



MK INTERNAL MEDICINE & CLINICAL SKILLS





MOSES KAZEVU

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By: Moses Kazevu

FOREWORD

This review book is designed for use by medical students and the junior medical doctor in the diagnosis, management and curative care of regional Adult internal medicine conditions.

The book serves as a good guide and revision tool for board/shelf/licentiate examinations.

Effort has been put in to simplify the literature and make it as practical as possible while maintaining scientific accuracy.

Despite all efforts, it is possible that certain errors may have been overlooked in this book. Please inform the authors of any errors detected.

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CHAPTER 1: INTRODUCTION

INTRODUCTION TO BEDSIDE MEDICINE

- The word "Patient" is derived from the Latin "patiens", meaning sufferance or forbearance.
- In order to relief this suffering (the purpose of medicine) it is imperative that:
  - A diagnosis is made to know how to approach treatment and design an appropriate scheme of management for each patient.
- It is also important to understand each person fully (with every social class or ethnic and cultural background).
- The role of the doctor is not only to elucidate the problems posed by disease but also apply his or her skill to advise patients and families how to manage these problems.
- No patient should leave a medical consultation feeling that nothing can be done to help them, even when the disease is incurable.
- Clinical methods are the skills doctors use to achieve this aim of excellence in clinical practice.
- Clinical methods are acquired by a combination of study and experience and there is always something new to learn.
- Initial aims of any first consultation are to understand the patient's own perception of their problem and to start or complete the process of diagnosis.
  - This requires sufficient knowledge of the disease and its patterns of presentation, together with an ability to interpret a patient's signs and symptoms.
- Difficulties posed by assessing the patients themselves, or by the variety of cultural and ethnic backgrounds found in modern life must be accepted and factored into the interpretation of the data acquired during the consultation.
- There are two main steps to making a diagnosis:
  a. To establish the clinical features by History taking and Examination-Clerking.
  b. To interpret the clinical database in terms of disordered function and potential causative pathologies.

SETTING THE SCENE

- Most medical consultations occur not only in the wards but in an outpatient or primary care setting.
- A suitable environment, waiting area and all the associated staff makes the process of clinical diagnosis easier.
- Meeting the patient in the waiting room allows the doctor to make an early assessment of their demeanor, their hearing, their walking and any accompanying persons.
- Offer a greeting and make an introduction.
- Patients are easily confused by medical titles and hierarchies. Quickly assess the following questions:
  - Does the patient smile or appear furtive or anxious?
  - Do they make good eye contact?
  - Are they frightened or depressed?
  - Are posture and stance normal?
  - Is the patient short of breath or wheezing?
- In some conditions e.g. congestive heart failure (CHF), uremia, severe jaundice etc. the nature of the problem is often immediately obvious.
- It is important to identify the patient correctly, especially if they have a name that is very common in the local community.
- Carefully check the full name, date of birth and address. Make sure any previous records you have are those of the correct patient, not of someone else with a similar name.
- It is important that both patient and doctor feel at ease and neither feels threatened by the encounter.
- Avoid having patients full-face across a desk.
- Note-taking is important during consultations while being able to see the patient and establish eye contact and to show sympathy and awareness of their needs during the discussion of symptoms, many of which may be distressing or even embarrassing.
- Arrange the seating so that it is clear the patient is the center of attention rather than any others present.

COMMUNICATION

- Communication is of two types: Verbal communication and Non-verbal communication.

NON-VERBAL COMMUNICATION

- Non-verbal communication is as important as what the patient says.
- There may be obvious contradiction e.g. a patient who does not admit to any worries or anxieties but who clearly looks as if they have many.
- Particular gestures during the description of pain symptoms can give vital clinical clues. (See box 1)
- While concentrating on the conversation with the patient, the doctor should remain aware of other clues.

BOX 1

Particular gestures useful in analyzing specific pain symptoms

- A squeezing gesture to describe cardiac pain
- Hand position to describe renal colic
- Rubbing the sternum to describe heartburn
- Rubbing the buttock and thigh to describe sciatica
- Arms clenched around the abdomen to describe midgut colic

VOCABULARY

- It is important to use vocabulary the patient will easily understand and use appropriately.
- The patient must understand the basic words used and their interpretation of those words must be understood and clarified by the doctor. (See Box 2)

BOX 2

Words and phrases that need clarification:

- Ordinary English words: Diarrhea, Constipation, Wind, Indigestion, Being sick, Dizziness, blackouts, headache, double vision, pins and needles, rash and blister

- Medical terms that may be used imprecisely by patients: Arthritis, Sciatica, Migraine, Fits, Stroke, Palpitation, Angina, Heart attack, Diarrhea, Constipation, Nausea, Piles/hemorrhoids, Anemia, Pleurisy, Eczema, Urticaria, Warts, Cystitis

- If the patient uses one of the ordinary English words listed in the box above their meaning must be clarified.
  - A patient who says they are dizzy could be describing actual vertigo, but could just mean light-headedness or a feeling that they were going to faint.
  - A patient saying that they have diarrhea could mean liquid stools passed hourly throughout the day and night, or could mean a couple of urgent soft stools passed first thing in the morning only.
- The doctor needs to use words that are almost certainly going to be clearly understood by the patient and must clarify any word or phrase the patient uses to avoid any possibility of ambiguity.

INDIRECT AND DIRECT QUESTIONS

- Questions asked by the doctor can be divided into:
  - Indirect or open-ended questions
    - Serve as an invitation for the patient to talk about the general area that the doctor indicates is of interest.
    - These questions often start with phrases such as 'Tell me more about', 'What do you think about", 'How does that make you feel', 'What happened next' or 'Is there anything else you would like to tell me'.
    - These questions inform the patient that the agenda is very much with them, that they can talk about whatever is important, and that the doctor has not prejudged any issues.
    - If skillfully used, and if the doctor is sensitive to the clues presented in the answers, a series of such questions should allow the doctor to understand the issues that are most important to the patient.
    - The patient will also be allowed to describe things in their own words. Always listen carefully, and maintain eye contact. Do not take too many notes!
  - Direct or closed questions
- Many patients are in awe of doctors and have a conscious or subconscious need to please and agree.
- If the doctor prejudges the patient's problem and tends to direct the conversation to fit the diagnosis that they have assumed too early, the patient can easily go along with this and give simple answers that do not fully describe the situation. The box below shows the extremely simple, common and important pitfall of history taking. (See Box 3, Table 1.1 and Table 1.2)

BOX 3

A general practitioner (GP) is seeing a 58-year-old man who is known to be hypertensive and a smoker. The receptionist has already documented that he is coming with a problem of chest pain. The GP makes an automatic assumption that the pain is most likely to be angina pectoris, because that is probably the most serious possible cause and the one that the patient is likely to be most worried about and starts taking the history with the specific purpose of confirming or refuting that diagnosis.

Table 1.1: Direct questioning

GP:	I gather you've had some chest pain?	The GP has only asked very direct and closed questions. Each answer has begun with "Yes". The patient has already been quite firmly tagged with a 'label' of angina, and anxiety has been raised by the specialist referral.
Patient:	Yes, it's been quite bad.	
GP:	Is it in the middle of your chest?	
Patient:	Yes.	
GP:	And does it travel to your left arm?	
Patient:	Yes- and to my shoulder	
GP:	Does it come on when you walk?	
Patient:	Yes.	
GP:	And is it relieved by rest?	
Patient:	Yes-usually.	
GP:	I'm afraid I think this is angina and I will need to refer you to a heart specialist.	

Table 1.2: Indirect questioning

GP:	Tell me why you have come today.	The GP has asked questions which are completely open-ended or leave the patient free to describe exactly what happens within a directed area of interest. Clarifying questions have been used. While being reassuring, the GP expresses some concern about angina and is clear about the exact reason for the specialist referral (for clarification).
Patient:	Well, I have been having some chest pain	
GP:	Tell me more about what it's like.	
Patient:	It's in the center of my chest and tends to go to my left arm. Sometimes it comes on when I've been walking.	
GP:	Tell me more about that.	
Patient:	Sometimes it comes when I am walking and sometimes when I'm sitting down at home after a long walk.	
GP:	If the pain comes on when you are walking, what do you do?	
Patient:	I usually slow down, but if I'm in a hurry I can walk on with the pain.	
GP:	I am a little worried that this might be angina but some things suggest it might not be, so I am going to refer you to a heart specialist to make sure it isn't angina.	

PATIENTS, ACCOMPANYING PERSONS AND ADVOCATES

ANGRY PATIENTS

- Not all patients are overtly angry when they see a doctor, but anger expressed during a consultation may be an important diagnostic clue while at the same time getting in the way of a smooth diagnostic process.
- It is always important to acknowledge anger, try and discover what underlies it, and apologize for simple things such as late running.
- In some patients, anger may be part of the symptomatology, or expressed as a reaction to the diagnosis or treatment.

THE WELL-INFORMED PATIENT

- 20 or more years ago doctors often looked after patients for a long time without really explaining their illness to them, and patients were reasonably happy about this, taking the attitude that 'the doctor knows best'.
- This approach is now unacceptable and the doctor must give the patient as much information about their illness as possible, particularly so that they can make informed choices about treatments.
- This change of approach has led to many patients seeking information about their problems from other sources, particularly the internet.
- The doctor should thus go through the information with the patient and help them by showing what is relevant and what is not.
- Generally, it is much easier and more rewarding to look after well-informed patients, provided they do not fall into the very small group who have such fixed and erroneous ideas about their problems that the diagnostic and treatment process is impeded.

ACCOMPANYING PERSONS

- Some people come to consultations alone, others with one or more friends or family members.
- Always spend time during the initial exchange of greetings to identify who is present and to get some idea of the group dynamics.
- There is always a reason why people come accompanied but if there appears to be too many people present or if the presence of others might threaten the relationship with the patient at any time in the consultation, it is appropriate to consider asking the others to leave, even if only briefly.
- Consider whether specific questions about history should be asked of those accompanying, either with the patient or separately with specific consent.
- Beware of a situation where the accompanying people answer all the questions, even if there is no language difficulty.
- Reasons for this may include embarrassment in front of those accompanying, such as a teenager accompanied by parents. In such circumstances it may be necessary to leave parts of the history until those accompanying can be reasonably asked to leave.

USING INTERPRETERS/ADVOCATES

- Consultation has to be undertaken with the help of an interpreter.
- The most immediate solution may be to use a family member, but if the issues are private or embarrassing this often does not work well and it is generally unwise to use an underage family member as an interpreter.
- The best solution is to have available an independent interpreter/advocate for the consultation, although in areas where many patients are not native speakers, many such interpreters may be needed for a range of languages.
- The history taken via an interpreter or advocate may be quite limited in subtlety by the exigencies of the double translation, and the doctor therefore often utilizes a much more direct style of questioning for which the answers will be unambiguous.
- Unfortunately, it is not unusual for the interpreter/advocate and the patient to have a few minutes of conversation following an apparently simple question from the doctor but then a very short answer is returned to the doctor.
- This leaves the doctor bemused as to what is really going on.
- History taking via an advocate/interpreter usually takes much longer than when the doctor and the patient speak the same language.

CLARIFYING DETAIL

- One of the basic principles of history taking is not to take what the patient says at face value but to clarify it as much as possible.
- Almost all of the history will involve clarification, but there are specific areas where this is particularly important.

PAIN

- Whenever a patient complains of pain you should follow a series of clarifying question such as ('SOCRATES'):
  - S-site
  - O- onset
  - C-Character
  - R-radiation
  - A-alleviating factors
  - T-time course
  - E-Exacerbating factors
  - S-severity and symptoms (Associated)
- Of all symptoms, pain is perhaps the most subjective and the hardest for the doctor to truly comprehend.
- Some painful conditions have a classic site for the pain and the radiation
  - Myocardial ischemia is classically felt in the center of the chest, radiating to the left arm
  - Pain from a hollow organ is classically colicky (such as biliary or renal colic)
  - The pain of subarachnoid hemorrhage is classically very sudden, 'like a hammer blow on the head'
- Some pains have clear aggravating or relieving factors
  - Duodenal ulcer pain is classically worse when hungry and better after food.
  - Gastric ulcer pain is classically worse during feed and better during hunger.
  - Pain for pericarditis is worsened by laying down and relieved by sitting and leaning forward
- Colicky right upper quadrant abdominal pain accompanied by jaundice suggests a gallstone obstructing the bile duct, headache accompanied by preceding flashing lights suggests migraine.
- Some of these points will come out in the open-ended part of the history taking, but others will need specific questions.

CHAPTER 2: HISTORY TAKING

HISTORY TAKING

- History taking is immensely skilled and fascinating.
- The medical history is the foundation of internal medicine. The answer to the patient's problems is in the history 90% of the time! The other 10% of the time, you will need to use investigations to help you figure the answer out.
- The extent of which history taking skill increases with experience is much greater than that for clinical examination.
- It is an art that has to be mastered to reach correct diagnosis.
- The sequence of history taking includes:
    1. Collection of demographic data (i.e. name, age, sex/gender, residence, religion, marital status)
    2. Presenting complaints (Complaining of-C/O)
    3. History of presenting complaints (Development of history) (HxPC)
    4. Review of systems (ROS)
    5. Past medical history (PMHx) and Past surgical history
    6. Drug history and Allergies (specially to drugs and other allergies to other material)
    7. Family history
    8. Social-economic history
    9. Summary of history

COLLECTION OF DEMOGRAPHIC DATA

- The process of history taking may begin by reading any referral documentation and with the immediate introduction of doctor and patient.
- Collection of demographic data includes asking questions involving the patient's details i.e. name, age, sex/gender, residence, religion, tribe and marital status.
- Collection of this information is vital in leading to the correct diagnosis for example, patients of a certain age, sex or even region of residence are prone to certain diseases and conditions.
    - Example 1: A Patients from the Eastern province presenting with signs and symptoms of hepatocellular carcinoma is most likely to have this malignancy. This is due to the storage of the groundnuts in the region which happen to contain afla-toxins produced by *Aspergillus* that participates in the development of this type of malignance.
    - Example 2: Most patients with sickle cell are from Northern, and Luapula province (i.e. the Bembas).
    - Example 3: Most patients with benign prostatic hypertrophy are from southern province (due to excessive use of herbal medicine to enhance sexual activity in an attempt to satisfy their polygamous marriage practices).
    - It is also important to know that most malignancies are most likely to occur at a certain age.
- With this demographic data, the physician is given a rough idea of how the presenting complaints could most likely be linked with certain factors such as age, sex, region of residence and tribe.
- The patient should be informed about the ongoing order of things in-order to prevent them from feeling that their pressing problems are being ignored.
    - A statement along the lines of 'Before we discuss why you come today, I want to ask you some background questions' should inform the patient satisfactorily.
- It is also important to indicate whether this is a hospital referral or a self-referral along with the date and time of which the history was taken.

PRESENTING COMPLAINTS

- Once social introductions are established the doctor will usually begin with a single open-ended question along the lines of 'Tell me what has led to you coming here today.'

- This gives the patient a chance to begin with what they feel is most important to them and avoids any pre-judgement of issues or exclusion of what at first may seem less important.
  - At this stage the patient may be very anxious and nervous and still making their own assessment of how they will react to the doctor as a person.
  - Therefore, a beginning that focuses on issues that may be more factual and less emotive (emotional) can be more rewarding and lead to a more satisfactory consultation.
- Try to understand the patient's mood: sometimes the response to your initial question will be vague or concrete or even hostile; the latter suggests emotional conflict and needs to be talked through.
- It is very tempting to interrupt too early but once interrupted the patient rarely completes what they were intending to say.
  - Even when they seem to have finished giving their reasons for the consultation always ask if there are any broader areas that still need discussion before discussing each in detail.
- Complaints must be in chronological order and should be recorded in the patient's own words.
- Taking the history along a "time-line" will often build up a much better picture of all the patient's problems, how they have developed and how they now interact with their life and work.
- It is also of importance to enquire about the duration of the complaint.
- These can be written in point form for example:
  - Cough complaints 2/52
- Writing the duration of the complaint must be in a particular manner e.g. 1/7 representing 1 day, 2/52 representing 2 weeks, or 4/12 representing 4 months.

HISTORY OF PRESENTING COMPLAINTS

- This should be a story about how the symptoms developed. Use the patient's own words as much as possible.
- Avoid medical terminology (like the word 'angina') unless the patient actually uses that word and when the patient uses medical terms it should be place in inverted commas e.g. 'orthopnea'.
- Usually a patient will say "chest pain" instead of "angina".

- Begin with the earliest symptoms related to the chief complain and proceed chronologically.
  - For example: "The patient described chest pain when walking up a hill four weeks ago. This resolved with rest and recurred with activity. Eventually the chest pain subsided and the patient began to experience shortness of breath when walking short distances. One week ago, the patient began to notice that they were short of breath when lying flat and began having swelling of his legs."
- Ask the patient to explain the illness in detail including:
  - Mode of onset: acute, subacute or insidious
  - Duration of illness
  - Whether the disease has progressed or remains the same
  - Associated symptoms
  - Aggravating and relieving factors
  - Positive history to rule out (r/o) involvement of other systems
- The history of presenting complaints must exhaust all possible symptoms of the presenting symptoms for example if a patient presents with diarrhea for a duration of 2 days, the history of presenting complaints must focus on the gastrointestinal system.

REVIEW OF SYSTEMS

- This is done in order to find out any other possible symptoms that may have been left out as well as to gather more details about the affected system of the presenting problem.
- The system that is involved in the presenting complaint should be reviewed within the history of presenting complaints.
- Usually the review of systems (ROS) is done from head to toe (Central nervous system [CNS], Cardiovascular system [CVS], Respiratory system [RS], Gastrointestinal tract [GIT], Genitourinary system [GUT], Musculoskeletal system and skin [MSS]).
- Review every system every time you take a history, but when you present the patient, only mention the ones that are important negatives and positives related to the presenting complaint.
- If you don't know which systems are relevant to the history of presenting complaint, it is always better to include more information than less.

DIRECT QUESTIONS ABOUT BODILY SYSTEMS

- Many diseases have features occurring in several bodily systems that at first may not seem to be related to the patient's main complaint.
- For example, a patient presenting with back pain may have had some hematuria from the renal cell carcinoma that has spread and is causing pain.
- For this reason, any thorough assessment must include questions about all bodily systems, and not just areas that the patient perceives as problematic.
- This area of questioning should be introduced with a statement such as 'Now I am going to ask you some extra questions.'

Table 2.1: Bodily systems and questions relevant to taking a full history from most patients. If the specific questions have been covered by the history of the presenting problem, they do not need to be included again. If the answers are positive then the characteristic of each must be clarified.

Cardiovascular system	-Chest pain: location, character, radiation to neck, shoulder and arm, alleviating and exacerbating factors? -Shortness of breath: on exercise or at rest? Amount of exertion? -Paroxysmal Nocturnal dyspnea: breathlessness at night that awakens the patient from sleep? - Orthopnea: difficulty in breathing especially when lying flat. -Intermittent claudication: pain caused by too little blood flow usually during exercise and especially in the legs -Palpitations: patient can feel their own heartbeat/ pounding heart? -Ankle swelling and swelling of legs -Bluish discoloration: tongue, lips, hands and ear lobes?
Respiratory system	-Cough- with or without sputum? -Hemoptysis- blood in sputum? -Pus in sputum -Fever with chills and rigors? -Night sweats? -Wheezing?
Gastrointestinal system	-Abdominal pain -Nausea and/ or vomiting: color, smell, content, blood, frequency? -Dysphagia: Difficulty in swallowing? -Change in appetite: increase or decrease - Weight loss or gain -Dyspepsia: indigestion? -Bowel pattern and any change: loose stools, constipation? -Rectal bleeding: Black stools (melena), blood in stools (hematochezia)?

	-Jaundice: Yellowish discoloration of skin and eyes?
Genitourinary system	-Hematuria: Blood in urine? -Nocturia: urination at night? -Polyuria: increased frequency of urination? -Dysuria: pain during urination? -Menstrual irregularity- women -Vaginal discharge in women -Urethral discharge- men -Suprapubic pain/ pain abdomen? -Dribbling of urine? -Delay in urination (urinary hesitancy)? -Change in color of urine?
Musculoskeletal system and Skin	-Joint pain -Change in mobility: Stiffness in joints? Difficult in walking? -Swelling of joints? -Back or neck pain? -Skin rash?
Central nervous system	-Seizure/ tremors -Collapse or blackouts or fainting -Dizziness and loss of balance -Transient loss of function (vision, speech, sight) -Paresthesia: tingling, "pins and needles" -Weakness or numbness in arms and legs -Wasting -Spasms and involuntary movements -Pain in limbs and back -Headache -Change in sleep patterns -Mood swings -Memory loss
Endocrine	-Swelling in the neck? -Increased sweating? -Intolerance to cold or hot weather? -Generalized weakness/fatigability? -Mood swings, irritability, restlessness? -Protrusion of eyes? -Skin changes?

- If other systems do not show any positive signs towards the presenting complaint it is vital to mention that the other systems were non-revealing.

PAST MEDICAL HISTORY

- There is a particular logic in taking the past medical history at this stage. For many conditions that patients may bring to a new doctor, the distinction between what is a current problem and what is past history is unclear and arbitrary.
  - For example, a patient presenting with an acute exacerbation of chronic obstructive pulmonary disease may have a history of respiratory problems going back many years.
- It is important to ask if the patient was having a similar complaint in the past and if they were treated for it.
- One way to figure out if they have any chronic medical problems is to ask if they have ever gone to the clinic or if they are on any medication.
- The past medical history should include past admissions, history of similar illness, chronic medical problems as well as history of blood transfusion.
- Area of interest may include History of Diabetes mellitus, Epilepsy, Asthma, Tuberculosis, Hypertension, Human immunodeficiency virus (HIV), and sickle cell disease (Remember D.E.A.T.H.S).
- At this point the patient will most likely continue to talk much more than the doctor but it still remains vital for the doctor to steer and mould the process so that the information gathered is complete, coherent and if possible logical.
- Some patients will present a clear, concise and chronologically perfect history with little prompting, although these are in a minority.
- For most patients the doctor will need to do a substantial amount of clarifying and summarizing, with statements such as:
  - 'You mean that'
  - 'Can I go back to when'
  - 'Can I check I have understood'
  - 'So up to that point you'
  - 'I am afraid I am not at all clear about'
  - 'I really do not understand; can we go over that again?"
- If the patient clearly indicates that they do not wish to discuss particular aspects of the history, this wish must be respected and the diagnosis based on what information is available.

PAST SURGICAL HISTORY

- Previous surgical procedures-indications, procedure and any complications involved.

DRUG, ALLERGIES AND TREATMENT HISTORY

- Past medication: What medication has the person taken for the condition or any other underlying condition?
- Current medication:
  - Is the patient on treatment now? What medication are they taking and what are the dosages?
  - Was the patient on alternative therapies like homeopathy and ayurvedic medication.
- History of allergy to drugs such as sulfur containing drugs e.g. Fansidar, septrin as well as penicillin associated allergies.
- It is also important to include history of previous immunization where applicable (especially in children).

GYNAE HISTORY (IF APPLICABLE)

- Include:
  - Last menstrual period
  - Regularity of periods
  - Amount and nature of flow
  - Use of contraceptives (especially oral)

FAMILY HISTORY

- Number of siblings.
- History of similar complaints in family members.
- Any major illness in family members (D.E.A.T.H.S).
- Cause and age of death of family members.

SOCIAL-ECONOMIC HISTORY

- Education status.
- Occupation- to rule out occupational diseases.
- Lifestyle-sedentary or hard work.
- Social and financial status.
- Living conditions: number of room, ventilation, source of water and toilet use (in door or outdoor).

- Diet- vegetarian or mixed diet.
- Smoking- duration, number of packs per day, type of cigarettes.
- Alcohol consumption- quantity, duration, type of alcohol
- Drug addictions.
- Tobacco and betel nut chewing.
- Sexual history including number of current partners (or number of partner in the past month).
- History of recent travel.

SUMMARY OF HISTORY

- This is one sentence that summarizes the important parts of the history. Include identifying information, presenting complaint, a very brief description of the history of presenting complaints plus essential details from ROS, PMHx, Family and social-economic Hx.
  - For example: "This is D. J a young male newly diagnosed with Pulmonary Tuberculosis, who presented with a 2-week history of difficult breathing which was associated with chest pain, fever, weight loss, night sweats and a TB contact."
- In the summary do not use the name (use initials) and use an estimated age range i.e.
  - <45 years: young age
  - 45-65 years: middle age
  - > 65 years: old age

IMMPRESSION AND DIFFERENTIALS

- These are based on the history given.
- The impression and differentials must be accurately related and correlated to the information obtained in the history.

PHYSICAL EXAMINATION

- This is a brief overview of the physical exam. More detailed information on each system is provided in the relevant subsequent chapter.

GENERAL EXAMINATION

- Always start with the general exam followed by Vitals.
- At the end of the general exam, report the vital signs. For example: "ill appearing middle aged male, who was extremely wasted and lying in bed. The vital signs are BP: 105/70mmHg, Pulse rate 105 beats/min (for pulse mention the rhythm i.e. regular/irregular, character i.e. volume and rate as well as presence of radial-radial synchronicity), Oxygen saturation of 92%, Temperature of 37.7 degrees Celsius."

SYSTEMIC EXAMINATION

- After reporting the general exam, report the systemic exam. Report the most affected organ systems first. If the patient presents with diarrhea, present GI first, then go on to other systems.
- Do a complete physical exam of each organs systems related to the presenting complaint and for abnormal findings in other systems.
- Each organ system ought to be examined in the same order:
  - Inspection
  - Palpation
  - Percussion
  - Auscultation
- As a junior medical student/ doctor, it is best to report "On inspection… On palpation…. On percussion… On auscultation…" this way you will not forget any part of the examination and you will keep things in the correct order.
- The only exception to this rule would be for the CNS. Also for the CVS exam we start out with the inverted J (check radial pulse, blood pressure and JVP, then proceed to Inspection, palpation, percussion and auscultation with the precordium and rest of the CVS exam).
- After all systemic examinations ALWAYS perform a bedside urinalysis.

SUMMARY

- This summary is two sentences. The first one is a repetition of the first summary, the second sentence is a summary of the physical findings.
  - For example, if the patient has a respiratory exam with decreased tactile fremitus, stony dullness on percussion, and decreased breath sounds on auscultation, you can say that they have exam findings consistent with a pleural effusion.
- In the summary do not use the name (use initials) and use an estimated age range i.e.
  - <45 years: young age
  - 45-65 years: middle age
  - > 65 years: old age

IMPRESSION/ DIFFERENTIALS/ PROBLEM LIST

- This includes the most likely causes of the presenting complaint.
- When listing differentials, it is important to list them in order of most likely cause to least likely cause.
- It is also important to ensure that each of the differentials can be correctly associated with the presenting complaints or any information elicited from the history and physical exam.

PLAN

- Your plan should include both investigations and treatments (pharmacological and non-pharmacological).
- It is best to organize your plan by starting with investigations and treatments you want for each of your impressions.
- For example, for Retroviral disease I want to send a CD4 count, viral load and get baseline labs (Full blood count, Urea & Electrolytes, Creatinine and Liver enzymes-AST, ALT), for Tuberculosis I want to get sputum for Acid fast bacilli (AFB), check Full blood count with differential count (FBC-DC), and get a chest x-ray.
- This will help you in the future because your plan will be the same every time you see that diagnosis.

CHAPTER 3: PHYSICAL EXAMINATION

PHYSICAL EXAMINATION

- It is important to develop a routine of physical examination that combines speed with thoroughness, sensitivity and alertness but which disturbs the patient no more than necessary.
- The examination must be carried out as gently as possible, without tiring the patient needlessly.
- In severely ill patients it may be necessary to postpone a routine examination and to perform only that required for provisional diagnosis and treatment.
- Different doctors use different routines in different circumstances. Start the examination in a manner that is relevant to the patient's symptoms e.g. if the presenting symptom is sciatica, start with the legs and the spine.
- A systematic approach to each functional system is essential in order to obtain information that is both complete and relevant. Always try to be thorough.

GENERAL APPROACH

- The physical examination starts from the moment you meet the patient- you will be able to notice aspects of their general demeanor (general condition), nutrition and personality at first acquaintance which will be important in your approach to the history.
- Every moment of your contact with patient, every gesture and every communication is full of information.
- Ideally a chaperone should be present when a male doctor is examining a female patient, both to reassure the patient and to protect the doctor from subsequent accusations of improper conduct.
  - A chaperone is essential when conducting an intimate examination such as vaginal or rectal examination.

- In considering the patient's general appearance, it is important to make a rapid assessment of the degree of illness. This is not making a diagnosis. Simply consider the question: 'Does this patient look well, mildly ill or severely ill, thus needing urgent attention?'
- Experienced nurses are often highly skilled in this kind of assessment and their opinion should never be ignored.
- Every moment of the consultation is important.
- Certain abnormalities may sometimes be recognized as soon as you meet the patient, and you may well notice things about them during history taking e.g. shortness of breath, pallor, jaundice, parkinsonism, stroke, skin rashes and other features may be recognized immediately.
- For a thorough examination the patient should be asked to undress completely, or at least to their underclothes and to lie or sit on the couch or bed partially covered with a sheet or dressing gown.
- For restricted examinations such complete exposure is not necessary.
- Watching the patient getting undressed or dressed is often revealing of neurological and rheumatological disorders and may also reveal the degree of any pain or shortness of breath.
- The examination begins on meeting the patient and continues until the consultation ends.
- An abnormal finding on examination may indicate the need for further questions- do not hesitate to revisit the history in the light of such findings at the end of the examination.
- The general examination is usually done in either sitting or lying position.
- A summary plan for the general physical examination include
  - General condition
  - Mental state
  - Nutrition status
  - Hands
  - Axillae
  - Neck
  - Face
  - Skin
  - Temperature
  - Pulse
  - Respiration
- The object of a routine examination is to check the different bodily systems to exclude abnormality.
- Always begin every examine by washing hands, requesting permission from the patient and placing the patient in the right position while having them exposed appropriately.

- Always remember for every examination begins at the foot end of the bed then this is followed by proceeding to the right side of the bed/patient.
- Examine both sides of the body and not just focus on one side.

GENERAL APPEARANCE

- Much can be learned from a general inspection of the patient's physique. Ask yourself the following questions:
  - Is the patient generally looking well, stable, ill, or toxic?
  - Is the appearance consistent with patient's chronological age?

MENTAL STATE

- Make some initial assessment of the patient's intelligence and mental and emotional state but recognize that this initial impression may be inaccurate.
  - Is the patient looking happy, sad/depressed or anxious?
  - Is the patient cooperative and following orders?
  - Is the person oriented in time, place and person? (O.T.P.P)

NUTRITIONAL STATUS

- Comment on the nutritional status and general physique of the patient
  - Is the nutrition fair, good or poor?
  - Is he or she tall, short, fat, thin, muscular or asthenic?
  - Is he or she wasted or obese?
- A history of weight gain or loss can be checked by observation, remembering that fluid retention (Edema) will increase weight.
- Obvious weight loss, even when food intake has increased, is a feature of thyrotoxicosis and diabetes mellitus.
- Psychogenic loss of appetite usually affecting girls (anorexia nervosa) causes extreme emaciation while physical activity remains unimpaired.

THE HANDS

- The patient's hands should be carefully examined (from the right side of the bed).
- A range of abnormalities may be present in the structure and function of the hands, including evidence of arthritis, neurological disease, liver disease anemia and acromegaly.
- Classic appearances that should always be sought include:
  - Finger clubbing,
  - Koilonychias, which occurs in long-standing iron deficiency anemia
  - Nailbed 'splinter' hemorrhages,
  - Dupuytren's contracture

- Also check for capillary refill type, peripheral cyanosis and palmar pallor.
- Tremor should be assessed carefully, distinguishing between a fine tremor such as that due to thyrotoxicosis and the coarse jerky tremor of metabolic encephalopathy.
- In hypertrophic pulmonary osteoarthropathy, bedside clubbing of the fingers there is tender thickening of the periosteum of the radius, ulna, tibia and fibula.
- At this moment you can also take vitals:
  - Temperature: the person febrile or afebrile to touch. Measure the axillary temperature.
  - Pulse: Count up to 30 seconds and multiple by 2. Comment on the Rate, volume, regularity of the pulse and presence radio-radial as well as radio-femoral synchronicity.
  - Respiratory rate: Count the patient's respiration for a full minute starting when their attention is directed elsewhere. This can be done the same time the pulse is being done.
  - Blood pressure: measure using appropriate cuff.

THE AXILLAE

- Before proceeding to examine the axilla, examine the epitrochlear lymph node.
- Examine the axillae.
- It is difficult to feel enlarged lymph glands unless the patient's arm is raised to allow the examining fingers to be pushed high into the axilla.
- The arm is then lowered in the flexed position to rest across the examiner's arm and palpation is continued downwards along the chest wall.

THE NECK

- The neck should be inspected and palpated.
- Swellings in the neck are usually best felt from behind.
- Careful note should be taken of lymph glands and the thyroid.
- Carefully assess the major arteries and veins palpable in the neck.

FACIAL APPEARANCE

- Observe the patient's face.
- The expression and particularly the eyes, indicating real feelings better than words. Some diseases e.g. Parkinson's disease, depression, hypothyroidism, thyrotoxicosis, acromegaly, CNIII and CNVII palsies and paralysis of the cervical sympathetic nerve (Horner's

syndrome) produce characteristic facial appearances.

- Check the eyes for pallor, jaundice
- Parotid swellings are obvious on inspection of the face.
- Check the mouth for cyanosis, dental caries, oral thrush, stigmata of anemia (angular stomatitis, atrophic glossitis) and any Kaposi's sarcoma lesions on the palate.
- The cheeks give information regarding the patient's health:
  - In anemia and hypopituitarism, they are pale
  - In nephrotic syndrome they are pale and puffy
  - In mitral stenosis there is sometimes a bright circumscribed flush over the malar bone
  - In many persons who lead an open-air life they are red and highly colored.
  - In congestive heart failure they may also be highly colored, but the color is of a bluish tint which cannot be mistaken for the red cheeks of weather-beaten people.
  - In some cases of systemic lupus erythematosus there is a red raised eruption on the bridge of the nose that extends on the cheeks in a 'butterfly' distribution.
  - Telangiectasia, minute capillary tortuosities or naevi, may be seen on the face in liver disease and rarely, as a hereditary disorder.

THE FEET

- The feet must not remain obscured under bedclothes or socks during the examination.
- Pitting edema may be recognized only in the ankles and dorsal surfaces of the feet.
- The condition of the skin of the feet is especially important in diabetics and the elderly.
- Peripheral vascular disease will make the skin shiny and hair does not grow on ischemic legs or feet.
- The dorsalis pedis and posterior tibial pulses may be reduced or absent.
- If the toes of an ischemic foot are compressed their dull purple color will blanch and only slowly return.
- Passive elevation of an ischemic leg will cause marked pallor of the foot as perfusion against gravity falls.
- Painless trophic lesions often with deep ulceration on the soles are seen frequently in diabetic peripheral neuropathy (the diabetic foot)

ORDOURS

- The odor of alcohol is easily recognizable on the breath although patients may try and mask it by sucking a mint but it does not necessarily mean the patient's condition is due to alcohol intoxication.
- The odor of diabetic ketosis has been described as 'sweet and sickly', that of uremia as 'ammoniacal or fishy' and that of hepatic failure as 'mousy' but too much reliance on such delicate distinctions is unwise.
- Halitosis (bad breath) is common in patients whose dental hygiene has been poor and is associated especially with chronic gingivitis (periodontal or gum disease)

AFTER EVERY EXAMINATION

- Always thank the patient and leave them covered.
- Always wash hands.
- Summarize your findings and offer a differential diagnosis based on your findings.
- The general examination is always followed by specific examination of each individual system. This will be discussed in each respective chapter.

CHAPTER 4: CARDIOLOGY

CARIDOVASCULAR CONDITIONS

APPROACH TO CARDIOVASCULAR DISEASE

CARDIAC SYMPTOMS

- The symptoms caused by heart disease result most commonly from myocardial ischemia from disturbance of contraction and/or relaxation of the myocardium, from obstruction to blood flow, or from an abnormal cardiac rhythm or rate.
- Ischemia is manifest most frequently as chest discomfort, while reduction of the pumping ability of the heart commonly leads to fatigability and shortness of breath or when severe produces cyanosis, hypotension, syncope and elevated intravascular pressure behind a failing ventricle.
- Failing of a ventricle results in abnormal fluid accumulation, which in turn leads to dyspnea, orthopnea and systemic or pulmonary edema.
- Obstruction to blood flow as in valvular stenosis, can cause symptoms resembling those resulting from congestive heart failure.
- Cardiac arrhythmias often develop suddenly, and the resulting signs and symptoms- palpitations, dyspnea, hypotension, presyncope and syncope- generally occur abruptly and may disappear as rapidly as they develop.
- Ischemic heart disease by far are the most common form of heart disease in adults may present with chest discomfort but also as heart failure, tachyarrhythmia and sudden cardiac death.
- Myocardial or coronary function that may be adequate at rest may be inadequate during exertion. Thus chest discomfort and/or dyspnea that appear only during activity are characteristic of heart disease, while the opposite pattern i.e. appearance of these symptoms at rest and their remission during exertion, is rarely observed in patients with organic heart disease.
- Many patients with cardiovascular disease may also be asymptomatic both at rest and during exertion, but may present an abnormal physical

finding such as a murmur, elevated arterial pressure or an abnormality of the electrocardiogram (ECG) or the cardiac silhouette on the chest X-ray.

- Patients may exhibit asymptomatic ischemia on an exercise stress test.
- In some asymptomatic patients the first clinical event may be catastrophic- sudden cardiac death, acute myocardial infarction or stroke.
- Dyspnea, one of the cardinal manifestations of heart failure, is not limited to patients with heart disease but is also observed in conditions as diverse as pulmonary disease, marked obesity and anxiety. Similarly, chest discomfort may result from a variety of causes other than myocardial ischemia.
- Whether heart disease is responsible for these symptoms can frequently be determined by carrying out a careful clinical examination as well as performing certain noninvasive tests such as electrocardiography, echocardiography, X-ray and myocardial imaging.

DIAGNOSIS

- As outlined by the New York Heart Association, the elements of a complete cardiac diagnosis include consideration of the following:
  - The underlying etiology: is the disease congenital, infectious, hypertensive or ischemic in origin?
  - The anatomic abnormalities: which chamber are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?
  - The physiologic disturbances: is an arrhythmia present? Is there evidence of congestive heart failure or of myocardial ischemia?
  - Functional disability (status): how strenuous is the physical activity required to elicit symptoms?

Table 4.1: New York Heart Association Functional classification	
Class I (No limitation)	No limitation of physical activity No symptoms with ordinary exertion
Class II (Mild limitation)	Slight limitation of physical activity Ordinary activity causes symptoms
Class III (Moderate limitation)	Marked limitation of physical activity Less than ordinary activity causes symptoms Asymptomatic at rest
Class IV (Marked limitation)	Inability to carry out any physical activity without discomfort Symptoms at rest

- The establishment of a correct and complete cardiac diagnosis often commences with the history and physical examination.

CARIDIOVASCULAR EXAMINATION

- Before starting the examination of the cardiovascular system
  - Wash hands and introduce yourself to the patient.
  - Confirm the patient's details.
  - Explain the examination and gain consent.
  - The entire cardiovascular examination is best performed with the patient sitting at 45 degrees in cardiac position. (remember when presenting don't forget to mention that you examined a patient propped up in bed at 45 degrees).
  - Ask the patient to expose the chest fully.
  - Always remember to start your examination at the foot end of the bed and then proceed to the right side of the bed.

GENERAL INSPECTION

- From the foot-end of the bed:
  - Look around for any ECG equipment, heart monitoring equipment, oxygen masks and tanks, urinary bags and catheters, cannula in situ, medicines, nutritional supplements and adjuncts that can be used for cardiovascular diseases.
  - Observe the patient's general appearance (age, state of health, nutritional status and any obvious signs).

- Is the patient comfortable?
- Is the patient in obvious discomfort or pain?
- Is the patient breathless or cyanosed?
- Are they in any obvious respiratory distress?

➢ Inspect the precordium for the presence of any abnormal pulsation and the chest for any scars, traditional markings, median sternotomy (which might have been performed for coronary artery bypass grafting, for valve surgery or for the repair of a congenital defect). DO NOT MISS A PACEMAKER IF IT IS THERE!

INSPECTION

INSPECTION AND EXAMINATION OF THE HANDS

- This would normally be done and reported as part of the general examination unless only a focused cardiovascular examination is done.
- From the right side of the bed, take both hands noting:
  - ➢ Temperature- febrile or afebrile to touch?
  - ➢ Color- presence of palmar erythema (chronic liver disease, polycythemia)
  - ➢ Presence of palmar pallor (Anemia)
  - ➢ Presence of finger clubbing (subacute infective [bacterial] endocarditis, cyanotic congenital heart disease- tetralogy of fallot, atrial myxoma [tumor])- there will be loss of Schamroth's window.
  - ➢ Presence Tar staining- smoking associated with atherosclerosis.
  - ➢ Presence of splinter hemorrhages (subacute infective endocarditis)
  - ➢ Presence of any nail signs- Leukonychia (hypoalbuminemia) or koilonychias (iron deficiency)
  - ➢ Check for capillary refill time (normal= <2s).
  - ➢ On the palms check for Janeway's lesion- non-tender small erythematous or hemorrhagic macular, papular, nodular lesions only a few mm in diameter (infective endocarditis) and Osler's node- painful, red, raised lesions found on the hands and feet caused by immune complex deposition (infective endocarditis, SLE, disseminated gonococcal infection).

INSPECTION AND EXAMINATION OF THE FOREARM AND ARM

- Determine the radial pulse and assess: count for 30 seconds and multiple by 2.
  - Rate: palpate the right radial artery. Note tachycardia (>100 bpm) or bradycardia (<60bmp).
  - Rhythm: note whether the rhythm is regular (no missed or extra beats) or irregular. If there is sinus arrhythmia, the heart rate will slow slightly whenever the patient breaths out.
  - Volume: Assess the volume (increased/decreased-full volume or thready?).
- Synchronicity: is the radial pulse synchronous with both the contralateral radial pulse and the femoral pulsation?
  - Radial-radial delay indicates aortic coarctation, aneurysm of aorta, atherosclerosis of aorta, pulseless disease (Takayasu's disease), peripheral embolism, pressure of axillary artery by tumor, lymph nodes
  - Radial-femoral delay indicates aortic coarctation (it is an important diagnostic clue in a young hypertensive), atherosclerosis of the aorta, thrombosis or embolism of aorta
- Radial, brachial, carotid, femoral, popliteal and pedal pulses commonly assessed.
- Check for collapsing pulse (aortic regurgitation)- feel the pulse on the left hand side then while doing this lift the arm and note the pulse. Before doing so ask patient if it is ok to do this and if they do not have any pain in the shoulder.
- At this point do not forget to palpate the epitrochlear lymph nodes.
- Measure blood pressure (state you would ideally do this in the exam of course if not done)
  - Blood pressure should be checked first in the sitting position in both arms. If you are concerned about hypovolemia, check the blood pressure and pulse in standing, sitting and lying positions.
  - Patients must be sitting with feet flat on the floor with blood pressure cuff above the elbow, with the width of the cuff being at least 40% of the circumference of the arm.
  - Place the diaphragm of the stethoscope over the brachial artery on the ventral surface of the elbow.

- Inflate the blood pressure cuff until the pulse is totally occlude, slowly deflate the cuff and listen for the appearance of the korotkoff sounds:
  - Phase 1: the first appearance of sound= the systolic blood pressure
  - Phase 2 and 3: increasingly loud sounds
  - Phase 4: abrupt muffling of the sounds
  - Phase 5: disappearance of the sounds= diastolic blood pressure

- At this point the axillary lymph nodes can be palpated.

INSPECTION AND EXAMINATION OF THE HEAD AND NECK

- Check carotid pulse- assess volume/character (assess each side individually) NEVER PALPATE BOTH CAROTID PULSES SIMULTANEOUSLY.
  - Waveform of the carotid pulse
    - Tardus et parvus: the carotid pulse is slow and small
    - Biphasic pulse: two systolic peaks
    - Alternating pulse: alternating high and low systolic peaks
    - Paradoxical pulse: more than 10mmHg decline in systolic blood pressure during inspiration
- Check jugular venous pressure
  - Observe for a visible JVP along the border of sternocleidomastoid
    - Have the patient to turn his head slightly to the left side, look at the internal jugular vein medial to the clavicular head of sternocleidomastoid. Assuming that the patient is at 45 degrees, the vertical height of the jugular distension from the sternal angle should be no greater than 4 cm.
    - Kussmaul's sign: paradoxical rise in jugular venous pressure during inspiration.
  - Check for hepato-jugular reflux:
    - Apply pressure to the liver (right upper quadrant)
    - Observe for a rise in JVP
    - Positive result= Sustained rise greater or equal to 4cm

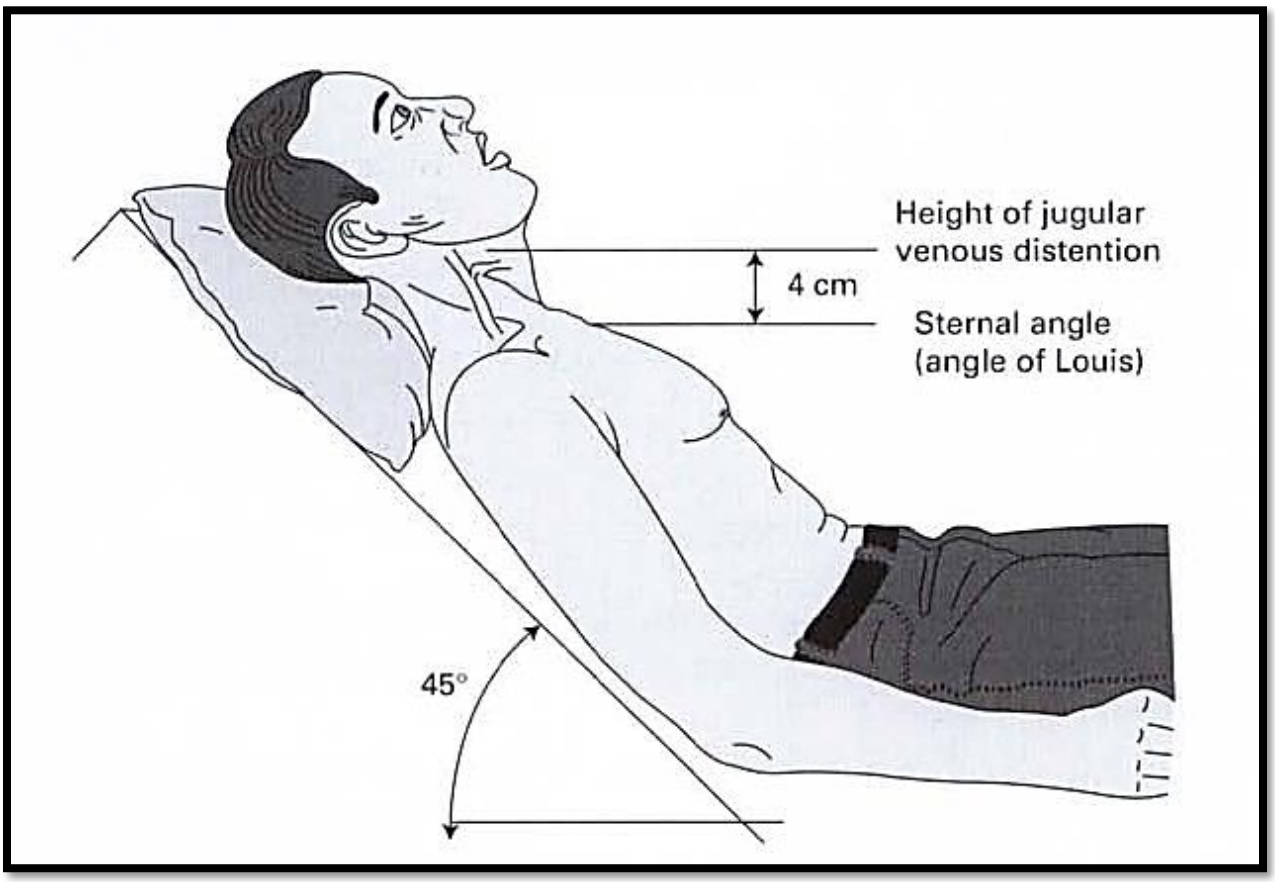


Figure 1: Position of the patient during a cardiac examination. Measurement of JVP. Normally JVP <4cm

- Waveform of JVP:
  - "a" and "v" waves separated by "x" and "y" descents.
    - a wave- right atrial contraction
    - c wave- closure of the tricuspid valve
    - x descent- atrial relaxation
    - v wave- ventricular systole (with passive venous filling of the atrium)
    - y descent- opening of the tricuspid valve with rapid emptying of the right atrium
  - JVP during inspiration declines.
  - Giant "a" wave: forceful contraction against a stenosed tricuspid valve or non-compliant hypertrophied right

ventricle, pulmonary hypertension, and pulmonary stenosis.

- Cannon "a" wave: atrial systole against a closed tricuspid valve caused by atrial-ventricular dissociation (complete heart block)
- Absent a waves: atrial fibrillation.
- Large c-v waves: tricuspid regurgitation.
- Giant "v" wave: sign of tricuspid regurgitation
- Prominent "x" and "y" descents: constrictive pericarditis.
- Absent y descent: cardiac tamponade.



Figure 2: JVP wave

- Kussmaul's sign: an increase in JVP during inspiration. Seen in chronic constrictive pericarditis, occasionally seen in tricuspid stenosis and CHF.
- After measuring the JVP check the ankles for edema.

INSPECTION AND EXAMINATION OF THE FACE

- Check cornea for corneal arcus (hyperlipidemia) / Xanthelasma (hypercholesterolemia)
- Check for conjunctival pallor-anemia and scleral jaundice
- Check Malar flush on cheeks-Mitral stenosis
- Check for central cyanosis (hypoxia), Check for dentures and oral hygiene (infective endocarditis), high arched palate, glossitis
- Check for angular stomatitis (iron deficiency anemia)
- Check neck for tracheal centrality

INSPECTION OF THE CHEST

- Inspect for scars: midline sternotomy/ infraclavicular, lateral thoracotomy.
- Inspect also for any tattoo marks.
- Chest deformities: pectus excavatum/ carinatum.
- Check for activity in the precordium
  - Normoactive precordium
  - Hyperactive precordium- left ventricular hypertrophy

PALPATION OF CHEST

- Place your right hand on the patient's left chest with the butt of the hand at the sternum and the fingers into the axilla.
  - Apex beat: the lowest most lateral point at which the cardiac impulse can be palpated. Normally located superior to the 5th intercostal space and medial to the midclavicular line.
    - A "tapping" apex beat is likely to indicate mitral stenosis, a "heaving" apex beat is likely to indicate left ventricular hypertrophy.
  - Double thrust: a palpable 3rd and 4th heart sound.
  - Left parasternal thrust: thrust appreciated just to the left of the sternum.
  - Thrill: palpable vibrations on the chest wall.
- Place your hand over the cardiac apex and on either side of the sternum (parasternal heave) and Feel for thrills (palpable murmurs) and heaves (ventricular hypertrophy)
  - A Thrill is a vibratory sensation on your hand frequently in the auscultatory areas of the valves. It is a murmur that you can feel.
  - A heave has to do with the upward push on your hand when you palpate the precordium suggesting the presence of hypertrophy e.g. parasternal heave in someone with severe pulmonary hypertension.

AUSCULATION OF CHEST

TECHNIQUE

- Diaphragm of the stethoscope (the flat big part containing the plastic) for high-pitched sounds.
- Bell of the stethoscope (the smaller part) to hear the low-pitched sounds.

SOUNDS

- S1- closing of the mitral and tricuspid valves.
- S2- closing of the aortic and pulmonary valves. Split S2 occurs during inspiration.
- S3 and S4
  - Low frequency sounds. Occur during diastole after S2. Either one is called a 'gallop'
  - Best heard with the bell of the stethoscope.
- Systolic clicks and opening snaps are abnormal
  - Early systolic click- can occur with aortic stenosis right before ejection murmur
  - Late systolic click- mitral valve prolapsed

- ➢ Early diastolic snap- mitral stenosis
- For every murmur there should be:
  - Location of maximal impulse point
  - Time of the murmur: systolic or diastolic
    - Systolic: midsystolic, pansystolic, late systolic
    - Diastolic: early diastolic, mid-diastolic or pre-systolic
    - Continuous: audible in both phases of the cardiac cycle
  - Pitch: This can be low-pitched, medium pitched or high pitched
  - Quality: the frequency
  - Grade of the murmur
    - Grade I: barely audible murmur
    - Grade II: soft and localized murmur
    - Grade III: murmur of moderate intensity that is immediately audible
    - Grade IV: murmur of loud intensity
    - Grade V: murmur of loud intensity with a palpable precordial thrill
    - Grade VI: as above, except that the murmur is audible even as the stethoscope is lifted from the chest wall
  - ➢ Radiation of murmur: what direction does the sound travel to? (neck, axilla, back?)

Aortic stenosis	Slow-rising pulse, heaving cardiac apex, mid-systolic murmur best heard in the aortic area and radiating to the carotids and cardiac apex
Mitral regurgitation	Displaced, thrusting cardiac apex, pan-systolic murmur best heard in the mitral area and radiating to the axilla
Aortic regurgitation	Collapsing pulse, thrusting cardiac apex, diastolic murmur best heard at the left sternal edge
Mitral valve prolapse	Mid-systolic click, late-systolic murmur best heard in the mitral area

Figure 3: Common murmurs

- Innocent murmurs: always mid-systolic, rarely greater than grade 3.

PROCEDURE

- Listen for heart sounds, additional sounds, murmurs and pericardial rub.
- Listen to heart sounds (with the diaphragm first and then with the bell)
  - Aortic valve: 2nd intercostal space (right sternal edge)
  - Pulmonary valve: 2nd intercostal space (left sternal edge)
  - Tricuspid valve: 5th intercostal space (left sternal edge)
  - Mitral valve: at region of apex heart beat
- While listening to the heart sound at the mitral area with the bell ask the patient to turn to the left side (accentuation maneuver), this helps one to hear a mid-diastolic murmur for mitral stenosis, ask them to take a deep breath in and the out and hold it.
- Auscultate the axilla to assess for radiation of murmurs
- Ask patient to lean forward (accentuation maneuver) and listen to the aortic area with the diaphragm. ask them to take a deep breath in and the out and hold it.
- Auscultate the carotids for murmur radiation/bruits using the bell

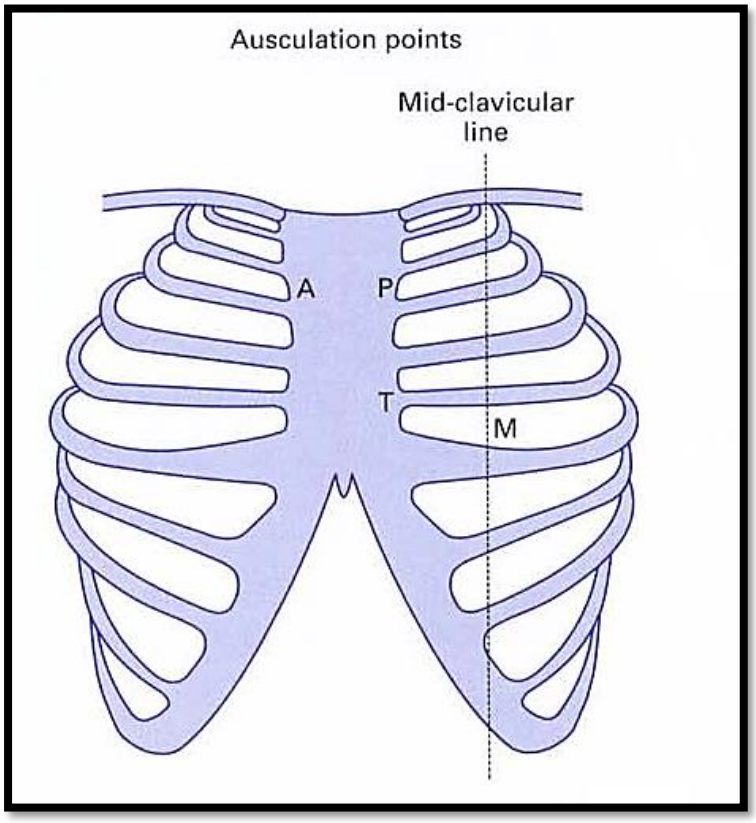


Figure 4: Auscultatory positions

- Positioning/maneuvers: some murmurs are louder when the patient is positioned differently
  - Lying on the left side: helps with mitral regurgitation
  - Inspiration: helps to hear tricuspid regurgitation
  - Leaning forward: helps to hear aortic regurgitation or pulmonic regurgitation
- Friction and venous harms
  - Best heard in maintained expiration with the patient leaning forward.
  - High-pitched scratching noise audible during any part of the cardiac cycle and over any part of the left precordium
  - Hyperkinetic venous hum can be heard at the base of the heart, and is particularly common in infants and usually disappears when lying flat.

OTHER ORGANS TO EXAMINE DURING A FOCUSED CARDIAC EXAM

- Percuss and auscultate the chest, especially at the lung bases (pulmonary edema and pleural effusions)- use diaphragm.
- Palpate the abdomen to exclude ascites and/or an enlarged liver
- Check for the presence of an aortic aneurysm.
- Ballot the kidneys and listen for any renal artery bruits.
- Palpate for sacral edema (right heart failure)
- Feel the temperature of the feet and then palpate the:
  - Femoral pulses
  - Popliteal pulses
  - Posterior tibial pulses
  - Dorsalis pedis pulses
- To complete the examination, point out other investigations that should have been done such as:
  - Urinalysis
  - Capillary blood glucose
  - 12 lead ECG
  - CXR
  - Echocardiogram
- Thank patient, cover them and ensure they are comfortable
- Summarize your findings and offer a differential diagnosis.

CARDIAC PULSES

PULSE	DESCRIPTION	CLINICAL SIGNIFICANCE
ARTERIAL PULSATIONS		
DMINISHED/EXAGGERATED/ASYMMETRIC PULSES		
Diminished pulses	Pulse is weak and thread Small volume pulse	• Atherosclerotic peripheral vascular disease, • Low cardiac output conditions (e.g. heart failure, cardiac tamponade, critical aortic stenosis)
Exaggerated pulses	Pulse is strong	• Aortic regurgitation • Coarctation (upper extremities only) • Patent ductus arteriosus • Hyperthyroidism • Arteriovenous fistulas
Asymmetric pulses	Radial-Radial/Femoral delay	• Severe atherosclerotic vascular disease • Takayasu's arteritis • Coarctation of the aorta
CAROTID PULSATONS		
Delayed upstroke	Delayed upstroke of carotid pulse	Aortic stenosis
Bisferiens pulse	Two palpable peaks during systole	• Mixed aortic stenosis, aortic regurgitation and hypertrophic cardiomyopathy
Dicrotic pulse	Two palpable peaks- one in systole and one in diastole	• Young patients with severe heart failure • Very low ejection fraction e.g. dilated cardiomyopathy 2^{o} to alcoholism
PERIPHERAL PULSES		
Corrigan (water-hammer) pulse	Rapid rise and fall of the radial pulse accentuated by wrist elevation	• Chronic, hemodynamically significant aortic regurgitation • Persistent ductus arteriosus • Aortic root aneurysm
Pulses paradoxus	Drop in BP of >10mmHg during normal inspiration	• Cardiac tamponade • Severe asthma • Constrictive pericarditis • COPD
Pulsus alternans	Alternation of amplitude with every other heartbeat	Severe systolic heart failure

HEART SOUNDS AND MURMURS

HEART SOUNDS

- 2 sounds are normally heard through a stethoscope during each cardiac cycle.
- Normally the valves on the left side of the heart close first. Valves on the right side open first.
- The first is a low, slightly prolonged "lub" (first sound), caused by vibrations set up by the sudden closure of the Atrioventricular valves at the start of ventricular systole.
  - The first sound has a duration of about 0.15s and frequency of 25 to 45Hz.
  - Even though the valves close with only a separation of about 0.01s, the human ear can appreciate only as a single sound.
  - It is soft when the heart rate is low because the ventricles are well filled with blood and the leaflets of the AV valves float together before systole.
- The second is a shorter, high-pitched "dup" (second sound) caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole.
  - The second sound last 0.12s with a frequency of 50Hz.
  - It is loud and sharp when the diastolic pressure in the aorta or pulmonary artery is elevated causing the respective valves to shut briskly at the end of systole.
  - The interval between aortic and pulmonary valve closure during inspiration is frequently long enough for the second sound to be reduplicated (physiologic splitting of the second sound).
  - The two sounds created by physiologic splitting originate from the aortic (A2 component) and pulmonic valves (P2 component). They are heard as a single sound during expiration but during inspiration the increased output of the right heart causes the physiologic splitting.
  - Splitting also occurs in various diseases e.g. pulmonary stenosis, atrial septal defect (Left to right shunt), and advanced aortic stenosis.

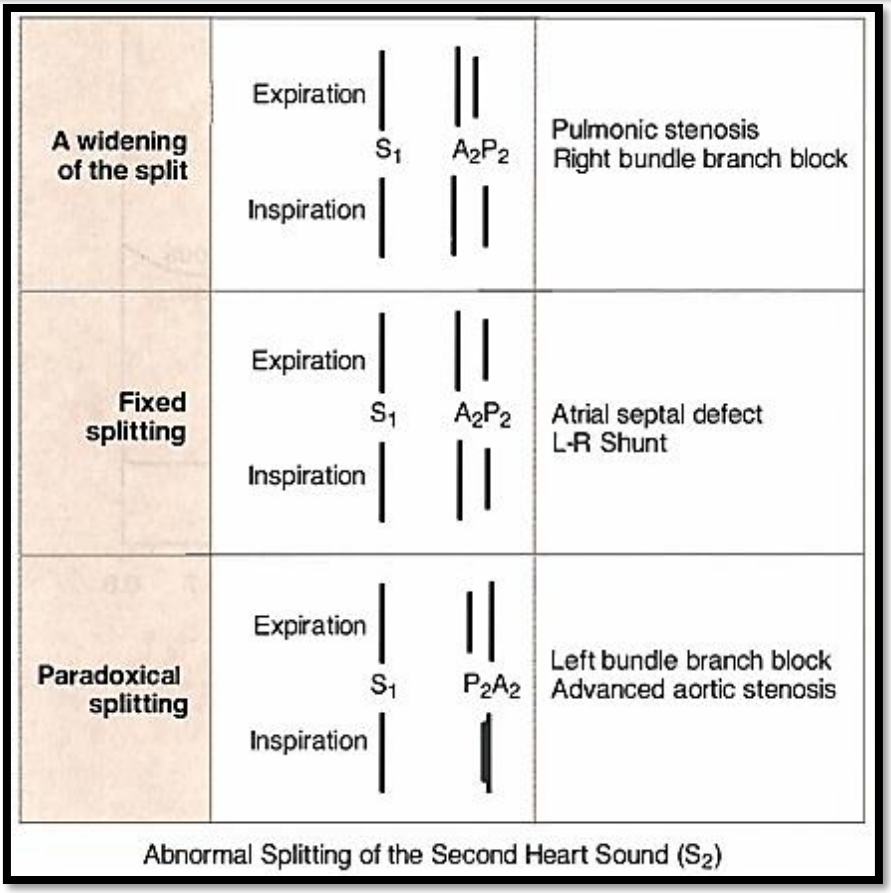


Figure 5: Splitting of the second heart sounds

- A soft, low-pitched third sound is heard about 1/3 of the way through diastole in many normal young individuals. It coincides with the period of rapid ventricular filling and is probably due to vibrations set up by the inrush of blood.
  - The third sound when present has a duration of 0.1s
  - In older adults it occurs with volume overload and often is a sign of cardiac disease.
  - A third heart sound is present in heart failure.
- A fourth sound can sometimes be heard immediately before the first sound when atrial pressure is high or the ventricle is stiff in conditions such as ventricular hypertrophy. It is due to ventricular filling and is rarely heard in normal adults.
- The third and fourth heart sound either singly or together will produce a gallop rhythm.

Heart sound	Cause	Duration and Frequency	Comments
First	Vibrations from closure of AV valves	0.15s and 25 to 45Hz	Prolonged and soft "Lub"
Second	Vibrations from closure of semilunar valves	0.12s and 50Hz	Short and high pitched "Dub". Can undergo physiological splitting during inspiration.
Third	Rapid ventricular filling phase	0.1s	Heard 1/3 way through diastole, Normal in young individuals. In adults it is pathological and a sign of heart failure
Four	Due to high atrial pressure or ventricular stiffening such as in ventricular hypertrophy		Rarely heard in normal individuals

CARDIAC MURMURS

- Murmurs or bruits are abnormal sounds heard in various parts of the vascular system.
- Even though the two terms are used interchangeable, a murmur denotes a noise heard over the heart whilst a bruits denotes a noise heard over blood vessels.
- Blood flow is laminar, non-turbulent and silent up to a critical velocity, above this velocity and beyond an obstruction, blood flow is turbulent and creates sounds. Blood flow speeds up when an artery or a heart valve is narrowed.
- A cardiac murmur or heart murmur is a sound produced when blood flows across one of the heart valves that are loud enough to be heard with a stethoscope.
- There are 2 types of murmurs:
  - Anatomical murmurs
    - These are murmurs due to structural defects in the heart
    - They can be due to narrowing or leaking of valves, or the presence of abnormal passages through which blood flows in or near the heart.

- Functional/ physiological murmurs
  - These are murmurs primarily due to physiological conditions outside the heart
  - Functional murmurs are benign ("innocent murmurs")
  - These are usually soft systolic murmurs, especially children, who have no cardiac disease. Systolic murmurs are also heard in anemic patients as a result of low viscosity of the blood and associated rapid flow.

ANATOMICAL MURMURS

- The major but certainly not the only cause of cardiac murmurs is disease of the heart valves.
- When the orifice of a valve is narrowed (stenosis), blood flow through it is accelerated and turbulent.
- When a valve is incompetent, blood flow through it backward (regurgitation or insufficiency) again through a narrow orifice that accelerated flow.
- The timing (systolic or diastolic) of a murmur due to any particular valve can be predicted from knowledge of the mechanical events of the cardiac cycle.
- Murmurs due to disease of a particular valve can generally be heard best when the stethoscope is directly over the valve.
- There are also other aspects of the duration, character, accentuation and transmission of the sound that help to locate its origin in one valve or another.

Valve	Abnormality	Timing of Murmur
Aortic or pulmonary	Stenosis	Systolic
	Insufficiency	Diastolic
Mitral or tricuspid	Stenosis	Diastolic
	Insufficiency	Systolic

Figure 6: Different murmurs

FUNCTIONAL MURMURS

- These are murmurs primarily due to physiological conditions outside the heart
- Functional murmurs are benign ("innocent murmurs")
- These are usually soft systolic murmurs, especially children, who have no cardiac disease. Systolic murmurs are also heard in anemic patients as a result of low viscosity of the blood and associated rapid flow.
- These murmurs never exceed grade 3.

GRADING OF MURMURS

- Grade I: barely audible murmur
- Grade II: soft and localized murmur
- Grade III: murmur of moderate intensity that is immediately audible
- Grade IV: murmur of loud intensity
- Grade V: murmur of loud intensity with a palpable precordial thrill
- Grade VI: as above, except that the murmur is audible even as the stethoscope is lifted from the chest wall.

DESCRIBING MURMURS

- Location of maximal impulse point
- Time of the murmur: systolic or diastolic
  - Systolic: midsystolic, pansystolic, late systolic
  - Diastolic: early diastolic, mid-diastolic or pre-systolic
  - Continuous: audible in both phases of the cardiac cycle
- Pitch: This can be low-pitched, medium pitched or high pitched
- Quality: the frequency
- Grade of the murmur
  - Grade I: barely audible murmur
  - Grade II: soft and localized murmur
  - Grade III: murmur of moderate intensity that is immediately audible
  - Grade IV: murmur of loud intensity
  - Grade V: murmur of loud intensity with a palpable precordial thrill
  - Grade VI: as above, except that the murmur is audible even as the stethoscope is lifted from the chest wall
- Radiation of murmur: what direction does the sound travel to? (neck, axilla, back?)

RHEUMATIC FEVER

- This is a delayed non-Suppurative autoimmune complication of upper respiratory infection with Lancefield group A beta-hemolytic streptococcus (Streptococcus pyogenes) characterized by inflammation of connective tissue.
- Rheumatic fever causes chronic progressive damage to the heart and its valves.
- The dramatic decline in the incidence of rheumatic fever in the developed world is thought to be largely due to antibiotic treatment of streptococcal infection, though it started to decline before the era of antibiotics probably due to improved socioeconomic status.
- Rheumatic fever predominantly affects the CNS, heart, blood vessels, joints, and skin.
- Rheumatic fever is the commonest cause of heart disease in the developing countries.
- The cause of rheumatic fever is unknown but this disease appears to be autoimmune in nature.

PATHOPHYSIOLOGY

- Acute rheumatic fever is a sequel of a previous group A streptococcal infection usually of the upper respiratory tract.
- One beta-streptococcal serotype (e.g. M types 3, 5, 18, 19 and 24) is linked directly to acute rheumatic fever.
- Rheumatogenicity of GAS is important fact as not all GAS pharyngitis is associated with development of rheumatic fever.
- Rheumatic fever follows Lancefield A Beta hemolytic streptococcus pharyngitis within the interval of 2-3 weeks.
- The mechanism is elusive however the following are proposed:
  - Dysfunction of the immune response
  - Antigenic (molecular) mimicry
    - Similarity between the carbohydrate moiety of GAS and glycoprotein of the heart valve.
    - Molecular similarity between some streptococcal antigens and sarcolemma or other moiety of human myocardial cells.
    - Antibodies produced in response to throat infection in a susceptible host against M protein cross react with tissues of the body.
- Several host related factors have been identified to have operated in relation to specific genetic function and difference in the immune response in individuals.

- The disease involves the heart, joints, central nervous system, skin and subcutaneous tissue. It is characterized by an exudative and proliferative inflammatory lesion of the connective tissues especially that of the heart, joints, blood vessels and subcutaneous tissue.

CLINICAL MANIFESTATIONS

- Acute rheumatic fever is associated with 2 distinct patterns of presentation:
  - Sudden onset: typically begins as polyarthritis 2-6 weeks after streptococcal pharyngitis and is usually characterized by fever and toxicity
  - Insidious onset: subclinical and initial abnormality is mild carditis
- Age at onset influences the order of complications. Younger children tend to develop carditis first, while older patients tend to develop arthritis first.

DIAGNOSIS: JONES CRITETERIA

- Major:
  - Sydenham's chorea
  - Carditis
  - Migratory polyarthritis
  - Subcutaneous nodules
  - Erythema marginatum
- Minor:
  - Clinical
    - Fever
    - Arthralgia
  - Laboratory
    - Elevated acute phase reactants: ESR, CRP
    - Prolonged PR interval
- For diagnosis: Supportive evidence of recent Group A streptococcal infection (e.g. positive throat culture or rapid antigen detection test and/or elevated or increasing Streptococcal antibody test-ASOT, AntiDNAse) plus
  - 2 Majors or
  - 1 Major + 2 minors

SYNDENHAM'S CHOREA

- Also known as St Vitus dance
- It is a characteristic movement disorder.
- It consists of rapid purposeless movements of the face and upper extremities.

- Onset may be delayed for several months to years and may cases when the patient is asleep.
- It is more common in females.
- Antibodies cross react with the basal ganglia

CARDITIS

- Occurs in 40-60% of patients and manifest as:
  - New murmur
  - Cardiomegaly
  - Congestive heart failure
  - Pericarditis with or without a pericardial rub and resolves with squeal of constriction
  - Valvular disease: mitral and aortic commonly affected. Heading of rheumatic valvulitis will lead to fibrous thickening and adhesions resulting in progressive valvular damage. In 80% mild valvulitis would resolve. There is a risk of developing endocarditis on a damaged valve.

MIGRATTORY POLYARTHRITIS

- Occurs in 75% of cases and involves many joints at a time. The larger joints are mainly affected.

SUBCUTANEOUS NODULES

- Occur in 10% of patients. They are firm painless nodules on the extensor surfaces of wrists, elbows and knees.

ERYTHEMA MARGINATUM

- Occurs in about 5% of cases.
- This is a non-pruritic rash that starts as pink to red macules with a pale center which may coalesce and spread centripetally with central clearing over the trunk and proximal limbs.

LABORATORY INVESTIGATIONS

- Throat swab for microscopy, culture and sensitivity (20-40% culture yield)
- Streptococcal antibody tests:
  - ASOT: positive in 80% of cases
  - Anti-DNAse beta and Anti-hyaluronidase is positive in 95% of cases
- Full blood count
  - Leukocytosis

  - Anemia due to suppression of erythropoiesis
- ECG: Prolonged PR interval
- Acute phase reactants (e.g. raised ESR and C-reactive protein)

TREATMENT

- Treatment of Group A streptococcal infection: regardless of organism detection
  - Ampicillin 500mg PO QID or Amoxicillin 500mg PO TID for 10 days or
  - Benzathine penicillin 1.2 million IU IM single dose
  - Erythromycin 500mg PO QID for 10 days (for penicillin allergic patients)
- Teat manifestation of acute rheumatic fever:
  - Arthritis: ASA 2g QID for 4-6 weeks, no indication for steroids
  - Carditis: severe carditis with congestive heart failure should be treated with
    - Prednisolone 60 to 80mg/day to be tapered as patient improves
    - Start ASA during tapering phase to be given for 4-6 weeks
    - CHF: treat with conventional therapy such as bed rest, dietary salt restriction, digoxin and diuretics
  - Sydenham's chorea: in most cases it is self-limiting however in symptomatic patients benzodiazepines (diazepam) or phenothiazine (haloperidol) may help control symptoms.
- Prophylaxis: for all patients with rheumatic fever:
  - First choice Benzathine penicillin 1.2 million IU IM every 4 weeks but if there is high risk of recurrence it can be given every 3 weeks
  - Oral penicillin V (250mg BID)
  - Oral sulfadiazine (1g/day)
  - Oral erythromycin for patients allergic to penicillin
  - Most recommend treatment till the age of 18 or 21 years but more recently lifelong prophylaxis has been advocated.
  - Note: in a patient with an established RHD, it is advisable to get the prophylaxis lifelong.

VALVULAR DISEASES

- Valvular heart disease involve outflow obstruction (stenosis) or incompetence (regurgitation) of one of the four valves of the heart.
- Valvular heart diseases of clinical significance thus include:
  - Mitral stenosis
  - Mitral regurgitation
  - Aortic stenosis
  - Aortic regurgitation
- The distribution of disease varies greatly based on population and risk factors.
- The most valvular disease are rheumatic, congenital or degenerative.
- The most common cause of valvular heart disease in Africa is Rheumatic heart disease.
- Even though the definitive management for most valvular heart diseases is surgical intervention to correct the underlying valvular abnormality, in the current Zambian setup this is not affordable and not available in the country hence the general management is treatment of congestive heart failure state.

MITRAL STENOSIS

- The mitral valve consists of the anterior and posterior leaflets, fibrous annulus, chordae tendinae and the papillary muscles.
- The mitral valve has a normal surface area of about 4-6 cm^{2}..
- Mitral stenosis is a valvulopathy that describes narrowing of the opening of the mitral valve between the left ventricle and the left atrium.
- Note: Mitral stenosis can co-exist with mitral regurgitation (Mixed valve disease).

ETIOLOGY

- The most common cause of mitral stenosis is rheumatic heart disease secondary to previous rheumatic fever due to infection with group A β-Hemolytic streptococcus.
  - The condition is more common in women than men.
  - It is very common in developing countries manifesting below the age of 20 whereas there is generally a latent period of 20 to 40 years between the occurrence of rheumatic fever and of mitral stenosis in developed countries.
  - Inflammation leads to commissural fusion and a reduction in mitral valve orifice area leading to the characteristic doming pattern (Fish mouth opening) seen on echocardiography.

  - Over many years the condition progresses to valve thickening, cusp fusion, calcium deposition, a severely narrowed (stenotic) valve orifice and progressive immobility of the valve cusps.
- Other causes of mitral stenosis:
  - Congenital mitral stenosis
  - Senile calcification and fibrosis of the valve, valve ring and subvalvular apparatus (chordae tendinae)
  - Autoimmune disease: Rheumatoid arthritis, SLE
  - Lutambacher's syndrome, which is the combination of acquired mitral stenosis and an atrial septal defect.
  - Mucopolysaccharidoses
  - Endocardial fibroelastosis
  - Carcinoid tumors metastasizing to the lung, or primary bronchial carcinoid. (note carcinoid tumors are more common in the GIT- Appendix thus they most commonly cause tricuspid stenosis)
    - Carcinoid tumors produce biologically active products that are growth factors for fibroblast.
- Most patients remain asymptomatic until atrial fibrillation develops or until pregnancy occurs when there is increased demand on the heart.

PATHOPHYSIOLOGY

- When the normal valve orifice area of 4-6 cm^2 is reduced to <2 cm^2, signs and symptoms begin to show and when it is reduced to <1 cm^2 severe mitral stenosis is present.
- Stenosis of the mitral valve results in outflow obstruction from the left atrium to left ventricle and therefore high atrial pressure. The elevated pressures lead to atrial dilatation and often atrial fibrillation. Elevated atrial pressure causes pulmonary pressures and pulmonary symptoms.
- In order that sufficient cardiac output will be maintained, the left atrial pressure increases and left atrial hypertrophy and dilatation occur.
  - Decreased filling of the left ventricle causes the left ventricle to generally becomes smaller than normal.
  - Stasis in the dilated atrium leads to the development of thrombi that can cause systemic thrombo-embolism to cerebral system, kidney, spleen, bone, lung and causing infarction in these areas.

  - Dilatation of the atria also predisposes the heart to atrial fibrillation (due to re-entry of current in the hypertrophied atrium), atrial fibrillation also increases stasis and this also contributes to formation of thrombi.
- Consequently, pulmonary venous, pulmonary arterial and right heart pressures also increase.
- The increase in pulmonary capillary pressure is followed by the development of pulmonary edema particularly when the rhythm deteriorates to atrial fibrillation with tachycardia and loss of coordinated atrial contraction.
- This is partially prevented by alveolar and capillary thickening and pulmonary arterial vasoconstriction (reactive pulmonary hypertension).
- Pulmonary hypertension leads to right ventricular hypertrophy, dilatation and failure with subsequent tricuspid regurgitation.

CLINICAL PRESENTATION

SYMPTOMS

- Symptoms are generally those of left-sided heart failure.
- Patient may present with Pulmonary edema
  - Exertional dyspnea: lungs are edematous and boggy making them difficult for respiratory muscles to expand lungs in addition during exertion right heart pumps more blood to the lungs and this further increases congestion and pulmonary edema in lungs.
  - Orthopnea: due to pulmonary edema
  - Paroxysmal nocturnal dyspnea: due to pulmonary edema
  - Cough with pink-frothy sputum
  - Frank hemoptysis: due to rupture of pulmonary vasculature as a result of pulmonary hypertension
  - Recurrent bronchitis: infection is more likely in edematous lungs.
- After progression of disease there may be signs of right sided heart failure such as ascites, tender hepatomegaly and pitting edema of the lower limbs.
- There may be hoarseness of the voice from recurrent laryngeal nerve compression

SIGNS

FACE

- Severe mitral stenosis with pulmonary hypertension is associated with the so-called mitral facies or malar flush.

- This is a bilateral, cyanotic or dusky pink discoloration over the upper cheeks that is due to arteriovenous anastomoses and vascular stasis.

PULSES

- Pulse may be associated with a small-volume which is usually regular early in disease in patients with sinus rhythm
- Atrial fibrillation as disease progresses results in irregularly irregular pulse.
- The development of atrial fibrillation in these patients often causes a dramatic clinical deterioration.

JUGULAR VEINS

- If right heart failure develops there is obvious distention of the jugular veins.
- If pulmonary hypertension or tricuspid stenosis is present, the 'a' wave will be prominent provided that atrial fibrillation has not supervened.

PALPATION

- There is a tapping impulse felt parasternally of the left side. This is the result of a palpable first heart sound combined with left ventricular backward displacement produced by an enlarging right ventricle.
- A sustained parasternal impulse due to right ventricular hypertrophy may also be felt.

AUSCULATATION

- If the mitral valve is still pliable there is a loud first heart sound.
- As the valve becomes calcific the sound is softer.
- When the valve suddenly opens with the force of the increased left atrial pressure, an 'opening snap' will be heard.
- This is followed by a low-pitched 'rumbling' mid-diastolic murmur best heard with the bell of the stethoscope held lightly at the apex with the patient lying on the left side.
- The P2 component of the second heart sound may be loud if there is pulmonary hypertension.
- If the patient is in sinus rhythm, the murmur becomes louder at the end of diastole as a result of atrial contraction (pre-systolic accentuation).

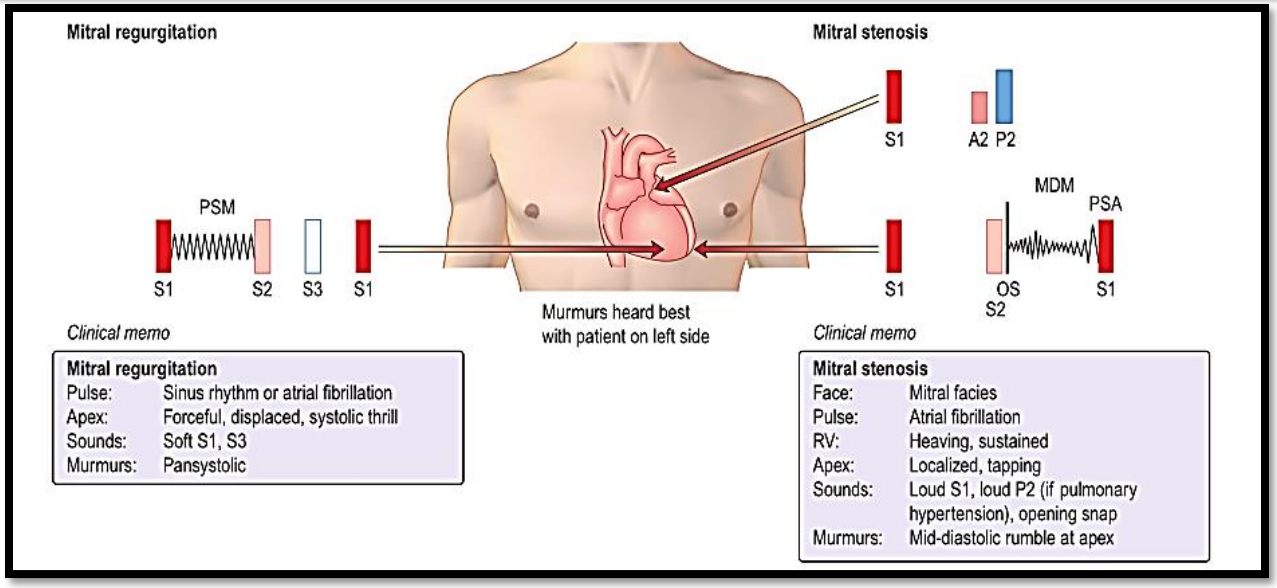


Figure 7: Mitral Regurgitation vs Mitral stenosis

INVESTIGATIONS

DIAGNOSTIC

BLOOD INVESTIGATIONS

- Antistreptolysin O titers (ASOT) to detect presence of rheumatic fever.

CHEST X-RAY

- Usually shows a generally small heart with an enlarged left atrium.
- Pulmonary venous hypertension is usually also present.
- Late in the course of the disease a calcified mitral valve may be seen on a penetrated or lateral view.
- The signs of pulmonary edema or pulmonary hypertension may also be apparent when the disease is severe.

ECHOCARDIOGRAM (IMAGING)

- It is the diagnostic tool of choice for diagnosing and assessing the severity of mitral stenosis. It is used to estimate valve area and to measure the transmitral pressure gradient. Mitral valve morphology on echocardiography determines a patient's suitability for percutaneous valvuloplasty.
- It also determines the left and right atrial and ventricular size and function.

	Normal	Mild	Moderate	Severe
Pressure half time (ms)	40–70	71–139	140–219	>219
Mean pressure drop (mmHg)		<5.0	5–10	>10
Valve area (cm^2)	4.0–6.0	1.6–2.0	1.0–1.5	<1.0

British Society of Echocardiography.

Figure 8: ECHO findings in Mitral stenosis

ELECTROCARDIOGRAM

- In sinus rhythm the ECG shows a bifid P wave (P- mitrale) owing to delayed left atrial activation.
- However, atrial fibrillation is frequently present.
- As the disease progresses the ECG features of right ventricular hypertrophy (right axis deviation and perhaps tall R waves in lead V1) may develop.

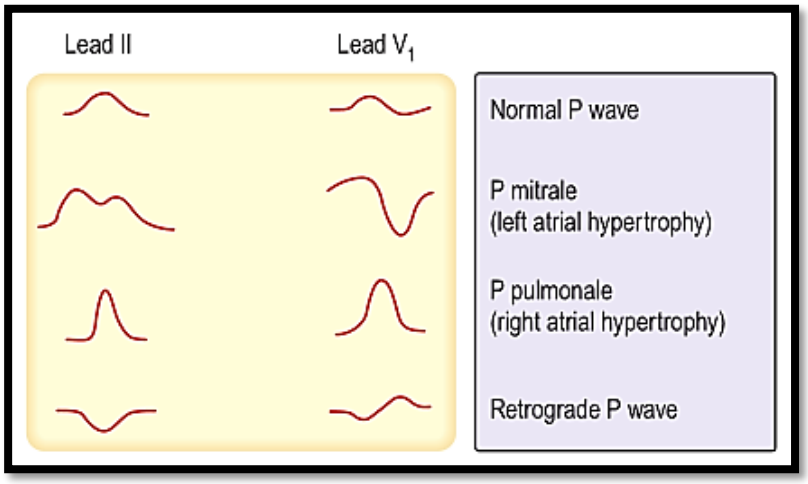


Figure 9: ECG findings in Mitral stenosis

CARDIAC CATHETERIZATION

- Rarely required and only used if co-existing cardiac problems (e.g. mitral regurgitation or coronary artery disease) are suspected.
- Right heart catheterization may be required to determine pulmonary artery pressure in patients referred for valve intervention

SUPPORTIVE

- Urinalysis
- FBC- to show infection
- U & Es

MANAGEMENT

- Management is both:
  - Medical and
  - Surgical

MEDICAL MANAGEMENT

- Asymptomatic patients
  - Annual checkups (history, physical examination, chest X-ray and ECG).
  - Endocarditis prophylaxis
  - Secondary prophylaxis for rheumatic fever
- Symptomatic patients:
  - Diuretics may be helpful in reducing left atrial pressure and decreasing symptoms. Long-acting nitrates can also be used for shortness of breath.
  - Digoxin is indicated for patients with atrial fibrillation to control the heart rate since tachycardia will further decrease left ventricular filling, reduce cardiac output and increase left atrial pressure leading to more symptoms.
  - Beta blockers or rate-limiting calcium channel blockers improve exercise tolerance
  - Anticoagulants e.g. Warfarin in patients with left atrium hypertrophy and atrial fibrillation to prevent atrial thrombus and systemic embolization.
  - Any addition lung infections especially pneumonia are treated with antibiotics.

SURGICAL MANAGEMENT

- If pulmonary hypertension develops or the symptoms of pulmonary congestion persist despite therapy, surgical relief of the mitral stenosis is advised.
- Indications:
  - Severe symptoms
  - Complications
- Surgical intervention includes:
  - Percutaneous balloon mitral commissurotomy: first line choice
  - Trans-septal balloon valvotomy.
  - Closed valvotomy
  - Open valvotomy (open commissurotomy-involves opening up the valve at the junction of its leaflets)
    - Contraindication of commissurotomy: left atrial thrombosis
  - Mitral valve reconstruction

- Mitral valve replacement

COMPLICATIONS

- Left atrial enlargement
  - Esophageal compression
  - Recurrent laryngeal nerve compression
  - Atrial fibrillation
- Pulmonary hypertension
- Right ventricular failure
- Tricuspid or pulmonary regurgitation
- Infective endocarditis

MITRAL REGURGITATION

- Mitral regurgitation can occur due to abnormalities of the valve leaflets, the annulus, the chordae tendinae or papillary muscles or the left ventricle.
- A small amount is common in the population but clinically significant in 2%.
- The most common causes of mitral regurgitation are:
  - Rheumatic heart disease
  - Ischemic heart disease
  - Infectious endocarditis
  - Degenerative (myxomatous) disease
- Other causes include:
  - Cardiomyopathies (dilated and hypertrophic)
  - Rheumatic autoimmune disease e.g. SLE, collagen disease e.g. Marfan's syndrome and Ehlers-Danlos syndromes
  - Drugs e.g. centrally acting appetite suppressants (fenfluramine) and dopamine agonist (cabergoline).

ETIOLOGY

- Primary causes:
  - Mitral valve prolapse (causes 50%)
  - Rheumatic heart disease
  - Calcification
  - Infective endocarditis
  - Congenital
  - Papillary muscle rupture due to MI
  - Appetite suppressants
  - Trauma
- Secondary causes (functional):
  - Left ventricular dilation due to Ischemic heart disease
  - Dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Aortic regurgitation

PATHOPHYSIOLOGY

- Regurgitation into the left atrium produces left atrial dilatation but little increase in left atrial pressure if regurgitation is long standing as the regurgitant flow is accommodated by the large left atrium.
- With acute mitral regurgitation the normal compliance of the left atrium does not allow much dilation and the left atrial pressure rises. In acute mitral regurgitation the left atrial v-wave is greatly increased and pulmonary venous pressure rises to produce pulmonary edema.
- A proportion of stroke volume is regurgitated, the stroke volume increases to maintain the forward cardiac output and left ventricle therefore enlarges.
- Chronic mitral regurgitation is a state of volume overload leading to the development of left ventricular hypertrophy. The left atrium also enlarges to accommodate the regurgitant volume. This compensated phase of mitral regurgitation varies in duration but may last many years.
- The prolonged state of volume overload may eventually lead to decompensated mitral regurgitation characterized by impaired left ventricular function, decreased ejection fraction and pulmonary congestion.

CLINICAL FEATURES

- Mitral regurgitation may be asymptomatic and present for many years as the cardiac dimensions greatly increase.
- Symptoms:
  - Palpitation: due to increased stroke volume which is sensed as a palpitation
  - Shortness of breath, Dyspnea and orthopnea: due to pulmonary venous hypertension occurring as a direct consequence of mitral regurgitation and secondarily to left ventricular failure.
  - Fatigue and lethargy: due to reduced cardiac output
  - Chest pain
  - Symptoms of Right heart failure (in later stages of disease) it can also leads to congestive cardiac failure.
    - Painful hepatic congestion, peripheral edema may occur in patients with MR who have associated pulmonary hypertension
  - Cardiac cachexia
  - Symptoms of atrial fibrillation (though this is commoner in mitral stenosis): palpitations and an irregularly irregular pulse. Thromboembolism is less common than in mitral stenosis but subacute infective endocarditis is much more common.

- Signs
  - Hyperdynamic apex beat that is laterally displaced (forceful) and diffuse.
  - If severe there may be a systolic thrill over the apex.
  - Soft S1 and widely split S2 (due to incomplete apposition of the valve cusps and their partial closure by the time ventricular systole begins)
  - Pansystolic (holosystolic) murmur best heard at the apex and radiates to the axilla (this is due to occurrence of regurgitation throughout the whole of systole)
    - It may also radiate to the upper sternal borders or the subscapular region.
  - With a floppy mitral valve there may be a mid-systolic click which is produced by the sudden prolapse of the valve and tensing of the chordae tendinae that occurs during systole.
  - LVF signs: S3 (Sudden rush of blood back into the dilated left ventricle-sometimes a short mid-diastolic flow murmur may follow S3), crackles
  - The signs related to atrial fibrillation, pulmonary hypertension and left and right heart failure develop later in the disease.
  - Acute mitral regurgitation e.g. due to infective endocarditis or papillary muscle rupture can present with pulmonary edema.

DDX of a Pansystolic murmur

- Mitral regurgitation
- Tricuspid regurgitation: Louder on inspiration
- VSD: usually younger patients and apex non-displaced

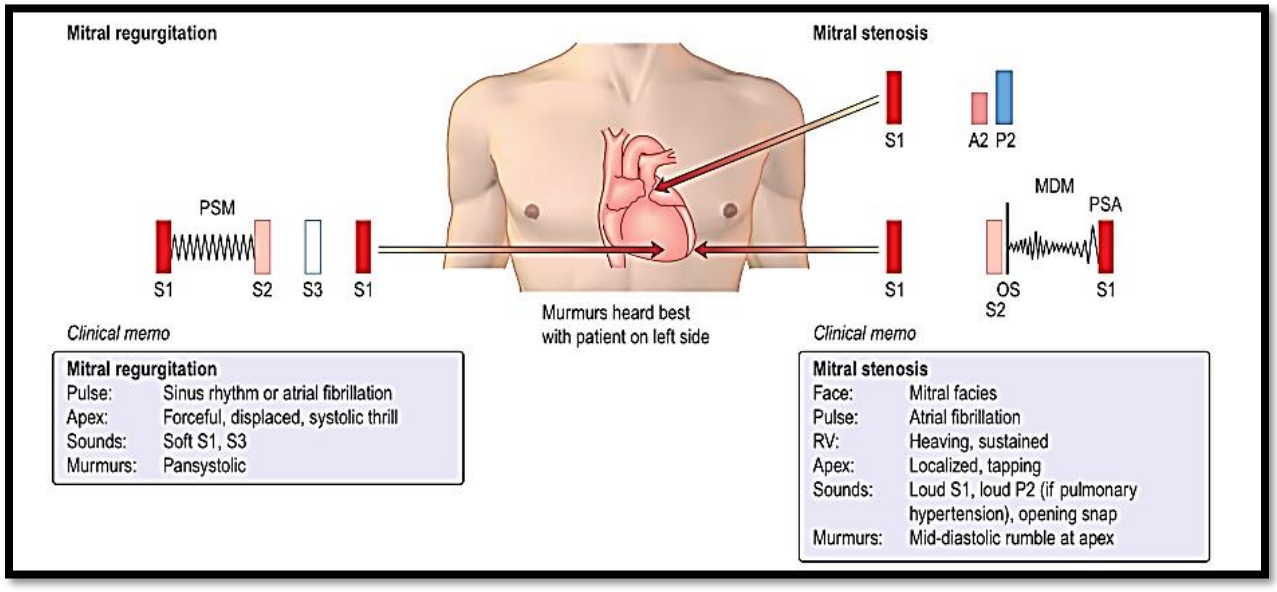


Figure 10: Mitral Regurgitation vs Mitral stenosis

INVESTIGATIONS

- Diagnostic: Echo
- Echo is used to determine the etiology and morphology of the mitral regurgitation which are important in determining suitability for mitral valve repair.
- Chest X-ray:
  - Enlarged left ventricle and atrium: double right heart border.
  - Increased cardiothoracic ratio
  - Valve calcification
  - Pulmonary venous congestion
  - Interstitial edema and Kerley B line
- ECG
  - P-mitrale if sinus rhythm: bifid/broad P wave due to large left atrium and left atrial delay.
  - Tall R waves in the left lateral leads (leads I and V6) and Deep S waves in the right sided precordial leads (e.g. leads V1 and V2) indicating left ventricular hypertrophy.
    - Note: SV1 plus RV5 or RV6 >35mm indicates left ventricular hypertrophy
  - Atrial fibrillation may occur
- Other tests:
  - Cardiac MRI, angiography and Catheterisation if indicated
  - BNP may provide prognostic information.

MANAGEMENT

- Can be
  - Medical
  - Surgical

MEDICAL MANAGEMENT

- Salt restriction
- Diuretics
- Digoxin: may be indicated in patients with severe regurgitation and dilated left ventricle without frank LV failure

- Vasodilators: Afterload reduction with vasodilators has shown to improve left ventricular performance. ACE inhibitors are the preferred vasodilators. Sodium nitroprusside can also be used.
- Manage atrial fibrillation and heart failure if present.
- Endocarditis prophylaxis is important essential.
- 6 monthly follow up and annual echo if severe.

SURGICAL MANAGEMENT

- Mitral valve replacement is the definitive treatment.
- Anticoagulation: 3 months after valve repair or bioprosthetic replacement, lifelong after metallic replacement.
- Indications:
  - Symptomatic MR
  - Acute severe MR (emergency)
  - MR complications such as LVF, new-onset AF, pulmonary hypertension. In MR secondary to ischemic HF, surgery should only be done alongside planned coronary artery bypass graft.

COMPLICATIONS

- Structural changes:
  - Left ventricular and atrial enlargement
  - Congestive heart failure
- Pulmonary hypertension
- Atrial fibrillation
- Infective endocarditis

AORTIC STENOSIS

- The aortic valve has an area of 3 to 4cm^3.
- Aortic stenosis is the commonest valve disease, affecting 4% of elderly.
- It is a chronic progressive disease that produces obstruction to the left ventricular stroke volume leading to symptoms of chest pain, breathlessness, syncope and pre-syncope and fatigue.

ETIOLOGY

- Rheumatic carditis
- Congenital stenosis of the aortic valve
- Congenital bicuspid valve
- Senile/calcific aortic stenosis which is idiopathic results in calcification and degeneration of the aortic leaflets.

PATHOPHYSIOLOGY

- Obstructed left ventricular emptying leads to increased ventricular pressure and compensatory left ventricular hypertrophy.
- This results in relative ischemia of the left ventricular myocardium and consequent angina, arrhythmias and left ventricular failure.
- The obstruction to left ventricular emptying is relatively more severe on exercise.
- Normally, exercise causes a many-fold increase in cardiac output but when there is severe narrowing of the aortic valve orifice the cardiac output can hardly increase.
- Thus, the blood pressure falls, coronary ischemia worsens, the myocardium fails and cardiac arrhythmias develop.
- Left ventricular systolic function is typically preserved in patients with aortic stenosis.

CLINICAL FEATURES

- No symptoms until stenosis is moderately severe (when the aortic orifice is reduced to 1/3 of its normal size i.e. less than 1.5cm^2)
- Symptoms: “SAD” triad
  - Syncope (may occur on exertion)
  - Angina
  - Dyspnea on exertion
- Sign:

- Pulse: carotid pulse is small volume and slow-rising or plateau in nature (Parvus et Tardus)
- Precordial palpation:
  - Apex beat is not usually displaced because hypertrophy (as opposed to dilation) does not produce noticeable cardiomegaly.
  - Sustained and obvious pulsations
  - Double impulse is sometimes felt because of S4 or atrial contraction ('kick')
  - Systolic thrill in the aortic area.
- Auscultation
  - Ejection systolic murmur that is usually 'diamond-shaped' (Crescendo-decrescendo): the murmur is usually longer when the disease is more severe as a longer ejection time is needed.
  - The murmur is usually rough in quality and best heard in the aortic area. It radiates to the carotid arteries and also the precordium.
  - Intensity of murmur is not a good guide to severity of the condition because it is lessened by a reduced cardiac output. In severe cases the murmur may be inaudible.
  - Other findings:
    - Systolic ejection click, unless the valve has becomes immobile and calcified.
    - Soft or inaudible aortic S2 when the aortic valve becomes immobile
    - Reversed splitting of S2 (splitting on expiration)
    - Prominent S4 (due to atrial contraction, it is heard unless co-existing mitral stenosis prevents this).

DDX of systolic murmur

- Aortic stenosis: loud on expiration
- Pulmonary stenosis: Pulmonary areaas, loud on inspiration
- Pan-systolic: mitral regurgitation, tricuspid regurgitation, VSD
- Late systolic: Mitral valve prolapse
- Hypertrophic cardiomyopathy: increases on standing.
- Aortic sclerosis: distinguished from aortic stenosis by lack of other signs

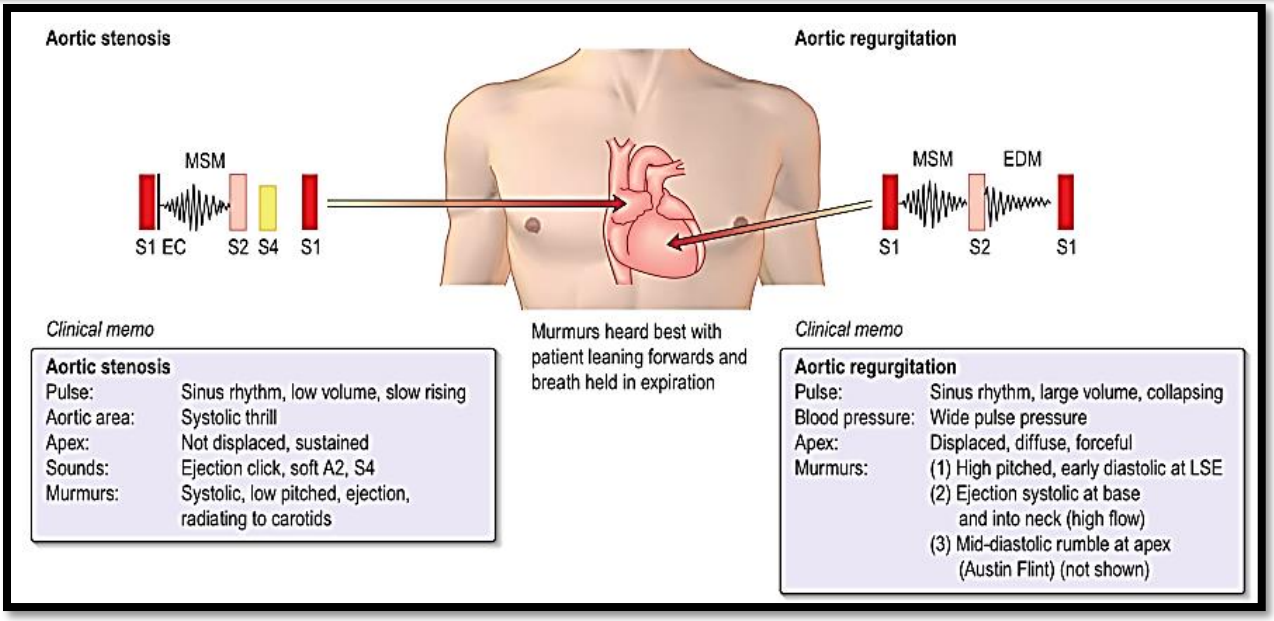


Figure 11: Aortic stenosis vs Aortic regurgitation

INVESTIGATIONS

- Imaging:
  - Chest X-ray:
    - Usually normal, otherwise LVH, calcified valve, dilated ascending aorta.
    - CXR may show a relatively small heart with a prominent dilated ascending aorta. This occurs because of turbulent blood flow above the stenosed aortic valve producing 'post-stenotic dilation'
    - The cardiothoracic ratio may be increased when there is heart failure
  - ECG: LVH and left atrial delay
    - P-mitrale (bifid P wave)
    - Left bundle branch block
    - AV block
    - Poor R wave progression
  - Echo with Doppler: confirms diagnosis and assesses degree of calcification, LV function, aortic velocity, pressure gradient and valve area. These factors help classify severity.
- Further investigations
  - Cardiac MRI, stress testing, angiography or Catheterisation if indicated.
  - Multi-slice CT can help evaluate severity and is useful when considering TAVI
  - BNP may provide prognostic information.

	Normal	Mild	Moderate	Severe
Peak velocity (m/s)	<1.7	1.7–2.9	3.0–4.0	>4.0
Peak pressure drop (mmHg)		<36	36–64	>64
Mean pressure drop (mmHg)		<25	25–40	>40
Valve area (cm^2)	>2.0	1.5–2.0	1.0–1.4	<1.0

British Society of Echocardiography.

Figure 12: ECHO severity of Aortic stenosis

MANAGEMENT

- It is
  - Medical
  - Surgical

MEDICAL MANAGEMENT

- Medical management is not effective and treatment with digitalis or cautiously administered diuretics may only reduce symptoms.
- Patients with severe aortic stenosis should limit vigorous physical activity
- Endocarditis prophylaxis
- Treat any secondary heart failure
- 6 monthly echo if severe

SURGICAL

- Aortic valve replacement is the only effective treatment that will relieve this mechanical obstruction.
- Indications:
  - Severe (<1cm^2 opening) + symptoms of LVSD
  - If severe but asymptomatic need to weight risks vs benefits. If undergoing coronary artery graft bypass might as well be done.

COMPLICATIONS

- Left ventricular failure or congestive heart failure
- Aortic root dilation due to hemodynamic changes around valve
- Infective endocarditis
- Sudden cardiac death

AORTIC REGURGITATION

- Aortic regurgitation may be acute or chronic.

ETIOLOGY

- Acute causes:
  - Infective endocarditis
  - Aortic dissection
- Chronic causes:
  - Congenital: bicuspid valve
  - Aortic root dilatation: Marfan's, Ehlers-Danlos
  - Inflammatory: SLE, RA or seronegative arthritis, rheumatic heart disease, Takayasu's, syphilis
  - Appetite suppressants
  - Hypertension

PATHOPHYSIOLOGY

- Aortic regurgitation is reflux of blood from the aorta through the aortic valve into the left ventricle during diastole.
- If net cardiac output is to be maintained, the total volume of blood pumped into the aorta must increase and consequently the left ventricular size must enlarge.
- Because of the aortic runoff during diastole, diastolic blood pressure falls and coronary perfusion is decreased.
- In addition, the larger left ventricular size is mechanically less efficient so that the demand for oxygen is greater and cardiac ischemia develops.

CLINICAL FEATURES

SYMPTOMS

- Symptoms occur late and do not develop until left ventricular failure occurs.
- Pounding of the heart because of increased left ventricular size and its vigorous pulsation.
- Angina pectoris
- Varying grades of dyspnea
- Arrhythmias are relatively uncommon

SIGNS

- Signs are due to Hyperdynamic circulation, reflux of blood into the left ventricle and increased left ventricular size.
- Signs:
  - De Musset's sign- head nodding with each heartbeat.
  - Becker's sign- visible pulsation of retinal arteries (through an ophthalmoscope)
  - Muller sign- pulsation or bobbing of the uvula that occurs during systole.
  - Dancing sign (Corrigan's sign)- visible carotid pulsation
  - Collapsing pulse (Waterhammer pulse/Corrigan's pulse): Hyperdynamic pulse with rapid increase then collapse. Reflects large volume pushing against little resistance through floppy valve then collapsing back down.
  - Quincke's sign- capillary pulsation in nail bed
  - Duroziez's sign- a to and fro murmur heard when the femoral artery is auscultated with pressure applied distally (if found it is a sign of severe aortic regurgitation)
  - Pistol shot femoral- sharp bang heard on auscultation over the femoral arteries in time with each heart beat
  - Hill sign: popliteal systolic blood pressure exceeds brachial systolic blood pressure by 60mmHg or greater. (This is the most sensitive sign of severe aortic regurgitation)

DDX of diastolic murmur

- Aortic regurgitation
- Aortic dissection (causing aortic regurgitation)
- Mitral stenosis
- Right sided valve disease: Pulmonary regurgitation, tricuspid stenosis

- There is a wide pulse pressure.
- The apex beat is displaced laterally and downwards and is forceful in quality.
- On auscultation:
  - High-pitched early diastolic murmur best heard at the left sternal edge in the fourth intercostal space with the patients leaning forward and the breath held in expiration
  - Because of the volume overload there is commonly an ejection systolic flow murmur. The regurgitant jet can impinge on the anterior mitral valve cusp causing a mid-diastolic murmur (Austin Flint rumble)

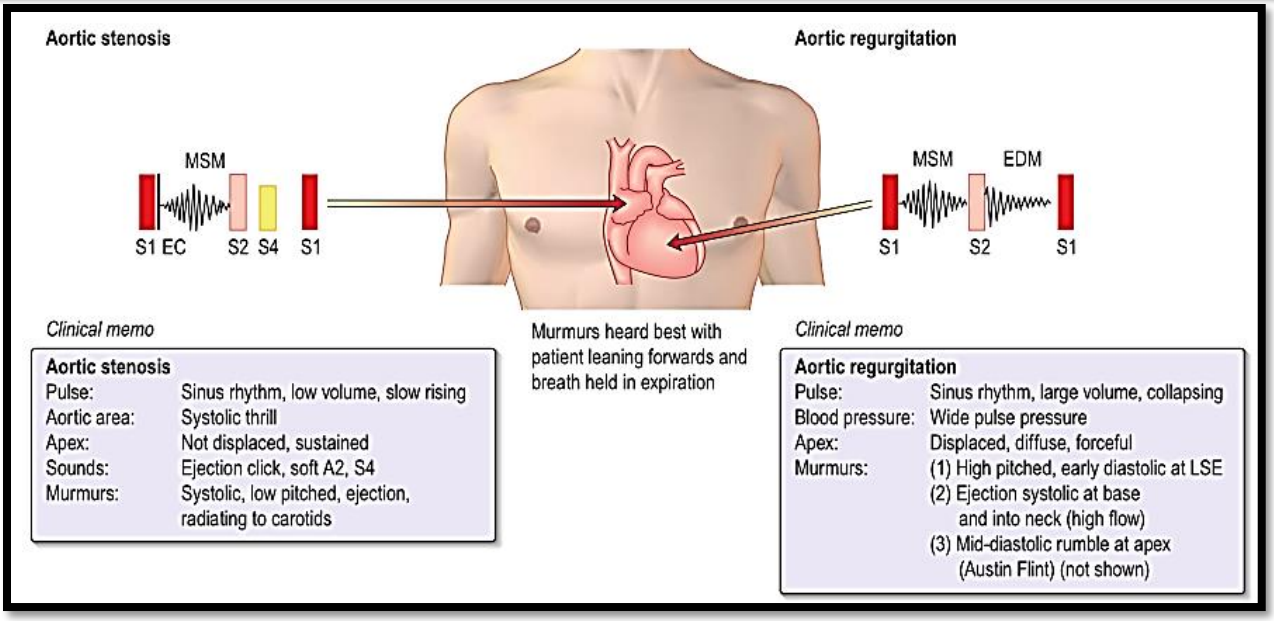


Figure 13: Aortic stenosis vs Aortic regurgitation

INVESTIGATIONS

- ECHO with Doppler ultrasonography is diagnostic and provides information about aortic valve morphology, aortic root size, and a semiquantitative estimate of the severity of aortic regurgitation. It provides valuable information about left ventricular size and function.
- ECG: LVH- tall R waves and deeply inverted T waves in left sided chest leads, and deep S waves in right sided leads. Normal sinus rhythm.
- CXR: LVH, dilated ascending aorta
- Multi-slice CT may help visualize aortic root dilation in Marfan's.

MANAGEMENT

- It is:
  - Medical
  - Surgical
- Medical:
  - Salt restriction
  - Diuretics
  - Digoxin: may be indicated in patients with severe regurgitation and dilated left ventricle without frank LV failure.

- Vasodilators: reduce afterload to improve left ventricular performance and reduce aortic regurgitation. ACEi are preferred. Therapy with long acting Nifedipine in particular has been shown to delay the needed for surgery by 2 or 3 years.
- Manage LVF if present: ACEi (especially in HTN), beta blockers (especially in Marfan's)
- Monitor regular echo, 6 monthly if severe or every 2 years if mild-moderate.

- Surgical:
  - Aortic valve replacement
    - Recall: patients with chronic AR usually do not become symptomatic until after the development of myocardial dysfunction
    - When delayed too long, surgical treatment often does not restore normal LV function therefore appropriate timing is necessary for surgical intervention.

OTHER VALVE PATHOLOGIES

MITRAL VALVE PROLAPSE

- This occurs when varying portions of one or both leaflets of the mitral valve extend or protrude abnormally above the mitral annulus into the left atrium.
- It is seen in 5% of the population.
- It has different causes including:
- Clinical features:
  - Common in females and more common in 14-30 age group
  - Clinical course is often benign
  - Most patients are asymptomatic and may remain so for their entire lives
  - Some may manifest features of mitral regurgitation. They may have palpitations and chest pain.
  - Arrhythmias like premature ventricular contraction and ventricular tachycardia may occur as complications.
  - Mid-systolic click often accompanied by a late systolic murmur is the auscultatory hallmark of mitral valve prolapse.
- Management:
  - Asymptomatic patients need only reassurance
  - Symptomatic with thickening of mitral valve:
    - Endocarditis prophylaxis
    - Beta blockers sometimes may relieve chest pain
  - Severe symptoms from secondary MR: surgical treatment may be needed (mitral valve repair and/or rarely replacement)

Feature	Pulmonary Stenosis	Pulmonary Regurgitation	Tricuspid stenosis	Tricuspid regurgitation
Etiology	• Rheumatic fever • Congenital: Tetralogy of Fallot, Noonan, rubella • Carcinoid syndrome	• Pulmonary hypertension (dilation of the pulmonary valve ring) • Dilated cardiomyopathy	• Rheumatic heart disease (Mitral and aortic valves are also affected) • Carcinoid syndrome • Tricuspid atresia • Atrial tumor • Infective endocarditis	• Functional: right ventricle dilation (cor pulmonale, myocardial infarction, pulmonary hypertension) • Organic: rheumatic heart disease, infective endocarditis, carcinoid syndrome, Ebstein's anomaly (congenitally malpositioned tricuspid valve) • Congenital anomalies (Tricuspid atresia)
Symptoms	• Asymptomatic (mild PS) • Fatigue • Syncope • Symptoms of right heart failure	• Mild • Asymptomatic	• Symptoms associated with left-sided rheumatic valve lesion • Abdominal pain (due to hepatomegaly) and swelling (due to ascites) • Peripheral edema • Dyspnea	• Symptoms of right heart failure including ascites and liver signs (enlarged, pulsatile, painful, jaundice)
Signs	• Harsh mid-systolic ejection murmur best heard on inspiration to the left of the sternum in the second	• Decrescendo diastolic murmur beginning with the pulmonary component of S2 that is difficult to distinguish	• Prominent jugular venous a wave • Pre-systolic pulsation may be felt over the liver • Mid-diastolic rumbling	• Large venous 'cv' wave • Palpable liver that pulsates in systole • Left Parasternal heave • Blowing pansystolic murmur best heard on inspiration at the lower left parasternal edge.

	intercostal space. • The murmur may be associated with a thrill and radiates to the left shoulder • Ejection click • Wide split S2: P2 is delayed due to slow emptying through narrow valve. • Prominent a in JVP • S4	from the murmur of aortic regurgitation.	murmur after opening snap. Best heard in left lower parasternal area. It is louder on expiration. It may be missed because of the murmur of mitral stenosis may co-exist.	• Atrial fibrillation is common
Investigations	• CXR: prominent pulmonary artery. • ECG: right atrial and ventricular hypertrophy although it may sometimes be normal even in severe PS. • Doppler Echo is investigation of choice		• CXR: prominent right atrial bulge • ECG: enlarged right atrium (peaked tall P waves >3mm in lead II) • ECHO: thickened and immobile tricuspid valve.	• Echo shows dilation of the right ventricle with thickening of valve
Medical management	• Salt restriction • Diuretic therapy	Treatment rarely necessary as it is asymptomatic	• Salt restriction • Diuretic therapy	• Treat functional cause

Surgical management	• Pulmonary valvotomy (balloon valvotomy or direct surgery)		• Tricuspid valvotomy • Tricuspid valve replacement	• Tricuspid valve replacement

SYSTEMIC HYPERTENSION

- This is persistent elevation in the arterial blood pressure that exceeds 140mmHg systolic or 90mmHg diastolic on more than one occasion (at least 2-3 times).
  - This is an arbitrary definition because a diastolic pressure of even 85mmHg may be associated with increased cardiovascular morbidity and mortality.
  - Unless acute end-organ damage e.g. hypertensive emergency is present or Blood pressure is above 220/115 mmHg the diagnosis of hypertension requires multiple blood pressure readings above 140/90mmHg on at least 2 different occasions.
- Hypertension is the most important modifiable risk factor for stroke, coronary heart disease, myocardial infarction, congestive heart failure, end-stage renal disease, retinopathy and peripheral vascular disease.
- Health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.
- The prevalence of hypertension increases in patients older than 60 years and it is higher in blacks than whites.
- The age-adjusted prevalence of hypertension is slightly higher in men than in women. The prevalence in women is closely related to age, with substantial increase occurring after age 50. This may be related to hormonal changes associated with menopause.
- The risk of hypertensive complications increases continuously throughout the BP range.
- All adults should have blood pressure measured routinely at least every 5 years until the age of 80 years. Seated blood pressure when measured after 5 minutes resting with appropriate cuff size and arm supported is usually sufficient but standing blood pressure should be measured in diabetic and elderly subjects to exclude orthostatic hypotension.
- The cuff should be deflated at 2mm/s and the blood pressure measure to the nearest 2mmHg.
- Two consistent blood pressure measurements are needed to estimate blood pressure and more are recommended if there is variation in the pressure.
- A non-pathological rise in blood pressure is seen during pain and anxiety (including white coat hypertension). However, this may suggest underlying problem so consider follow up.

CLASSIFICATION

- Hypertension is classified according to
  - Etiology
  - Degree of elevation of blood pressure

ETIOLOGY

- This is divided into
  - Essential (primary) hypertension- most common (90-95%) and is due to a combination of genetic, environmental factors and age. It usually develops after the age of 30 but can develop earlier.
    - A number of factors modulate the blood pressure including humeral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity and neural stimulation.
    - Genetic factors- tends to run in families
    - Fetal factors- low birth weight is associated with subsequent high blood pressure. This relationship may be due to fetal adaptation to intrauterine undernutrition with long-term changes in blood vessel structure or in the function of crucial hormonal systems.
    - Environmental factors- obesity, alcohol intake, salt intake, stress, sedentary life style, smoking.
      - There is evidence that a high potassium diet can protect against the effects of a high sodium intake.
  - Secondary hypertension- this is due to other causes (5-10%). All patients below the age of 30 with hypertension and those with hypertension not sufficiently controlled on 3 drugs should be assessed for these conditions.
    - Renal:
      - Chronic kidney disease (most common)
      - Chronic pyelonephritis
      - Diabetic nephropathy
      - Acute and Chronic glomerulonephritis
      - Chronic tubulointerstitial nephritis
      - Polycystic kidney disease
      - Urinary tract obstruction
      - Renovascular disease- renal artery stenosis
      - Renin-producing tumor

- Endocrine:
  - Cushing's syndrome- hypercortisolemia
  - Acromegaly
  - Hyperthyroidism or hypothyroidism
  - Hyperparathyroidism
- Adrenal:
  - Conn's syndrome- hyperaldosteronemia
  - Pheochromocytoma- catecholamine producing tumor
  - Adrenal hyperplasia
- Cardiovascular -coarctation of the aorta, vasculitis, and collagen vascular disease
- Neurogenic: psychogenic, increased intracranial pressure, acute spinal cord section
- Drugs: NSAIDs, oral contraceptives, cyclosporine, nasal decongestants e.g. ephedrine, cocaine, amphetamines, steroids, erythropoietin, carnenoxalone, liquorice, sympathomimetic, vasopressin, monoamine oxidase inhibitors (with tyramine)
- Others: Obstructive Sleep apnea, Pregnancy or Pre-eclampsia

DEGREE OF EVELATION

CLASS	BLOOD PRESSURE	
	SYSTOLIC	DIASTOLIC
Blood pressure:		
▪ Optimal	<120	<80
▪ Normal	120-129	80-84
▪ Pre-hypertensive	130-139	85-89
Hypertension:		
▪ Stage 1: mild	140-159	90-99
▪ Stage 2: moderate	160-179	100-109
▪ Stage 3 severe	>180	>110
Isolated systolic hypertension:		
▪ Stage 1	140-149	<90
▪ Stage 2	>160	<90

- When systolic and diastolic blood pressure levels fall into different categories, the higher category should be selected to classify the individual's blood pressure status.
  - E.g. 160/92 mmHg should be classified as Stage 2 (moderate) hypertension
  - 174/120 mmHg should be classified as stage 3 (severe) hypertension
- Isolated systolic hypertension is defined as systolic blood pressure 140mmHg or greater and diastolic blood pressure less than 90mmHg and staged approximately (e.g. 170/82 mmHg is defined as stage 2 isolated systolic hypertension).
- The progression begins with prehypertension in persons aged 10-30 years (by increased cardiac output) to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent) to established hypertension in person aged 30-50 years, and finally to complicated hypertension in persons aged 40-60 years.
- Hypertensive urgency- severe hypertension (diastolic pressure greater than 130mmHg) but no end organ damage. The blood pressure should be lowered over 24 hours.
- Hypertensive emergency- severe hypertension (diastolic pressure greater than 130mmHg) with end organ damage. The blood pressure should be lowered aggressively over minutes to hours.
  - Usually does not occur unless sudden increase in diastolic blood pressure to <130mmHg. Was called malignant hypertension in the past.
  - Signs of end organ damage include encephalopathy (headache, visual impairment, seizures), blurry vision/retinal hemorrhage, angina, heart failure, pulmonary edema, aortic dissection and acute kidney injury.
- Hypertensive crises: this is a diastolic pressure of 130mmHg with fundoscopic findings of papilledema. Change in neurologic and mental status and abnormal renal sediments are the hallmarks of hypertensive crisis.
  - When associated with hemorrhages and exudates it is termed accelerated hypertension however when associated with papilledema it is termed malignant hypertension.

PATHOPHYSIOLOGY

- The pathogenesis of essential hypertension remains unclear.
- Hypertension is caused by a combination of cardiac output, peripheral vascular resistance and sodium retention (regulated by the renin-angiotensin system).
- Peripheral vascular resistance and sodium retention are more important.
- All treatment of hypertension targets these factors.

RISK FACTORS OF HYPERTENSION

- Modifiable:
  - Age
  - Gender: male sex
  - Race: black race
- Non-modifiable:
  - Arteriosclerosis
  - Dyslipidemias/hypercholesterolemia
  - Diabetes mellitus
  - Smoking
  - Obesity
  - Sedentary lifestyle
  - Excess alcohol intake
  - Stress

CLINICAL FEATURES

- Most patients with hypertension are asymptomatic.
- The signs and symptoms may be attributed to end organ damage or associated with the underlying secondary disease.
- The only reliable sign of hypertension is the blood pressure.
- Some symptoms:
  - Headache: though popularly considered symptom of high BP, it is a characteristic of only severe hypertension. Such headaches are localized to the occipital region and present when the patient awakens in the morning but subsides spontaneously after several hours.
  - Blurred vision, Postural hypotension, Dizziness, palpitations, shortness of breath sweating, easy fatigability and impotence
- Signs:
  - Tachycardia
  - Cerebral vascular insufficiency
  - Lung crepitations
  - Hypertensive retinopathy
- Symptoms related to vascular disease or evidence of target organ damage:
  - Epistaxis, hematuria
  - Retinal changes => blurring of vision
  - Cerebrovascular disease:

- TIAs: episodes of weakness or dizziness or stroke may occur (hemorrhagic or ischemic)

➢ Cardiovascular damages: chest pain/angina pectoris or myocardial infarction which may cause dyspnea due to heart failure

➢ Pain due to dissecting aorta

Underlying disease	Comments
Chronic pyelonephritis	• History of repeated UTIs
Pheochromocytoma	• History of Sweating, labile hypertension, headache, nervousness, postural dizziness, palpitations and weight loss
Aldosteronism	• History of polyuria, polydipsia and muscle weakness secondary to hypokalemia
Cushing's syndrome	• History of weight gain, and emotional labiality
Hypo- or hyperthyroidism	• History of cold or heat intolerance, sweating, lack of energy, bradycardia or tachycardia
Drugs	• Look for history of drug ingestion including oral contraceptives, licorice and sympathomimetics
• There may be a history of known renal disease, abdominal masses, anemia and urochrome pigmentation.	

DIAGNOSIS

- Hypertension is diagnosed if the blood pressure is elevated on 3 separate occasions. Once the diagnosis of hypertension has been made the following tests should be ordered:
  - ➢ Full blood count
  - ➢ Urinalysis including microscopy, protein, blood and glucose
  - ➢ Fasting blood glucose
  - ➢ Urea and Creatinine: to check the function of kidneys
  - ➢ Electrolytes
  - ➢ Liver enzymes
  - ➢ Lipid profile: Serum cholesterol, triglycerides, HDL and LDLs
  - ➢ Chest X-ray
  - ➢ ECG
  - ➢ ECHO to detect left ventricular hypertrophy
  - ➢ Fundoscopy

- Special investigations to determine secondary cause:
  - Thyroid function tests for hypo- and hyperthyroidism
  - Renal ultrasound (with dopplers) for Renovascular disease,
  - 24-hours urine assay of metanephrines and catecholamines for pheochromocytoma.
  - Overnight dexamethasone suppression test or 24-hour urine cortisol for Cushing's syndrome
  - Serum renin/aldosterone for primary Aldosteronism,
- "Burn out" hypertension- occurs in patients who have had severe, long standing hypertension but have now progressed to CCF (usually with dilated ventricles) with decreased systolic function and a blood pressure that is now normal or low.

COMPLICATIONS OF HYPERTENSION

- End organ/target organ damage involves: the CNS, the eyes, the heart and the kidneys.
- CNS complications:
  - Hypertensive encephalopathy: this consists of severe hypertension, altered state of consciousness, increased intracranial pressure with papilledema and seizures. Focal neurologic deficits are not common.
  - Cerebrovascular accident:
    - Transient ischemic attack: episodic dizziness, unilateral blindness, hemiparesis etc.
    - Stroke: ischemic stroke (due to atherosclerosis of cerebral blood vessels) or hemorrhagic stroke (as a result of elevated arterial pressure and formation of vascular micro-aneurysms).
  - Cerebrovascular insufficiency
- Eye complications: Blurry vision, Retinal hemorrhage and Hypertensive retinopathy (Grading below)

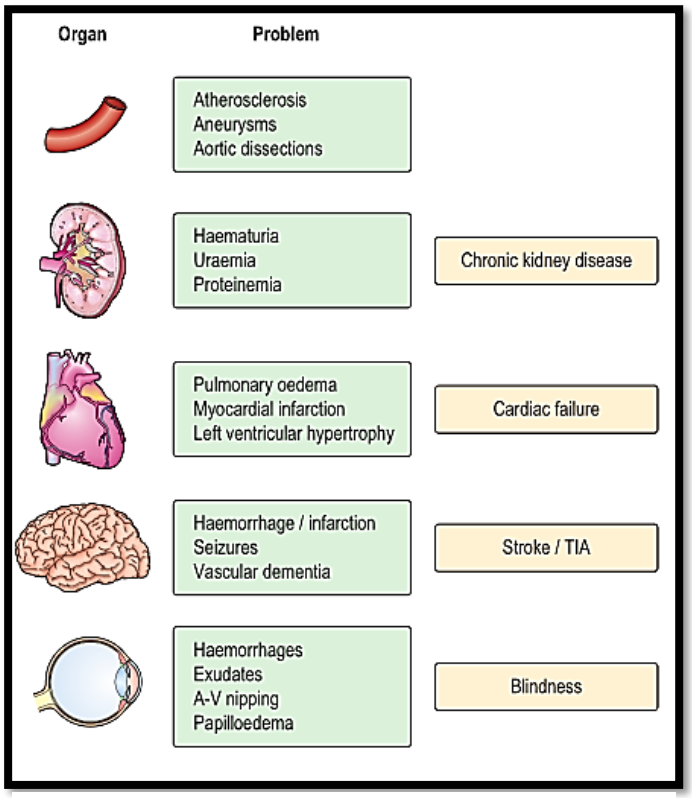


Figure 14: Target organ damage in hypertension (Image adapted from Kumar and Clark)

- Grade 1: Silver wiring/increased reflectiveness (thickening of arterioles-copper wiring=> silver wiring) and tortuosity
- Grade 2: grade 1 + Arteriovenous nipping produced when thickened retinal arteries pass over the retinal veins
- Grade 3: grade 2 + cotton wool spots (flame-shaped hemorrhages and soft exudates) due to small infarcts
- Grade 4: grade 3 + papilledema (blurring of the margins of the optic disc)



Figure 15: Fundus showing hypertensive changes: Grade 4 retinopathy with papilledema, hemorrhages and exudates

Note: Grades 3 and 4 are diagnostic of malignant hypertension.

- Cardiovascular complications:
  - Coronary artery disease/ischemic heart disease: angina pectoris and myocardial infarction
  - Aortic dissection
  - Pulmonary edema
  - Heart failure
  - Peripheral vascular insufficiency
- Kidneys: hypertensive nephropathy and renal failure

- Arteriosclerosis (hyperplastic arteriolosclerosis) of the afferent and efferent arterioles and the glomerular capillary tuft impairs renal function.
- Patients may have proteinuria and microscopic hematuria and later on develop chronic renal failure.

MANAGEMENT

- Evaluation involves:
  - Diagnosis of hypertension
  - Patient evaluation: Assessing lifestyle and other cardiovascular risk factors or other diseases that will affect management (diabetes, hyperlipidemia, smoking)
  - Identify secondary cause of hypertension
  - Assess for the presence of target-organ and cardiovascular disease (heart, brain, kidney, peripheral vascular disease, retinopathy)

DIAGNOSIS OF HYPERTENSION

- Diagnosis is confirmed after an elevated blood pressure greater than 140/90mmHg, properly measured has been documented on at least 3 separate occasions (based on the average of 2 or more readings at each of 2 or more visits after initial screening).
- For accurate diagnosis ensure:
  - Several determinations are made over a period of several weeks
  - The patient should rest quietly for at least 5 minutes before the measurement.
  - The proper cuff size is used (it must be large enough so that the bladder of the cuff encircles more than 30% of the arm), as the improper cuff size may influence blood pressure measurement, a wider cuff is preferable, particularly if the patient's arm circumference exceeds 30cm. If the cuff is too small the blood pressure will be falsely elevated.
  - Although somewhat controversial, the common practice is to document phase V (a disappearance of all sounds) of Korotkoff sounds as the diastolic pressure.
  - At any given visit an average of 3 blood pressure readings taken 2 minutes apart using a mercury manometer is preferable.
  - Blood pressure should be measured in both the supine and sitting positions, auscultating with the bell of the stethoscope.

- On the first visit, blood pressure should be checked in both arms and in one leg to avoid missing the diagnosis of coarctation of aorta or subclavian artery stenosis.

PATIENT EVALUATION

- Predisposing factors for hypertension:
  - Strong family history of hypertension
  - Age: secondary hypertension often develops before the age of 35 or after 55
- Associated cardiovascular risk factors:
  - Cigarette smoking
  - Lipid abnormality or hypercholesterolemia
  - Diabetes mellitus
  - Family history of early deaths due to cardiovascular diseases
  - Alcoholism
  - Obtain a history of over the counter medication use, current and previous unsuccessful antihypertensive medication trials.
- Physical examination
  - General appearance:
    - Round face and truncal obesity suggest Cushing syndrome
    - Muscular development in the upper extremities out of the proportion of the lower extremities suggestive coarctation of the aorta.
  - Proper measurement of blood pressure:
    - Compare the BP and pulses in the two upper extremities and in supine and standing position.
    - A rise in diastolic pressure when the patient goes from supine to standing position is most compatible with essential hypertension while a fall in BP in the absence of antihypertensive medication suggests secondary hypertension
  - Fundoscopic evaluation of the eyes:
    - Grade 1: Silver wiring/increased reflectiveness (thickening of arterioles-copper wiring=> silver wiring) and tortuosity
    - Grade 2: grade 1 + Arteriovenous nipping produced when thickened retinal arteries pass over the retinal veins
    - Grade 3: grade 2 + cotton wool spots (flame-shaped hemorrhages and soft exudates) due to small infarcts
    - Grade 4: grade 3 + papilledema (blurring of the margins of the optic disc)

- Palpation of all peripheral pulses should be performed: mainly palpation and auscultation of carotid arteries. Femoral pulses should be felt and compared with radial pulse. Radio femoral delay suggests coarctation of the aorta.
- Cardiac examination: this is performed to evaluate the signs of left ventricular hypertrophy. These include displacement of apex, a sustained and enlarged apical impulse and the presence of an S4. Occasionally a tambour S2 is heard with aortic root dilatation.
- Abdominal examination:
  - Look for renal artery bruit over the upper abdomen. The presence of a unilateral bruit with both a systolic and diastolic component suggests renal artery stenosis.
  - Palpate for an abdominal aneurysm, enlarged kidneys of polycystic kidney diseases.

LIFESTYLE MODIFICATION

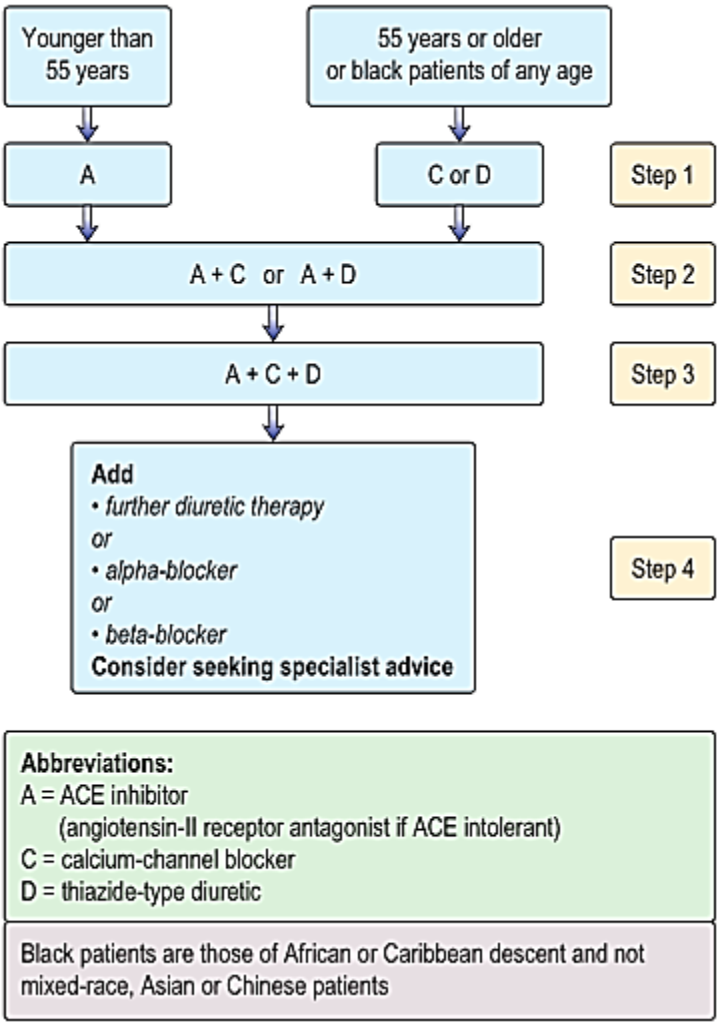
- The goal of blood pressure management is to reduce blood pressure to <140/90mmHg or <130/80mmHg in patients with diabetes, renal disease or cardiovascular disease.
- All patients with prehypertension and stages 1 and 2 hypertension should be counseled about lifestyle modification.
  - Salt restriction (intake not more than 2.4g sodium or 6g sodium chloride): no added salt or low-sodium diet
  - Weight reduction: if over the ideal BMI (BMI 20-25)
  - Exercise: aerobic physical activity (brisk walk for 30-45 minutes most days of the week i.e. 3-4 times a week)
  - Decrease of alcohol consumption (<3 units/day for men and <2 units/day for women): alcohol potentiates the action of catecholamines and may exacerbate hypertension
  - Cessation smoking
  - Stress relaxation techniques
  - DASH diet (Dietary Approaches to Stop hypertension): a diet rich in fruits, vegetables and low-fat dairy products with decreased saturated and unsaturated fat.
- Patients with mild to moderate (grade 1-2) hypertension should be given 3 months to see if they respond to behavioral modification.
- If a brief trial of nonpharmacologic therapy fails, medications should be added for those with stage 1 or stage 2 hypertension.

- In general, any patient with severe (Grade 3) hypertension and/or signs of complications (Stroke, Chronic kidney disease, Coronary artery disease, Congestive cardiac failure, retinopathy etc.) should be started on antihypertensive treatment immediately.
- Other modifiable cardiovascular risk factors (diabetes, hyperlipidemia, smoking), should be screened and treated in hypertensive individuals.
- Patients should be counseled that, if they start antihypertensives, they will likely need to take medication every day for life to prevent complications. They need to take the medication even if they feel well. If they have side effects they should come directly to see the doctor and not stop the medications until they are seen.

PHARMACOLOGICAL THERAPY

PRINCIPLES

- Classes of antihypertensives used include
  - ACE inhibitors
  - Angiotensin receptor antagonists
  - Beta-blocker
  - Calcium channel blocker
  - Diuretics
- Step 1:
  - Young Caucasians are more likely to have high renin hypertension and older patients and black patients usually have low renin hypertension.
  - If a drug with each pair is not tolerated, the alternative drug type can be used (e.g. If an ACE inhibitor is not tolerated an angiotensin receptor antagonist can be used)
  - If a drug is not effective, a drug from the other group should be selected. Thus, if a calcium-channel blocker is not helpful, an ACE inhibitor/angiotensin receptor antagonist should be tried. Almost all patients will need more than one drug to effectively lower blood pressure.



- Step 2: involves combining two drugs from different groups.
- Step 3: an ACE inhibitor (or angiotensin receptor antagonist) is combined with a calcium channel blocker and diuretic. If triple therapy is not sufficient to achieve target blood pressure readings, an alpha blocker, beta-blocker or spironolactone or another agent may be used. It is not advised to combine a diuretic with a beta-blocker since both aggravate diabetes.
- Step 4: add diuretic therapy, alpha blocker or beta blocker.
- Note: if the blood pressure remains elevated despite maximal dose of a first drug, add another drug and then titrate to its maximal dose.

DRUG CLASS	IMPORTANT CONSIDERATIONS
DIURETICS	• Thiazide diuretics low dosage are well-established agents and reduce risk of stroke in patients with hypertension. • Side effects with higher doses: increased serum cholesterol, impaired glucose tolerance, hyperuricemia (which may precipitate gout) and hypokalemia • Loop diuretics do have a hypotensive effect but are not routinely used to manage Primary HTN • Potassium sparing diuretics are not effective agents with monotherapy treatment except spironolactone in the treatment of hypertension and hypokalemia associated with primary hyperaldosteronism • Always monitor electrolytes with thiazide diuretics
BETA-ADRENOCEPTOR BLOCKERS	• No longer preferred as initial therapy for HTN but may be useful in younger people particularly those that cannot tolerate ACE and ARBs as well as women of child bearing potential. • Should not be combined with thiazide type diuretics as they increase the risk of developing diabetes (should be combined with calcium channel blockers) • Beta-blockers exert their effect by attenuating the effects of the sympathetic nervous system and the RAAS system. • Major side effect: bradycardia, bronchospasm, cold extremities, fatigue, bad dreams and hallucinations • Always monitor heart rate • These agents are especially useful in the treatment of patients with both hypertension and angina.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS	• Block the formation of angiotensin II a potent vasoconstrictor. They also block the degradation of bradykinin, a potent vasodilator. • There is evidence that black African patients respond less well to ACE inhibitors unless combined with diuretics. • Useful in diabetics with nephropathy where they slow disease progression and in patients with symptomatic or asymptomatic left ventricular dysfunction. • Profound hypotension following first dose is occasionally seen in sodium-depleted patients or in those on treatment with large doses of diuretics. • Renal function should be monitored during therapy as deterioration may occur in patients with severe bilateral renovascular disease (in whom the production of angiotensin II is playing a major role in maintaining renal perfusion by causing efferent arteriolar constriction at the glomerulus) • Most common side effect is a mild dry cough due to their effect on bradykinin.
ANGIOTENSIN II RECEPTOR ANTAGONISTS	• Share many actions of ACE inhibitors but since they do not have any effect on bradykinin they do not cause cough. • They are used as an alternative in patients that cannot tolerate ACE inhibitors • Angioneurotic edema and renal dysfunction are encountered less with this class as opposed to ACE inhibitors
CALCIUM CHANNEL BLOCKERS	• Reduce blood pressure by causing arteriolar dilation as well as reduce cardiac contractility. • They are useful in patients with concomitant ischemic heart disease • Major side effects (seen mostly with short acting): headache, sweating, swelling of ankles, palpitations and flushing
ALPHA BLOCKER	• These agents cause postsynaptic alpha-1 receptor blockade with resulting vasodilation and blood pressure reduction.

	• Earlier short acting agents cause serious first dose hypotension but the newer longer acting agents are far better tolerated.
RENIN INHIBITORS	• Aliskerin is the first orally active renin inhibitor which directly inhibits plasma renin activity. • It reduces the negative feedback by which angiotensin II inhibits renin release. It has been used in combination with ACE inhibitors and ARBs with a significant reduction in blood pressure. However, a recent FDA warning suggests avoiding these drugs with aliskerin • Side effects are few but hypokalemia occurs.
OTHER VASODILATORS	• Reserved for patients resistant to other forms of treatment. • Hydralazine can be associated with tachycardia, fluid retention and a systemic lupus erythematosus-like syndrome. • Minoxidil can cause severe edema, excessive hair growth and coarse facial features.
CENTRALLY ACTING DRUGS	• Methyldopa acts on central alpha-2 receptors usually without slowing the heard and is usually reserved for patient with hypertension in pregnancy.

- Calcium channel blockers (like Nifedipine or Amlodipine) are all very effect in Africans and good first antihypertensive drugs if you want to lower BP rapidly (as in hypertensive urgency).
- For patients with DM or CCF and a normal or stable creatinine, ACE inhibitors (like captopril or Lisinopril) are the best first antihypertensive.
- In patients with CAD, beta blockers are the first antihypertensive as they reduce the risk of death from CAD
- Of note, most antihypertensives take 2-4 weeks to reach maximal effect so it is good to wait 1 month before increasing the dose of a medicine or adding another one.

STEP ONE

- Option 1: Diuretics: start diuretics
  - Amiloride and hydrochlorothiazide (5/50mg) PO OD
  - Hydrochlorothiazde 25mg PO OD and Spironolactone 25-50mg PO BD to QID
- Option 2: Calcium channel blocker
  - Nifedipine retard 20mg PO BD or
  - Amlodipine 2.5-10mg PO OD
- Option 3: Angiotensin converting enzyme inhibitors
  - Captopril 25-50mg PO BD or TDS alternatively Enalapril 2.5-40mg PO OD.
  - Those who cannot tolerate angiotensin converting enzyme inhibitors may be given Angiotensin receptor antagonists [Losartan potassium 50-100mg PO OD]

STEP TWO

- Use a combination of drugs from different groups:
  - Diuretics + ACE inhibitors/ AR blocker
  - Calcium channel blocker + ACE inhibitors/AR blocker
  - Calcium channel blocker + Diuretic

STEP THREE

- Use a combination of diuretic + ACE inhibitor/ AR blocker + Calcium channel blocker

STEP FOUR

- If not controlled as above, optimize the dose, add further diuretic therapy or
- Alpha blocker [Prazosin 0.5mg BD or TDS PO] initial should be at bed time to avoid postural hypotension- then increase to 1-3mg BD or TDS after 3 to 7 days, maximum daily dose 20mg or
- Add beta blocker- Atenolol 50-100mg PO OD, Propranolol 40-80mg PO BD or TDS or
- Hydralazine 25-50mg PO BD or TDS
- Note: beta blockers are no longer preferred as a routine initial therapy for hypertension, however can be used in younger people, patients with cardiovascular risk or existing ischemic heart disease

Drug	Dose	Conditions favouring use	Cautions/contraindications
Alpha-blockers			
Doxazosin	1.0–16 mg daily	Benign prostatic hypertrophy	Postural hypotension, urinary incontinence
Indoramin	25–100 mg ×2 daily		
Phenoxybenzamine	1 mg/kg i.v. over >2 h	Phaeochromocytoma crisis	Profound hypotension
Phentolamine	2.0–5.0 mg i.v.		
Aldosterone antagonists			
Spironolactone	50–400 mg daily	Primary hyperaldosteronism, heart failure	Hyperkalaemia
Eplerenone	50–100 mg daily		
Angiotensin-converting enzyme inhibitors			
Enalapril	5.0–40 mg daily	<55 years old, Caucasian, heart failure or left ventricular dysfunction, myocardial infarction or cardiovascular disease, diabetic nephropathy, chronic renal disease, stroke secondary prevention	Renal failure (monitor electrolytes), peripheral vascular disease (if renovascular disease), pregnancy
Lisinopril	2.5–40 mg daily		
Perindopril	2.0–8.0 mg daily		
Ramipril	1.25–10 mg daily		
Angiotensin II receptor blockers			
Losartan	50–100 mg daily	ACE inhibitor intolerant, <55 years old, Caucasian, hypertension with LVH, heart failure or left ventricular dysfunction, myocardial infarction, diabetic nephropathy, chronic renal disease	Renal failure (monitor electrolytes), peripheral vascular disease (if renovascular disease), pregnancy
Candesartan	2.0–32 mg daily		
Valsartan	40–320 mg daily		
Olmesartan	10–40 mg daily		
Telmisartan	40 mg daily		
Beta-blockers			
Atenolol	25–100 mg daily	Coronary heart disease (post myocardial infarction or angina), heart failure (bisoprolol and carvedilol)	Diabetes, peripheral vascular disease, asthma/COPD, heart block, unstable heart failure
Bisoprolol	1.25–20 mg daily		
Carvedilol	12.5–50 mg daily		
Labetalol	100–200 mg ×2 daily (max. 2.4 g/day)	Hypertension in pregnancy	
Calcium channel blockers			
Amlodipine	5.0–10 mg daily	>55 years, black patients, angina	
Nifedipine (long acting)	20–90 mg daily		
Diltiazem (long acting)	90–180 mg ×2 daily		Bradycardia, heart block, heart failure, beta-blockers (verapamil)
Verapamil	120–240 mg ×2 daily		
Centrally acting			
Methyldopa	250 mg–1 g ×3 daily	Hypertension in pregnancy, breastfeeding	Monitor blood counts and liver function tests
Moxonidine	200–600 µg daily	Resistant hypertension, insulin resistance	Renal or heart failure, glaucoma, angioedema, bradycardia
Diuretics			
Bendroflumethiazide	2.5 mg daily	>55 years, black patients, heart failure, stroke secondary prevention	Gout, diabetes, hypokalaemia
Chlortalidone	25 mg daily		
Furosemide	40–80 mg daily	Heart failure, renal dysfunction	Hypokalaemia
Renin inhibitors			
Aliskiren	150–300 mg daily	Resistant hypertension	Renal failure, pregnancy
Vasodilators			
Hydralazine	25–50 mg ×2 daily	Black patients, heart failure (when combined with nitrates)	SLE
Minoxidil	5.0–50 mg daily	Severe hypertension (with a diuretic and beta-blocker)	Pregnancy
Sodium nitroprusside	0.3–5 µg/kg per min i.v.	Hypertensive crisis	Needs intra-arterial BP monitoring, avoid prolonged use

MANAGEMENT OF HYPERTENSIVE CRISES

- Hypertensive urgency- severe hypertension (diastolic pressure greater than 130mmHg) but no end organ damage. The blood pressure should be lowered over 24 hours.
- Hypertensive emergency- severe hypertension (diastolic pressure greater than 130mmHg) with end organ damage. The blood pressure should be lowered aggressively over minutes to hours.
  - Usually does not occur unless sudden increase in diastolic blood pressure to <130mmHg. Was called malignant hypertension in the past.
  - Signs of end organ damage include encephalopathy (headache, visual impairment, seizures), blurry vision/retinal hemorrhage, angina, heart failure, pulmonary edema, aortic dissection and acute kidney injury.
- Hypertensive crises: this is a diastolic pressure of 130mmHg with fundoscopic findings of papilledema. Change in neurologic and mental status and abnormal renal sediments are the hallmarks of hypertensive crisis.
  - When associated with hemorrhages and exudates it is termed accelerated hypertension however when associated with papilledema it is termed malignant hypertension.
- Note: in any patient with BP>222/120mmHg (very severe hypertension), assess for signs of end organ damage and consider admission to the hospital. Hypertensive emergency usually does not occur unless diastolic blood pressure >130. Keep in mind that urgency is much more common than emergency.
- Signs of end organ damage:
  - Hypertensive encephalopathy: visual impairment, confusion, headache and seizures
  - Acute retinal hemorrhage: sudden onset of blurry vision, massive hemorrhage on ophthalmoscopy
  - Myocardial ischemia or infarction: chest pain and ECG changes
  - Pulmonary edema: shortness of breath, Chest X ray with pulmonary edema
  - Acute kidney injury: recent onset of oliguria or anuria, elevated creatinine, blood on urinalysis

APPROACH TO THE PATIENT

- Rapid assess of the patient with brief history and targeted physical examination (of the CNS, CVS, retina).
- Laboratory investigations:
  - Full blood count
  - Urinalysis
  - Renal function test
  - ECG
- General measures: look if the patient is in a stressful situation. Place the patient in a quiet room and reevaluate after initial interview. Some patient's BP lowers below a critical level after relaxation.
- If the patient has hypertensive urgency (no signs of end organ damage) aim to lower MAP by 25% over 2-3 days using oral medications. Start with Nifedipine 20mg PO BD and add other meds as necessary.
- If the patient has hypertensive emergency (signs of end organ damage), lower the MAP by 25% over 1-2 hours using IV medication. Do not drop the diastolic pressure to less than 95mmHg.
- Pharmacologic treatment:
  - Start with Labetalol 50mg IV over at least a minute repeated after 5 minutes if necessary, maximum dose is 200mg or
  - Hydralazine 10mg IV stat followed by 5 mg IV every 30 minutes until diastolic BP is 110mmHg or less or
  - Sodium nitroprusside 0.5-8 micrograms/kg/min through continuous IV infusion till BP is lowered to desired level.
  - Furosemide 40-80mg IV may be used as adjunctive therapy as a stat dose.
- As the patient's BP stabilizes start long term oral anti-hypertensive agents.
- Those patients with urgency could be discharged with close follow- up and oral medication.

$$MAP \simeq DP + \frac{1}{3}(SP - DP)$$

or equivalently

$$MAP \simeq \frac{2}{3}(DP) + \frac{1}{3}(SP)$$

or equivalently

$$MAP \simeq \frac{(2 \times DP) + SP}{3}$$

or equivalently

$$MAP \simeq DP + \frac{1}{3}PP$$

where PP is the pulse pressure, $SP - DP$

HEART FAILURE

- This is a complex clinical syndrome caused by a structural or functional abnormality in the cardiac muscle that impairs its ability to function as a pump and meet the metabolic needs of the body.
- The body, sensing inadequate organ perfusion, activates multiple systemic neuro-hormonal pathways which compensate initially by redistributing blood flow to vital organs but later exacerbate the patient's symptoms and lead to clinical deterioration.
- Heart failure is a syndrome and not a complete diagnosis in itself: it's important to determine the underlying cardiac abnormalities.
- The incidence of CCF increases with age.
- The term 'congestive heart failure' is ill-defined but typically refers to heart failure with fluid overload especially pulmonary edema.

CLASSIFICATION

- Heart failure can be classified:
  - Anatomically
    - Right sided heart failure
    - Left sided heart failure
    - Biventricular heart failure
  - Functionally
    - Heart failure with reduced ejection fraction (systolic heart failure)
    - Heart failure with preserved ejection fraction (diastolic heart failure)
    - High output heart failure

ETIOLOGY

UNDERLYING CAUSES

- The most common causes of heart failure include:
  - Ischemic heart disease (35-40%)
  - Cardiomyopathies (Dilated) (30-34%)
  - Hypertensive heart disease (15-20%)
- Other causes include:
  - Hypertrophic and restrictive cardiomyopathies
  - Valvular heart lesions (mitral, aortic, tricuspid)
  - Congenital heart disease (ASD, VSD)
  - Alcohol and drugs (chemotherapy- doxorubicin)

- Hyperdynamic state (anemia, thyrotoxicosis, hemochromatosis, Paget's disease)
- Right ventricular heart failure (RV infarct, pulmonary hypertension, Pulmonary embolism, COPD)
- Tricuspid incompetence
- Pericardial disease (constrictive pericarditis, pericardial effusions)

LEFT VENTRICULAR FAILURE

- Manifestations are seen in the pulmonary circuit.

HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF)

- Left ventricular ejection fraction <40%. (normal ejection fraction ≥50%)
  - Ejection fraction between 40-49% is a 'mid-range' grey area
- It is also known as systolic heart failure or left ventricular systolic dysfunction (LVSD)
- Causes:
  - Ischemic heart disease (IHD)/Myocardial infarction: commonest cause
  - Hypertension
  - Diabetes usually via IHD
  - Valve disease
  - Arrhythmias
  - Drugs or alcohol
- Systolic heart failure: there is reduced cardiac contractility.
- The manifestations of systolic heart failure include: weakness, fatigue, reduced exercise tolerance and other symptoms of hypoperfusion.

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

- Left ventricular relaxation failure leads to inadequate filling which decreases stroke volume normal ejection fraction (≥50%).
- It is also known as diastolic heart failure.
- Causes:
  - Hypertension: commonest cause
  - Diabetes
  - Constrictive pericarditis
  - Cardiac tamponade

  - Restrictive cardiomyopathy
- Much more common in women than men, especially elderly women with hypertension.

ETIOLOGY OF CHF	CAUSES
Systolic dysfunction (inability to expel blood)	Hypertension (common) Ischemic heart disease Idiopathic cardiomyopathy (like HIV) Dilated cardiomyopathy Valvular disease (common) Alcoholic cardiomyopathy Drug-associated cardiomyopathy Myocarditis
Diastolic dysfunction (abnormal filling)	Hypertension Fibrosis Ischemia Aging process Constrictive pericarditis (like in TB-common) Restrictive pericarditis (like in EMF-common) Hypertrophic cardiomyopathy

RIGHT VENTRICULAR FAILURE

- Manifestations are seen in the systemic circuit.
- Right ventricular systolic dysfunction due to:
  - Cor pulmonale: primary lung disease (e.g. COPD) causing vasoconstriction in poorly ventilated lung tissue to correct the decreased V/Q (ventilation perfusion ratio) leading to pulmonary hypertension and right ventricular failure
  - Left ventricular failure due to pulmonary hypertension causing right ventricular failure.
  - Pulmonary valve stenosis (uncommon)

HIGH OUTPUT HEART FAILURE

- Normal heart but increased needs due to:
  - Anemia
  - Pregnancy

- Hyperthyroidism

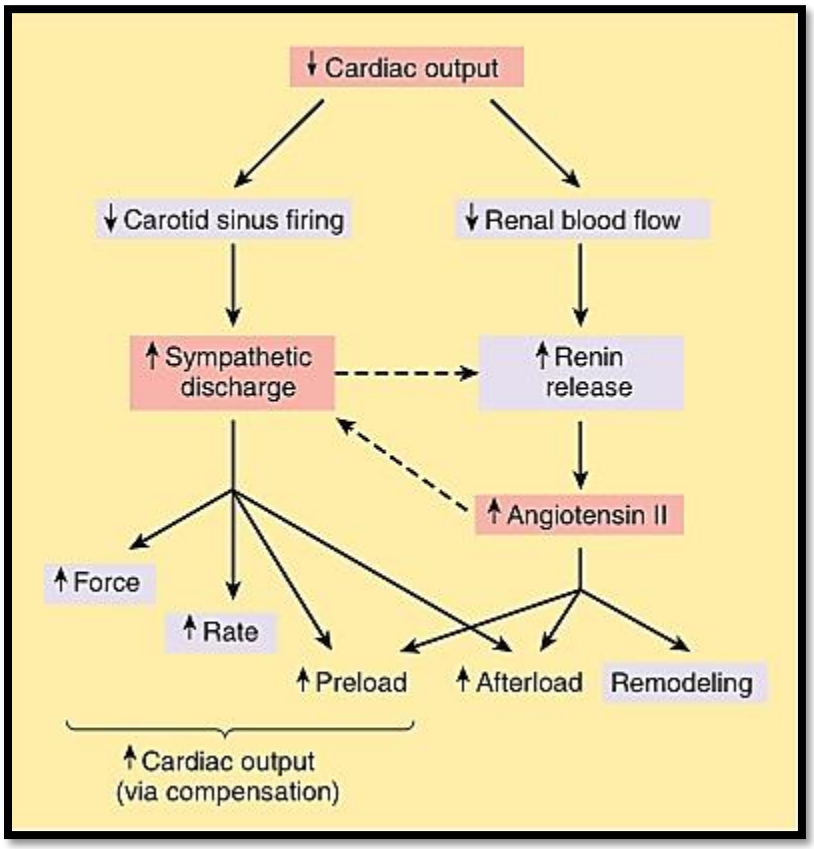
PRECIPITATING CAUSES

- The most common causes include
  (1) H-Hypertension (systemic)
  (2) E- Endocarditis (infection)
  (3) A-Anemia
  (4) R- Rheumatic fever and myocarditis
  (5) T- thyrotoxicosis and pregnancy
  (6) F-fever (infections)
  (7) A-Arrhythmias (atrial fibrillation, complete heart block, sick sinus syndrome)
  (8) I-infarction (myocardial)
  (9) L- Lung infection
  (10) E- Embolism (pulmonary)
  (11) S-Stress (emotional, physical, environment, dietary, fluid excess)

PATHOPHYSIOLOGY

- Heart failure may be classified as 'acute' or 'chronic', based on the time course of the development of symptoms.
- Heart failure may be transient and reversible or permanent and thus chronic.
- When the heart fails, considerable changes occur to the heart and peripheral vascular system in response to the hemodynamic changes associated with heart failure.
- These physiological changes are compensatory and maintain cardiac output and peripheral perfusion.
- The heart depends on a number of adaptive mechanism for maintenance of its pumping function:
  - Intrinsic mechanism
    - The Frank-starling mechanism (cardiac dilation): increase in venous return or end-diastolic volume results in increase in stroke volume and cardiac output. It is the mechanism that matches cardiac output to venous return.
    - Myocardial hypertrophy: increase in muscle mass helps maintain cardiac performance. However, after initial beneficial effect, hypertrophy can lead to ischemic changes, impairment of diastolic filling and alterations in ventricular geometry.
  - Extrinsic mechanism

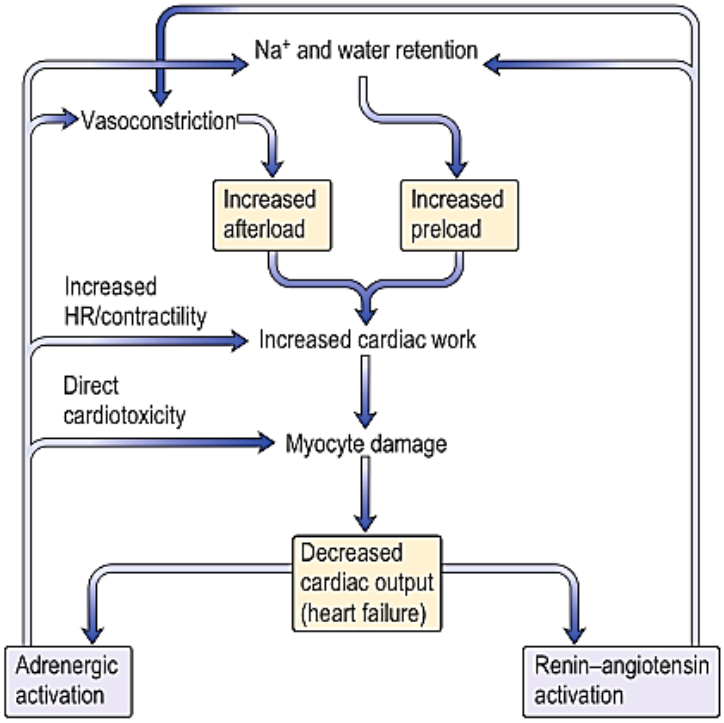
- ♦ Baroreceptor reflex: increases release of catecholamines, activation of renin—angiotensin-aldosterone system and other neuro-humoral adjustments.
- ♦ Renin-angiotensin aldosterone system.



- To compensate for the decreased cardiac output, the activity of the sympathetic nervous system is elevated and the renin-angiotensin-aldosterone system is activated.
- The change in activity of the sympathetic nervous system and the subsequent stimulation of the adrenal medulla to release noradrenaline and adrenaline, results in increased heart rate (tachycardia), increased contractility of the heart and pronounced peripheral vasoconstriction in order to maintain blood pressure.
- The renin-angiotensin-aldosterone system is activated to correct the poor perfusion to the kidneys due to the decrease in cardiac output.
- Vascular tone is further increased by angiotensin II and endothelin, a potent vasoconstrictor released by vascular endothelial cells.
  - ➢ Vasoconstriction increases afterload, which further reduces ejection fraction and cardiac output.

- The retention of salt and water are potentiated by the secretion of aldosterone leading further congestion and edema.
- The stretch of the heart chamber walls leads to the release of atrial natriuretic factor from the atrial wall and brain natriuretic factor from the ventricular wall.
  - These peptides induce a decrease in blood volume and blood pressure through sodium and water excretion as well as vasodilation of arterioles and venules.
- Unfortunately, in the long term most of these compensatory mechanisms amplify the problem rather than overcome it.
- The marked vasoconstriction increases the workload of the heart (afterload), it is now harder to push blood out into the smaller-diameter vasculature than before because of increased resistance.
- The heart also works harder when the heart rate increases.
- The increase in workload (afterload) means the myocardium requires more oxygen but coronary blood flow is depressed due to the decrease in cardiac output.
- There is also a progressive reduction in the sensitivity of the arterial baroreceptor reflex to changes in blood pressure. This reflex is important in inhibiting sympathetic activation when blood pressure rises. As a consequence, sympathetic nervous system activity remains elevated in heart failure sufferers as do plasma renin levels.

- Coupled with the increased ventricular filling pressure caused by poor ventricular emptying and the expansion of the intravascular volume, the ventricular chamber wall is subjected to increased stress.
- These stresses trigger myocardial remodeling. As a consequence, there is hypertrophy of the ventricular myocardium, dilation of the affected chamber (or chambers) and further reductions in contractility.
- An increased mass of cardiac muscle also places increased demands on oxygen consumption.
- Thus, the compensatory mechanisms that (in a normal heart) act to increase cardiac output actually perpetuate and worsen the heart failure.



Neuro-humoral changes	Favorable effect	Unfavorable effect
Increased sympathetic activity	Increased heart rate, contractility, and vasoconstriction leading to increased venous return and filling	Arteriolar constriction increases afterload which increases the oxygen demand of the myocardium
Increased Renin-Angiotensin-Aldosterone system	Salt and water retention leading to increase venous return	Vasoconstriction leading to increased afterload and cardiac remodeling
Increased Vasopressin (ADH)	Salt and water retention leading to increase venous return	Vasoconstriction leading to increased afterload
Increased interleukins and TNFs	May have roles in myocytes hypertrophy	Apoptosis
Increased Endothelin	Vasoconstriction leading to increased venous return	Vasoconstriction leading to increased afterload

- Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy and fibrosis.
- This prompts additional neurohormonal activation creating a vicious cycle that if left untreated, leads to death.
- The severity of the clinical manifestations are commonly described according to criteria developed by the New York Heart Association.

THE NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

- Class I- no limitation in physical activity. Normal physical exercise does not cause fatigue, dyspnea or palpitations.
- Class II- mild limitation of physical activity. Comfortable at rest but normal physical activity produces fatigue, shortness of breath or palpitations. (i.e. when long distance walking, climbing 2 flights of stairs)
- Class III- marked limitation of activity. Comfortable at rest but gently exertion causes marked symptoms of heart failure. (i.e. short distance walking, climbing one flight of stairs
- Class IV- symptoms of heart failure occur at rest and are exacerbated by any physical activity.

Grade	Symptoms
I	No symptoms
II	Slight limitation, mild symptoms
III	Marked limitation, symptoms with minor activity
IV	Severe limitation, symptoms at rest

CLINICAL FEATURES

- CCF is characterized by shortness of breath, fatigue and signs of fluid retention.
- Most patients present with left heart failure which can progress to right heart failure.
- Heart failure can be either compensated (when the patient is stable) or decompensated (when the patient suddenly gets worse).
- Signs and symptoms of heart failure are:
  - Symptoms: Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue

- Signs: cardiomegaly, S3 & S4 heart sounds, Elevated JVP, tachycardia, hypotension, bi-basal crepitations, pleural effusion, peripheral ankle edema, ascites, tender hepatomegaly

	Left sided heart failure	Right sided heart failure
Symptoms	• Respiratory symptoms: ➢ shortness of breath, ➢ Orthopnea (ask how many pillow they sleep with) ➢ Paroxysmal nocturnal dyspnea (PND) and nocturnal cough ➢ Pink frothy sputum ➢ Wheeze • Other symptoms: ➢ Palpitations ➢ Poor exercise tolerance ➢ Fatigue ➢ Weight loss (cachexia) or weight gain (fluid retention)	• Liver congestion leads to nausea, anorexia, early satiety and right upper quadrant pain • Epistaxis • Nocturia: on lying flat, fluid backs up from legs to kidneys
Signs	• Cachexia • Cold peripheries • Pulses Alternans: Arterial Amplitude Strong then Weak • Displaced apex beat (lateral displacement) • Crepitations (bi basal) • S3 heart sound (‘gallop rhythm) • S4 is commoner in diastolic heart failure • Crepitations	• Increased JVP • Peripheral edema • Ascites • Hepatomegaly • Right ventricular heave due to pulmonary hypertension

- Note: in biventricular failure there are features of both right sided and left sided heart failure.

DIAGNOSIS

- History and clinical examination
- Blood:
  - FBC: anemia may mimic or exacerbate symptoms
  - U+E and LFTs: liver and kidney function can be affected in heart failure and are differential for fluid retention
  - Thyroid function test: thyrotoxicosis can cause high output failure, while hypothyroidism may cause symptoms of fatigue and edema
  - Investigate cardiac risk factors: cholesterol, blood glucose
- Imaging
  - Chest X ray
    - Prominent pulmonary vessels (dilatation of pulmonary vessels) and interstitial edema.
    - Vascular redistribution (cephalization).
    - Cardiomegaly (enlarged cardiac silhouette): increased cardiothoracic ratio (normal ratio<50%)
    - Pulmonary congestion: upper lobe diversions, fluid in fissures, Kerley B lines, pleural effusions
  - Echocardiography- wall thickness, cavity dimensions, ventricular function (systolic <40% and diastolic dysfunction≥50%)
  - ECG- abnormal in 80%
    - Usually non-specific changes: Previous MI or AF (common) or axis deviation (less common)
    - Left ventricular failure
      - Voltage criteria are met if the combined height of (S in V1) + (R in V5 or V6) is at least 7 large squares (35mm)
      - LV strain pattern is ST depression and T inversion in V5-6
      - Less commonly there is the mirror image ST elevation in V1-V3
    - Right ventricular failure
      - Tall R in V1 (>7 small squares or R>S in V1)
      - Large S waves in V4-6.
      - RV strain pattern is ST depression or T inversion in V1-3

FRAMINGHAM CRITERIA FOR CHF

- Validate CHF with (2 major criteria) or (1 major and 2 minor)
  - Major: paroxysmal nocturnal dyspnea or orthopnea, Elevated JVP, pulmonary rales, S3, cardiomegaly on chest X-ray
  - Minor: peripheral edema, night time cough, dyspnea on exertion (DOE), pleural effusions, HR> 120, weight loss>4.5 kg in 5 days with diuresis.

MANAGEMENT

- Principles:
  - Identify and treat the precipitating factors
  - Control the congestive state
  - Improve myocardial performance
  - Prevention of deterioration of myocardial function (slowing progression of heart failure)
  - Treat underlying cause

GENERAL MEASURES

- Counseling
  - Dietary salt restriction (<2g/day)
  - Moderate fluid restriction. Get help if rapid gain e.g. 2kg in 3 days.
  - Daily weighing
  - Weight loss in obese patients (Avoid excess physical exertion, Note: exercise may be advised within limit of the patient's cardiac function)
  - Stop smoking and alcohol
- Administration of oxygen if needed, exercise as tolerated for Class I and II.
- Treat co-morbidities such as IHD, AF and dyslipidemia.

PHARMACOLOGICAL THERAPY

HEART FAILURE WITH REDUCED EJECTION FRACTION

- Most patients are on four agents, all which except diuretics have a mortality benefit.

CONTROL CONGESTIVE STATE

- Diuretics: are used in relieving congestion and reducing or preventing edema. Most patients with heart failure have some degree of symptomatic congestion and benefit from diuretic therapy.
  - Usually a loop diuretic is required with the addition of a thiazide diuretic in patients refractory to loop diuretics.

- Furosemide
  - Initial dose 20-40mg PO OD/BD or 20mg IV
  - Maximum dose 400mg PO/day or 80mg IV/day
- Hydrochlorothiazide
  - Initial dose 25mg PO/day
  - Maximum dose 100mg PO/day
- Note: Loop and thiazide diuretics are useful for symptomatic relief; however, they have not been shown to improve survival
- Side effects: azotemia, hypokalemia, metabolic alkalosis and elevation of neurohormones
- Spironolactone: is an aldosterone inhibitor, reduces mortality in patients with advanced heart failure. This drug should be reserved for patients with moderately severe or severe heart failure (Class IV symptoms)
  - Initial dose: 25mg PO/day or every other day
  - Maximum dose: 50mg PO BD or higher
  - Side effects: hyperkalemia (common so monitor potassium, the serum potassium level is essential. As a result, this drug should be used in patients with a creatinine above 2.5mg/dl), gynecomastia (in men)

ENCHACEMENT OF MYOCARDIAL CONTRACTILITY

- Digoxin:
  - Inotropic effect and acts by inhibiting the Sodium-potassium ATPase and increases intracellular calcium. This increases myocardial contractility.
  - Neurohormonal modulation of centrally mediated parasympathomimetic and sympathetic activity. By doing so it blocks the AV node and delays AV conduction.
    - Initial dose: 0.125mg PO/day
    - Maximum dose: 0.25mg PO/day
  - The use of digoxin can improve symptoms, reduce the duration and the need for hospitalization in patients with heart failure but no effect on long term survival.
  - Digoxin is renally excreted and so dose adjustment is necessary in renal failure.
  - Digoxin use is recommended for patients with left ventricular systolic dysfunction, particularly if they have atrial fibrillation.
  - It is relatively contraindicated in some cardiac disease
    - Cardiac outflow obstruction in MS (in the absence of atrial fibrillation)

    - Cor pulmonale
  - Because of its narrow therapeutic index, it is associated with different side effects
    - GI: anorexia, vomiting, weight loss
    - Neuralgia, delirium
    - Yellow vision, Gynecomastia
    - Arrhythmias of different types
  - When electrolyte imbalance is suspected, digoxin should be withheld, and patient observed for some days before reinitiating with a lower dose. One should also give KCL as hypokalemia increases digoxin toxicity
- Vasodilator therapy: mainstay of chronic therapy, reduces mortality. May be used in patients with severe heart failure. Through vasodilation there is a reduction in the peripheral resistance and after load and improving cardiac performance.
  - ACE inhibitors (1st line)- but must follow renal function. Enalapril has most evidence and should be offered to all, and titrated to evidence-based dose. ARBs can be substituted if intolerant.
  - Isosorbide dinitrate
    - Initial dose 10mg PO QID
    - Maximum dose 80mg PO TDS
  - Hydralazine (rarely used)
    - Initial dose 10mg PO TDS
    - Maximum dose 80mg PO TDS
  - Hydralazine and nitrates in combination are effective afterload reducing agents used in ACE intolerant patients

PREVENTION OF DETERIORATION OF MYOCARDIAL FUNCTION

- The following drugs prevent deterioration in myocardial function by inhibiting the neurohumeral mechanisms which causes cardiac remodeling and progression of heart failure
- ACE inhibitors: improve mortality, symptoms and hospitalizations. They also reduce afterload and cause neurohormonal modulation. The dose of ACE inhibitors should be titrated to the maximum that can be tolerated symptomatically or the target dose
  - Captopril
    - Initial dose: 6.25mg PO/day or every other day
    - Maximum dose: 50-100mg PO QID

  - Enalapril:
    - Initial dose: 2.5mg PO BD
    - Maximum dose: 10-20mg PO BD
  - Side effects: angioedema, acute renal failure in patients with bilateral renal artery stenosis. It is contraindicated in patients with creatinine >3mg/dl, cough
  - Contraindications:
    - Angioedema or anuric renal failure
    - Pregnancy, Hypotension
    - Creatinine >265mol/L (2mg/dl)
  - Note the first 2 side effects are serious and necessitate immediate cessation of the drug.
- Angiotensin II receptor blockers: these drugs are useful in patients who cannot tolerate ACE inhibitors due to different side effects like cough, angioedema and leukopenia.
  - Losartan dose 25-50mg PO OD/BD
- Beta-blockers: for chronic therapy in patients with non-valvular CHF, not acute, decompensated heart failure, reduces mortality. They are not indicated in unstable heart failure, hypotensive states, severe fluid overload, sinus bradycardia, AV block and asthma
  - Carvedilol (best), metoprolol, atenolol
  - Metoprolol dosage:
    - Initial dose 6.25mg PO BD
    - Maximum dose: 75mg PO BD

RIGHT VENTRICULAR FAILURE AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

- There is little evidence based treatment for RVF or heart failure with preserved ejection fraction except for symptomatic relief with diuretics, management of co-morbidities and lifestyle changes
- Long term oxygen therapy is beneficial in cor-pulmonale.

DRUGS CONTRAINDICATED IN HEART FAILURE

- NSAIDs especially diclofenac. Low dose aspirin is ok
- Steroids
- Most calcium channel blockers especially rate-limiting (verapamil, diltiazem)
- Pioglitazone, TCAs, Beta-agonists

TREATMENT GUIDLINES

NYHC	Comments	Management
Class I	Asymptomatic	• Most patients do not require medicine but will require lifestyle modifications
Class II	Symptomatic on moderate exertion	• Captopril 12.5mg to 15mg PO BD or • Lisinopril 5-10mg PO daily or • Enalapril 5-20mg PO daily (if patient develops a persistent dry cough replace with Losartan 50mg PO daily) • Hydrochlorothiazide 25mg PO daily or oral Furosemide 20-40mg PO daily • Beta blockers (Carvedilol 3.125mg PO BD, increase dose at least every 2 weeks to 25mg BD, if patient is over 85kg then maximum dose 50mg BD or use metoprolol 50-100mg PO daily)
Class III	Symptomatic on mild exertion	• Captopril 25mg PO BD/TDS or • Lisinopril 10-20mg PO daily or • Enalapril 5-20mg PO daily (if patient develops a persistent dry cough replace with Losartan 50mg PO daily) • Furosemide 40-80mg PO BD (monitor potassium levels) • Digoxin 0.125mg-0.25mg PO daily • Isosorbide nitrate 5mg to 10mg BD + hydralazine 5mg to 10mg BD orally if patient cannot tolerate ACE inhibitors • ASA 75mg PO OD
Class IV	Symptomatic at rest	• Captopril 25mg PO BD/TDS or • Lisinopril 10-20mg PO daily or • Enalapril 5-20mg PO daily (if patient develops a persistent dry cough replace with Losartan 50mg PO daily) • Furosemide 40-80mg IV BD (monitor potassium levels) • Digoxin 0.125mg-0.25mg daily • Isosorbide nitrate 5mg to 10mg BD + hydralazine 5mg to 10mg BD orally if patient cannot tolerate ACE inhibitors • Spironolactone 25-50mg PO OD/BD • ASA 75mg PO OD • Beta blockers should not be used in class IV CHF

CARDIOMYOPATHIES

- Cardiomyopathies are a group of diseases affecting the myocardium that are not a result of hypertension, valvular lesions, coronary heart disease, or pericardial abnormalities.
- Cardiomyopathies are frequently associated with myocardial dysfunction and subsequently heart failure.
- With few exceptions, histologic findings are non-specific, with myocyte hypertrophy, cellular necrosis and fibrosis.

CLASSIFICATION

- Cardiomyopathies are classified into
  - Primary myocardial involvement
    - Idiopathic (causes Dilated (D), Restrictive (R) and hypertrophic (H) cardiomyopathy)
    - Familial (D, R, H)
    - Eosinophilic endomyocardial disease (Loeffler syndrome) (R)
    - Endomyocardial fibrosis (R)
  - Secondary myocardial involvement
    - Infective (D)
      - Viral (HIV), bacterial, fungal, protozoal (Chagas), metazoan, myocarditis
      - Spirochetal disease
      - Rickettsia disease
    - Metabolic (D)
    - Familial storage disease (D, R):
      - Glycogen storage disease (D, R)
      - Mucopolysaccharidoses
      - Hemochromatosis
      - Fabry's disease
    - Deficiency (D)
      - Electrolytes
      - Nutritional (vitamin B1 deficiency)
    - Connective tissue disorders (D):
      - SLA
      - Polyarteritis nodosa

        - Rheumatoid arthritis
        - Progressive systemic sclerosis
        - Dermatomyositis
    - Infiltrations and granulomas (R, D)
        - Amyloidosis
        - Sarcoidosis
        - Malignancy
    - Neuromuscular (D)
        - Muscular dystrophy
        - Myotonic dystrophy
        - Friedreich's ataxia (H, D)
    - Sensitivity and toxic reactions (D):
        - Alcohol
        - Radiation
        - Drugs
    - Peripartum heart disease (D)
- Clinical classification of Cardiomyopathies also divides them into:
    - Dilated/congestive cardiomyopathy (DCM):
        - Pathological dilatation and impaired contraction of the left or both ventricles.
        - There is global hypokenisia of the myocardium (global impairment in the contractility of the myocardium- "Large but hypokinetic heart".)
            - Remember segmental impairment in contraction is indicative of ischemic heart disease.
        - There is a systolic failure (as there is failure in pumping of the heart but reserved diastolic filling action)- reduce ejection fraction.
        - Caused by familial/genetic, viral and/or immune, alcoholic/toxic or unknown factors or is associated with recognized cardiovascular disease.
    - Hypertrophic obstructive cardiomyopathy (HCM)
        - Left and/or right ventricular hypertrophy.
        - It is often asymmetrical hypertrophy which usually involves the upper part of the interventricular septum.
        - Recall hypertrophy due to conditions like hypertension, valvular lesion have symmetrical hypertrophy (normal shaped cavity).
        - "hyperkinetic heart"
        - Mutations in sarcoplasmic proteins cause disease in many patients.
        - In all there is cases there is a mutation (autosomal dominant mutation)

        - 50% of the cases are familial
        - 50% of the cases are sporadic
    - As ventricle contracts strongly, septum becomes shorter and the obstruction in 30-40% of patients bulges into the cavity producing a dynamic obstruction to outflow of blood (hypertrophic obstructive cardiomyopathy).
    - This is the most common cause of sudden unexplained death especially in young athletes during vigorous activity (exercise)
        - During vigorous activities Heart becomes more dynamic and obstruction becomes more pronounced and less blood is ejected from the ventricle, pressure in aorta decreases and so very little heart reaches myocardium this may precipitate severe myocardial ischemia, arrhythmias and eventually death.
- Restrictive cardiomyopathy (RCM)
    - This is due to pathologic infiltration (by amyloid, hemochromatosis, sarcoid, granulomas) in the myocardium leading to myocardium thickening with restricted filling and reduced diastolic size of either or both ventricles with normal or near-normal systolic function. (diastolic failure)
    - It is idiopathic or associated with other diseases e.g. amyloidosis, endomyocardial disease, sarcoidosis.

DILATED (CONGESTIVE) CARDIOMYOPATHY

- There is impaired left and/or right ventricular systolic dysfunction characterized by an ejection fraction <40% with dilation of left ventricle.
- This is the most common type of cardiomyopathy.

PATHOPHYSIOLOGY

- Dilated cardiomyopathy (congestive) represents the final common morphologic outcome of a variety of biological insults.
- It is a combination of myocyte apoptosis and necrosis with increased myocardial fibrosis, produced mechanical function.
- Causes include (A, B, 3C, D, H, P):
    - A-alcohol
    - B- Beriberi (thiamine Deficiency-Vitamin B1)
    - C- cocaine use
    - C-coxsackie virus

- C-Chagas disease
- D-drugs (anticancer drugs-doxorubicin/Adriamycin, amphetamines),
- H-HIV, HCV, hemochromatosis (bronze diabetes)
- P- Peripartum dilated cardiomyopathy (pregnancy)
- Genetic mutations- in dystrophin, and myocardium generally as well as enzymes participating in oxidative phosphorylation, and beta-oxidation of fatty acids.

CLINICAL MANIFESTATION

- A carful history is essential with particular emphasis on
  - Family history of similar illness
  - Exposure to cardiotoxins such alcohol
  - Protracted "flu-like illness" or respiratory tract infection may suggest previous myocarditis
  - History of recent delivery or being in the last trimester of pregnancy
- Symptoms (similar to CHF/BVHF):
  - Exertional dyspnea, fatigue, syncope, decreased exercise tolerance and edema.
- Physical examination
  - Hypotension, tachycardia
  - Cardiomegaly (displaced apex beat)
  - Findings of CHF: narrow pulse pressure, raised JVP, S3 and S4 gallops, holosystolic murmur of mitral regurgitation.
  - Functional mitral or tricuspid regurgitation.
  - Evidence of fluid overload (e.g. crackles on lung exam, lower extremity edema, ascites) and evidence of atrial fibrillation (irregularly irregular pulse) or other arrhythmias.

COMPLICATIONS

- Syncope may result from arrhythmias (stretching the heart muscle).
- Systemic embolization often emanating from ventricular thrombus may occur.
- Mitral and tricuspid valve regurgitation (due to overstretching of the muscle from the dilatation).

INVESTIGATIONS

- Chest radiography: enlargement of cardiac silhouette and evidence of pulmonary congestion
- ECG:

  - Sinus tachycardia or atrial fibrillation,
  - Ventricular arrhythmias,
  - ST segment and T wave abnormalities
  - Conduction disorders (Wide QRS, LBBB)
- Echocardiogram: left ventricular dilatation and dysfunction (ejection fraction <40%)
- Other LAB investigations:
  - Full blood count
  - HIV test
  - Renal function test- urea, electrolytes and creatinine
  - Blood glucose (fasting or random)
  - Lipid profile glucose
  - Thyroid function tests

TREATMENT

- Medical therapy: standard therapy of systolic heart failure
  - Salt restriction
  - Diuretics
  - Digitalis
  - ACE inhibitors or Angiotensin II receptor antagonists
  - Spironolactone
  - Alcohol should be avoided
  - Identify and treat underlying cause if it is treatable
- Surgical therapy: cardiac transplantation provides a median 10-year survival and is effective palliation in appropriately selected individuals.

HYPERTROPHIC CARDIOMYOPATHY

- This is an autosomal-dominant disorder of myocardial structural proteins that causes premature, severe left ventricular hypertrophy.
  - A subset of hypertrophic cardiomyopathy cases may have asymmetric septal hypertrophy and dynamic outflow tract obstruction.
- This is characterized by left ventricular hypertrophy (myocardial thickness greater than 1.5 cm) typically of none dilated chamber without obvious causes.
- Other etiologies of left ventricular hypertrophy such as long-standing hypertension and aortic stenosis need to be excluded before one can diagnose hypertrophic cardiomyopathy.

GENETIC PREDISPOSITION

- Hypertrophic cardiomyopathy is the most common genetic cardiovascular disease.
- Half of patients with hypertrophic cardiomyopathy have a positive family history with autosomal dominant transmission.

PATHOPHYSIOLOGY

- Generally ventricular hypertrophy involves the proximal portion of the interventricular septum.
- As the septum thickens, it may narrow the outflow tract.
- In addition, systolic anterior motion of the mitral valve may occur and result in left ventricular outflow tract obstruction and mitral regurgitation.
- When systolic anterior motion occurs, the mitral valve leaflets are pulled or dragged anteriorly toward the ventricular septum, producing the obstruction.
- Consequently, the left ventricle has to generate much greater pressure to overcome the outflow obstruction and to pump blood to the systemic circulation.
- Premature closure of the aortic valve may occur and is caused by the decline in pressure distal to the left ventricular outflow obstruction.

CLINICAL FEATURES

- Clinical course is variable.
- Most patients are asymptomatic.
- Most common symptom is dyspnea on exertion.
- Patients may also complain of chest pain with exertion, syncope or near syncope or palpitations.
- Congestive heart failure and atrial fibrillation along with their accompanying symptoms may be part of the natural history of hypertrophic cardiomyopathy.
- Unfortunately, the first clinical manifestation of the disease may be sudden cardiac death frequently occurring in young children and young adults often during or after physical exertion. (this is usually common in athletes e.g. wrestlers)
- Physical examination:
  - Unless congestive heart failure has developed the lungs are usually clear and the JVP is normal.
  - Pulses Bisferiens: rapidly rising carotid pulse followed by a collapse in the pulse and then a secondary rise.
  - The point of maximal impulse may be double or triple, forceful and sustained

- S4 gallop may be present
- Systolic murmur: the classic auscultatory findings for hypertrophic cardiomyopathy is a crescendo-decrescendo systolic murmur along the left sternal border that intensifies with a reduction in left ventricular volume e.g. with the Valsalva maneuver or when standing and diminishes with increased left ventricular volume e.g. hand grip or raising the legs when the patient is in a supine position). In young adults, hypertrophic cardiomyopathy is the most common etiology for sudden cardiac death

DIFFERANTIAL DIAGNOSIS

- Valvular aortic stenosis: the murmur of aortic stenosis radiates to the neck. Aortic stenosis also has weak and delayed carotid upstrokes (parvus et Tardus).
- Hypertensive heart disease: not typically associated with asymmetric septal hypertrophy or outflow tract obstruction.

DIAGNOSIS

- Chest X-ray
  - May suggest left ventricular hypertrophy but will often be normal because the hypertrophy in HCM involves the ventricular septum.
- ECG:
  - Atrial fibrillation may be present as one of the complications of HCM.
- Echocardiography (gold standard at the diagnosis of HCM): on transthoracic ECHO, the clinician should note:
  - The thickness of the septum, location, and pattern of hypertrophy,
  - Site and degree of left ventricular outflow tract obstruction,
  - Presence of systolic anterior motion of the mitral valve,
  - Presence of premature closure of the aortic valve and any change in severity of obstruction with amyl nitrite.
  - Pattern of hypertrophy varies, in classic obstructive phenotype the septum is asymmetrically hypertrophied, the left ventricular cavity is small and hypercontractile, often with diastolic dysfunction.

TREATMENT

MEDICAL

- Avoid competitive sport and strenuous exercise.
- Avoid dehydration, use diuretic with caution.

- Beta-blockers are considered first-line therapy. By decreasing contractile force, beta blockers decrease the outflow gradient and decrease oxygen demand. Beta blockers also lengthen diastolic filling by slowing the heart rates. They help to control chest pain.
- Calcium channel blocker: second-line therapy include verapamil and diltiazem. Nifedipine, amlodipine and felodipine should be avoided because they cause peripheral vasodilation which may result in decreased left ventricular filling and worsening of symptoms of outflow tract obstruction.
- Atrial fibrillation is a common complication of HCM. Treatment of persistent atrial fibrillation in HCM includes anticoagulation and rate control, preferably with beta blockers.
- Digoxin should be avoided in HCM patients, particularly in those with resting or latent obstruction because of its positive inotropic effect.
- Patients with HCM should receive prophylactic antibiotics for endocarditis prevention before dental or invasive procedures. Turbulent flow through left ventricular outflow tract striking the aortic valve as well as the mitral regurgitation from systolic anterior motion of the mitral valve predispose to endocarditis.

SURGICAL

- Septal myomectomy/myotomy may cause lasting symptomatic relief in ¾ of severely symptomatic patients
- Alcohol ablation: ethanol injection in to the septal artery has also been reported to reduce obstruction.

PREVENTION

- First degree relative of patients with HCM should be screened with ECHO.

RESTRICTIVE CARDIOMYOPATHY

- Restrictive cardiomyopathy is a disease of the myocardium that is characterized by restrictive filling and reduce diastolic volume of either or both ventricles with normal or near-normal systolic function.

CAUSES

- Infiltrative and granulomas:
  - Amyloidosis
  - Sarcoidosis: granulomas
  - Hemochromatosis

- Scleroderma
- Endocardial fibroelastosis (children): endocardium is massively fibrosed with elastic tissue
- Radiation
- Fibrosis following cardiac surgery
- Eosinophilic endomyocardial disease (Loeffler syndrome)
- Familial
- Idiopathic

PATHOPHYSIOLOGY

- Infiltration or fibrosis of the myocardium causes impaired ventricular filling with preserved systolic function.
- In end-stage disease, systolic dysfunction may develop.
- Restrictive cardiomyopathies present with a clinical heart failure syndrome that is frequently indistinguishable from that caused by systolic dysfunction.

CLINICAL FEATURES

- History:
  - Patients present with dyspnea, fatigue and peripheral edema (with predominant ascites).
  - Exercise intolerance and dyspnea are the prominent symptoms.
- Examination:
  - Enlarged tender and pulsatile liver. (hepatosplenomegaly)
  - JVP is elevated and it doesn't fall normally during inspiration (Kussmaul's sign)
  - Ascites
  - The heart sounds may be distant but apical impulse is easily palpable unlike in constrictive pericarditis.

DIFFERENTIAL DIAGNOSIS

- The clinical features are very similar to constrictive pericarditis.
  - Clinical presentation and physical exam may yield findings identical to those of restrictive cardiomyopathy.
  - MRI shows pericardial thickening (>5mm) and right heart catheterization demonstrates equalization of diastolic pressures in constrictive pericarditis.
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy

DIAGNOSTIC WORK UP

- Chest X-ray: mild cardiac enlargement.
- ECG: low voltage (low QRS voltage), nonspecific ST-T wave changes and conduction defects (AV conduction delay, bundle branch block).
- Echocardiography: increases left ventricular wall thickness, normal or mildly reduced systolic function. Infiltrative causes can present with the characteristic granular appearance of myocardium.
- Myocardial biopsy: detects infiltrative disease such as amyloidosis and sarcoidosis.

TREATMENT

- Treat the underlying disease process (e.g. amyloidosis, sarcoidosis)
- Diuretics: reduce symptoms from venous congestion but overdiuresis leads to decreased cardiac output due to preload dependence
- Beta blocker/calcium channel blockers: may improve diastolic function early in disease process by slowing heart rate and increasing ventricular filling time. Caution should be used in administration as this may result in a fall in cardiac output. Avoid use of calcium channel blockers in amyloid heart disease because they can cause significant negative chronotropy.
- Cardiac transplantation: remains an option for patients with intractable heart failure without severe systemic disease.

FEATURE	DILATED	HYPERTROPHIC	RESTRICTIVE
Characteristics	Left and/or right ventricular enlargement, impaired systolic function, CHF, arrhythmias, emboli	Disproportionate left ventricular hypertrophy, typically involving the septum more than the free wall, with or without an intraventricular systolic pressure gradient, usually of a non-dilated left ventricular cavity	Endomyocardial scarring or myocardial infiltration in restriction to left and or right ventricular filling with preserve systolic function
Etiology	A-alcohol B- beriberi (thiamine Deficiency-Vitamin B1) C- Coxsackie virus, Chagas, cocaine D-drugs (Doxorubicin-Adriamycin) H- HIV, HC, hemochromatosis P-Pregnancy (postpartum)	Idiopathic Familial	Amyloidosis, hemochromatosis Sarcoidosis
History	• Exertional Dyspnea • Fatigue • Syncope • Decreased exercise tolerance • Edema	• Dyspnea • Chest pain • Syncope	• Dyspnea • Fatigue • Peripheral edema (usually ascites)
Physical examination	• Elevated JVP • Displaced apex beat • S3, S4 gallops • Holosystolic murmur of mitral regurgitation • Pulmonary basal Crepitations	• Crescendo-decrescendo murmur that intensifies with a reduction in left ventricular volume e.g. standing, valvular maneuver and diminishes with	• Raised JVP that does not drop on Inspiration (Kussmaul's sign) • Hepatosplenomegaly • Peripheral edema

	• Irregularly irregular pulse (atrial fib)	increased left ventricular volume e.g. hand grip or raised legs in supine position • Pulsus Bisferiens • S4 and sustained apical impulse	
CXR	• Enlarged cardiac silhouette • Evidence of pulmonary congestion	• Normal (ventricular hypertrophy cannot be visualized because involves ventricular septum)	• Mild cardiac Silhouette enlargement
ECG	• Evidence of left ventricular enlargement • Conduction disorders (wide QRS, LBBB) • Arrhythmias (atrial fib, non-sustained VT)	• Left ventricular hypertrophy and left atrial enlargement along with a broad, deep Q wave in leads I and I and in left precordial leads.	• Low voltage QRS complex • Conduction defects (AV conduction delay, bundle branch block)
ECHO	• Dilated left ventricle • Decreased ejection fraction (<40%)	• Left ventricular hypertrophy with systolic anterior motion of mitral valve and left ventricular outflow tract obstruction.	• Increased left ventricular wall thickness • Normal or mildly reduced systolic function

ARTERIOSCLEROSIS

- This literally means "hardening of the arteries", it is a generic term reflecting arterial wall thickening and loss of elasticity.
- 3 distinct types are seen:
  - Arteriolosclerosis: affects small arteries and arterioles and may cause downstream ischemic injury.
    - The two anatomic variants are hyaline and hyperplastic arteriolosclerosis.
      1. In Hyaline arteriolosclerosis there is deposition of eosinophilic material which does not have any structural detail, the underlying medial histology is obscure, arteries become hard. This is seen in aging, essential hypertension and diabetes mellitus
      2. Hyperplastic arteriolosclerosis is an indication of malignant hypertension.
  - Monckeberg medial calcific sclerosis: Characterized by the presence of calcific deposits in medium sized muscular arteries (e.g. radial artery or ulnar artery), typically in persons older than 50.
    - The lesions cause changes that are non-stenotic and so it is of little clinical importance.
  - Atherosclerosis: this is the most frequent and clinically important pattern. It is a disease of intima in which there is formation of fibro-fatty plaque in intima.
    - It involves elastic arteries (aortic, carotid, and iliac arteries) and medium sized muscular artery (coronary artery, popliteal artery, Circle of Willes artery).

ARTERIOLOSCLEROSIS

- This characterized by hyaline thickening or proliferative changes of small arteries and arterioles, especially in the kidneys and is usually associated with hypertension or diabetes mellitus.
- Consist of two types:
  - Hyaline arteriolosclerosis
  - Hyperplastic arteriolosclerosis
- Hyaline arteriolosclerosis is characterized by:
  - Hyaline thickening of arteriolar walls. In the kidneys it is referred to as "Benign nephrosclerosis" and is associated with hypertension.

- Hyperplastic arteriolosclerosis is marked by:
  - Concentric, laminated, "onionskin" thickening of the arteriolar wall.
  - Necrotizing arteriolitis, intramural deposition of fibrinoid material in arterioles with vascular necrosis and inflammation.
  - In the kidneys it is called "malignant nephrosclerosis" and is associated with malignant hypertension

ATHEROSCLEROSIS

- It is characterized by the presence of intimal lesions called atheromas (or atheromatous or atherosclerotic plaques).
  - The atheromatous plaques are raised lesion composed of soft yellow, grumous lipid cores (mainly cholesterol and cholesterol esters with necrotic debris) covered by fibrosis.
- Atherosclerotic plaques can mechanically obstruct vascular lumina and are prone to rupture, resulting in catastrophic vessel thrombosis.
- Plaques also weaken the underlying media, sometimes leading to aneurysm formation.
- Atherosclerosis begins as an intimal process, the changes in the media occur secondary to changes in the intima.
- Because coronary artery disease is an important manifestation of atherosclerosis, epidemiologic data related to atherosclerosis mortality typically reflect deaths caused by ischemic heart disease (IHD).
  - Atherosclerosis causes more morbidity and mortality (roughly half of all deaths) in the western world than any other disorder.

MAJOR CONSTITUTIONAL RISK FACTORS

NONMODIFIABLE FACTORS

- Age: between ages 40 and 60, the incidence of myocardial infarction in men increases fivefold.
- Gender: premenopausal women are relatively protected against atherosclerosis and its consequences compared with age-matched men. Thus, myocardial infarction and other complications of atherosclerosis are uncommon in premenopausal women in the absence of other predisposing factors such as diabetes, hyperlipidemia or severe hypertension.
- Genetics: well-established familial predisposition to atherosclerosis and IHD is multifactorial such as hypertension or diabetes, familial hypercholesterolemia, that result in excessively high blood lipid levels.

MAJOR MODIFIABLE FACTORS

- Hyperlipidemia: especially hypercholesterolemia; major risk factor for development of atherosclerosis and is sufficient to induce lesion in the absence of other risk factors.
  - LDL cholesterol- "bad cholesterol"
  - HDL cholesterol- "good cholesterol"
- Hypertension: can increase the risk of IHD by approximately 60%. Hypertension also is the major cause of left ventricular hypertrophy (LVH) which also can contribute to myocardial ischemia.
- Cigarette smoking: prolonged (years) smoking of one pack of cigarettes or more daily increases the death rate from IHD by 200%.
- Diabetes mellitus: induces hypercholesterolemia, the incidence of myocardial infarction is twice as high in diabetic as in non-diabetic individuals.
- Abdominal obesity.

ADDITIONAL FACTORS

- Inflammation as marked by C reactive protein.
- Hyperhomocystinemia
- Lipoprotein A
- Factors affecting hemostasis

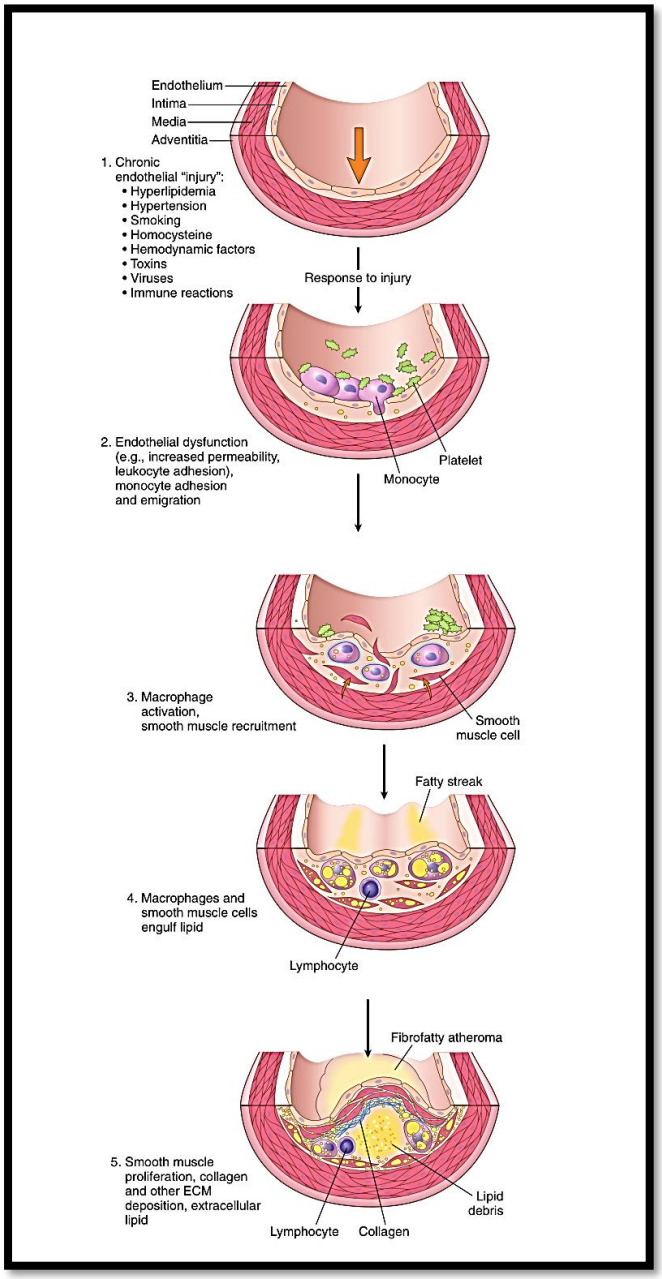
Other factors: lack of exercise, living a competitive, stressful lifestyle ("Type A" personality) and obesity

PATHOGENESIS

- There are 2 dominant theories regarding atherogenesis, one emphasizing intimal cellular proliferation in response to endothelial injury and the other focusing on repeated formation and organization of thrombi.
- The contemporary theory incorporates some aspects of both theories and also includes risk factors. This theory is called the response to injury hypothesis.
- It views atherosclerosis as a chronic inflammatory response of the arterial wall to endothelial injury.
- Lesion progression involves interaction of modified lipoproteins, monocyte-derived macrophages, T lymphocytes and cellular constituents of the arterial wall.

RESPONSE TO INJURY HYPOTHESIS

- Atherosclerosis results from the following pathological events:
  - Chronic endothelial injury- and resultant endothelial dysfunction, leading to increased permeability, leukocyte adhesion and thrombosis.
  - Accumulation of lipoproteins (mainly oxidized LDL and cholesterol crystals) in the vessel wall
  - Platelet adhesion
  - Monocyte adhesion to the endothelium, migration into the intima and differentiation into macrophages and foam cells.
  - Lipid accumulation with macrophages, which release inflammatory cytokines.
  - Smooth muscle cell recruitment (from media or circulating precursors) due to factors released from activated platelets, macrophages and vascular wall cells.
  - Smooth muscle proliferation and ECM production



MORPHOLOGY

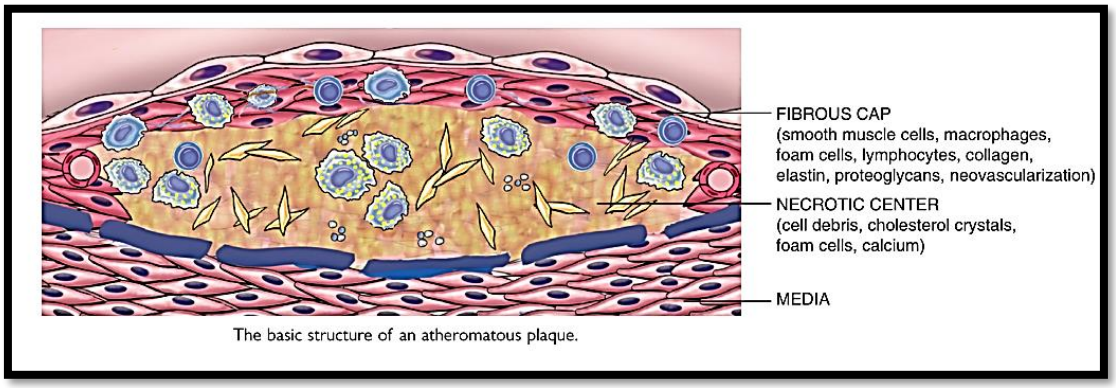
GENERAL MORPOLOGY

- Grossly recognizable atherosclerosis begins as a fatty streak and progress to a fibroatheroma.
  - Fatty streaks: begin as minute yellow, flat macules that coalesce into elongated lesions, 1cm or more in length. They are composed of lipid filled macrophages (foam cell) but are only minimally raised and do not cause any significant flow disturbance.
  - Atherosclerotic plaque (fibrous or fibro-fatty plaque): intimal thickening and lipid accumulation. They are white to yellow raised lesions ranging from 0.3

to 1.5 cm in diameter but can coalesce to form larger masses. Thrombus superimposed over the surface of ulcerated plaques is red-brown in colour.

- Atherosclerotic plaques have 3 principal components:
  a. Cells, including smooth muscle cells, macrophages and T cells.
  b. Extracellular matrix including collagen, elastic fibers and proteoglycan
  c. Intracellular and extracellular lipid

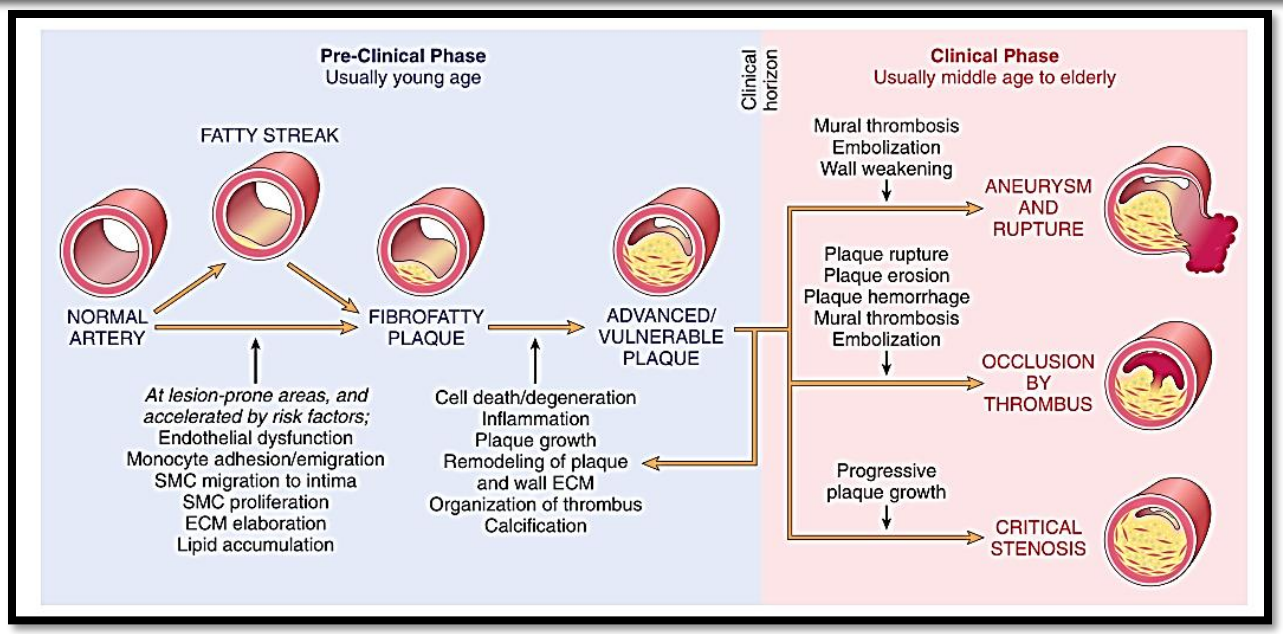
- Microscopic morphology
  - Superficial fibrous cap: a thick fibrous cap is more stable and less likely to develop complications (e.g. hemorrhage or rupture). The fibrous cap is composed of smooth muscle cells and extracellular matrix (e.g. collagen).
  - Atheromatous core: contains extracellular lipid, macrophages with intracellular lipid and necrotic tissue (debris from dead cells, foam cells, fibrin, variably organized thrombus, and other plasma proteins). The cholesterol content is frequently present as crystalline aggregates that are washed out during routine tissue processing and leave behind only empty clefts.
  - Shoulder of plaque: has macrophages, leukocytes (T-lymphocytes) and blood vessels (due to neovascularization at the periphery of plaque).



The basic structure of an atheromatous plaque.

COMPLICATIONS OF ATHEROSCLEROSIS

- Complications include:
  - Occlusion of vessel: symptoms, signs and results depend upon organ supplied.
  - Disruption of plaque: hemorrhage within plaque or rupture or ulceration of plaque (with exposure of the thrombogenic components) can result in thrombus formation.
    - Myocardial infarction (coronary artery)
    - Stroke (middle cerebral artery)
  - Emboli: plaque can break free and carried in the blood stream farther down the vessel.
  - Aneurysm: Atherosclerosis begins as an intimal process but over time the thickened intima puts pressure on and causes atrophy of the media, often resulting in an aneurysm (i.e. dilation or saccular outpouching of vessel). Aneurysm may rupture.
  - Stenosis of medium sized vessels:
    - Peripheral vascular disease e.g. popliteal
    - Angina: coronary artery
    - Ischemic bowel disease: mesenteric
  - Peripheral vascular disease
    - Clinical presentation: Claudication which is characterized by ache or cramping in the extremities with exertion that is relieved by standing still. Patients also have cool extremities, diminished distal pulses, and shiny, hairless skin. Patients with severe peripheral vascular disease have pain at rest. Ischemic ulcerations are a common cause of morbidity.
    - Cause: atherosclerosis of vessels of lower extremities.



PREVENTION OF ATHEROSCLEROTIC VASCULAR DISEASE

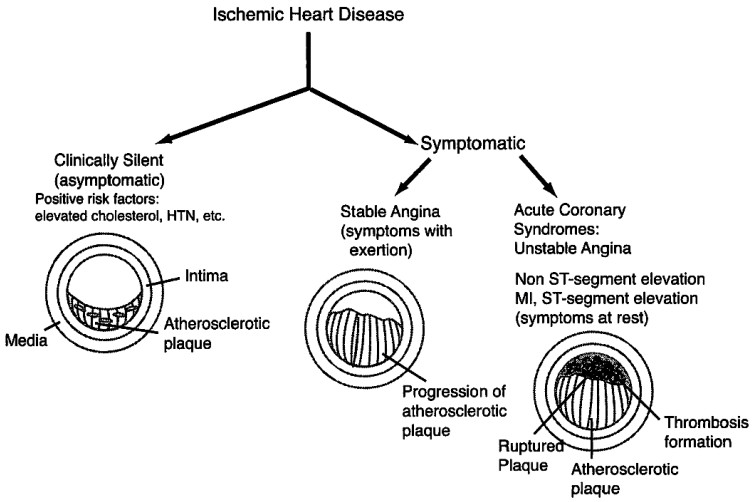
- Primary prevention programs:
  - Cessation of cigarette smoking
  - Control of hypertension
  - Weight loss
  - Exercise
  - Lowering total and LDL blood cholesterol levels while increasing HDL (e.g. by diet or through statins)
- Secondary prevention programs: these can successfully reduce recurrent myocardial or cerebral events
  - Use of aspirin (Anti-platelet agent)
  - Statins and beta-blockers (to limit cardiac demand)
  - Surgical interventions (e.g. coronary artery bypass surgery, carotid endarterectomy)

ISCHEMIC HEART DISEASE/CORONARY HEART DISEASE

- Ischemic heart disease (also known as coronary heart disease, coronary artery disease) is the presence of symptoms or signs of cardiac ischemia.
- Ischemic heart diseases manifest due to an imbalance in myocardial oxygen supply and demand that results in myocardial hypoxemia.
- Commonest cause of ischemia is atherosclerosis, the formation of lipid-laden plaques in coronary artery walls.
  - Other causes of mechanical obstruction include:
    - Thrombosis
    - Embolus
    - Spasm
    - Coronary arteritis (e.g. in SLE)
    - Coronary ostial stenosis
  - Other cause can be due to decrease in flow of oxygenated blood to the myocardium due to:
    - Anemia
    - Carboxyhemoglobulinemia
    - Hypotension causing decreased coronary perfusion pressure
- Symptoms occur when plaques:
  - Grow and obstruct the vessel causing angina or
  - Rupture and form a thrombus occluding the vessel and causing an acute coronary syndrome
- IHD can present with
  - Angina
    - Stable angina (classical angina)
    - Prinzmetal angina/Vasospastic angina
  - Acute coronary syndrome (ACS)
    - Unstable angina
    - ST segment elevation myocardial infarction (STEMI)
    - Non-ST segment elevation myocardial infarction (NSTEMI)

PATHOPHYSIOLOGY

- Myocardial ischemia reflects an imbalance between myocardial oxygen supply and demand. Myocardial oxygen demand is mainly determined by heart rate, the force of ventricular contraction, and ventricular wall tension which is proportional to the ventricular volume and pressure.
- Unless there is a proportionate rise in oxygen supply, conditions that increase oxygen demand such as physical exertion result in ischemia.
- Atherosclerosis of coronary artery (CAD) is the most common cause of IHD.
- Atherosclerosis is focal narrowing of arteries which results from a plaque formation. In CAD, atherosclerosis disrupts the normal functioning of the vascular endothelium.
- Plaques are formed as a result of:
  - Intimal smooth muscle proliferation probably as a result of endothelial damage
  - Lipid (cholesterol esters) are deposited at the center of plaques and also within smooth muscle cells and macrophages (foam cells)
  - A fibrous cap made of connective tissue covering the plaque
- As the stenotic lesion grows, perfusion pressure distal to the lesion decreases in response, coronary arterioles dilate to maintain adequate blood flow preventing ischemic symptoms at rest.
- During exertion the myocardial oxygen demand increases which cannot be matched by the perfusion via the narrowed coronary artery.
- The resulting myocardial ischemia results in chest pain called angina pectoris which is relieved by rest.
- Sometimes atherosclerotic plaques may rupture and a fibrin thrombus is formed over the plaque which completely blocks the narrowed coronary artery and results in myocardial infarction.
- Note: for symptoms to occur occlusion of coronary artery lumen should exceed 70%.



RISK FACTOR

- Modifiable risk factors:
  - Hypertension: increases the risk of CAD both in men and women
  - Dyslipidemia: increase in LDL, Increase in total cholesterol, increase in total cholesterol: HDL ratio, and a reduction in HDLs.
  - Diabetes mellitus: is associated with significant increase in risk of CAD
  - Smoking: cigarette smokers are 60% more likely to develop CAD than non-smokers.
  - Excess alcohol
  - Obesity
  - Oral contraceptive pills: use of OCP is associated with increased risk of CAD.
  - Gout
- Non-modifiable risk factors:
  - Age: the risk of CAD increases progressively with age. The risk of death from CAD is 1.5 in 1000 individuals at age 50.
  - Gender: IHD is more prevalent in men than in women. The difference is more marked in premenopausal women compared to men of similar age.
  - Ethnicity: especially South Asian ethnicity
  - Medical history of atheroma: MI, stroke, or Pulmonary thromboembolism
  - Family history: MI in 1st degree relative, male<55 years, female<65 years

ANGINA PECTORIS

- This is a chest pain or pressure produced by myocardial ischemia.
- It is usually caused by atherosclerosis i.e. ischemic heart disease (IHD). Less commonly due to:
  - Valve disease (especially aortic stenosis)
  - Arrhythmias
  - Hypertrophic cardiomyopathy
  - Anemia
  - Coronary vasospasm (e.g. cocaine-induced)
- It affects 1/10 over 65 years old and is commoner in males.
- Anginal pain is often precipitate by exertion. Other factors that increase myocardial oxygen demand (e.g. emotional stress, eating meal, sexual intercourse) may also precipitate angina.

CLINICAL FEATURES

- The chest pain in angina is squeezing in type or a feeling of pressure or tightness in the chest. Sometimes it can be burning in nature or felt as epigastric discomfort.
- Radiation: the pain radiates to the left shoulder, left jaw, teeth or to the left arm. Sometimes it may radiate to the right arm.
- The pain in angina is often reproducible with the same degree of physical exertion. The symptom usually begins with low intensity, increases over 2-3 minutes and often lasts less than 15minutes. Episodes lasting more than 30 minutes suggest myocardial infarction may have occurred.

DIAGNOSTIC BOX:

- Angina pain is intermittent, stable with 3 classic features, remember 'ECG':
  - E- exertion as a precipitant
  - C- constricting discomfort of anterior chest, which may radiate to neck, shoulders, jaw or arms
  - G- Getting rest or Nitrates reliefs pain
- 3/3= typical angina, 2/3= atypical angina, 1/3= not angina

TYPES OF ANGINA

- Chronic stable angina: angina which recurs under similar circumstances and with similar frequency over time.
- Silent ischemia: for every episode of symptomatic ischemia that the patient suffers, there are usually 4 to 5 episodes of silent (asymptomatic) ischemia. This episode can be detected by ECG including stress ECG. Such episodes are less severe in nature and shorter in duration.
- Unstable angina: this is when a change in status occurs. Unstable angina is progressive and it may be ominous feature of imminent myocardial infarction:
  - New onset angina: progresses in severity, duration or frequency over 1- or 2 months
  - Resting angina: particularly worrisome because it implies decreased supply rather than increased demand is causing angina. This suggests possible occlusion is imminent.
- Prinzmetal angina (Vasospastic angina):
  - This is a type of angina resulting from transient coronary spasm, which usually but not always associated with fixed atherosclerotic lesion. The spasm produces total but transient coronary occlusion.
  - It usually occurs at rest (often at night) and episodes are frequently complicated with ventricular arrhythmias.

HISTORY

- A history of recurrent chest pain, obtain a detailed symptom history including: onset, quality, location, duration, radiation and precipitating and relieving factors.
- Determine the presence or absence of each of the 3 of the following symptoms complex characteristics: remember 'ECG':
  - E- exertion as a precipitant
  - C- constricting discomfort of anterior chest, which may radiate to neck, shoulders, jaw or arms
  - G- Getting rest or Nitrates reliefs pain
- 3/3= typical (definite) angina, 2/3= atypical (probable) angina, 1/3= not angina
- If patients' symptoms are consistent with typical angina sub-classify the angina as:
  - Stable (unchanged for 2 or more months)
  - Unstable:
    - Rest
    - New onset
    - Increasing
- In patients with typical (Definite) or atypical (probable) angina, ask about functional limitation.
- Ask about any episodes of dyspnea, palpitations or dizziness with or without chest pain. If the patient has experienced any such episodes, ask about the same symptom variables that are applicable to typical angina.
- Assess potential risk factors of CAD: lifestyle, habits, past medical history, family history and hormone therapy.
- Ask about a history of symptoms such as exertional dyspnea, orthopnea and bilateral leg swelling that suggest left ventricular (LV) dysfunction or heart failure and nocturia.
- Ask about other potential causes of chest pain, especially if the symptoms have changed, new symptoms have arisen or the patient is at low risk for CAD.

PHYSICAL EXAMINATION

- Complete physical examination
- Assess vital signs especially for hypertension, tachycardia, bradycardia, arrhythmia and tachypnea.
- Examine the head and neck especially for:

  - Signs of anemia (mucous membrane pallor)
  - Thyroid disease (exophthalmos, thyromegaly)
  - Hypercholesterolemia (xanthelesma which is the deposit of lipids in the skin of the eyelids)
  - Atherosclerosis (Carotid bruit)
- Perform a general and peripheral vascular examination to identify signs of generalized or peripheral atherosclerosis e.g. inequality of blood pressure in arms, diminished pedal pulse and abdominal aneurysm.
- Examine the heart for evidence of hypertrophy, murmurs, S3 and S4 heart sounds.
- Examine the lungs for crackles and other abnormal breath sounds.
- Examine the lower extremities for dependent (Ankle) edema, tendinous xanthomas (lipid deposit), weak pulses or cutaneous signs of ischemia or necrosis.

DIFFERENTIAL DIAGNOSIS

- Pleurisy
- Pneumonia
- Pericarditis
- Ischemia associated with aortic stenosis or hypertrophic cardiomyopathy

INVESTIGATIONS

- Blood investigations:
  - Full blood count: to rule out anemia and infections
  - Fasting blood glucose: for diabetes
  - Serum lipid profile: for dyslipidemias
  - Urea and electrolytes + creatinine: co-morbid CKD, ACEi baseline
- Imaging:
  - Chest X ray: in patients with symptoms and signs of congestive heart failure
  - Stress echocardiography (+ exercise or dobutamine stress)
  - ECG: may be normal or may show Q waves or ST-T changes
    - Resting ECG: This is an ECG taken when the patient is not in pain, it may be normal. The presence of new horizontal or down sloping of ST segment depression and new T-wave inversion are suggestive of myocardial ischemia. ST segment elevation associated with pain which returns to normal as the pain waves suggest variant angina.

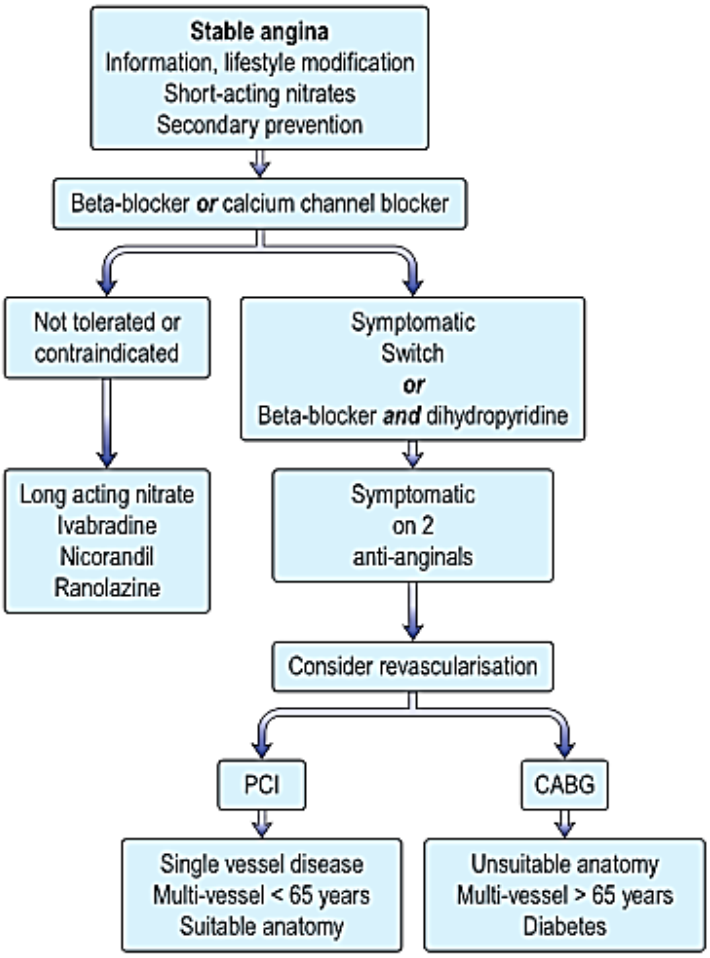
- ♦ Stress ECG: recording ECG during exercise increases the sensitivity and specificity of ECG. This helps to quantify the patient's exercise tolerance. The presence of new horizontal or down slopping ST segment depression has sensitivity of 70% and specificity of 90%.
- ➢ Stress radionuclide ventriculography
- ➢ Cardiac catheterization

MANAGEMENT

- This is aimed at either reducing myocardial oxygen demand or to compensate for impaired flow through diseased coronary arteries or at increasing myocardial oxygen supply (i.e. blood flow).

GENERAL MEASURES

- Lifestyle modification:
  - ➢ Counsel patient about cessation of smoking
  - ➢ Diet ('healthy' diet like low fat and low caloric diet with increased habit of eating fruits and vegetables)
  - ➢ Regular exercise: about 30 minutes a day but below angina threshold
  - ➢ Weight reduction
- Treat comorbidities that can provoke or exacerbate angina (e.g. hypertension, diabetes mellitus, hyperthyroidism, pulmonary disorders, anemia)
- Short-acting nitrate:
  - ➢ Glyceryl trinitate (GTN) Spray or sublingual tablets
  - ➢ Use before planned activity and when symptomatic
  - ➢ If pain continues for 5 minutes after 1st dose call ambulance and take 2nd dose



Algorithm for management of patients with stable angina. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. *(From NICE draft guideline: http://www.nice.org.uk/nicemedia/live/11878/52141/52141.pdf.)*

- Side effects: headache, flushing and lightheadedness

MEDICAL THERAPY

- Anti-anginals:
  - First line: Beta blockers and/or calcium channel blockers. Use both if one is insufficient
  - Second line: Isosorbide mononitrate, nicorandil (potassium channel opener), ivabradine (Funny channel blocker) or Ranolazine ('late' sodium channel blocker). Can be used as monotherapy or in combination with 1st line drugs.
  - Consider revascularization if not controlled by 2 drugs. Percutaneous coronary intervention (PCI) for one or two vessels, coronary artery bypass graft (CABG) for left main or triple vessel disease. Both relieve symptoms but only CABG reduces mortality.
- CVD prevention:
  - Aspirin for all (clopidogrel 2nd line) and consider statins and ACEi.

SURGICAL INTERVENTIONS

- Percutaneous transluminal coronary angioplasty
- Artherectomy
- Coronary artery bypass surgery

PROGNOSTIC INDICATORS

- The status of left ventricular (LV) function
- The location and severity of coronary artery narrowing
- The severity or activity of myocardial ischemia
- The presence of complex arrhythmias

	Mechanism of action	Dose	Indications and side effects
FIRST LINE			
Beta blockers			
Atenolol	Inhibit beta-adrenoreceptors, reducing heart rate, BP, and myocardial oxygen consumption	25-100mg daily	Indications: First line drug Caution: COPD, acute heart failure, AV conduction Side effects: fatigue, peripheral vasoconstriction (cold peripheries), erectile dysfunction, bronchospasm
Bisoprolol		2.5-10mg daily	
Metoprolol		25-100mg BD or TDS	
Propranolol		20-80 mg PO BD to QID	
Calcium channel blockers (Consider CCB when beta blockers are contraindicated or not tolerated)			
Verapamil (Phenylalkylamines)	Inhibit calcium channels in myocardium, cardiac conductive tissue and vascular smooth muscle. Diltiazem and verapamil also slow down the heart rate Note: drugs are effective especially in preventing coronary spasms in variant angina	80-120mg TDS (or 240-480mg daily slow release)	Diltiazem and verapamil-contraindicated in severe bradycardia, left ventricular failure with pulmonary congestion, 2nd or 3rd degree AV block Side effects: constipation (verapamil), ankle edema (amlodipine, diltiazem), reflex tachycardia (amlodipine)
Diltiazem (benzothiapines)		60-120mg TDS	
Amlodipine (dihydropyridine)		5-10 mg daily	
SECOND LINE			
Nitrates/vasodilator			
Glyceryl trinitrate	Cause vasodilation through nitric oxide and cGMP cascade. They produce venodilation and to a lesser extent arteriolar dilation. These effects reduce BP and reduce cardiac size.	0.3-1.0 mg sublingual 2.0-3.0mg buccal	Indications: Prophylaxis and treatment of angina-rapid onset. Repeat after 5 min if symptomatic Side effects: headache and flushing due to vasodilation
Isosorbide mononitrate		10-60mg BD	Indications: prophylaxis of angina Side effects: headache and flushing Contraindicated with phosphodiesterase type 5 inhibitors

Other second line			
Ivabradine	Inhibits the pacemaker funny current (I_f) in the SA node	2.5-7.5mg BD	Indications: use in sinus rhythm with or without a beta blocker Side-effects: bradycardia Contraindications: sick sinus syndrome, AV block
Nicorandil	Activates ATP sensitive potassium channels and has nitrate properties- peripheral and coronary vasodilation	5-30mg BD	It is used as adjunctive therapy Side-effects: headache, flushing, oral ulceration.
Ranolazine	May inhibit late sodium channels in cardiac cells	375-750mg BD	Used as an adjunct Metabolized by cytochrome P450 3A4 Side-effects: constipation, dizziness, lengthens QT
SECONDARY PREVENTION			
Aspirin	Antiplatelet	75mg daily	Side-effects: gastrointestinal bleeding
ACE inhibitor	Block ACE enzyme	Variable	Used to treat other conditions e.g. hypertension, heart failure, chronic kidney disease
Statins	HMG CoA inhibitor	Variable	Used to reduce total cholesterol to below 4mmol/L and LDL cholesterol to below 2mmol/L

ACUTE CORONARY SYNDROME

- This is usually due to rupture of atheromatous plaque in coronary artery leading to thrombus formation and vessel occlusion locally or elsewhere in the heart.
- There are 3 acute coronary syndromes:
  - ST segment elevation myocardial infarction (STEMI): increased troponin and ST elevation on ECG. In practice ST elevation alone is sufficient to treat as troponins take time to rise.
  - Non-ST segment elevation myocardial infarction (NSTEMI): increased troponin and ischemic symptoms or ECG changes
  - Unstable angina: prolonged, severe angina, usually at rest, possibly with ECG changes.
- NSTEMI and unstable angina are often grouped together as non-ST elevation ACS (NSTEACS)

Initial phase of infarction leads to subendocardial necrosis involving <50% of the myocardial thickness (subendocardial infarction). ECG shows ST-segment depression.

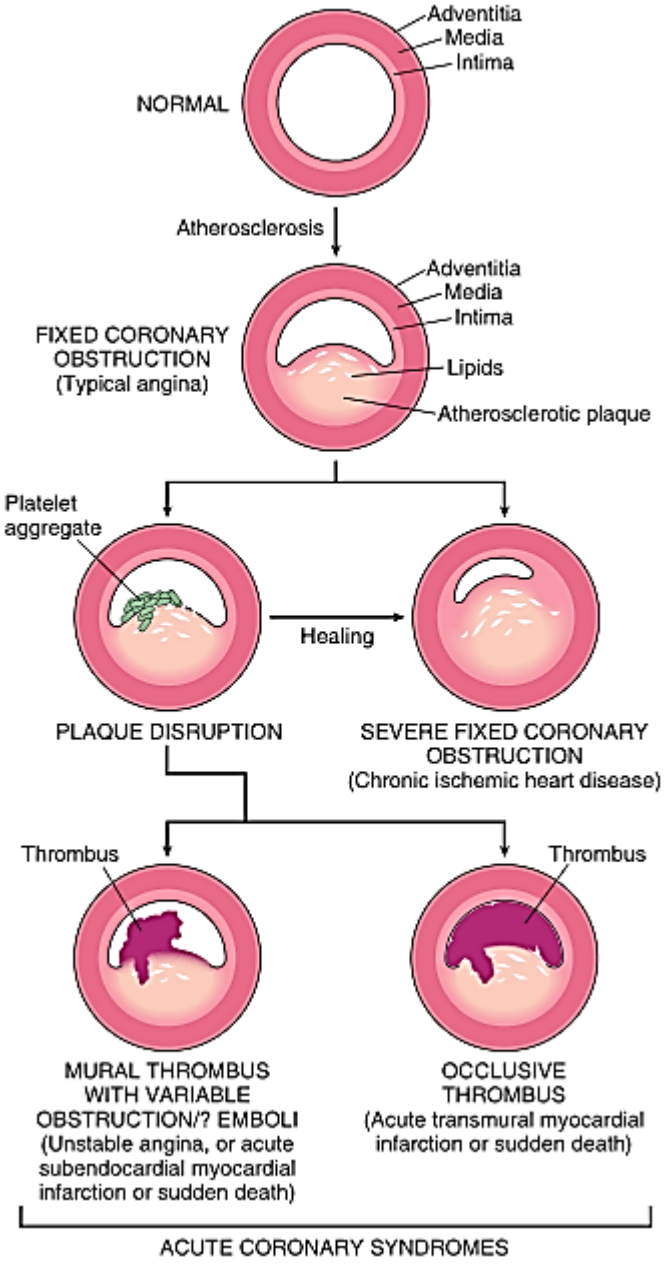
Continued or severe ischemia leads to transmural necrosis involving most of the myocardial wall (transmural infarction). ECG shows ST segment elevation

CLINICAL FEATURES

- Chest pain. It must be evaluated using SOCRATES
  - Site: central
  - Onset: usually sudden but can be more gradual.
  - Character: tight, crushing, but not sharp.
  - Radiation: left arm, neck, jaw. Less commonly right arm, epigastrium, back
  - Associated symptoms: sweating, clamminess, SOB, dizziness, faint, angor animi (an impending sense of doom)
  - Timing: duration >15 minutes
  - Exacerbating factor: Exertion, Emotion, Eating. Relieving factors: ACS less likely if relieved by glyceryl trinitrate <5 mins.
  - Severity: high but can atypically be low.
- Atypical presentations, more commonly seen in elderly or diabetic patients:
  - Little or no chest pain
  - SOB
  - Sweating
  - Nausea and vomiting
- Signs:
  - Heart rate and blood pressure may be increased or decreased
  - Pallor
  - S3or S4 heart sounds (especially in STEMI)

INVESTIGATIONS

- ECG: do immediately and if negative repeat after 20 minutes if pain continues or suspicion is high.
  - ECG is diagnostic in 85% of cases.
  - Transmural MI: ST segment elevation in those leads reflecting the area of myocardial infarction. As ST segments fall, Q waves appear and T waves become inverted
  - Subendocardial infarction: ECG findings are less certain and ST segment depression may be the only finding.
- Cardiac enzymes:
  - Troponin T and I are cardiac specific. Test on admission and at 3-6 hours. Troponin peaks at 12-24 hours then declines over 10 days. Troponin I is the most sensitive and specific marker for MI, levels rise 2-4 hours.
  - Causes of raised troponin: "HEART DIES"
    - H-heart failure
    - E-embolus (pulmonary)
    - A-Atrial fibrillation
    - R- Renal failure (due to decreased clearance)
    - T-Thrombus
    - D- dissection of the aorta
    - I- Inflammation (myo/pericarditis)
    - E-Exercise (very strenuous)
    - S-Sepsis
  - Creatinine phosphokinase elevation appears 6 hours after infarction
  - AST elevates 12 hours after infarction
  - Lactate dehydrogenase starts elevation 24 hour after infarction



- Cardiac imaging:
  - Chest X-ray: rule out other causes and check for heart failure.
- Blood investigations:
  - Full blood count: decrease hemoglobin may exacerbate heart strain and baseline Hb and PLT needed before anticoagulation
  - U and Es: baseline before anticoagulants and ACEi, and screens for co-morbid renal disease from hypertension.
  - Glucose: tight control improves outcomes.
  - Lipids: check on admission, as cholesterol can dip 24 hours post-MI
- Exercise tolerance test: consider in decreased risk patients.

MANAGEMENT

Management of ACS

M-morphine

O- oxygen

N- Nitrates

A-Aspirin

- General measures:
  - Reassure and make the patient comfortable
  - Supply oxygen by mask
  - Secure IV line
  - Give aspirin 160-325mg tablets- helps to prevent further platelet aggregation. Also give $P2Y_{12}$ inhibitor (Clopidogrel, Ticagrlor or prasugrel) loading dose
  - If patient is tachycardic/hypertensive beta-blockers IV can be given (but not if unstable)
- Treatment of pain:
  - Give morphine sulphate PRN: it is very effect analgesic for pain associated with ACS. It is administered in small doses of 2-4mg IV every 5 minutes.
  - Nitrates (Oral spray, sublingual tablets or IV infusion) can be added to refractory cases. Nitroglycerin sublingual up to 3 times doses of 0.4mg should be administered at about 5 minutes intervals for up to 3 doses.
- Anticoagulation:
  - Unfractioned heparin or bivalirudin IV in those going for immediate or early angiography. GP IIb/IIIa inhibitor IV (eptifibatide, tirofiban or abciximab) is sometimes added as adjunctive antiplatelet but not routinely.
  - Enoxaparin or fondaparinux SC for those without angiography planned
- Reperfusion with:
  - Percutaneous coronary intervention (PCI) i.e. dilation of artery with balloon catheter +/- stent placement for STEMI presenting within 12 hours of onset.
    - If PCI not available within 120 minutes, consider thrombolysis (alteplase, reteplase, or tenecteplase) and transfer to PCI center.

        - Thrombolytic agents: such as Streptokinase, t-plasminogen activator, urokinase: these drugs are given to dissolve the occlusive thrombus and promote reperfusion of the infarct related artery reduces mortality from MI when administered within 6 hours of the onset of chest pain
        - Contraindication: history of cerebrovascular hemorrhage, marked hypertension, bleeding disorder
    - Patients persisting beyond 12 hours are essentially managed like NSTEMI.
- Angiography +/- revascularization within 48 hours ('early invasive strategy). Revascularization is usually PCI but sometimes coronary artery bypass graft (CABG) if left main or triple vessel disease can be done for NSTEACS.
    - Immediate PCI if unstable, refractory chest pain, or acute severe heart failure
    - Conservative management otherwise.

- Secondary prevention
    - ASA 75-150mg PO OD
    - Beta blockers have short term and long term benefits for patients with AMI
        - Short term benefit is they relieve pain and decrease the risk of malignant arrhythmias
        - Long term benefits: improved myocardial performance and facilitate the healing process in post MI patients
        - Metoprolol-25-200mg BD
        - Atenolol 50-150mg PO OD
        - Contraindications: Severe CHF, AV block
    - ACE inhibitors: reduces mortality and improves long term survival post MI by preventing cardiac remodeling which may have led to progressive heart failure. They should be prescribed with 24 hours and maximum benefit is achieved when they are given at higher doses than are recommended. In patients with CHF ACE inhibitors are given indefinitely.
        - Captopril: start with smaller dose 12.5mg PO day to gradually escalate to 75mg PO BD
        - Enalapril: start with 2.5mg PO daily and escalate gradually to 40mg PO OD
    - Statins. Evidence of short-term benefit is unclear, but it will be needed for secondary prevention anyway.

PROGNOSIS

- Depends on 2 factors:
  - Extent of coronary artery disease in terms of the number of vessels affected.
  - The extent of ventricular damage: left ventricular ejection faction (especially <40% doubles yearly mortality)

COMPLICATIONS

SHORT TERM COMPLICATIONS

ELECTRICAL

- Heart block or sinus bradycardia following inferior MI (right coronary artery) as supply to the AV and SA node is disrupted.
- Bundle branch block (Right or left bundle branch) following anterior MI (left anterior descending artery)
- Ventricular fibrillation

STRUCTURAL

- Acute mitral regurgitation: may occur if the papillary muscles are affected by infarction.
- Papillary muscle rupture
- Ventricular aneurysm: blood pools under dyskinetic, thin area of the left ventricle walls. Causes persistent (>6 weeks) ST elevation. The infarcted myocardium may evaginate and heal with fibrous connective tissue. It may be a source of cardiac emboli
- Ventricular free wall rupture leading to hemopericardium
- Ventricular septal rupture. Causes pan-systolic murmur. May lead to cardiogenic shock later

INFLAMMATORY

- Peri-infarction pericarditis
- Dressler's syndrome: post AMI pericarditis which is believed to be autoimmune in origin

LONG TERM COMPLICATIONS

- Myocyte death and decreased stroke volume leads to decreased heart rate and blood pressure.
- The decreased in BP results in a sympathetic neurohumoral response and left ventricular changes that result in heart failure.

MANAGEMENT OF COMPLICATIONS

- Malignant arrhythmias:
  - Cardiac defibrillation
  - Prophylactic defibrillation
  - Prophylactic lidocaine
  - Other antiarrhythmic agent: bertyluim tosylate and procainamide
- Conduction disturbances:
  - Sinus bradycardia: Atropine 2mg IV may restore conduction and restore heart rate
  - AV block: transcutaneous cardiac pacemakers
- Heart failure:
  - Diuretics, salt restriction, ACE inhibitors, vasodilators. Use of digoxin is controversial.
- Cardiogenic shock: do echocardiography to assess the ventricular function
  - IV infusion of fluids to maximize left ventricular filling
  - Use of vasopressors: Dobutamine, dopamine in IV infusion
  - Intra-aortic balloon pumping
  - Percutaneous transluminal angioplasty

CARDIAC DYSRHYTHMIAS

- The heart beat is normally initiated by an electrical discharge from the sinoatrial node (SA node). The atria and ventricle then depolarize sequentially as electrical depolarization passes through specialized conducting tissue.
- The sinus node acts as a pacemaker and its intrinsic rate is regulated by the autonomic nervous system, vagal activity decreases the heart rate and sympathetic activity increases it via cardiac sympathetic nerves and circulating catecholamines.
- Normally the parasympathetic system predominates, resulting in slowing of the spontaneous discharge rate from approximately 100 to 70 b/m. A reduction of parasympathetic tone or an increase in sympathetic stimulation leads to tachycardia, conversely, an increased parasympathetic tone and decreased sympathetic stimulation produces bradycardia.
- The sinus rate in women is slightly faster than in men.
- Normal sinus rhythm is characterized by P waves that are upright in leads I, and II of the ECG but inverted in the cavity leads aVR and V1.
- If the sinus rate becomes unduly slow, another, more distal part of the conducting system may assume the role of pacemaker. This is known as an escape rhythm and may arise in the atrioventricular (AV) node or His bundle (junctional rhythm) or the ventricles (idioventricular rhythm).
- A dysrhythmia is an abnormality of the cardiac rhythm.
- The heart may seem to skip a beat or beat irregularly or beat very fast or very slow.
- Dysrhythmias may cause sudden death, dizziness, syncope, heart failure, chest pain, palpitations or no symptoms at all.
- There are 2 main types of
  - Tachyarrhythmias: the heart rate is fast (>100 b/m)
  - Bradyarrhythmias: the heart rate is slow (<60 b/m during the day or <50 b/m at night)
- Some dysrhythmias occur in patients with apparently normal hearts, and in others arrhythmias originate from diseased tissue such as a scar, as a result of underlying structural heart disease.
- When myocardial function is poor, arrhythmias are symptomatic and are potentially life-threatening.

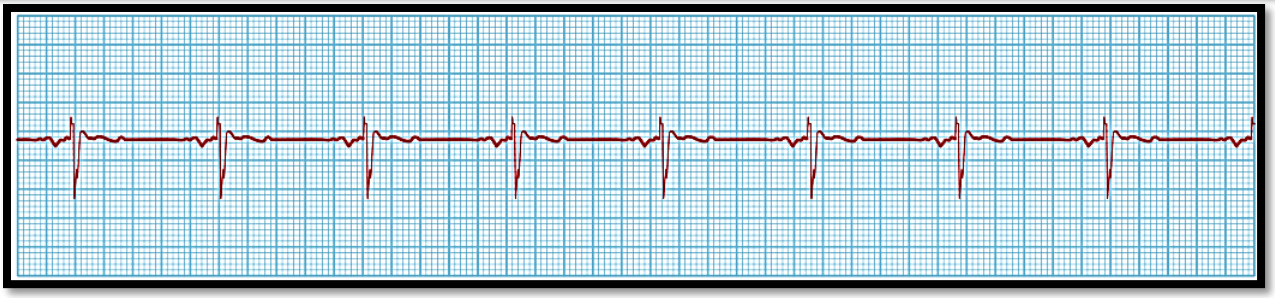


Figure 16: An ECG showing normal sinus rhythm (PR interval <0.2s). P waves preceding each QRS complex. The inversion of P waves is normal in leads aVR and V1 (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

CLASSIFICATION OF DYSRHYTHMIAS

- Arrhythmias can be classified by:
  - Heart rate:
    - Tachyarrhythmias (Heart rate >100bpm)
      - Simple Tachyarrhythmias 100-150bpm
      - Paroxysmal Tachyarrhythmias 250-350bpm
      - Flutter (Atrial and ventricular) 250-350bpm
      - Fibrillation (Atrial and ventricular) >350bpm
    - Bradyarrhythmias (Heart rate <60bpm)
      - Mild Bradyarrhythmias 40-60bpm
      - Moderate Bradyarrhythmias- 20-40bpm
      - Severe Bradyarrhythmias <20bpm
  - Location:
    - Supraventricular dysrhythmias
      - SA node dysrhythmias: Sick sinus rhythm, Sinus tachycardia, Sinus bradycardia
      - Atrial dysrhythmias
        - Paroxysmal atrial tachycardia
        - Atrial flutter
        - Atrial fibrillation
      - Nodal/Junctional dysrhythmias:
        - AV nodal re-entry tachycardia (paroxysmal supraventricular tachycardia)
        - Wolff-Parkinson-White syndrome
        - Heart block

- Ventricular dysrhythmias:
  - Premature ventricular contraction
  - Ventricular tachycardia
  - Ventricular fibrillation
  - Torsades de point

SICK SINUS SYNDROME (SINOATRIAL DISEASE)

- Sinoatrial disease can occur at any age but is common in older people. This is due to fibrosis, degenerative changes or ischemia of the SA node.
- The condition is characterized by a variety of arrhythmias including:
  - Paroxysmal atrial tachycardia
  - Paroxysmal atrial fibrillation
  - Sinus bradycardia
  - Sinus arrest (sinoatrial block)
  - Atrioventricular block
- It may present with palpitations, dizzy spells or syncope, due to intermittent tachycardia, bradycardia, or pauses with no atrial or ventricular activity (SA block or sinus arrest).
- A permanent pacemaker may benefit patients with troublesome symptoms due to spontaneous bradycardias or those with symptomatic bradycardia induced by drugs required to prevent Tachyarrhythmias.
- Atrial pacing may prevent episodes of atrial fibrillation. Pacing improves symptoms but not improve prognosis and is not indicated in patients who are asymptomatic.

TACHYARRHYTHMIAS

- Tachyarrhythmias are more symptomatic when the arrhythmia is fast and sustained.
- Tachyarrhythmias cause rapid palpitations, dizziness, chest discomfort or breathlessness. Extreme tachycardias can cause syncope because the heart is unable to contract or relax properly at extreme rates. Extreme tachycardias can precipitate sudden death or cardiac arrest.
- Tachyarrhythmias are subdivided into:
  - Supraventricular tachycardias: which arise from the atrium or the atrioventricular junction. These usually produce narrow QRS complex because the ventricles are depolarized in their normal sequence via the AV node and bundle of His. Occasionally, however a supraventricular rhythm can produce a broad or wide QRS complex due to coexisting bundle branch block or the presence of an additional atrioventricular connection (accessory pathway). Though this technically includes atrial fibrillation and flutter, SVT usually refers to other causes especially atrial tachycardia, AV nodal reentry tachycardia. Important SVTs include:
    - Atrial tachycardia:
      - Sinus tachycardia (regular rhythm)
      - Paroxysmal atrial tachycardias
      - Atrial flutter
      - Atrial fibrillation
    - Atrioventricular junction Tachyarrhythmias
      - AV nodal re-entry tachycardia (paroxysmal supraventricular tachycardia)

  - Ventricular tachycardias: which arise from the ventricles. These usually produced broad, bizarre QRS complexes because the ventricles are activated in an abnormal sequence.
    - Premature ventricular contraction
    - Ventricular tachycardia
    - Ventricular fibrillation
    - Torsades de pointes

PATHOPHYSIOLOGY OF TACHYARRHYTHMIAS

- There are 3 main mechanisms of tachycardia:
  - Increased automaticity: the tachycardia is produced by repeated spontaneous depolarization of an ectopic focus, often in response to catecholamines. Increased automaticity is thought to produce sinus tachycardia, escape rhythms and accelerated AV nodal (junctional) rhythms.
  - Re-entry/circus movements: the tachycardia is initiated by an ectopic beat and sustained by a re-entry circuit. Re-entry results in regular paroxysmal tachycardias.
    - Re-entry can occur when there are 2 alternative pathways with different conducting properties (e.g. the AV node and an accessory pathway or an area of normal and an area of ischemic tissue).
    - Here, pathway A conducts slowly and recovers quickly, while pathway B conducts rapidly and recovers slowly.
    - In sinus rhythm, each impulse passes down both pathways before entering a common distal pathway.
    - As the pathways recover at different rates, a premature impulse may find pathway A open and B closed.
    - Pathway B may recover while the premature impulse is travelling selectively down pathway A.
    - The impulse can then travel retrogradely up pathway B, setting up a closed loop or re-entry circuit.
    - This may initiate a tachycardia that continues until the circuit is interrupted by a change in conduction rates or electrical depolarization.

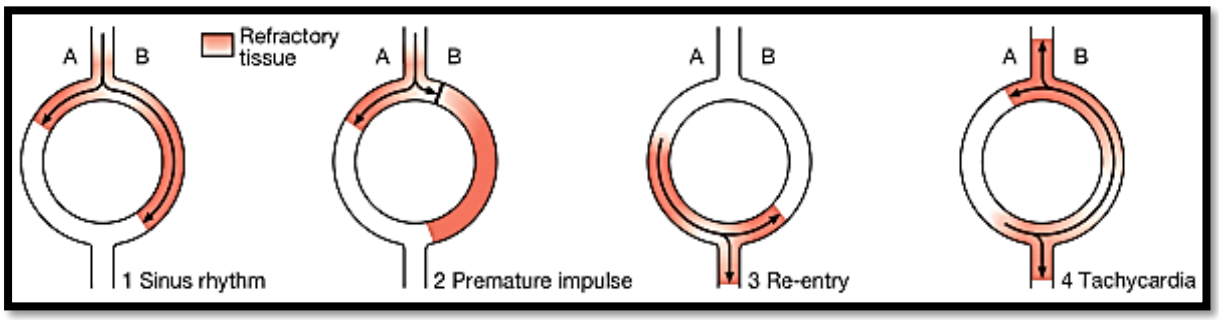


Figure 17: Mechanism of re-entry (Adapted from Davidson's Principles of Medicine 22nd Edition)

  - Triggered activity: this can cause ventricular arrhythmias in patients with coronary artery disease. It is a form of secondary depolarization arising from an incompletely repolarized cell membrane.

- Myocardial damage can result in oscillations of the transmembrane potential at the end of the action potential. These oscillations which are called 'after depolarization', may reach threshold potential and produce an arrhythmia.
- If they occur before the transmembrane potential reaches its threshold (at the end of phase 3 of the action potential), they are called 'early after depolarizations'.
- When they develop after the transmembrane potential is completed they are called 'delayed after depolarizations'.

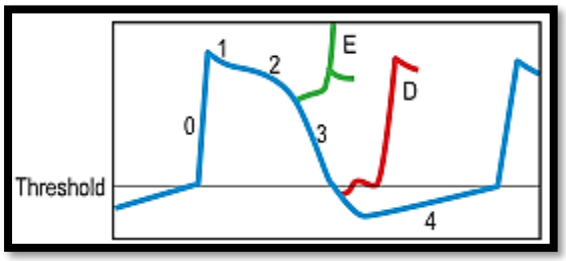


Figure 18: Triggered activity due to early (E) or delayed (D) after depolarization reaching threshold potential. (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

SUPRAVENTRICULAR TACHYCARDIA

- Supraventricular tachycardia (SVT) arises from the atrium or the atrioventricular junction.
- Conduction is via the HIS-Purkinje system, therefore the QRS shape during tachycardia is usually similar to that seen in the same patient during baseline rhythm.
- They are usually associated with a narrow QRS complex and are characterized by a re-entry circuit or automatic focus involving the atria.

Cardiac	Non-cardiac
Hypertension	Thyrotoxicosis
Congestive heart failure	Phaeochromocytoma
Coronary artery disease and myocardial infarction	Acute and chronic pulmonary disease (pneumonia, chronic obstructive pulmonary disease)
Valvular heart disease	Pulmonary vascular disease (pulmonary embolism)
Cardiomyopathy: dilated, hypertrophic	Electrolyte disturbances (hypokalaemia)
Myocarditis and pericarditis	Increased sympathetic tone (exercise, adrenergically mediated arrhythmia)
Wolff–Parkinson–White syndrome	Increased parasympathetic tone (vagally induced and postprandial arrhythmia)
Sick sinus syndrome	Alcohol misuse ('holiday heart' and long-term use)
Cardiac tumours	Caffeine, smoking, recreational drug use, e.g. cannabis
Cardiac surgery	Myotonic dystrophy type 1
Familial tachyarrhythmia (e.g. lone atrial fibrillation)	Chagas' disease
Genetic predisposition	

Figure 19: Causes of atrial tachyarrhythmias

SINUS TACHYCARDIA

- Fluctuations of autonomic tone result in phasic changes of the sinus discharge rate.
- During inspiration, parasympathetic tone falls and the heart rate quickens and on expiration the heart rate falls.
- This variation is normal particularly in children and young adults. Typically, sinus arrhythmia results in predictable irregularities of the pulse.
- In inappropriate sinus tachycardia there is a persistent increase in resting heart rate unrelated to or out of proportion with the level of physical or emotional stress.
- Sinus rate acceleration to more than 100b/min is known as sinus tachycardia.
- It is usually due to an increase in sympathetic activity associated with exercise, emotion, pregnancy or pathology.
- Young adults can produce a rapid sinus rate, up to 200 b/min during intense exercise.
- Etiology:
  - Cardiac
    - Acute heart failure
  - Systemic
    - Anxiety
    - Exercise
    - Emotion
    - Pain
    - Hypovolemia, hypoxia
    - Fever
    - Infections
    - Pulmonary embolism
    - Hyperthyroidism
    - Anemia
    - Thyrotoxicosis
    - Pheochromocytoma
    - Drugs e.g. Beta-agonist (bronchodilators)

- ECG findings:
  - Rate: >100b/min
  - Rhythm: Regular
  - P waves: normal (upright and uniform)
  - PR intervals: normal (0.06-0.10 sec)
  - QRS: normal (0.06-0.10 sec)
  - Decreased RR interval

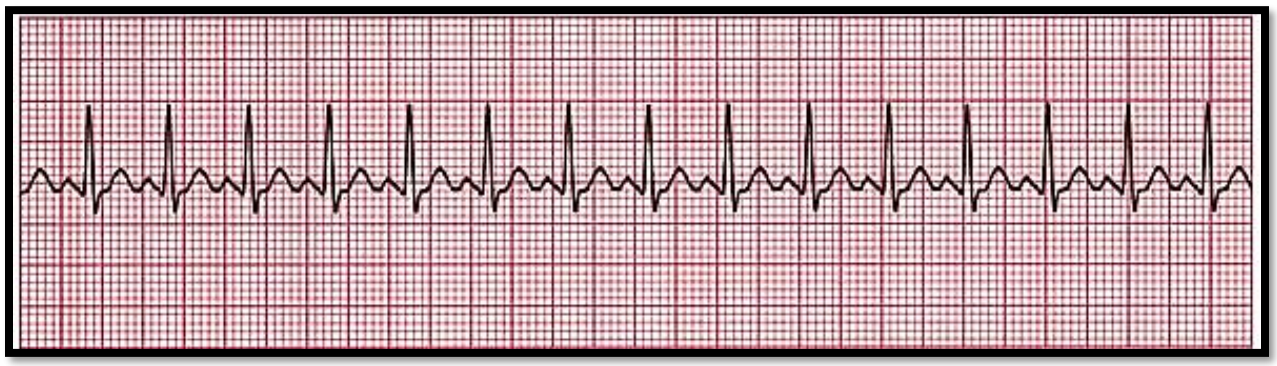


Figure 20: Sinus tachycardia

- Treatment should address underling cause.
- If necessary, beta-blockers may be used to slow the sinus rate e.g. in hyperthyroidism, ivabradine an I_f (funny current/pacemaker current) blocker may be useful when beta-blockade cannot be tolerated.

PAROXYSMAL ATRIAL TACHYCARDIA

- A series of early beats in the atria speed up the heart rate.
- In paroxysmal tachycardia, repeated periods of very fast heartbeats begin and end suddenly.
- These arrhythmias are sudden onset, often occurring in patients with otherwise normal heart and characterized by a heart rate of 150-250b/min.
- Common causes:
  - Exercise
  - Fever
  - Anxiety
  - Thyrotoxicosis
  - Hypoxemia
  - Hypotension
  - Heart failure
- Diagnosis: ECG faster rate with P waves followed by narrow QRS complexes
- Treatment
  - If patient is stable- no need for treatment, identify and treat the underlying cause.
  - If the patient is hemodynamically unstable- there is need for treatment.
    - The patient should be kept in a quiet room
    - Mechanical treatment
      - Carotid sinus massage
      - Valsalva maneuver: abrupt voluntary increase in intrathoracic and intra-abdominal pressure by straining.
      - Head immersion in cold water
    - Medical therapy
      - Adenosine (drug of choice) 6mg IV push if no response give 12mg IV push.
      - Beta blockers-1-2mg IV bolus
      - Calcium channel blockers (Verapamil 15-20mg IV over 2 minutes and diltiazem)
      - Digoxin can be helpful

ATRIAL FLUTTER

- Rapidly fired signals cause the muscles in the atria to contract quickly, leading to a very fast, steady heartbeat.
- It is characterized by an atrial rate of 250-350b/min and is usually conducted to ventricles with block so that the ventricular rate is a fraction of the atrial rate.
- The block is usually regular so the ventricular rate is regular. Sometimes there may be a varying block resulting irregular ventricular beat.
- Causes of atrial flutter:
  - Coronary artery disease
  - Pericarditis
  - Valvular heart diseases
  - Cardiomyopathy
- ECG: classic saw tooth pattern: 2 or 3 P waves (F waves) are followed by QRS complex. The block is often in a ratio of 2:1 with an atrial rate of 240 b/min and ventricular rate of 120b/min.

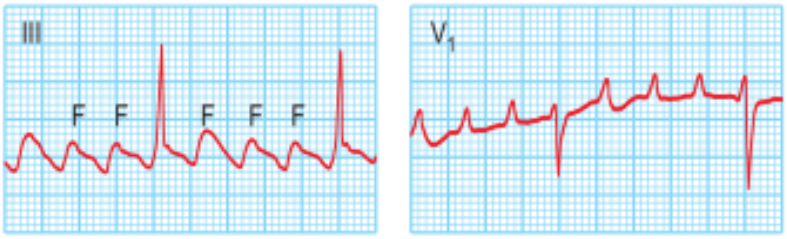


Figure 21: Atrial flutter. Some flutter waves are marked with an F. In this case the flutter frequency is 240/min. Every fourth flutter wave is transmitted to the ventricles and the ventricular rate is therefore 60bpm.

- Therapy:
  - Drugs:
    - Digoxin, esmolol, or verapamil to control ventricular rate
    - Quinidine or other anti-arrhythmic agents (amiodarone) to restore sinus rhythm
  - Direct current cardioversion: if the patient is hemodynamically unstable

ATRIAL FIBRILLATION

- Electrical signals in the atria are fired in a very fast and uncontrolled manner. Electrical signals arrive in the ventricles in a completely irregular fashion, so the heart beat is completely irregular.
- This is a supraventricular tachyarrhythmia with chaotic and irregular conduction of depolarization through the atrium and the ventricles.
- It is the commonest arrhythmia affecting 10% over 80 years old and is commoner in men.

ETIOLOGY

- Common causes 'PIRATES':
  - P: Pulmonary (PE, Pleural effusion, COPD, lung cancer, pneumonia)
  - I: ischemic heart disease (including acute MI/coronary artery disease) and other cardiac diseases (HTN, HF, cardiomyopathy, pericardial disease, myxoma, mitral stenosis/regurgitation/prolapse)
  - R: rheumatic valve disease and mitral stenosis
  - A: alcohol ("holiday heart"), smoking, caffeine
  - T: thyrotoxicosis
  - E: electrolyte imbalance (hypokalemia and hypomagnesemia)
  - S: sugar (diabetes), Sepsis, Stress
  - Idiopathic (lone) atrial fibrillation

CLASSIFICATION

- It is classified by time frame as:
  - Acute Atrial fibrillation:
    - Onset within previous 48 hours either 'new-onset' or 'recurrent episodes'
  - Chronic atrial fibrillation: sub-classified as
    - Paroxysmal Atrial fibrillation: self-terminates <7 days, usually 48 hours.
    - Persistent Atrial fibrillation: lasts >7 days or <7 days but requires cardioversion, 'Long standing' if >1 year.
    - Permanent Atrial fibrillation: refractory to cardioversion.

CLINICAL FEATURES

- Symptoms:
  - Palpitations
  - Syncope
  - Shortness of breath
  - Angina reflecting rate-related ischemia.

  - 20% are asymptomatic
- Signs:
  - Pulse: increased heart rate, irregularly irregular and apical pulse may be faster than radial
  - Decreased blood pressure
  - Absent 'a' waves in JVP
- Symptoms of complications
  - TIA/Stroke
  - Pulmonary edema (acute heart failure)

INVESTIGATIONS

- ECG:
  - Absent P waves, replaced with small irregular f waves reflecting depolarization beginning randomly at various foci in the atrium.
  - Irregularly irregular RR interval
  - If HR>100, known as AF with rapid ventricular response or 'fast AF'. Prolonged episodes may lead to transient ischemic changes such as ST depression, though persistent changes (and a compatible history) may suggest MI as the underlying cause of the AF.
  - If the ECG is normal but paroxysmal AF is suspected, use 24 ambulatory ECG or consider an event recorder if episodes >24 hr apart.



Figure 22: Atrial fibrillation. Note absolute rhythm irregularity and bassline undulations (f waves)

- Blood:
  - FBC: anemia may exacerbate heart failure
  - U + E and TSH to look for cause
  - Investigate other CVS factors: lipids, glucose
  - LFTs and coagulation profile (pre warfarin)
- Imaging:
  - Transthoracic echo: look for cardiac causes and complications. Especially important if there is a suspicion of structural disease or pre-cardioversion. Consider transesophageal echo if abnormality found.

- Chest X-ray may show heart failure

MANAGEMENT

- Rate and rhythm control:
  - Rate- slowing the heart is the first line for most patients.
    - First line options: Beta blockers, Rate-limiting calcium channel blockers (Verapamil and diltiazem), consider digoxin if they are sedentary. In active patients it is ineffective at slowing sympathetic driven increased heart rate.
      - Digoxin 0.125-0.25mg PO OD / BD or
      - Verapamil 40-80mg PO TDS or
      - Diltiazem 60mg PO TDS
    - Second line: combine any 2 of: beta blocker, diltiazem and/or digoxin
    - As an alternate to continuous therapy in patients with paroxysmal AF, offer PRNN sotalol or flecainide ("Pill in the pocket") if they meet the following criteria:
      - Infrequent episodes
      - Understand how and when to take it
      - No structural (LVF, valvular) or ischemic heart disease
      - SBP>100 and HR>70
    - Consider no treatment at all if episodes are very infrequent.
  - Rhythm control- regularizing the arrhythmia is an alternative in certain patients.
    - Offered if rate control has been unsuccessful or as an alternative 1st line treatment for:
      - New-onset AF (<48 hours)
      - AF with a reversible cause
      - AF leading to HF or hemodynamic instability: reduced BP, chest pain, loss of consciousness
      - Patients in whom it is considered more suitable based on clinical judgement e.g. younger patients especially if active and want to avoid rate control.
    - Electrical cardioversion:
      - Preferred if patient hemodynamically unstable: SBP<90mmHg, syncope, acute HF, MI.
      - Shock carried out under short-acting general anesthetic followed by second shock with higher joules if no success with first

        - If not anticoagulated give heparin or LMWH first but not if this delays treatment in a life-threatening situation.
    - Pharmacological cardioversion
        - Indications: if symptoms are milder and situation is less urgent. Bolus followed by infusion if AF continues. Again, anticoagulated first.
        - Drugs used: Flecainide or propafenone IV (Class Ic) if there is no structural heart disease. Amiodarone (Class III) if there is no structural or ischemic heart disease. It is given through central line as it carries the risk of thrombophlebitis if given peripherally
            - Amiodarone 200mg PO TDS 1st week then reduce to 200mg PO BD (maintenance dose 200 to 400mg daily)
    - Anticoagulants: if the atrial fibrillation has stayed for more than 1 week to prevent thromboembolism.
        - Warfarin 2.5mg-10mg PO OD (to maintain INR 2.5 to 3.5)
        - ASA 75-150mg PO OD
        - Use ASA if INR is not available
    - Catheter ablation can be done for cases that do not respond to medical therapy. As well as young individuals to avoid lifelong medication.
        - Methods: radiofrequency, cryotherapy or microwave. Often targets an area around the insertion of the pulmonary vein.
        - 'Ablate and pace'- ablation of the AV node followed by pacemaker insertion can be considered in permanent AF with LV dysfunction

COMPLICATIONS

- Stroke (5 times risk)
- Acute heart failure
- Pulmonary edema
- Cardiomyopathy and heart failure

VENTRICULAR TACHYARRHYTHMIAS

- Tachyarrhythmias originate from the ventricles.
- These include:
  - Premature ventricular contraction
  - Ventricular tachycardia
  - Ventricular fibrillation
  - Torsades de pointes

PREMATURE VENTRICULAR CONTRACTION

- Premature ventricular contractions (PVC) is a type of arrhythmia in which occasional cardiac impulses are originating directly from the ventricles by passing the normal conduction system.
- These are among the commonest arrhythmias.
- ECG: wide and bizarre QRS appearing in a relatively normal looking ECG.
- Therapy: most isolated PVCs are benign and need no treatment.
- If symptomatic or frequent:
  - beta-blockers (propranolol 40-80mg PO TDS)
  - Amiodarone 200mg PO TDS for 5-7 days then reduce to 200mg PO BD (maintenance dose 100-200mg daily)
  - Monitor for possible side effects: thyroid function test, LFTs, consult ophthalmologist and CXR once a year.

VENTRICULAR TACHYCARDIA

- Ventricular tachycardia arises from the ventricles (ventricular ectopic focus), it occurs paroxysmal and exceeds 120b/min (100-180bpm) with regular rhythm.
- It often occurs in a structurally abnormal heart. Injury to the ventricular myocardium can leave strands of functioning tissue among damaged tissue, creating the possibility of a re-entrant loop which is the commonest trigger for VT.
- There is AV dissociation and the ventricular arrhythmia proceeds independently of the normal atrial rhythm.
- During ventricular tachycardia, the ventricles do not have enough time to relax, ventricular filling is impaired and the cardiac output significantly decreases. When the ventricular tachycardia lasts for more than 30 seconds or requires control because of hemodynamic collapse it is called sustained ventricular tachycardia.

- ECG: bizarre and wide QRS complexes coming in succession with no constant relation to P waves.
- Therapy: since this is a life threating situation urgent intervention is needed.
  - In cardiac arrest recall that ventricular fibrillation and pulseless VT are shockable rhythm. Defibrillate at 50-100 + 200.
  - If patient is stable, pharmacological treatment:
    - Amiodarone 300mg IV over 10 min followed by infusion at 1mg/min for 6 hours
    - Lignocaine 100mg IV bolus followed by infusion of 4mg/min for 30 min, 2mg/min for 2hours, then 1 mg/min
  - In cases of multifocal ventricular tachycardia use magnesium sulfate 1-2 g IV.
  - Correct reversible causes hypokalemia, digoxin toxicity.

VENTRICULAR FIBRILLATION

- Electrical signals in the ventricles are fired in a very fast and uncontrolled manner, causing the heart to quiver rather than beat and pump blood.
- It is characterized by lack of ordered contraction of the ventricles. Therefore, there is no cardiac output.
- The patient is pulseless and becomes rapidly unconscious and respiration ceases (cardiac arrest)
- Ventricular fibrillation is synonymous with death unless urgent conversion to effective rhythm can be accomplished.
- There is irregular, chaotic ventricular activity without effective cardiac output and without identifiable P waves, QRS or T waves on ECG. It is usually provoked by a ventricular ectopic beat.

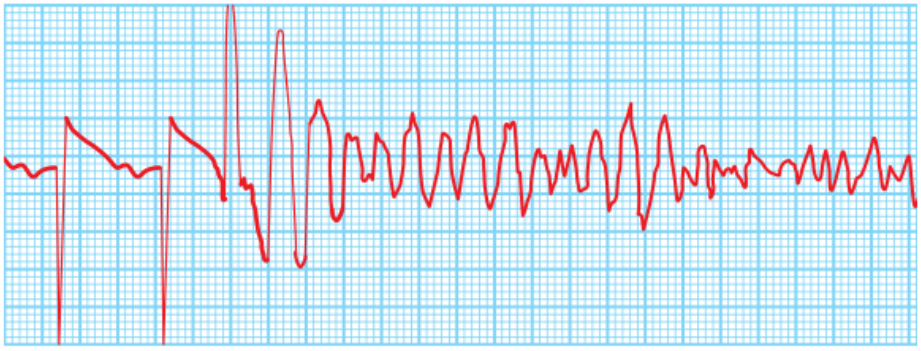


Figure 23: Ventricular fibrillation. Four beats of sinus rhythm followed by a ventricular ectopic beat that initiates ventricular fibrillation. The ST segment during sinus rhythm is elevated owing to acute myocardial infarction in this case.

- Therapy: patients need cardiorespiratory resuscitation
  - Cardiac resuscitation
  - Mechanical ventilation
  - Cardiac compression and intracardiac adrenaline
  - DC cardioversion (Electrical defibrillation) using high voltage (recall ventricular fibrillation is a shockable rhythm)

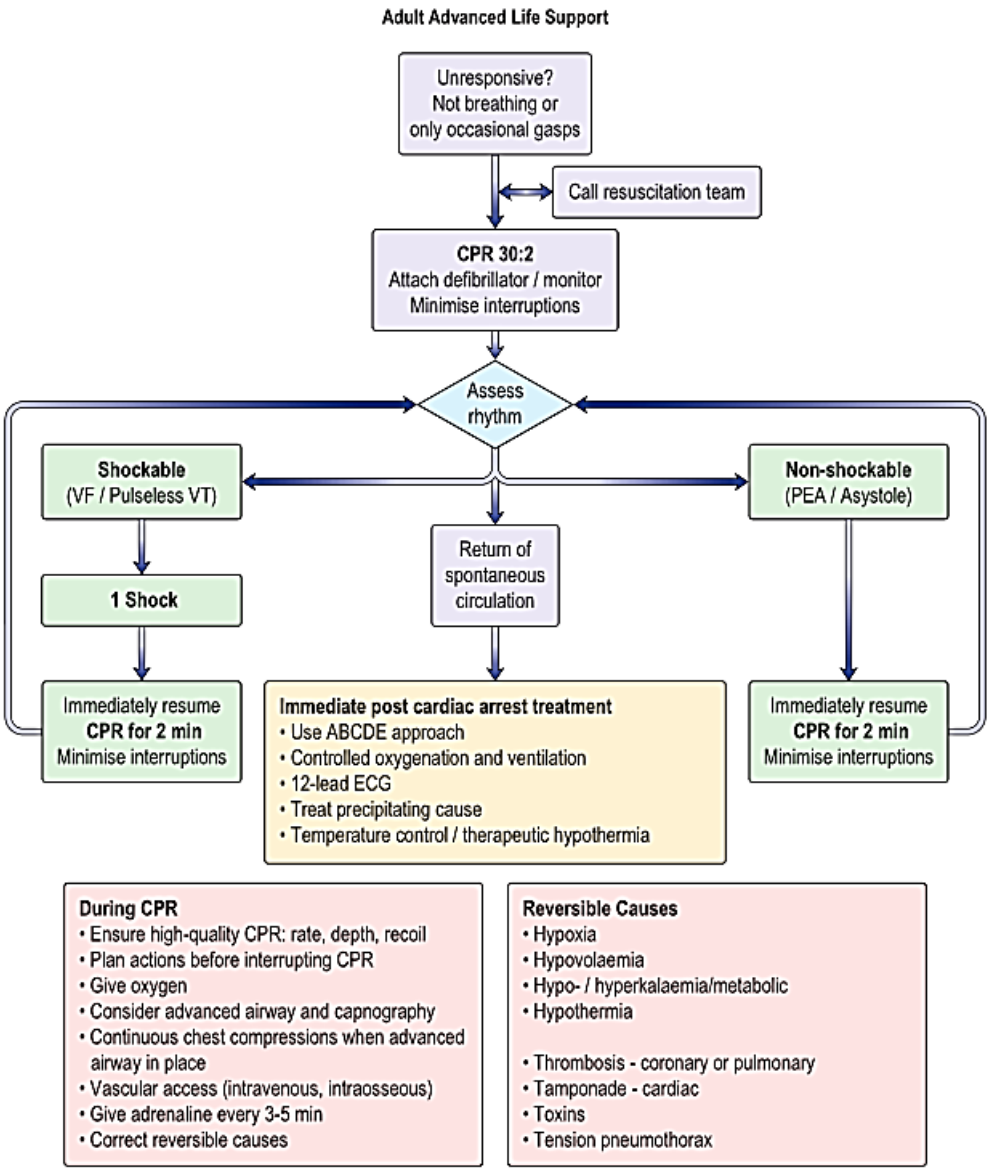
CARDIAC RESUSCITATION

- Check if patient is unresponsive by shaking him/her and shouting into one ear. If no response perform ABCs.
- Call for help.
- A- airway and B-breathing
  - Ensure airway is clear and patent
  - Perform jaw thrust /chin lift to keep head in "sniffing air in the morning" position.
  - Endotracheal intubation or Supraglottic airway tube should be instituted.
- C-circulation
  - If patient is unresponsive with absent or abnormal breathing, then external chest compression should be started.
    - The heel of one hand is placed over the center of the chest and the heel of the second hand is placed over the first with the fingers interlocked.
    - The arms are kept straight and the sternum is rhythmically depressed by 5-6 cm at a rate of approximately 100-120/min allowing for complete recoil.
    - Respiratory and circulatory support is continued by providing 2 effective breaths for every 30 cardiac compressions (30:2 for one or two persons, 15:2 in pediatric patients). Compressions alone is good as compressions with rescue breaths (American Heart Association updated guidelines)
  - Gain venous access and start an intravenous infusion in a large peripheral or central vein (an intraosseous needle may be used if IV access is not possible)
- Continuous ECG monitoring
- If the ECG shows a shockable rhythm- ventricular fibrillation or pulseless ventricular tachycardia, then an unsynchronized shock of 150-200J biphasic (360 J monophasic) is delivered without delay via paddles or self-adhesive pads followed immediately by 2 minutes of CPR.
  - Intravenous amiodarone is the first-line drug in refractory VF/Pulseless VT.

  - When treating VF/VT cardiac arrest, adrenaline 1mg is given after the third shock and then every 3-5 min.
  - Amiodarone 300mg is also given after the third shock, particularly if VT/VF have recurred after defibrillation.
- For non-shockable rhythm- asystole or pulseless electrical activity, 2 minutes of CPR is delivered with 1mg of intravenous adrenaline (epinephrine)
- For both sides of algorithm, it is necessary to maintain:
  - CPR,
  - Ensure oxygenation and to
  - Exclude/treat reversible causes (hypoxia, hypovolemia, hyper or hypokalemia, hypothermia, Tension pneumothorax, tamponade, toxins, thromboembolism)

POST RESUSCITATION

- Involves:
  - Use of the ABCDE approach
  - Controlled oxygenation and ventilation
  - 12 lead ECG
  - Treat precipitating cause
  - Temperature control/therapeutic hypothermia
- Studies have supported the use of therapeutic hypothermia in unconscious adult patients with spontaneous circulation after an out-of-hospital cardiac arrest due to ventricular fibrillation
- These patients should be cooled with careful temperature monitoring to 32-34ºC for 12-24 hours.
- External cooling methods including the use of cooling blankets, ice packs to the groin, axillae and neck, wet towels and a cooling helmet.
- Invasive methods include intravenous infusions and peritoneal and pleural lavage.
- Shivering should be prevented by the use of a neuromuscular blocker and sedation to reduce oxygen consumption,



- When an arrhythmia cannot be controlled by other treatments, there may be a place for surgery. After locating the heart tissue that is causing the arrhythmia, the tissue is altered or removed so that it will not produce the arrhythmia.

TORSADES DE POINTES

- Polymorphic VT with a characteristic pattern of QRS complex of increasing and decreasing magnitude.
- A complication of congenital or acquired long QT syndrome (LQTS)
- Clinical features:
  - Sudden decrease in BP, dizziness and syncope
  - Usually self-resolves but can progress to sustained VF or VF
- Management: IV magnesium sulphate

BRADYARRHYTHMIAS

- Bradyarrhythmias are a result of inadequate sinus impulse production or from blocked impulse propagation.
- The heart beats slower than normal.
- They are not usually cause of concern unless the patient develops syncope or presyncope.
- They include:
  - Sinus bradycardia
  - Sinus pause (arrest)
  - AV block
- The incidence of bradycardia increases with age
- Etiologies include:
  - Cardiac:
    - Idiopathic senile degeneration,
    - Ischemia (usually involving the inferior wall),
    - Infectious processes (endocarditis, Chagas' disease, Lyme disease),
    - Infiltrative diseases (sarcoidosis, amyloidosis, hemochromatosis),
    - Autoimmune disease (SLE, RA, scleroderma),
    - Iatrogenic factors (heart transplant, surgery),
    - Inherited/congenital disease (myotonic muscular dystrophy),
    - Conditioned heart (trained athletes).
  - Systemic:
    - Autonomic (neurocardiac, carotid sinus hypersensitivity, situational),
    - Medication (beta blockers, calcium channel blockers, clonidine, digoxin, antiarrhythmics),
    - Metabolic (electrolyte abnormalities),
    - Metabolic (hypothyroidism, hypothermia),
    - Neurologic (increased ICP, obstructive sleep apnea).

- Symptoms of bradycardia may include dizziness, weakness, fatigue, heart failure, syncope or presycope. Other symptoms are related to underlying cause of bradycardia.
- When performing a physical examination look for evidence of decreased pulse rate and evidence of the underlying cause of bradycardia.

PATHYPHYSIOLOGY OF BRADYARRHYTHMIAS

- Bradycardia may be due to:
  - Reduced automaticity e.g. sinus bradycardia
  - Blocked or abnormally slow conduction e.g. AV block

SINUS BRADYCARDIA

- A sinus rate of <60b/min during the day or <50 b/min at night is known as sinus bradycardia.
- It is usually asymptomatic unless the rate is very slow.
- It is normal in athletes owing to increased vagal tone.

ETIOLOGY

- Causes are divided into:
  - Cardiac
    - Myocardial infarction: acute ischemia and infarction of the sinus node
    - Sinus node disease (sick sinus syndrome): chronic degenerative changes such as fibrosis of the atrium and SA node.
  - Systemic
    - Hypothermia
    - Hypothyroidism
    - Hyperkalemia
    - Cholestatic jaundice
    - Raised intracranial pressure (Cushing reflex)
    - Drugs e.g. beta-blockers, alpha agonists (clonidine), digoxin, verapamil, amiodarone, antiarrhythmic drugs, opioids and benzodiazepines.
    - Neurally mediated syndromes e.g. carotid sinus syndrome, vasovagal syndrome (syncope)
    - Physiological states: high levels of fitness, pain
    - Anorexia nervosa
- Sinus bradycardia can be acute and reversible or chronic and degenerative.

- In sinus bradycardia the ECG shows normal P wave configuration consistent with origin in sinus node area. The RR interval is increased.

MANAGEMENT

- Management of sinus bradycardia is first to identify and if possible remove any extrinsic causes.
- Asymptomatic sinus bradycardia requires no treatment.
- Symptomatic acute sinus bradycardia (HR<35b/m) usually responds to intravenous atropine 1mg IV may temporarily increase the sinus.
- Patients with recurrent or persistent symptomatic sinus bradycardia should be considered for pacemaker implantation.
- Thromboembolism is common in tachy-brady syndrome and patients should be anticoagulated unless there is a contraindication.

SINUS PAUSE (SINUS ARREST)

- This is failure of the impulse formation (Sinus arrest) or conduction from (Sinoatrial exit block) the SA node.
- Its causes overlap with those of sinus bradycardia including:
  - Sick sinus syndrome
  - Hyperkalemia
  - Inferior MI
  - CVS drugs
- ECG findings:
  - Rhythm: irregular whenever a pause (arrest) occurs
    - Escape rhythm may take over,
      - Junctional-narrow QRS 45-60bpm
      - Ventricular- wide QRS 30-45bpm
  - P waves: normal (upright and uniform) except in areas of pause (Arrest)
  - PR intervals: normal (0.12-0.20 sec)
  - QRS: normal (0.06-0.10 sec)

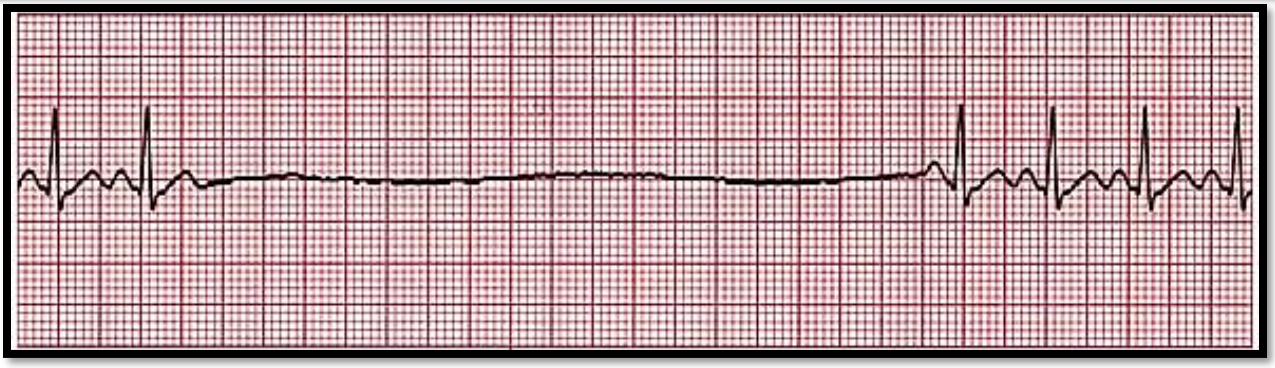


Figure 24: Sinus pause (Arrest)

HEART BLOCK

- Heart block or conduction block may occur at any level in the conducting system.
- Block in either the AV node or the His bundle results in AV block, whereas block lower in the conduction systems produces bundle branch block.
- Causes:
  - RCA infarct (inferior MI) as this supplies the AV node
  - Myocarditis
  - Drugs: beta-blockers, calcium channel blockers, adenosine, digoxin, cholinesterase inhibitors
  - Idiopathic

ATRIOVENTRICULAR BLOCK

- There are 3 forms:
  - First degree AV block: occurs between SA node and the AV node (i.e. within the atrium)
  - Second degree AV block
    - Type I: occurs in the AV node. This is the only piece of conductive tissue in the heart which exhibits the ability to conduct at different speeds.
    - Type II: occurs after the AV node in the bundle of HIS or Purkinje fibers
  - Third degree (complete) AV block: occurs anywhere from AV node down causing complete blockage of conduction

FIRST DEGREE AV BLOCK

- This is simple prolongation of the PR interval to >0.20s (200ms i.e. >5 small squares).
  - Recall the normal PR interval is 120-200ms (3-5 small squares)
- Every atrial depolarization is followed by conduction to the ventricles but with delay.
- Etiology: medication, CHF, ischemia, electrolyte abnormalities.
- It rarely causes symptoms.
- ECG findings:
  - Rate: depends on rate of underlying rhythm
  - Rhythm: regular
  - P waves: normal (upright and uniform)
  - PR interval: Prolonged (>0.20 sec)
  - QRS: normal (0.06-0.10s)

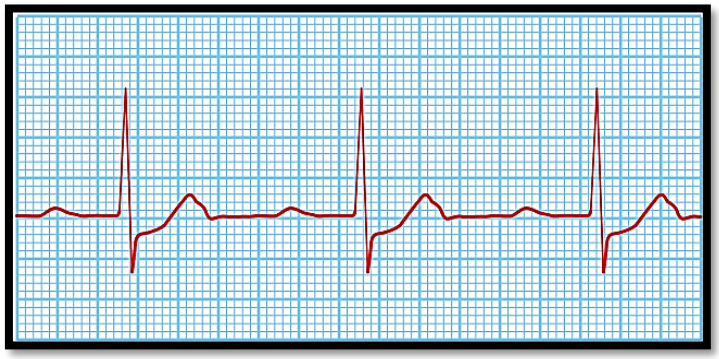


Figure 25: First degree AV block with a prolonged PR interval. Note ST depression is also present (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

- No therapy is needed.

SECOND-DEGREE AV BLOCK

- This occurs when some P waves conduct and others do not.
- There are several forms:
  - Mobitz I block (Wenckebach block phenomenon)
  - Mobitz II block
- Acute myocardial infarction may produce second-degree heart block.
- In inferior myocardial infarction, close monitoring and transcutaneous temporary back up pacing are all that is required.

- In anterior myocardial infarction, second-degree heart block is associated with a high risk of progression to complete heart block and temporary pacing followed by permanent pacemaker implantation is usually indicated.
- The conduction ratio is the number of P waves to QRS complexes e.g. 4:3
- A conduction ratio of 2:1 is untypable as it is hard to determine if there is progressive PR prolongation.
- High grade second degree block is when 2 consecutive P waves fail to conduct to the ventricles.
- The P waves are regular, distinguishing it from ectopic atrial contractions.

MOBITZ I BLOCK (WENCKEBACH BLOCK PHENOMENON)

- There is progressive PR interval prolongation until a P wave fails to conduct i.e. the PR interval slowly increases then there is dropped QRS complex.
- The PR interval before the blocked P wave is much longer than the PR interval after the blocked P wave.
- Etiology: medication, electrolyte abnormalities, ischemia.
- The phenomenon may be physiological and is sometimes observed at rest or during sleep in athletic young adults with high vagal tone.
- ECG findings:
  - Rate: depends on rate of underlying rhythm
  - Rhythm: irregular
  - P waves: normal (upright and uniform)
  - PR interval: Progressively longer until one P-wave is blocked and a QRS is dropped (blocked beat)
  - QRS: normal (0.06-0.10sec)

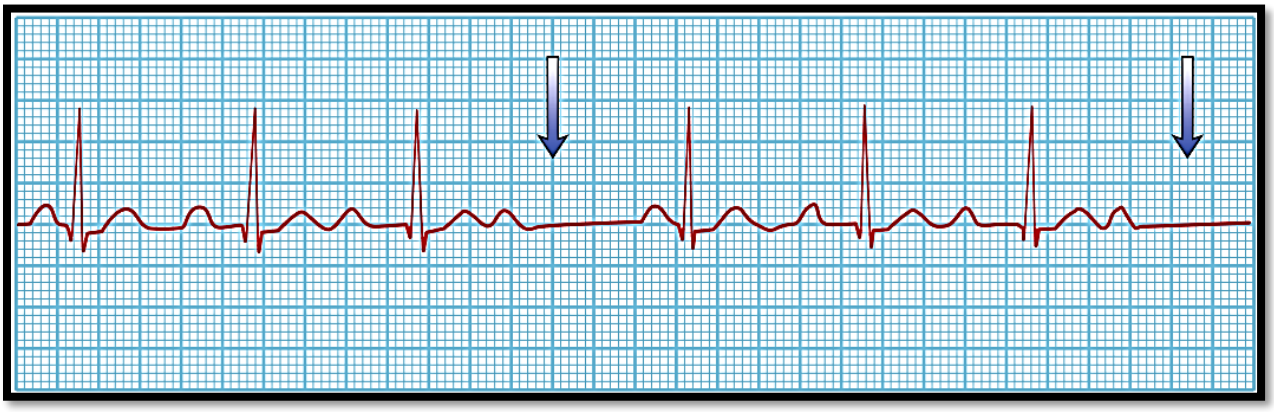


Figure 26: Mobitz type I AV block. The PR interval gradually prolongs until the P wave does not conduct to the ventricles (arrows) (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

- It can be hard to distinguish from Mobitz 2 when increase in PR are small. Look for the biggest increase, which is between the 1st and 2nd PR after the missed QRS.
- If symptomatic give atropine (0.5-2mg IV) or isoproterenol (1-4 microgram/min IV).
- Persistent symptoms often require permanent pacemakers.

MOBITZ II BLOCK

- Occurs when a dropped QRS complex is not preceded by progressive PR interval prolongation i.e. the PR interval is fixed but there are dropped beats.
- Always clarify the frequency of dropped beats e.g. 2:1, 3:1, 4:1.
- Etiology: ischemia, conduction system disease.
- ECG findings:
  - Rate: atrial rate (usually 60-100b/min), faster than ventricular rate.
  - Rhythm: atrial regular and ventricular irregular
  - P wave: Normal (upright and uniform), more P waves than QRS complexes
  - PR interval: normal or prolonged but constant
  - QRS: usually wide (>0.10 sec)

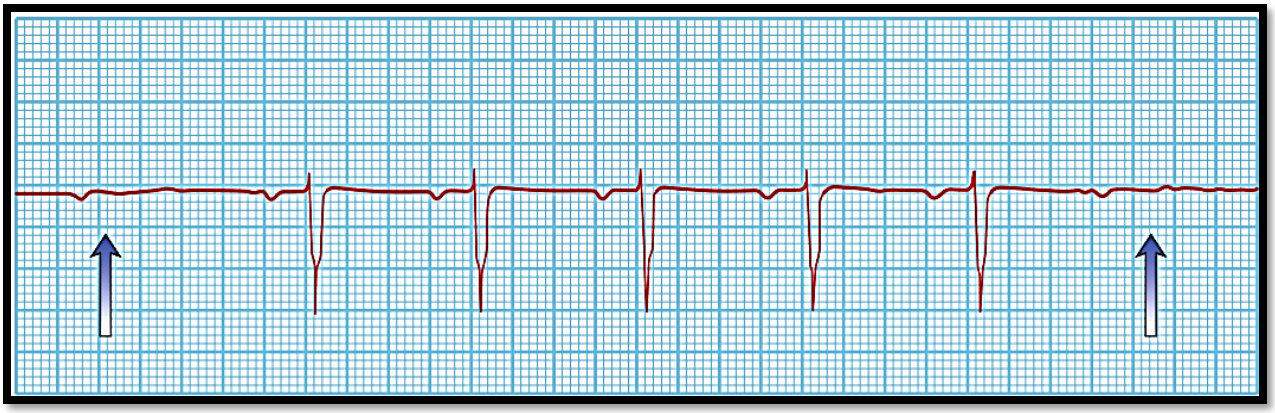


Figure 27: Mobitz type II AV block. The P waves that do not conduct to the ventricles (arrows) are not preceded by gradual PR interval prolongation. (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

- High risk of progression to 3rd degree heart block so often requires pacemaker treatment.
- Treatment: pacemaker

THIRD DEGREE (COMPLETE) AV BLOCK

- Complete heart block occurs when all atrial activity fails to conduct to the ventricles.
- There is dissociation of atrial beats and ventricular beats as the atrial impulses fail to conduct to the ventricles and the ventricles beat on their own with a slower rate.
- In patients with complete heart block the etiology needs to be established.
- In this situation life is maintained by a spontaneous escape rhythm.
- The heart rate drops significantly to a range of 20-40 b/min and patients become symptomatic.
- ECG findings:
  - Rate: Atrial (60-100 b/min), ventricular (40-60b/min) if escape focus is junctional <40b/min. P wave rate>QRS rate.
  - Rhythm: usually regular but atria and ventricles act independently.
  - P waves: normal (upright and uniform) may be superimposed on QRS complexes or T waves.
  - PR interval: varies greatly
  - QRS: can be narrow or wide
- Narrow complex escape rhythm (<0.12s QRS complex) implies that it originates in the HIS bundle and therefore that the region of block lies more proximally in the AV node.

- The escape rhythm occurs with an adequate rate (50-60 b/min) and is relatively reliable.
- Broad complex escape rhythm (>0.12s) implies that the escape rhythm originates below the HIS bundle and therefore that the region of block lies more distally in the HIS-purkinje system.
- The resulting rhythm is slow (15-40b/min) and relatively unreliable. Dizziness and blackouts (Stokes-Adams attacks)
- Cannon A waves may be visible in the neck and the intensity of the first heart sound varies due to loss of AV synchrony.
- Treatment: depends on etiology
  - Recent- onset narrow complex AV block due to transient causes may respond to intravenous atropine 0.5-2mg but temporary pacing facilities should be available for the management of these patients.
  - Chronic narrow complex AV block requires permanent pacing (dual chamber) if it is symptomatic or associated with heart disease.
  - Pacing is also advocated for isolated, congenital AV block even if asymptomatic.
  - Broad complex AV block requires permanent pacemaker implantation.

Aetiology of complete heart block

Congenital
- Autoimmune (e.g. maternal SLE)
- Structural heart disease (e.g. transposition of the great vessels)

Idiopathic fibrosis
- Lev's disease (progressive fibrosis of distal His–Purkinje system in elderly patients)
- **Lenegre's disease** (proximal His–Purkinje fibrosis in younger patients)

Ischaemic heart disease
- Acute myocardial infarct
- Ischaemic cardiomyopathy

Non-ischaemic heart disease
- Calcific aortic stenosis
- Idiopathic dilated cardiomyopathy
- Infiltrations (e.g. amyloidosis, sarcoidosis, neoplasia)

Cardiac surgery
- e.g. following aortic valve replacement, CABG, VSD repair

Iatrogenic
- Radiofrequency AV node ablation and pacemaker implantation

Drug-induced
- e.g. digoxin, beta-blockers, non-dihydropyridine calcium-channel blockers, amiodarone

Infections
- Endocarditis
- Lyme disease
- Chagas' disease

Rheumatic autoimmune disease
- e.g. SLE, rheumatoid arthritis

Neuromuscular diseases
- e.g. Duchenne muscular dystrophy

SLE, systemic lupus erythematosus; CABG, coronary artery bypass graft surgery; VSD, ventricular septal defect; AV, atrioventricular.

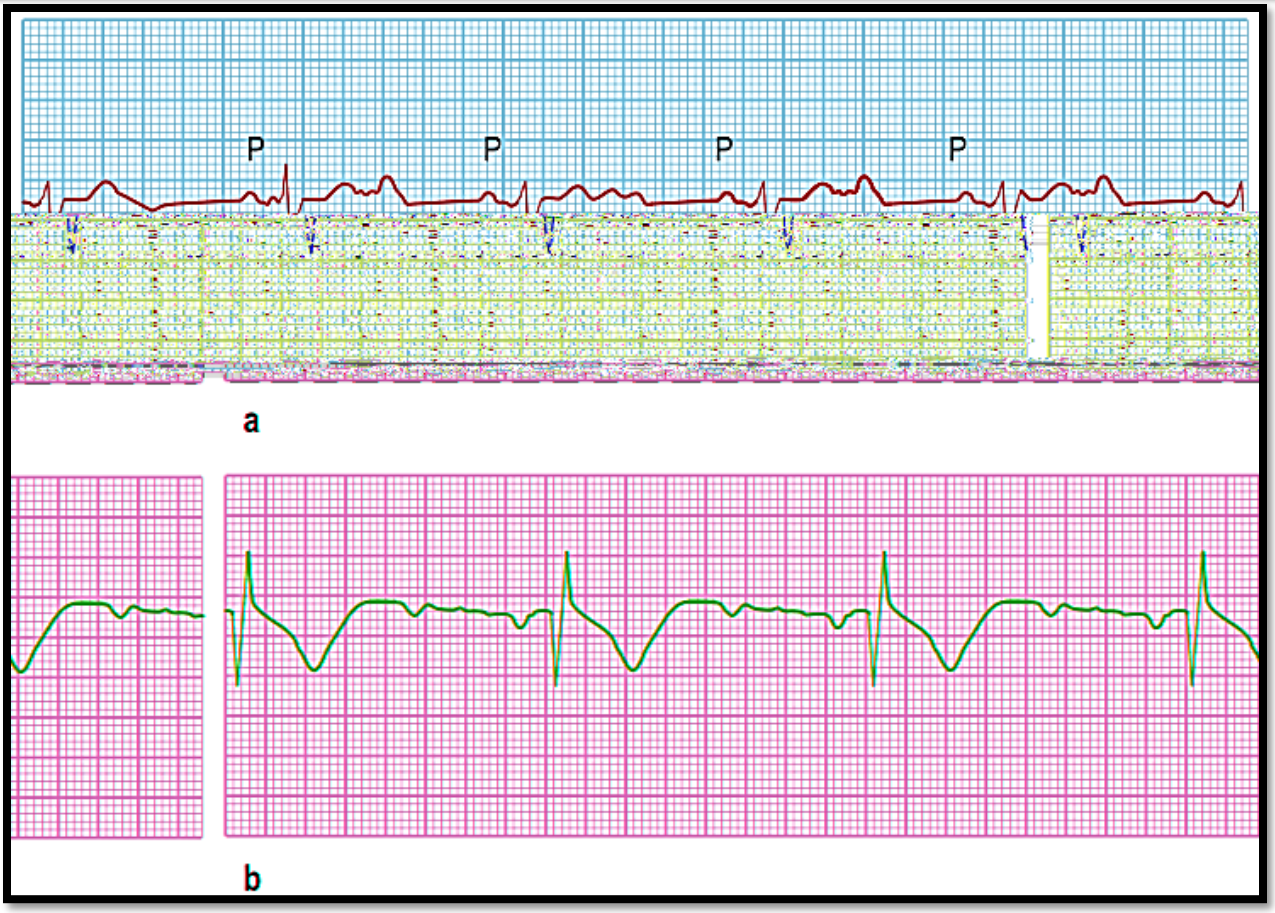


Figure 28: Complete heart block. (a) congenital complete heart block. The QRS complex is narrow (0.08s) and the QRS rate is relatively rapid (52b/min) (b) Acquired complete heart block. The QRS complex is broad (0.13s) and the QRS rate is relatively slow (38b/min) (Adapted from Kumar and Clark's Clinical Medicine 8th Edition)

BUNDLE BRANCH BLOCK

- The HIS bundle gives rise to the right and left bundle branches.
- The left bundle subdivides into the anterior and posterior division of the left bundles.
- Abnormalities seen in the bundle branch include:
  - Bundle branch conduction delay (incomplete bundle branch block)
  - Complete bundle branch block
  - Hemiblock
  - Bifascicular block
- Bundle branch blocks are usually asymptomatic.
- Right bundle branch block causes wide but physiological splitting of the second heart sound.

- Left bundle branch block may cause reverse splitting of the second sound.
- Patients with intraventricular conduction disturbances may complain of syncope. This is due to intermittent complete heart block or to ventricular tachyarrhythmias.
- Causes of bundle branch block are similar to those of complete heart block.

Causes of bundle branch block

Right	Left
It is a normal finding in 1% of young adults and 5% of elderly adults	**Left ventricular outflow obstruction**
Congenital heart disease	Aortic stenosis
Atrial septal defect	Hypertension
Fallot's tetralogy	**Coronary artery disease**
Pulmonary stenosis	Acute myocardial infarction
Ventricular septal defect	Severe coronary disease (two- to three-vessel disease)
Pulmonary disease	
Pulmonary hypertension	
Pulmonary embolism	
Myocardial disease	
Myocardial infarction	
Cardiomyopathy	
Conduction system, fibrosis	
Chagas disease	

- In Bundle branch blocks there is blockage in the bundle branches which lie between the Bundle of His and the Purkinje fibers.
- Depolarization instead spreads via the (slower) myocardium causing broad QRS complexes
- The altered depolarization sequence also leads to altered repolarization and hence ST-T changes.

BUNDLE BRANCH CONDUCTION DELAY (INCOMPLETE BUNDLE BRANCH BLOCK)

- This produces slight widening of the QRS complex (up to 0.11s).
- It is known as incomplete bundle branch block.

COMPLETE BUNDLE BRANCH BLOCK

- This is associated with a wider QRS complex (>0.12s).
- The shape of the QRS depends on whether the right or the bundle is blocked.

RIGHT BUNDLE BRANCH BLOCK (RBBB)

- Right bundle branch block occurs as an isolated congenital anomaly or is associated with cardiac or pulmonary conditions.
- Causes:
  - Increased RV pressure: Primary pulmonary hypertension, cor pulmonale, pulmonary embolism.
  - Acquired heart disease: anterior MI (Left anterior descending), myocarditis, cardiomyopathy.
  - Congenital
  - Iatrogenic e.g. cardiac catheterization
  - It can also be a normal ECG variant in healthy individuals
- Produces late activation of the right ventricle. This is seen as deep S waves in leads I and V6 and as a tall late R wave in lead V1 (late activation moving towards right and away from left sided leads).
- Right bundle branch block alone does not alter the electrical axis of the heart. Axis deviations signify right ventricular hypertrophy (RV overload) or co-existent fascicular block.
- The combination of right bundle branch block with left axis deviation is associated with ostium primum atrial septal defects.

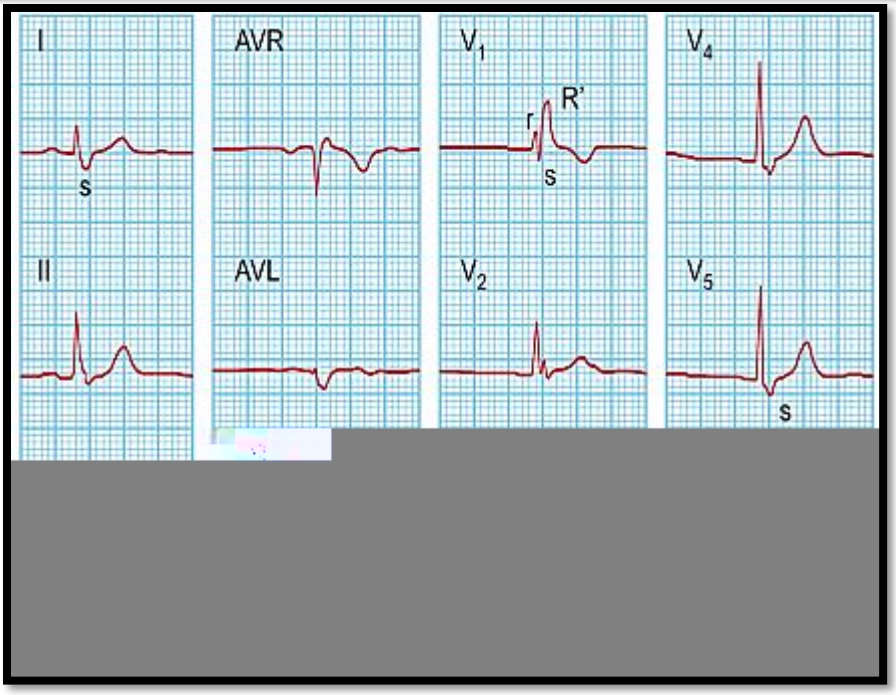


Figure 29: Right bundle branch block: Note an rsR' pattern with the tall R' in lead V1-V2 and the broad S waves in leads I and V5-V6 (Adapted from Kumar and Clark's Clinical Medicine)

LEFT BUNDLE BRANCH BLOCK

- Complete left bundle branch block is often associated with extensive left ventricular disease.
- Causes:
  - Anterior MI (LAD) may be the initial ECG sign
  - Hypertension
  - Myocarditis
  - Cardiomyopathy
  - Aortic valve disease
- Left bundle branch block produces the opposite- a deep S wave in V1 and a tall late R wave in leads I and V6. Because left bundle branch conduction is normally responsible for the initial ventricular activation, left bundle branch block also produces abnormal Q waves.

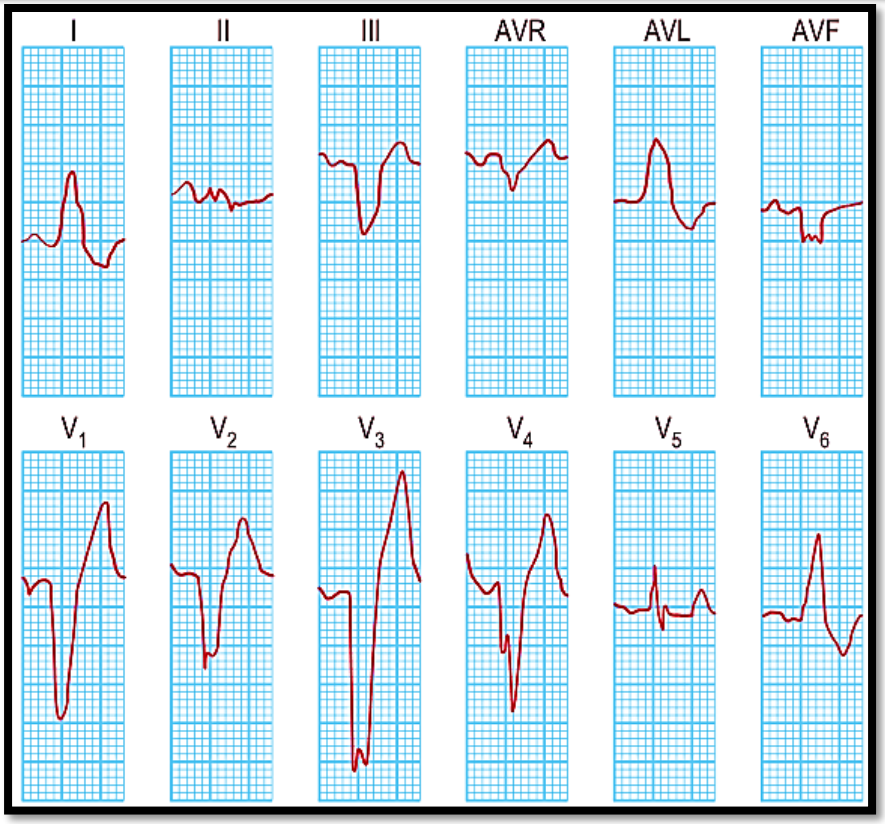


Figure 30: Left bundle branch block. The QRS duration is >0.12s. Note the broad notched R waves with ST depression in leads I, AVL and V6 and the broad QS waves in V1-V3 (Adapted from Kumar and Clark's Clinical Medicine 8th edition)

HEMIBLOCK

- Delay or block in the divisions of the left bundle branch produces a swing in the direction of depolarization (cardiac axis) of the heart.
- When the anterior division is blocked (left anterior hemiblock), the left ventricle is activated from inferior to superior. This produces a superior and leftwards movement of the axis (left axis deviation).
- Delay or block in the postero-inferior division swings the QRS axis inferiorly to the right (right axis deviation).

BIFASCICULAR BLOCK

- This is a combination of a block of any 2 of the following:
  - Right bundle branch
  - Left anterosuperior division
  - Left postero-inferior division

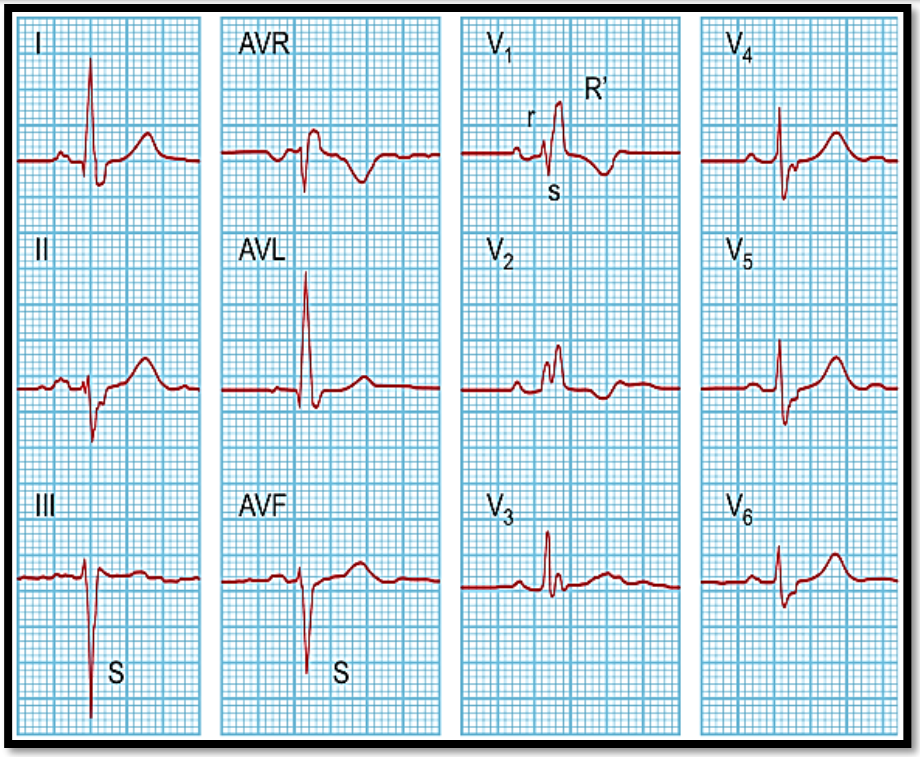


Figure 31: Bifascicular block. In addition to right bundle branch block, note left axis deviation and deep S waves in leads III and AVF typical for left anterior hemiblock. (Adapted from Kumar and Clark's Clinical Medicine)

INFECTIVE ENDOCARDITIS

- This is infection and inflammation of the endocardial surface of the heart usually a valve, most commonly the mitral or aortic.
- Infective endocarditis usually follows transient bacteremia and turbulent flow past valves leading to formation of vegetations on valves, containing bacteria, fibrin and platelets.
- It can affect natural valves or prosthetic valves.
- Individuals with prosthetic or abnormal valves are at high risk, but half the cases occur in those with normal valves.
- Disease is often systemic due to septicemia, and mutli-system due to septic or sterile emboli and immune-complex deposition.

CLASSIFICATION

- The classic clinical presentation and clinical course of infective endocarditis is divided into:
  - Acute infective endocarditis (50% of cases): has a rapid onset and develops over days-weeks. It is usually seen in normal heart valves and is due to *Staphylococcus aureus*. It is a rapidly progressive illness with destruction of valvular structures.
  - Subacute infective endocarditis (Subacute bacterial infective endocarditis): it has an insidious onset and develops over weeks to months. It usually seen in abnormal valves and due to *Streptococcus viridans*.

ETIOLOGY

- Bacterial:
  - *Streptococcus viridans* (this is the commonest cause in those with valve disease, it is a bacterium which is a normal flora of the oral cavity. It accounts for 50-60% of cases of subacute infective endocarditis)
  - *Staphylococcus aureus* (this is commonest cause in IV drug users, acute infective endocarditis and in individuals with prosthetic valve. 35-50% of *Staph* bacteremia is complicated by infective endocarditis. In more than half of cases endocarditis due to *S. aureus* occurs in the absence of underlying valvular disease. Mortality range 40-50%)
  - *Enterococci* are another common cause.
  - *Group D streptococci* (the source for bacterium is the GIT or GUT. Causes Subacute infective endocarditis)

  - *Coagulase-negative S. aureus:* causes approximately 30% of prosthetic valve cases and 5% of natural valve cases. It causes subacute infective endocarditis.
  - *HACEK organisms (Haemophilus species, Actinobacillus, actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella species).* These group of organisms usually cause subacute disease and account for 5% of infective endocarditis.
- Fungi:
  - *Candida*
  - *Aspergillus*
- Non-infective:
  - SLE
  - Cancer

PATHOPHYSIOLOGY

- All cases of infective endocarditis develop from a common shared process:
  - Bacteremia (nosocomial or spontaneous) that delivers the organisms to the valve's surface
  - Adherence of the organism to valvular structures
  - Eventual invasion of the valve leaflets and formation of vegetations.
- Infective endocarditis develops most commonly on the mitral valve, closely followed in descending order of frequency by the aortic valve, the combined mitral and aortic valve, the tricuspid valve and rarely the pulmonic valve. Mechanical prosthetic and bioprosthetic valves exhibit equal rates of infection.
- Turbulence in blood flow damages valvular surface and endocardium which creates a favorable situation for formation of sterile thrombus (vegetation) made of platelets and fibrin.
- The micro-organisms that most commonly produce endocarditis resist the bactericidal action of complement and possess fibronectin receptor for the surface of fibrin and platelet thrombus.
- Either a spontaneous bacteremia or one that is the result of an invasive procedure gives access to the bacteria to adhere to the sterile platelet/fibrin vegetation. Most cases of subacute disease are secondary to the bacteremia that develop from the activities of daily living (e.g. brushing teeth, bowel movements)
- The complications of acute bacterial endocarditis result from intracardiac disease and metastatic infection produced by suppurative emboli. Because of their shortened course, immunological phenomena are not a part of acute infective endocarditis.

RISK FACTORS

- Increased turbulent flow:
  - Valve disease
  - Prosthetic valves
  - Structural disease: unrepaired PDA, VSD, HCM
  - Rheumatic heart disease
- Increased pathogen entry and bacteremia:
  - IV drug use
  - Hemodialysis
  - Dermatitis
- Chronic disease:
  - Diabetes
  - Kidney disease

CLINICAL FEATURES

SUBACUTE INFECTIVE ENDOCARDITIS

- The patient suspected of subacute bacterial infective endocarditis (SBE) should be asked about invasive procedures that may be causing bacteremia. Most causes are due to *S. viridans* related to dental procedures.
- Symptoms of are subtle and non-specific.
- SBE is suggestive by a history of a slowly progressive process characterized by:
  - Fever (low grade), rigors and night sweats
  - Fatigue/malaise
  - Anorexia
  - Back pain
  - Weight loss

Key diagnostic features of infective endocarditis: Murmur + fever

- Less common developments are a cerebrovascular accident or congestive heart failure.
- When appropriate therapy is delayed for weeks or months, additional clinical features, embolic or immunological in origin develop
- Common physical findings:
  - Fever: low grade. 3-15% of patients may have normal or subnormal temperature.
  - Murmurs: seen in 99% of cases. The absence of a murmur should cause clinicians to reconsider the diagnosis of IE. The major exception is right-

sided infective endocarditis in which only 1/3 of cases have detectable murmur.

- Peripheral stigmata suggestive of SBE (rare now because of introduction of antibiotics)
  - Petechiae: most common peripheral lesion. Seen in palpebral conjunctivae, the dorsa of the hands and feet, the anterior chest, abdominal walls, oral mucosa and soft palate.
  - Splinter hemorrhages (Subungual hemorrhages): these are linear and red lesions that do not extend for the entire length of the nail
  - Finger and toe clubbing: especially in patients with extended course of untreated infective endocarditis.
  - Janeway lesions: painless ('Gentle') plantar/palmer lesions
  - Osler's nodes: painful ('Ouch') infarcts in distal phalanges of fingers/toes
  - Arthritis: asymmetrical and limited to 1-3 joints
  - Splenomegaly

- Embolic manifestations: causes infarcts and abscesses most commonly affecting brain (stoke), lung and spleen.
  - Acute meningitis with sterile spinal fluid
  - Hemiplegia due to embolization in distribution of the middle cerebral artery
  - Unilateral blindness caused by occlusion of a retinal artery
  - Myocardial infarction resulting from embolization to a coronary artery
  - Splenic infarction
  - Renal regional infarcts producing pain
- Immunological manifestations: this is due to immune complex disposition and vasculitis. It is suggestive of SBE:
  - Petechiae and splinter hemorrhages: commonest signs
  - Janeway lesions
  - Osler's nodes
  - Roth spots: retinal hemorrhages with pale centers
  - Glomerulonephritis
  - Presence of rheumatoid factor

ACUTE INFECTIVE ENDOCARDITIS

- History of antecedent procedures or illicit drug use must be investigated
- Aggressive disease.
- Onset of illness is abrupt with rapidly progressive destruction of the infected valve.
- The valve leaflets are destroyed rapidly by bacteria that multiply very fast within the ever-growing friable vegetations.
- Clinical symptoms of acute IE result from either embolic or intracardiac suppurative complications.
- There is an acute onset of high grade fever and chills and rapid onset of congestive heart failure.
- Complications develop within a week and they include
  - Dyspnea and fatigue of severe congestive heart failure
  - Neuropsychiatric complications from CNS involvement
  - Roth spots
  - Murmurs: most commonly murmur of aortic regurgitation. Because of rapid onset, the left ventricle does not have a chance to dilate. In this situation the classic findings of increased pulse pressure that are seen in chronic AR are absent.
  - Janeway lesions
  - Acute septic monoarticular arthritis
  - Purulent meningitis

RIGHT-SIDED INFECTIVE ENDOCARDITIS

- Is associated with a very low rate of congestive heart failure and valvular perforation.
- Pulmonary infarcts may result from emboli of right-sided infective endocarditis.

INVESTIGATIONS

- Blood cultures: gold standard for diagnosis for documentation of a continuous bacteremia (>30 min in duration)
  - Draw 3-5 different sets from at least 3 different sites before starting antibiotics over 6 hours if subacute
  - Draw 3 sets from different sites before stating antibiotics over 1 hour 30 minutes if acute.
  - There is a 90% sensitivity

- Echocardiography: Transthoracic echo then transesophageal echo if negative (Transesopheal echo mores sensitive at detecting IE)
- Electrocardiography: increased PR interval. Monitor this to decide whether surgery is required.
- CXR: cardiomegaly
- Bloods:
  - FBC: normocytic anemia, increased neutrophils
  - Increased ESR/CRP
  - Rheumatoid factor may be positive (due to IE itself or RA)

DIAGNOSIS: DUKE CRITERIA

- Diagnosis requires any 2 of:
  - 2 major
  - 1 major plus 3 minor
  - 5 major
- Major:
  - Positive blood culture for typical microorganisms that cause IF from 2 separate blood cultures or persistent.
  - Positive Echocardiogram:
    - Definitive vegetation (oscillating intracardiac mass on valve or supporting structure)
    - Abscess
    - New partial dehiscence of prosthetic valve
    - New valvular regurgitation (increase or change in pre-existing murmur not sufficient)
- Minor:
  - Predisposition: predisposing heart condition or IV drug abuse
  - Fever greater than 38.0^{o}C
  - Embolic phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
  - Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
  - Microbiologic evidence: positive blood culture not meeting major criterion (e.g. 1 positive culture)
  - Echocardiogram: consistent with IF but not meeting major criterion (i.e. positive echo for other abnormality)

MANAGEMENT

- Admit and treat as inpatient to allow monitoring of the development of complications and the response to the antibiotic therapy.
- General measures:
  - No special diet however if CCF develops then sodium restriction may be necessary.
  - Limitation of activity is determined by the severity of illness, complications (e.g. stroke) and the presence of significant CCF.
- Medical therapy:
  - Aimed at:
    - Eradicating the infectious agent from the thrombus
    - Treating the complications of valvular infection
  - Intravenous antibiotics
    - Treat for 4-6 weeks including at least 2 weeks IV initially.
    - SBE:
      - Crystalline penicillin 3-4 million IU IV every 4 hours for 4-6 weeks' plus
      - Gentamicin 1mg/kg (80mg) IV TDS for 2 weeks' plus
    - Prosthetic valve endocarditis:
      - Vancomycin 1g IV BD for 6 weeks' plus
      - Gentamicin 1mg/kg (80mg) IV TDS for 2 weeks' plus
      - Rifampicin 300mg PO/TDS for 6 weeks
    - Acute IF where S. aureus is suspected e.g. hospital acquire infection
      - Flucloxacillin if native valve add rifampicin 300mg PO TDS 2 weeks and gentamicin 1mg/kg (80mg) IV TD for 2 weeks if prosthetic valve.
  - Treating complications
    - Mild CHF resulting from valvular insufficiency or myocarditis may be managed with standard medical therapy for CHF.
    - Although thrombosis is a key element of infective endocarditis, anticoagulation with heparin or Warfarin is controversial and it should be avoided
- Surgery (needed in 15-25% of patients with IE)
  - Debridement, repair or replacement may be required.
  - Indications
    - Acute AR with sever heart failure

- Fungal endocarditis
- Refractory Heart failure
- Persistent sepsis or emboli despite adequate antibiotic therapy
- Poor response to antibiotics
- Mobile vegetation >10mm in size
- Prosthetic valve dysfunction associated with CHF
- Valve ring abscess near a prosthetic valve

PREVENTION

- Prophylactic antibiotics for high-risk dental procedure in patients at risk of IE e.g. prosthetic valve is controversial some recommend for it while others don't.

MYOCARDITIS

- Myocarditis is inflammation of the myocardium often resulting from infectious process, which subsequently leads to myocardial destruction and a dilated cardiomyopathy.
- The acute picture is nonspecific unless overt congestive heart failure develops.

ETIOLOGY

- Infectious:
  - Viral infections: Coxsackievirus B, HIV myocarditis (overt involvement is seen in 10 % of HIV patients)
  - Bacterial myocarditis: Not common usually occurs as a complication of infective endocarditis. Diphtheric myocarditis may develop in ¼ of patients with diphtheria
  - Fungal myocarditis
  - Protozoal myocarditis: Chagas disease caused by a protozoon *Trypanosoma cruzi* and transmitted by an insect vector. It is one of the most common causes of heart disease in Central and South America.
  - Rickettsial myocarditis: associated with Typhus, Lyme disease
  - Spirocheatal myocarditis: associated with Relapsing fever.
- Non-infectious:
  - Hypersensitivity and toxic reactions to:
    - Drugs: Doxorubicin (anti- neoplastic agent)
    - Radiation
  - Giant cell myocarditis: is a rare form of myocarditis of unknown etiology

PATHOPHYSIOLOGY

- Myocarditis is defined as inflammatory changes in the heart muscle.
- It characterized by an interstitial mononuclear cell infiltrate with an attendant myocyte necrosis.
- It is not known whether the infiltrate is caused by a direct invasion of the infective agents or by a systemic immune response.
- In the chronic stage, cytotoxic T lymphocytes infiltrate the myocardium and mediate an autoimmune response with myocardial autoantibody activity directed against cardiac myosin. This autoimmune process persists after the viral particles are no longer detected.
- Coronary artery thrombus formation, luminal obstruction, ischemia, and

dysrhythmias compound the deleterious effects of the inflammatory response.

CLINICAL FEATURES

- Variable presentation.
- Patients may present with a nonspecific illness characterized by fatigue, mild dyspnea, or fulminant congestive heart failure (CHF).
- Myocarditis may even cause sudden death in some patients.
- Majority of cases of myocarditis are subclinical.
- An antecedent viral syndrome has been documented in 60% of patients with myocarditis.
- The typical time interval between the onset of the viral illness and cardiac involvement is 2 weeks.
- Fever is present in 20% of cases. Fatigue, myalgia and, malaise are common symptoms
- Chest pain or chest discomfort is reported in 35% of cases.
  - The chest pain is often pleuritic quality with precordial pain of a sharp stabbing nature. Sometimes it may be substernal and squeezing, more typical of ischemic pain.
- Dyspnea on exertion is common and orthopnea and shortness of breath at rest may be noted if CHF is present.
- Palpitations are common.
- Syncope signals development of AV block or malignant dysrhythmias and may lead to sudden death in patients with myocarditis.
- Physical examination:
  - Patients with mild cases of myocarditis have a nontoxic appearance and simply may appear to have a viral syndrome.
  - Tachypnea and tachycardia are common. Tachycardia is often out of proportion to fever.
  - More acutely ill patients have signs of left ventricular failure including:
    - Raised JVP, bilateral basal crepitations on the chest, ascites and peripheral edema.
    - S3 gallop may be noted with significant cardiac enlargement (displaced apical impulse).
    - S1 is soft or muffled.
    - Cyanosis may be noticed.

- Hypotension caused by left ventricular dysfunction is uncommon in the acute setting. A poor prognosis is indicated when hypotension is present.
- Cardiogenic shock is observed in fulminant cases and has a high mortality.
- Murmurs of mitral or tricuspid regurgitation may be present due to ventricular dilation.

➢ In cases where a dilated cardiomyopathy has developed, signs of peripheral or pulmonary thromboembolism may be found.

➢ Associated pericarditis may manifest with a pericardial friction rub. Pericardial effusion is common, but signs of tamponade (e.g., hypotension, jugular venous distention, muffled heart sounds) are rare. Pleural friction rub might be heard because Pleuritis can occur with cases of acute myocarditis.

DIAGNOSIS AND INVESTIGATIONS

- Since many cases of myocarditis are not clinically obvious, a high degree of suspicion is required for the making a diagnosis of acute myocarditis.
- Erythrocyte sedimentation rate (ESR) is elevated in 60% of patients with acute myocarditis.
- Leukocytosis is present in 25% of cases.
- Chest x-ray: often reveals a normal cardiac silhouette, but pericarditis or overt clinical CHF may be associated with cardiomegaly. Vascular redistribution, interstitial and alveolar edema and pleural effusion may also be noticed.
- Echocardiography: Dilated chambers and reduced ejection fraction indicating left ventricular systolic dysfunction.
- ECG: Sinus tachycardia is the most frequent finding. ST-segment elevation without reciprocal depression, particularly when diffuse, is helpful in differentiating myocarditis from acute myocardial infarction

MANAGEMENT

- Patients with mild symptoms and no signs of cardiac failure or dysrhythmia may be treated on an outpatient basis.
- The medical treatment of myocarditis is directed towards amelioration of associated complications including CHF and cardiogenic shock, arrhythmias, and thromboembolism.
- Left ventricular dysfunction with signs of CHF should be treated with;
  - ➢ Low sodium diet

- Limitation or avoidance of exercise as exercise may have deleterious effect.
- Diuretics
- Digoxin: should be given with caution as patients with myocarditis are sensitive for digitalis toxicities.
- ACE inhibitors and vasodilators
- In general, sympathomimetic and beta-blocker drugs should be avoided because they increase the extent of myocardial necrosis and mortality.

- Arrhythmias:
  - Detection of dysrhythmia with inpatient cardiac monitoring.
  - Medical therapy for arrhythmias
  - Implantation of cardiac pacemakers.
- Avoiding risk of thromboembolism:
  - Anticoagulants such as Warfarin or Heparin may be given.
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in the early course of disease because of inhibition of prostaglandin production, worsened myocyte function, and increased myocardial necrosis.

PERICARDITIS AND PERICARDIAL EFFUSION

- Pericarditis is an inflammation of the pericardium surrounding the heart.
- Pericarditis is most commonly due to secondary causes. Primary pericarditis is almost invariably due to viral infection.
- Pericarditis is one cause of fluid accumulation in the potential space and cardiac tamponade is the hemodynamic result of fluid accumulation

PATHOPHYSIOLOGY

- The pericardium consists of an outer fibrous layer (parietal pericardium) and an inner serious layer (visceral pericardium). Normally the 2 layers are separated by a small quantity of fluid (15-50ml).
- The pericardium serves as a protective barrier from the spread of infection or inflammation from adjacent structures. It also prevents sudden dilation of the cardiac chambers during exercise and hypervolemia. It restricts the anatomic position of the heart and minimizes friction with the surrounding structures.
- Approximately 120ml of additional fluid can accumulate in the pericardium without an increase in pressure.
- Further fluid accumulation can result in marked increases in pericardial pressure, eliciting decreased cardiac output and hypotension (Cardiac tamponade). The rapidity of fluid accumulation influences the hemodynamic effect.

CLASSIFICATION

- Pericarditis can be classified according to:
  - Etiological classification
  - Clinical classification

ETIOLOGICAL CLASSIFICATION

- Infectious pericarditis
  - Viral: Coxsackie, Herpesviridae (CMV, EBV, HSV), Flu, mumps, HIV
  - Pyogenic: *Staphylococcus aureus*, *Streptococcus*, *Haemophilus*
  - Tuberculous (this is common in HIV positive patients)
  - Fungal
- Non-infectious pericarditis
  - Uremia
  - Acute myocardial infarction and post MI (Dressler's syndrome)
  - Neoplasm
  - Drugs: procainamide, hydralazine

  - Hypothyroidism
  - Idiopathic
- Hypersensitivity/autoimmune
  - Rheumatic fever
  - Rheumatoid arthritis
  - SLE
  - Sarcoidosis
  - Posttraumatic

CLINICAL CLASSIFICATION

- Acute pericarditis (<6 weeks)
  - Effusive (serous or sanguineous)
    - Serous pericarditis is associated with SLE, rheumatic fever, Scleroderma, uremia, tumors and a variety of viral infections. It is characterized by production of clear, straw-colored, protein-rich exudate containing small numbers of inflammatory cells.
  - Fibrinous or serofibrinous pericarditis: is characterized by a fibrin-rich exudate. It may be caused by uremia, myocardial infarction, radiation to chest (e.g. in the treatment of breast cancer and mediastinal tumor) or acute rheumatic fever.
  - Purulent or suppurative pericarditis is characterized by grossly cloudy or frankly purulent inflammatory exudate. It is almost always caused by bacterial infection
  - Hemorrhagic pericarditis is characterized by a bloody inflammatory exudate. It usually results from tumor invasion of the pericardium, but can also result from TB or other bacterial infection.
- Subacute pericarditis (6 weeks to 6 months)
  - Effusive-constrictive
  - Constrictive
- Chronic pericarditis (over 6 months)
  - Constrictive
  - Effusive
  - Adhesive (non-constrictive)

CLINICAL FEATURES

- Retrosternal or precordial chest pain which is described as sharp or stabbing.

  - Pain may be sudden or gradual onset and may radiate to the back (left trapezial ridge), neck, left shoulder or arm
  - Movement or inspiration may aggravate the pain
  - Pain may be most severe when the patient is supine and can be relieved when the patient leans forward while sitting.
- Associated symptoms:
  - Low grade intermittent fever
  - Dyspnea
  - Cough
  - Dysphagia
- In TB pericarditis: fever, night sweats and weight loss are commonly seen (80%)
- Some patients may present with acute abdominal pain.
- Cardiac tamponade:
  - May present with anxiety, dyspnea, orthopnea, fatigue or altered mental status.
  - History of medical illness associated with pericardial disease e.g. end stage renal disease.
  - Traumatic tamponade may present with acute dyspnea or altered mental status.
  - A waxing and waning clinical picture may be present in intermittently decompressing tamponade
- Physical findings
  - Pericarditis:
    - Pericardial friction rub (classic sign of acute pericarditis): this is scratchy, leathery sound heard during both systole and diastole. It is best heard at the lower sternal border or apex when the patient is positioned sitting forward. Friction rub may be distinguished from a cardiac murmur by its changing character from heartbeat to heartbeat and patient position changes. A friction rub is closer to the ear on auscultation than a murmur.
    - Fever: usually low grade but it can reach 39°C
    - Tachypnea and dyspnea. Dyspnea may be severe with myocarditis, pericarditis and tamponade.
    - Ewart signs: Dullness and bronchial breathing between the tip of the left scapula and the vertebral column.
    - Hepatomegaly and ascites may be found
    - Cardiac arrhythmias: premature atrial and ventricular contractions occasionally are present

- Cardiac tamponade:
  - As volume of pericardial fluid increases the capacity of the atria and ventricles to fil is mechanically compromised, leading to reduce stroke volume and tamponade. It is influenced by volume and rate of accumulation.
  - Beck triad:
    - Jugular venous distention: increased JVP
    - Hypotension
    - Muffled heart sounds
  - Neck vein distension is a common finding but Kussmaul's sign is absent.
  - Hypotension to the extent of shock: may occur when the cardiac stroke volume is significantly reduced and tissue perfusion is compromised.
  - Pulses paradoxus: abnormal fall in blood pressure by more than 10mmHg during inspiration
  - Narrow pulse pressure: indicates reduced left ventricular stroke volume
  - Cyanosis
  - Varying degrees of altered consciousness

INVESTIGATIONS

- Blood investigations:
  - Full blood count with differential
  - ESR: elevated
  - HIV testing
  - Antinuclear antibody (ANA)
  - Rheumatoid factor
- Imaging:
  - Chest X-ray
    - Bottle-shaped heart can be seen with excessive pericardial fluid accumulation.
    - In cardiac tamponade (or large effusions), the chest X-ray may demonstrate an enlarged cardiac silhouette after 200-250ml of fluid accumulation. This occurs in patients with slow fluid accumulation compared to a normal cardiac silhouette seen in patients with rapid accumulation and tamponade. Thus the chronicity of the effusion may be suggested by the presence of a huge cardiac silhouette.
  - ECHO: minimal pericardial effusion in pericarditis and significant pericardial effusion in chronic pericarditis or cardiac tamponade.

- ECG
  - Acute pericarditis: diffuse ST segment elevation with reciprocal depression and depression of PR segment is unique to acute pericarditis in 80% of viral pericarditis.
  - Cardiac tamponade or massive effusion: electrical alternans is pathognomic of cardiac tamponade and is characterized by alternating levels of ECG voltage of the P wave, QRS complex and T wave. This is a result of the heart swinging in a large effusion. Low voltage of ECG.

TREATMENT

- Acute pericarditis:
  - Treatment of pain and inflammation
    - NSAIDs: ASA, indomethacin and ibuprofen are effective in reducing the inflammation and reliving the chest pain
    - Steroid therapy: intractable cases of pericarditis that fail to respond to NSAID.
  - Specific therapy should be directed towards the cause of pericarditis. E.g. patients with TB pericarditis should be treated with anti TB along with steroids.
- Cardiac tamponade: Patients with evidence of cardiac tamponade need emergency Pericardiocentesis i.e. removal of fluid from pericardial sac.
- Prognosis largely depends upon the etiology of the pericardial infection or inflammation as well as the presence of a pericardial effusion and/or tamponade.

COMPLICATIONS

- Recurrence (15-32%)
- Cardiac tamponade
- Chronic constrictive pericarditis
- Cardiac perforation at time of Pericardiocentesis
- Bronchopericardial fistula: this was noted as complication of MDR TB in a patient with HIV

SHOCK AND HYPOTENSION

- Hypotension is a state of low blood pressure with systolic blood pressure (SBP) <90mmHg or mean arterial pressure <65.
  - In relative hypotension the SBP is >30mmHg below baseline
- Shock is a state of cardiovascular failure resulting in impaired tissue perfusion and disturbed cellular metabolism and function as a result of decreased oxygen supply.
- Clinically shock can be defined as a 20% sudden blood loss or shift from peripheral circulation.
- Adequate blood flow to tissues depends on:
  - Blood volume
  - Myocardial contractility
  - Peripheral resistance
- Any disturbance in the above 3 can lead to shock.
  - Pump failure leads to cardiogenic or obstructive failure
  - Peripheral circulatory failure leads to hypovolemic (decreased blood volume) or distributive shock (decreased peripheral resistance).

CLASSIFICATION OF SHOCK

- Shock can be classified into:
  - Hypovolemic (Oligemic) shock: due to diminished blood volume (loss of fluid/blood- hemorrhagic shock)
  - Cardiogenic shock: due to inefficient myocardial function (decreased cardiac contractility)
  - Distributive shock: due to peripheral blood pooling. Can either be
    - Septic shock: due to systemic infection
    - Neurogenic shock: due to peripheral vasodilation, reduced peripheral resistance and peripheral pooling of blood.
    - Anaphylactic shock: due to antigen-antibody reaction that also leads to peripheral pooling of blood e.g. injection of anti-tetanic serum
    - Endocrinal shock: due to acute severe hormonal imbalance e.g. in adrenal insufficiency or pituitary failure. It may present with a combination of any of the above types.
  - Obstructive shock: due to decreased blood flow to the left ventricle as in cardiac tamponade, pulmonary embolism, and tension pneumothorax.
- **Patients may have more than 1 type of shock e.g. hypovolemic and septic**.

PATHOPHYSOLOGY

- This includes cellular changes, microcirculatory changes, acid-base imbalances and systemic changes.
- Cellular changes:
  - Tissue hypo-perfusion resulting in a decrease in oxygen delivery to the tissue and cells undergo anaerobic metabolism producing lactic acid (causing metabolic acidosis).
  - This continues until cellular glucose is depleted resulting in stoppage of cell metabolism release of auto-digestive enzymes and rupture of plasma and lysosomal membranes.
- Microcirculatory changes:
  - Under the effect of catecholamines the precapillary sphincters constrict, less blood enters the capillaries and the capillary circulation becomes sluggish.
  - Untreated hypovolemia thus leads to hypoxia.
  - Under normal conditions only one third of the capillary bed is open at a time.
  - Under ischemic conditions however the body reacts by opening more capillaries this results in:
    - Further slowing of the capillary circulation, the so called slugging of blood.
    - Slugging encourages spontaneous coagulation of blood in these capillaries.
    - If extensive, it is called disseminated intravascular coagulation (DIC).
    - This depletes coagulation factors and induces bleeding in the rest of the body (consumption coagulopathy)
  - A sluggish circulation and DIC compound tissue hypoxia and affect the function of capillary endothelium. The result of the latter is leakage of large protein molecules from the vessels into interstitial space dragging with them huge amounts of fluid. This third space loss of fluid reduces blood volume.
- Acid-base imbalance: Shock is accompanied by metabolic acidosis which is caused by accumulation of lactic acid as a result of anaerobic metabolism and renal failure as a result of prolonged ischemia, aggravates acidosis.
- Systemic changes:
  - Sympathetic response: release of catecholamines & stress hormones (Cortisol, glucagon), release of ADH and activation of renin-angiotensin-aldosterone system.

- Cardiovascular: reduced coronary artery perfusion and direct depression of myocardium by tumor necrosis factor
- Respiratory: metabolic acidosis results in tachypnea which causes carbon dioxide washout and compensatory respiratory alkalosis. Leakage and swelling can develop in the lungs, causing difficulty in breathing (respiratory distress- ARDS)
- GIT: mucosal hypoperfusion causes mucosa death and stress ulcers. Mucosal death may also result in bacterial translocation, septicemia and multi-organ failure.
- Liver: ischemic hepatic dysfunction
- Renal: renal hypoperfusion decreases GFR, urine output and may lead to pre-renal failure and acute tubular necrosis.
- Ischemic perfusion syndrome:
  - It is due to systemic hypoperfusion, tissue hypoxia and local activation of inflammatory mediators.
  - Further injury occurs once normal circulation is restored to tissues:
    - Myocardial depression
    - Cellular and humoral elements activated by hypoxia are flushed back into circulation causing more endothelial injury e.g. acute lung injury, acute renal injury
  - It only can be minimized by decreasing the period of hypoperfusion.

STAGES OF SHOCK

- Initial: decreased oxygen and increased lactate.
- Compensatory stage:
  - Increased respiratory rate
  - Sympathetic response: increased heart rate, fluid retention
  - Increased renin and ADH secretion
- Progressive/decompensated stage: If compensatory mechanisms and treatment are unsuccessful.
  - Worsening hypotension due to vasodilation, blood pooling in capillaries, and fluid leak from vessels.
  - Altered mental status
  - Electrolyte imbalances
- Refractory: irreversible

GENERAL CLINICAL FEATURES OF SHOCK

- Change in mental status: a continuum from agitation, confusion/delirium, obtundation/coma.
- Hypotension: absolute (systolic blood pressure <90mmHg) or relative (a drop in systolic blood pressure >40mmHg), which is why a patient may be in shock with a high or normal blood pressure.
- Increased heart rate, pulse may be thread (barely perceptible). Capillary refill >2s
- Oliguria (<30ml/hr)- from shunting of renal flow to other vital organs, intravascular volume depletion or both.
- Cool, clammy skin- compensatory peripheral vasoconstriction redirects blood from the peripheral to the vital organs (heart, brain, splanchnic). However, in early distributive shock or terminal shock the skin may be flushed or hyperemic due to failure of compensatory vasoconstriction.
- Metabolic acidosis- increased lactate production from anaerobic respiration when shock progresses to circulatory failure and tissue hypoxia along with decreased clearance of lactate by the liver, kidneys and skeletal muscle.

APPROACH TO THE PATIENT WITH SHOCK

HISTORY

- Look for underlying causes, try to classify the type of shock. Often limited due to confusion or obtundation.
- Ask for any history of:
  - Bleeding? Trauma? Hematemesis? Hematochezia? Melena? (if so suspect hypovolemic shock)
  - Coronary artery disease? Valvular heart disease? CCF? (if so suspect cardiogenic shock)
  - History of fever? Pneumonia? Meningitis? (if so suspect septic shock)

EXAMINATION

- General examination: ill appearing, confused, lethargic, unresponsive and temperature >38ºC or <36ºC.
- Neurologic: meningism and focal neurologic deficits
- Cardiac: Tachycardic (HR> 100), hypotensive (SBP <100), Dizziness, Orthostatic hypotension, S3 heart sound, murmur, Extremities may be warm/well perfused or cold/blue, Capillary refill brisk or slow, Chest pain
- Pulmonary: Evidence of pneumonia, use of accessory muscles of respirations, Respiratory rate >30, Oxygen saturation <95%.

- Gastrointestinal: Abdominal pain, Tense/Rigid abdomen (may indicate perforated viscus, hemorrhage, peritonitis), rebound tenderness, guarding, melena or blood on rectal exam.
- Renal: Flank tenderness (pyelonephritis), Urine output <0.5ml/kg/hr or <30ml/h

INVESTIGATIONS

- Blood investigations:
  - Urea and electrolytes (Sodium, potassium, chloride and bicarbonate) + Creatinine
  - Liver enzymes
  - Serum glucose
  - Full blood count (leukocytes and bandemia in sepsis)
  - Clotting profile: Bleeding time, Prothrombin time and activated partial thromboplastin time to rule out bleeding tendencies
  - Blood culture
  - Cardiac enzymes
  - Arterial blood gas/lactate (if available)
- Imaging:
  - Chest and abdominal X-ray
  - ECG
  - Echocardiogram
  - Ultrasound- Focused assessment with sonography for trauma (FAST)
- Septic work up: CXR, blood culture, sputum microscopy culture and sensitivity, urine dipstick, microscopy, culture and sensitivity, lumbar puncture.

MANAGEMENT

- Management depends entirely on the type of shock.
- Shock is always an emergency and must be treated rapidly as it is life threatening.
- Treat the underlying cause
- Management includes:
  - Frequent monitoring of vital signs
  - 2 large bore IV cannulas- 18 gauge (green) or greater.
  - Foley catheter and monitoring of urine output.
  - Aggressive colloid (normal saline or ringers lactate) fluid resuscitation for hypotension- especially in hypovolemic + septic shock (may require >10 L)
  - Intubation if in respiratory distress
  - Packed red cells if bleeding/hypovolemic

- Stop any antihypertensive or diuretics. Give pressors (dopamine, dobutamine, epinephrine, neosynephrine etc.) if shock is present despite aggressive fluid resuscitation.
- Hypovolemic shock:
  - IV fluids
  - Check electrolytes
  - Fix underlying condition e.g. diabetic ketoacidosis
  - Send for X-match for urgent transfusion if hemorrhage (most common cause of hypovolemic shock)
- Cardiogenic shock:
  - IV fluids may be harmful
  - IV Lasix and or dopamine may help
  - Fix underlying cause e.g. valve replacement
- Septic shock:
  - Search for source and start empiric antibiotics based on likely type of infection.
  - Give IV fluids
- Anaphylactic shock:
  - IV fluids
  - Subcutaneous epinephrine 0.3ml 1: 1000 solution if severe
  - Antihistamines and corticosteroids may help
- Adrenal insufficiency: give hydrocortisone 100mg TDS x 5/7
- Obstructive shock
  - IV fluids
  - Urgent ECG
  - CXR to confirm
  - Thrombolysis for Pulmonary embolism
  - Chest tube for tension pneumothorax
  - Pericardiocentesis for tamponade.

HYPOVOLEMIC SHOCK

ETIOLOGY

- This is due to diminished blood volume as a result of:
  - Whole blood loss i.e. hemorrhage which can be traumatic or pathological
    - Trauma
    - Ruptured abdominal aortic aneurysm
    - Aortic dissection
    - Upper GI bleeding
    - Ruptured ectopic pregnancy
  - Plasma loss as in burns, heat exhaustion or peritonitis
  - Water and electrolyte loss (especially Sodium) as in: severe vomiting, diarrhea, intestinal obstruction and fluid sequestration (as in acute pancreatitis).

STAGES

- Compensated stage: in this stage the body employs the physiological mechanisms, in a trial to restore blood volume or at least, preserve the normal function of the vital organs (brain, kidneys, heart and lung). With loss of >15% of blood volume, the compensatory mechanisms usually fail.
- Decompensated stage (40% blood loss): if the cause of shock is not treated successfully and after failure of compensatory mechanisms there will be progressive poor perfusion and micro-circulatory changes with deterioration of functions of the brain, kidney, heart and lung.
- Refractory stage: The shock can no longer be reversed. Failure of vital organs and death occurs imminently.

CLINICAL FEATURES

- Of shock
  - Symptoms:
    - Weakness and fainting
    - The patient feels cold and thirsty
  - Signs:
    - Patient is cold and clammy with a narrow pulse pressure
    - Decrease in blood pressure: SBP<90 or 60 below normal
    - Orthostatic hypotension can be an early sign of hypovolemia.
    - Capillary refill>2s
    - Oliguria: <30ml/hr

  - Altered mental status (may vary from anxious to drowsy but the patient usually remains alert).
  - Hypotension, tachycardia (increased heart rate, pulse may be thread-barely perceptible) and decreased pulse pressure (thready pulse)

- Of the cause
  - Sites of bleeding
  - Signs of internal hemorrhage
  - Burns
  - Intestinal obstruction
  - In hemorrhagic shock, trauma or signs of GI bleeding (melena, abdominal pain)
- Of complications:
  - Anuria
  - Acute respiratory depress syndrome

INVESTIGATIONS

- Blood investigations:
  - Full blood count (check Hemoglobin, hematocrit)
  - Cross match (for blood transfusion) as well as group and save
  - Urea and electrolytes (Sodium, potassium, chloride and bicarbonate) + creatinine
  - Clotting profile: Bleeding time, Prothrombin time and activated partial thromboplastin time to rule out bleeding tendencies
  - Liver function tests
  - Serum glucose
  - Arterial blood gasses: lactate >2 suggests hypoperfusion
- Imaging:
  - Chest X-ray and ECG: to exclude cardiogenic causes
  - Abdominal ultrasound: to rule out internal hemorrhage
  - Head CT scan: if the patient with head injury or unconscious

MANAGEMENT

RESUSCITATION

- ABCs
  - Airway should be patent by: Pulling the tongue forward, aspiration of secretions, and tracheostomy if needed

- Breathing should be maintained by: oxygen mask and ambu bag. Administer oxygen.
- Circulation:
  - 2 large bore IV cannula 18G (green) or bigger: one for IV fluids and the other for sampling (if no veins available/all collapsed)
  - Stop any external bleeding by compression.
- Drugs: analgesics for any pain

- Insert an NGT to evacuate the stomach (if surgery may be needed)
- Insert a urinary catheter to monitor urine output
- Elevate legs and head down to restore cerebral blood flow (Trendelenburg's position)
- Give sufficient warmth (but avoid over warmth)

Recall:

60% of the body is fluid. It is distributed in 3 compartments:

- 2/3 is intracellular fluid
- 1/3 is extracellular fluid
  - ¾ (75%) of ECF is in the interstitium
  - ¼ (25%) of ECF is in the intravascular compartment

FLUID ADMINISTRATION

- Crystalloids: may be the only fluid given to patients with hypovolemia caused by loss of water and electrolytes.
  - Normal saline: to replenish equivalent loss of both water and electrolytes.
  - Ringer: gives potassium supply (after ensuring good urine output) in prolonged shock
  - Lactated Ringer's solution: also a buffer, in prolonged shock and acidosis
  - Note: Glucose 5% is not used in shock because glucose is rapidly redistributed this leads to an increase in the amount of ECF (without electrolytes) causing dilutional hyponatremia and increased ICF with brain edema and increased intracranial pressure.
- Fluid therapy:
  - Resuscitation:
    - 500ml crystalloid bolus over <15minutes. 250ml if old or heart failure.
    - Reassess and re-give up to 2L
    - Don't wait until SBP is under 90. A SBP of 110 in the presence of increased heart rate suggests impaired output.
  - Replacement:
    - Estimate fluid losses, and replace gradually over 2-3 days i.e. in addition to maintenance fluids.
  - Maintenance:
    - Basic needs:

        - 25-30ml/kg/day water. 20-25ml/kg/day if old, kidney or heart failure or malnourished. So just over 1ml/kg/hr
        - 1mmol/kg/day of sodium, potassium and chloride. In general, don't give >10mmol/hr
        - 50-100g/day of glucose.
    - Management:
        - Usually need around 2-3 liters per day so around 100ml/hr is typical e.g. 1L over 8-10 hours. 500ml over 8 hours if old or heart failure.
        - 1L of normal saline contains 154mmol of both sodium and chloride and 1 L of Hartmann's solution contains 131 mmol of sodium and 111mmol of chloride (plus 5 mmol of potassium). So 500ml of each roughly covers daily needs.
        - Typical daily regimen may be 1L 5% dextrose with 20mmol potassium, then 500ml normal saline with 20mmol potassium, then 1L 5% dextrose with 20 mmol potassium.
        - Monitor potassium to determine needs
        - Monitor increase in chloride daily if on normal saline due to risk of increased chloride ions.
- Colloids: contain large insoluble molecules increasing oncotic pressure and in theory keeping the fluid in the intravascular compartment longer. In clinical trials, however, colloids have shown no benefit (and sometimes harm) relative to crystalloids.
    - Plasma substitutes: needs matching and adequate storage
    - Dextran (polysaccharide polymers): high molecular and low molecular weight
- Blood and blood products:
    - Red blood cells
        - Indications:
            - Decreased Hb (Hb<7g/dl)
            - Hb <8g/dl in patients with ACS
            - Major hemorrhage (given in combination with FFP and platelets)
        - 1 unit of blood increases Hb by 1g/dl
        - 1 unit of whole blood is around 450ml while 1 unit of packed cells is 250-300ml.
        - Prescribe 1 unit at a time, checking response (symptoms and/or Hb) after each.
        - If unused must return to fridge within 30 minutes for reuse.

- RBCs typically given over 2-3 hours but can be up to 4 hours most other products are given over 30 minutes.
- Assess patient at baseline, 15 minutes and at the end of transfusion.

➢ Fresh frozen plasma (FFP)
- Human plasma which contains clotting factors (II, V, VIII, IX, X, XI and antithrombin III)
- Indications
  - Major hemorrhage
  - Warfarin reversal (INR>1.5)
- Cryoprecipitate is another alternative to FFP, though less used now. It is the precipitate from human plasma, and contains fibrinogen, factor VIII (8), vWF and factor XIII (13)

➢ Platelets
- Indications:
  - Platelet <50K/µL and bleeding
  - Platelet <20 K/µL and septic
  - Platelet <10 K/µL
  - Stop any anti-platelets if giving

Transfusion reaction	Signs	Management
Mild	• <2ºC rise in temperature • Rash/Urticaria	• Pause transfusion and assess patient • Consider paracetamol or chlorphenamine • Re-start transfusion with close observation
Severe	• >2ºC rise in temperature • Rigors • Loin or back pain • Anxiety or angor animi • Unexpected increased heart rate • Infusion site pain	• Stop transfusion and replace any fluid needs with saline • Call hematology, contact lab to return product, and complete incident report

- Transfusion associated circulatory overload (TACO):

➢ Commonest cause of transfusion-associated death

  - Presents with 6 hours of transfusion with acute respiratory distress, pulmonary edema, increased heart rate and increased BP.
  - Risk factors: age <3 or >60, low birth weight, heart failure, kidney failure
  - Blood products are prescribed in mls in neonates to reduce TACO
- Transfusion-related acute lung injury (TRALI)
  - Very uncommon
  - Respiratory distress, decreased BP
  - Usually due to FFP or platelets
- Other complications:
  - Anaphylaxis
  - Hemolytic anemia
  - Increased potassium
  - Infection

MONITORING

- Monitor:
  - Pulse and ECG
  - Blood pressure
  - Temperature
  - Urine output (optimum urinary output= 0.5-1ml/kg/hr)
  - Arterial blood gasses (normal PO_2=80-100mmHg, normal PCO_2= 35-45mmHg)

DRUGS

- Drugs that increase BP by increasing cardiac contractility (inotropes) and/or vasoconstriction (vasopressors). Many also increase heart rate (positive chronotropy).
- Indicated in shock for which IV fluids are insufficient or inappropriate.
- Delivery is typically as an infusion through a central line.
- Many commonly used agents are synthetic versions of endogenous catecholamines

Drug	Mechanism of action	Dosage	Side-effect
Noradrenaline (norepinephrine) First line agent for shock in many ICUs	Vasopressor via alpha 1 agonism but also inotropy via Beta 1 agonism at higher doses. Reflex bradycardia from increased BP typically cancels out chronotropic effect.	0.05-1.0mcg/kg/min	Peripheral administration carries a risk of extravasation and hence tissue necrosis via vasoconstriction. However short term delivery via a large, proximal peripheral line is sometimes acceptable. Ischemia especially to the GIT, kidney and extremities Atrial and ventricular arrhythmias
Adrenaline (epinephrine) Most commonly used for anaphylaxis and cardiac arrest	Acts on all adrenergic receptors. At lower doses works primarily on beta 1 (inotropy and chronotropy) and beta 2 (airway and vessel dilation) and alpha 1 (vasoconstriction) at higher doses (including cardiac arrest dose)	0.05-1.0mcg/kg/min	
Dobutamine Used in acute heart failure	Inodilator with inotropy via beta 1 agonism and vasodilation via beta 2.	Dobutamine 5-10 microgram/kg/min IV infusion	
Dopamine	DA agonist at lower doses, alpha and beta effects at higher doses	Give dopamine 5-10 micrograms/kg/min IV infusion (dilute 400mg in 500ml of 5% dextrose infusion rate to be calculated according to body weight) • Start 5mcg/kg/min, titrate to effects.	Risk of Tachyarrhythmias Evidence suggests that dopamine inhibits secretion of prolactin and could increase lymphocytes apoptosis (impairment of immune response to sepsis)

TREAMENT OF CAUSE AND COMPLICATIONS

- Treat the underlying cause.

CARDIOGENIC SHOCK

- This is due to inadequate blood flow to vital organs due to inadequate cardiac output despite of normal blood volume.
- It is characterized by
  - SBP <90mmHg
  - Mean arterial pressure drop >30mmHg
  - Urine output <0.5ml/kg/hr
  - Heart rate >60bpm

ETIOLOGY

- Primary pump failure due to:
  - MI (commonest cause) or its complications e.g. ventricular septal rupture
  - Severe arrhythmias
  - Massive pulmonary embolism
  - Cardiac tamponade
  - Myocarditis
  - Severe valve disease
  - Trauma
  - High spinal anesthesia

CLINICAL FEATURES

- Of shock:
  - Clinical picture similar to hypovolemic shock.
  - Comatose
  - Patient is cold and clammy and pulse pressure may be narrow
  - Peripheral cyanosis
  - Poor urine output
  - Increased JVP and decreased heart rate
- Of the cause: enlarged liver, chest pain, pulsus alternans, 'gallop' rhythm, murmur, basal crackle, pulmonary edema.

INVESTIGATIONS

- Blood investigations:
  - Full blood count (check Hemoglobin, hematocrit)
  - Cross match (for blood transfusion) as well as group and save
  - Urea and electrolytes (Sodium, potassium, chloride and bicarbonate) + creatinine

  - Clotting profile: Bleeding time, Prothrombin time and activated partial thromboplastin time to rule out bleeding tendencies
  - Liver function tests
  - Serum glucose
  - Arterial blood gasses: lactate >2 suggests hypoperfusion
- Imaging:
  - Cardiorespiratory: ECG, CXR (enlarged heart, pulmonary venous congestion) and echo
  - Abdominal ultrasound: to rule out internal hemorrhage
  - Head CT scan: if the patient with head injury or unconscious

MANAGEMENT

- Management aims at:
  - Improving cardiac output:
    - Correct dysrhythmias
    - Optimize preload
    - Improve contractility
    - Reduce afterload
  - Minimizing cardiac work:
    - Maintain normal temperature
    - Sedation
    - Intubation and mechanical ventilation
    - Correct anemia
- ICU care
- Give oxygen
- Regular monitoring of temperature, heart rate, blood pressure and cardiac monitoring.
- Give dopamine 5-10 micrograms/kg/min IV infusion (dilute 400mg in 500ml of 5% dextrose infusion rate to be calculated according to body weight)
  - Start 5mcg/kg/min, titrate to effects.
  - Evidence suggests that dopamine inhibits secretion of prolactin and could increase lymphocytes apoptosis (impairment of immune response to sepsis).
- Dobutamine 5-10 microgram/kg/min IV infusion
- Prophylactic anticoagulation with ASA 75mg PO OD.
- Treat underlying cause
- If in heart failure and BP goes above 90mmHg treat as class IV.

- Captopril 25mg BD/TDS or Lisinopril 10-20mg OD or Enalapril 5-20mg OD (if patient develops dry cough Losartan 50mg OD)
- Furosemide IV 40-80mg OD or BD (monitor potassium levels)
- Digoxin 0.125mg-0.25mg daily
- Isosorbide dinitrate 5-10mg BD + hydralazine 25-50mg BD orally if patient cannot tolerate ACEi.
- Spironolactone 25-50mg OD or BD
- ASA 75mg OD

DISTRIBUTIVE SHOCK

- Vasodilation leads to a relative (though not absolute) deficiency in volume.

SEPTIC SHOCK (ENDOTOXIC SHOCK)

- Septic shock is a type of distributive shock though it may also include an element of hypovolemic shock as altered capillary permeability leads to volume loss from the vasculature.
- It is the most serious type of shock and the most difficult to treat.

ETIOLOGY

- Gram negative bacilli (commonest cause)
- *Staphylococci*
- *Candida*

PREDISPOSING FACTORS (IMMUNOSUPPRESION)

- Extremes of age
- Malignancy
- Malnutrition
- Diabetes mellitus
- Chemotherapy, corticosteroids or immunosuppressants
- HIV infection

PATHOPHYSIOLOGY

- Bacterial endotoxins are released when immune cells (i.e. macrophages) kill gram negative bacteria.
- Immune cells release cytokine, TNF and IL-2 which damage capillary endothelium leading to edema and vasodilation (rapid shifting of blood bypassing capillary) and tissue ischemia.

- Septic shock starts as maldistribution of blood followed by myocardial depression and hypovolemia.

CLINICAL FEATURES

- Hyper-dynamic (warm) septic shock (early phase): diagnosis is difficult and high index of suspicion is required to detect it at early stage.
  - Restless and confusion
  - Skin: flushed, warm and dry
  - Vitals:
    - Fever >38ºC + Chills
    - Mild decreased in arterial blood pressure, pulse pressure may be wide with a low DBP.
    - Tachycardia
    - Tachypnea
  - High cardiac output
- Hypo-dynamic "cold" septic shock (Late phase): picture similar to hypovolemic shock with reduced cardiac output
  - Skin: cold and clammy
  - Vitals:
    - SBP<90mmHg
    - Tachycardia
    - Tachypnea
  - Oliguria
  - Multi-organ failure starts at this stage.

DIAGNOSIS

- To diagnose septic shock, the following 2 criteria must be met
  - Evidence of infection, through a positive blood culture
  - Refractory hypotension (Despite adequate fluid resuscitation and cardiac output)
- In addition to the 2 criteria above 2 or more of the following must be met (SIRS)
  - RR >20bpm (high respiratory rate)
  - WBC <4000 cells/mm^3 or > 12 000 cells/mm^3
  - Temperature >38ºC or <36ºC
  - HR>90b/min
  - Arterial blood gasses $PaCO_2$ <32mmHg

MANAGEMENT

- Give oxygen
- Give fluids:
  - Ringer's lactate + Plasma
  - If low hematocrit packed RBCs or whole blood transfusion
- Drugs
  - Inotropes and vasopressors: dopamine and dobutamine
  - Give if patient remains hypotensive despite adequate fluid replacement.
  - Give dopamine 5-10 micrograms/kg/min IV infusion (dilute 400mg in 500ml of 5% dextrose infusion rate to be calculated according to body weight)
    - Start 5mcg/kg/min, titrate to effects.
    - Evidence suggests that dopamine inhibits secretion of prolactin and could increase lymphocytes apoptosis (impairment of immune response to sepsis).
  - Dobutamine 5-10 microgram/kg/min IV infusion
- Antibiotics: parenteral combined broad-spectrum started early without waiting for culture and sensitivity results (3rd generation cephalosporin e.g. ceftriaxone + Aminoglycoside e.g. gentamicin + Metronidazole) then changed to culture and sensitivity.
- Monitor vitals and urine output regularly.
- ASA 75mg OD for DVT prophylaxis
- Proton pump inhibitors to prevent stress ulcers.
- Use of corticosteroids in septic shock remains controversial.

CHAPTER 5: HEMATOLOGY

HEMATOLOGICAL CONDITIONS

- Blood is a connective tissue in fluid form.
- It consists of:
  - Plasma: plasma proteins, water, electrolytes, complement system and coagulation factors.
  - Formed elements: red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes/megakaryocytes).
- Plasma is the liquid component of blood which contains soluble fibrinogen. Serum is what remains after the formation of the fibrin clot.
- In adults red blood cells, many white blood cells and platelets are formed in the red marrow of the bone marrow.
- In the fetus, blood cells are formed in the mesoderm cells of the yolk sac (in the first trimester), the liver and spleen (in the second trimester) and the bone marrow (in the third trimester).
- Synthesis of blood cells outside the bone marrow is termed extra-medullary hematopoiesis.
- The bone marrow of essentially all the bones produces blood cells until the age of 5 and then afterwards only the axial skeleton (vertebrae, sternum, pelvis, ribs, cranial bones) and the proximal ends of the limb retain hemopoeitic function.

INTEPRETATION OF A HEMOGRAM

- The 8 parameter cell counter will give the following:

- WBC count: white blood cell count
- RBC count: red blood cell count
- Hb: Hemoglobin
- Hct: Hematocrit / Packed cell volume (PCV)
- MCV: Mean cell volume
- MCH: Mean cell hemoglobin
- MCHC: Mean cell hemoglobin concentration
- RDWt: red blood cell distribution width

- In addition to these above parameters the 18 parameter cell counter also has
  - White blood cell Differentials:
    - Neutrophils count and percentage
    - Lymphocyte count and percentage
    - Monocytes count and percentage
    - Eosinophil count and percentage
    - Basophils count and percentage
  - Pct: Plateletcrit

WHITE BLOOD CELL COUNT

- This is the number of white blood cells in 1 cubic mm of whole blood.
- The normal value is 4.0-11.0 million cells per microliter ($10^6/\mu L$).
- A rise in this number (lymphocytosis) may indicate an infection
- A decrease in this number (leukopenia) may indicate bone marrow failure.
- On its own is not a useful parameter.
- The differential count is more specific:
  - Neutrophils= 3-6 ($10^9/L$)
  - Lymphocytes= 1.5- 4 ($10^9/L$)
  - Monocytes= 0.3-0.6 ($10^9/L$)
  - Eosinophils= 0.15-0.30 ($10^9/L$)
  - Basophils= 0-0.1 ($10^9/L$)

RED BLOOD CELL COUNT

- This is the number of erythrocytes in 1 cubic mm of whole blood.
- The normal values include:

  - Men= 4.5-6.0 million cells per microliter (10^6/μL)
  - Women= 3.9-5.0 million cells per microliter (10^6/μL)
- RBC count will be low with iron deficiency, blood loss, hemolysis and bone marrow suppression
- RBC count increases when one moves to a higher altitude or after prolonged physical exercise and can also reflect the body's attempt to compensate hypoxia (such as is seen in the obese and smokers)
  - It increases with erythrocytotic states such as polycythemia vera, eyrthrocytosis of chronic hypoxia, dehydration, stress polycythemia and thalassemia minor.

HEMOGLOBIN

- Normal hemoglobin values:
  - Men= 13.5-17.5 g/dl
  - Women= 11.5- 16.0 g/dl
- In anemia there is a decrease of hemoglobin.
- In polycythemia there is an increase of hemoglobin.

HEMATOCRIT/ PACKED CELL VOLUME (PCV)

- Normal PCV
  - Men= 0.4-0.54 L/L (45-54%)
  - Women= 0.37-0.47 L/L (37-47%)
- Normal value of PCV is 45% but in females it is slightly lower due to their reduced RBC count.
- PCV is increased in polycythemia and severe dehydration.
- It is reduced in anemia.

BLOOD INDICES

MEAN CELL VOLUME (MCV)

- Indicates the average volume of a single RBC.
- It is expressed in cubic microns.
- The normal value is 80-96 fL
- An alteration of MCV helps in identification of microcytic, normocytic and macrocytic anemia.

MEAN CELL HEMOGLOBIN (MCH)

- This gives an idea about the average hemoglobin content in a single red cell.
- Normal range varies between 27 and 32 pico grams.

MEAN CELL HEMOGLOBIN CONCENTRATION

- It indicates the relative percentage of hemoglobin in the red cell.
- This is the most important absolute value in the diagnosis of anemia.
- Its normal value is 32.0-36.0 mg/L.
- When MCHC is normal the RBC is normochromic.
- When MCHC decreases the RBC is known as hypochromic.
- A single RBC cannot be hyperchromic because the amount of hemoglobin cannot increase beyond normal.

RED BLOOD CELL DISTRIBUTION WIDTH (RDW)

- This shows the variation in red cell size. This is calculated by dividing the standard deviation of the red cell width by the mean cell width x 100. An elevated RDW suggests variation in red cell size (anisocytosis)
- The normal value is 11-15%.
- In sickle cell anemia, and iron deficiency there is increased RDW.
- In beta-thalassemia trait, the RDW is usually normal.

PLATELETS

- The normal platelet count is 150-400 (10^9/L).
- Platelet increase (thrombocytosis) and decrease (thrombocytopenia) is seen in different pathological states.

THROMBOCYTOPENIA	THROMBOCYTOSIS
• Decrease in platelet count below 150 000/cu mm of blood • Occurs in: ➢ Acute infections ➢ Acute leukemia ➢ Aplastic and pernicious anemia ➢ Chicken pox and smallpox ➢ Splenomegaly	• Increase in platelet count over 450 000/cu mm of blood • Occurs in ➢ Allergic conditions ➢ Asphyxia ➢ Hemorrhage ➢ Bone fractures ➢ Surgical operations

➢ Scarlet fever ➢ Typhoid fever ➢ Tuberculosis ➢ Purpura ➢ Gaucher's disease	➢ Splenectomy ➢ Rheumatic fever ➢ Trauma (wound or injury or damage caused by external damage) ➢ Parturition

RED BLOOD CELL DISORDERS: ANEMIA

- Erythropoiesis is the process which produces red blood cells (erythrocytes).
- We make approximately 10^{12} new red cells each day.
- The process of erythropoiesis is stimulated by hypoxia (a decrease in oxygen partial pressure) which is detected by the kidneys, which then secretes the hormone erythropoietin (EPO). EPO stimulates the proliferation, differentiation and release of red cell precursors into erythrocytes. 90% of EPO is produced in the peritubular interstitial cells of the kidney and 10% in the liver and elsewhere.
- All blood cells are derived from pluripotent stem cells. These stems cells have 2 properties- the first is self-renewal, i.e. the production of more stem cells and the second is its proliferation and differentiation into progenitor cells, committed to one specific cell line.
- In the process of red blood cell maturation, a cell undergoes a series of differentiations:
  - A pluripotent hematopoietic stem cell (hematocytoblast) becomes
  - A common myeloid progenitor cell and then
  - A unipotent stem cell, then
  - A pronormoblast also commonly called a proerythroblast or a rubriblast.
  - This becomes an early normoblast (basophilic normoblast) and then
  - An intermediate normoblast (polychromatophilic normoblast), then
  - A late normoblast (orthochromatic normoblast). At this stage the nucleus is expelled before the cell becomes

- A reticulocyte.

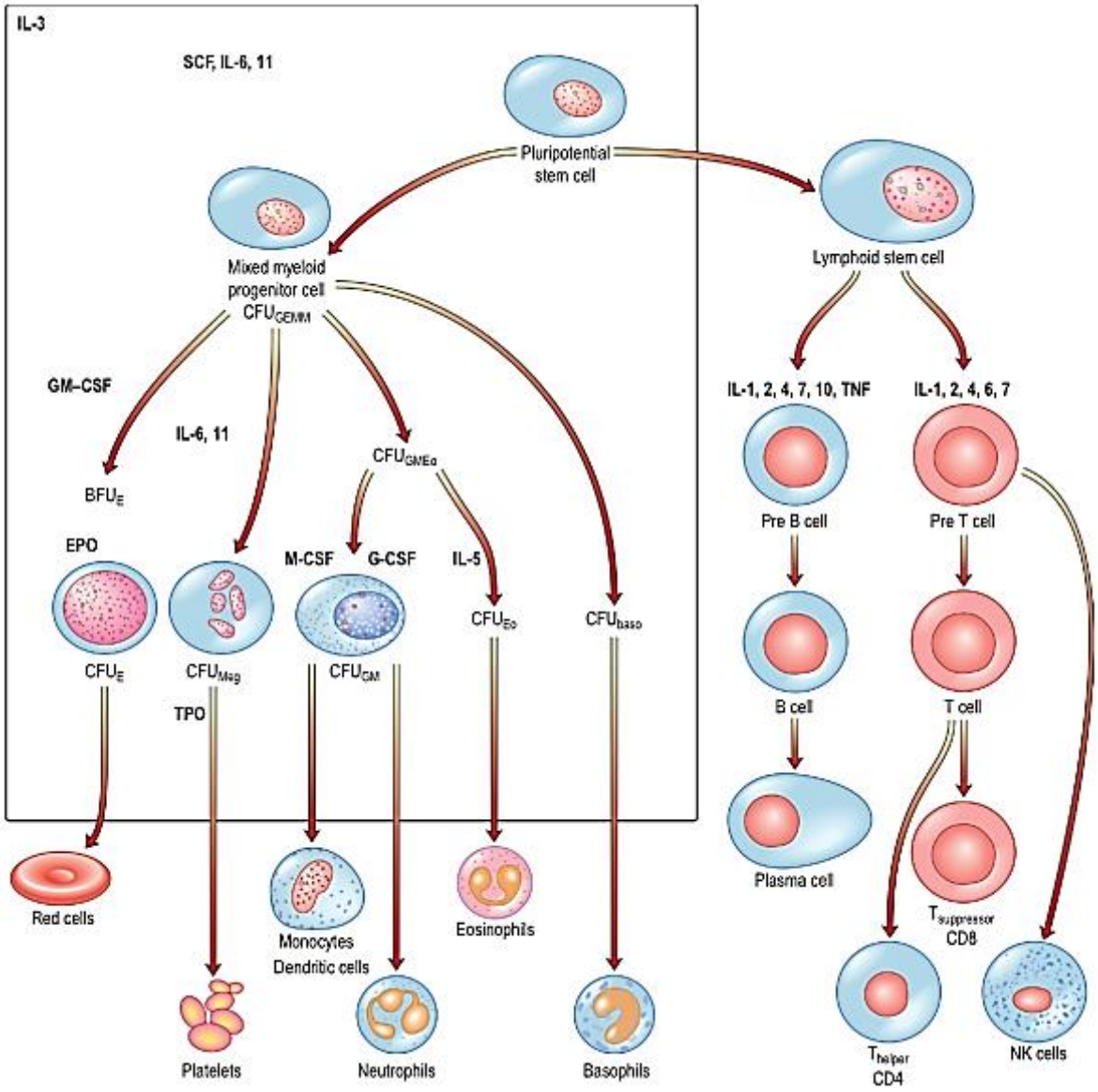


Figure 32: Hematopoiesis

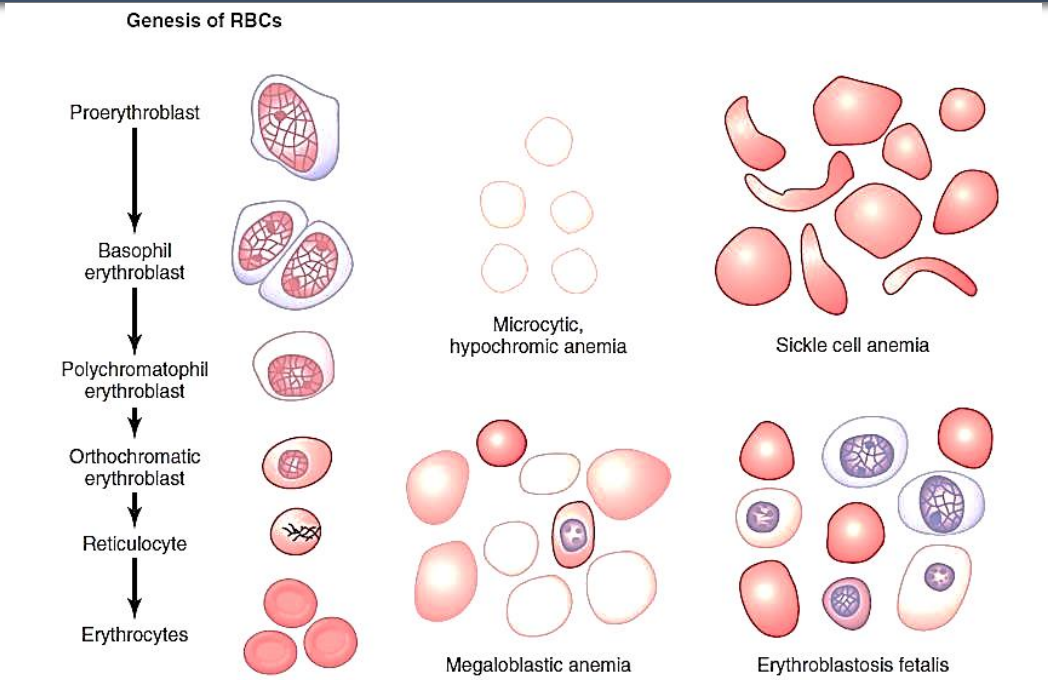


Figure 33: Genesis of normal RBCs and characteristics of RBCs in different types of anemia. Image adapted from Guyton and Hall Textbook of Medical Physiology

- Normoblasts progressively contain more hemoglobin (which stains pink) in the cytoplasm, the cytoplasm stains paler blue as it loses its RNA and protein synthetic apparatus while nuclear chromatin becomes more condensed.
- The nucleus is fully extruded from the late normoblast within the marrow and a reticulocyte stage results which still contains some ribosomal RNA and is still able to synthesize hemoglobin.
- A single pronormoblast usually gives rise to 16 mature red blood cells.
- The whole process of erythropoiesis takes 7 days.
- The stage from the pluripotent hematopoietic stem cell to reticulocyte takes roughly about 5 days. Reticulocytes are released into the circulation and they mature into erythrocytes in 1-2 days.
- Reticulocytes account for 1% of the red blood cells in the circulation.
- As erythrocytes are differentiating and maturing their size reduces and their color changes from basophilic to polychromatic to eosinophilic (orthochromatic) because of the appearance of hemoglobin and the loss of protein synthetic apparatuses.
- The process of erythropoiesis requires vitamin B12 (cobalamin), Vitamin B8 (folic acid) and iron.

- A feedback loop involving erythropoietin helps regulate the process of erythropoiesis so that in non-disease states, the production of red blood cells is equal to the destruction of red cells and the red cell number is sufficient to sustain adequate tissue oxygen levels but not so high as to cause sludging, thrombosis or stroke.
- Erythropoietin is bound by circulating red blood cells therefore low circulating numbers leads to a relatively high level of unbound EPO, which stimulates the production of RBCs in the bone marrow.
- Recent studies show that a peptide hormone called hepcidin may play a role in the regulation of hemoglobin production and thus erythropoiesis.
- The liver produces hepcidin.
- Hepcidin controls iron absorption in the GUT and iron release from the reticuloendothelial tissue.
- Hepcidin is implicated in the pathophysiology of anemia of chronic disease.
- Anemia is a disorder of the red blood cell. It is a significant reduction in red cell mass and a corresponding decrease in the oxygen carrying capacity of the blood.
- Anemia is present when there is a decreased level of hemoglobin in the blood below the reference level for the age, sex and pregnancy state of the individual.
  - In women of child bearing age, their blood values are 10% lower than men. Therefore, anemia may be defined as HCT of less than 10% below the mean values for age, sex and altitude.

TABLE: CRITERIA OF ANEMIA IN ADULTS AT SEA LEVEL

Factor	Women	Men
RBC x 10^{12}/L	< 4.0	<4.5
Hgb (g/dl)	<12	<14
Hct (%)	<37	<40

- Note:
  - From the age 2 years to puberty, Hb less than 11g/dl indicates anemia
  - As newborn infants have a high hemoglobin (Hb), 14g/dl is taken as the lower limit at birth.
  - Alterations in total circulating plasma volume as well as of total circulating hemoglobin mass determine the hemoglobin concentration.
  - Reduction in plasma volume (as in dehydration) may mask anemia or even cause (apparent, pseudo) polycythemia conversely an increase in plasma

volume (as with splenomegaly or pregnancy) may cause anemia even with a normal total circulating red cell and hemoglobin mass.

- After acute major blood loss, anemia is not immediately apparent because the total blood volume is reduced. It takes up to a day for the plasma volume to be replaced and so for the degree of anemia to become apparent. Regeneration of hemoglobin takes substantially longer.
- The initial clinical features of major blood loss are therefore a result of reduction in blood volume rather than anemia.

- Anemia is a manifestation of an underlying pathological condition; it results from:
  - Under production
  - Increased destruction/ hemolysis
  - Blood loss/bleeding
  - Multifactorial: a combination of these

APPROACH TO ANEMIA

HISTORY

- Obtain a thorough history to help determine underlying cause.
  - Geographic location: parasites e.g. schistosomiasis

PRESENTING SYMPTOMS

- Depend on acuteness and severity of anemia. Also depend on the age of patient, presence of underlying disease.
- Symptoms can occur when anemia is chronic, most patients are asymptomatic.
- Non-specific symptoms include lightheadedness, dizziness, throbbing headache, syncope, tinnitus, fatigue, palpitations, chest pain (angina), exercise and cold intolerance, dyspnea, intermittent claudication (limping), ankle swelling and visual disturbances (due to retinal hemorrhages).
- Other symptoms include anorexia, indigestion, nausea, bowel irregularity (Due to shunting of blood from the splanchnic bed), irritability, difficult in concentration, worsened dementia, menstrual irregularities and impotence or decreased libido.

PAST MEDICAL, SURGICAL AND DRUG HISTORY

- History of similar illness
- Underlying disease
- Exposure to drugs/toxins e.g. methyldopa

FAMILY HISTORY

- Family history of anemia

OBSTETRIC AND GYNAE HISTORY

- Pregnancies (multiple pregnancies, grand Multiparity)
- Menstrual history: excessive menstrual bleeding, prolonged menses

NUTRITION HISTORY

- Diet: amount, quality and frequency

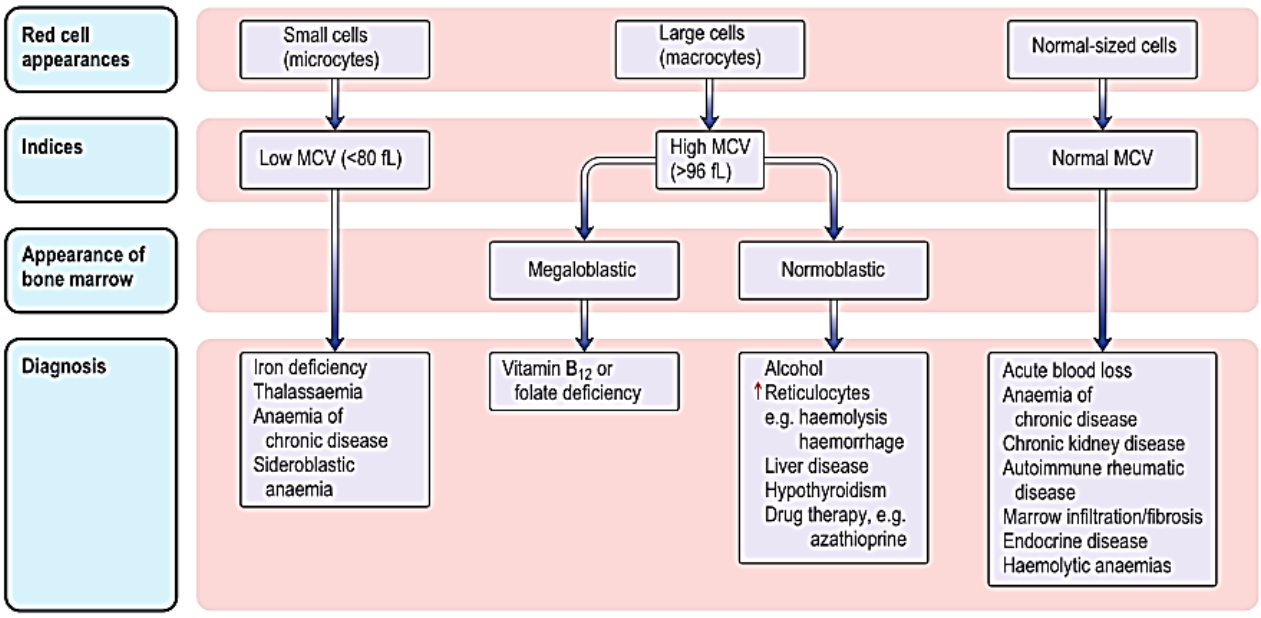
PHYSICAL EXAMINATION

- A comprehensive examination with emphasis to the following should be made.
- General: pallor of mucus membranes, bleeding sites, signs of Hyperdynamic circulation (tachycardia, bounding pulse, cardiomegaly and systolic flow murmur), heart failure (S3 gallops), orthostatic hypotension.
- Specific:
  - Iron deficiency: koilonychias (spoon shaped nails), angular stomatitis
  - Folate: glossitis
  - Vitamin B12: glossitis, neurologic abnormalities (peripheral neuropathy- pins and needles)
  - Hemolytic anemia: Jaundice
  - Thalassemia: bone deformities
  - Sickle cell disease: leg ulcers
  - Bleeding disorder: splenomegaly, petechiae/purpura

INVESTIGATIONS

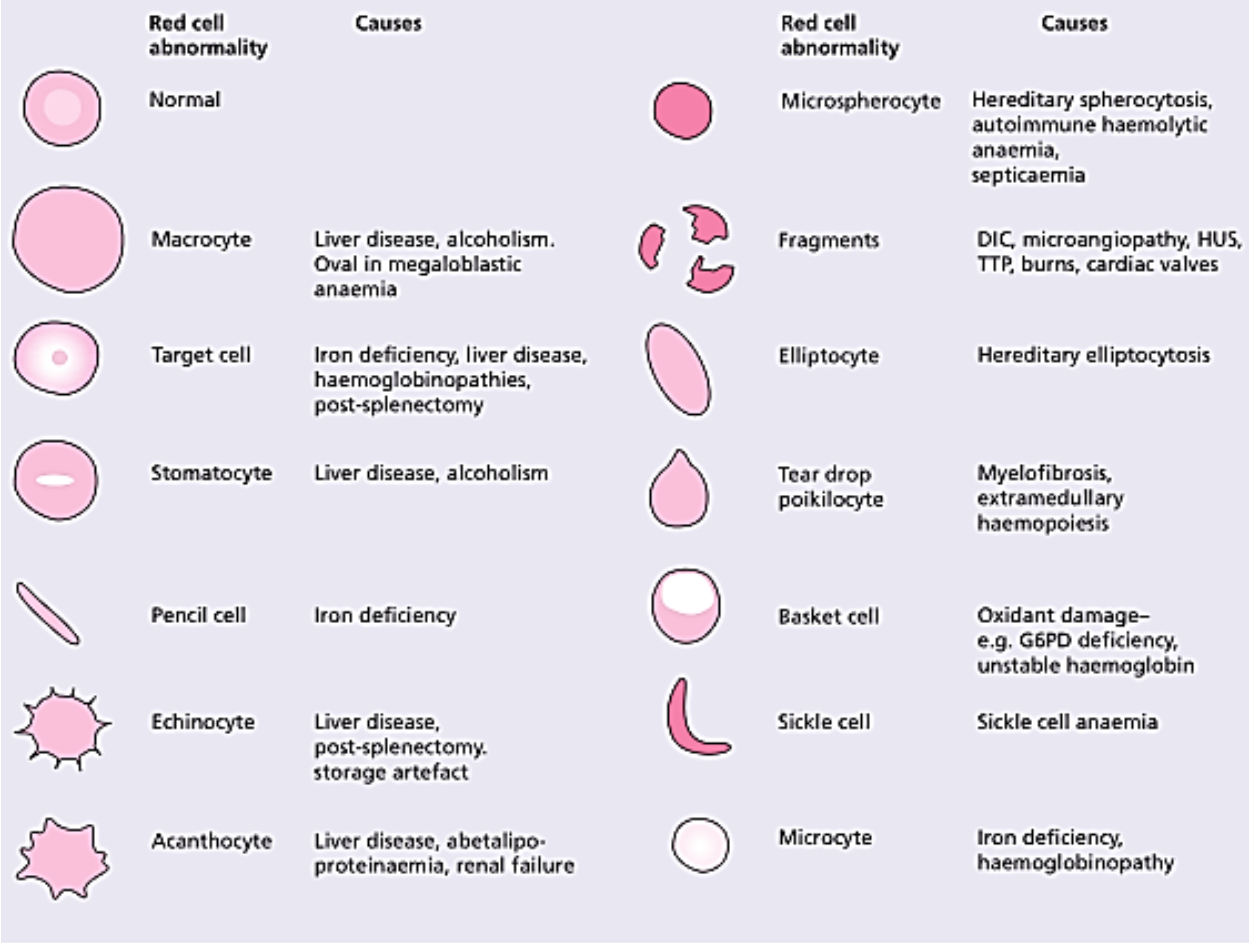
- Full blood count
  - Hb
  - RBC indices: MCV (normal 80-96 fL), MCH (27-32pg), MCHC (31-35), Hct- 32-36%
  - Platelet count
  - WBC differential
- Peripheral blood smear: RBC morphology
  - Normochromic normocytic: normal individual and in anemia of chronic disease
  - Anisopoikilocytes: variation in size and shape may be seen in iron deficiency anemia
  - Hypochromic microcytic anemia: iron deficiency, anemia of chronic disease, thalassemia and sideroblastic anemia (SBA)
  - Macrocytic RBC- Macro-ovalocytes with hypersegmented neutrophils indicate megaloblastic anemia and myelodysplasia
  - Schistocytes (fragmented RBC/ Helmenth cells)- microangiopathies, DIC, vasculitis, prosthetic heart valve

- Consider colonoscopy/endoscopy, urinalysis/urine cytology for hematuria, pelvic ultrasound for fibroids.



Classification of anaemia. MCV, mean corpuscular volume.

- NOTE: Anemia is not a diagnosis and a cause must be found.



Red cell abnormality	Causes	Red cell abnormality	Causes
Normal		Microspherocyte	Hereditary spherocytosis, autoimmune haemolytic anaemia, septicaemia
Macrocyte	Liver disease, alcoholism. Oval in megaloblastic anaemia	Fragments	DIC, microangiopathy, HUS, TTP, burns, cardiac valves
Target cell	Iron deficiency, liver disease, haemoglobinopathies, post-splenectomy	Elliptocyte	Hereditary elliptocytosis
Stomatocyte	Liver disease, alcoholism	Tear drop poikilocyte	Myelofibrosis, extramedullary haemopoiesis
Pencil cell	Iron deficiency	Basket cell	Oxidant damage– e.g. G6PD deficiency, unstable haemoglobin
Echinocyte	Liver disease, post-splenectomy. storage artefact	Sickle cell	Sickle cell anaemia
Acanthocyte	Liver disease, abetalipo-proteinaemia, renal failure	Microcyte	Iron deficiency, haemoglobinopathy

Figure 34: Some Red Cell Anomalies

- Anemia can be classified according to:
  - Etiology
  - Severity
  - Red cell size

CLASSIFICATION OF ETIOLOGIES

- Anemia can arise due to either:
  - Decreased production/ impaired RBC production
  - Increased destruction or blood loss

Decreased production	Increased destruction of loss
Nutritional deficiencies	Blood loss
• Iron deficiency* • Vitamin B12 deficiency • Folate deficiency*	• Acute or chronic GI bleeding* • Menstrual bleeding* • Trauma
Bone marrow suppression	Hemolysis
• Infections*: HIV, tuberculosis, malaria, schistosomiasis, hookworm, hepatitis • Drugs: isoniazid, chloramphenicol, alcohol, zidovudine, 5-Flucytosine, hydroxyurea • Chronic disease*: renal and liver disease, rheumatologic diseases, hypothyroidism	➢ Hereditary hemolytic anemia ♦ Hemoglobinopathies: sickle cell disease*, thalassemia ♦ Enzymopathies: G6PD deficiency*, Pyruvate kinase deficiency ♦ Membranopathies: hereditary spherocytosis, eliptocytosis ➢ Acquired ♦ Microangiopathic hemolytic anemia: TTP, HUS, DIC, eclampsia, HELLP syndrome ♦ Autoimmune hemolytic anemia ♦ Paroxysmal nocturnal hemoglobinuria ♦ Hypersplenism ♦ Infections: Malaria*
Hemoglobinopathies: Thalassemias Myelodysplastic syndromes	

* These are common causes of anemia in adults in Africa.

CLASSIFICATION OF ANEMIA ACCORDING TO SEVERITY

- Anemia is classified as follows:
  - Mild: 8-12g/dl hemoglobin
  - Moderate: 7-8g/dl hemoglobin
  - Severe: <6g/dl hemoglobin

CLASSIFICATION OF ANEMIA BY SIZE

- This classification gives a good indicator of the underlying etiology.
- Anemia can be divided into
  - Microcytic anemia: MCV< 80-96 fL
  - Normocytic anemia: MCV= 80-96 fL
  - Macrocytic anemia: MCV> 80-96 fL

MICROCYTIC ANEMIA

- Microcytic anemias are due to decreased production of hemoglobin (either due to iron, protoporphyrin, or the globin part)
  - RBC progenitor cells in the bone marrow are large and normally divide multiple times to produce smaller mature cells (MCV= 80 to 100 fL)
  - Microcytosis is due to an "extra" division which occurs to maintain hemoglobin concentration. (to keep the RBC "nice and pink").
- Microcytic anemia includes:
  1. Iron deficiency
  2. Anemia of chronic disease
  3. Sideroblastic anemia
  4. Thalassemia

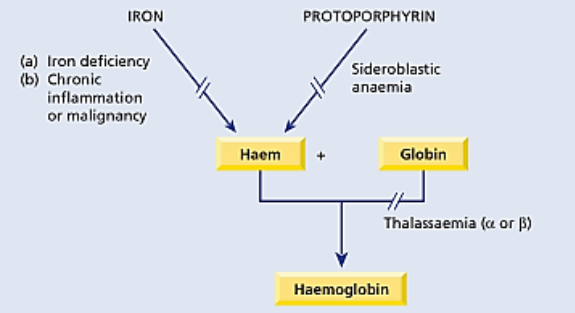


Figure 35: Causes of microcytic anemia

IRON DEFICIENCY ANEMIA

- This is the most common type of anemia worldwide.
- Iron deficiency anemia occurs when the body iron stores become inadequate for the need of normal RBC production.
- It is due to decreased levels of iron. Decreased iron leads to decreased heme and hemoglobin thus resulting in a microcytic anemia.
- Iron deficiency anemia is a manifestation of disease, not by itself a complete diagnosis (i.e. it is always secondary to something).

IRON METABOLISM

- Daily 10-30mg iron ingested, 5-10% absorbed to balance precisely

the amount lost (1 mg) under physiologic condition. Absorption may be increased to20-30% in iron deficiency and pregnancy.

- Amount absorbed can increase up to 5-fold if the body iron stores are depleted or erythropoiesis is accelerated.
- Iron is consumed in heme (meat-derived) and non-heme (vegetable-derived and cereals fortified with iron) forms.
  - Absorption of heme occurs in the duodenum while that of non-heme occurs in the proximal jejunum
  - Enterocytes have heme (Haem carrier protein 1-HCP1) and non-heme (divalent metal transporter 1- DMT1) transports. The heme form is more readily absorbed.
  - Absorption is facilitated by: stomach acidity (keeps iron in reduced ferrous state Fe^{2+} and not ferric state Fe^{3+}), Vitamin C (Ascorbic acid), Citrates.
  - Absorption is limited by: phosphates, oxalates, tannates (tea) and pyrates (plant food)
  - Enterocytes transport iron across the cell membrane into blood via ferroportin.
  - Transferrin transports iron in the blood and delivers it to liver and bone marrow macrophages for storage.
- Stored intracellular iron is bound to ferritin, which prevents iron from forming free radicals via the phenton reaction.
  - 2/3 is stored as ferritin and 1/3 as hemosiderin.
  - Ferritin is a water soluble complex of iron and protein. It is more easily mobilized than hemosiderin for Hb formation. It is present in small amounts in plasma.
  - Hemosiderin is an insoluble iron protein complex found in macrophages in the bone marrow, liver and spleen. Unlike ferritin it is visible by light microscopy in tissue sections and bone marrow films after staining by Perls' reaction

STAGES OF IRON DEFICIENCY ANEMIA

- Storage iron is depleted- decreased ferritin and increased total iron binding capacity.
- Serum iron is depleted- decreased serum iron and decreased iron saturation.
- Normocytic anemia- bone marrow makes fewer, but normal-sized RBCs (Iron deficient erythropoiesis).
- Microcytic, hypochromic- bone marrow makes smaller and fewer RBCs.

ETIOLOGY

- Poor diet:
  - Infants- breastfeeding (human milk is low in iron as such it is seen in infants where introduction of mixed feeding is delayed).
  - Children- poor diet.
  - Other causes: malnutrition, malabsorption (celiac disease) and gastrectomy (Acid aids iron absorption by maintaining the Fe^{2+} state which is more readily absorbed than Fe^{3+}).
- Chronic bleeding:
  - Adults (20-50 years)- peptic ulcer disease in males and menorrhagia or pregnancy in females.
  - GIT e.g. esophageal varices, hiatal hernia, peptic ulcer disease, aspirin ingestion, carcinoma of stomach, caecum, colon or rectum, Hook worm (*Ancyclostoma duodenale* and *Nector americanus*) and schistosomiasis infestation, colitis, piles, diverticulosis.
  - Rarely hematuria, hemoglobinuria, pulmonary hemosiderosis, self-inflicted blood loss.
- Increased demands:
  - Prematurity in newborns
  - Rapid growth (as in adolescent) growth spurt
  - Pregnancy
- Decreased absorption e.g. post-gastrectomy

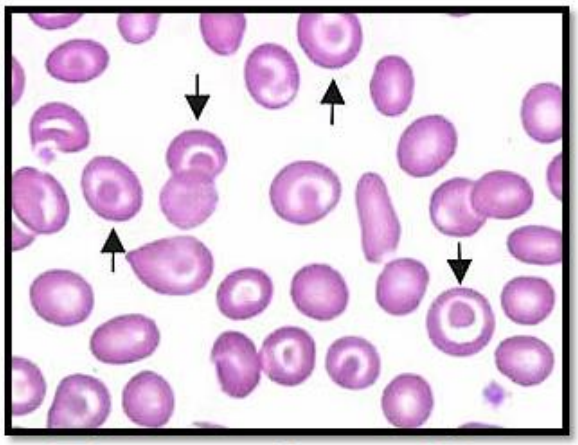
CLINICAL FEATURES

- Insidious onset and progressive in course.
- Patients often present with nonspecific symptoms (mentioned earlier on) along with/without some specific symptoms:
  - Pica: craving for unusual food substance (amylophagia, geophagia, pagophagia)
  - Brittle nails, Koilonychia, atrophy of papillae of tongue (atrophic glossitis), brittle hair.
  - Angular stomatitis
  - Plummer-Vinson syndrome- iron deficiency anemia with esophageal web (dysphagia) and atrophic glossitis, presents with anemia, dysphagia and a beefy red-tongue. It is also known as Paterson-Kelly syndrome.
- The diagnosis of iron deficiency anemia relies on a clinical history which should include questions about:
  - Dietary intake,
  - Self-medication with NSAIDs (GIT bleeding),
  - Presence of blood in feces (may be a sign of hemorrhoids or carcinoma of bowel)
  - In women a careful enquiry about the duration of periods,

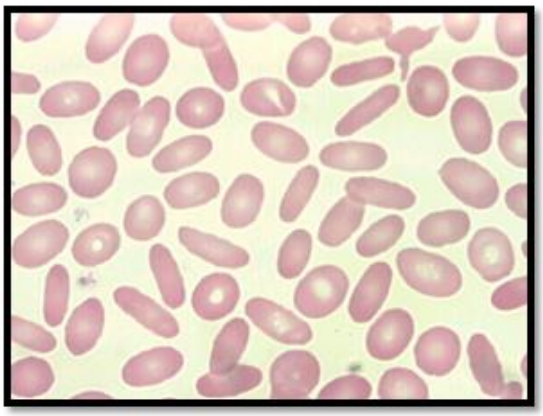
the occurrence of clots and the number of sanitary towels or tampons (normal 3-5/day) used should be made.

INVESTIGATIONS

- Full blood count:
  - Decreased MCV, MCH, MCHC, reticulocyte count
- Diagnosis: MCV< 80fL, blood smear shows hypochromic red cells, pencil shaped (Poikilocytosis), anisocytosis, target cells.



Target cells



Poikilocytosis

- Laboratory measurements of iron status:
  - Serum iron- measure of iron in the blood. (normal- 13-32 µmol/L)
  - Total iron binding capacity (TIBC)- measure of transferrin molecules in the blood. Each transferrin molecule binds 2 atoms of ferric iron.
  - % saturation- percentage of transferrin molecules that are bound by iron (normal is 33%)
  - Serum ferritin- reflects iron stores in macrophages and the liver.
- Laboratory findings:
  - Microcytic hypochromic RBCs with target cells and increased red cell distribution width (as above)
  - Decreased serum iron
  - Decreased ferritin
  - Increased total iron binding capacity
  - Decreased % saturation (<19%)
  - Increased free erythrocyte protoporphyrin (FEP): it is increased during early phase of iron deficiency, lead poisoning, sideroblastic anemia and in erythropoeitic porphyria.

- Investigations to establish the underlying cause:
  - Stool for occult blood
  - Stool for ova and parasites
  - CXR to exclude pulmonary hemosiderosis
  - U/A for hematuria or hemosiderinuria
  - Pelvic- gynecologic studies
  - Upper and lower GI radiologic and endoscopic studies
  - Bronchoscopy

MANAGEMENT

- Identify and treat underlying cause.
- Iron replacement: ferrous sulfate 200mg TDS (This gives 180mg ferrous iron).
  - Side effect: GI upset, nausea, dyspepsia, constipation/diarrhea. If these side effects are not tolerable, reduce dose or change brand e.g. to ferrous gluconate (300mg BD giving 70mg iron) or ferrous lactate syrup
- Response to treatment: an expected daily rise of hemoglobin by 0.1-0.2g/dl.
  - An increase in Hb concentration of at least 2gm/dl after 3 weeks of therapy is considered as a good response
  - Treatment should be continued for 3 months after resolution of anemia to replenish the iron stores.
  - Inadequate response may imply:
    - Continuing hemorrhage
    - Non-compliance
    - Wrong diagnosis
    - Mixed deficiency-associated folate or Vit B12 deficiency
    - Another cause for anemia e.g. malignancy, inflammation
    - Malabsorption-rare cause
    - Use of slow release preparations
- Parenteral iron:
  - Indications: oral iron intolerance despite modification in dosage regimen, malabsorption, inability or unwillingness to take orally.
  - Iron-dextran complex or iron sorbitol citrate can be used IM or IV
    - Dose (ml)= 0.0442 (desired Hb- Observed Hb) x weight (kg) + (0.26 x weight Kg)

ANEMIA OF CHRONIC DISEASE

- This is associated with chronic inflammation (e.g. endocarditis or autoimmune conditions) or malignant disease.
- It is the most common type of anemia in hospitalized patients.

- Etiologies:
  - Infectious: TB, lung abscess, osteomyelitis, pneumonia, bacterial endocarditis.
  - Non-infectious: rheumatoid arthritis, lupus, connective tissue disease, sarcoidosis, Crohn's disease, malignancy (carcinoma, lymphoma, sarcoma).

PATHOGENESIS

- Chronic disease results in production of acute phase reactants from the liver, including hepcidin.
  - Hepcidin sequesters iron in storage sites by (1) limiting iron transfer from macrophages to erythroid precursors and (2) suppressing erythropoietin (EPO) production.
  - The aim is to prevent bacteria from accessing iron, which is necessary for their survival.
  - Decreased availability of iron results in microcytic anemia.
- Other cytokines produced during inflammation reduce life span of RBC (80 days) rendering erythropoietin inadequate.

CLINICAL FEATURES

- Clinical features: normocytic anemia (Early stages) and microcytic anemia (Late stages)
- Laboratory findings:
  - Reduced serum iron and TIBC,
  - Normal or raised ferritin because of the inflammatory process,
  - Decreased % saturation and
  - Increased free erythrocyte protoporphyrin.

MANAGEMENT

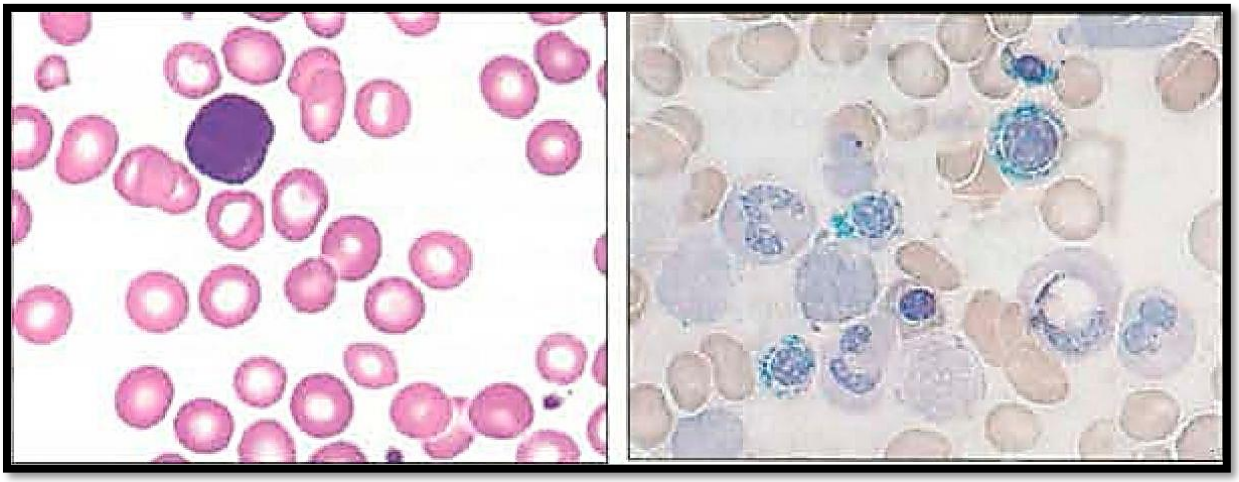
- Treatment is treat underlying cause,
- Exogenous recombinant EPO therapy is useful in a subset of patients especially those with cancer and anemia of renal disease as well as inflammatory disease (rheumatoid arthritis, inflammatory bowel disease).
- Correct reversible contributors (iron, folate, cobalamin supplements if necessary)

SIDEROBLASTIC ANEMIA

- Anemia due to defective protoporphyrin synthesis (heme synthesis).
- Decreased protoporphyrin leads to microcytic anemia.
- They can be inherited or acquired disorders.

SYNTHESIS OF PROPTOPORPHYRIN

- Protoporphyrin is synthesized via a series of reactions:
  - Aminolevulinic acid synthetase (ALAS) converts succinyl CoA to aminolevulinic acid. This is the rate limiting step and requires vitamin B6 as a co-factor.
  - Aminolevulinic acid dehydrogenase (ALAD) converts Aminolevulinic acid to porphobilinogen.
  - Additional reactions convert porphobilinogen to protoporphyrin.
  - Ferrochelatase attaches protoporphyrin to iron to make heme (final reaction occurs in the mitochondria).
- Iron is transferred to erythroid precursors and enters mitochondria to form heme. If protoporphyrin is deficient, iron remains trapped in mitochondria.
  - Iron-laden mitochondria form a ring around the nucleus of erythroid precursors, these cells are called ringed sideroblasts (hence the term sideroblastic anemia)- Stain used is Prussian blue (Pearls' reaction).



CLASSIFICATION

- Sideroblastic anemia can be classified as congenital or acquired
  - Congenital defect most commonly involves ALAS (rate-limiting enzyme)- sex linked recessive trait
  - Acquired causes include:
    - Primary: myelodysplasia (myelodysplastic syndromes),
    - Secondary
      - Malignant diseases of the marrow (myeloproliferative disorders, myeloid leukemia)
      - Drugs e.g. cycloserin, lead (inhibits ALAD and Ferrochelatase), alcohol (mitochondrial poison)
      - Vitamin B6 deficiency- required cofactor for ALAS, most commonly seen as a side effect of isoniazid treatment for tuberculosis.

LABORATORY FINDINGS

- Laboratory findings:
  - Increased ferritin
  - Decreased TIBC
  - Increased serum iron
  - Increased % saturation
  - A similar picture is seen in hemochromatosis (iron overload state)

MANAGEMENT

- Treat the underlying cause.
- Pyridoxine (100-400mg PO daily in divided doses), folic acid therapy (5mg PO daily): may bring some response
- Repeated transfusion is ultimate choice.

STATE	FERRITIN	TIBC	SERUM IRON	% SATURATION
Normal	30-300 µg/L (11.6-114nmol/L) in males, 15-200 µg/L (5.8-96 nmol/L)	300 pg/dl	13-31 µmol/L	33
Iron deficiency anemia	Low	High	Low	Low
Anemia of chronic disease	Normal or High	Low	Low	Low
Sideroblastic anemia	High	Normal	High	High

THALASSEMIA

- Heterogeneous group of genetic disorders (autosomal recessive) which results from a reduced rate of synthesis/dysfunction of alpha (coded for by 4 alleles on chromosome 16) or beta chains (coded for by 2 alleles on chromosome 11) of adult hemoglobin (HBA).
  - Alpha thalassemia: leads to impaired oxygen transport and extravascular hemolysis (splenic clearance).
  - Beta thalassemia: leads to failed erythropoiesis with the buildup of alpha chains causing cell destruction. Compensatory erythroid hyperplasia (increased immature RBCs) cases bone growth.
- Changes in normal ratio results in each of the disorders. Normally, there is balanced (1:1) production of alpha and beta chains. The defective synthesis of globin chains in thalassemia leads to 'imbalanced' globin chain production, leading to precipitation of globin chains with red cell precursors and resulting in ineffective erythropoiesis.
- Precipitation of globin chains in mature red cells leads to hemolysis.
- Due to inherited mutations carriers are protected against *Plasmodium falciparum* malaria.
- Thalassemias are divided into alpha and beta Thalassemias.
- Alpha Thalassemias are common in South-east Asia, Africa and India.

- Beta Thalassemias are common in Mediterranean, Middle east, Central and South Asia, China.
- Normally there are 3 types of hemoglobin:
  - HbF (2alpha, 2 gamma)-1%,
  - HbA (2 alpha, 2 beta)-97-99% and
  - HbA2 (2 alpha and 2 delta)-2.5%.
- In thalassemia there is a decrease in the amount of either alpha or beta chain. As a result, HbA is reduced, while there is an increase in variant forms of hemoglobin such as HbA2 and HbF.
- Severity of the disease reflects how many alleles are affected: out of 4 for alpha (which has 2 genes) and out of 2 for beta (just 1 gene).
- In general symptoms are worse in beta-thalassemia patients, as the most severe alpha-thalassemia doesn't survive pregnancy or early life.

ALPHA THALASSEMIA

- Alpha Thalassemia leads to impaired oxygen transport and extravascular hemolysis (via splenic clearance).
- Alpha thalassemia is usually due to gene deletion, normally 4 alpha genes are present on chromosome 16.
- One gene deleted (Alpha thalassemia silent carriers/ alpha thalassemia Minima)- asymptomatic
  - Clinical course: Normal life span
  - Hematocrit- 28-40%
  - Hemoglobin electrophoresis: normal
  - Blood picture is usually normal
- Two genes deleted (alpha thalassemia trait/ alpha thalassemia minor)- mild anemia (Microcytic anemia may be the only sign) with slightly increased RBC count.
  - Cis deletion is when both deletions occur on the same chromosome, seen in Asians.
  - Trans deletion is when one deletion occurs on each chromosome, seen in Africans including African Americans.
  - HbH bodies may be seen on staining a blood film with brilliant cresyl blue.
- Three genes deleted (Hemoglobin H disease)- moderate to severe anemia, beta chains form tetramers (HbH) that damage RBCs. HbH is seen on electrophoresis.
  - Clinical course: chronic hemolytic anemia (Hb 7-11mg/dl), exacerbated by stress, and splenomegaly

  - Hematocrit- 22-32%
  - Hemoglobin electrophoresis- 10-40% HbH
  - HbH does not transport oxygen and precipitates in erythroblasts and erythrocytes.
- Four genes deleted- lethal in utero (hydrops fetalis), gamma chains form tetramers (Hb Barts) that damage RBCs. Hb Barts is seen on electrophoresis.
  - Clinical course: universally lethal as neonate due to intrauterine hemolytic anemia
  - Hb Barts cannot carry oxygen and is incompatible with life. Infants are either stillborn at 28-40 weeks or die very shortly after birth. They are pale, edematous and have enormous livers and spleens- a condition called hydrops fetalis.

BETA THALASEMMIA

- Usually due to gene mutations (point mutations in promoter or splicing sites) seen in individuals of African and Mediterranean descent.
  - The mutations result in defects in transcription, RNA splicing and modification, translation via frame shift and nonsense codons producing highly unstable beta-globin which cannot be utilized.
- Two beta genes are present on chromosome 11, mutations result in absent (β^0) or diminished (β^+) production of the beta-globin chain.
- There is an excess of alpha chains which precipitate in erythroblasts and red cells causing ineffective erythropoiesis and hemolysis. The excess alpha chains may combine with whatever beta, delta and gamma chains produced resulting in increased quantities of HbA2, and HBF at best small amounts of HbA.
- Beta thalassemia minor (trait) (β/β^+) is the mildest form of the disease and is usually asymptomatic with an increased RBC count.
  - Here one allele is normal and one allele is reduced in function.
  - Microcytic hypochromic RBCs (low MCV and MCH) and target cells are seen on blood smear.
  - Clinical notes: asymptomatic, mild microcytic anemia. They are not transfusion dependent and live a normal lifespan.
  - Hemoglobin electrophoresis shows:
    - Slightly decreased HbA (28-80%, normal 97-99%)
    - Increased HbA2 (4-8%, normal 2.5%) and
    - HbF (1-5%, normal 1%).
- Beta thalassemia intermedia (β^+/β^+):

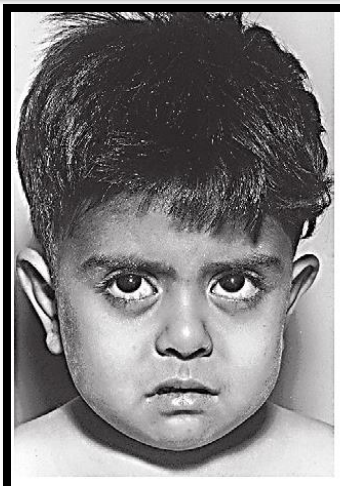
- Here both alleles are reduced in function.
- Thalassemia intermedia may be due to a combination of homozygous mild β+ and α-thalassemia, where there is reduce α-chain precipitation and less ineffective erythropoiesis and hemolysis.
- Hematocrit is variably low
- Clinical notes: they present earlier with Mild bony anomalies and mild hepatosplenomegaly and moderate anemia (Hb 7-10mg/dl).
- Recurrent leg ulcers, gallstones and infections are also seen. It should be noted that these patients may be iron overloaded despite a lack of regular blood transfusions. This is caused by excessive iron absorption which results from the underlying dyserythropoiesis.
- Lifespan: adult
- Hemoglobin electrophoresis shows:
  - HbA 0-20%
  - HbA2 0-10%
  - HbF 90-100%
- These patients may variably be dependent on transfusions.

- Beta thalassemia major (Cooley's anemia) (β^0/β^0) is the most severe form of disease and presents with severe anemia a few months after birth (3-6 months), high HbF at birth is temporarily protective.
  - Here both alleles are absent.
  - Hematocrit is <10% without transfusions.
  - Clinical notes: These present very early, bony anomalies, hepatosplenomegaly, jaundice and transfusional iron overload.
  - Hemoglobin electrophoresis shows:
    - HbA 0%
    - HbA2 4-10%
    - HbF 90-96%
  - Life span: 20-30 years
  - This condition is transfusion dependent
  - Alpha tetramers aggregate and damage RBCs resulting in ineffective erythropoiesis and extravascular hemolysis (removal of circulating RBCs by the spleen)
  - Massive erythroid hyperplasia ensues resulting in (1) expansion of hematopoiesis into the skull (reactive bone formation leads to hair-on end appearance on X-ray) and facial bones ('chipmunk face') and (3) risk of aplastic crisis with parvovirus B19 infection of erythroid precursors.

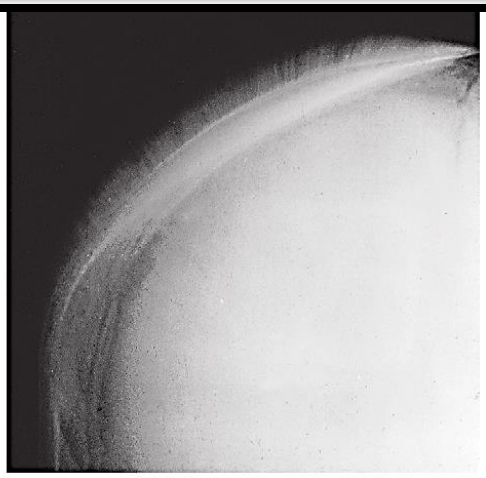
- Chronic transfusions are often necessary leading to risk for secondary hemochromatosis.
- Smear shows microcytic, hypochromic RBCs with target cells and nucleated RBCs.
- Hb electrophoresis shows little or no HbA with increased HbA2 and HbF.
- Presents with hepatosplenomegaly, bone expansion, infections

CLINICAL PRESENTATION

- Presents anytime from neonate to adult, but later onset tends to be milder.
- In general symptoms are worse in beta-thalassemia patients, as the most severe alpha-thalassemia doesn't survive pregnancy or early life.
- Signs and symptoms:
  - Hemolytic anemia: fatigue, shortness of breath, pallor, jaundice (commoner in beta thalassemia)
  - Splenomegaly (alpha thalassemia) or hepatosplenomegaly with abdominal distension (beta thalassemia)
  - Failure to thrive, growth restriction
  - Facial dysmorphia: frontal bossing, maxillary hypertrophy, large head. (Commoner and more prominent in beta thalassemia)
  - Osteopenia (beta thalassemia)



Thalassemia facial features



Hair-on end appearance



X-ray of hand showing expansion of the marrow and a thinned cortex

Differential Diagnosis of α-Thalassemias

	α-Thalassemia Trait	Hemoglobin H Disease	Hydrops Fetalis
α-globin chains	2–3	1	0
Hematocrit	28–40%	22–32%	N/A
Hemoglobin electrophoresis	**Normal**	10–40% HbH	N/A
Clinical course	Normal life span	Chronic hemolytic anemia, exacerbated by stress	Universally lethal as neonate

Differential Diagnosis of β-Thalassemias

	β-Thalassemia Major (Cooley's Anemia)	β-Thalassemia Intermedia	β-Thalassemia Minor
β-globin synthesis	Almost complete absence	Moderately ↓	Near normal (heterozygous)
Hematocrit	< 10% without transfusions	Variably low	28–40%
HbA	0%	0–30%	80–95%
HbA_2	4–10%	0–10%	4–8%
HbF	90–96%	90–100%	1–5%
Life span	20–30 years	Adult	Normal
Transfusion dependent	Yes	Variable	No
Clinical notes	Bony anomalies, hepatosplenomegaly, jaundice, transfusional iron overload	Mild bony anomalies; mild hepatosplenomegaly	Asymptomatic; mild microcytic anemia

INVESTIGATIONS

- Diagnosis:
  - Hb electrophoresis
  - Gap-PCR detects common deletion to confirm diagnosis. Other mutations may require DNA sequencing.
- Bloods:
  - FBC: decreased Hb, Decreased MCV, decreased MCH. Unlike iron deficiency, RBC count may be normal or high
  - Increased Reticulocytes
  - Peripheral smear: Microcytosis, hypochromia and basophilic stippling (Beta thalassemia only). With increasing severity increased nucleated RBCs, tear

drop (dacrocytes-this is a type of poikilocyte shaped like a teardrop) and target cells are seen.
  - LFT: increased unconjugated bilirubin (beta thalassemia). Increased liver enzymes if there is iron overload.
  - Iron studies: increased iron and increased ferritin in severe disease. Due to disease itself or frequent transfusions
- Imaging:
  - Skull x ray: bone abnormalities
  - Chest x ray: rib deformities, cardiomegaly
  - Abdominal Ultrasound: for organomegaly
  - ECG and ECHO for cardiac function
- Note: Liver biopsy and/or MRI can be done if there is iron overload.

MANAGEMENT

- Asymptomatic carriers require no specific treatment. Just avoid iron supplements.
- Long term folic acid supplements are required.
- Regular transfusions should be given to keep the Hb above 10mg/dl. Blood transfusions may be required every 4-6 weeks.
- Transfusion indications:
  - Symptomatic anemia, or aplastic or hyperhemolytic crisis.
  - Regular transfusion for thalassemia major or if there is growth impairment.
- Iron chelation if there is overload:
  - Parenteral desferrioxamine is given as an overnight subcutaneous infusion on 5-7 nights each week. Ascorbic acid 200mg daily given as it increases the urinary excretion of iron in response to desferrioxamine.
  - Deferiprone an oral iron chelator can be taken once a day and is similar in effectiveness to desferrioxamine.
  - May cause hearing loss and visual impairment so check both regularly.
- Splenectomy:
  - Indication: Hypersplenism with increasing transfusion requirements,
  - Splenectomy is usually delayed until after the age of 6 years because of the risk of infection. Prophylaxis against infection is required for patients undergoing splenectomy.
  - Avoid if possible.
  - Patients with thalassemia major are at an increased risk for development of post-splenectomy syndrome. This syndrome is characterized by severe

infections with encapsulated organisms (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*)

- Bone marrow transplantation:
  - Used in sever, transfusion-dependent disease
  - Curative
- Parental diagnosis and gene therapy should also be done.
- Patients' partner should be tested: if both partners have beta-thalassemia trait, there is one in four chance of such pregnancy resulting in a child having beta-thalassemia major. Therefore, couples in this situation must be offered prenatal diagnosis.

COMPLLICATIONS AND PROGNOSIS

- Complications:
  - Iron overload affecting liver, heart, pancreas, and pituitary gland
  - High-output heart failure
  - Gallstones
  - Hypersplenism
  - Aplastic crisis due to parvovirus B19 infection
- Prognosis:
  - HbH: generally, good
  - Beta thalassemia major: without treatment, death occurs in less than 5 years from heart failure or anemia. Regular transfusions and iron chelation allow near-normal life expectancy.

	Mechanism	Electrophoresis	Epidemiology	Clinical Characteristic	Treatment
Beta-Thalassemia Minor	• Heterozygotes • Loss of one of the two beta-globin genes	• ↓ HbA • ↑↑ HbA2 • ↑ HbF	• Mediterranean, sub-Saharan African, Indian subcontinent, or Southeast Asian descent	• Mild hypochromic microcytic anemia • No evidence of clinical disease	• None
Beta-Thalassemia Major	• Homozygotes • Loss of both beta-globin genes	• ↓↓ HbA • ↓↓ HbA2 • ↑↑ HbF		• Severe clinical disease • Hemolytic anemia • Growth delay • Cardiac failure • Iron overload from transfusions • Premature death	• Transfusion dependent • Chelation therapy for iron overload • Bone marrow transplant may be an option
Alpha-Thalassemia Trait	• Two functioning alpha-globin genes	• Normal	• African or Southeast Asian descent	• Mild hypochromic, microcytic anemia	• None
Hemoglobin H Disease	• Only one functioning alpha-globin gene • Four beta-globin complex together as dysfunctional homo-tetramers (HbH)	• ↑ HbF • ↑ HbH		• Moderate to severe hypochromic, microcytic anemia • Hemolytic anemia	
Hydrops Fetalis	• Loss of four alpha-globin genes • Formation of excess gamma-globin chains (hemoglobin Bart)	• ↓↓ HbA • ↓↓ HbA2 • ↓↓ HbF		• The most severe form of alpha thal-assemia • Neonatal demise	

MACROCYTIC ANEMIA

- This is anemia with MCV>100.
- It can be divided into megaloblastic and non-megaloblastic types depending on bone marrow findings.

MEGALOBLASTIC ANEMIA

- Characterized by presence of erythroblasts with delayed nuclear maturation because of defective DNA synthesis (megaloblasts) in the bone marrow.
- Megaloblasts are large and have large immature nuclei. The nuclear chromatin is more finely dispersed than normal and has open stippled appearance. In addition, giant metamyelocytes are frequently seen in megaloblastic anemia. These cells are about twice the size of normal cells and often have twisted nuclei.
- Causes include:
  - Vitamin B 12 deficiency or abnormal vitamin B12 metabolism,
  - Folate deficiency or abnormal folate metabolism.
  - Other defects of DNA synthesis such as congenital enzyme deficiencies such as congenital enzyme deficiencies in DNA synthesis (e.g. orotic aciduria) or resulting from therapy with drugs interfering with DNA synthesis (e.g. hydroxycarbamide (hydroxyurea), azathioprine, Zidovudine-AZT)

- Myelodysplasia due to dyserythropoeisis

- Folate and vitamin B12 are necessary for synthesis of DNA precursors.
  - Folate circulates in the serum as methyltetrahydrofolate (methy THF), removal of the methyl group allows for participation in the synthesis of DNA precursors.
  - Methyl group is transferred to Vitamin B12 (Cyanocobalamin).
  - Vitamin B12 then transfers it to homocysteine producing methionine.
- Lack of folate or vitamin B12 impairs synthesis of DNA precursors
  - Impaired division and enlargement of RBC precursors leads to megaloblastic anemia.
  - Impaired division of granulocytic precursors leads to hypersegmented neutrophils.
  - Megaloblastic change is also seen in rapidly-dividing (e.g. intestinal) epithelial cells.

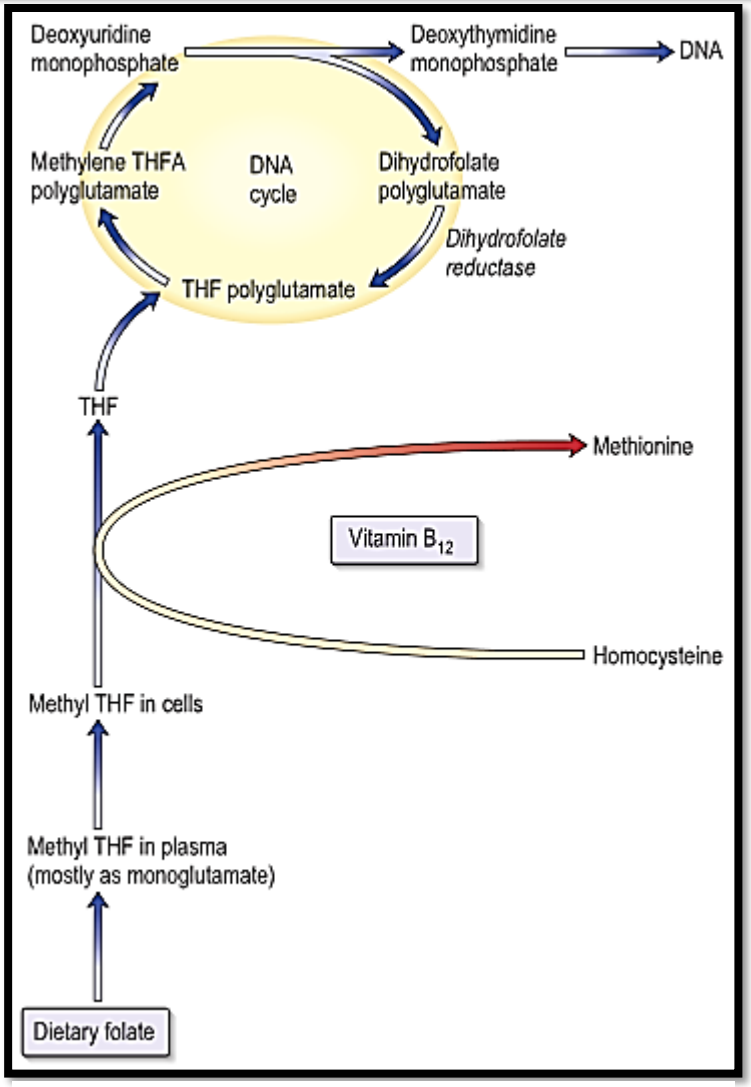


Figure 36: DNA precursor synthesis

- Pathogenesis:
  - It's a descriptive morphologic term in which maturation of the nucleus is delayed relative to that of the cytoplasm. The delay in maturation of the nucleus is attributed to defective DNA synthesis. This condition leads to megaloblastic marrow and ineffective erythropoiesis.
  - The immature erythroblasts are destroyed within the bone marrow (intramedullary hemolysis) which results in megaloblastic anemia.
- Laboratory findings:
  - Anemia (MCV >96fL unless there is co-existing cause of microcytosis when there may be a dimorphic picture with a normal/low average MCV)
  - Leucopenia and thrombocytopenia if severe.

- The peripheral blood film shows oval macrocytes with hypersegmented polymorphs with 6 or more lobes in the nucleus.



Figure 37: Macrocytes and a hypersegmented neutrophil (Arrowed) on a peripheral blood film

VITAMIN B12 DEFICIENCY

- Vitamin B12 is synthesized by certain microorganisms, and humans are ultimately dependent on animal sources.
- It is found in meat, fish, eggs and milk but not in plants. It is not usually destroyed by cooking.
- Daily diet contains 5-30 micrograms of Vitamin B12 of which 2-3 micrograms is absorbed.
- The average adult stores some 2-3mg mainly in the liver and it may take 2 years or more after absorptive failure before B12 deficiency develops, as the daily losses are small (1-2 micrograms).
- Dietary vitamin B12 is complexed to animal-derived proteins.
  - Salivary gland enzyme (e.g. amylase) liberate vitamin B12, which is then bound to R-binder (also from the salivary gland) and carried through the stomach.
  - Pancreatic proteases in the duodenum detaches vitamin B12 from R-binder.
  - Vitamin B12 binds intrinsic factor (made by gastric parietal cells) in the small bowel, the intrinsic Factor-Vitamin B12 complex is absorbed in the ileum.
- Vitamin B12 deficiency is less common than folate deficiency and takes years to develop due to large hepatic stores of vitamin B12.
- For Vitamin B12

  - Source: animal products (meat, dairy products)
  - Daily requirements= 2-5 micrograms
  - Body storage= 3-5 (4) mg
  - Time to develop anemia= 3-4 years
  - Cooking: little effect
- For folate
  - Source: vegetables, fruits and animal products
  - Daily requirements= 100mg (50-200mg)
  - Body storage= 5-20mg
  - Time to develop anemia= 4-6 months
  - Cooking: easily destroyed

CAUSES OF VITAMIN B12 DEFICIENCY

- Nutritional: especially in vegans, alcoholics
- Malabsorption
  - Gastric causes
    - Adult (addisonian) pernicious anemia: this is the most common cause
    - Congenital lack or abnormality of intrinsic factor
    - Total or partial gastrectomy
  - Intestinal causes
    - Chronic tropical sprue
    - Ileal resection and Crohn's disease
    - Increased competition (fish tapeworm, intestinal bacterial overgrowth)
    - Pancreatic insufficiency and damage to the terminal ileum (e.g. Crohn disease or *Diphyllobothrium latum*-fish tapeworm)
- Pernicious anemia is the most common causes of vitamin B12 deficiency. Malabsorption of vitamin B12 because of pancreatitis, coeliac disease or treatment with metformin is mild and does not usually result in significant vitamin B12 deficiency.
  - Pernicious anemia is an autoimmune destruction of parietal cells (body of stomach) leads to intrinsic factor deficiency.
  - It is seen in all races but frequently in fair-haired and blue-eyed individuals and those who have blood group A. It is more common in females than males.
  - There is an association with other autoimmune disease, particularly thyroid disease, Addison's disease and vitiligo.

  - Parietal cell antibodies are present in the serum in 90% of patients. Conversely, intrinsic factor antibodies although found in only 50% of patients are specific for this diagnosis.
  - 2 types of intrinsic factor antibodies are found:
    - A blocking antibody which inhibits binding of intrinsic factor to B12
    - Precipitating antibody which inhibits the binding of B12-intrinsic factor complex to its receptor site in the ileum
- Clinical features: neurologic changes (numbness, paresthesia, decreased vibratory and positional sense, ataxia)- subacute combined degeneration of the spinal cord, glossitis
- Smear shows hypersegmented neutrophils.
- Treatment: replacement of B12.
  - Dose: initial dose: 6 x 1000micrograms over 2-3 weeks and maintenance: 1000microgram every 3 months for the rest of their life.
  - Alternatively, oral B12 2mg/day is used as 1-2% of an oral dose is absorbed by diffusion and therefore does not require intrinsic factor. (compliance in elderly patients is a problem)
  - Clinical improvement may occur within 48 hours and a reticulocytosis can be seen some 2-3 after starting therapy peaking at 5-7 days. Improvement of the polyneuropathy may occur over 6-12 months but longstanding spinal cord damage is irreversible. Hypokalemia can occur and if severe supplements should be given. Hyperuricemia also occurs but clinical gout is uncommon.
- Prophylactic therapy is indicated with total gastrectomy and Ileal resection.
- Additional measures:
  - Correct underlying cause
- Antibiotics for bacterial overgrowth and treatment of fish tapeworm.

FOLATE DEFICIENCY

- Dietary folate is obtained from green vegetables and some fruits.
  - Absorbed in the jejunum.

- Folate deficiency develops within months (4-6 months) as body stores are minimal.
- Etiology: malnutrition (alcoholic, elderly), decreased absorption (sprue), impaired metabolism (methotrexate- folate antagonist that inhibits dihydrofolate reductase, trimethoprim, antimalarials), increased demand (pregnancy, cancer and hemolytic anemia)
- Clinical and laboratory findings include:
  - Macrocytic RBCs and hypersegmented neutrophils (>5 lobes)
  - Glossitis
  - Decreased serum folate
  - Increased homocysteine
  - Normal methylmalonic acid
  - Unlike B12 deficiency, neuropathy does not occur.

Causes of folate deficiency

Nutritional (major cause)	Excess utilization
Poor intake	**Physiological**
Old age	Pregnancy
Poor social conditions	Lactation
Starvation	Prematurity
Alcohol excess (also causes impaired utilization)	**Pathological**
Poor intake due to anorexia	Haematological disease with excess red cell production, e.g. haemolysis
Gastrointestinal disease, e.g. partial gastrectomy, coeliac disease, Crohn's disease	Malignant disease with increased cell turnover
Cancer	Inflammatory disease
Antifolate drugs	Metabolic disease, e.g. homocystinuria
Anticonvulsants:	Haemodialysis or peritoneal dialysis
Phenytoin	**Malabsorption**
Primidone	Occurs in small bowel disease, but the effect is minor compared with that of anorexia
Methotrexate	
Pyrimethamine	
Trimethoprim	

- Treatment: folate repletion.
  - 5mg PO daily
  - Treatment should be given for about 4 months to replace body stores. Treat any underlying cause.
- Prophylactic therapy is indicated in pregnancy, severe hemolytic anemia in patients with dialysis and premature newborns.
- Response to therapy:
  - Feeling of general well-being is restored in 48 hours.
  - Reticulocytosis begins in 3-4 days and peaks in 7-10 days.
  - If both folate and vitamin B12 deficiency present give Vitamin B12 first.

MACROCYTOSIS WITHOUT MEGALOBLASTIC CHANGES

- A raised MCV with macrocytosis on the peripheral blood film can occur with a normoblastic rather than a megaloblastic bone marrow.
- A common physiological cause of macrocytosis is pregnancy. Macrocytosis may also occur in newborn
- Common pathological causes:
  - Alcohol excess
  - Liver disease

  - Reticulocytosis
  - Hypothyroidism
  - Some hematological disorders (e.g. aplastic anemia, sideroblastic anemia, pure red cell aplasia)
  - Drugs (e.g. hydroxyurea, azathioprine)
  - Cold agglutinins due to autoagglutination of red cells (the MCV decreases to normal with warming of the sample to 37 ºC)
- In all these conditions, normal levels of Vitamin B12 and folate will be found. The exact mechanisms in each case are uncertain but in some there is increased lipid deposition in the red cell membrane.
- An increased number of reticulocytes also leads to a raised MCV because they are large cells.
- A high alcohol consumption is a frequent cause of a raised MCV and in such patients the MCV can be used as a surrogate marker for monitoring excessive alcohol consumption. A full blown megaloblastic anemia can also occur in people who use alcohol to excess, this is due to a toxic effect of alcohol on erythropoiesis and/or to dietary folate deficiency.

NORMOCYTIC ANEMIA

- This is anemia with normal-sized RBCs (MCV= 80-100fL)
- It is due to increased peripheral destruction or underproduction
  - Reticulocyte count helps to distinguish between these 2 etiologies.
- Includes anemia of chronic disease, endocrine disorders (hypothyroidism, hypopituitarism and hypoadrenalism), acute blood loss and Hematological disorder (pure cell anaplasia and some hemolytic anemias).
- Anemia of chronic disease as above.
- Hypothyroidism: treatment is thyroid replacement.
- Acute blood loss: can be normocytic before iron stores are reduced.
- Pure red cell aplasia: destructive antibodies or lymphocytes leading to ineffective erythropoiesis, associated with thymoma and parvovirus.
  - Diagnosis: lack of erythroid precursors on bone marrow biopsy
  - Treatment: supportive care

ANEMIA DUE TO MARROW FAILURE (APLASTIC ANEMIA)

- Aplastic anemia is defined as pancytopenia with hypocellularity (aplasia) of the bone marrow.
- There are no leukemic, cancerous or other abnormal cells in the peripheral blood or bone marrow. It is usually an acquired condition but may rarely be inherited.
- It is due to a reduction in the number of pluripotential stem cell together with a fault in those remaining or an immune reaction against them so that they are unable to repopulate the bone marrow.
- Failure of one cell lineage can also happen, when it affects the red cell precursors it is called pure red cell aplasia.

CAUSES

- Primary:
  - Inherited e.g. Fanconi's anemia
  - Idiopathic acquired (67% of cases)
- Secondary:
  - Chemicals e.g. benzene, toluene, glue sniffing
  - Drugs
    - Chemotherapeutic antibiotics e.g. chloramphenicol, gold, penicillamine, phenytoin, carbamazepine, carbimazole, azathioprine
  - Insecticides
  - Ionizing radiation
  - Infections:
    - Viral e.g. hepatitis, EBV, HIV, erythrovirus
  - Paroxysmal nocturnal hemoglobinuria
  - Miscellaneous e.g. pregnancy

CLINICAL FEATURES

- Features of marrow failure:
  - Anemia
  - Bleeding
  - Infection
- Bleeding is often the predominant initial presentation of aplastic anemia with bruising with minimal trauma or blood blisters in the mouth.
- Physical findings:
  - Ecchymoses
  - Bleeding gums

  - Epistaxis
- Mouth infections are common. Lymphadenopathy and hepatosplenomegaly are rare in aplastic anemia.

INVESTIGATIONS

- FBC: Pancytopenia
- The virtual absence of reticulocytes
- Bone marrow aspirate: a hypocellular or aplastic bone marrow with increased fat spaces.

TREATMENT

- Treat underlying cause if possible
- Supportive care while awaiting bone marrow recovery and specific treatment to accelerative recovery.
  - Transfusions of red cells and platelets as necessary.
- Prevent and Treat infections promptly with broad-spectrum parenteral antibiotics.
- Definitive treatment is bone marrow transplantation for patients under the age of 40 with an HLA identical sibling donor where it gives a 75-90% chance of long-term survival. Immunosuppressive therapy used is antithymocyte globulin (ATG) and cyclosporine. It is recommended for:
  - Patients with severe disease over the age of 40
  - Younger patients with severe disease without an HLA-identical sibling donor
  - Patients who do not have severe disease but who are transfusion dependent.
- Steroids should not be used to treat severe aplastic anemia except for serum sickness due to ATG.
- The most reliable determinants for the prognosis are the number of neutrophils, reticulocytes, platelets and the cellularity of the bone marrow.
- Bad prognosis (severe aplastic anemia) is associated with presence of 2 of the following:
  - Neutrophil count $<0.5 \times 10^9/L$
  - Platelet count of $<20 \times 10^9/L$
  - Reticulocyte count of $< 40 \times 10^9/L$

HEMOLYTIC ANEMIA

- Due to red cell destruction and increased red cell turnover. Bone marrow is able to compensate 5 times the normal rate.
- The red cell normally survives about 120 days but in hemolytic anemias the red cell survival times are considerably shortened.
- Breakdown of normal red cells occurs in the macrophages of the bone marrow, liver and spleen.
- Shortening of the red cell survival does not always cause anemia as there is a compensatory increase in red cell production by the bone marrow. If the red cell loss can be contained within the marrow's capacity for increased output, then a hemolytic state can exist without anemia (compensated hemolytic disease).
- The bone marrow can increase its output 6 to 8 times by increasing the proportion of cells committed to erythropoiesis (erythroid hyperplasia) and by expanding the volume of active marrow.
- Immature red cells (Reticulocytes) are released prematurely. These cells are larger than mature cells and stain with a light blue tinge on a peripheral blood film (the description of this appearance on a blood film is polychromasia) due to the presence of residual ribosomal RNA.
- Reticulocytes may be counted accurately as a percentage of all RBCs on blood film using a supravital stain for residual RNA (e.g. new methylene blue).
- Hemolysis can occur due to:
  - Extravascular hemolysis: red cells are hemolyzed by macrophages in the reticuloendothelial system particularly in the spleen.
  - Intravascular hemolysis: res cells are hemolyzed in circulation. The liberated hemoglobin is liberated. It initially binds to plasma haptoglobins but these soon become saturated. Excess free plasma hemoglobin is filtered by the renal glomerulus and enters urine, although small amounts are reabsorbed by the renal tubules. In the renal tubular cells, hemoglobin is broken down and becomes deposited in cells as hemosiderin. Some of the free plasma hemoglobin is oxidized to methaemoglobin.
- Clinical features: jaundice, hepatosplenomegaly, dark urine.
- Etiology can be classified as:
  - Congenital
    - Hemoglobinopathies: sickle cell disease*, thalassemia
    - Enzymopathies: G6PD deficiency*, Pyruvate kinase deficiency
    - Membranopathies: hereditary spherocytosis, elliptocytosis

- In born errors of metabolism

➢ Acquired

- Microangiopathic hemolytic anemia: TTP, HUS, DIC, eclampsia, HELLP syndrome
- Autoimmune hemolytic anemia
  - Warm type
  - Cold type
- Alloimmune
  - Hemolytic transfusion reactions
  - Hemolytic disease of the newborn
  - After allogenic bone marrow or organ transplantation
- Paroxysmal nocturnal hemoglobinuria
- Hypersplenism
- Infections: Malaria*

- Labs: increased reticulocyte count, indirect hyperbilirubinemia, Schistocytes on blood smear.
- Treatment: treatment of underlying cause of hemolysis.

Type of anemia	Treatment
Hereditary spherocytosis and Elliptocytosis	• Splenectomy • Vaccines for encapsulated organisms e.g. pneumococci and lifelong penicillin prophylaxis.
G6PD	• Any offending drug should be stopped • Underlying infection should be treated • Blood transfusion may be life-saving • Splenectomy is not usually helpful
Pyruvate kinase deficiency	• Blood transfusions may be necessary during infections and pregnancy. Splenectomy may improve the clinical condition and is usually advised for patients requiring frequent transfusions.
Autoimmune	• Corticosteroids (Prednisolone in doses of 1mg/kg daily) • Splenectomy is the most effect second-line therapy • Immunosuppressive drugs e.g. azathioprine and rituximab may be effective when patients fail to respond to steroids and splenectomy • Blood transfusion
Paroxysmal nocturnal hemoglobinuria	• Blood transfusion

SICKLE SYNDROMES

- Sickle cell disease is a hereditary form of chronic hemolysis ranging from asymptomatic to severe, overwhelming crisis. It is characterized by irreversibly sickled cells and recurrent painful crises.
- Sickle cell disease is an autosomal recessive hereditary disease.
- Sickle cell hemoglobin (HbS) results from a single-base mutation of adenine to thymine on chromosome 11, which produces a substitution of valine to glutamic acid at the sixth codon of the beta chain.
- In the homozygous state (sickle cell anemia) both genes are abnormal (HbSS), whereas in the heterozygous state (sickle cell trait HbAS) only one chromosome carries the gene.
  - Carriers are protected against *Plasmodium falciparum*.
- As the synthesis of HbF is normal, the disease usually does not manifest itself until the HbF decreases to adult levels at about 6 months of age.
- The sickle cell gene is commonest in Africans (up to 25% frequency in some populations).
- Depending on the type of hemoglobin chain combinations, 3 clinical syndromes occur:
  - Homozygous HbSS have the most severe disease.
  - Combined heterozygosity (HbSC) for HbS and C who suffer intermediate symptoms.
  - Heterozygous HbAS (sickle cell trait) have no symptoms.

PATHOGENESIS

- Deoxygenated HbS molecules are insoluble and polymerize. This increases viscosity.
  - Polymer formation at concentrations exceeding 30g/dl.
  - Polymers form a gel-like substance containing Hb crystals called tachoids.
- Flexibility of the cells is decreased and they become rigid and take up their characteristic sickle appearance.
- This process is initially reversible but with repeated sickling the cells eventually lose their membrane flexibility and become irreversibly sickled.
  - This is due to dehydration, partly caused by potassium leaving the red cells via

calcium activated potassium channels called the Gados channel.

- These irreversibly sickled cells are dehydrated and dense and will not return to normal when oxygenated.
- Sickling produces:
  - Shortened red cell survival
  - Impaired passage of cells through the microcirculation, leading to obstruction of small vessels and tissue infarction
- Precipitating factors for sickling:
  - Hypoxia
  - Dehydration
  - Cold
  - Acidosis
  - Infection and fever
  - Living at high altitude
- A crisis may occur without the presence of these factors.
- Adhesion proteins on activated endothelial cells (VCAM-1) may play a role particularly in vaso-occlusion when rigid cells are trapped, facilitating polymerization.
- HbS releases its oxygen to the tissues more easily than does normal Hb and patients therefore feel well despite being anemic (except of course during crises or complications).

CLINICAL FEATURES OF SICKLE CELL ANEMIA

- The physiological changes in RBCs result in a disease with the following cardinal signs
  - Hemolytic anemia
  - Painful vaso-occlusive crisis (most common clinical manifestation)
  - Multiple organ damage from microinfarcts, including heart, skeleton, spleen and central nervous system.

VASO-OCCLUSIVE CRISES

- An early presentation may be acute pain in the hands and feet: dactylitis due to vaso-occlusion of the small vessels. (hand-foot syndrome)
- Severe pain in other bones e.g. femur, humerus, vertebrae, ribs, pelvis occurs in older children/adults.
- Attacks vary from person to person.
- Fever often accompanies the pain.
- Triggers of vaso-occlusive crisis include:
  - Hypoxemia: may be due to acute chest syndrome or respiratory complications
  - Dehydration: acidosis results in a shift of the oxygen dissociation curve
  - Changes in body temperature

PULMONARY HYPERTENSION

- This occurs in about 30-40% of patients and is associated with an increased mortality.
- The hyperhemolytic paradigm (HHP) proposes that hemolysis in sickle cell disease leads to increased cell-free plasma Hb which consumes NO, leading to a state of NO deficiency, endothelial dysfunction and a high prevalence of pulmonary hypertension.

ACUTE CHEST SYNDROME

- This is caused by infection, fat embolism from necrotic bone marrow or pulmonary infarction due to sequestration of sickle cells.
- It comprises shortness of breath, fever, cough, chest pain, tachypnea, leukocytosis, hypoxia, pulmonary infiltrates in the upper lobes and new chest X-ray changes due to consolidation.
- The presentation may be gradual or very rapid, leading to death in a few hours
- Management is with
  - Pain relief
  - High flow supplemental oxygen and antibiotics (ANcefotaxime and clarithromycin) which should be started immediately.
  - Exchange transfusion will reduce the amount of HbS to <20% if there is no improvement
  - Ventilation (CPAP) may be necessary
- Infections can be due to *Chlamydia* and *mycoplasma*, as well as *Streptococcus pneumoniae*.

ANEMIA

- Chronic hemolysis produces a stable hemoglobin level usually 6-8mg/dl but an acute fall in Hb level can occur due to:
  - Splenic sequestration
  - Bone marrow aplasia
  - Further hemolysis due to drugs, acute infection or associated G6PD deficiency.

SPLENIC SEQUESTRATION

- Vaso-occlusion produces an acute painful enlargement of the spleen.
- There is a splenic pooling of red cells and hypovolemia, leading in some to circulatory collapse and death.
- There will be severe hemolysis, rapid splenomegaly and a high reticulocyte count.
- The condition occurs in childhood before multiple infarctions have occurred.
- Multiple infarctions lead to a fibrotic non-functioning spleen.
- Treatment is by splenectomy but this predisposes the patient to infection especially by

encapsulated organisms e.g. *Haemophilus influenza*, *Streptococcus pneumoniae* and *Salmonella*

- Liver sequestration can also occur.

BONE MARROW APLASA (APLASTIC CRISIS)

- This most commonly occurs following infection with erythrovirus B19 (previously called Parvovirus B19) which invades proliferating erythroid progenitors.
- There is a rapid fall in hemoglobin with no reticulocytes in the peripheral blood, because of the failure of erythropoiesis in the marrow

LONG TERM PROBLEMS

- Growth and development: young children are short but regain their height by adulthood. They however remain normal weight. There is often delayed sexual maturation which may require hormone therapy.
- Bones: vaso-occlusive episodes lead to chronic infarcts causing avascular necrosis of hips, shoulders, compression of vertebrae and shortening of bones in the hands and feet. Osteomyelitis is common in SCD and is caused by *Staphylococcus aureus* and *salmonella*.
  - Hypoxia causes bone marrow changes exacerbated by episodic occlusion of the micro-circulation by the abnormal sickle cells leading to infarction of bone and marrow.
  - There is compensatory bone marrow hyperplasia, secondary osteomyelitis and secondary growth defects.
- Infections are common in tissues susceptible to vasooclusion e.g. bones, lungs, kidneys.
- Eye: background retinopathy, proliferative retinopathy, vitreous hemorrhages and retinal detachments all occur. Regular yearly eye checks are required.
- Cardiac problems: cardiomegaly, arrhythmias, dilation of both ventricles & left atrium and iron overload cardiomyopathy. Myocardial infarctions occur due to thrombotic episodes which are not secondary to atheroma.
- Neurological complications: in 25% there are transient ischemic attacks, fits, cerebral infarction, cerebral hemorrhage and coma. Strokes occur in about 11% of patients under 20 years of age. Most common finding is obstruction of a distal intracranial internal carotid artery or a proximal middle cerebral artery. Other complications include ptosis

- GIT: Cholelithiasis-pigment stones occur as a result of chronic hemolysis, Chronic hepatomegaly and liver dysfunction are caused by trapping of sickle cells
- Genitourinary: Chronic tubulointerstitial nephritis occurs, kidneys lose concentrating capacity (isosthenurea).
- Priapism: an unwanted painful erection occurs from vasooclusion and can be recurrent. This may result in impotence. Treatment is with an alpha-adrenergic blocking drug, analgesia and hydration.
- Dermatological: Leg ulcers occur spontaneously or following trauma and are usually over the medial or lateral malleoli. They often become infected and are quite resistant to treatment, sometimes blood transfusion may facilitate ulcer healing
- Pregnancy: impaired placental blood flow causes spontaneous abortion, intrauterine growth retardation, pre-eclampsia and fetal death. Painful episodes, infections and severe anemia occur in the mother.

INVESTIGATIONS

- Hb electrophoresis (diagnostic)
- Hemoglobin solubility testing/sickling test
- Peripheral smear
- FBC: low Hb levels (6-8mg/L) and a high reticulocyte count (10-20%)
- Urea and electrolytes
- Liver function tests (ALT & AST)
- Pulmonary function tests
- CT before lumbar puncture
- Blood cultures
- Chest XR
- MRI: for early bone marrow changes
- CT for subtle regions of osteonecrosis and to exclude renal medullary carcinoma in patients presenting with hematuria.
- Tc bone scan to detect early osteonecrosis.
- Transcranial Doppler U/S: to detect risk of stroke in children
- Abdominal U/S: for cholecystitis, cholelithiasis, or an ectopic pregnancy and to measure splenomegaly and hepatomegaly.
- Echocardiography for pulmonary hypertension

MANAGEMENT PRINCIPLES

1. Avoid and treat precipitating factors quickly.
2. Rehydration
3. Pain control: opioids (morphine), NSAIDs
4. Oxygen and antibiotics are only given if specifically, indicated
   - Antibiotics: cefuroxime, amoxicillin/clavulanate,

penicillin VK, ceftriaxone, azithromycin, cefaclor

5. Prophylaxis is with penicillin 500mg daily and vaccination with polyvalent pneumococcal and Haemophilus influenzae type b vaccine
6. Folic acid is given to all patients with hemolysis
7. Transfusion: for sudden, severe anemia due to acute splenic sequestration, aplastic crisis or hyperhemolytic crisis.
8. Bone marrow transplantation is the only cure

- Hydroxyurea has been given to patients with SCD, it increases HbF but has carcinogenic effect (leukemia)
  - 15mg/kg/day increased by 2.5mg over 12 weeks depending on response

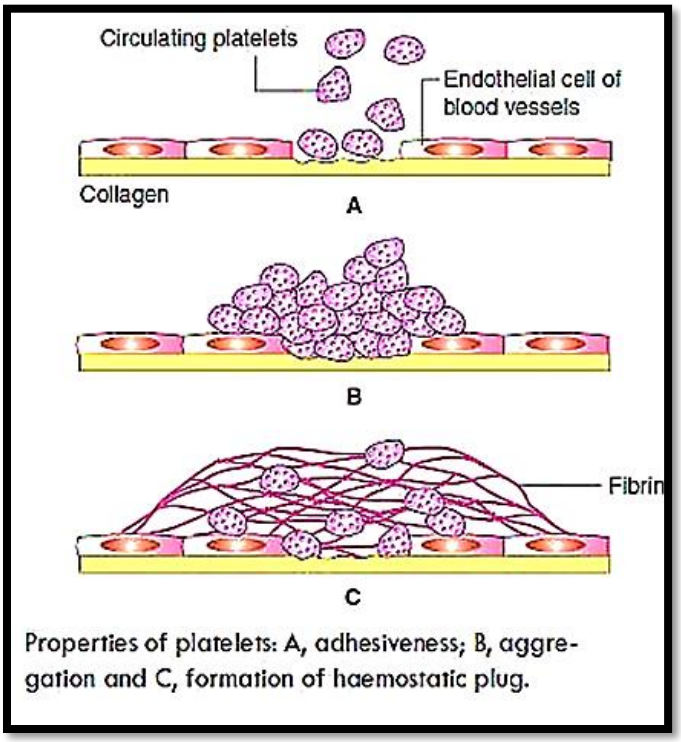
LEUKEMIAS

- There are 4 main subtypes:
  - Acute myeloid leukemia (AML)
  - Acute lymphoblastic leukemia (ALL)
  - Chronic myeloid leukemia (CML)
  - Chronic lymphocytic leukemia (CLL)

LYMPHOMA

HEMOSTATIC DISORDERS

- Platelets (small plates) or thrombocytes are formed elements of blood.
- 1/3 of platelets are sequestered in the spleen and 2/3 circulates for about 7 to 10 days.
- They are the smallest blood cells (2-5 microns) and are colorless.
- They have several shapes (spherical, rod shaped, oval, disk-shaped when inactivated, dumbbell shaped, comma shaped, cigar shape of any other unusual shape).
- They have no nucleus.
- Inactivated platelets are without processes/filopodia and activated platelets develop filopodia/Processes.
- Normal platelet count: 150 000 to 400 000/mm^3 of blood.
- Platelets life span varies from 8 to 12 days with an average of 10 days.
- Platelets are destroyed by tissue macrophage system in the spleen.
- Splenomegaly causes reduction in the platelet count.
- Splenectomy is followed by an increase in the platelet count.
- Platelets have the following properties:
  - Adhesiveness: when platelets come in contact with any wet surface or rough surface, these are activated and stick to the surface. Factors responsible for adhesiveness are collagen, thrombin, ADP, thromboxane A2, calcium ions and vonWillebrand factor.
  - Aggregation: platelets stick to each other. This occurs due to ADP and thromboxane A2
  - Agglutination: clumping together of platelets. This occurs due to the actions of some platelet-activating factors.



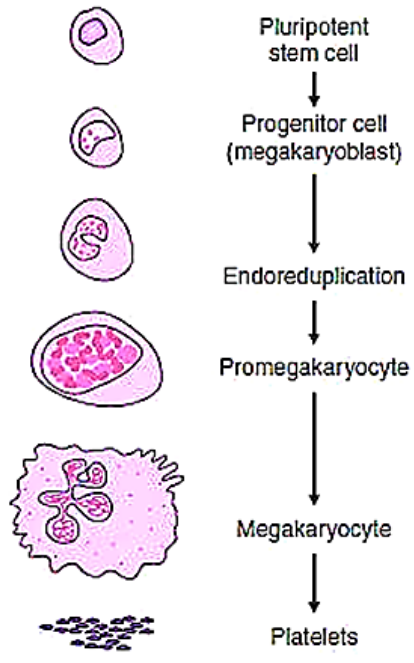
Properties of platelets: A, adhesiveness; B, aggregation and C, formation of haemostatic plug.

- Physiological variations:
  - Age: platelets are less in infants and each normal level at the 3rd month after birth.
  - Sex: no difference in count between males and females however it rises during ovulation and is reduced during menstruation in females

- High altitude: increases platelets
- After meal: platelet count increases

THROMBOCYTOPENIA	THROMBOCYTOSIS
• Decrease in platelet count below 150 000/cu mm of blood • Occurs in: ➢ Acute infections ➢ Acute leukemia ➢ Aplastic and pernicious anemia ➢ Chicken pox and smallpox ➢ Splenomegaly ➢ Scarlet fever ➢ Typhoid fever ➢ Tuberculosis ➢ Purpura ➢ Gaucher's disease	• Increase in platelet count over 450 000/cu mm of blood • Occurs in ➢ Allergic conditions ➢ Asphyxia ➢ Hemorrhage ➢ Bone fractures ➢ Surgical operations ➢ Splenectomy ➢ Rheumatic fever ➢ Trauma (wound or injury or damage caused by external damage) ➢ Parturition

- Pathologically platelets are also influenced by nutritional state: Decreased in severe iron, folic acid or vitamin B12 deficiency.
- Platelets are acute phase reactants hence may be increased in patients with systemic inflammation, tumors, bleeding and mild iron deficiency hence the term secondary or reactive thrombocytosis is used. It is mediated by cytokines IL-3, 6 and 11.



Stages of thrombopoiesis.

HEMOSTASIS

- Integrity of the blood vessel is necessary to carry blood to tissues.
- Damage to the wall of blood vessels is repaired by hemostasis which involves formation of a thrombus (clot) at the site of vessel injury.

- Hemostasis is the spontaneous arrest or prevention of bleeding from the injured/damaged vessels by the physiological process.
- Hemostasis occurs in 3 steps:
  - Vasoconstriction
  - Platelet plug formation (Primary hemostasis)
  - Coagulation of blood (Secondary hemostasis)

VASOCONSTRICTION

- Immediately after injury the blood vessel constricts (initial constriction) and decreases the loss of blood from the damaged portion.
- Usually arterioles and small arteries constrict.
- Vasoconstriction is purely a local phenomenon. It is brought about by:
  - Neural reflex resulting in release of vasoconstrictors.
  - Local smooth muscle spasm due to injury
  - Release of endothelin from injured endothelium
- When blood vessels are cut, the endothelium is damaged and collagen is exposed.
- Platelets adhere to the exposed collagen and become activated.
- Activated platelets secrete serotonin and other vasoconstrictor substances to cause vasoconstriction
- Adherence of platelets to collagen is accelerated by VonWille brand factor (this factor acts as a bridge between a specific glycoprotein present on the surface of platelets and collagen fibrils).
  - During adhesion, Platelets use GPIb receptor to bind to VonWille brand factor
  - Note: VonWille brand factor is derived from alpha granules of platelets and endothelial cell (Weibel-Palade bodies)

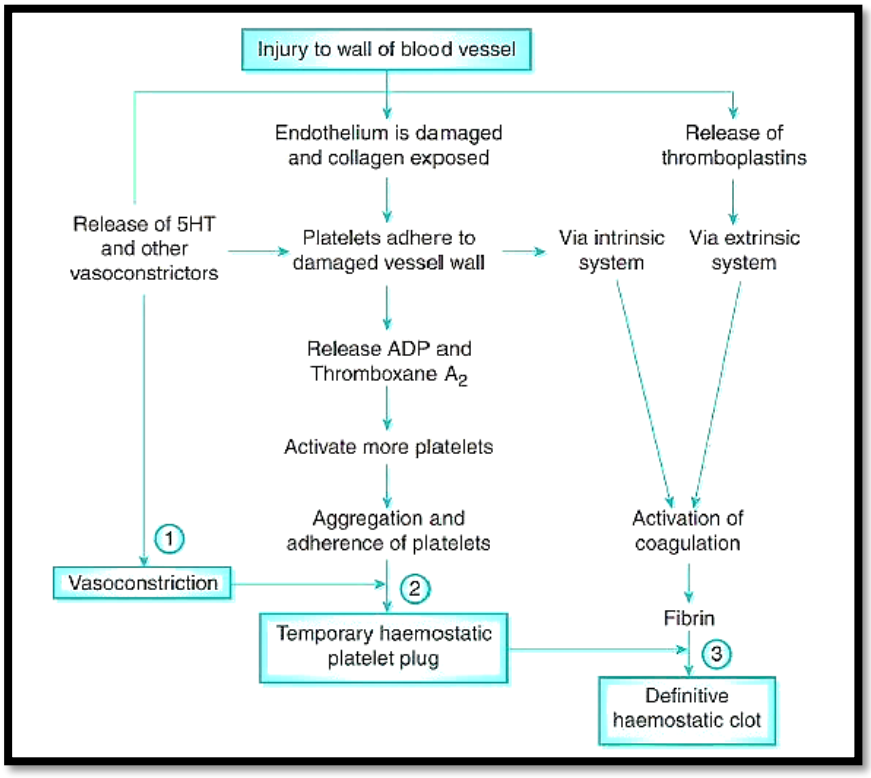
PLATELET PLUG FORMATION

- Following injury platelets come in contact with damaged collagen fibers and endothelial cells of the vessel wall and change their characteristics (they begin to swell and assume irregular forms with large number of pseudopodia protruding to the surface)
- Contractile proteins of platelets contract and cause dense granules inside the platelet containing multiple factors including ADP and thromboxane A2.
- Note: Phospholipase A2 converts phospholipids to arachidonic acid and eventually forms thromboxane A2 in the cyclooxygenase pathway.
- ADP and thromboxane A2 attract more and more platelets and activate them.

- ADP also induces the platelets to produce GPIIb/IIIa receptor which is essential for platelet aggregation. The linker molecules between these platelets is fibrinogen.
- All the platelets aggregate to form a loose temporary platelet plug or a temporary hemostatic plug which closes the ruptured vessels and prevents further blood loss.
- Platelet activating factor (PAF) a cytokine released by neutrophils, monocytes and platelet cell membrane lipids accelerates platelet aggregation.

BLOOD COAGULATION

- Coagulation is a process by which soluble fibrinogen is converted to fibrin.
- Note: blood coagulation does not necessarily need platelets, red blood cells and white blood cells.
- In coagulation the temporary platelet plug is converted into a definitive hemostatic plug by the process of clot formation (blood coagulation) which involves a complex series of events.
- Fibrinogen is converted to fibrin. Fibrin threads get attached to the loose platelet plug, which blocks the ruptured part of the blood vessel and prevents further blood loss.



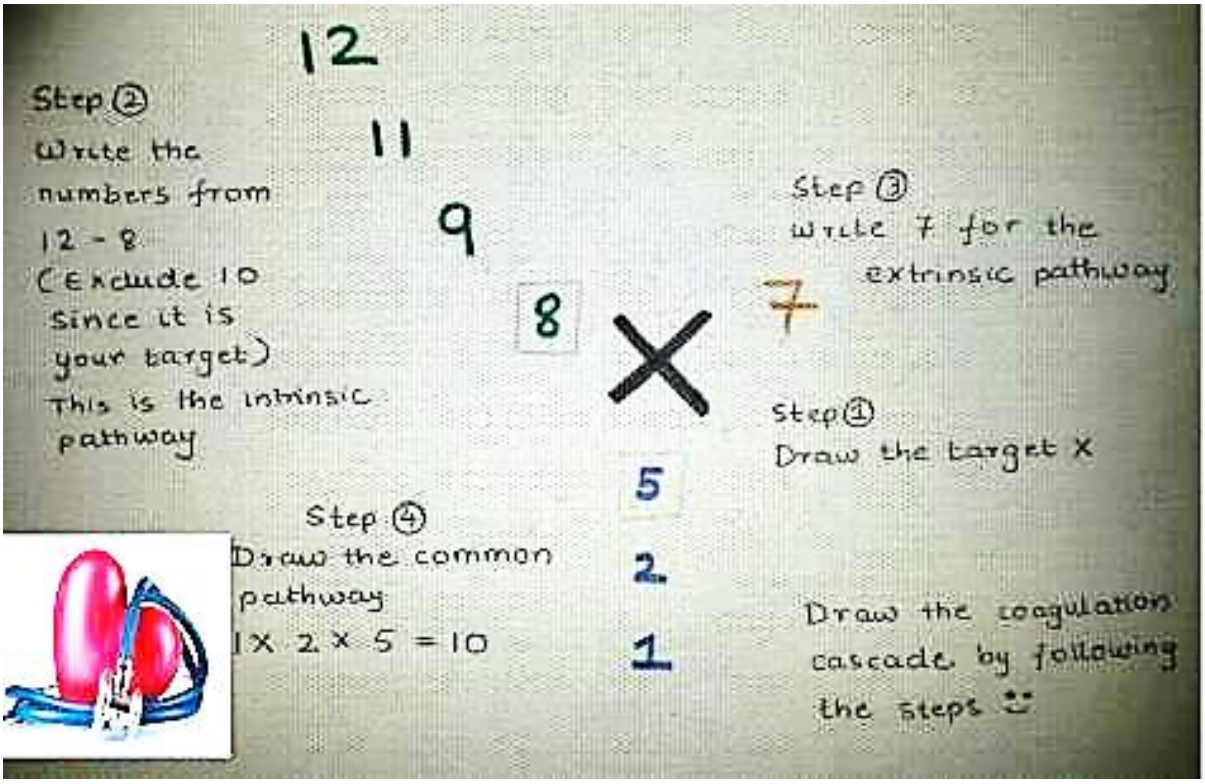
CLOTTING FACTORS

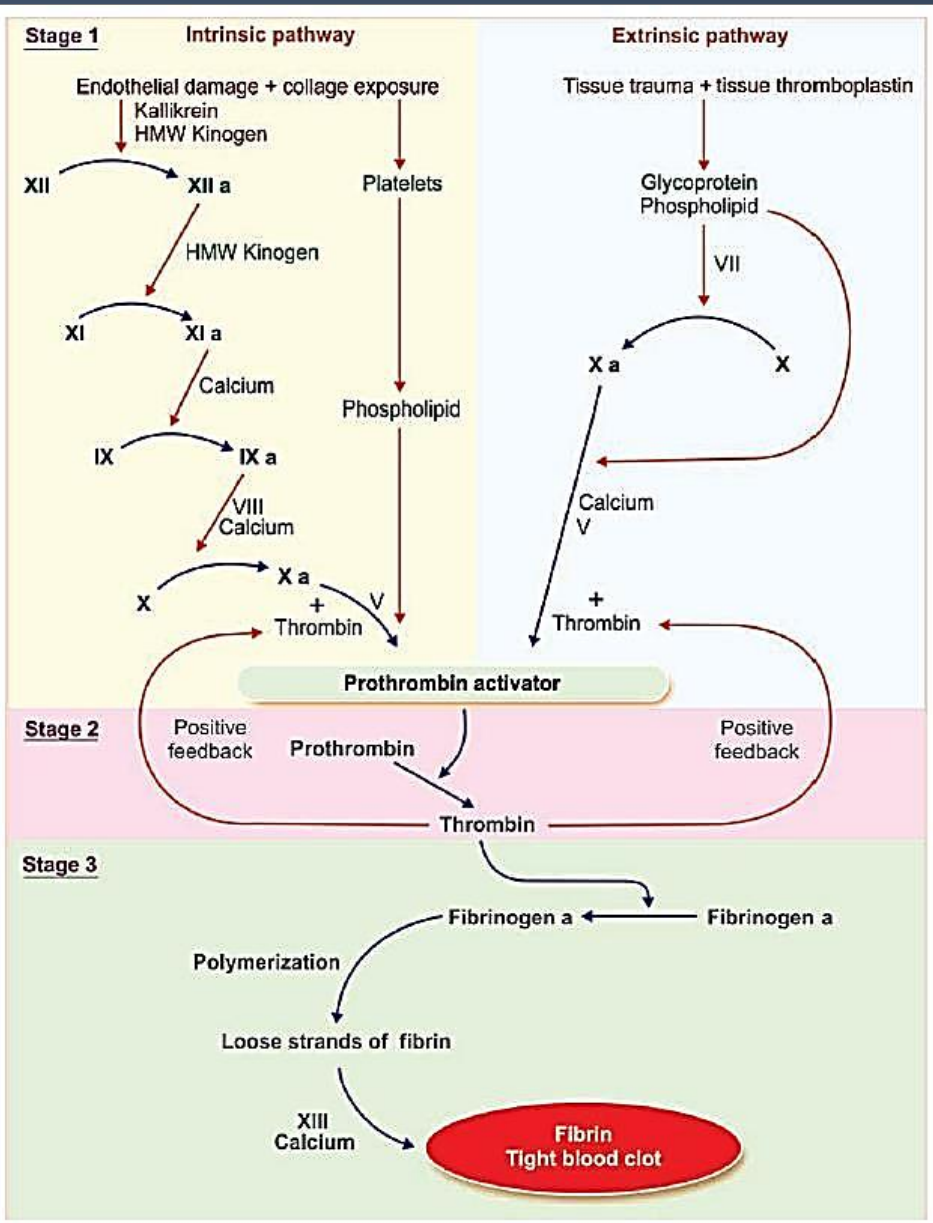
- There are 13 clotting factors involved in the coagulation of blood, they are given roman numeral.
- To indicate the activated form of the factor, a small letter "a" is added after the roman numeral such as factors VIIa to indicate activated factor VII.
- Clotting factors were named after the scientist who discovered them or as per the activity except for factor IX (Christmas Factor) which was named after the patient in whom it was discovered.
- They include:
  - Factor I- fibrinogen
  - Factor II- prothrombin
  - Factor III- Tissue factor/Thromboplastin
  - Factor IV- Calcium
  - Factor V- labile factor
  - Factor VI- presence has not been proven
  - Factor VII- stable factor
  - Factor VIII- antihemophilic factor
  - Factor IX- Christmas factor
  - Factor X- Stuart Prower factor
  - Factor XI- plasma thromboplastin antecedent
  - Factor XII- Hageman factor
  - Factor XIII-fibrin stabilizing factor
- To remember these factors, use the mnemonic: "Foolish People Try Climbing Long Slopes After Christmas Some People Have Fallen"
  - Note: This mnemonic does not include factor VI because its presence has not been proven
- Note: Factor II, VII, IX and X are vitamin K dependent factors.

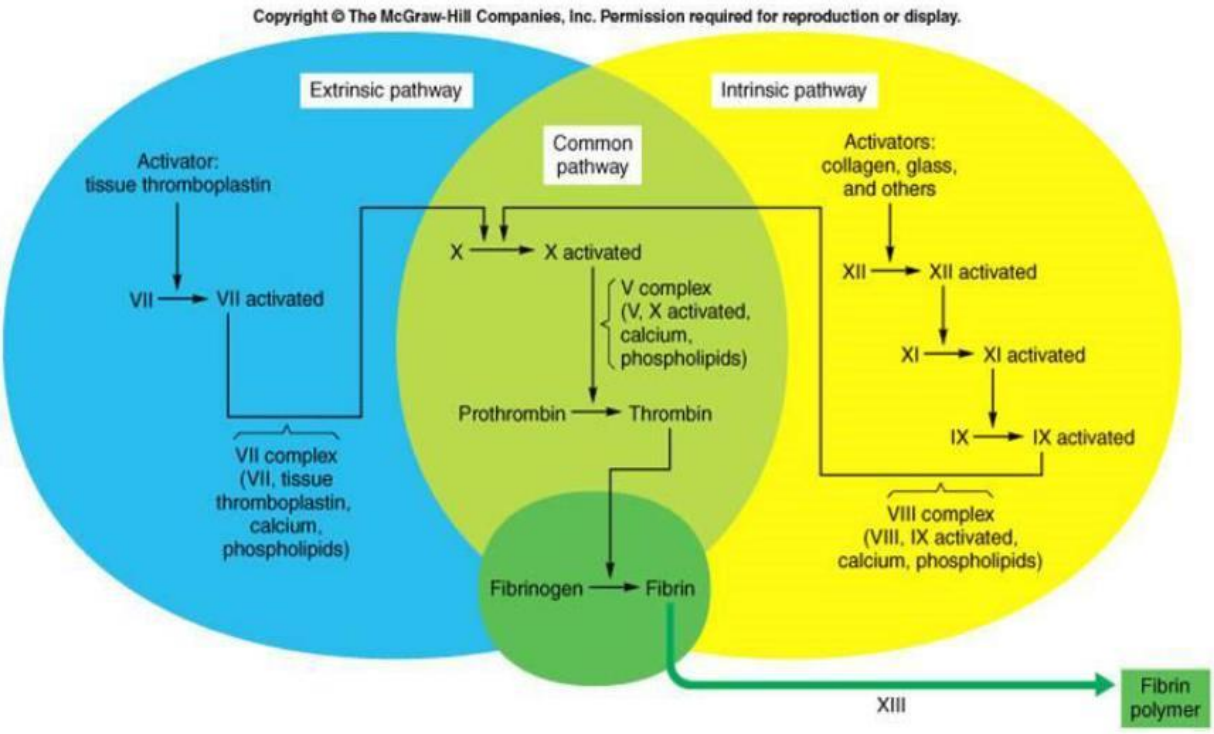
MECHANISM OF ACTION

- Clot formation is initiated under the following conditions:
  - Trauma to the vascular wall and adjacent tissue
  - Trauma to blood
  - Contact of blood with damaged endothelial cells or collagen or other tissue elements outside the vessels.
- Blood clotting involves a cascade of reactions in which activation of one factor leads to activation of subsequent factor

- Most of the clotting factors are proteins in form of enzymes that exist in an inactive proenzyme form.
- The conversion of an inactive enzyme to an active enzyme leads to activation of subsequent enzymes in a "water-fall sequence" until the final active enzyme thrombin is formed from prothrombin.
- Stages of clotting:
  - Formation of prothrombin activators
  - Conversion of prothrombin to thrombin
  - Conversion of fibrinogen into fibrin
- Prothrombin activators convert prothrombin to thrombin.
- Formation of prothrombin activators occurs through 2 pathways:
  - Extrinsic
  - Intrinsic
- These 2 pathways converge into a common pathway.

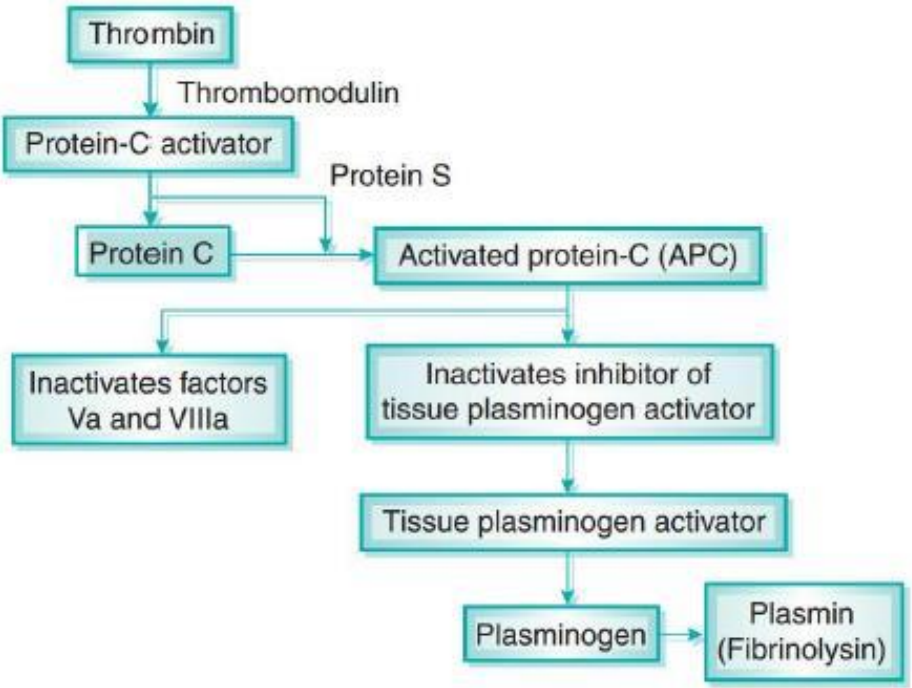



Stage 1
Intrinsic pathway
Extrinsic pathway
Endothelial damage + collage exposure
Kallikrein
HMW Kinogen
Tissue trauma + tissue thromboplastin
XII
XII a
Platelets
Glycoprotein
Phospholipid
HMW Kinogen
VII
XI
XI a
X a
X
Calcium
Phospholipid
IX
IX a
Calcium
V
VIII
Calcium
X
X a
+
Thrombin
V
+
Thrombin
Prothrombin activator
Stage 2
Positive
feedback
Prothrombin
Positive
feedback
Thrombin
Stage 3
Fibrinogen a
Fibrinogen a
Polymerization
Loose strands of fibrin
XIII
Calcium
Fibrin
Tight blood clot



FIBRINOLYSIS

- Fibrinolytic mechanisms are also put into place to remove the blood clot.



LABORATORY TESTS

- Bleeding time: this is the time between a skin prick and the arrest of bleeding. Normal bleeding time is 1 to 6 minutes. It indicates the platelet count and their function as well as health of capillaries.
- Prothrombin time: this is the time taken by blood to clot after adding tissue thromboplastin to it. Normal prothrombin time is 11-16s. It is a marker of the extrinsic pathway.
- Partial thromboplastin time/ activated partial thromboplastin time: this is the time taken for blood to clot after adding an activator such as phospholipid, along with calcium to it. Normal PTT is about 40s. PTT is used to monitor heparin therapy. It is a marker of the intrinsic pathway.
- International normalization ratio (INR): this is the ratio of a patient's PT to mean PT for the lab raised to the power of the international sensitivity index.
  - Normal population: 0.8-1.2
  - Standard therapy: 2.0-3.0
  - High dose therapy: 3.0- 4.5

PRIMARY HEMOSTATIC DISORDERS

- Disorders of primary hemostasis are defects of initial platelet plug formation i.e. the platelet or vessel endothelium.
- It is characterized by bleeding from small vessels and capillaries resulting in mucocutaneous bleeding.
- Petechial (pinpoint or punctate) hemorrhages occur in the skin and mucus membranes with bleeding and oozing from the nose (epistaxis), gums, genitourinary (hematuria and menorrhagia) and gastrointestinal tract (hemoptysis, GI bleeding).
- Multiple petechial subcutaneous hemorrhages may sometimes be described as a "rash".
- Bleeding begins immediately after trauma and either responds to simple measures such as pressure and packing or requires systemic therapy with glucocorticoids, desmopressin, plasma fraction and platelet concentrate.

- Petechiae: pinpoint hemorrhages which do not go white when pressed.
- Purpura: purple coloring of the skin similar to a bruise measuring 3mm or more and can be cause by blood disease and not by trauma.
- Ecchymoses: bleeding under skin greater than 1cm.

- Primary hemostasis disorders are characterized by:
  - Prolonged bleeding time (test has suboptimal accuracy and is rarely performed clinically)
  - Normal prothrombin time (PT)
  - Normal activated partial thromboplastin time (APTT or PTT)
- Causes of primary disorders of hemostasis include:
  - Lesions of vasculature
  - Platelet disorders:
    - Quantitative disorder (thrombocytopenia)
    - Qualitative disorder (platelet dysfunction)

LESIONS OF VASCULATURE

- Usually no laboratory abnormalities are associated with bleeding due to small blood vessel dysfunction but a prolonged bleeding time is sometimes noted.
- Examples include:
  - Simple purpura: easy bruising, especially of the upper thighs in otherwise health persons
  - Senile purpura: Hemorrhagic areas on the back of the hands and forearms of older persons. This condition is presumed to arise from age-dependent atrophy of vascular supportive tissues.
  - Scurvy:
    - Due to Vitamin C deficiency.
    - Clinical characteristics:
      - Extensive primary hemostatic bleeding with gingival hemorrhages
      - Bleeding into muscles and subcutaneous tissue
      - Hemorrhagic perifollicular hyperkeratotic papules, each papule surrounding a twisted, corkscrew-like hair.
  - Henoch-Schonlein purpura (allergic purpura)
    - This condition is a form of hypersensitivity (type III-immune complex) vasculitis resulting from an immune reaction that damages the vascular endothelium.
    - Characteristic features include hemorrhagic urticarial (palpable purpura), the purpuric rash is on the buttock and extensor surfaces accompanied by fever, arthralgia (painful joint swelling) and gastrointestinal (abdominal pain) and renal involvement (joint pain).
    - It is usually self-limiting however sometimes may cause renal failure.

- Hereditary hemorrhagic telangiectasia: This is an autosomal dominant disorder marked by localized malformation of venules and capillaries of the skin and mucous membranes, often complicated by hemorrhage.
- Connective tissue disorders: Includes Ehlers-Danlos syndrome, an inherited disorder caused by abnormalities of collagen or elastin and manifested by vascular bleeding, articular hypermobility, dermal hyper-elasticity and tissue fragility.
- Amyloidosis: Can cause vessel damage
- Rickettsial and meningococcal disease:
  - Include Rocky mountain spotted fever and meningococcemia.
  - These disorders involve vascular endothelium and immune complex deposition, leading to necrosis and rupture of small blood vessels.

PLATELET DISORDERS

QUANTITATIVE DISORDER

- Thrombocytopenia may follow 1 of 3 mechanisms:
  - Decreased bone marrow production
    - This is commonly associated with stem cell injury.
    - It affects multiple hematopoietic cell lines, hence varying degrees of accompanying anemia and leucopenia.
    - Bone marrow aspirate or biopsy shows a reduce number of megakaryocytes.
    - Common causes:
      - Marrow aplasia
      - Fibrosis
      - Infiltration of the marrow with malignant cells
    - Less common:
      - Cytotoxic drug use
      - Rarely congenital megakaryocytic hypoplasia and thrombocytopenia
  - Increased splenic sequestration
    - Usually follows condition causing splenomegaly e.g. portal hypertension and splenic infiltration with tumor cells as in myeloproliferative disorders or lymphoproliferative ones.
  - Accelerated destruction of platelets
    - Non-immunologic: associated with abnormal vessels, fibrin thrombi and valve prosthesis. Examples include vasculitis, hemolytic uremic syndrome, TTP and DIC

  - Immunologic: platelets coated with antibody, immune complexes or compliments are rapidly cleared by mononuclear phagocytes in the spleen or other tissues, may follow viral or bacterial infections, drugs etc.
  - Drug induced thrombocytopenia: these include chemotherapeutic agents (especially carboplatin, alkylating agents, anthracycline and antimetabolites), antibiotics (sulfonamides, penicillines and cephalosporines), Heparins (highest incidence is with unfractionated products) and cardiovascular agents (thiazide diuretics rarely angiotensin converting enzyme inhibitors). Most drugs induce thrombocytopenia by eliciting an immune response in which platelets are innocent bystanders. The best proof of drug induced thrombocytopenia is prompt rise in the platelet count when the suspected drug is discontinued.

- To determine the etiology one should do
  - An estimate of splenic size by bed side palpation supplemented by ultrasound.
  - Platelet count
  - Bleeding time
  - Blood smear
  - Assessment of marrow morphology by examination of an aspirate or biopsy
- Dominant features include petechial cutaneous bleeding, intracranial bleeding (with severe thrombocytopenia) and oozing from mucosal surfaces.
  - Petechiae are a sing of thrombocytopenia and are not usually seen with qualitative disorders.
- Quantitative platelet disorders are characterized by:
  - Decreased platelet count. When platelet count is reduced there will be reactive marrow megakaryocytosis.
    - Bone marrow aspiration reveals decreased megakaryocytes when caused by decreased platelet production and increased megakaryocytes when caused by increased platelet destruction.
  - Prolonged bleeding time.
- Implicated conditions: acute leukemia, myelopthisis, aplastic anemia, splenic sequestration, Multiple transfusion, Disseminated intravascular coagulation (DIC), idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP)

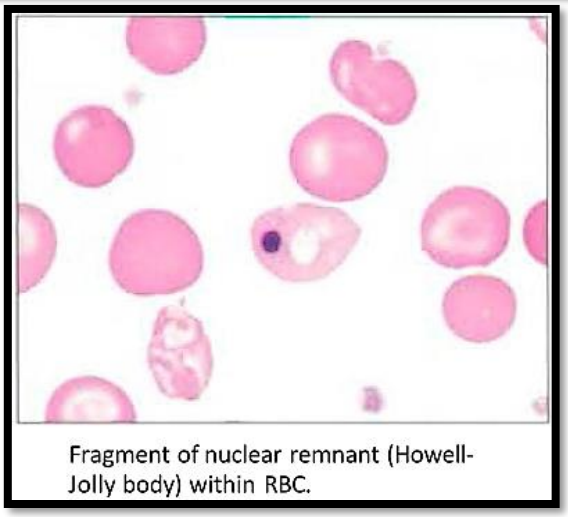
- Acute leukemia: causes decreased production because of replacement of bone marrow by blast cells.
- Myelopthisis: causes decreased production because of bone marrow replacement usually by tumor cells.
- Aplastic anemia: often caused by exposure to toxic agents such as benzene. It can also be due to autoimmune destruction by cytotoxic T-cells.
- Splenic sequestration: results in loss of circulating platelets.
- Multiple transfusions result in dilution
- Disseminated intravascular coagulation (DIC): Results in depletion of platelets through consumption
- Thrombocytopenia can be secondary to other disease e.g. AIDS and systemic lupus erythematosus.

IDIOPATHIC/IMMUNOLOGIC THROMBOCYTOPENIC PURPURA (ITP)

- This is also known as immune (or autoimmune) thrombocytopenic purpura. It is an autoimmune production of IgG against platelet antigens e.g. GPIIb/IIIa.
- The IgG antibodies are produced by the plasma cells in the spleen. The antibody platelets are consumed by splenic macrophages resulting in thrombocytopenia.
- It is the most common cause of thrombocytopenia in children and adults.
- In children (2-6 years), it is usually acute, self-limiting reaction to viral infection or immunization.
  - It accounts for 90% of pediatric cases
  - 60% recover in 4 to 6 weeks and over 90% recover within 3 to 6 months.
- In adults it is a chronic disorder.
  - It runs an indolent course.
  - Women aged 20-40 are afflicted most commonly and outnumber men by a ratio of 3:1.
  - It presents acutely or more often with prior history of easy bruising and menometrorrhagia.
  - There is immune mediated platelet destruction as well as platelet dysfunction.
- Characteristics:
  - Antiplatelet antibodies that coat and damage platelets, which are then selectively removed by splenic macrophages
  - Maternal IgG antibodies in affected mother can cause fetal thrombocytopenia
- ITP shows thrombocytopenia with normal or increased megakaryocytes.

- For a diagnosis of ITP there shouldn't be an exposure to thrombocytopenic agents, or splenomegaly.
- Investigations:
  - Platelet count: decreased, often <50 000/microliter
  - Full blood count
  - Normal PT and PTT
  - Serology for HIV and screening for SLE
    - HIV infection is a common cause of immunologic thrombocytopenias in young adults.
  - Ultrasound of the abdomen to look for splenomegaly
  - Bone marrow aspirate to look for reactive thrombocytosis (increased megakaryocytes)
- Treatment:
  - Depends on age, severity and anticipated natural history.
  - Specific treatment may not be necessary unless platelet count is <20 000/ml
  - Steroids:
    - Symptomatic patients with ITP are placed on prednisolone 60mg/day for 4 to 6 weeks then tapered slowly over another few weeks.
    - Children respond well but adults may show early response, but often relapse.
    - Those patients who fail to maintain a normal platelet count after a course of steroids are eligible to splenectomy (steroids responsive but dependent patients are most likely to respond to splenectomy)
  - Intravenous immunoglobulins (IVIG) or anti-Rho (win Rho) (reserved for those with severe thrombocytopenia and clinical bleeding who are refractory to other measures) it is used to raise the platelet count in symptomatic bleeding but its effect is short lived. The spleen destroys the infused immunoglobulins and not the platelets.
  - Platelet transfusion is considered only in those with eminent CNS bleeding as a temporary measure.
  - Emergency splenectomy: for those who are desperately ill and refractory to medical measures.
    - Splenectomy eliminates primary source of antibody and site of destruction.

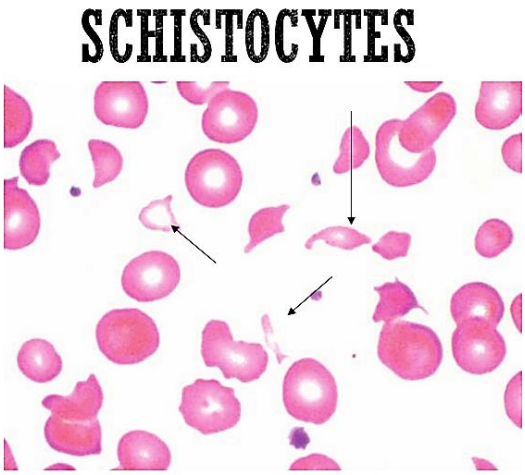
- Note: failure to respond to splenectomy may signify presence of accessory spleen which may be evidenced by peripheral blood smear examination for Howell Jolly body (fragments of nuclear material in RBCs) which appears in the circulation of asplenic patients. Such patients may need immunosuppressive therapy or plasmapheresis.


Fragment of nuclear remnant (Howell-Jolly body) within RBC.

- Antiretroviral treatment for those dually infected with HIV increases platelet count.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- Characteristics:
  - Platelet derived hyaline microaggregates in small vessels (microvascular platelet thrombi)
  - Thrombocytopenia: platelets are consumed as microthrombi are formed.
  - Microangiopathic hemolytic anemia: the microcirculatory lesions produce mechanical damage to red blood cells as they squeeze through narrowed vessels, resulting in helmit cells and Schistocytes.



- Causes include deficiency of von Willebrand factor metalloprotease. Enzyme deficiency results in accumulation of very high molecular weight multimer of vWF, promoting platelet microaggregate formation.
- Note: microangiopathic hemolytic anemia is seen also in hemolytic uremic syndrome (HUS)
  - HUS is due to endothelial damage by drugs or infection.
  - Classically seen in children with E. coli O157:H7 dysentery, which results from exposure to undercooked beef.
  - E. coli verotoxin damages endothelial cells resulting in platelet microthrombi.
- Clinical findings (HUS and TTP):
  - Skin and mucosal bleeding

  - Microangiopathic hemolytic anemia
  - Fever
  - Renal insufficiency (more common in HUS)- thrombi involve vessels of the kidney
  - CNS abnormalities (more common in TTP)- thrombi involve vessels of the CNS
- Laboratory findings:
  - Thrombocytopenia with increased bleeding time
  - Normal PT/PTT (coagulation cascade is not activated)
  - Anemia with Schistocytes
  - Increased megakaryocytes on bone marrow biopsy
- Treatment involves plasmapheresis and corticosteroids, particularly in TTP.

QUALITATIVE DISORDER

- These platelet-mediated bleeding disorders occur in spite of a normal platelet count.
- They result in mucocutaneous bleeding and are often associated with a prolonged bleeding time.
- Causes:
  - Defects of platelet adhesion:
    - Von Willebrand disease (discuss under combined hemostasis disorders), an autosomal recessive disorder characterized by unusually large platelets lacking platelet-surface glycoprotein needed for platelet adhesion.
    - Bernard-Soulier syndrome is due to a genetic GPIb deficiency required for platelet adhesion. Blood smear shows thrombocytopenia with enlarged platelets.
  - Defects of platelet aggregation: can either be
    - Acquired (aspirin induced- inhibition of COX-1 and COX-2 leading to failure of synthesis of thromboxane A2)
    - Inherited (Glanzmann thrombasthenia, inaggregability of platelets due to hereditary deficiency of platelet surface GPIIb-IIIa required for formation of fibrinogen bridges between adjacent platelets)
- Uremia disrupts platelet function and causes both adhesion and aggregation impairment.

SECONDARY HEMOSTATIC DISORDERS

- Secondary hemostasis stabilizes the weak platelet plug. It occurs via the coagulation cascade.
  - Coagulation cascade generates thrombin which converts fibrinogen in the platelet plug to fibrin.
  - Fibrin is then cross-linked, yielding a stable platelet-fibrin thrombus
- Factors of the coagulation cascade are produced by the liver in an inactive state. Activation requires:
  - Exposure to an activating substance
    - Tissue thromboplastin activates factor VII (extrinsic pathway)
    - Subendothelial collagen activates factor XII (intrinsic pathway)
  - Phospholipid surface of platelets
  - Calcium (derived from platelet dense granules)
- Disorders of secondary hemostasis are caused by deficiencies of plasma clotting factors.
- Manifestations include:
  - Bleeding from larger vessels resulting in hemarthroses (blood in joints)
  - Large hematomas
  - Large ecchymoses
  - Extensive bleeding with trauma (rebleeding after surgical procedures)
- Bleeding time or platelet count is not affect (thus distinguishing secondary hemostatic disorders from primary hemostatic disorders).
- Laboratory results:
  - Abnormalities in PT: It measures the extrinsic (factor VII) and the common pathway (Factors II, V, X and fibrinogen). It reflects deficiency of fibrinogen or factors, II, V, VII and X
    - PT is a better measure of Warfarin therapy
  - Abnormalities in APTT (or PTT): It measures the intrinsic (Factors XII, XI, IX, VIII) and common pathway (Factors II, V, X and fibrinogen). It reflects deficiency of all the coagulation factors except factors VII and XIII
    - PTT is a better measure of Heparin therapy
  - Thrombin time: reflects deficiency of fibrinogen
- They include:
  - Classic hemophilia (Hemophilia A, Factor VIII deficiency)
  - Christmas disease (Hemophilia B, Factor IX deficiency)
  - Vitamin K deficiency

CLASSIC HEMOPHILIA

- This is an X-linked recessive disorder with worldwide distribution and varies in severity depending on the factor VIII activity (absence or low level of plasma factor VII).
- Characteristics include: bleeding into muscles, subcutaneous tissue and joints. As well as postsurgical bleeding.
- Clinical features:
  - Profuse post circumcision hemorrhage in infants
  - Recurrent painful hemarthroses and muscle hematomas
  - Spontaneous intracerebral hemorrhage is an important cause of death
  - Transfusion related disorders: hepatitis (HBV, HCV) and HIV infection are frequent complications of repeated coagulation factors transfusions.
- The disorder is associated with a prolongation of APTT (PTT) and normal bleeding time, platelet count, PT and thrombin time. There is a decrease in factor VIII amounts.
- Because 30% of cases are attributable to new mutations, a positive family history may not always be present. If family history is present inheritance is X-linked recessive.
- Female carrier usually have >50% factor VII activity and usually fall within normal range. Females may rarely be symptomatic due to homozygosity, hemizygosity (Turner syndrome) and asymmetric lionization.

Coagulation factor activity (% of normal)	Clinical manifestations
<1	• Severe disease • Frequent spontaneous bleeding • Episode from early life • Joint deformity and crippling
1-5	• Moderate disease • Post-Traumatic bleeding • Occasional spontaneous episodes of bleeding
5-20	• Mild disease • Post-Traumatic bleeding

- Treatment:
  - Factor VII replacement
    - Spontaneous bleeding is usually controlled if patient's factor VIII activity is >20%
    - For major surgery or serious post-traumatic bleeding or hemorrhage occurring in dangerous sites.
    - Factor VIII level should be raised to 100% and maintained above 60% until healing occurs.
  - Desmopressin

CHRISTMAS DISEASE

- This is a deficiency of clotting factor IX (Christmas factor).
- Incidence is approximately one fifth that of classic hemophilia.
- Hemophilia B is indistinguishable from classic hemophilia in mode of inheritance and clinical features.

VITAMIN K DEFICIENCY

- Vitamin K is activated by epoxide reductase in the liver.
- Activated Vitamin K gamma carboxylates factors II, VII, IX, X and proteins C and S. Gamma carboxylation is necessary for factor function.
- In adults, Vitamin K deficiency is most often caused by fat malabsorption from pancreatic or small-bowel disease (recall fat soluble vitamins are A, D, E, K). Long-term antibiotic therapy-disrupts vitamin K producing bacteria in the GI tract.
- In neonates, vitamin K deficiency cause hemorrhagic disease of the new born, which is due to deficient exogenous vitamin K in breast milk in association with incomplete intestinal colonization by vitamin K synthesizing bacteria.
  - Vitamin K injection is given prophylactically to all newborns at birth to prevent hemorrhagic disease of the new born.
- Results in decreased activity of factors II, VII, IX and X and are reflected by prolongation of the PT and APTT.

Features	Hemophiliac	Factor IX deficiency	Von Willebrand's disease
Inheritance	Sex linked recessive	Sex linked recessive	Autosomal dominant
Site of bleeding	Body cavities, joint & intramuscular spaces	Body cavities, joint & intramuscular spaces	Both mucocutaneous and other mentioned sites
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Prothrombin Time	Normal	Normal	Normal
Partial thromboplastin time	Prolonged	Prolonged	Prolonged or normal
VIII	Low	Normal	Low
VWF	Normal	Normal	Low
Factor IX	Normal	Low	Normal

COMBINED HEMOSTATIC DISORDER

- Include:
  - Von Willebrand disease
  - Coagulopathy of liver disease
  - Disseminated intravascular coagulation
  - Dilutional coagulopathy

VON WILLEBRAND DISEASE

- This is the most common hereditary bleeding disorder.
- It is an autosomal disorder marked by deficiency of vWF, a large multimeric protein synthesized by endothelial cells and megakaryocytes.
- vWF is a carrier protein for factor VIII (antihemophilic factor) and the two proteins circulate together as a complex. It also mediates adhesions of platelets of subendothelium at sites of vascular injury.
- Characteristics:
  - Impaired platelet adhesion
  - Prolonged bleeding time
  - Functional deficiency of factor VIII

THROMBOTIC DISORDERS

THROMBOSIS

- Thrombi can occur in an artery or vein.
- Thrombosis occurring in the veins is commonly seen in the veins of the leg and the pelvis.
- Thrombosis is a pathologic formation of an intravascular blood clot.
- Most common locations are in the deep veins (DVT) of the leg below the knee.
- The thrombus is characterized by:
  - Lines of Zahn: characterized by alternating layers of platelets/fibrin and RBCs
  - Attachment to vessel wall
- Both features distinguish thrombus from postmortem clot.
- There are 3 major risk factors for thrombosis (Virchow's triad):
  - Disruption in blood flow (stasis)
  - Endothelial cell damage
  - Hypercoagulable state

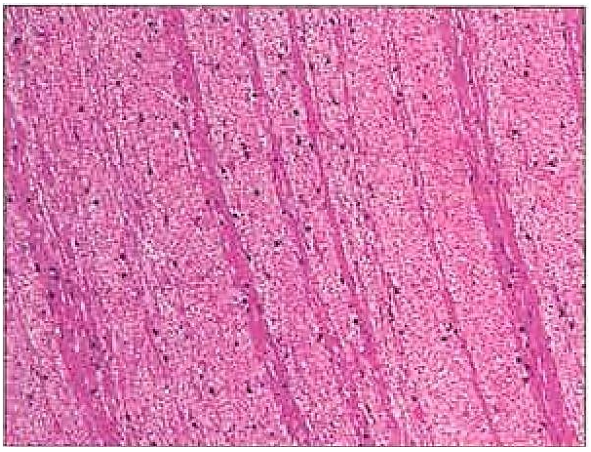


Figure 38: Lines of Zahn (alternating layers of platelets/fibrin and RBCs)

DISRUPTION IN BLOOD FLOW

- Stasis or turbulence of blood flow increases risk for thrombosis.
- Examples:
  - Immobilization- increased risk for DVT
  - Cardiac wall dysfunction e.g. arrhythmia i.e. atrial fibrillation or myocardial infarcation
  - Aneurysm

ENDOTHELIAL CELL DAMAGE

- Endothelial damage disrupts the protective function of endothelial cells, increasing the risk for thrombosis.
- Endothelial cells prevent thrombosis by several mechanisms:
  - Block exposure to subendothelial collagen and underlying tissue factor
  - Production of prostacyclin (PGI_2)- blocks platelet aggregation and NO- causes vasodilation

- Secretion of heparin-like molecules- augment antithrombin III (ATIII) which inactivates thrombin and coagulation factors
- Secretion of Tissue plasminogen activator (tPA)- converts plasminogen to plasmin which
  - Cleaves fibrin and serum fibrinogen
  - Destroys coagulation factors
  - Blocks platelet aggregation
- Secretion thrombomodulin- redirects thrombin to activate protein C, which inactivates factors V and VIII

- Causes of endothelial damage include atherosclerosis, vasculitis and high levels of homocysteine
  - Vitamin B12 and folate deficiency result in mildly elevated homocysteine levels, increasing the risk for thrombosis.
    - Recall: folic acid (tetrahydrofolate, THF) circulates as methyl-THF in the serum
    - Methyl is transferred to cobalamin (vitamin B12) allowing THF to participate in the synthesis of DNA precursors
    - Cobalamin transfers methyl to homocysteine resulting in methionine
    - Lack of vitamin B12 or folate leads to decreased conversion of homocysteine to methionine resulting in buildup of homocysteine
  - Cystathionine beta synthase (CBS) deficiency results in high homocysteine levels with homocystinuria
    - CBS converts homocysteine to cystathionine, enzyme deficiency leads to homocysteine buildup
    - It is characterized by vessel thrombosis, mental retardation, lens dislocation and long slender fingers

HYPERCOAGULABLE STATE

- Due to excessive pro-coagulant proteins or defective anticoagulant proteins.
- It may be inherited or acquired.
- Classica presentation is recurrent DVTs or DVT at a young age. Usually occurs in the deep veins of the legs. Other sites include the hepatic and cerebral vein
- Examples:
  - Protein C and S deficiency (autosomal dominant) decreases negative feedback on the coagulation cascade
    - Protein C and S normally inactivate factors V and VIII
    - Increased risk for warfarin skin necrosis

        - Warfarin blocks epoxide reductase in the liver that blocks the ability to activate vitamin K (factors II, VII, IX and X, protein C and S cannot be synthesized effectively)
        - Initial stage of warfarin therapy results in a temporary deficiency of proteins C and S (due to shorter half-life as protein C and S degrade faster in comparison to the factors) relative to factors II, VII, IX and X
        - In pre-existing C or S deficiency, a severe deficiency is seen at the onset of warfarin therapy increasing risk for thrombosis, especially in the skin.
    - Factor V leiden is a mutated form of factor V that lacks the cleavage site for deactivation by protein C and S. This is a common inherited cause of hypercoagulable state.
    - Prothrombin 20210A is an inherited point mutation in prothrombin that results in increased gene expression. Increased prothrombin results in increased thrombin, promoting thrombus formation
    - Antithrombin III deficiency:
        - Decreases the protective effect of heparin-like molecules by the endothelium, increasing the risk for thrombus.
        - Heparin-like molecules normally activate ATIII which inactivates thrombin and coagulation factors.
        - In ATIII deficiency, PTT does not with standard heparin dosing.
        - Pharmacologic heparin works by binding and activating ATIII
        - High doses of heparin activate limited ATIII, Coumadin is then given to maintain an anticoagulated state.
    - Oral contraceptives are associated with a hypercoagulable state: Estrogen induces increased production of coagulation factors, thereby increasing the risk for thrombus
- Note: heparin therapy is monitored using the PTT and you would expect it to rise.

SUPERFICIAL THROMBOPLEBITIS

- This commonly involves the saphenous veins and is often associated with varicosities.
- Occasionally the axillary vein is involved usually as a result of trauma. There is local superficial inflammation of the vein wall, with secondary thrombosis.
- The clinical picture is of a painful, tender, cord-like structure with associated redness and swelling.
- The condition usually responds to symptomatic treatment with rest, elevation of the limb and analgesics (e.g. NSAIDs)
- Fodaparinux 2.5mg OD SC has been seen to significantly reduce the rate of thromboembolic events (pulmonary embolism and deep vein thrombosis)

DEEP VEIN THROMBOSIS

- This is formation of an intravascular thrombus (blood clot) in the deep veins.
- A thrombus forms in the vein and any inflammation of the vein wall is secondary to this.
- Thrombosis commonly occurs after periods of immobilization but it can occur in normal individuals for no obvious reasons.
- A deep vein thrombosis in the legs occurs in 50% of patients after prostatectomy (without prophylactic heparin) or following a cerebral vascular event or an obstetric operation.
- Thrombosis can occur in any vein of the leg or pelvis, but is particularly found in veins of calf. Around 10% progress to the proximal leg and become (more) symptomatic.
- Axillary vein thrombosis occasionally occurs, sometimes related to trauma but usually for no obvious reason.
- 50% of untreated proximal thrombi progress to pulmonary embolism (PE), the commonest type of venous thromboembolism.
- Less commonly, PEs are caused by fat, fluid, or infective emboli.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

- Non-modifiable
  - Age >60years
  - Personal history or first degree relative with a history of venous thromboembolism
- Modifiable
  - Active cancer or cancer treatment: there is activation of thrombin. Prostate and ovarian are particularly associated.
  - Critical care admission (immobility), immobility leads to venous status
  - Dehydration
  - Known thrombophilia
  - Obesity (BMI >30)
  - Significant medical comorbidities e.g. heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases, inflammatory conditions, IBD, Nephrotic syndrome, Polycythemia rubra vera.
  - Use of hormone replacement therapy or estrogen containing contraceptive therapy: estrogen increases fibrinogen, prothrombin and clotting factor levels.
  - Varicose veins with phlebitis
  - Pregnancy/childbirth

Virchow's triad for thrombi formation

- Endothelial dysfunction (damage)
- Stasis
- Hypercoagulabile state

CLINICAL FEATURES

- The individual may be asymptomatic, presenting with clinical features of pulmonary embolism.
  - Sudden onset of unexplained dyspnea (this may be the only sign)
  - Pleuritic chest pain and Hemoptysis are present only when infarction has occurred.
  - Tachypnea, pleural rub, coarse crepitation, pericardial effusion, tachycardia, atrial fibrillation, pulsus paradoxus, raised JVP, right ventricular heave, gallop rhythm, widely split second heart sound or signs of right ventricular overload with a right ventricular heave and loud pulmonary second sound may be seen on examination
- A major presenting feature is pain in the calf, often with swelling, redness and engorged superficial veins.
- The affected calf is often warmer and there may be ankle edema.

- Homan's sign (pain in the calf on dorsiflexion of the foot) is often present but is not diagnostic and occurs with all lesions of the calf.
  - The Moses' sign (Bancroft's sign) is also found in patients with DVT of the lower leg involving the posterior tibial veins. The sign is positive if pain is elicited when the calf muscle is compressed forwards against the tibia but not when the calf muscle is compressed from side to side. This sign is neither sensitive or specific for DVT.
  - The Lowenberg's sign is also a clinical sign found in patients with DVT of the lower leg. The sign is positive when pain is elicited rapidly when a blood pressure cuff is placed around the calf and inflated to 80mmHg. This sign is neither sensitive or specific for DVT.
  - These signs should be carried out with caution as they run the risk of dislodging the thrombus complicating into pulmonary embolism.
- Thrombosis in the illiofemoral region can present with severe pain but there are often few physical signs apart from occasional swelling of the thigh and/or ankle edema.
- Complete occlusion particularly of a large vein can lead to a cyanotic discoloration of the limb and severe edema, which can very rarely lead to venous gangrene.

INVESTIGATIONS

- Clinical diagnosis is unreliable but combined with D-dimer level it has a sensitivity of 80%.
  - D-dimer are products of thrombolysis and once seen are indicative of a lysis of a thrombi
- Confirmation of an illofemoral thrombosis can usually be made with B mode venous compression ultrasonography or Doppler ultrasound with a sensitivity and specificity over 90%.
- Below-knee thromboses can be detected reliably only by venography with non-invasive techniques, ultrasound, fibrinogen scanning and impedance plethysmography have a sensitivity of only 70%.
- A venogram is performed by injecting a vein in the foot with contrast which will detect virtually all thrombi that are present.
- Chest X-ray in suspected PE: may show wedge-shaped infarct (rare) but more for ruling out other conditions.
- Other investigations:
  - Baseline aPTT before heparin and baseline INR before warfarin.

- ECG in PE: most commonly sinus tachycardia (50%). Less commonly (20-30% each), RV strain (T wave inversion in V1-V3), S1Q3T3 (Prominent S in lead I, and Q wave and inverted T in lead III), right bundle branch block and right axis deviation.
- Unprovoked venous thromboembolism: consider thrombophilia screen. Look for underlying cancer only if suggested by history, exam and basic bloods.
- Arterial blood gasses in PE: decreased oxygen and carbon dioxide partial pressure, increased pH.

TREATMENT

- The main aim of therapy is to prevent pulmonary embolism and all patients with thrombi above knee must be anticoagulated.
- Anticoagulation of below-knee thrombi is now recommended for 6 weeks as 30% of patients will have an extension of the clot proximally.
- Bed rest is advised until the patient is fully anticoagulated.
- The patient should then be mobilized with an elastic stocking giving graduated pressure over the leg.
- Low molecular weight heparin e.g. Enoxaparin have replaced unfractionated heparin as they are more effective, they do not require monitoring and there is less risk of bleeding.
  - Enoxaparin 1.5mg/kg SC every 24 hours until INR> 2 for >24 hours.
  - Alternatively, 1mg/kg SC every 12 hours
  - It should be administered the same time each day.
- DVTs are being treated at home with LMW heparin.
- Warfarin is started after 1 or 2 days of heparin therapy and the heparin stopped when the INR is in the target range.
  - Warfarin should not be started alone because it is pro-coagulant in the first days, it inhibits the synthesis of factors II, VII, IX and X as well as Protein C and protein S. The half-lives of already synthesized Protein C are shorter than the clotting factors so there is increased risk for coagulation.
  - Warfarin should be started within 72 hours of starting Enoxaparin.
  - Continue enoxaparin and warfarin for a minimum of 5 days and until therapeutic oral anticoagulation effect has been achieved (INR 2.0-3.0, Target INR should be 2.5)
  - Average administration is up to 7 days. Stop heparin after and continue with Warfarin.

- Anticoagulants do not lyse the thrombus that is already present
- Unfractionated heparin should only be used if LMWH is unavailable
  - Loading dose 5000 units SC followed by 15 000 units every 12 hours with Lab monitoring preferably on a daily basis and dose adjusted accordingly.
  - Alternatively loading dose 75units/kg IV injection, followed by continuous intravenous infusion 18 units/kg/hour, with Lab monitoring preferably on a daily basis and dose adjusted accordingly

- Warfarin dosage:
  - Initial dose (induction dose): 2-5mg PO every day for 2 days or 10mg PO for 2 days in healthy individuals
  - Maintenance dose 2-10 mg PO per day
- The duration of warfarin treatment is debatable-3 months is the period usually recommended but 4 weeks is long enough if a definite risk factor (e.g. bed rest) has been present.
- Recurrent DVTs need permanent anticoagulants.
- Thrombolytic therapy is occasionally used for patients with a large illiofemoral thrombosis.

Medications	Pros	Cons	Test used to monitor
Unfractionated heparin	Short half-life, can turn off quickly if the patient bleeds. Although falling out of favor, still appropriate for acute coronary syndromes, cardiopulmonary bypass, acute thrombotic events, mechanical heart valves and anticoagulation in renal failure	Requires continuous IV infusion Long-term use is associated with osteoporosis Carries a risk of heparin induced thrombocytopenia	Need to monitor PTT and platelet count at least daily (for heparin induced thrombocytopenia) Reversible with protamine sulfate.
LMWH	No need to monitor PTT as dosing is weight based.	Excretion is impaired in renal failure (Creatinine clearance should be greater than 30ml/min)	Will not prolong PTT, if monitoring is required, measure- Factor Xa activity

		Not reversible with protamine. Requires injection.	
Warfarin	Oral	Slow to reach therapeutic effect, requires the addition of heparin with starting for an acute clot. Teratogenic, many drug interactions. Warfarin skin necrosis (Rare)	Monitor with INR, appropriate INR and duration vary by clinical situation Reversible with FFP or vitamin K
Direct thrombin inhibitors (Leepirudin or argatroban)	Used for anticoagulation in patients with heparin induced thrombocytopenia	Irreversible thrombin inhibitors, require continuous IV infusion	Monitor with PTT

COMPLICATIONS

- Cellulitis/ thrombophlebitis: can resemble, cause or follow DVT.
- Post-thrombotic syndrome: varicose vein-like symptoms (itch, swelling, dull pain), venous ulcers. It can occur up to 12 months post DVT. Prevention: compression stockings on the affected leg for 2 years after DVT, though the evidence is weak.

PROPHYLAXIS

- Patients at risk for venous thromboembolism
  - Medical patients with reduced mobility for more than 3 days or if their mobility is reduced and they have more than 1 risk factor for venous thromboembolism
  - Surgical and trauma patients are at risk:
    - If they undergo surgical procedure with a combined anesthetic and surgery of >90min (60 min if surgery on pelvis or lower limb)
    - If they are admitted with an acute inflammatory or intra-abdominal condition
    - If they have significantly reduced mobility
    - If they have more than 1 risk factor for venous thromboembolism.
- Patients at risk should be considered for pharmacological prophylaxis (fondaparinux or LMW heparin or unfractionated heparin if renal impairment) unless they have a risk factor for bleeding that outweighs the benefits of venous thromboembolism prophylaxis.
- Risk factors for bleeding:
  - Active bleeding
  - Acquired bleeding disorders (e.g. acute liver failure)
  - Concurrent use of anticoagulants (such as warfarin with INR >2)
  - Lumbar puncture/epidural/spinal anesthesia within the previous 4 hours or expected within 12 hours
  - Acute stroke
  - Thrombocytopenia (Platelets <75 x 10^9/L)
  - Uncontrolled systolic hypertension (>230/120 mmHg)
  - Untreated inherited bleeding disorders (hemophilia and von Willebrand's disease)
- Patients should also be encouraged to mobilize where possible and mechanical venous thromboembolism (anti-embolism stockings (thigh or knee length), foot impulse devices, intermittent pneumatic compression devices (thigh or knee length) may be appropriate in certain patients.
- On discharge patients should be provided with advice on the signs and symptoms of venous thromboembolism and if prescribed pharmacological or mechanical prophylaxis advice on their usage.

CHAPTER 6: PULMONOLOGY

RESPIRATORY CONDITIONS

APPROACH TO RESPIRATORY CONDITIONS

- Patients with disease of the respiratory system generally present because of symptoms, an abnormality on a chest radiography or both.
- Most patients with respiratory disease will present with one or more of the following symptoms:
  - Breathlessness
  - Cough
  - Sputum
  - Hemoptysis
  - Wheezing
  - Pain in chest
- Dyspnea (shortness of breath) and cough are common presenting symptoms for patients with respiratory system disease.
- Less common symptoms include hemoptysis (coughing up blood), and chest pain, often with a pleuritic quality.

ASSESSING RESPIRATORY SYMPTOMS

DYSPNEA

- Breathlessness inappropriate to the level of physical exertion or even occurring at rest is called dyspnea.
- Its mechanisms are complex and not just dependent on lowered blood oxygen tension (hypoxia) or raised blood carbon dioxide tension (hypercapnia).
- People with cardiac disease may become dyspneic as well as those with primary respiratory problems.
- To assess dyspnea a few questions, need to be asked:
  - Is the dyspnea related only to exertion?
  - How far can the patient walk at a normal pace on the level?

- Is there variability in the symptom? Are there good days and bad days and very importantly, are there any times of day or night that are usually worse than others?
  - Variable airways obstruction due to asthma is very often worse at night and in the early morning.
  - People with pre-dominantly irreversible airways obstruction due to chronic obstructive pulmonary disease (COPD) will often say that as long as they are sitting in bed they feel quite normal; it is exercise that troubles them.

- When evaluating a patient with shortness of breath, one should determine:
  - Time course over which the symptom has become manifest:
    - Patients who were well previously and developed acute shortness of breath (over a period of hours to days) can have acute disease affecting the airways (an acute attack of asthma), the pulmonary parenchyma (acute pulmonary edema or an acute infectious process such as bacterial pneumonia), the pleural space (a pneumothorax), or the pulmonary vasculature (a pulmonary embolus)
    - A subacute presentation (over days to weeks) can suggest an exacerbation of preexisting airways disease (asthma or chronic bronchitis), an indolent parenchymal infection (PCP in AIDS, mycobacterial or fungal pneumonia), a noninfectious inflammatory process that proceeds at a relatively slow pace (Wegener's granulomatosis, Eosinophilic pneumonia, bronchiolitis obliterans with organizing pneumonia and many others), neuromuscular diseases (Guillain-Barre syndrome, myasthenia gravis), pleural disease (pleural effusion from a variety of possible causes) or chronic cardiac disease (CHF).
    - Chronic presentation (over months to years) often indicates COPD, chronic interstitial lung disease or chronic cardiac disease. Chronic disease of airways (not only COPDs but also asthma) are characterized by exacerbations and remissions. Patients often have periods when they are severely limited by shortness of breath, but these may be interspersed with periods in which symptoms are minimal or absent.
    - Many diseases of the pulmonary parenchyma are characterized by a slow but unavoidable progression.

COUGH

- Cough may indicate the presence of lung disease, but cough per se is not useful for the differential diagnosis.
- A cough may be dry or it may be productive.
- The presence of sputum accompanying the cough often suggests airway disease and may be seen in asthma, chronic bronchitis, or bronchiectasis.
- Other further questions can be asked to assess cough, such as:
  - How long has the cough been present? A cough lasting a few days following a cold has less significance than one lasting several weeks in a middle-aged smoker, which may be the first sign of malignancy.
  - Is the cough worse at any time of day or night? A dry cough at night may be an early symptom of asthma, as may cough that comes in spasms lasting several minutes.
  - Is the cough aggravated by anything, for example dust, pollen or cold air? The increased reactivity of the airways seen in asthma, and in some normal people for several weeks after viral infections may present in this way.
  - Is the cough productive or not? If productive what is the nature of the sputum? Blood or mucopurulent?
- Severe coughing, whatever its cause, may be followed by vomiting.

HEMOPTYSIS

- Hemoptysis (coughing of blood in sputum) should never be dismissed without very careful evaluation of the patient.
- The potentially serious significance of blood in the sputum is well known and fear often leads patients not to mention it: a specific question is always necessary:
  - Is there any blood in the sputum?
  - Is it fresh or altered?
  - How often has it been seen?
  - For how long?
- Blood may be coughed up alone, or sputum may be bloodstained.
- Sometimes patients may find it difficult to describe whether it comes from gums, nose or even from the stomach.
  - They should always be asked about associated conditions such as epistaxis (nosebleeds), subsequent development of melena (altered blood in the stool) which occurs in the case of upper GI (gastrointestinal) bleeding.
- Hemoptysis can originate from disease of the airways, the pulmonary parenchyma or the vasculature.

- Diseases of the airways can be inflammatory (acute or chronic bronchitis, bronchiectasis, or cystic fibrosis) or neoplastic (bronchogenic carcinoma or bronchial carcinoid tumors).
- Parenchymal disease causing hemoptysis may be either localized (pneumonia, lung abscess, tuberculosis or infection with Aspergillus) or diffuse (Good pasture's syndrome, idiopathic pulmonary hemosiderosis)
- Vascular diseases potentially associated with hemoptysis include pulmonary thromboembolic disease and pulmonary arteriovenous malformations.

SPUTUM

- Is sputum produced?
- What does it look like?
  - Children and some adults swallow sputum, but it is always worth asking for a description of its color and consistency.
  - Yellow or green sputum is usually purulent.
  - People with asthma may produce small amounts of very thick or jelly-like sputum, sometimes in the shape of a cast of the airways. Eosinophils may accumulate in the sputum in asthma, causing a purulent appearance even when no infection is present.
- How much is produced?
  - When severe lung damage in infancy and childhood was common, bronchiectasis was often found in adults. The amount of sputum produced daily often exceeded a cupful. Bronchiectasis is now rare and chronic bronchitis causes the production of smaller amounts of sputum.

WHEEZING

- Always ask whether the patient hears any noises coming from the chest.
- Even if a wheeze is not present when you examine the patient, it is useful to know that they have noticed it on occasions.
- Sometimes wheezing will have noticed by others (especially by a partner at night, when asthma is worse) but not by the patient.
- Sometimes stridor may be mistaken for wheezing by both the patient and doctor. This serious finding usually indicates narrowing of the larynx, trachea or main bronchi.
  - Stridor is an abnormal, high pitched musical breathing sound caused by upper airway narrowing or obstruction. It is often heard during inspiration frequently without the aid of a stethoscope.

- Wheezing refers the high-pitched sound which is most prominent during expiration. It is usually heard clearly upon auscultation (with a stethoscope) although at times it may be audible, especially to the patient without any need for a stethoscope.

CHEST PAIN

- Chest pain is caused by disease of the respiratory system usually originating from involvement of the parietal pleura. As a result, the pain is accentuated by respiratory motion and is often referred to as pleuritic.
- Pleuritic pain is sharp and stabbing.
- Common examples include primary pleural disorders such as neoplasms or inflammatory disorders involving the pleura or pulmonary parenchymal disorders that extend to the pleural surface such as pneumonia or pulmonary infarction.
- A spontaneous pneumothorax causes pain which is worse on breathing but which may have more of an aching character than the stabbing pain of pleurisy.
- If a pulmonary embolus causes infarction of the lung, pleurisy- and hence pleuritic pain-may occur but an acute pulmonary embolus can also cause pain which is not stabbing in nature.

PHYSICAL EXAMINATION OF THE RESISPIRATORY SYSTEM

- Before the examination ensure that you wash your hands.
- Always greet the patient, and introduce yourself.
- Confirm patient details
- Explain the procedure and gain consent.
- When examining a female patient presence of chaperone is a must to avoid any misunderstandings.
- Always perform examination standing on the right side of the patient.
- Adequate exposure (expose the chest area) is a necessity but try to avoid unnecessary exposure. Cover the patient after finishing the examination.
  - A bare below the elbows dress code should be adopted.

GENERAL EXAMINATION

GENERAL INSPECTION

- Ideally the patient is examined in sitting position.
  - Position the patient at 45 degrees and ask him/her to remove his/her top(s).
- From the foot-end of the bed comment on the presence of any respiratory adjuncts (oxygen tank), sputum containers, inhalers or other medicines.
  - Ask if any items identified belong to the patient or they have just been placed there.
  - Inspect sputum containers for mucus if present.
    - Mucoid sputum is characteristic in patients with chronic bronchitis when there is no active infection. It is clear and sticky and not necessarily produced in a large volume.
    - Sputum may become mucopurulent or purulent when bacterial infection is present in patients with bronchitis, pneumonia, bronchiectasis or a lung abscess.
    - In bronchiectasis and lung abscess the quantities may be large and the sputum is often foul-smelling.
    - Occasionally asthmatics have a yellow tinge to the sputum, owing to the presence of many eosinophils. A particularly tenacious form of mucoid sputum may also be produced by people with asthma and sometimes they cough up casts of the bronchial tree particularly after an attack.

  - Patients with bronchopulmonary *aspergillosis* may bring up black sputum or sputum with black parts in it: this is the fungal element of the *Aspergillus*.
  - When sputum is particularly foul-smelling the presence of anaerobic organisms should be suspected.
  - Pink or white frothy sputum may be brought up by very ill patients with pulmonary edema, for example in acute left ventricular failure.
  - Rusty-colored sputum is characteristic of pneumococcal lobar pneumonia.
  - Blood may be coughed up alone, or bloodstained sputum produced, with bronchogenic carcinoma, pulmonary tuberculosis, pulmonary embolism, bronchiectasis or pulmonary hypertension (e.g. with mitral stenosis).

- Observe the position the patient assumes during respiration.
  - Patients with severe asthma or COPD exacerbation may sit and lean forward with shoulders arched forward to assist accessory muscles of respiration.
- Examine the following:
  - Look for any obvious discomfort or pain
  - Use of accessory muscles of respiration (pectoralis, sternocleidomastoid, scalene and trapezius)
  - Is the patient breathless (Shortness of breath) or cyanosed (hypoxia)?
  - Is the patient coughing?
  - Inspect the sputum for color, volume, blood and type (mucoid, purulent or mucopurulent)
  - Listen to the patient's voice for presence of hoarseness
    - Hoarseness is commonly seen in recurrent laryngeal nerve palsy in cases of carcinoma lung.
  - Stridor
    - Ask the patient to cough and then breathe deeply with mouth wide open. Listen for any stridor.
    - Stridors are high pitches, creaking sounds, predominantly of inspiratory origin.
  - Note:
    - The rate, depth and regularity of the patient's breathing.
    - The normal rate of respiration in a relaxed adult is about 14-16 breaths per minute.

        - Tachypnea is increased rate of respiration observed by the doctor.
        - Dyspnea is the symptom of breathlessness experienced by patient.
        - Apnea is a cessation of respiration.
    - Any deformities, thoracotomy scars and markings of the chest and spine
        - Barrel chest
        - Pectus excavatum
        - Pectus carinatum
        - Kyphosis
    - Any asymmetry of chest expansion

INSPETION AND EXAMINATION OF THE HANDS

- From the right side of the bed, take both hands and assess them for color and temperature.
- Examine both hands for:
    - Clubbing
        - Clubbing is seen in respiratory conditions such as bronchial carcinoma (squamous cell type), fibrosing alveolitis, chronic Suppurative lung disease (bronchiectasis, lung abscess, empyema), pulmonary fibrosis (e.g. idiopathic lung fibrosis), pleural and mediastinal tumors (e.g. mesothelioma) and cryptogenic organizing pneumonia.
    - Pallor
    - Peripheral cyanosis: which is caused by poor peripheral perfusion.
    - Tar staining on the fingers and nails seen in chronic smokers.
    - Radial pulse (rate, rhythm and character of the radial pulse) and respiration rate
        - A bounding pulse is due to carbon dioxide retention.
        - In a significant asthma attack the pulse rate is usually raised. The systolic blood pressure also falls during the severe inspiratory effort of acute asthma, and the degree of this fall (the degree of pulsus paradoxus) can be used as a measure of asthma severity.
    - Check the Blood pressure
- Examine for tremors in arms
    - Ask patient to hold their arms stretched out with hands at the same level and their fingers splayed out.
    - You can even place a paper on top to check for tremors.

  - Tremors indicate use of beta-agonists.
- Examine for flapping tremors (Asterixis)
  - Ask the patient to stretch the arms in front of them with the wrist dorsiflexed and fingers extended.
  - Presence of irregular jerky flexion-extension movements at wrist and metacarpophalangeal joints is a positive sign.
  - It is seen in patients with hypercapnic respiratory failure (carbon dioxide retention)/ severe COPD, severe cirrhosis of liver and hepatic encephalopathy.
- At this point one can even palpate the epitrochlear lymph nodes.
- Palpate axillary lymph nodes and lymph nodes in the neck. Note for the size, consistency and whether they are fixed to the surrounding structure.
- Palpate for the scalene lymph nodes, its enlargement may be the first sign of metastatic lung cancer.

INSPECTION OF THE HEAD AND NECK

- Look for signs of secondary polycythemia as well as central cyanosis
  - Examine the eyes for pallor (Anemia) and jaundice
  - Examine the eyes also for an injected conjunctiva (a sign of polycythemia seen in chronic smokers especially)
- Examine the nose for:
  - Deviated nasal septum
  - Nasal polyp
  - Post nasal drip
- Examine the oral cavity for:
  - Hygiene
  - Dental caries
  - Tonsils
  - Purple lesions on the palate (Kaposi's sarcoma)

INSPECTION OF THE CHEST

- Inspect the position of the trachea:
  - Trail's sign: it is the prominence of clavicular head of sternocleidomastoid muscle to the side to which the trachea is deviated.
- Inspect the chest movements and note any scars (e.g. lobectomy), markings and chest deformities
  - Ask patient to place hands on the hips and bring the elbows forward.

- Inspect for symmetrical chest expansion.

PALPATION OF THE CHEST

- Feel the position of the trachea. This is done by placing the index and ring finger on the medial ends of the clavicle and feeling for the tracheal rings with the middle finger. Crico-sternal distance (3/4 fingers=normal).
- Palpate for the apex beat which is normally in the 5th intercostal space midclavicular line as it may be displaced due to pneumothorax, or a massive pleural effusion.
- Check the symmetry of the chest movements by palpation.
  - Start by placing hands on lower chest with the thumbs touching each other in the midline and ask the patient to take deep breaths.
  - Observe symmetry of thumb movement.
  - Move your arms upwards and repeat the process.
  - A unilateral decrease in expansion may signify a consolidation or collapse.
  - Bilateral decrease in expansion may signify COPD/Pulmonary fibrosis.
- Check for tactile fremitus
  - It is the palpation of chest wall for vibrations transmitted from larynx through the lungs on the chest wall.
  - To check for vocal fremitus, use the ulnar border of the hand (or the flat of the hand) to palpate over the chest wall.
  - Keep your ulnar boarder of the hand on the chest and ask the patient to repeat words like 'One one one'.
  - Feel the vibrations on the chest wall.
  - Increased tactile fremitus is seen in consolidation (pneumonia) and decreased tactile fremitus is seen in pleural effusion, COPD or severe asthma.

PERCUSSION OF THE CHEST

- Percuss the anterior chest and axillae.
  - Press the middle finger of your left hand firmly over the intercostal spaces parallel to the ribs, with other fingers not touching the chest. This finger is called the plexímeter.
  - Strike the center of the middle phalanx of the left finger with your right middle finger at 90 degrees.
  - The striking movement must be loose swinging movement at the wrist joint and not the elbow joint.

- The striking finger must be moved immediately to prevent dampening of the produced sounds. The striking finger is called the plexor.
- Always percuss from resonant to dull areas for better appreciating the change in note of percussion.
- Always compare by percussion on the opposite side.
- With the patient sited with arms on the side percuss the medial third of the clavicle, infra-clavicular noting:
  - Resonant sound (normal)
  - Hyperresonant (pneumothorax)
  - Dull (consolidation/ collapse)
  - Stony dull (pleural effusion)

- Tenderness during percussion is a sign of emphysema or parietal pleural effusion.

AUSCULTATION

- Listen to the breath sounds. Assess breath sound quality (vesicular/bronchial)
  - Use the diaphragm of the stethoscope (even though the bell is preferred for auscultation of breath sounds).
  - While auscultating, make sure that the patient is relaxed and is breathing through the mouth
  - Avoid auscultating within 3cm of midline anteriorly and posteriorly as breath sounds are directly transmitted from the trachea or bronchi in this region.
  - Auscultate each side alternately and compare the findings.
  - Auscultation after asking the patient to cough helps differentiate coarse crepitation and rhonchi from pleural rub.
  - Crepitation and rhonchi disappear after coughing whereas pleural rub persists.
  - When auscultating note the following:
    - Intensity/loudness
    - Character
    - Comparison of inspiration and expiration element in terms of intensity, duration and pitch
    - Presence of intermediatory pause between inspiration and expiration
    - Presence of added sounds.
  - Auscultation areas-
    - Anterior: from above clavicle down to 6^{th} rib
    - Lateral- up to 8^{th} rib
    - Posterior- from above the scapula to the level of 11^{th} rib
  - Abnormal sounds:

  - Crepitations/Crackles, Rales- Can be coarse or fine
  - Rhonchi
  - Pleural rub: gratting sound of pleural membranes rubbing against each other.
- Check for vocal resonance:
  - Every time the stethoscope is placed on the patients' chest the patient says 'one one one'.
  - Increased vocal resonance is indicative of consolidation
  - Decreased vocal resonance is indicative of pleural effusion

- Note: after examination of the front chest, ask the patient to lean forward and place their hands crossed on their shoulder
  - Inspect the posterior chest wall for deformities, scars and chest markings
  - Check for tactile fremitus
  - Percuss the back of the chest
    - This is done by making the patient sit with his hands over his shoulder and head bent forwards. This position helps increasing the surface area between the scapulae for percussion.
    - Percuss in-between the spine and the scapular.
    - Avoid percussing in the midline as the spine and musculature produces dull note.
  - Listen to the breath sounds
  - Check for vocal resonance
- Thank the patient and ensure they are dressed or appropriately covered.
- To complete examination perform:
  - Oxygen saturation
  - Sputum analysis
  - Chest X-ray
- Summarize findings and offer differential diagnosis.

INTERPRETING THE SIGNS

- Developing an appropriate differential diagnosis on the basis of the signs you have elicited requires practice.
- Keep the following in mind
  - If movements are diminished on one side, there is likely to be an abnormality on that side.
  - The percussion note is dull over a pleural effusion and over an area of consolidation- the duller the note, the more likely it is to be a pleural effusion.
  - Over a pneumothorax, the percussion note is more resonant than normal but the breath sounds, vocal resonance and tactile vocal fremitus are quite or reduced. Pneumothorax is easily missed.
  - The breath sounds, the vocal resonance and the tactile vocal fremitus are quitter or less obvious over a pleural effusion and louder or more obvious over an area of consolidation.

INVESTIGATIONS

- Any patient with the following should have chest x-ray:
  - Severe or persistent shortness of breath
  - Cough
  - Hemoptysis
  - Chest pain
  - Chest trauma
  - Evidence of tuberculosis or malignancy by history or pulmonary findings on physical examination
- See radiology chapter 14 for interpretation of chest X-rays.
- Other pulmonary investigations include:
  - Sputum analysis: Microscopy, culture and sensitivity
  - Spirometry
  - Bronchoscopy
  - CT/MRI of the thorax

PULMONARY INFECTIONS

PNEUMONIA

- This is an acute inflammation of the lung parenchyma distal to the terminal bronchioles including respiratory bronchioles, alveolar ducts, alveolar spaces and interstitial tissue.
- It can affect:
  - The entire lobe: **lobar pneumonia**
  - A segment of a lobe: **Segmental/lobular pneumonia**
  - Alveoli contiguous (adjacent) to Bronchi-**Bronchopneumonia**
  - Interstitial tissue- **Interstitial pneumonia/atypical**
- The differences between the above are made on X-ray.
- Pneumonia is usually caused by bacteria but can also be caused by viruses and fungi.
- Clinically, it usually presents as an acute illness with cough, purulent sputum (rusty color), breathlessness and fever together with physical signs or radiological changes compatible with consolidation of the lung.
  - A pulmonary consolidation is a region of lung tissue (normally compressible) that has been filled with fluid instead of air. It occurs through accumulation of inflammatory cellular exudate in the alveoli and adjoining ducts.
  - The liquid can be pulmonary edema, inflammatory exudate, pus, inhaled water or blood (from bronchial tree or hemorrhage from a pulmonary artery)
  - Consolidation must be present to diagnose pneumonia.
- In the elderly there is a subtler presentation of symptoms.
- About 50% of pneumonia is pneumococcal.

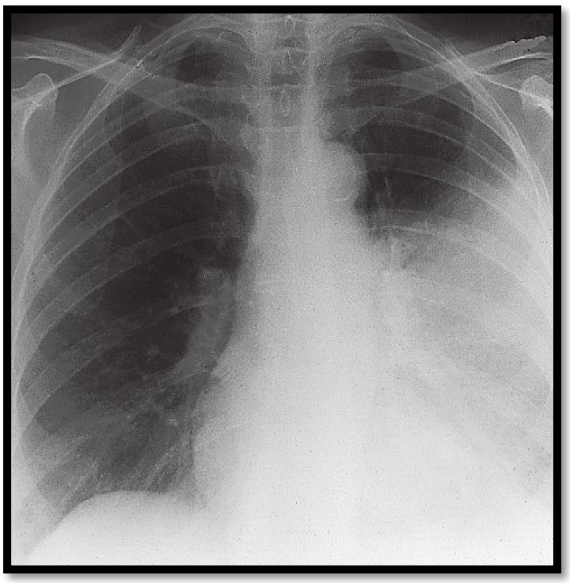


Figure 39: Chest X-ray showing lobar pneumonia (left lower lung zone)

PREDISPOSING FACTORS FOR PNEUMONIA

- Preceding respiratory viral infections
- Alcoholism
- Cigarette smoking
- Underlying diseases such as heart failure, COPD
- Age extremes
- Immunosuppressive therapy and disorders
- Decreased consciousness, coma, seizure etc.
- Surgery and aspiration of secretions

CLASSIFICATION OF PNEUMONIA

- Pneumonia can be classified:
  - Morphologically/anatomical
  - Etiologically
  - Setting in which it is contracted

MORPHOLOGICAL/ ANATOMICAL CLASSIFICATION

- Pneumonia can be classified as:
  - Lobar pneumonia: involving the entire lobe
  - Segmental/lobular pneumonia: involving part of the lobe
  - Bronchopneumonia: involving the alveoli contiguous (adjacent) to Bronchi
  - Interstitial pneumonia: involving the interstitial tissue.

ETIOLOGICAL CLASSIFICATION

- Cause of pneumonia can be
  - Infectious
  - Non-infectious

INFECTIOUS

- Bacterial:
  - *Streptococcus pneumoniae (50%)*
  - *Haemophilus influenzae (7%)*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Legionella pneumophilia (3%)*
  - *Staphylococcus aureus (2%)*
  - *Moraxella catarrhalis (2%)*

- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Chlamydophila psittaci*
- *Coxiella burnetti (Q fever)*

- Viral:
  - Influenza viruses (A and B)
  - Parainfluenza virus
  - Cold viruses: adenovirus, corona virus, Astrovirus

- Fungal/Parasitic
  - *Pneumocystis Jirovercii pneumonia*
  - Aspergillosis

NON-INFECTIOUS

- This includes aspiration pneumonia
  - Chemical insult such as in the aspiration of vomit
    - Aspiration pneumonia is seen in patients at risk for aspiration (e.g. alcoholics and comatose patients)
    - Most often due to anaerobic bacteria in the oropharynx (e.g. *Bacteroides, Fusobacterium* and *Peptococcus*) and other microbes such as *Enterobacteriacae, S. pneumoniae, S. aureus*
    - Classically results in a right lower lobe abscess: anatomically the right main stem bronchus branches at a less acute angle than the left.
- Radiotherapy
- Allergic mechanisms

SETTING ACQUIRED

- Pneumonia is usually classified by the setting in which the person has contracted their infection:
  - Community acquired pneumonia: with no underlying immunosuppression or malignancy.
  - Hospital acquired pneumonia
  - Pneumonia in the immunocompromised (through genetic defect, immunosuppressive medication or acquired immunodeficiency such as HIV)

COMMUNITY ACQUIRED PNEUMONIA

- Occurs across all ages however is commoner at the extremes of age.
- Pneumonia can be classified either according to the organisms responsible for the infection or by the site of disease.
- Classification according to etiology includes:
  - Bacterial pneumonia: pneumococcus is the commonest cause overall. Usually produce lobar or bronchopneumonia.
    - *Streptococcus pneumoniae* (*pneumococcal pneumonia*)-50% of cases
    - *Haemophilus influenza*-7% of cases
    - *Staphylococcus aureus*-2% of cases
    - *Mycoplasma pneumoniae*- 5-15% of cases
    - *Chlamydia pneumoniae*-10% of cases
    - *Legionella pneumophila*-3% of cases
    - Oral anaerobic bacteria
    - *Mycobacterium tuberculosis*
  - Viral pneumonia: usually produce atypical pneumonia.
    - Influenza A + B
    - Respiratory syncytial virus
  - Fungal pneumonia: *Pneumocystis Jirovercii* (causing pneumocystis pneumonia-PCP) which is common in the immunosuppressed.
- Classification according to site of disease includes:
  - Lobar pneumonia: consolidation affects one whole lobe
  - Segmental/lobular: lobules of the lung are affected, and the infection is centered on the bronchi and bronchioles.
  - Bronchopneumonia: the alveoli adjacent to the bronchi are affected.
  - Interstitial pneumonia (atypical pneumonia): inflammation within the interstitium- there is an increase in lung markings on CXR.

LOBAR PNEUMONIA

- This is characterized by consolidation of an entire lobe of the lung.
- Usually bacterial, most common causes are *Streptococcus pneumoniae* (95%) and *Klebsiella pneumoniae*.
- Classic gross phases of lobar pneumonia:
  - Congestion- due to congested vessels and edema. This lasts less than 24 hours.
  - Red hepatization- due to exudate, neutrophils, and hemorrhage filling the alveolar air spaces, giving the normally spongy lung a solid consistency.

There is a firm, 'meaty' and airless appearance of the lung (it looks like a liver).

- Gray hepatization- due to macrophage mediated degradation of red cells and fibrin within the exudate. There is less hyperemia.
- Resolution- lysis and removal of the fibrin via sputum and lymphatics. It begins after 8-9 days (without antibiotics) and there is sudden improvement of the patient's condition.

- This type of pneumonia usually develops in the distal airspaces adjacent to the visceral pleura and then spreads to produce consolidation of all or part of the lobe.
- On X-ray this appears as:
  - Unifocal (but may be multifocal)
  - Homogenous lung opacity limited by fissures with air bronchograms (which become less obvious as the disease progresses).
  - Round shaped pneumonia that may simulate a lung mass. (cavitations are unlikely)
  - A Parapneumonic effusion
  - Note: lobar volume usually remains unchanged (but rarely it increases)

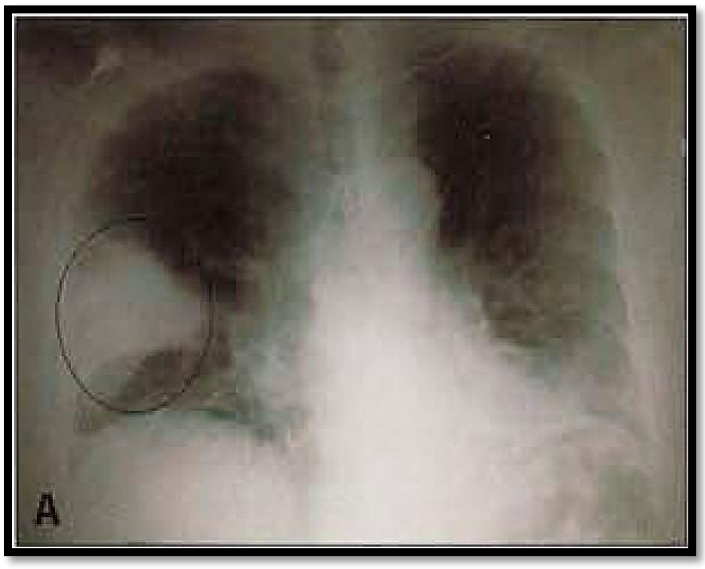


Figure 40: Lobar pneumonia: note the consolidation of the right lung.

- Radiographic resolution is fairly rapid- 1 week; total resolution happens within 2-6 weeks.
  - Chest X-ray must be repeated 6 weeks after discharge unless complications occur to rule out an underlying bronchial malignancy predisposing to pneumonia by causing obstruction.

BRONCHOPNEUMONIA/LOBULAR

- Characterized by scattered patchy consolidation centered around bronchioles, often multifocal and bilateral. With worsening disease, the opacities may become more homogenous.
- Pleural effusion or empyema, cavitation, pneumothorax and atelectasis are common.
- Caused by a variety of bacterial organisms.



Figure 41: Bronchopneumonia

INTERSTITIAL PNEUMONIA (ATYPICAL PNEUMONIA)

- Characterized by diffuse interstitial infiltrates.
- Presents with relatively mild upper respiratory symptoms (minimal sputum and low fever), 'atypical presentation'.
- Most often caused by bacteria or viruses.

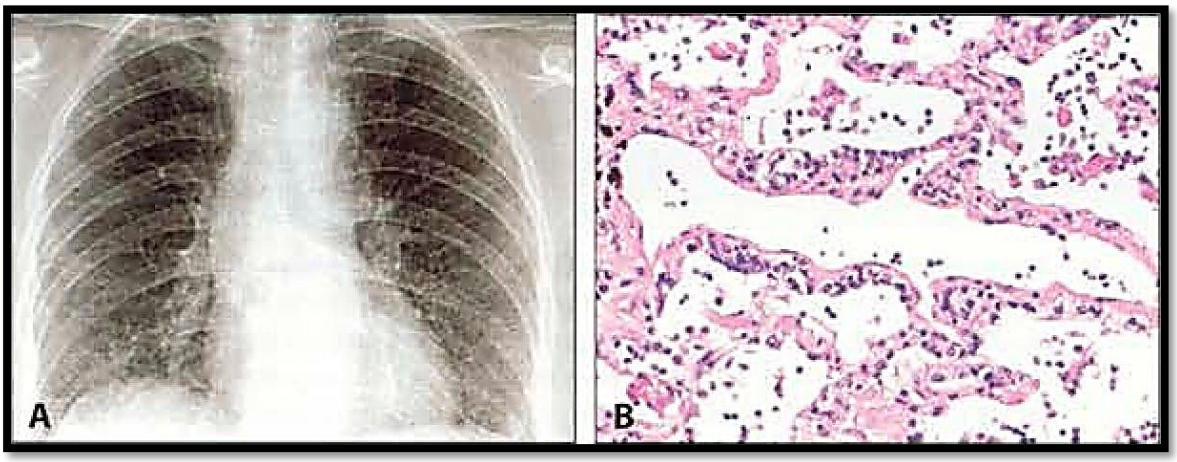


Figure 42: Atypical pneumonia

TYPES OF PNEUMONIA	
CAUSES OF LOBAR PNEUMONIA	
ORGANISM	COMMENTS
Streptococcus pneumoniae	• Most common cause of community acquired pneumonia. • Seen in middle-adults and elderly.
Klebsiella pneumoniae	• Affects malnourished and debilitated individuals, especially elderly in nursing homes, alcoholics and diabetics (enteric flora that is aspirated) • Thick mucoid capsule results in gelatinous sputum (current jelly) • Often complicated by abscess.
CAUSES OF BRONCHOPNEUMONIA	
ORGANISM	COMMENTS
Staphylococcus aureus	• Most common cause of secondary pneumonia (bacterial pneumonia superimposed on a viral upper respiratory tract infection) • Often complicated by abscess or empyema
Haemophilus influenza	• Common cause of secondary pneumonia and pneumonia superimposed on COPD (leads to exacerbation of COPD)
Pseudomonas aeruginosa	• Pneumonia in cystic fibrosis patients
Moraxella catarrhalis	• Community-acquired and pneumonia superimposed on COPD (leads to exacerbation of COPD)
Legionella pneumophila	• Community-acquired pneumonia • Pneumonia superimposed on COPD or pneumonia in immunocompromised states. • Transmitted from water source. • Intracellular organism that is best visualized by silver stain.
CAUSES OF INTERSTITIAL (ATYPICAL) PNEUMONIA	
ORGANISM	COMMENTS
Mycoplasma pneumoniae	• Most common cause of atypical pneumonia, usually affects young adults. • Complicates include autoimmune hemolytic anemia (IgM against antigen on RBCs causes cold hemolytic anemia) and erythema multiforme. • Not visible on gram stain due to lack of cell wall
Chlamydia pneumoniae	• Second most common cause of atypical pneumonia in young adults
Respiratory syncytial virus	• Most common cause of atypical pneumonia in infants.
Cytomegalovirus	• Atypical pneumonia with post-transplant immunosuppressive therapy

Influenza virus	• Atypical pneumonia in elderly, immunocompromised and those with preexisting lung disease. • Also increases risk for superimposed *S aureus or H influenza bacterial pneumonia*
Coxiella burnetti	• Atypical pneumonia with high fever (Q fever). • Coxiella is a Rickettsial organism that causes pneumonia and does not require arthropod vector for transmission and does not produce a skin rash.

RISK FACTORS FOR COMMUNITY ACQUIRED PNEUMONIA	
AGE	<16 or >65 years
CO-MORBIDITIES	HIV infection, diabetes mellitus, chronic kidney disease, malnutrition, recent viral respiratory infection
OTHER RESPIRATORY CONDITIONS	Cystic fibrosis, bronchiectasis, COPD, obstructing lesion (endoluminal cancer, inhaled foreign body)
LIFESTYLE	Cigarette smoking, excess alcohol, intravenous drug use
IATROGENIC	Immunosuppressant therapy (including prolonged corticosteroids)

CLINICAL FEATURES

- Clinical features vary according to the immune state of the patient and the infecting agent.
- Symptoms:
  - Fever and chills: this can be as high as 39.5- 40.5^{o}C. If swinging fevers are present, this often indicates empyema.
  - Cough: may be dry or productive and hemoptysis can occur.
    - In pneumococcal pneumonia, sputum is characteristically rust-colored or yellow-green (indicating pus).
  - Chest pain: pleuritic in nature due to inflammation of pleura (mediated by bradykinin and prostaglandin E_2).
    - The pleuritic chest pain is worsened during inspiration and coughing
  - Breathlessness: alveoli become filled with pus and debris, impairing gas exchange.

- In the elderly community acquire pneumonia (CAP) can present with confusion or nonspecific symptoms such as recurrent falls. CAP should always be considered in the differential diagnosis of sick elderly patients given their frequently atypical presentation.
- Where symptoms have been present for several weeks or have failed to respond to standard antibiotics, the possibility of Tuberculosis should always be remembered.

- Signs:
  - Tachypnea and increased pulse rate
  - Cyanosis may be present
  - There will be dullness to percussion
  - Bronchial breathing (Increased breath sounds): may be heard over areas of consolidated lung.
  - Coarse crepitations are often heard on auscultation, due to consolidation of the lung parenchyma.
  - A pleural rub may be heard early on in the illness
  - Elevated WBC count.
  - Extrapulmonary manifestation: may be indicative of causative agent.

Pneumonia	Manifestations
Legionella pneumonia	• Myalgia, arthralgia and malaise • Headache • Meningoencephalitis and other neurological abnormalities (less common) • Abdominal pain, diarrhea and vomiting (common) • Hepatitis
Mycoplasma pneumonia	• Myalgia, arthralgia and malaise • Myocarditis and pericarditis • Erythema multiforme and erythema nodosum • Stevens-Johnson syndrome (Rare complication of pneumonia)
Pneumococcal pneumonia	• Labial herpes simplex reactivation

- The type and extent of depends on the severity of the illness, which also guides where the patient should be managed and predicts their outcome.
- Severity is commonly assessed by CURB-65 or CRB=65 score. The CRB=65 score is used in the community where the serum urea level is not usually available. 1 point for each
  - *C- confusion present (abbreviated mental test score <8/10)*
  - *U- urea levels >7 mmol/L*
  - *R- respiratory rate >30/min*
  - *B- systolic BP <90 or diastolic BP <60*
  - *65- age>65*
- **Score 0-1: treat as outpatient**
- **Score 2: Admit to hospital**
- **Score 3+: Often require ICU care. Mortality rates increase with increasing score.**
- Other severity scores are also used e.g. Pneumonia Severity index (PSI)

INVESTIGATIONS

- The clinical presentation varies between different causative organisms but there is considerable overlap.
- *Streptococcus pneumoniae* is the commonest single cause and all treatment and investigation strategies need to cover this. The most likely causative pathogens must be treated while considering alternative less common infectious causes (such as tuberculosis) or an alternative pathology (e.g. lung cancer).
- All patients admitted to hospital should have a chest X-ray, blood tests and microbiological tests.
  - Chest X-ray: must be repeated 6 weeks after discharge unless complications occur to rule out an underlying bronchial malignancy predisposing to pneumonia by causing obstruction
    - ***Strep. Pneumoniae***: consolidation with air bronchograms, effusions and collapse due to retention of secretions can all be seen. Radiological abnormalities can lag behind clinical signs. A normal CXR on presentation should be repeated after 2-3 days where community acquired pneumonia is suspected.
    - ***Mycoplasma***: Usually one lobe is involved but infection can be bilateral and extensive

- ***Legionella***: There is lobar and then multi-lobar shadowing with the occasional small pleural effusion. Cavitation is rare.

➢ Sputum gram stain and culture: required for all patients
- ***S. pneumoniae***: gram positive diplococci
- ***S. aureus***: gram positive organisms commonly in clusters like a bunch of grapes or in rods.
- Blood culture should be done for all patients who have moderate to severe community acquired pneumonia, ideally before antibiotics are administered. In *S. pneumoniae* infection, positive blood culture indicates more severe disease with greater mortality.

➢ Blood tests: Full blood count, urea & electrolytes, biochemistry, C-reactive protein, HIV testing
- *Strep pneumoniae*: WBC> 15 $x10^9$/L (90% polymorphonuclear leukocytosis), ESR> 100mm/hour, CRP> 100mg/L.
- *Mycoplasma*: WBC is usually normal. In the presence of anemia, hemolysis should be ruled out (direct Coomb's test and measurement of cold agglutinins).
- *Legionella*: there is Lymphopenia without marked leukocytosis, hyponatremia, hypoalbuminemia and high serum levels of liver aminotransferases.

➢ Pulse oximetry and arterial blood gas analysis is necessary if oxygen saturation is below 94%.

MANAGEMENT OF PNEUMONIA

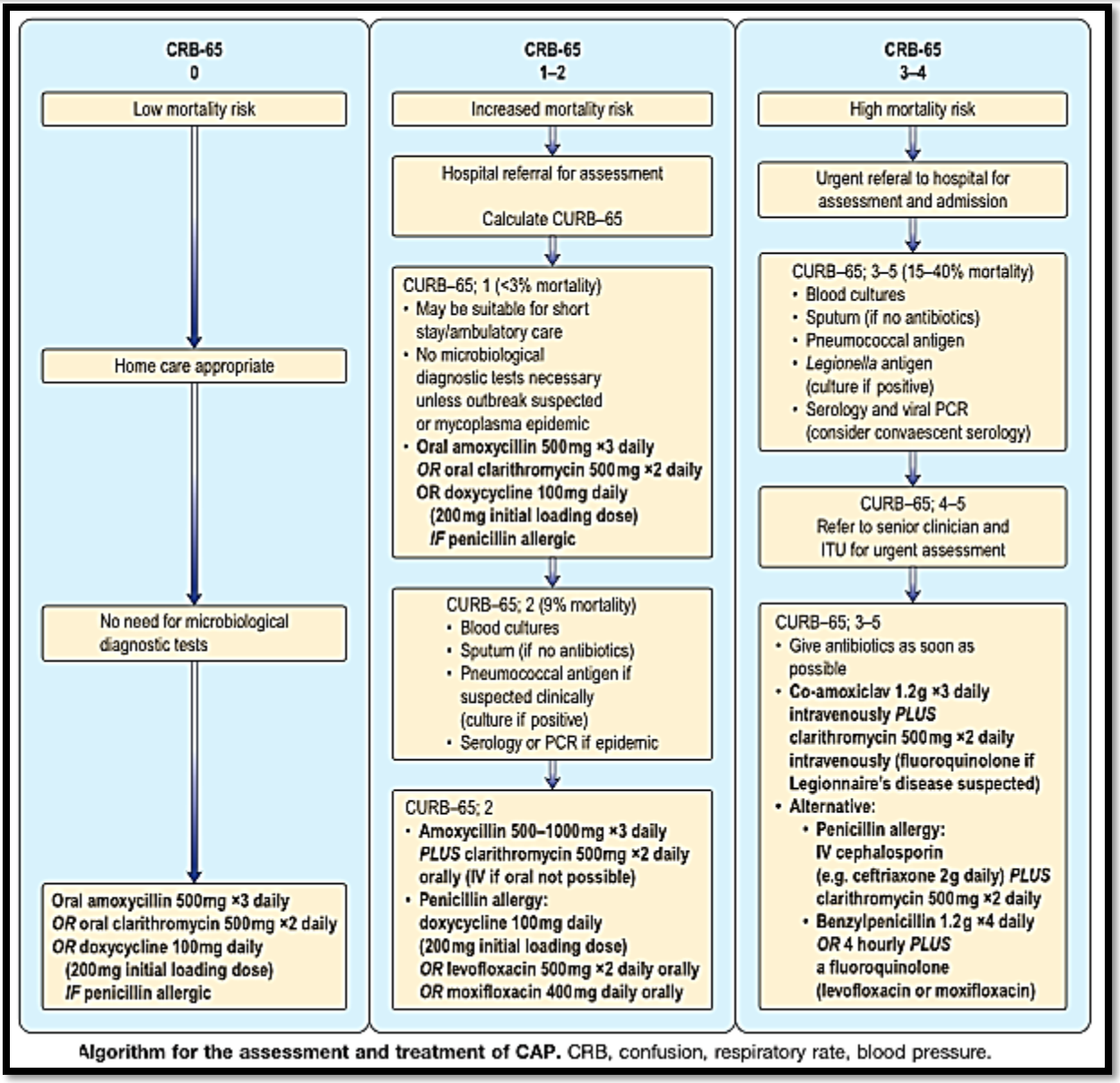
- Antibiotics
  - ➢ Administer first dose within 4 hours of presentation in hospital and treatment should not be delayed while investigations are awaited.
  - ➢ The antibiotic regimen should be adjusted specifically once culture and sensitivity results are available.

TYPE OF PNEUMONIA	MANAGEMENT
EMPERICAL TREATMENT	• Benzyl penicillin 1-2 MU IV QID for 5 days (as soon as the symptoms and respiratory rates are controlled change to oral medication i.e. Amoxicillin 500mg for remaining days) or • Ceftriaxone 1-2g daily for 7 days. If allergic to penicillin use • Erythromycin 500mg PO QID for 7 days
MILD FORM OF COMMUNITY ACQUIRED PNEUMONIA	
Uncomplicated "Typical" pneumonia	• Can be treated as outpatient • Amoxicillin 500mg PO TDS for 7-10 days or • Ampicillin 500mg PO QID for 7-10 days or • Procaine penicillin 600, 000 IU IM every 12 hours • Supportive therapy
"Atypical Pneumonia"	• Erythromycin 500mg PO QID for 7-10 days or • Doxycycline 100mg PO BD for 7-10 days • Supportive therapy
SEVERE FORMS OF COMMUNITY ACQUIRED PNEUMONIA	
Community acquired	• High dose of crystalline penicillin 3-4 million IU IV every 4-6 hours or • Ceftriaxone 1g IV daily or BD or • Ampicillin 500mg IV QID or Cefotaxime • In severely ill patients erythromycin or a fluoroquinolone can be added. • Choice of antibiotics may be modified based on culture and sensitivity results if available • If the patient improves IV treatment can be changed to oral after 3-4 daus to complete a 7-10 days course
Aspiration pneumonia	• Gentamycin 5mg/kg BD or 10mg IM OD • Ciprofloxacin 10mg/kg TDS

SUPPORTIVE THERAPY

- Oxygen: supplemental oxygen should be administered to maintain saturations between 94% and 98% provided the patient is not at risk of carbon dioxide retention due to loss of hypoxic drive in COPD. In patients with known COPD, oxygen saturations should be maintained between 88% and 92%, normally with controlled oxygen via fixed percentage delivery mask.

  - Ensure adequate oxygenation to patients with cyanosis, significant hypoxemia, severe dyspnea, circulatory disturbance or delirium.
- Intravenous fluids: required in hypotensive patients showing evidence of volume depletion.
- Thromboprophylaxis if admitted for more than 12 hours subcutaneous low molecular weight heparin should be prescribed unless contraindications exist.
- Physiotherapy: chest physiotherapy is not needed unless sputum retention is an issue.
- Nutritional supplementation
- Antipyretics should be given.
- Analgesia: paracetamol or NSAIDs help treat pleuritic pain, thereby reducing the risk of further complications due to restricted breathing because of pain e.g. sputum retention, atelectasis or secondary infection.
  - Paracetamol 500mg to 1g PO TDS/QID



Algorithm for the assessment and treatment of CAP. CRB, confusion, respiratory rate, blood pressure.

COMPLICATIONS OF PNEUMONIA

LOCAL COMPLICATIONS

- Parapneumonic effusion and empyema: early indications of empyema are ongoing fever and rising or persistently elevated inflammatory markers despite appropriate antibiotic therapy.
  - Thoracentesis should be performed to make a diagnosis.
  - Light's criteria can be applied to assess whether an effusion is transudative or exudative.

  - If empyema develops the fluid should be urgently drained to prevent further complications such as development of a thick pleural ring or prolonged hospital admission. The presence of empyema further increases mortality risk.
- Lung abscess: severe localized suppuration within the lung associated with cavity formation visible on the chest X-ray or CT scan, often with a fluid level (which always indicated an air-liquid interface). Causes include
  - Aspiration pneumonia: rare complication, a history of severe alcohol consumption or impaired swallowing in a patient with pneumonia suggests aspiration.
  - Tuberculosis
  - Staph pneumonia or Klebsiella pneumonia
  - Foreign body inhalation
  - Bronchial obstruction by an endoluminal cancer
  - Spread from an amoebic liver abscess in right lower lobe from transdiaphragmatic spread.
  - Septic emboli usually containing Staphylococci: can cause multiple lung abscesses. The presence of multiple lung abscesses in an injecting drug user should prompt investigation for infective endocarditis or the tricuspid valves (or rarely pulmonary). Infarcted areas of lung (due to pulmonary emboli) occasionally cavitate and become infected.
- Emphysema

DISTANT COMPLICATIONS

- Septic arthritis
- Meningitis
- Pneumonia can progress to sepsis, sometimes with septic shock
- Heart failure (Cor pulmonale)

HOSPITAL ACQUIRED PNEUMONIA

- This is defined as new onset of cough with purulent sputum along with a compatible X-ray demonstrating consolidation in patients who are beyond 2 days (48 hours) of their initial admission to hospital or who have been in a healthcare setting within the last 3 months.
- Hospital acquire pneumonia (HAP) includes the presence of a new progressive infiltrate of chest X-ray plus at least 2 of the following:
  - Fever> 37.8 ^{o}C
  - Leukocytosis >10, 000/mm^{3}
  - Production of purulent sputum
- Other findings: dyspnea, hypoxemia and chest pain
- Hospital acquired pneumonia is the second most common form of hospital-acquired infection after urinary tract and carries a significant mortality risk, particularly in the elderly or those with co-morbidities such as stroke, respiratory disease or diabetes.
- The causative agents differ from those of community acquired.
- Viral or fungal pathogens are not responsible in immunocompetent host.
- Aerobic Gram-negative bacilli are commonly involved (e.g. *P. aeruginosa, E. coli, Klebsiella* and *Acinetobacter* species).
- Staphylococcus aureus is increasingly recognized in hospital acquired pneumonia especially *methicillin-resistant S. aureus* (MRSA).
- HAP due to *S. aureus* is more common in patients with diabetes mellitus, head trauma and patients in intensive care units.
- Empirical antimicrobial therapy should be tailored accordingly.
- Other conditions should be excluded including aspiration of gastric contents due to impaired swallowing or bulbar weakness.
- Treatment:
  - Antibiotics: should be initiated empirically which latter on may be modified based on culture and sensitivity result.
  - The selection of drugs should be guided by an understanding of local patterns of antibiotic resistance.
  - Antibiotics should cover at least gram negatives and S. aureus
    - Ceftriaxone 1g IV BD daily plus Cloxacillin or methicillin or
    - Levofloxacin 500mg IV/day
  - When resistant organisms are suspected:
    - Cefotaxime 750mg IV TDS plus vancomycin 1g IV BD.

- Prevention:
  - Strict hand washing protocols by health care providers
  - Extubate an intubated patient as soon as the patient is stable
  - Remove NG tubes when the patient is stable
  - Proper aseptic handling of IV lines

PNEUMONIA IN IMMUNOCOMPROMISED

- Immunocompromised patients are at risk of pneumonia from the usual organisms as well as the opportunistic pathogens which would not be expected to cause disease.
  - Pathogens like *Streptococcus pneumonia*, which cause pneumonia in immunocompetent people, are still responsible for the majority of pneumonia in compromised patient.
- These opportunistic pathogens can be commonly occurring microorganisms or bacteria, viruses and fungi that are less often.
- The symptom pattern may resemble community acquired pneumonia or may be more non-specific.
- A high degree of clinical suspicion is therefore necessary when assessing an ill patient who is immunocompromised.
- Immunocompromised host include patients with AIDS, acute leukemia, cancer chemotherapy, diabetes, sickle cell disease, Hodgkin's disease and corticosteroids treatment.
- Diagnosis:
  - Sputum examination and culture are used but they are not specific.
  - Transtracheal aspirate, bronchoscopy and biopsy have high accuracy, however these are done only in specialized hospitals.
- Acutely ill patients who have suspected bacterial infections are often treated with antibiotics selected on the basis of probability and the findings with sputum gram stain and culture. Later treatment is adjusted on the basis of more definitive diagnostic evaluation.

PNEUMOCYSTIS JIROVECI

- Pneumocystis pneumonia (PCP) is one of the most common opportunistic infections encountered in clinical practice.
- It affects patients on immunosuppressant therapy such as long-term corticosteroids, monoclonal antibody therapy, or methotrexate for autoimmune disease, those on anti-rejection medication post-solid organ transplantation or

following stem cell transplantation and patients infected with HIV (with CD4 counts less than 200/mm^3).

- *Pneumocystis Jirovercii* is found in the air, and pneumonia arises from re-infection rather than reactivation of persisting organisms acquired in childhood.
- Clinically the pneumonia is associated with a high fever, breathlessness and dry cough.
- A characteristic feature on examination is rapid desaturation on exercise or exertion.
- The typical radiographic appearance is of a diffuse bilateral alveolar and interstitial shadowing beginning in the perihilar regions and spreading out in a butterfly pattern.
- Other chest X-ray appearances include localized infiltration, nodules, cavitation or a pneumothorax.
- Empirical treatment is justified in very sick high-risk patients but wherever possible the diagnosis should be confirmed by indirect immunofluorescence on induced sputum or Bronchoalveolar lavage fluid.
- First-line treatment of PCP is with high-dose co-trimoxazole (Septrin).
  - Cotrimoxazole 960 mg every 12 hours (or 3 tablets 480mg PO QID) for 21 days in combination with a steroid i.e. Prednisolone for PCP starting with 40mg per day and reducing by 5mg every 3 days for adults.
    - Co-trimoxazole= (Trimethoprim 1 part + 5 parts sulfamethoxazole)
    - (Trimethoprim 160mg/ Sulfamethoxazole 800mg)-960mg
    - (Trimethoprim 80mg/Sulfamethoxazole 400mg)- 480mg
    - Single-strength tables of TMP-SMX (Septrin) are effective and may be less toxic than double-strength tablets.
- Alternatively, dapsone +/- pyrimethamine or pentamidine nebulizers or atovaquone can be used.
- Adjunct therapy: Supplemental oxygen.

TUBERCULOSIS

- This is a chronic necrotizing disease caused by *Mycobacterium tuberculosis* complex usually affecting the lungs and sometimes some other organs.
- Tuberculosis is caused by a range of mycobacterium including the species *M. tuberculosis* (most common), *M. bovis* (reservoir cattle), *M. africanum* (reservoir human) and *M. microti*.
- *M. tuberculosis* is an encapsulated obligate aerobe, facultative intracellular pathogen rod-shaped, non-spore forming, thin bacterium measuring 0.5µm by 3µm.
- The mycolic acid in the cell wall and the capsule impede phagocytosis.
- They are slow growing with a generation time of 12-18 hours.
- Due to high lipid content in the cell wall, they are relatively impermeable and stain only weakly with Gram-stain.
- The bacterium is demonstrated by acid fast staining technique.
- When stained with a dye combined with phenol and washed with acidic organic solvents, they resist decolorization and therefore are termed 'acid-fast bacilli'-AFB.
- TB can be classified into:
  - Primary tuberculosis (PTB): 80% of cases
    - 75-80% of all PTB cases are smear-positive PTB.
    - 20-25% of all PTB cases are smear-negative PTB.
  - Extra-pulmonary TB (EPTB)-20% of cases.

TRANSMISSION

- Adults with smear positive TB such as cavitory TB and laryngeal TB are the sources of infection.
- Patients who are culture-negative pulmonary TB and extra pulmonary disease are not infectious.
- *M. tuberculosis* is commonly transmitted from a patient with infectious tuberculosis to a healthy individual through:
  - Inhalation of droplets excreted via coughing, sneezing or speaking.
  - Only a small number of bacteria need to be inhaled to develop infection but not all those who are infected develop active disease.
  - The outcome is dependent on a number of factors including the host's immune response.

- Drinking non-sterilized infected cow milk could also transmit *M. bovis* but the incidence seems to be decreasing because of health education on boiling or pasteurizing milk.
- Factors that facilitate transmission of PTB are:
  - Presence of a contact
  - Infectivity of the contact (patients with heavy bacterial load)
  - Duration of contact (prolonged exposure)
  - Intimacy (how close the source and the subject are)
  - Environment: overcrowding, poor ventilation
- Patients who acquire the infection may not develop the disease. The rate of clinical disease is highest during late adolescence and early adulthood but the reasons are not clear.
- Infections are more common in young women than men.
- Conditions that increase the likely hood of developing active TB include:
  - HIV (co-infection) due to suppression of cellular immunity.
  - Hematologic and other malignancies: lymphoma, leukemia, malignancies.
  - Chronic renal failure
  - Diabetes mellitus
  - Immune suppressive drugs like long-term corticosteroids (e.g. prednisolone)
  - Old age: decreased immunity
  - Malnutrition is a very important factor for the development of disease.
  - Alcohol

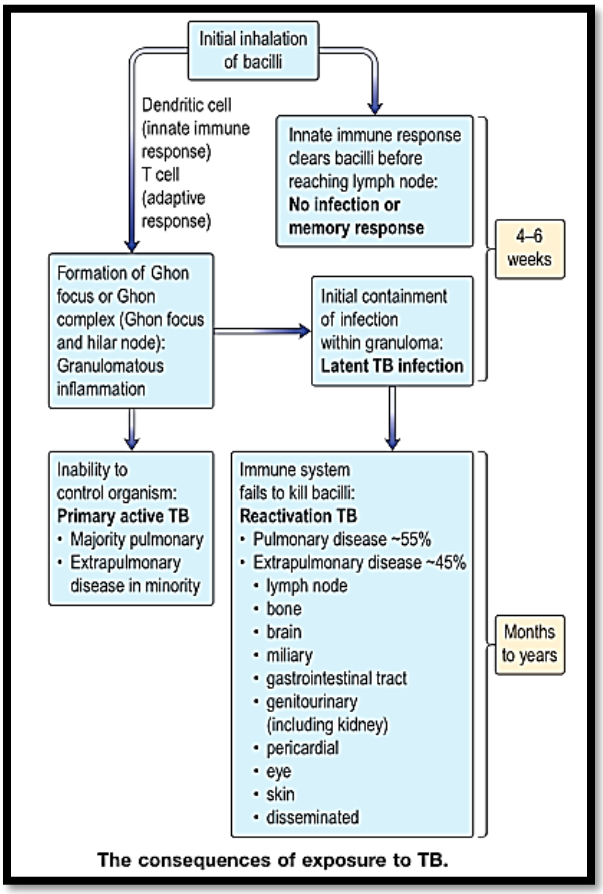
PATHOGENESIS

- Transmission is through droplet infection. Only a small number of bacteria need to be inhaled to develop infection but not all those who are infected develop active disease.
- *M. tuberculosis* interacts with host immune system immediately after entry. It initiates the recruitment of macrophages and lymphocytes.
- Activated alveolar macrophages ingest the bacilli, after which they release neutrophil chemo-attractants and cytokines to activate other immune system components and try to control the infection or multiplication of bacilli.
- This process will recruit cells (cell mediated immune response).
- Macrophages present the antigen to the T-lymphocytes.
- Macrophages undergo transformation into epithelioid and Langerhans cells which aggregate with lymphocytes to form the classical tuberculous granuloma.

- A delayed hypersensitivity-type reaction occurs resulting in tissue necrosis and formation of a granuloma.
- Activated cells aggregate around the lesion and the center becomes necrotic, soft cheese like material called caseous necrosis.
- Granulomatous lesions consist of a central area of necrotic material (caseation), surrounded by epithelioid cells and Langhans' giant cells with multiple nuclei, both cells being derived from macrophages. Lymphocytes are present and there is a varying degree of fibrosis.
- Numerous granulomas aggregate to form a primary lesion or 'Ghon focus' characteristically situated in the periphery of the lung.
- Spread of organisms to the hilar lymph node is followed by a similar pathological reaction and the combination of the Ghon focus and regional lymph nodes is referred to as the 'Primary complex of Ranke'.
- The primary complex is encapsulated in a fibrous capsule, limiting the spread of the bacilli, so called latent TB.
- The primary complex of Ranke is seen in 'healed' primary pulmonary tuberculosis and is a later manifestation of the ghon complex (Ghon focus + ipsilateral calcified mediastinal nodes).
- If no further complication arises the lesion may eventually be calcified and is clearly seen on X-ray
- The center however may still contain live bacteria that become dormant.
- These bacteria will flare up and multiply when the person's immunity is depressed.
- But if the bacteria inside the macrophage multiply rapidly, they will kill the macrophage and are released but to be taken up by other macrophages again. If this process is not arrested, patients may develop disseminated infection.
- On initial contact with infection <5% of patients develop active disease. This percentage increases to 10% within the first year of exposure.
- In the majority of people who are infected by mycobacterium spp, the immune system contains the infection and the patient develops cell mediated immune memory to the bacteria. This is termed latent tuberculosis.
- The majority of TB cases are due to reactivation of latent infection. The initial contact usually occurred many years or decades earlier. In patients with HIV infection newly acquired TB infection is also

common. This is called reactivation tuberculosis.

Latent infection	Active disease
Bacilli present in Ghon focus	Bacilli present in tissues or secretions
Sputum smear and culture negative	Sputum commonly smear and culture positive in pulmonary disease MTb can usually be cultured from infected tissue
Tuberculin skin test usually positive	Tuberculin skin test usually positive (and can ulcerate)
Chest X-ray normal (small calcified Ghon focus frequently visible)	Chest X-ray shows signs of consolidation/cavitation/ effusion in pulmonary disease
Asymptomatic	Symptomatic – night sweats, fevers, weight loss and cough common
Not infectious to others	Infectious to others if bacilli detectable in sputum



The consequences of exposure to TB.

CLINICAL MANIFESTATIONS

PULMONARY TUBERCULOSIS

- Patients are frequently symptomatic with a productive cough and occasionally hemoptysis along with systemic symptoms of weight loss, fever and sweats (commonly at the end of the day and through the night).
- This can be classified as
  - Primary Pulmonary tuberculosis
  - Secondary/ Re-activation Tuberculosis
- Note: extrapulmonary involvement is far less common in primary disease and is usually only seen in regions of high endemnicity.

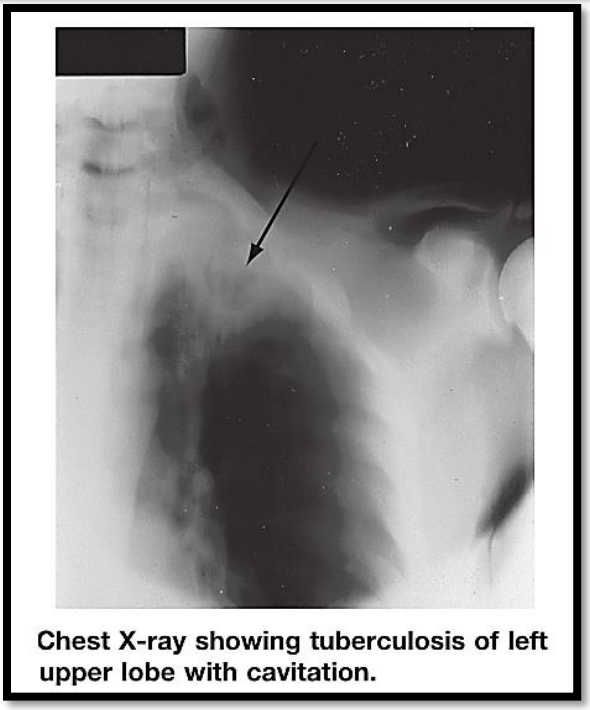
PRIMARY PULMONARY DISEASE

- Clinical illness follows after primary tuberculosis (no history of prior TB infection).
- This is common in children <4 years of age, it results from an initial infection.
- Frequently it involves the middle and lower lung zones.
- In the majority it heals spontaneously leaving a healed scar on the lung called Ghon lesion.

- It may be contained by immunity into dormant stage only to flare up in immunocompromised state (re-activation).
- In children or in immune compromised individuals the disease is usually rapid involving lungs, pleura and mediastinal lymph nodes.
- It may disseminate into the blood stream and cause miliary tuberculosis.
  - Characterized by 2-3 weeks of fever, night sweats, anorexia, weight loss and a dry cough.

SECONDARY/RE-ACTIVATION PULMONARY TUBERCULOSIS

- If no clinical disease is developed after primary infection, dormant bacilli may persist for years or decades before being reactivated when this happens, it is called secondary (post primary) tuberculosis.
- It is more common in adults and typically involves the apical lobes, where oxygen tension favors survival of the strictly aerobic organism but any portion of the lungs can be involved.
- The disease could extend from small infiltrates to large cavitory lesions. Patients with cavitory lesion expectorate tuberculosis bacilli with sputum.
- Early in the course patients may have intermittent fever, night sweats, weight loss, anorexia and weakness. Most patients have cough which may be dry at first but later becomes productive of whitish sputum, it is frequently blood streaked.
  - Patients may have exertional dyspnea, and hoarseness of the voice if there is laryngeal involvement.
- Physical examination:
  - Chronically sick patient
  - Pallor
  - Finger clubbing
  - Inspiratory crepitations are seen in some cases
- Laboratory findings:
  - ESR: raised
  - Full blood count: Anemia, Leukocytosis
  - Sputum examination (microscopy, culture and sensitivity) may be positive for AFB
  - GeneXpert
  - CXR findings are non-specific:
    - Infiltrations,
    - Consolidation with or without cavitation
    - Pleural effusion
    - Thickening or widening or the mediastinum caused by hilar or paratracheal adenopathy



Chest X-ray showing tuberculosis of left upper lobe with cavitation.

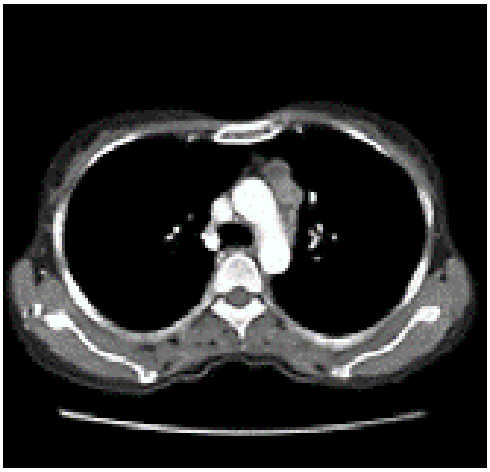
EXRAPULMONARY TUBERCULOSIS

- Accounts for about 20% of cases in those who are HIV-negative but is more common in HIV-positive individuals.
- Commonly affected organs are lymph nodes, pleura, meninges, genitourinary tract, bones, joints, adrenal glands and peritoneum.

LYMPH NODE TUBERCULOSIS (TB LYMPHADENITIS)

- This is the second most common site of infection.
- Seen more in HIV patients.
- Extrathoracic nodes are more commonly involved than intrathoracic or mediastinal.
- The commonest sites are cervical and supraclavicular.
- Other sites include axillary and inguinal.
- The nodes are usually painless (non-tender) and initially mobile but become matted together overtime, sometimes pus may be discharging (the overlying skin is frequently indurated or there can be sinus tract formation).
- The node becomes necrotic centrally and can liquefy and be fluctuant if peripheral.
- Characteristically there is no erythema (cold abscess formation)
- Half the cases do not have any constitutional features such as fever or night sweats.
- The diagnosis is made by fine needle aspiration (under radiological guidance) and/or lymph node biopsy. Histocytopathological examination as well as culture can be done on the sample.
- Mediastinal nodal sampling (endobronchial ultrasound transbronchial needle aspiration mediastinoscopy/mediastinotomy)
- Nodes typically can be enlarged for several months prior to diagnosis.

- On CT imaging, the central area appears necrotic.



PLEURAL TUBERCULOSIS

- Pleural involvement may be asymptomatic or patients could have fever, pleuritic chest pain and dyspnea.
- On physical examination, typically there will be decreased tactile fremitus, dullness and decreased breath sounds on the affected side.
- Fluid should be aspirated from pleural space (thoracentesis) and analyzed.
- Chest X-ray is also helpful in diagnosis; it may show homogenous opacity with meniscus sign.
- Empyema (pus in the pleural space) may complicate tuberculosis occasionally.

GENITOURINARY TUBERCULOSIS

- Can involve any part of the system.
- Dysuria, intermittent hematuria and flank pain are common presentations.
- But it may be asymptomatic for a long period of time.
- Urinalysis shows pyuria and hematuria without bacteria in majority of cases (commonly called sterile pyuria).
- Diagnosis may be reached by culturing urine repeatedly for *M. tuberculosis*.
- It affects more females and may present as infertility or pelvic pain.

SKELETAL TUBERCULOSIS

- It is usually reactivation of hematogenous site or extension from a nearby lymph node. The most common sites are spine, hips and knees.
- Spinal tuberculosis is called Pott's disease or tuberculous spondylitis. In adults, lower thoracic and lumbar vertebrae are commonly affected. Patients may present with swelling (Gibbus) and pain on the back with or without paraparesis or paraplegia due to cord compression.
- Tuberculosis in other bones or joints usually presents with pain and swelling.
- Joint tuberculosis- any joint can be affected but weight bearing joints, particularly the hip and knee joints are commonly involved.

- Patients present with progressive joint swelling, usually with pain and limitation of movement. If left untreated, the joint may be destroyed.
- TB arthritis occurs as the primary disease in children. In adults, it is usually due to hematogenous spread from secondary pulmonary or renal lesions.
  - The onset is insidious and diagnosis often delayed.
  - The organism invades the synovium or intervertebral disc.
  - There are caseating granulomas and rapid destruction of cartilage and adjacent bone.
  - Some patients develop a reactive polyarthritis (Poncet's disease).
  - The Hip or knee (30%) is quite commonly affected but around 50% develop spinal disease.
  - The patient is febrile, has night sweats, is anorexic and loses weight.
  - The usual risk factors for TB apply- debility, excess alcohol use or immunosuppression especially with HIV/AIDs.
  - Investigations should include culture of fluid and culture & biopsy of synovium.
  - A chest X-ray should be performed. Initially joint or spinal X-rays may be normal but joint space reduction and bone destruction develop rapidly if treatment is delayed.
  - MRI shows the abnormality earlier in the spine and CT-guided biopsy from the affected disc is often necessary to obtain cultures.
  - Treatment is as for pulmonary tuberculosis with therapy for 9 months. The joint should be rested and the spine immobilized in the acute phase.
- TB osteomyelitis:
  - This is usually due to hematogenous spread from a reactivated primary focus in the lungs or gastrointestinal tract.
  - The disease starts in intra-articular bone.
  - The spine is commonly involved (Pott's disease), with damage to the bodies of two neighboring vertebrae leading to vertebral collapse and acute angulation of the spine (gibbus).
  - Pus can tract along tissue planes and discharge at a point far from the affected vertebrate.
  - Symptoms consist of local pain and later swelling if pus has collected. Systemic symptoms of malaise, fever and night sweats occur.

- Treatment is as for pulmonary tuberculosis but extended to 9 months together with initial immobilization.

TUBERCULOSIS MENINGITIS

- It is commonly seen in children and immune-compromised people particularly patients with HIV.
- More than half have evidence of disease in the lungs.
- Patients with TB meningitis present with headache, behavioral changes and neck rigidity for about two weeks or more. Patients may have cranial nerve paralysis and seizure.
- Cerebral spinal fluid (Lumbar puncture) analysis
  - Increased WBC count predominantly lymphocytes and very high protein (usually >2-3g/L) and low glucose content (<1/2 blood glucose). But any of these could be normal in the presence of the disease.
  - AFB can be seen in sediment CSF in only 20% of cases, this percentage increases if examined CSF volume is increased. Culture may be positive in about 80% but it takes 4 to 6 weeks to grow.

GASTROINTESTINAL TUBERCULOSIS

- TB can affect anywhere from the mouth to the anus.
- Bacteria could reach GI by swallowing sputum, hematogenously or by ingesting raw milk. The commonest sites are terminal ileum and cecum. The colon can also be affected.
- Patients usually present with Abdominal pain (right iliac fossa pain), anemia, diarrhea, symptoms of intestinal obstruction and hematochezia (frank blood on stool) may be presenting symptoms.
- One-third of patients present acutely with intestinal obstruction or generalized peritonitis. 50% have X-ray evidence of pulmonary TB.
- There could be associated fever, night sweats, weight loss and anorexia. There could be a palpable mass in the abdomen. Patient could have involvement of the peritoneum, liver and spleen.
- Differential diagnosis includes Crohn's disease and cecal carcinoma.
- A small bowel follow-through may show transverse ulceration, diffuse narrowing of the bowel with shortening of the cecal pole.
- Ultrasound or CT shows additional mesenteric thickening and lymph node enlargement.
- Histology and culture of tissue is desirable but not always possible.

- Specimen can be obtained by colonoscopy or laparoscopy but laparotomy is required in some cases.

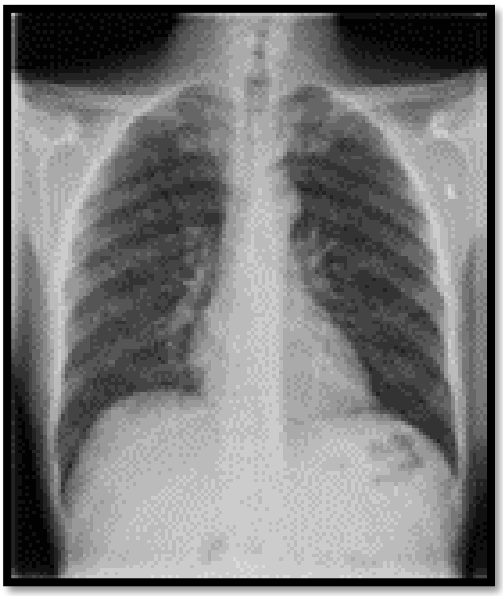
PERICARDIAL TUBERCULOSIS (TB PERICARDITIS)

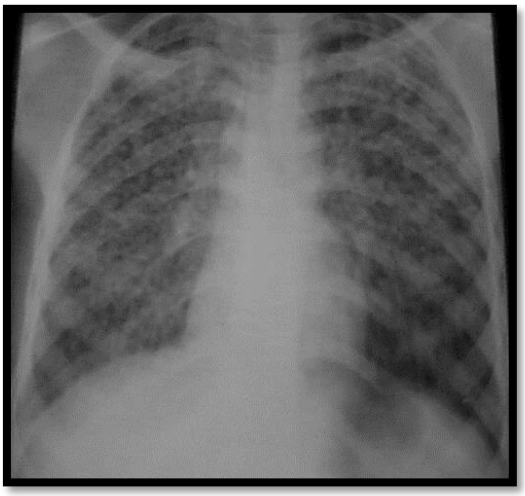
- Arises from ruptured abdominal lymph node or hematogenous dissemination.
- Patients usually present with chronic low-grade fever (particularly in the evening), associated with feature of acute pericarditis, retro-sternal pain, cough, dyspnea and generalized edema because of pericardial effusion. Cardiac tamponade may appear later.
- Constrictive pericarditis may develop as a complication of TB pericarditis even after treatment and patients can present with symptoms and signs of right sided heart failure.
- Diagnosis is usually reached by analyzing the pericardial effusion. It may show lymphocytosis but yield for AFB is low.
- Chest X ray may show enlarged heart shadow which suggests effusion. Ultrasound should be done when available and it demonstrates effusion.
- Treatment is as for pulmonary TB but prednisolone 60mg daily for 2-6 weeks is added.

MILIARY TUBERCULOSIS

- This is secondary to hematogenous dissemination of the bacilli to multiple sites, including the central nervous system in 20% cases.
- It is more common in children and immune-compromised patients.
- Manifestations are nonspecific with fever, night sweats, anorexia, weakness and weight loss. Patients may or may not have respiratory symptoms.
- Physical examination:
  - Seriously sick patient with hepatomegaly,
  - splenomegaly and
  - lymphadenopathy.
- Since symptoms and signs are not specific, high index of suspicion is required for the diagnosis.
- Systemic upset is the rule, with respiratory symptoms in the majority. Other findings are liver and splenic microabscesses with deranged liver enzymes or cholestasis and GI symptoms.
- Chest X-ray usually shows miliary pattern of infiltration bilaterally (millet seed like lesions)

- Diagnosis:
  - Blood cultures
  - Bronchoalveolar lavage fluid (usually smear negative but culture-positive)
  - Lumbar puncture should be performed in all cases unless contraindicated to assess for CNS involvement (affects treatment duration)
  - Sampling of other involved organs often necessary.





- Differential diagnosis for miliary TB on X-ray includes:
  - Miliary tuberculosis
  - Histoplasmosis
  - Sarcoidosis
  - Pneumoconiosis
  - Pulmonary siderosis
  - Bronchoalveolar carcinoma
  - Hematogenous metastasis from primary thyroid cancer, kidney, trophoblast and some sarcomas.

SKIN MANIFESTATIONS OF TB

- TB can occasionally cause skin manifestations:
  - Lupus vulgaris: usually arises as a post-primary infection. It usually presents on the head or neck with red-brown nodules that look like apple jelly when pressed with a glass slide ('diascopy'). They heal with scarring and new lesions slowly spread out to form chronic solitary erythematous plaque. Chronic lesions are at high risk of developing squamous cell carcinoma.
  - Tuberculosis verrucosa cutis: arises in people who are partially immune to TB but who suffer a further direct inoculation in the skin. It presents as warty lesions on a 'cold' erythematous base.

- Scrofuloderma: arises when an infected lymph node spreads to the skin causing ulceration, scaring and discharge.
- The tuberculides: are a group of rashes caused by an immune manifestation of TB rather than direct infection. Erythema nodosum is the commonest. Erythema induratum ("Bazin's disease) produces similar deep red nodules but these are usually found on the calves rather than the shins and they often ulcerate.

DIAGNOSIS

- Patients who have suggestive symptoms and signs for tuberculosis should undergo further tests.
  - AFB microscopy
    - Specimen: sputum, pleural, peritoneal, CSF and body discharges.
    - Stains used Ziehl-Neelsen.
    - Definitive diagnosis depends on detection of *M. tuberculosis* from a culture of specimen. Since culture routinely takes 4-6 weeks to grow, the culture is often not available to guide initial therapy. It is also necessary in order to do sensitivity testing.
    - Sputum (more than 2 samples are taken to increase diagnostic yield). Induced sputum (inhale hypertonic saline which induces coughing) gives more diagnostic yield than bronchoscopic samples.
    - Bronchoalveolar lavage fluid if cough unproductive and induced sputum not possible.
    - Aspiration of pleural fluid and pleural biopsy.
    - Gastric aspirates may be useful in pediatric disease.
    - Nasoendoscopic or bronchoscopic examination/biopsy of vocal cords with biopsy for smear/culture and histology in laryngeal disease
  - Gene expert: PCR
  - Chest X-ray: varies but typically there will be nodular infiltrates and cavities in the upper lobe, pleural effusion is also common. Chest X-ray findings do not confirm diagnosis of TB.
  - Raise ESR: non-specific, there could also be anemia of chronic illness.
  - Do not use PPD testing to diagnose acute cases of TB. PPD is relatively insensitive

and nonspecific with acute illness.

- Adenosine deaminase test (ADA) can also be done.
  - ADA is an enzyme present in the body whose main function is to aid in purine metabolism.
  - It helps in the breakdown of adenosine from food and thereby facilitates the turnover of nucleic acids in different body tissues.
  - In humans, the primary function of ADA is to keep the immunity system developed and maintained. It also has minor function functions such as gestation maintenance, the release of amino acids in the body, neurotransmission, and epithelial cell differentiation.
  - ADA test is done to measure the level of ADA in pleural fluid in the diagnosis of TB. In very rare cases it is done to test other infections.
  - In rare cases ADA test can also be done on cerebrospinal fluid or peritoneal fluid.
  - Normal range is less than 40µ/L.
  - If levels are increased in pleural fluid the result is indicative of Mycobacterium tuberculosis infection in the pleural.
  - In sarcoidosis, pulmonary embolus, cancer or lupus ADA levels may be mildly or moderately high.
- Urine LAM can also be done
  - This detects the lipoarabinomannan (LAM) antigens in urine samples
- Other important tests:
  - Full blood count
  - Liver function tests
  - Kidney function tests (Urea, electrolytes and creatinine)

ANTITUBERCULOSIS CHEMOTHERPAY

- Patients with fully sensitive TB require 6 months of treatment excluding TB meningitis for which the recommended duration is at least 12 months.
- In CNS and pericardial disease, corticosteroids are used as adjunct treatment to reduced long-term complications. (Prednisolone 60mg PO for 2-6 weeks then taper)
- Drugs currently in use include: streptomycin (S), Ethambutol (E), Isoniazid (H), Rifampicin (R) and pyrazinamide (Z)
- The treatment of tuberculosis through drug observed therapy has 2 phases:
  - The intensive (initial) phase: 4 fixed drug combination (4FDCs) are given for the first 2 months or until sensitivity testing is known.

    - Drugs include: Rifampicin, Isoniazide, Pyrazinamide and Ethambutol (given if sensitivity is not known)
  - The continuation phase: 2 drugs are used for the remaining 4 months.
    - Drugs include Rifampicin and Isoniazide
- The only forms of TB that definitely must be treated for longer than 6 months are TB meningitis (12 months), TB in pregnancy (9 months) and osteomyelitis.
- HIV positive persons may be treated for 6-9 months, there is no clear evidence that 9 months is necessary even in HIV positive persons, 6 months therapy is effective.
- Isoniazide should be given with Vitamin B6 (Pyridoxine 10mg OD) to prevent peripheral neuropathy that can be a side effect of isoniazid.
- Side effects:
  - All TB medications can cause liver toxicity except streptomycin and ethambutol. Isoniazide also causes peripheral neuropathy because of pyridoxine deficiency.
  - Rifampicin is associated with causing a benign change in the color of all bodily fluids to orange/red. This color is dangerous only because it could stain contact lenses and white underwear.
  - Ethambutol is associated with optic neuritis which can cause color blindness and other visual disturbances.
  - Pyrazinamide can cause benign hyperuricemia. Don't treat the hyperuricemia unless there are symptoms of gout associated with it, which rarely occurs.

Site of disease	Duration of therapy	Drug choice
Pulmonary[a] Extrapulmonary (excluding CNS disease) Miliary (excluding CNS involvement)	6 months (may be extended to 9 months in certain situations): patient smear positive 2 months into treatment some patients with HIV co-infection high burden of disease	Fully sensitive strain: 2HRZE + 4HR[b] *Or* 2HRZE + 7HR
CNS TB	12 months	2HRZE + 10HR *Plus* Prednisolone (20–40 mg o.d.) weaning over 2–4 weeks
Latent TB	3 months *Or* 6 months	3RH *Or* 6H

CNS, central nervous system; E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide.
[a]For pulmonary TB, 2HRZE + $4(HR)_3$, i.e. 3x weekly for 4HR is acceptable.
[b]2HRZE + 4HR, 2 months of HRZE + 4 months of HR.

DRUG	SIDE EFFECT	PREVENTIVE MEASURE
RIPAMPICIN (inhibits DNA-dependent RNA polymerase- transcription inhibitor)	Major: Hepatitis (inducer of P450), acute renal failure, shock, purpura (thrombocytopenia)	Stop Rifampicin if transferases are >3 times elevated.
	Minor: orange, pink or red discoloration of tears, sweat and urine + nausea, abdominal pain	Reassurance and advice patient to take drugs with a small meal
ISONIAZID: inhibits mycolic acid synthesis (Cell wall synthesis inhibitor)	Major: Jaundice and hepatitis (age dependent)	Stop isoniazide
	Minor: burning sensation in the feet (peripheral neuropathy), sideroblastic anemia	Give pyridoxine (Vitamin B6) 10mg OD
PYRAZINAMIDE (unknown mode of action)	Major: hepatotoxicity/ jaundice, hyperuricemia	Stop pyrazinamide
	Minor: Joint pain (pyrazinamide reduces the renal excretion of urate and may precipitate hyperuricemia gout)	Analgesics
ETHAMBUTOL (Inhibits the synthesis arabinogalactan-a cell wall component)	Major: optic neuritis: visual impairment (dose-related optic retrobulbar neuritis that presents with color blindness for green, reduction in visual acuity and a central scotoma-commoner at doses of 25mg/kg)	Stop ethambutol

	Minor: none	
STREPTOMYCIN (aminoglycoside- protein synthesis inhibitor)	Major: Ototoxicity: vertigo and hearing impairment, neuromuscular blockade (by decreasing acetylcholine release)	Stop streptomycin
	Minor: mild skin rash, perioral paresthesia	symptomatic treatment

- Streptomycin should not be given to pregnant women and patients with renal failure and ear problems. It should be replaced by ethambutol. Streptomycin dose should not be more than 750mg if the patient's age is >50 years.
- Children who are 6 years or below should not be given ethambutol because of damage to the eyes and children may not complain of it.
- Streptomycin is used only if patients are very ill, have multidrug-resistant TB or are not responding adequately to therapy.
- Patients should be strictly followed after initiation of the drugs.
- Corticosteroids are added to the anti-TB in meningitis, pericarditis and spinal TB to reduce long term complications. Adrenal TB patients should have replacement therapy.
- Close follow-up is needed and frequently children are put on Direct Observed therapy (DOTS) where nursing staff observe the therapy being given 3 times a week.
  - During the intensive phase the health worker or trained person watches as the patient swallows the drugs in his presence
  - During the continuation phase the patient is issued medicines for one week in a multi-blister combo-pack of which the first dose is swallowed by the patient in the presence of the health worker or trained person.
  - The consumption of medicines in the continuation phase is also checked by return of the empty multi-blister combo-pack when the patient comes to collect medicine for the next week.
  - DOTS is required especially for:
    - Patients thought unlikely to comply
      - History of serious mental illness
      - History of non-adherence of TB therapy in past or during current treatment course
    - Street or shelter-dwelling homelessness
    - Multi-drug resistant TB

- Drug resistant TB accounts for possibly only 2% of the million cases of TB in the world.
- It arises due to incomplete or incorrect drug treatment and can be spread from person to person.
- Factors associated with an increased risk of drug-resistant TB:
  - History of prior drug treatment of TB (particularly if unsupervised, self-administered treatment)
  - Co-infection with advanced HIV and previous TB treatment
  - Infection acquired in region with high rates of drugs resistance
  - Contact with a known case of resistant TB
  - Failure to respond to empiric TB therapy despite documented adherence
  - Exposure to multiple courses of fluoroquinolone antibiotics for presumed community acquired pneumonia
  - Healthcare workers exposed to cases of resistant TB.
- Types of drug resistance:
  - Primary drug resistance: infected with TB which is already drug resistant
  - Secondary (Acquired) drug resistance: drug resistance develops during treatment
- Drug resistant TB denotes resistance to one of the first line TB drugs (being Rifampicin or isoniazid)
- Multidrug resistant (MDR) TB denotes resistance to at least 2 main first line TB drugs i.e. rifampicin and isoniazide.
- Extreme drug resistant (XDR) TB denotes MDR-TB + resistance to any fluoroquinolone and at least 1 of the 3 injectable second-line drugs (amikacin, kanamycin or capreomycin)
- The second line drugs include:
  - Oral: fluoroquinolones
    - Ciprofloxacin
    - Levofloxacin
    - Movifloxacin
    - Gatifloxacin
  - Injectables
    - Amikacin
    - Kanamycin
    - Capreomycin
    - Streptomycin

- TB defaulter: this a patient whose treatment is interrupted for more than 2 consecutive months.
- Treatment failure in TB: This is the presence of continued or recurrently positive cultures during the course of antituberculosis therapy.
  - After 3 months of multi-drug therapy for PTB caused by drug susceptible organisms, 90-95% of patients will have negative cultures and show clinical improvement.
  - All patients with positive cultures after 3 months of appropriate treatment must be evaluated carefully to identify the cause of the delayed conversion.
  - Patients whose sputum culture remains positive after 4 months of treatment should be classified as treatment failure.
  - The reasons for this include:
    - Non-adherence
    - Drug resistance
    - Malabsorption of drugs
    - Laboratory errors
    - A few patients take a long time to respond as part of extreme biological variation.
- TB relapse: this is a patient who has become (and remained) culture negative while receiving therapy but after completion they become culture positive or have clinical or radiological deterioration that is consistent with active TB.
- Chemoprophylaxis can be offered to reduce the risk of active infection especially in patients at risk e.g. individuals with TB contact.
  - 300mg daily for 6 months, alternatively 300mg daily for 3 months, to be taken in combination with rifampicin.
- The BCG vaccine is a live attenuated vaccine derived from *M. bovis* that has lost its virulence. It has variable efficacy but it is still recommended in certain situations in developed countries. It has been shown to reduce the risk of disseminated and CNS TB in babies and children and is therefore used worldwide. There are safety concerns in babies with HIV. Its efficacy in adults is very variable.

COMPLICATIONS OF TUBERCULOSIS

- Pulmonary complications:
  - Pleurisy
  - Pleural effusion
  - Empyema
  - Pneumothorax
  - Aspergillosis
  - Endobronchitis
  - Bronchiectasis
  - Laryngitis
  - Cor pulmonale
  - Ca bronchus
  - Miliary TB

CHRONIC OBSTRUCTIVE PULMONARY DISORDERS

- COPDs are conditions characterized by chronic partial/complete irreversible airway obstruction causing an increased resistance to outflow of air.
  - The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
  - The obstruction can occur at any level (from the trachea to the terminal and respiratory bronchioles)
- These disorders include: emphysema, chronic bronchitis and asthma (although changes in asthma are reversible it is therefore not essentially a true COPD)
- COPDs can occur together in the same individual in a variable proportion but the manifestations of one often predominates the clinical picture.
- The older terms 'chronic obstructive airway disease' and 'chronic obstructive lung disease' are synonymous with COPD.
- Previous (before 1979) patients with COPD were often classified by:
  - Symptoms:
    - Chronic bronchitis
    - Chronic asthma
  - Pathological changes: emphysema
  - Physiological correlates
    - Pink Puffers
    - Blue bloaters
- Recognition that these entities overlapped and often co-existed led to introduction of the term COPD.
- COPDs can occur with a number of co-morbidities e.g. ischemic heart disease, hypertension, diabetes, heart failure and cancer, suggestive that it may be part of a generalized systemic inflammatory process.
- COPDs are a major health problem especially in Western societies because of the effect of cigarette smoking and aging.
- Males are affected more than females which could be attributed to the high prevalence of smoking in males. Nowadays, the incidence of this disease in females is increasing because of the increasing smoking habit.
- In patients with chronic obstructive pulmonary disorders, forced vital capacity (FVC) is either normal or slightly decreased while forced expiratory volume in 1second is significantly decreased.
- The FEV1/FVC ratio is characteristically decreased (FEV1/FVC<80%)

- The residual volume is increased but the total lung capacity may remain normal or increase (air trapping).
- The condition eventually leads to hypercapnic respiratory failure with pCO_2 of >45mmHg.
- Mechanisms of airflow limitation:
  - Loss of elastic recoil: emphysema
  - Increased resistance:
    - "Large" airways (>2mm): chronic bronchitis
    - "Small" airways (<2 mm): small airway disease

EMPHYSEMA

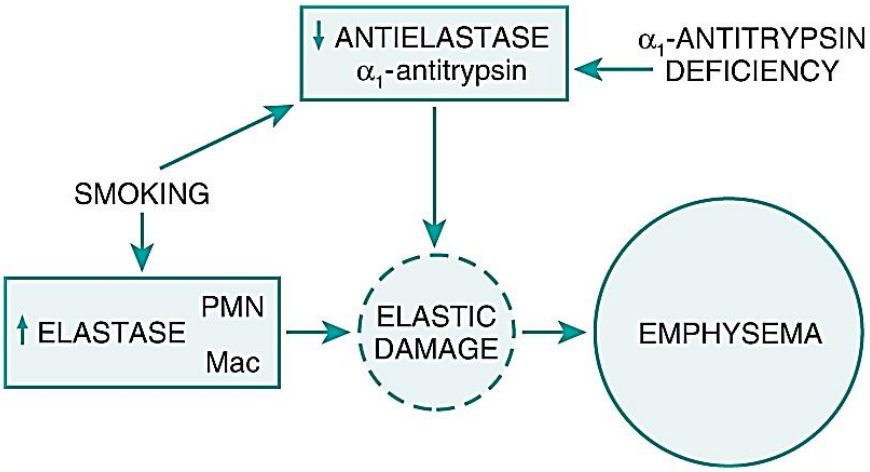
- Pulmonary emphysema is permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and alveolar septa without obvious fibrosis.
- Recent evidence suggests that the enlargement of the distal air spaces is a secondary result of small airway inflammation and destruction.

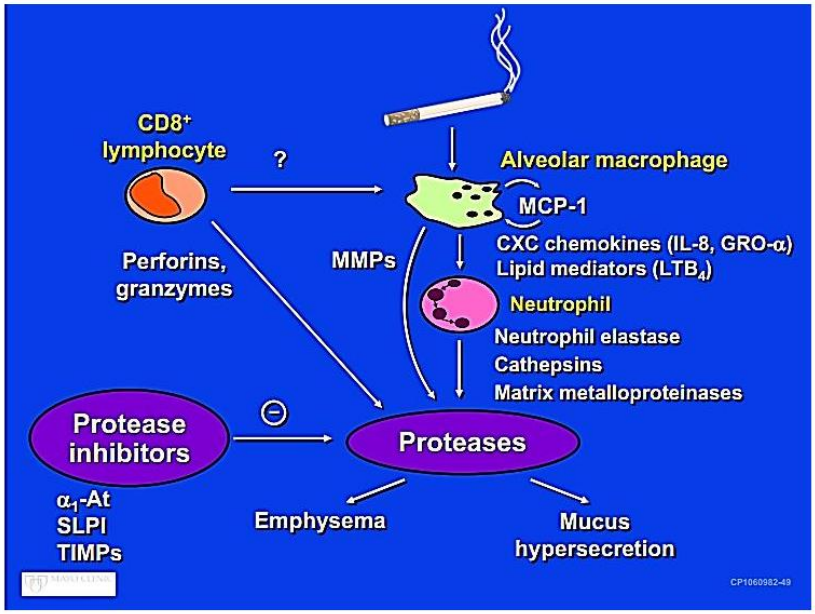
ETIOLOGY

- Any factor leading to chronic alveolar inflammation would encourage development of an emphysematous lesions.
- Smoking has adverse effects on lung defenses, leading to emphysematous change.
  - In developed countries, cigarette smoking accounts for over 90% of cases. In developing countries other factors such as inhalation of smoke from biomass fuels used in heating and cooking in poorly ventilated areas are also implicated.
  - Only 10-20% of heavy smoker develop COPD indicating individual susceptibility.
  - The development of COPD is proportional to the number of cigarettes smoked per day. The risk of death from COPD in patients smoking 30 cigarettes daily is 20 times that of a non-smoker.
- Congenital enzyme defects such as alpha-1 antitrypsin deficiency are also risk factors for the disease.
- 10-15% are occupational. Due to many of the same dusts that cause interstitial lung disease.

PATHOPHYSIOLOGY

- Emphysema is characterized by destruction of alveolar septa and distension of alveoli resulting in reduced surface area and loss of vessels, the later causing reduced perfusion.
  - Irritants from cigarette smoke, tobacco smoke or inhaled pollutants induce an ongoing inflammation. Tumor necrosis factor and IL -8 activate neutrophils which produce damaging proteases (especially elastase).
  - Nicotine also inactivates anti-proteases and produces reactive oxygen species which inactivate proteases and deplete antioxidants.
  - The loss of pulmonary parenchyma causes a loss of elastic recoil when the patient breathes out the airways collapse, trapping air (hyperinflation) because of reduced driving pressure (elastic recoil).
  - Changes are irreversible.
  - In alpha-1 antitrypsin deficiency there are low levels of protease inhibitor (Pi). Liver cirrhosis may also be present.
- In addition, emphysema causes mucus production and airway narrowing with accompanying reduction in ventilation. This leads to retention of carbon dioxide in the blood and severe dyspnea from reduced tissue perfusion
- These patients however, do not suffer from hypoxia and acidosis and have less chance of development of pulmonary hypertension and cor-pulmonale. However, patients usually have a mixed picture of emphysema and chronic bronchitis.





TYPES OF EMPHYSEMA

- It is classified according to the site of damage:
  - Centri-acinar emphysema: distension and damage of lung tissue is concentrated around the respiratory bronchioles whilst the more distal alveolar ducts and alveoli tend to be well preserved. This form is extremely common. When of modest extent it is not necessarily associated with disability. Severe centri-acinar emphysema is associated with substantial airflow limitation. It mostly affects the upper lobes particularly in the apical segments and is most commonly seen in smokers.
  - Pan-acinar emphysema: the acini are uniformly enlarged from the level of the respiratory bronchioles to the terminal blind alveoli. it affects the lower lung zones mostly and is associated with alpha-1 antitrypsin deficiency.
  - Distal acinar emphysema: proximal portion is normal but distal part is primarily involved. More severe in upper half of the lungs and may be associated with spontaneous pneumothorax in young adults.
  - Irregular emphysema: acinus is irregularly involved and is almost invariably associated with scarring such as that resulting from healed inflammatory disease. Although clinically asymptomatic this may be the most common form of emphysema.
  - Bullous emphysema: this results from any form of emphysema that produces large sub-pleural spaces more than 1cm in diameter. Such blebs represent localized accentuations of 1 of the 4 forms of emphysema. Most blebs are sub-pleural near the apex and on occasion they may rupture leading to pneumothorax.

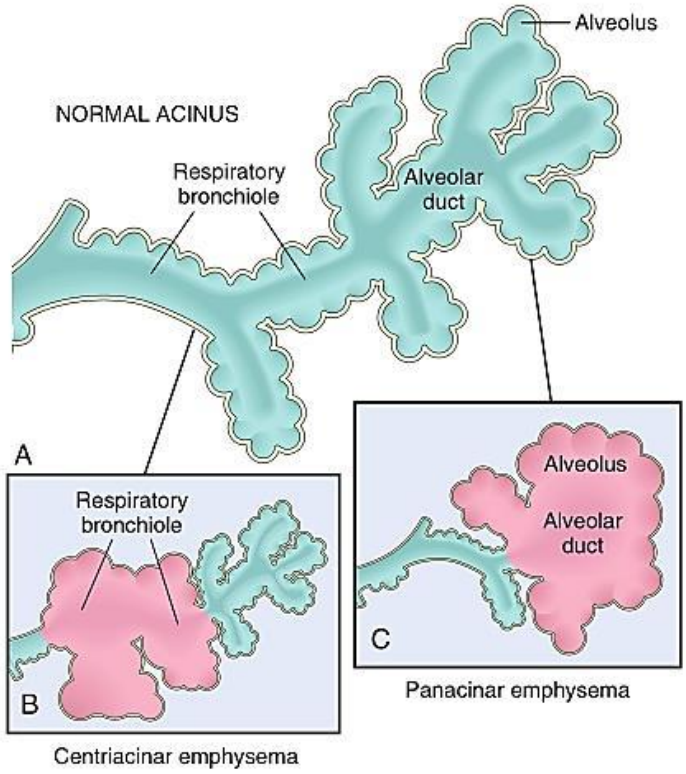


Figure 43: Types of emphysema

CLINICAL FEATURES

- Dyspnea: usually the first symptoms. It begins insidiously but is steadily progressive.
- Patients have prolonged expiration sitting forward in a hunched-over position, attempting to squeeze the air out of the lungs with each expiratory effort
- Rapid respirations with pursed lips.
- Because of prominent dyspnea (frank cyanosis and hypoxia) and adequate oxygenation of hemoglobin, there is secondary eyrthrocytosis (polycythemia) and these patients appear plethoric and are sometimes called "Pink puffers"
- Weight loss is common and may be severe to suggest a hidden malignancy ("Lots of calories just to breath")
- On examination they may have:
  - Barrel-shaped chest due to hyperinflation and trapped air.
  - Finger clubbing
  - Tachypnea and use of accessory muscles
  - Pulsus paradoxus
  - Chest is Hyper-resonant to percussion
  - Wheeze/Rhonchi
  - Prolonged expiration (normally <4 seconds)
  - Diminished vesicular breath sounds and distant heart sounds
  - In advanced emphysema the chest may be remarkably "quiet"



Figure 44: Pink Puffers of Emphysema

CHRONIC BRONCHITIS

- Chronic bronchitis is due to chronic excess mucus secretion in the bronchial tree.
- It is defined by the presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years ('Smoker's cough').
- It is common among cigarette smokers and urban dwellers in smog-ridden cities.
- 20-25% of men in the 40 to 65-year-old age group have the disease.

- In the early stages of disease, the productive cough raises mucoid sputum but airflow is not obstructed.
- Some patients with chronic bronchitis may demonstrate hyperresponsive airways with intermittent bronchospasms and wheezing.
- A subset of bronchitis patients especially heavy smokers develop chronic obstruction usually with associated emphysema.

ETIOLOGY

- Sufficient exposure to bronchial irritate particularly cigarette smoke, most persons develop some degree of chronic bronchitis with signs of inflammation of the airways.
- In developing countries household smoke from fire wood is said to be a major contributing factor.

PATHOPHYSIOLOGY

- There is hypersecretion of mucus beginning in the large airways.
- Although the single most important cause is cigarette smoking (chronic irritation), other air pollutants such as sulfur dioxide and nitrogen dioxide may contribute.
- Bacterial and viral infections are triggers of acute exacerbation.
- These environmental irritates induce hypertrophy of mucus glands in the trachea and main bronchi leading to a marked increase in mucin-secreting globlet cells in the surface epithelium of smaller bronchi and bronchioles.
- The irritants also cause inflammation with infiltration of CD8+ lymphocytes, macrophages and neutrophils. In contrast to asthma there are no eosinophils in chronic bronchitis.
- Mucus hypersecretion is primarily a reflection of large bronchial involvement. Accompanying alterations in small airways leads to bronchiolitis which can result in earlier manifestations of chronic obstruction.
- Obstruction of airway by mucus leads to bronchiectasis (pathological dilation airways) or atelectasis (collapse).
- In chronic bronchitis alveoli are often spared and no vessel loss and lung perfusion remains normal but ventilation is very much reduced. This leads to abnormal V/Q (arteriovenous shunt) and patients usually suffer from hypoxemia (manifested with cyanosis) and acidosis which causes pulmonary hypertension and right heart failure in the long term.

CLINICAL FEATURES

- Prominent productive cough (for 3month in past 2 years). Sputum is copious and purulent.
- Shortness of breath
- Patients tend to be obese
- Hypercapnia, hypoxemia and in severe cases cyanosis (hence the term 'blue bloater')
- In advanced stages chest may be "noisy".
- On examination:
  - Cyanosis
  - Finger clubbing
  - Normal RR
  - Rhonchi/Wheezing
- With progression chronic bronchitis is complicated by pulmonary hypertension and cardiac failure (Cor pulmonale).
- Recurrent infections and respiratory failure are constant threats



Figure 45: Blue bloater of Chronic bronchitis

Feature	Predominant emphysema	Predominant chronic bronchitis
Age	60 +/-	50 +/-
Body habitus	Thin	Obese
Cough	After dyspnea	Before dyspnea
Sputum	Scanty, mucoid	Copious, purulent
Appearance	Pink, tachypnic (Pink Puffers)	Cyanosed, normal RR (blue bloaters)
Physical examination	• Increased Anteroposterior diameter • Use of accessory muscles of respiration • Silent chest • Hyper-resonant • Decreased cardiac dullness	
CXR	• Long narrowed tubular heart • Low diaphragm (flat diaphragm) • Dark lung fields (translucent) with loss of peripheral vascular markings	• Enlarged heart • Large pulmonary artery • Increased bronchovascular markings
Hematology	Normal Hct	Increased Hct
Blood gasses	PaO_2= 65-75 mmHg $PaCO_2$= 35-40mmHg	PaO_2= 40-60 mmHg $PaCO_2$=50-60 mmHg
Complications	• Less bronchial infection • Terminal respiratory insufficiency +/- cor-pulmonale	• Frequent bronchial infection • Repeated respiratory insufficiency • Frequent cor-pulmonale

- Distinction from asthma:
  - Suggest COPD: smoker, cough, older (>35 years old), chronic productive cough, progressive SOB.
  - Suggest asthma: nocturnal symptoms. Significant diurnal or day to day variability in symptoms.

DIAGNOSIS

- Diagnosis is based on history and spirometry.
- History of chronic productive cough and/or exertional dyspnea of unknown etiology, or whose physical examination reveals evidence of prolonged forced expiration.

INVESTIGATIONS

- Pulmonary spirometry: FEV1/FVC <0.7, decreased FEV1 and decreased TLC.
  - Classification by % of FEV1 predicted
    - Mild: ≥80%. Symptoms must be present for diagnosis
    - Moderate: <80% (50-79%)
    - Severe: <50% (30-49%)
    - Very severe: <30%
- Chest X-ray: findings are very variable. In the early stages it is normal.
  - Hyperinflation: >6 anterior ribs and flat/tented diaphragm, generalized radio-lucency of the lung fields is common usually late in the disease process.
  - In patients with recurrent chest infections, a variety of non-descriptive post-inflammatory abnormalities (referred to as 'dirty lung') may be noted on the film.
  - Other findings: large pulmonary arteries, bullae, loss of lung markings (emphysema) and cardiomegaly (cor pulmonale)
- Sputum for microscopy, culture and sensitivity
- ECG: RVH, may show P pulmonale (Tall P waves of pulmonary hypotension), Right bundle branch block.
- Bloods:
  - Full blood count: increased RBC and elevated hematocrit in chronic hypoxemic patients.
  - Baselines:
    - U+Es: for Kidney function
    - Liver function tests and liver enzymes for alpha-1 antitrypsin deficiency
  - Alpha-1 antitrypsin levels.
  - Arterial blood gasses: decreased oxygen and increased carbon dioxide.

- Other investigations:
  - CT: not needed for diagnosis but emphysema may be incidental finding which prompts consideration for COPD

MANAGEMENT

- There is no curative treatment.
  - Therapy is direct at relieving symptoms, controlling potentially fatal exacerbation, and slowing of the progression of the disorder.
  - Avoidance of bronchial irritants especially cessation of smoking is of primary importance.
  - Vaccination: one-off pneumococcal and annual flu.
  - Hydration with oral fluids.
- Stepwise medical treatment
  - SOB or exercise limitation: PRN inhalers, either one of:
    - Short acting Beta 2 agonists e.g. salbutamol (200µg every 4-6 hours) which is continued at all stages
    - Short acting muscarinic antagonist e.g. ipratropium (40 µg QID)
  - Persistent SOB or exacerbations: regular inhalers either one of:
    - Combination of long acting muscarinic antagonist e.g. tiotropium (17 µg BD) (an M3 antagonist) + Long acting beta 2 agonist e.g. salmeterol (50 µg BD), formoterol (12 µg BD). First line for most.
    - Combination of Long acting beta 2 agonist + inhaled corticosteroid e.g. Seretide (salmeterol + Beclometasone-40 µg) or Symbicort (formoterol + budesonide)
      - Consider if there are asthmatic features such as prior diagnosis of asthma or atopy, eosinophilia or substantial FEV1 or peak flow variability.
      - Inhaled corticosteroids increase the risk of pneumonia in COPD but does not affect (or even reduces) mortality risk.
  - Still persist: triple therapy
    - Long acting antimuscarinic e.g. tiotropium + Long acting beta 2 agonist e.g. salmeterol + Inhaled corticosteroid e.g. beclometasone
  - Further options in severe disease:
    - Home nebulizers
    - Oral immunomodulators:

        - Prednisolone 30mg should be given for 2 weeks, with measurements of lung function before and after the period of treatment.
        - Roflumilast (PDE 4 inhibitor)
    - Antibiotics: to treat infections
        - Co-trimoxazole 980mg PO BD or TTC or Ampicillin 250-500mg QID for 10days for infections
        - Cefaclor 500mg 8 hourly or Cefixime 400mg OD. Co-amoxiclav can be used as an alternative.
        - Long-term treatment with antibiotics remain controversial.
    - Oxygen therapy: 2L/min via nasal prongs
    - Theophylline PO if inhaled therapy not possible
    - Diuretic therapy for all edematous patients with daily weighing.
    - Carbocisteine (2.25g daily) a mucolytic if there is no chronic productive cough
- Surgical treatment
    - Lung volume reduction surgery (LVRS) namely upper lobe resection. Offer if SOB and severe COPD but well enough for surgery (6-minute walk test >140m).
    - Bullectomy like LVRS removes areas of dead air space but is more limited. Offer if SOB and bulla >1/3 of hemithorax
    - Transplant if nothing else works in severe disease.

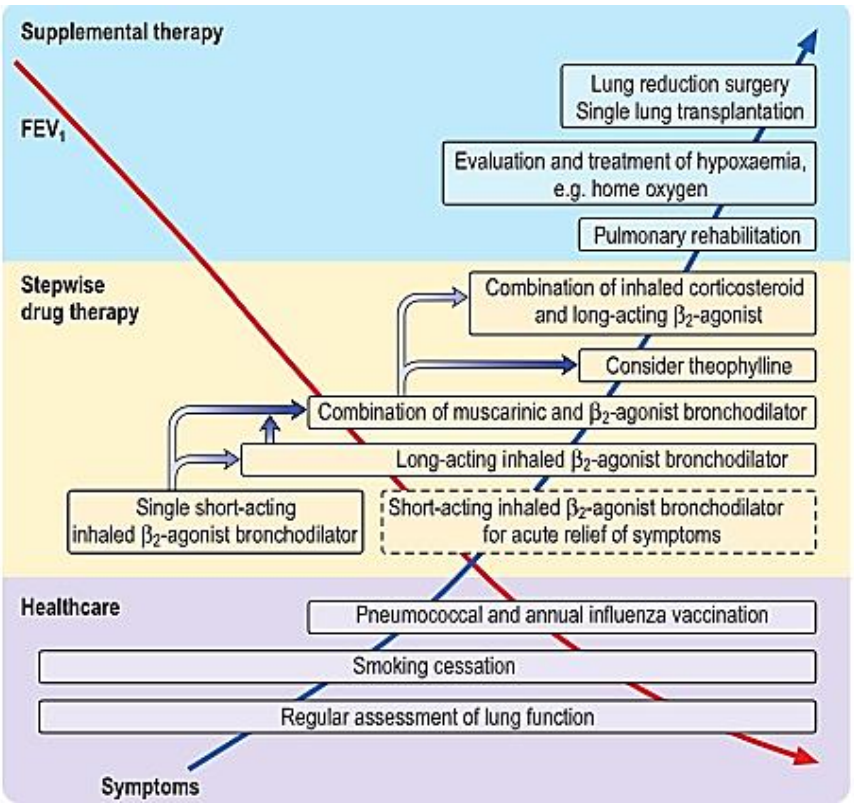


Figure 46: COPD management algorithm

COMPLICATIONS

- Exacerbations
- Chronic type 2 respiratory failure: respiratory acidosis is compensated for with raised bicarbonate ion and hence normal pH but this can decompensate in exacerbations

- Pulmonary hypertension and right heart failure (cor pulmonale)
- Anxiety and depression
- Bullae: dilated air spaces in lung which may require surgical excision due to compression of surrounding lung.

ACUTE EXACERBATION OF COPD

- Causes:
  - Upper or lower respiratory tract infections due to viruses or bacteria such as *S. pneumoniae*, *H. influenzae* or *Moraxella catarrhalis*.
  - Pollution
  - Drug changes
  - Co-morbidities: Heart failure, pulmonary embolism
- Indications for admission
  - Severe SOB
  - Oxygen saturation <90%
  - Cyanosis
  - Generally unwell, reduced activity or altered mental status
  - Not coping especially if living alone
  - Worsening edema
  - On long term oxygen therapy
- Investigate fully
  - Bloods: FBC, U +E, arterial blood gasses
  - Imaging: ECG, CXR and consider Echo
  - Microbiology: sputum microscopy/culture/Sensitivity and blood culture if fever
- Treatment: 'A VENTS'
  - A-antibiotics i.e. Erythromycin 500mg while awaiting sputum results.
  - Ve- ventilation with 24-28% oxygen through venturi mask if stats <90%. (target O_2 stats=88-92%). Suction any fluid from the airway.
  - N- nebulize with short acting beta 2 agonist +/- short acting antimuscarinic agent. Stop long acting antimuscarinic agent when using short acting antimuscarinic agent.
  - T- Theophylline IV if there is poor response
  - S-Steroids, ideally prednisolone PO 1-2 weeks
    - Hydrocortisone 200mg 4 hourly for 24 hours and maintain on oral prednisolone 30mg on alternate days.
  - At discharge arrange 6 week follow up.

ASTHMA

- This is a chronic inflammatory condition of the airways characterized by:
  - Airflow limitation: which is usually reversible, spontaneously or with treatment.
  - Airway hyperresponsiveness to a wide range of stimuli
  - Bronchial inflammation with T lymphocytes, mast cells, eosinophils with associated plasma exudation, edema, smooth muscle hypertrophy, matrix deposition, mucus plugging and epithelial damage.
- Note: In chronic asthma, inflammation may be accompanied by irreversible airflow limitation as a result of airway wall remodeling that may involve large and small airways and mucus impaction.
- Symptoms include wheeze, chest tightness, cough and shortness of breath often worse at night.
- Asthma commonly starts in childhood (it affects 15% of children) between the ages of 3 to 5 years and may either worsen or improve during adolescence.
  - It is not usually diagnosed in those under 2 years old due to the difficulty of distinguishing from viral-induced wheeze and frequent upper respiratory tract infections.
- Asthma can occur at any age but it usually starts early in life. About 50% of patients develop asthma before the age of 10 and another 35% before the age of 40.
- Males are affected twice as common as females in early life, this sex difference equalizes by age 30. Most causes of asthma are associated with personal or family history of allergic disease such as eczema, rhinitis and urticarial.

CLASSIFICATION

- Can be classified as:
  - Extrinsic asthma
  - Intrinsic asthma
- Previously it was classified as:
  - Allergic (Atopic)
  - Non-allergic (idiosyncratic)
  - Mixed

EXTRINSIC ASTHMA

- Occurs most frequently in atopic individuals (i.e. those with positive skin-prick reactions to common inhalant allergens such as dust mite, animal danders, pollens and fungi)
- 90% of children and 70% of adults with persistent asthma have positive skin prick tests to inhalant allergens.
- Childhood asthma is often accompanied by eczema (Atopic dermatitis).
- Sensitization to chemicals or biological products in work place is a frequently overlooked cause of late-onset asthma in adults.

INTRINSIC ASTHMA

- Often starts in the middle age
- Many patients with adult-onset asthma show positive allergen skin test and on close questioning some of these will give a history of childhood respiratory symptoms suggesting they have extrinsic asthma.
- Non-atopic individuals may develop asthma in middle age from extrinsic causes such as:
  - Sensitization to occupational agents e.g. toluene diisocyanate
  - Intolerance to NSAIDs e.g. aspirin or because they were given a Beta blocker for concurrent hypertension or angina that block the protective effect of endogenous adrenergic agonists.
  - Viral infection which causes epithelial damage and mucosal inflammation
  - Emotional upset which mediates excess parasympathetic input
  - Exercise which causes water and heat loss from the airways
  - Cold weather
- Extrinsic causes must be considered in all cases of asthma and where possible avoided.

ETIOLOGY AND TRIGGERS

- The 2 main causes of asthma symptoms are:
  - Hyperreponsiveness: this is an increased tendency of the airway to react to stimuli or triggers to cause an asthma attack.
  - Bronchoconstriction: narrowing of the airways that causes airflow obstruction.
- Asthma has a strong genetic predisposition or familial tendency.

- Triggers:
  - Allergens: seasonal allergens such as pollen green. Non-seasonal animal feathers, dust mites, molds.
  - Pharmacologic stimuli: Tatrazin (coloring agent), beta blockers such as propranolol etc.
  - Environmental and air pollution: in industrial and heavily populated areas. The common pollutants are ozone, nitrogen dioxide and sulfur oxide.
  - Infections: respiratory infections are the most common of stimuli that evoke acute exacerbation of asthma. Respiratory viruses are the major factors.
  - Exercise: this is a very common precipitant of acute episodes of asthma
  - Emotional stress: psychological factors can worsen or ameliorate asthma

PATHOPHYSIOLOGY

- Asthma results from a state of persistent subacute inflammation of the airways.
- The hallmark of this is an IgE type 1 hypersensitivity reaction.
- Exposure to an antigen or allergen leads to sensitization and production of IgM. With subsequent exposure to the same antigen or allergen IgE is produced.
- IgE via its Fc portion can bind to the surface of mast cells and basophils via the Fc receptors (FcR1). Cross-linkage of adjacent bound antibodies provides the signal to cause mast cell degranulation (histamine and heparin are release) and release of chemical mediators of inflammation resulting in vasodilation, increased pulmonary capillary permeability, viscous mucus production and severe constriction of bronchioles.
- In an acute attack there are 2 phases:
  - Early phase characterized by bronchospasm. This phase lasts 2 to 3 hours. This is due to interaction of mast cells and trigger leading to release of preformed mediators of inflammation, bronchospasms and increased mucus production.
  - Late phase associated with inflammation. This phase lasts 4 to 8 hours. It is due to infiltration of T lymphocytes, monocytes and eosinophil. There is airway hyperactivity.
- The airway obstruction in asthma is due to a combination of factors.
- The cells thought to play important part in the inflammatory response are mast cells, eosinophils, lymphocytes and airway epithelial cells.
- The mediators involved include histamine, prostaglandins, platelet activating factors and leukotrienes.

- These inflammatory mediators cause:
  - Bronchoconstriction (spasm of airways smooth muscle)
  - Vascular congestion and edema of airway mucosa
  - Increased mucus production
  - Injury and desquamation of the airways epithelium and impaired muco-ciliary transport.
- The epithelium lining the airway can become damaged and smooth muscle can undergo hypertrophy.
- In chronic state this can lead to airway remodeling.

CLINICAL FEATURES

- Attacks vary greatly in frequency and duration. Some patients only have 1 or 2 attacks a year that last for a few hours while others have attacks lasting for weeks.
- Some patients have chronic persistent symptoms, on top of which there are fluctuations.
- An attack usually begins acutely with paroxysms of wheezing, coughing, and shortness of breath or insidiously with slow increasing manifestations of respiratory distress.
- The asthmatic first notices dyspnea, tachypnea, cough, and tightness in the chest and may even notice audible wheezes.
- Symptoms:
  - Episodic shortness of breath
  - Wheezing
  - Chest tightness
  - Dry cough
- Symptoms are usually worst during the night and early morning, especially in uncontrolled disease.
- Cough is a frequent symptom that sometimes predominates especially in children in whom nocturnal cough can be a presenting feature.
- Signs:
  - Varying degrees of respiratory distress: tachypnea, tachycardia, and audible wheezes (or can be heard with a stethoscope as a rhonchi) are often present.
  - Dehydration may be present because of sweating and tachypnea
  - In more severe episodes, patients may be unable to speak more than a few words without stopping for breath.
  - Cyanosis is a late sign of hypoxia

- Confusion and lethargy may indicate the onset of progressive respiratory failure
- Pulsus paradoxus in a severe attack (An exaggeration in the normal variation in pulse pressure seen with inspiration such that there is drop in systolic blood pressure of greater than 10mmHg)
- Chest examination:
  - Prolonged expiratory phase with relatively high pitched wheeze throughout inspiration and most of expiration.
  - Reduced air entry due to mucous plug in attack
  - Less wheezing (silent chest) might indicate mucous plug or patient fatigue with less airflow and is a sign of impending respiratory failure.
  - The presence, absence or prominence of wheezes does not correlate precisely with the severity of the attack.
- The most reliable clinical signs which can be confirmed by arterial blood gas analysis are:
  - Degree of dyspnea at rest
  - Cyanosis
  - Difficult in speaking
  - Use of accessory muscles

INVESTIGATIONS

- Spirometry: FEV1/FVC ratio <0.7 confirms obstructive airway disease. Then do bronchodilator reversibility (BDR) test with more than 12% improvement in FEV1 is positive for asthma.
- Chest X-ray: varies from normal to hyperinflation. Atelectasis and pneumothorax may be seen in complicated cases.
- Full blood count: eosinophilia
- Sputum: is tenacious, rubbery and whitish or may be yellowish, eosinophils are present in sputum.

DIAGNOSIS

- Asthma should be considered in anyone who wheezes. A family history of allergy, rhinitis or asthma can be elicited in most asthmatics.
- Differential diagnosis:
  - In children
    - Foreign body obstruction
    - Viral upper respiratory tract infection (URTI) including epiglottis (croup) and bronchiolitis (RSV infection)
  - In adults: (physical examination should search for heart failure signs and signs of chronic hypoxemia (clubbing), unilateral wheezes indicate obstruction by foreign bodies or tumors)
    - COPD
    - Heart failure
    - Endobronchial TB
    - Malignancies

MANAGEMENT

- General principles:
  - Assessing the severity of the attack is paramount in deciding management
  - Bronchodilators should be used in orderly progression
  - Decide when to start corticosteroids. Inhaled corticosteroids reduce nocturnal symptoms quickly but wider effects take months so users need to know to be patient
  - Teach inhaler technique as many patients have trouble
- General measures: Remove any identifiable trigger, stop smoking. Routine antibiotics are not recommended.
- Mild cases: no acute distress, pulse rate <100 b/min, no cyanosis or dehydration
  - Salbutamol 2-4mg PO TDS
  - Salbutamol inhaler 2 puffs stat. Followed by 1 puff 4-6 hourly
  - Note: inhaled corticosteroids e.g. beclomethasone, 2 puffs given 10 minutes after salbutamol inhaler may be used.
  - The patient must be taught how to use the inhaler. Check that he can use it correctly. If he/she cannot learn, use oral salbutamol 4mg TDS daily though it may cause extrapyramidal symptoms.

- Stepwise medical therapy:
  - Principles
    - Most people are at steps 1-2
    - Start at a level appropriate to disease severity
    - Remember you can move down as well as up!
  - Step 1: Inhaled short acting Beta agonist (SABA) as required
    - Salbutamol 100µg/puff. Use 2 puffs before exercise if likely to bring on symptoms
    - Salbutamol tablets (4mg PO TDS/QID) can be used as an alternative.
    - Move to step 2 if using >3 times/week, waking at night or has acute asthma exacerbation
  - Step 2: SABA + Inhaled corticosteroid (ICS)
    - Fluticasone, beclometasone or budesonide.
    - Start at low dose
  - Step 3: SABA + ICS + leukotriene receptor antagonist (LTRA)
    - Monteleukast or Zafirlukast
  - Step 4: add long acting beta agonist (LABA)
    - Salmeterol or formoterol in combination in combination inhaler with ICS.
    - Continue LTRA if felt to be effective
  - Step 5: increase ICS dose until effective or trial further drug (theophylline or long-acting muscarinic antagonist)
  - Step 6: refer to specialist for consideration of systemic immunomodulators such as prednisolone PO and monoclonal antibodies: Omalizumab (anti IgE) and Reslizumab (anti-IL5)

USE OF INHALERS

- Basics:
  - First ask what they broadly know about asthma and inhaler use.
  - Detach metal canister to show and check the date on the drug.
  - Ensure lips and teeth are around mouthpiece.
  - Ensure slow breath
  - Praise correct behavior
  - Advise them to follow a steroid inhaler with mouth wash (e.g. Canestan-Fluconazole) to prevent thrush

- Metered dose inhaler:
  - Remove inhaler cap and shake inhaler
  - Breath out gently
  - Place mouthpiece in mouth, start breathing in then press canister and continue slow, deep inhalation.
  - Hold breath 10 seconds then breath out slowly
  - Wait 30 seconds then repeat all steps including the shake.

ACUTE SEVERE ASTHMA

- This is a term used to describe an exacerbation of asthma that has not been controlled by the use of standard medication.
- Patients with acute severe asthma typically have:
  - Inability to complete a sentence in one breath
  - Respiratory rate ≥25breaths/min
  - Tachycardia ≥110beats/min (pulsus paradoxus is not useful as it is only present in 45% of cases)
  - Use of accessory muscles of respiration
  - Paradoxical movement of the chest and the abdomen
  - PEFR <50% of predicted normal or best

- Features of life-threatening attacks are:
  - A silent chest, cyanosis or feeble respiratory effort
  - Exhaustion, confusion or coma
  - Bradycardia or hypotension
  - Presence of complications: pneumothorax, atelectasis
  - PEFR <30% of predicted normal or best (approximately 150L/min in adults)

- Features of a very severe life threatening attack:
  - A high P_aCO_2 >42mmHg
  - Severe hypoxemia (PaO_2<60mmHg) despite treatment with oxygen, SaO_2 < 90%
  - A low and falling arterial pH

- Arterial blood gases should always be measured in asthmatic patients requiring admission to hospital, with particular attention paid to the P_aCO_2. Pulse oximetry is useful in monitoring oxygen saturation during the admission and can reduce the need for repeated arterial puncture.

MANAGEMENT

- Assess the patient and admit patient
- Humidified Oxygen100%-3L/min is given through a mask (Aim for SpO_2 94-98%)
- Fluid and electrolyte balance. Avoid over hydration.
  - 3L/day (1-liter NS and 2L 5% Dextrose)
  - 20 mmol potassium chloride added to 1L of any of above fluids in 24 hours
- Calm patient and reassure the patient.
- Measure oxygen saturation with a pulse oximeter.
- Nebulized Salbutamol 5mg or Terbutaline 10mg stat followed by Salbutamol 2.5mg 4-hourly
- Add nebulized ipratropium bromide 0.5mg to nebulized salbutamol/terbutaline
- Hydrocortisone 200mg (4mg/kg) IV is given 4-hourly for 24 hours
- Prednisolone is continued at 60mg orally daily for 2 weeks then taper
- Aminophylline in doses of 1mg/kg/hr in a continuous IV infusion should be given.
  - Aminophylline 250mg IV over 5-10mins followed by maintenance dose of 100mg (less than 500mg over 24 hours)
  - If the patient has heart disease, liver disease or is taking beta blockers reduce the dose.
  - Always give oxygen with aminophylline. Patients who have taken oral aminophylline in the last 8 hours should not be given the loading dose.
- Respiratory tract infections precipitate acute asthmatic attacks are predominantly viral, but if patient expectorate yellowish, green or brown sputum antibacterial therapy is indicated. Ampicillin is first line, alternative TTC, erythromycin or Cotrimoxazole. CXR should be taken if there is suspicion of pneumonia or complications
- If patient does not improve consider endotracheal intubation and mechanical ventilation, they should be admitted to ICU
- One of the following IV infusion is given if no improvement is seen:
  - Salbutamol 3-20 µmg/min or
  - Terbutaline 1.5-5.0 µmg/min or
  - Magnesium sulphate 1.2-2g over 20 min

Management of a severe asthmatic attack 'O SHIT'

O-oxygen

S-salbutamol

H-hydrocortisone

I-Ipratropium

T-Theophylline/Aminophylline

COMPLICATIONS DURING AN ACUTE ATTACK OF ASTHMA

- Pneumothorax
- Mediastinal and subcutaneous emphysema due to alveolar rupture
- Atelectasis due to obstruction
- Dilated right chamber (Cor pulmonale) from chronic hypoxemia and pulmonary hypertension
- Respiratory failure

INTERSTITIAL LUNG DISEASES

PNEUMOCONIOSIS

- These are occupational lung disease in which inhalation of certain mineral dust that initiates an inflammatory process (tissue reaction) that eventually leads to lung fibrosis excluding bronchitis and emphysema.
- They are environmental disease caused by inhalation of inorganic dust particles.
- They usually appear 20-30 years after constant exposure to offending agents but can develop in less than 10 years when dust exposure is extremely high.
- History is of primary importance in assessing possible occupational lung diseases.
- Not all dusts are pathogenic. For example, silica is highly fibrogenic whereas iron (siderosis), tin (stannosis) and barium (baritosis) are almost inert.
- Coal dust has an intermediate fibrogenic effect. Exposure to silica or asbestos leads to extensive fibrosis and disability.
- The most important pneumoconiosis includes:
  - Coal miner's lung/coal worker's pneumoconiosis (CWP)
  - Asbestosis
  - Silicosis
  - Berylliosis: causes interstitial granulomatous disease similar to sarcoidosis.
- Alveolar macrophages engulf offending agents, causing inflammation and fibrosis of the lung parenchyma in pneumoconiosis. Respiratory insufficiency is the ultimate consequence of silicosis and the other pneumoconiosis.
- They are characterized by dyspnea, shortness of breath, cough, sputum production, cor pulmonale and clubbing.
- The hallmark of these restrictive lung diseases is an increase in the FEV1/FVC ratio (FEV1: FVC >80%)

  - This is because there is a decrease in Forced expiratory volume in 1 second (FEV 1) however, this decrease is not less than the decrease in Forced vital capacity (FVC)
  - There is also a decrease in Total lung capacity (TLC)
  - Recall in COPDs FEV1/FVC <80%
- Hypoxemia is evident with an increased atmospheric-alveolar partial pressure gradient.
- In many types of pneumoconiosis, a long period of dust exposure is required before radiological changes appear and these may precede clinical symptoms.
- Chest X-ray findings include: small irregular opacities, interstitial densities, ground glass appearance and honeycombing.

COAL MINER'S LUNG/COAL WORKER'S PNEUMOCONIOSIS

- This is caused by inhalation of coal dust which contains both carbon and silica.
- The risk of development and progression of CWP is related to the amount of coal dust exposure, higher rank (hardness) of coals and increased silica content of inhaled dust.
- The disease is caused by dust particles approximately 2-5 μm in diameter that are retained in the small airways and alveoli of the lung.
- The incidence of the disease is related to total dust exposure which is highest at the coal face, particularly if ventilation and dust suppression are poor.
- Clinical features: dyspnea, shortness of breath, cough, sputum production, cor pulmonale and clubbing
- 2 different syndromes result from the inhalation of coal
  - Simple pneumoconiosis:
    - This is deposition of coal dust in the lung.
    - It is the most common type of pneumoconiosis.
    - It is marked by coal macules around the bronchioles formed by ingestion of coal dust particles by macrophages. In most cases it is inconsequential and produces no disability.
    - It produces fine micronodular shadowing on the chest X-ray. It is graded on the Chest-X-ray appearance:
      - 1- small round opacities definitely present but few in number
      - 2- small round opacities numerous but normal lung markings still visible
      - 3- small round opacities very numerous and normal lung markings partly or totally obscured

- Simple pneumoconiosis can progress to development of progressive massive fibrosis. It almost never occurs with category 1 but occurs with 7% of patients in category 2 and 30% of patients in category 3.
- Miners with category 1 pneumoconiosis are unlikely to receive compensation unless they have evidence of COPD. Those with more extensive radiographic changes are compensated solely on basis of their X-ray appearances.

➢ Progressive massive fibrosis:

- This is marked by fibrotic nodules filled with necrotic black fluid.
- Patients develop round fibrotic masses several centimeters in diameter, almost invariably in the upper lobes and sometimes having necrotic central cavities.
- Pathogenesis still not understood though some fibrogenic promoting factors in individuals developing the disease lead to formation of immune complexes, analogous to the development of large fibrotic nodules in coal miners with rheumatoid arthritis (Caplan's syndrome).
- Pathologically there is apical destruction and disruption of the lung resulting in emphysema and airway damage.
- Lung function tests show a mixed restrictive and obstructive ventilator defect with loss of lung volume, irreversible airflow limitation and reduced gas transfer.
- The patient with PMF suffer considerable effort dyspnea usually with cough. The sputum may be black (melanoptysis).
- The chest X-ray appearance may be confused with lung cancer, tuberculosis and granulomatosis with polyangiitis.
- The disease can result in bronchiectasis, pulmonary hypertension or death from respiratory failure or right sided heart failure.

- Chest X-ray: small round densities are seen in the parenchyma usually involving the upper half of the lungs. Complicated or progressive massive fibrosis is diagnosed by the presence of larger densities from 1 cm in diameter to the entire lobe.
- Associated immunologic abnormalities: increased levels of IgA, IgG, C3, antinuclear antibodies (ANA) and rheumatoid factor.

- In Caplan syndrome there are rheumatoid nodules (rounded fibrotic nodules 0.5-5cm in diameter) in the periphery of the lung in a patient with rheumatoid arthritis and coexisting pneumoconiosis.
  - The rheumatoid nodules show central necrosis, palisading histiocytes and a peripheral rim of lymphocytes and plasma cells.
  - This syndrome may also occur in other types of pneumoconiosis.

ASBESTOSIS

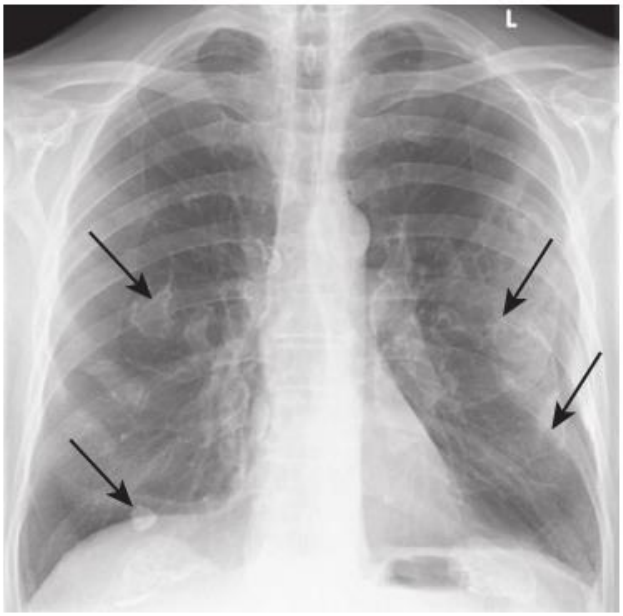
- This is caused by inhalation of asbestos fibers.
- Its fibers may be classified as either:
  - Chrysotile (white asbestos)-90% of the world's production
  - Serpentine (crocidolite or blue asbestos, and amosite or brown asbestos)
- Asbestos fiber exposure maybe seen in mining, milling, foundry work, shipyards, or application of asbestos products to pipes, brake lining, insulation and boilers.



Figure 47: Ferruginuous (asbestos) bodies. These asbestos fiber inclusions are coated with protein and iron and will appear blue when stained with Prussian blue.

- Previously some roofing of houses were built using asbestos material.
- History of exposure to asbestos is needed to consider the diagnosis.

- This disease is initiated by uptake of asbestos fibers by alveolar macrophages. A fibroblastic response occurs probably from release of fibroblast-stimulating growth factors by macrophages and leads to diffuse interstitial fibrosis, mainly in the lower lobes.
- Clinical features: exertional dyspnea and reduced exercise tolerance, cough and wheezing (especially among smokers), chest wall pain, and ultimately respiratory failure.
- On examination there may be finger clubbing and bilateral basal end inspiratory crackles.
- It is characterized by ferruginous bodies, yellow-brown, rod-shaped bodies with clubbed ends that stain positively with Prussian blue, these arise from iron and protein coating on fibers.
- Dense hyalinized fibrocalcific plaques of the parietal pleura are also present.



Asbestos-related benign pleural plaques. Chest X-ray showing extensive calcified pleural plaques ('candle wax' appearance – arrows), particularly marked on the diaphragm and lateral pleural surfaces.

- On chest x-ray diffuse or local pleural thickening, pleural plaques and calcifications at the level of the diaphragm are seen. Pleural effusions are commonly seen, and the interstitial lung process associated with asbestosis usually involves the lower lung fields.
- Asbestosis results in marked predisposition to bronchogenic carcinoma (adenocarcinoma or squamous cell carcinoma) and to malignant mesothelioma of the pleura or peritoneum.
- Cigarette smoking further increases the risk of bronchogenic carcinoma.
- A lung biopsy is usually necessary for the diagnosis in which the classic barbell-shaped asbestos fiber is found.
- No specific treatment is offered, though corticosteroids are often prescribed. It is important that patients with asbestos exposure stop smoking since the risk of lung cancer is 75 times higher than that of the normal population.

SILICOSIS

- This is a chronic occupational lung disease caused by exposure to free silica dust, it is seen in miners, quarry workers, glass and pottery manufacturers, sandblasting workers and stone cutters.

- The dust is highly fibrogenic. For example, a coal miner can remain healthy with 30g of coal dust in his lungs but 3g of silica is sufficient to kill.
- This disease is initiated by ingestion of silica dust by alveolar macrophages, damage to macrophages initiates an inflammatory response mediated by lysosomal enzymes and various chemical mediators.
  - These reactions cause susceptibility to tuberculosis.
- Silicosis will cause similar symptoms to asbestosis (or any other pneumoconiosis) except the acute form of silicosis, which is caused by massive exposure that causes lung failure in months.
- Silicotic nodules that enlarge and eventually obstruct the airways and blood vessels are characteristics.
- Silicosis is associated with increased susceptibility to tuberculosis, the frequent concurrence is referred to as silicotuberculsos.
- Chest X-ray findings: in silicosis there are nodules (1-10mm) seen throughout the lungs that are most prominent in the upper lobes. A characteristic finding is eggshell calcifications (rare). In progressive massive fibrosis, densities are 10mm or more and coalesce in large masses.
- There is no effective therapy for silicosis. Death occurs usually because of progressive respiratory insufficiency.

BERYLLIOSIS

- Beryllium-copper alloy has a high tensile strength and is resistant to metal fatigue, high temperature and corrosion.
- It is used in the aerospace industry, in atomic reactors and in many electrical devices.
- When beryllium is inhaled, it can cause a systemic illness with a clinical picture similar to sarcoidosis.
- Clinically there is progressive dyspnea with pulmonary fibrosis. However, strict control of levels in the working atmosphere has made this disease a rarity.

PLEURISY AND PLEURAL EFFUSION

- Pleural effusion is the presence of excess fluid in the pleural space.
  - The visceral pleura: covers the lung parenchyma including the fissures
  - The parietal pleura: lines the inside of the thoracic cavity
  - Normally 10-20ml of fluid is spread in a thin layer between the 2 layers of pleurae. It acts as a lubricant allowing smooth movement of the lung during respiration.
  - The pleural fluid is from different sources include:
    - Pleural capillaries
    - Interstitial spaces of the lungs
    - Intrathoracic lymphatics/blood vessels: disruption of the thoracic duct, injury to the blood vessel etc.
    - Peritoneal cavity: requires there to be free fluid in the abdomen and openings in the diaphragm
  - Hydrostatic and oncotic pressure balance the movement of fluid into the pleural space. Pleural fluid is reabsorbed normally by pleural lymphatics.

Pleurisy is pain arising from any disease of the pleura. The localizaed inflammation produces sharp localized pain which is worse on deep inspiration, coughing and occasionally on twisting and bending movements.

Common causes are pneumonia, pulmonary infarct and carcinoma. Rarer causes include rheumatoid arthritis and SLE

- Pleural effusions are as a result of excess production of pleural fluid or less commonly due to reduced clearance e.g. in lymphatic obstruction due to TB or cancer.
- Pleural effusions are classified based on laboratory analysis as (see common procedure chapter 13-Thoracentesis):
  - Transudates
  - Exudates

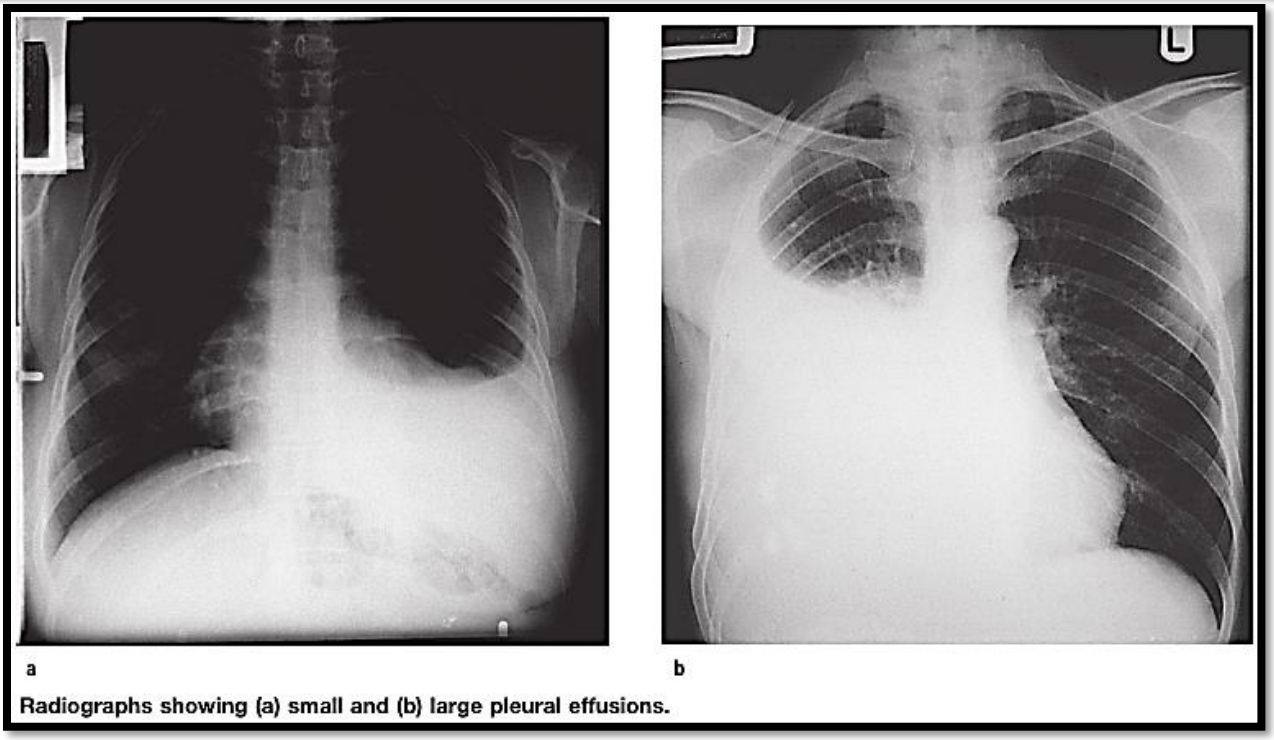
Transudative effusion	Exudative effusion
• Results from elevation in hydrostatic pressure or decrease in oncotic pressure	• Due to pleural inflammation (pleurisy) with increased permeability of the pleural surface to protein. • Pleurisy is seen in infections such as pneumonia, infections of the esophagus, mediastinum or sub-diaphragmatic areas, traumatic injuries and extension of infections from adjacent organs. • Initially pleurisy tends to be dry but fluid starts to collect subsequently.
• Heart failure • Cirrhosis of the liver • Nephrotic syndrome • Myxedema (hypothyroidism) • Hypoproteinemia • Constrictive pericarditis • Ovarian tumors producing right sided pleural effusion- Meigs' syndrome	• Infection (Parapneumonic, TB, fungal, empyema) • Esophageal rupture • Pulmonary embolism • Neoplasms e.g. mesothelioma • Autoimmune (Systemic lupus erythematosus) • Rheumatoid pleural effusion • Esophageal rupture • Sub-diaphragmatic abscess • Pancreatitis • Uremic pleural effusion • Hemothorax • Chylothorax (thoracic duct injury) • Radiation and drugs

CLINICAL FINDINGS AND DIAGNOSIS

- Underlying causes should be suspected from the history.
- Shortness of breath (dyspnea), Pleuritic chest pain and dry non-productive cough are the most common symptoms but many pleural effusions are asymptomatic and discovered on physical examination or chest X-ray.
- Physical examination:
  - Decreased chest motion on affected side
  - Tracheal deviation (if effusion is large)
  - Decreased/Absent tactile fremitus
  - Stony Dullness to percussion
  - Decreased or absent breath sounds
  - Reduced or absent vocal resonance
  - At the superior border of the fluid, there may be bronchial breath sounds- may be secondary to increased conductance of breath sounds through a partially collapsed lung
  - Pleural rub
- There may be signs of underlying e.g. raised JVP in heart failure, clubbing in lung cancer
- Clinically it can be detected when 500ml or more of pleural fluid is present.

INVESTIGATIONS

- Chest X-ray:
  - Homogenous opacity with a meniscus sign and obliteration of the costophrenic angle.
  - Large pleural effusions may result in complete opacification of the hemithorax and mediastinal shift to the opposite side.
  - An air-fluid level indicates bronchopleural fistula, pneumothorax, rupture of the esophagus into pleural space, gas forming organisms.
  - At least 200ml of fluid needs to be present for the lateral costophrenic angle to be blunted on a CXR. Ultrasound is more sensitive than CXR in detecting pleural effusions
  - The best way to identify and localize a loculated pleural effusion (when there are adhesions between the visceral and parietal pleural and the pleural fluid becomes encapsulated especially when there is pleural inflammation/pleurisy) is with ultrasonography



Radiographs showing (a) small and (b) large pleural effusions.

- Pleural thoracentesis (aspiration of fluid):
  - Should be performed to confirm the presence of fluid and to determine its characteristics including color and consistency.
    - Clear yellow fluid is described as serous
    - Bloody or blood-tinged fluid as sanguineous or serosanguineous. Some of the causes include pulmonary infarction and pleural carcinomatosis
    - Translucent or opaque, thick fluid as purulent.
  - Microscopic examination of the fluid is important including Gram stain and culture (if possible)
  - Total and differential cell counts should be obtained.
    - Predominance of Polymorphonuclear leukocytes suggests an underlying pneumonia with a Parapneumonic effusion.
    - The presence of small mature lymphocytes, particularly with few mesothelial cells strongly suggests tuberculosis
  - It is important to determine where the fluid is a transudate or exudate (using Light's criteria)

Light's Criteria: Exudate if any of the 3 are found		
	Transudate	Exudate
Protein (Pleural/Serum)	≤0.5	>0.5
Lactate dehydrogenase (Pleural/Serum)	≤0.6	>0.6
	Pleural LDH ≤ two thirds of upper limit of serum LDH	Pleural LDH > two-thirds of upper limit of serum LDH
Common causes	• Hypoalbuminemia (Cirrhosis, Nephrotic syndrome) • Congestive heart failure • Constrictive pericarditis • Myxedema (hypothyroidism) • Ovarian tumors producing right sided pleural effusion- Meigs' syndrome	• Infection (Parapneumonic, TB, fungal, empyema) • Esophageal rupture • Pulmonary embolism • Neoplasms • Autoimmune (Systemic lupus erythematosus) • Rheumatoid pleural effusion • Esophageal rupture • Sub-diaphragmatic abscess • Pancreatitis • Uremic pleural effusion • Hemothorax • Chylothorax (thoracic duct injury) • Radiation and drugs

Note: in resource limited setting where LDH is often not available: Total protein effusion >30g/L is often used to indicate an exudate effusion whilst that <30g/L is a transudate.

- Full blood count: for infection
- Total Serum protein
- Serum Lactate dehydrogenase
- Liver function tests and U + Es

Etiology	Appearance	WBC	RBC	pH	Glucose	Comments
CHF	Clear, straw	<1000	<5000	Normal	Normal	Bilateral, cardiomegaly
Parapneumonic	Turbid	5-40, 000 Neutrophils	<5000	Normal/low	Normal	
Empyema	Pus	25-100,000 Neutrophils	<5000	<7.2	Low	Needs drainage!
TB	Serosangeous	5-10, 000 Lymphocytes	<10,000	Normal	Normal or low	+ AFB
Malignancy	Bloody	1-100, 000 Lymphocytes	<100,000	Normal	Normal	+ Cytology
Pulmonary embolism	Sometimes bloody	1-50, 000 Neutrophils	<100,000	Normal	Normal	
Hemothorax	Bloody	1-50,000	>100,000	Normal	Normal	Hct ratio
Esophageal rupture	Turbid	5-50, 000	<10,000	Very low	Low	High amylase

TREATMENT

- Therapeutic thoracentesis should be done in massive effusion to relieve respiratory distress.
- Removal should be limited to 1200 to 1500ml at a time.
- Definitive treatment of pleural effusion requires identifying the underlying condition and administration of specific therapy.
  - TB effusion should be treated with anti-TB drugs
  - Parapneumonic effusions and other bacterial infections in the pleural space should be treatment with long course of antibiotics
  - Empyema (purulent fluid in the pleural cavity) is treated with high dose of parenteral antibiotics coupled with surgical drainage (chest tube insertion).
- Malignant pleural effusions that reaccumulate and are symptomatic can be aspirated to dryness followed by the instillation of a sclerosing agent such as tetracycline or talc. Effusions should be drained slowly since rapid shift of the mediastinum causes severe pain and occasionally shock. The treatment produces only temporary relief.

PNEUMOTHORAX

LUNG NEOPLASMS

- Lung cancer is one of most common cause of cancer mortality.
- Metastatic tumors are more common than primary tumors of the lungs with the commonest primary sites being the breast, thyroid, stomach, colon carcinoma, prostate and ovary.
  - Present as multiple 'Cannon-ball nodules on imaging'
- 90-95% of primary lung tumors are malignant epithelial tumors collectively called bronchogenic carcinomas.
- The remaining are bronchial carcinoids, mesenchymal tumors (lymphomas, sarcomas, leiomyomas, lipomas, fibromas and liomyosarcomas), and bronchial hamartomas, the last being benign tumors with aberrant differentiation of the bronchial tissues.
- Neoplasms are common between the age range of 65-75 years and affect men more than women (2:1)

ETIOLOGY AND RISK FACTORS

- Cigarette smoking- cigarettes contain at least 55 carcinogens and the risk of lung cancer increases to 20 fold for people who smoke more than 40 cigarettes/day.
- Exposure to Radon (from radioactive decay of Uranium) in underground Uranium miners (occupational) or indoors (in basements as a colorless odorless gas).
- Exposure to other carcinogens:
  - Asbestos
  - Polycyclic aromatic hydrocarbons (these are mutagenic and present in cigarette smoke and arsenic)
  - Ni, Co, Cr
  - Silica
  - Mustard gas (World war I)

PATHOLOGICAL FEATURES OF BRONCHOGENIC CARCINOMAS

- Classic division of lung carcinoma:
  - Small cell carcinoma/Oat cell (15%)
  - Non-Small cell carcinoma (85%): Adenocarcinoma, squamous carcinoma, large cell carcinoma and carcinoid tumor
- These originate from the bronchial epithelium and have 4 main histological types:
  - Adenocarcinoma including the bronchoalveolar carcinoma (30-35%)
  - Squamous cell carcinoma (25-30%)
  - Small (Oat cell) carcinoma (15-25%)
  - Large cell carcinoma (10-15%)
- Others include:
  - Mixed cell type (squamous and small cell or squamous cell and adenocarcinoma) 5-10%
  - Pleomorphic carcinoma (mixed carcinoma and sarcomatoid pattern) 0.5%
- Note: Differentiating between small cell and non-small cell carcinoma (Adenocarcinoma, squamous cell carcinoma and large cell carcinoma) is very important because small cell carcinoma is responsive (At least initially) to chemotherapy.
- All lung neoplasms are very aggressive, invasive and widely metastasizing commonly to liver, adrenals, brain and bones. They also produce bioactive hormones and other products.

Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma
• Glands or mucin production • Common in women than men • Develops in the periphery of the lung • Commonest lung cancer in non-smokers • Some adenocarcinomas arise from area of pulmonary fibrosis/scar (old infarcts, asbestosis, or on healed TB scars) which are referred to as scar cancers • Located peripherally • Distant organ metastases occur in 50% especially to the brain • Poor prognosis (5 year survival is 10-12%)	• Keratin pearls or intercellular bridges (desmosomal connections between squamous cells) on histology • More common in males than females • Strongly associated with cigarette smoking • Arise centrally in the major or segmental bronchi and spread to hilar lymph nodes in 70-90% of cases or distant mets in 50-60% or to viscera • May produce parathyroid hormone related peptide (leading to hypercalcemia) • Poor prognosis (5 year survival 5-8%)	• Poorly differentiated small cells arising from neuroendocrine (Kulchitsky) cells • Very aggressive • Early mets • Strongly associated with cigarette smoking • Centrally located • Commonly associated with paraneoplastic syndromes (ADH or ACTH or cause Eaton-Lambert syndrome) • Poor prognosis (5 year survival 5-8%)	• Anaplastic (undifferentiated) tumors and occur in smokers • No keratin pearls, intercellular bridges, glands or mucin • Central or peripheral locations • Metastasizes very rapidly and widely • Poor prognosis

- Bronchoalveolar carcinoma:
  - Columnar cells that grow along pre-existing bronchioles and alveoli. It arises from Clara cells.
  - Not related to smoking
  - Located peripherally
  - May present with pneumonia-like consolidation on imaging, excellent prognosis

- Carcinoid tumor:
  - Tumor of well-differentiated neuroendocrine cells,
  - Chromogranin positive,
  - Not related to smoking
  - Central or peripheral location, classically forms a polyp-like mass in the bronchus.
  - Low grade malignancy, rarely can cause carcinoid syndrome

CLINICAL FEATURES

- Clinical features are variable.
- Presentations:
  - Local pulmonary symptoms:
    - Depend on location of the tumor
    - When tumors are endobronchial cough, hemoptysis, stridor, wheezes, dyspnea and non-resolving pneumonia may predominate.
    - Pleuritic chest pain is common with peripheral tumors.
    - Local tumor invasion and obstruction:
      - Recurrent laryngeal nerve palsy causing hoarseness of voice
      - Phrenic nerve paralysis with diaphragm paralysis
      - Esophageal obstruction causing dysphagia
      - Superior vena cava obstruction presenting with edema
      - Pancoast syndrome is said to exist when apical lung tumors infiltrate spinal nerves (C8-T1) and cause shoulder pain and cervical sympathetic nerves causing Horner's syndrome (anhidrosis- absence of sweating, ptosis- eyelid drooping and miosis on the affected side)
      - Pericardial or pleural effusions and bronchial obstruction leading to atelectasis, pneumonia and lung abscess
  - Metastatic symptoms
  - Ectopic hormone secretions (paraneoplastic syndromes):
    - Occur in 10-15% of bronchogenic carcinoma and manifestations are related to ectopic hormone secretions by tumors.
    - The manifestations can be systemic or related to different systems.
    - Systemic symptoms: anorexia, cachexia, weight loss and fever in 30% of cases.
    - Another 1/3 of patients may present with endocrine manifestations like hypercalcemia or hypocalcemia (from ectopic secretion of parathyroid

hormone or calcitonin), Cushing's syndrome (from ectopic secretion of ACTH), gynecomastia (from ectopic secretion of gonadotrophins) and inappropriate release of ADH (SIADH) causes sodium and water retention.

- Additionally, patients may present with clubbing, migratory thrombophlebitis, cerebellar degeneration, neuropathies, and myopathies such as Eaton-Lambert myasthenic syndrome (this is an autoimmune condition characterized by the production of autoantibodies against the presynaptic voltage gated calcium channels thus impairing the release of acetylcholine at the neuromuscular junction resulting in proximal muscle weakness, and depressed tendon reflexes), Myasthenia gravis (autoantibodies against Nicotinic Acetylcholine receptors on post-synaptic membrane at the neuromuscular junction resulting in muscle weakness), anemia and thrombocytopenic purpura.

- About 10-15% of lung tumors are detected by chance (a coin shaped lesion on chest X-ray)
  - Benign lesions (e.g. in the young can also present as a coin lesion): Granuloma (TB, Histoplasma) and bronchial hamartoma (often calcified)

DIAGNOSIS

- Screening
  - For all men over 45 years and those smoking more than 40 cigarettes/day/
  - Can be done by:
    - Cytology (to detect malignant cells)-50% sensitivity
    - CXR:
      - Solitary pulmonary nodule (Coin shaped lesion 2-5cm) and about 35% of such cases are due to bronchogenic carcinoma
        - Compare with past X-rays if coin lesion has not changed it is most likely a benign entity, however if it has changed or is new there is a possibility of bronchogenic carcinoma that would warrant a biopsy to confirm.
      - Effusion, lobar collapse or mediastinal/hilar lymphadenopathy may be seen
- Other investigations for diagnosis and staging (TMN staging):
  - Blood investigations:
    - Basics: FBC, U+Es, LFT

  - LDH may be raised especially in small cell lung carcinoma due to tissue necrosis
  - Calcium may be increased (squamous) or reduced
  - Tumor markers
- Lung biopsy
- Lymph node biopsy from enlarged or supraclavicular lymph node to detect mets
- Bronchoscopy with biopsy or lavage if CT shows an accessible lesion or node.
- Thoracentesis to collect fluid for cytology
- Pleural biopsy
- Mediastinoscopy

MANAGEMENT

- Prevention: cessation of smoking
- Non-small cell carcinoma
  - Surgical excision is curative for patient with ipsilateral lymph node involvement but without local/distant spread or contralateral lymph node involvement
  - Intrathoracic disease- radiotherapy is palliative
  - Pancoast syndrome (tumor in the lung apices)- radiotherapy/chemotherapy
  - Extrathoracic disease- analgesics, radiotherapy, dexamethasone, obliteration of the pleural cavity
- Small cell carcinoma
  - By the time of diagnosis 95% of tumors have metastasized.
  - Responsive for chemotherapy +/- radiotherapy
- Bronchial adenomas, carcinoids need surgical resection

CHAPTER 7: GASTROENTEROLOGY

GASTROINTESTINAL CONDITIONS

GASTROINTESTINAL PHYSICAL EXAMINATION

- Before starting:
  - Introduce yourself to the patient.
  - Explain the procedure to the patient and ask the patient for permission to examine his/her abdomen (Gain consent).
  - Wash hands and say to the examiner that you would normally expose the patient from nipples to knees, but for modesty sake you are going to limit yourself to exposing the patient to the groins.
  - Position the patient so that they are lying flat on the couch, with their arms at side and head supported by a pillow (Anatomical position).
  - Ensure that the patient is comfortable.

GENERAL INSPECTION

- From the foot-end of the bed, inspect and make general comments about the surrounding (Drains/ vomit/ NG tube).
- Observe and make comments on:
  - The patient's general appearance: Healthy/ Obese/ Cachexic
  - Are they comfortable or in any respiratory distress
  - Age, state of health (is the general condition of the patient stable or unstable), nutritional status (Good, fair or poor) and any other obvious signs (such as jaundice- indicating hepatic/ biliary disease).
  - Abdomen- is abdomen distended and are there are obvious scars, markings, or masses observed from the foot end of the bed.

INSPECTION AND EXAMINATION OF THE HANDS

- From the right side of the bed, take both hands, looking for:
  - Finger Clubbing (Inflammatory bowel disease)
  - Palmar erythema (Chronic liver disease)
  - Dupuytren's contracture (Liver cirrhosis)
  - Nail signs (leukonychia- hypoalbuminemia, koilonychias- iron deficiency)

- Test for Asterixis or "liver flap" (hepatic failure- hepatic encephalopathy) by showing the patient how to extend both arms with the wrists dorsiflexed and the palms facing forwards.
- Check for any needle track marks (Hepatitis B/C), Bruising/ Petechiae (Thrombocytopenia)
- Feel for the epitrochlear lymph nodes
- Check axilla for acanthosis nigricans (GI malignancy)

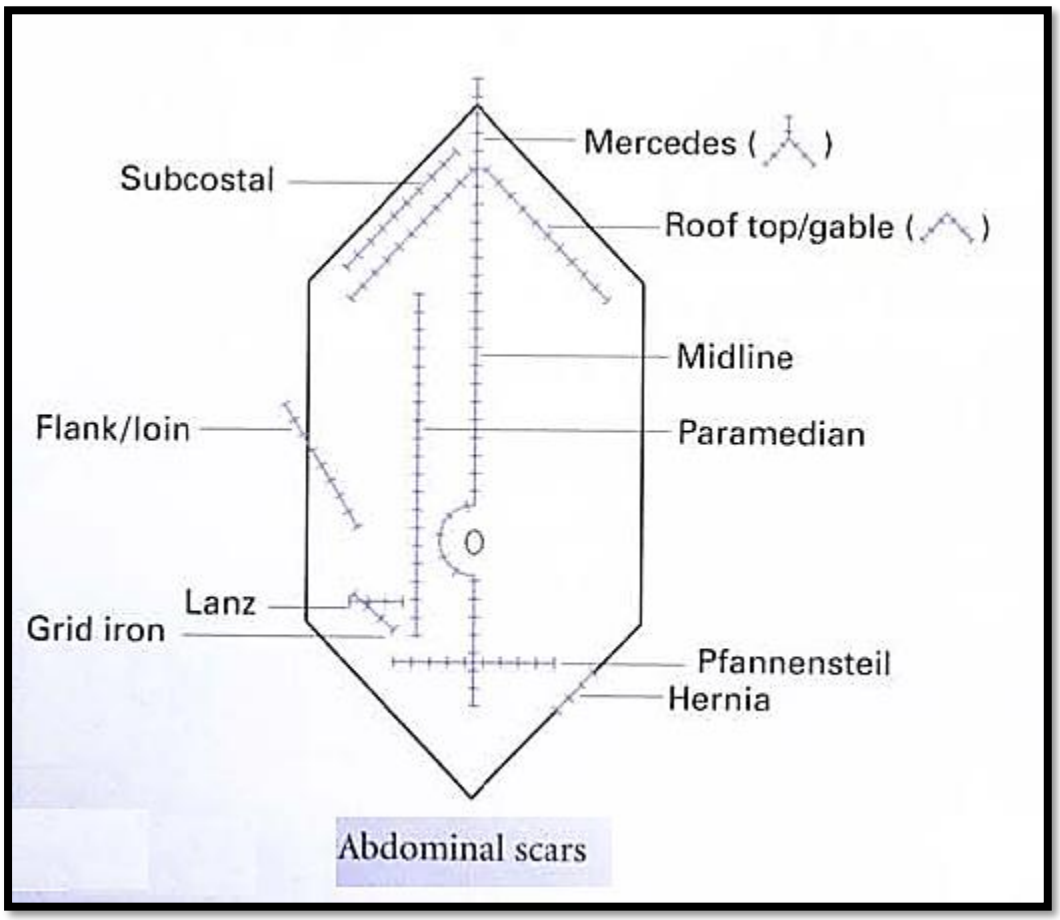
INSPECTION AND EXAMINATION OF THE HEAD, NECK AND UPPER BODY

- Inspect the sclera and conjunctivae for signs of jaundice or anemia.
- Inspect the mouth, looking for
  - Ulcers (Crohn's disease),
  - Angular stomatitis (nutritional deficiency),
  - Atrophic glossitis (iron deficiency, vitamin B12 deficiency, folate deficiency),
  - Furring of the tongue (loss of appetite)
  - State of the dentition
  - Purple lesions on the palate (Kaposi sarcoma)
- Palpate cervical lymph nodes (lymphadenopathy- Infection/ malignancy), Virchow's node (gastric malignancy) and check for parotid swelling (paratomegaly-in alcoholic liver disease).
- Examine the upper body for:
  - Gynecomastia: (Chronic liver disease)
  - Spider naevi- (>5 chronic liver disease)
  - Caput medusa (Portal hypertension)
  - Stretch marks
  - Stomas (Ileostomy vs Colostomy)

INSPECTION OF THE ABDOMEN

- Inspect the abdomen for its contours and any obvious distension (Ascites/ organomegaly), localized masses, scars and skin changes. Ask the patient to lift his head to tense the abdominal muscles. When inspecting the abdomen, you should crouch down to be at the same level as the abdomen.
  - Comment on any distension (Causes of abdominal distension -5Fs- Fluid, Fat, Fetus, Flatus and Fecal matter). Measure abdominal girth with measuring tape if abdomen is distended.

- Comment on presence of flank fullness
- Comment on symmetry
- Comment on movement with respiration



PALPATION OF THE ABDOMEN

- Ask the patient if he has any abdominal pain (Always start furthest from this region) and fix upon his face as you palpate his abdomen.
- Palpate with the palmar surface of your fingers whilst sitting or kneeling beside the patient.
- Light palpation- Begin by examining the segment furthest away from any pain or discomfort and systematically palpate the four quadrants and the umbilical area. Look for tenderness, guarding and any masses.
- Deep palpation- for greater precision. Describe and localize any masses
  - On deep palpation ask the patient to take deep breaths.
  - Assess masses for size, shape and consistency.

PALPATION OF THE ORGANS

- Liver- ask the patient to breathe in and out, starting in the right lower quadrant, feel for the liver edge leading with the index finger. The liver edge, if felt, can be described in terms of regularity, nodularity and tenderness. Note the degree of extension below the costal margin (cm)
- Gallbladder- palpate for tenderness over the gallbladder region that is at the tip of the right ninth rib.
- Spleen- palpate for the spleen as for the liver, again starting in the right lower quadrant feel for the splenic edge moving towards your index finger during inspiration.
- Kidneys- Position the patient close to the edge of the bed and ballot each kidney using the technique of deep bimanual palpation.
- Aorta- palpate the descending aorta between the thumb and the index of your right hand at a point midway between the xiphisternum and the umbilicus.

PERCUSSION

- Percuss the liver area, also remembering to detect its upper border (usually found in the fourth intercostal space). This is to estimate the size (liver span).
- Percuss the spleen to assess splenomegaly starting from the right iliac fossa ascending diagonally.
- Percuss the suprapubic area for undue dullness (bladder distention). Start in the midline and descend.
- If the abdomen appears distended, test for shifting dullness (ascites). Shifting dulling can be tested for by percussing down the right side of the abdomen. If an area of dullness is detected, keep two fingers on it and ask the patient to roll over to his left. Re-percuss the area which should now sound tympanic.
- Check for fluid thrills.

AUSCULTATION

- Auscultate in the mid-abdomen for abdominal sounds. Listen for 60 seconds before concluding that they are normal, hyperactive, hypoactive or absent.
  - Hypoactive bowel sound: constipation, drugs such as anticholinergics & opiates, General anesthesia, abdominal surgery, Paralytic ileus (absent bowel sounds)
  - Hyperactive bowel sounds: diarrhea of any cause, inflammatory bowel disease, GI bleeding, Mechanical bowel obstruction (high pitched bowel sounds)

  - Normally there are 5 to 30 bowel sounds in a minute.
- Listen over the abdominal aorta for aortic bruits suggestive of arteriosclerosis or an aneurysm.
- Listen for renal artery bruits 2.5 cm above and lateral to the umbilicus- a bruit suggests renal artery stenosis.
- Inspect for pedal edema.

- The following are not usually performed in an abdominal examination station, but they should nevertheless be mentioned at this stage.
  - Examination of the groins and genitals
  - Assess hernia orifices
  - Perform a Rectal examination (PR)

- After the examination
  - Cover the patient up.
  - Thank the patient.
  - Ask the patient if he/she has any questions or concerns.
  - State that you would test the urine and order some key investigations e.g. ultrasound scan, FBC, LFTs, U&Es, and clotting screen.
  - Summarize your findings and offer a differential diagnosis.

- Most common conditions likely to appear on an abdominal examination station:
  - Chronic liver disease
  - Splenomegaly
  - Polycystic kidney
  - Renal transplant
  - Scars
  - Hernias

DIARRHEAL DISEASES

- Diarrhea is an increase in stool frequency (>3 stools per day) and volume (>200-250grams/day).
  - Normal stool volume is 100-200grams/day.
  - Normal bowel habits= 3 times/day to 3 times/week.
  - Stool weight is affected by fiber contents of diet, gender (higher in males), medications, possibly exercise and stress.
  - About 9 liters of fluid is presented to the GIT daily (7L from the secretion and 2 liters from diet). Of this only 100-200ml of fluid is excreted with feces and the rest will be reabsorbed.
  - Fluid absorption follows sodium absorption which is co-transported with chloride ion, glucose and amino acids and through sodium channels.
  - Sodium-glucose co-transport is unaffected by many diarrhea diseases.
- Sudden onset of bowel frequency associated with crampy abdominal pains and a fever will point to an infective cause, bowel frequency with loose blood-stained stools to an inflammatory basis and the passage of pale offensive stools that float often accompanied by loss of appetite and weight loss, to steatorrhea.
- Nocturnal bowel frequency usually points to an organic cause. Passage of frequent small-volume (often formed) points to a functional cause.

CLASSIFICATION OF DIARRHEA

- Diarrhea can be classified according to:
  - Duration of symptoms
  - Etiology
  - Pathophysiological mechanism of diarrhea

BASED ON DURATION

ACUTE DIARRHEA

- Tis is diarrhea of sudden onset, it is very common, often short-lived and requires no investigation or treatment.
- Occurs within 14 days (2 weeks).
- It is usually infectious in origin.
  - Bacterial: *E. coli (enteropathogenic, enteroaggregative, 014:H1, Enteroinvasive, Enterotoxigenic and enterohemorrhagic), Campylobacter* (associated with Guillain-Barre syndrome), *Salmonella, Shigella, C. difficile* (due to antibiotic use), *C. perfringes, C. botulinum, Bacillus cereus, Vibrio cholerae, Yersinia, Aeromonas*.
  - Viral: Adenovirus, Rotavirus, Norwalk virus
  - Parasitic: *Entamoeba histolytica* (associated with liver abscess), *Giardia lamblia*, *Cryptosporidium parvum*, *Isospora belli*, *Microsporidium* and *Mycobacterium avium* complex in those with AIDS.
- Other causes include: antibiotics, NSAIDs, quinine, beta blockers, magnesium based antacids, Proton pump inhibitors, colchicine, theophylline, acarbose, and food allergies.
- Although dietary causes should be considered, diarrhea due to viral agents may also last 24-48 hours.
- Symptoms/Exam:
  - Diarrhea accompanied by urgency, tenesmus, abdominal bloating, pain and vomiting
  - Exam may reveal tachycardia, orthostasis, decreased skin turgor with dehydration, abdominal pain and distention.
    - Alarming features: fever >38.5ºC, severe abdominal pain, bloody diarrhea, immune compromise, age >70 years or severe dehydration
    - No alarming features (short duration, non-bloody diarrhea, nontoxic exam): treat with oral rehydration and symptomatic therapy. It no improvement is seen, evaluation is indicated.
- Resolves with or without intervention.
- If diarrhea is particularly severe, dehydration can be a problem particularly in the very young and very old.
- Investigations are necessary if diarrhea lasts more than 1 week:
  - Stool for microscopy, culture and sensitivity
  - Stool for Ova, cysts and parasites

  - Full blood count
- Viral and bacterial infective diarrheas do not last more than 2 weeks.

CHRONIC DIARRHEA

- Diarrhea has an insidious onset and lasts more than 2 weeks (14 days).
- Common causes include malabsorption, inflammatory bowel disease (ulcerative colitis), irritable bowel syndrome, pancreatic insufficiency, colonic cancer and HIV/AIDS.
- Infectious causes are not common causes of chronic diarrhea (excluding HIV GI OIs).
- Symptoms/Exam:
  - Presents with diarrhea accompanied by abdominal bloating and pain,
  - Exam reveals tachycardia, orthostasis, decreased skin turgor with dehydration, abdominal pain and distension.

PERSISTENT DIARRHEA

- Diarrhea starts off as acute and lasts more than 14 days.

BASED ON ETIOLOGY

INFECTIOUS

- Bacterial
  - *Vibrio cholerae*
  - *E. coli: enterotoxigenic, enteroinvasive, enterohemorrhagic**
  - *Shigella**
  - *Clostridium perfringens*
  - *Clostridium difficle*
  - *Salmonella typhi and paratyphi*
  - *Campylobacter jejuni**
- Viral
  - Norwalk and Rota virus
    - Invade and damage villous epithelial cells.
    - Causes diarrhea by interfering with absorption through selective destruction of absorptive villous tip cells with sparing of secretory crypt cells.
    - Stool is usually water and its content resembles those of non-invasive diarrhea, with few inflammatory cells, probably because of absence of colonic damage

  - Cytomegalovirus*
  - Enteric adenovirus
  - Astrovirus
  - Coronavirus
  - Picornavirus
  - HIV
- Parasitic
  - *Giardia lamblia*
    - Few organisms need for infection
    - Multiples in small intestines and attaches to it and occasionally invades the mucosal cells.
    - Clinical features: acute diarrheal illness, chronic diarrhea associated with malabsorption and weight loss.
    - Diagnosis based on identification of organisms either in stool or duodenal mucus or by small intestine biopsy.
    - Cysts or trophozoites can be identified in the stool and treatment should be given in both cases.
  - *Entamoeba histolytica**
    - Symptoms range from Mild diarrhea to fulminant amoebic colitis with multiple bloody stools, fever and severe abdominal pain.
  - *Cryptosporidium parvum* and *Isospora belli*
    - Occasionally causes self-limited acute diarrheal illness in otherwise healthy individuals. They may cause voluminous life threatening diarrheal diseases in patients with AIDS. Modified acid fast staining of the stool will identify both organisms.
- NOTE '*' denotes causative agents that cause bloody diarrhea

NON-INFECTIOUS

- Include:
  - Drugs: antibiotics (erythromycin)
  - Food allergy
  - Surgical conditions: Appendicitis
  - Inflammatory bowel disease*
  - Hyperthyroidism
  - Diabetes mellitus
  - Malabsorption syndromes: celiac disease, lactose intolerance

PATHOPHYSIOLOGY OF DIARRHEA

TYPE OF DIARRHEA	MECHANISM
SECRETORY DIARRHEA	• Occurs due to the secretion of fluid and electrolytes or decrease in normal absorptive capacity of the bowel. • It usually follows stimulation by mediators like enteric hormones, bacterial enterotoxins (e.g. cholera, heat labile E. coli toxin, Salmonella enterotoxin), vasoactive intestinal peptide (VIP) or laxatives. These agents activate the adenylyl-cyclase cAMP system. • The mediators block sodium chloride absorption and induce chloride secretion. These events can result in massive diarrhea, without evidence of cell injury as shown by the ability of the cell to absorb sodium if coupled to nutrients (sodium to glucose, sodium to amino acids) that is why cholera and other forms of diarrhea can be treated with oral solutions containing sodium and glucose. • Diarrhea of secretory type persists even if the patient fasts
OSMOTIC DIARRHEA	• It is due to presence of poorly absorbed or non-absorbable substances in the intestine which are osmotically active, resulting in secondary accumulation of fluid and electrolytes, • Such non-absorbable substances include lactose in patients with lactase deficiency. • This type of diarrhea is usually caused by malabsorption and disappears when patient fast for 48-72 hours.
EXUDATIVE DIARRHEA	• Inflammations or infectious conditions that result in damage to the intestinal mucosa cause diarrhea by several mechanisms. • There is loss of blood, mucous proteins and serum proteins • Mucosal damage can interfere with absorption, induce secretion and affect motility all of which contribute to diarrhea.
ABNORMAL INTESTINAL MOTILITY	• Causes or contributes to diarrhea seen in diabetes mellitus, irritable bowel syndrome, postvagotomy states, carcinoid syndrome and hyperthyroidism. • If small bowel peristalsis is too rapid, an abnormal large amount of fluid and partially digested foodstuffs may be delivered to the colon.

	• Extremely slow peristalsis may allow bacterial overgrowth to occur and bile salts deconjugation to cause secondary malabsorption. • Rapid colonic motility may not allow adequate time for the colon to absorb fluid delivered to the cecum (normally 90% of the fluid is absorbed)

PATHOPHYSIOLOGY OF INFECTIOUS DIARRHEA

- Microbes cause diarrhea either directly by invasion of gut mucosa or indirectly through elaboration of different types of toxins: secretory enterotoxins, cytotoxins and inflammatory mediators.

Type of diarrhea	Comments	Examples
Secretory toxin induced diarrhea	• Patients seldom have fever or major systemic symptoms • Little or no inflammatory response • The organisms colonize the intestinal mucosa but do not invade the intestinal wall	• *Vibrio cholerae*: produces enterotoxins which stimulate adenylate cyclase which results in massive intestinal secretion • *Enterotoxigenic E. coli* is the major cause of Traveler's diarrhea • Non- typhoidal salmonella like S. *typhimarium* • *Shigella dysenterae* may initially cause secretory diarrhea
Cytotoxin induced diarrhea	• Cytotoxins are soluble factors that directly destroy mucosal epithelial cells	• *Shigella dysentrae* produces Shiga toxin which causes destructive colitis • *Enterohemorrhagic E.coli* • *Clostridium perfringens, Vibrio parahemolyticus* • *Clostridium difficle* causes pseudomembranous colitis in individuals treated with antibiotics
Diarrhea cause by invasive pathogens	• Characterized by fever and other systemic symptoms like headache and myalgia.	• Acute *shigellosis* • Acute *salmonellosis* • *Campylobacter jejuni:* Responsible for up to 10% of

	• The diarrhea is frequent but small in volume. It is associated with crampy abdominal pain and tenesmus. • These pathogens induce marked inflammatory response and stool usually contains pus cells, proteins and often gross blood.	acute diarrhea worldwide. It invades both the small and large intestines. • *Enterohemorrhagic E. coli:* it produces bloody diarrhea without evidence of mucosal inflammation (grossly bloody stool with few or no leucocytes)

EVALUATION OF A PATIENT WITH DIARRHEA

HISTORY

- History should include:
  - Duration of diarrhea
    - <2 weeks is acute and suggests an infectious causes and resolves with or without intervention
    - >2 weeks consider chronic diarrhea disease and infectious causes are unlikely (also consider HIV status). In most cases cause includes malabsorption, inflammatory Bowel disease (ulcerative colitis), Irritable Bowel syndrome, Colonic cancer, and immunosuppression like AIDS
  - Number of stool per day
    - Large volume indicates small bowel or proximal colonic disease
    - Scanty, frequent stools associated with urgency suggests left colon or rectal diseases
  - Diurnal variation
    - Nocturnal- organic causes
    - Non-nocturnal- functional causes like irritable bowel syndrome
  - Nature of diarrhea- Watery or blood?
    - Bloody diarrhea is usually inflammatory or ischemic in origin and causes by invasive organisms, ulcerative colitis or neoplasms
  - Association with specific meal
    - Fat diet- due to fatty intolerance
    - Sweet diet- it is due to osmotic diarrhea
    - Milk and milk products- due to lactase deficiency
  - History of drug intake
    - Penicillin may be associated with pseudomembranous colitis
    - Laxatives

    - Chemotherapeutic agents
  - Presence of co-morbidities: diabetes mellitus

PHYSICAL EXAMINATION

- Physical examination:
  - Assess severity of dehydration
  - Weight loss and other associated signs in patients with chronic diarrhea
  - Digital rectal examination

INVESTIGATIONS

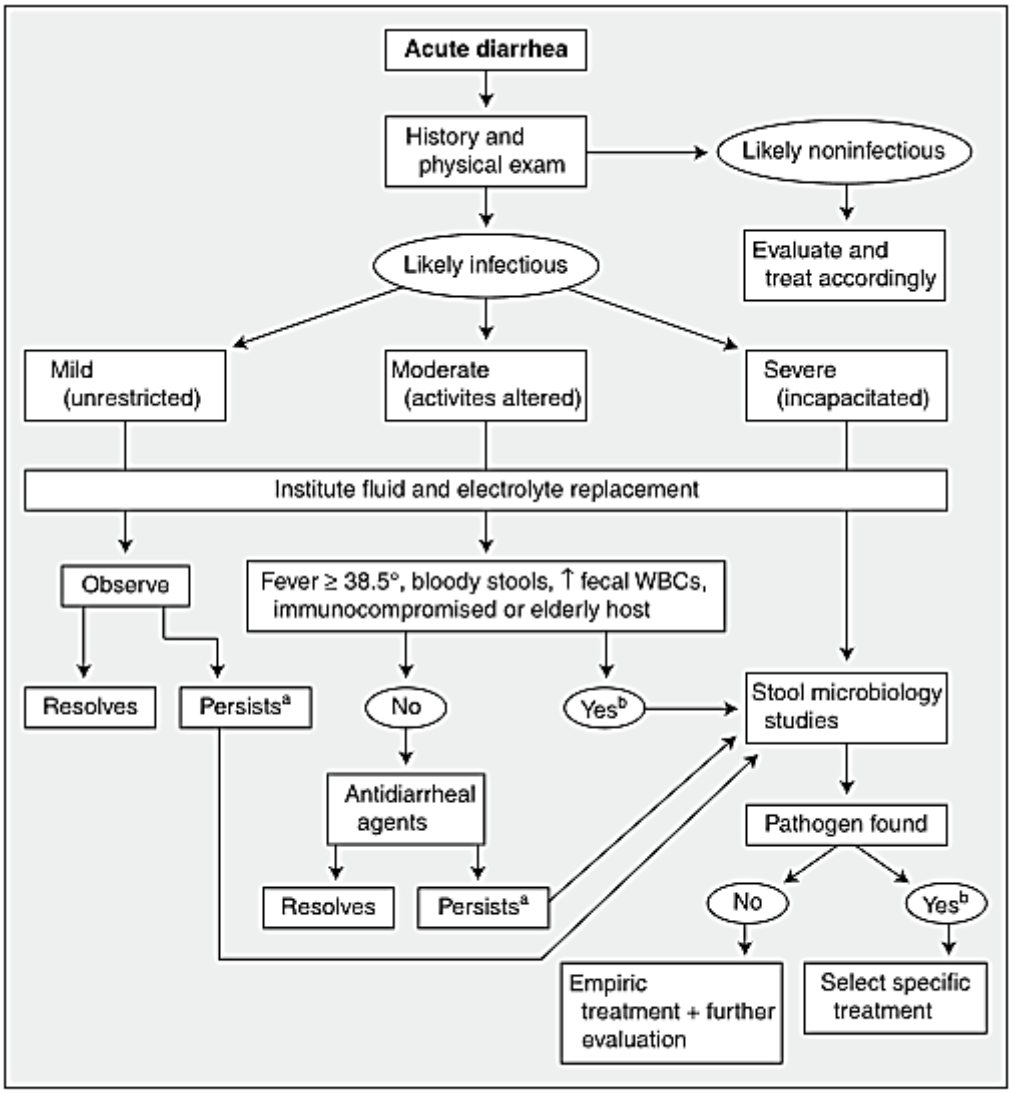
1. Stool microscopy, culture and sensitivity for:
   - Ova and parasites
   - Pathogenic bacterial strains
2. Stool for occult blood test
3. Full blood count, Urea, Electrolytes, Creatinine and liver enzymes
4. Proctosidmoidoscopy to exclude or confirm the diagnosis of inflammatory bowel diseases.

MANAGEMENT

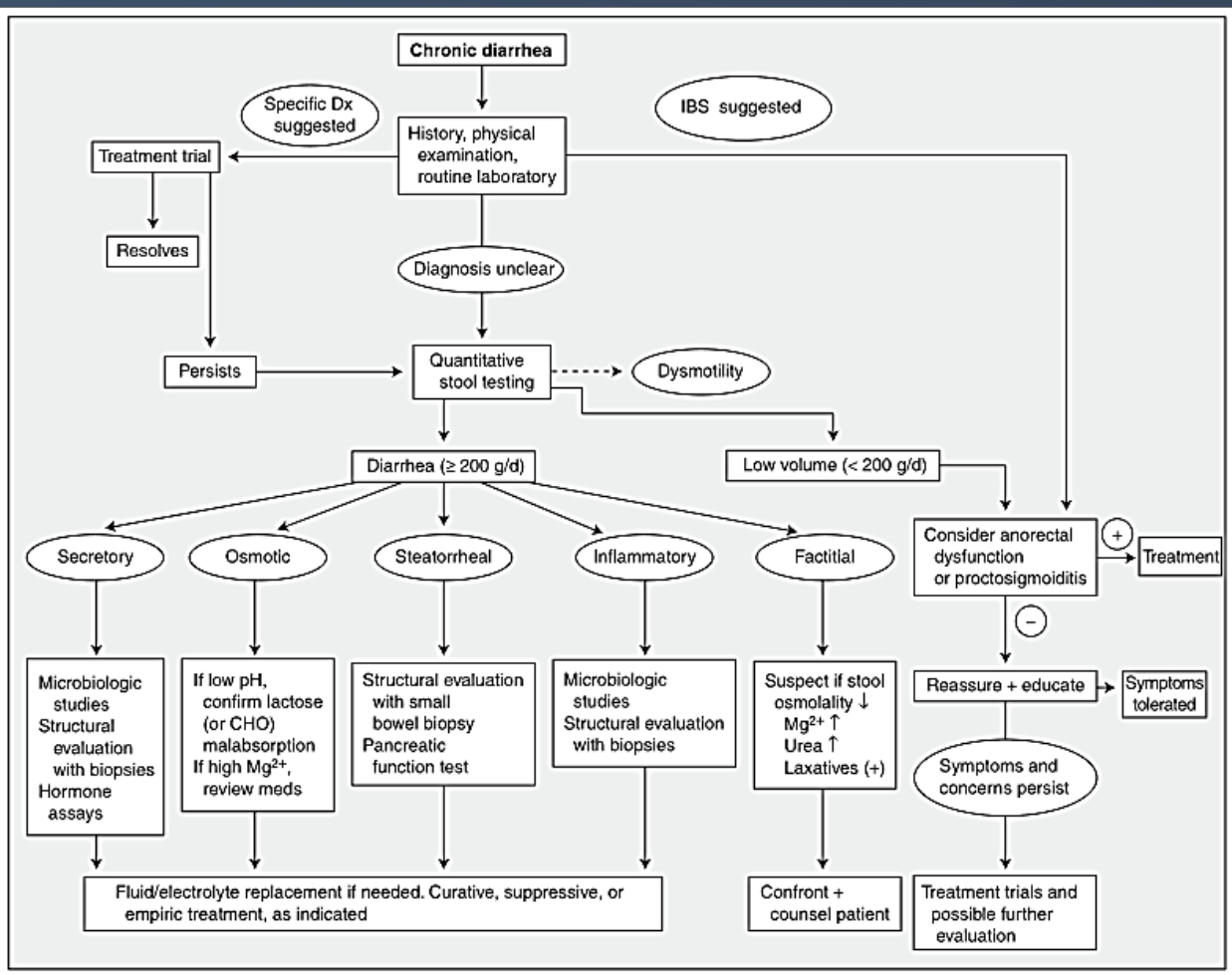
- Rehydration
  - IV fluids: Ringer's lactate or normal saline for patients with massive diarrhea and vomiting with hypotension.
  - For patients without hypotension oral fluid containing sodium, glucose, potassium and chloride ions (ORS) are preferred.
- Antimicrobial therapy
  - Antibiotics
    - Most acute infectious diarrheal diseases do not require antibiotic therapy because the majority of them are self-limited and viral in nature.
    - Of the non-invasive bacterial diarrhea, antibiotics decrease the volume only in cholera. Doxycycline 300mg single dose is the drug of choice.
    - For invasive bacterial diarrhea causes by *E. coli* and *Shigella* (bacillary dysentery) Ciprofloxacin 500mg or Norfloxacin 400mg TDS for 3-5 days is indicated.
  - Anti-protozoal
    - *Entamoeba histolytica*: metronidazole 500 mg PO TDS for 7 days.
    - *Giardia lamblia*: Metronidazole 250mg TDS for 5 days or Tinidazole 2g once

- *Isospora belli*: Co-trimoxazole 960mg QID for 10 days then 960mg BD for additional 3 weeks. In immunocompromised patients continue maintenance dose of the same drug three times a week.
- Nitazoxanide for Cryptosporidiosis

- When no specific therapy is available or no cause is identified it's appropriate to give empirical therapy e.g.
  - Antibiotics for possible bacterial overgrowth or Metronidazole for Giardia, Cholestyramine for bile acid malabsorption
    - Metronidazole 500mg TDS for 7 days
    - Ciprofloxacin 500mg TDS for 5 days
  - Non-specific therapy with constipating agents such as loperamide, diphenoxylate and in more severe cases codeine or long acting somatostatin analogue
    - Loperamide 4mg initially and then 2mg after each stool (maximum 8 mg/day)



[a]Consider empiric treatment with metronidazole before evaluation.
[b]Consider empiric treatment with quinolone before evaluation.


Chronic diarrhea
Specific Dx suggested
IBS suggested
History, physical examination, routine laboratory
Treatment trial
Resolves
Diagnosis unclear
Persists
Quantitative stool testing
Dysmotility
Diarrhea (≥ 200 g/d)
Low volume (< 200 g/d)
Secretory
Osmotic
Steatorrheal
Inflammatory
Factitial
Consider anorectal dysfunction or proctosigmoiditis
+
Treatment
−
Microbiologic studies
Structural evaluation with biopsies
Hormone assays
If low pH, confirm lactose (or CHO) malabsorption
If high Mg2+, review meds
Structural evaluation with small bowel biopsy
Pancreatic function test
Microbiologic studies
Structural evaluation with biopsies
Suspect if stool osmolality ↓
Mg2+ ↑
Urea ↑
Laxatives (+)
Reassure + educate
Symptoms tolerated
Symptoms and concerns persist
Fluid/electrolyte replacement if needed. Curative, suppressive, or empiric treatment, as indicated
Confront + counsel patient
Treatment trials and possible further evaluation

ENTERIC FEVER

- Enteric fever is an acute illness characterized by fever, headache and abdominal discomfort caused by *Salmonella typhi*.
  - This is a member of the family Enterobacteriacae.
  - It is an encapsulated facultative anaerobic non-spore forming gram negative bacilli.
  - Like other organisms in the family the bacterium has:
    - Somatic antigen (O antigen)
    - Flagella antigen (H antigen)
    - Capsular antigen: Vi (K)
- The disease was initially called typhoid fever because of its clinical similarity to typhus. The name enteric fever was proposed as an alternative designation to distinguish typhoid fever from typhus however, to this day the two designations are used interchangeably.
- The term enteric fever is a misnomer, in that the hallmark features of this disease-fever and abdominal pain are variable.
- Infection by *S. paratyphi* A, B or C also causes illness although it is less severe.
- Man is the only natural host for *S. typhi*.

PATHOGENESIS

- Transmission: ingestion of contaminated food or water (Fecal-oral route).
- Incubation period is 3-21 days.
- After ingestion, the bacteria invade the small bowel wall via Peyer's patches (specifically the mononuclear phagocytes- M cells in the terminal part of the ileum) from where they spread to the regional lymph nodes (especially the mesenteric lymph nodes) and then to the blood (bacteremia).
  - Gastric acid is protective so for infection to happen its either there is low gastric acid, immunocompromise or a large inoculum.
  - The Vi antigen is important in preventing antibody mediated opsonization and complement mediated lysis.
- The bacteria also spread to the phagocytes of the liver, gallbladder and spleen.
- The usual site of carriage is the gallbladder (chronic carrier is associated with gall stones).
  - In some areas endemic for urinary schistosomiasis chronic carriage is in the urinary bladder.
- The pathogen can be excreted into bile and feces further transmitting the disease.

CLINICAL FEATURES

- Infection begins in the small intestine but few gastrointestinal symptoms occur.
- A prodrome of non-specific symptoms often precedes fever and include:
  - Chills
  - Headache
  - Anorexia
  - Cough
  - Weakness
  - Sore throat
  - Dizziness
  - Muscle pain
- The onset of illness is insidious (causing harm without showing any obvious signs) and nonspecific with persistent step-ladder fever (lasting more than 1 week caused by endotoxins), headache, asthenia (severe weakness), insomnia, anorexia, epistaxis and abdominal pain.
- Fever and constipation (due to hypertrophy of Peyers patches) rather than vomiting and diarrhea predominate.
- Diarrhea may occur early but usually disappears by the time the fever and bacteremia occur.
- After the first week, as the bacteremia becomes sustained, high fever, delirium, tender abdomen and enlarged spleen occur.
- Rose spots i.e. rose-colored macules on the abdomen are associated with typhoid fever but occur only rarely.
- Physical findings in the early stages include:
  - Abdominal tenderness
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Scanty maculopapular rash (‘rose spots’)
- Within 3 weeks without treatment serious complications can arise:
  - Meningitis and encephalitis
  - Coma
  - Bronchitis and Lobar pneumonia
  - Hepatitis
  - Myocarditis
  - Intestinal perforation and peritonitis
  - Intestinal hemorrhage

  - Nephritis
  - Osteomyelitis and arthritis
  - Parotitis and orchitis
- The 4th weeks of illness is characterized by gradual improvement but 30% of infected will die and 10% of untreated will relapse.
- After clinical recovery 5-10% of patients will continue to excrete the pathogen for several months (convalescent carriers)
- 1-4% will carry organisms for more than 1 year (chronic carriage) in the gall bladder and urinary bladder.

DIAGNOSIS

- Diagnosis can be suggested by the presence of:
  - Persistent fever
  - Relative bradycardia
  - Rose spots
  - Leucopenia
- The definitive diagnosis requires culture of *S. typhi* or *S. paratyphi* from the patient.
  - Blood culture is positive in most cases in the first 2 weeks
  - Culture of intestinal secretions, feces and urine is also used, although care must be taken to distinguish acute infection from chronic carriage.
  - Bone marrow culture is more sensitive than blood culture but is rarely required except in patients who have already received antibiotics
- Full blood count: Leukopenia and anemia are often seen.
- Liver function tests (LFTs) are often abnormal indicating hepatic involvement
- Chest X-ray to rule out pneumonia
- Serological tests such as the Widal antigen tests are of little practical value, are easily misinterpreted and should not be used. They check for the somatic O and flagella H antigens.
  - Widal antigen could be positive due to infection by other Salmonellae, recent vaccination for typhoid, past typhoid (already treated)

Use the mnemonic "BUS" to help remember the specimen to take for culture during the first 3 weeks

B- blood/bone marrow in 1st week

U- urine in 2nd Week

S- stool in 3rd week

DIFFERENTIAL DIAGNOSIS

- Malaria

- Urinary tract infection
- Lower respiratory tract infection
- Dengue fever

MANAGEMENT AND PREVENTION

- Increasing antibiotic resistance has been noted.
- Chloramphenicol, Cotrimoxazole, and amoxicillin may all still be effective in some cases but quinolones (e.g. ciprofloxacin 500 mg twice daily) are now the treatment of choice.
- Antibiotic therapy is curative. The drugs are given either orally or intravenous depending on the patient condition (able to take orally or not), severity of the disease.
- First line: Quinolones and third generation cephalosporin
  - Ciprofloxacillin PO 500mg BD for 10 days or
  - Ceftriaxone 1-2gm IM or IV for 10-14 days or
  - Cefixime PO 1g/day in 2 divided doses for 10-14 days
- Alternatives
  - Azithromycin 1gm PO daily for 5 days
  - Chloramphenicol 500mg PO QID for 14 days (initial doses of 3-4g/day for adults with clinical response observed in 24-48 hours after initiation. Dose should be reduced to 2g/day when fever starts to decrease usually after 5-6 days and continued to complete 2 weeks treatment)
  - Norfloxacin 400mg BD for 14 days
- IV drugs are recommended for critically sick patients who are admitted or for patients who are unable to take oral drugs.
  - Ceftriaxone 2-4g OD for 3 days and then 1-2 g IV/IM for a total of 10-14 days
  - IV chloramphenicol 1g IV QID for 2-3 days then start PO medication as soon as the patient can take oral medication.
- Quinolones are not recommended for use in children and pregnant women because of their observed potential damaging effect on cartilage of the growing

animals. However, in severe infections especially by MDR strains, we have to outweigh the benefits and the potential risks.

- With resistance to quinolones azithromycin may be effective.
- The patient's temperature may remain elevated for several days (4-6 days) after starting antibiotics and this alone is not a sign of treatment failure.
- Prolonged antibiotic therapy may eliminate the carrier state but in the presence of gall bladder disease it is rarely effective.
- Cholecystectomy may be necessary to abolish the chronic carrier state.
- Prevention is mainly through improved sanitation and clean water.
- Vaccination with either injectable inactivated or oral live attenuated vaccines give partial protection.

CHOLERA

- Cholera is an illness characterized excessive diarrhea and vomiting.
- It is caused by the curved, flagellated Gram-negative bacillus, *Vibrio cholerae*.
- The organism is killed by temperatures of 100°C in a few seconds but can survive in ice for up to 6 weeks
- 1 major pathogenic serogroup possess a somatic antigen (O1) with 2 biotypes
  - Classical
  - El tor: infection causes milder symptoms but can still cause severe and life-threatening disease.

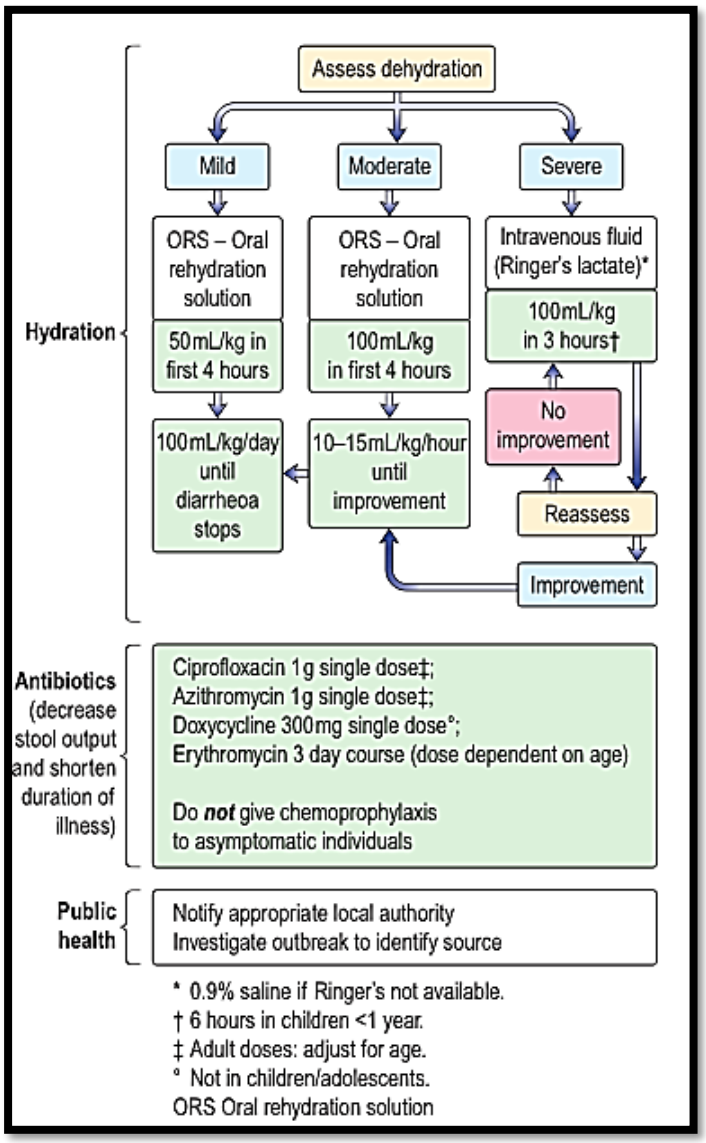
PATHOGENESIS

- Transmission is by fecal-oral route
  - Contaminated water plays a major role in the dissemination of cholera, although contaminated foodstuffs and contacts carriers may contribute in epidemics.
- Achlorrhydria or hypochlorhydria facilitates passage of cholera bacilli into the intestines
- In the intestines they proliferate, elaborating an exotoxin which produces massive secretion of isotonic fluid into the intestinal lumen
  - The toxin has an alpha and beta subunit
  - The cholera toxin binds to its receptor (monosialoganglioside Gi) via fimbria (toxin co-regulated pilus) on its beta-subunit
  - This activates the alpha stimulatory subunit (or the Gs protein) which activates the cAMP cascade.
  - This in turn activates protein kinase and there is an influx of calcium into the cytosol which then acts on the apical membrane causing chloride secretion (with water) and inhibition of sodium and chloride absorption.
- Cholera toxin also releases serotonin (5-HT) from enterochromaffin cells in the gut, which activates a neural secretory reflex in the enteric nervous system. This may account for at least 50% of cholera toxin's secretory activity.
- *V. cholerae* also produces other toxins (zona occcludens toxins, ZOT and accessory cholera toxin, ACT) which contribute to its pathogenic effect.

CLINICAL FEATURES

- The incubation period is from a few hours to 6 days.
- Cholera may present as a mild illness indistinguishable from diarrhea due to other causes.

- Classically it has 3 phases
  - Evacuation phase: characterized by abrupt onset of painless, profuse watery diarrhea associated with vomiting in severe forms. Stools may be rice-water, flecked with mucus.
  - Collapse phase: is reached if appropriate treatment is not given. It is characterized by features of circulatory shock (cold clammy skin, tachycardia, hypotension and peripheral cyanosis) and dehydration (sunken eyes, hollow cheeks and diminished urine output). There may also be muscle cramps. Children may also have convulsions due to hypoglycemia. Complications such as renal failure and aspiration of vomitus may occur.
  - Recovery phase: occurs if the patient survives the collapse phase. With adequate treatment the prognosis is good, with a gradual return to normal clinical and biochemical parameters in 1-3 days.



DIAGNOSIS

- Largely clinical.
- Examination of freshly passed stools may demonstrate rapidly motile organisms (although this is not diagnostic, as *Campylobacter jejuni* may give a similar appearance).
- A rapid dipstick test is now also available.
- Stool and rectal swabs should be taken for culture to confirm the diagnosis and to establish antibiotic sensitivity.
- Cholera should always be reported to appropriate public health authority

MANAGEMENT

- Mainstay of treatment is rehydration. Give Oral rehydration salts (ORS) solution or any fluids after each loose stool. ORS and other fluids should be continued until diarrhea stops.
  - Assess dehydration

  - Mild dehydration: give ORS 50ml/kg in first 4 hours then 100ml/Kg/day until diarrhea stops.
  - Moderate dehydration: give ORS 100ml/kg in first 4 hours then 10-15ml/kg/hour until improvement then give 100ml/kg/day until diarrhea stops
  - Severe dehydration: intravenous fluid (Ringer's lactate or normal saline if RL is not available): 100ml/kg in 3 hours and reassess if no improvement repeat, if improvement is seen give 10-15ml/kg/hr ORS until improvement then give 100ml/kg/day ORS till diarrhea stops
- Monitor the patient frequently
- Reassess the patient after 4 hours using the classification of dehydration. If signs of dehydration are present repeat the same management. If patient shows signs of severe dehydration change management of that severe dehydration
- Patients should be encouraged to eat and drink as much as they want.
- Drugs only given according to sensitivity patterns
  - Doxycycline 300 mg single dose (drug of choice except in pregnant women)
  - Azithromycin 1g single dose
  - Tetracycline 500mg QID for 3 days
  - Erythromycin QID for 3 days (Dose depends on age): this is recommended when other recommended antibiotics are not available or where *V. cholerae* is resistant to them.
- Immunization is now recommended by the WHO in potential or actual outbreak situations. Live attenuated and killed vaccine (both oral) are available: neither protect against the O139 strain.
- The best preventive measures are good hygiene and improved sanitation.

DYSENTERY

- Dysentery is the passage of bloody diarrhea or mucus or both in stool.
- There are two types of dysentery:
  - Bacillary dysentery
  - Amoebic dysentery

BACILLARY DYSENTERY

- Bacillary dysentery is caused by the bacteria *Shigella* which has a short incubation period usually being 2 days.
- Shigella are enteroinvasive bacteria, which cause classical bacillary dysentery.
- The principle species are:
  - *S. dysenteriae*
  - *S. flexneri*
  - *S. sonnei*
- They all cause a similar syndrome, as a result of damage to the intestinal mucosa. Some strains of *S. dysenteriae* also secrete a Cytotoxin affecting vascular endothelium.
  - Initially it multiples in the small intestine causing secretory diarrhea later it invades colonic epithelium causing bloody diarrhea
- Transmission is strongly associated with poor hygiene. The organism is spread from person to person and only small numbers need to be ingested to cause illness (<200 compared with 10^4 for campylobacter and >10^5 for salmonella).
- The illness is usually self-limiting in 7-10 days but in children in developing countries mortality may be as high as 20%.

CLINICAL FEATURES

- Acute onset (symptoms start 24-48 hours after ingestion and typically consist of frequent small-volume stools containing blood and mucus)
- Malaise
- Fever
- Watery diarrhea
- Bloody diarrhea with mucus
- Fecal urgency
- Severe cramping abdominal pain
- Nausea
- Vomiting

- Headache
- Convulsions (in children)
- Tenesmus
- Mild or moderate dehydration: dehydration is not as significant as in the secretory diarrheas but systemic symptoms and intestinal complications are worse.

DIAGNOSIS

- Stool microscopy may show leukocytes
- Stool culture and susceptibility test

MANAGEMENT

- Antibiotics relieve symptoms, shorten illness, reduce mortality in children and decrease transmission.
- The first drug of choice is Ciprofloxacillin 500mg BD for 3 days
  - Alternatives
    - Ampicillin 500mg PO QID
    - Azithromycin 500mg PO OD
    - Co-trimoxazole 960 mg PO BD
- Nalidixic acid 1g PO QID for 7 days is no longer the preferred drug of choice due to increased resistance
- Prevention:
  - Drink clean, boiled/chlorinated water
  - Good sanitation
  - Good personal hygiene

COMPLICATIONS

- Shigella type 1:
  - Encephalopathy
  - Conjunctivitis
  - Hemolytic uremic syndrome
  - Metabolic disorders
  - Septicemia
  - Arthritis
  - Colonic perforation
  - Toxic mega colon
  - Rectal prolapse in children

AMOEBIC DYSENTRY

- This is caused by the parasite *Entamoeba histolytica*.

CLINICAL FEATURES

- Bloody diarrhea with mucus
- Low grade fever
- Dehydration is unusual

DIAGNOSIS

- Stool microscopy
- Sero diagnosis

MANAGEMENT

- Metronidazole 800mg PO TDS for 5 days followed by diloxanide furoate 500mg TDS for 10 days (for eradication of cysts) or
- Tinidazole 2g PO daily 2-3 days
- Avoid use of anti-diarrhea agents
- Supportive
  - Fluid replacement
  - Analgesics

COMPLICATIONS

- Fulminant colitis
- Colon perforation
- Peritonitis
- Chronic infection
- Stricture formation
- Severe hemorrhage
- Amoebic liver abscess
- Amoeboma

PREVENTION

- Good disposal of excreta-good pit latrine, flush toilets
- Provision of clean water
- Boiling water. This kills amoeba cysts if water is boiled for at least 10 minutes.
- Chlorination of water- effects variable on amoeba

- Personal hygiene- washing of hands after use of toilet, when preparing food and before eating.

DIFFERENCES BETWEEN BACILLARY AND AMOEBIC DYSENTRY

Feature	Bacillary dysentery	Amoebic dysentery
Causative organism	Usually *Shigella* but can also be caused by enterohemorrhagic *E.coli, Vibrio parahemolyticus, Campylobacter jejuni*	*Entamoeba histolytic*
Onset	Acute	Chronic
Fever	High grade	Low grade
Dehydration	Frequent	Moderate
Number of stools	Over 10 motions per day	6-8 motions per day
Amount	Small	Relatively copious
Odor	Odorless	Offensive
Color	Bright red	Dark red
Nature	Blood and mucus no feces	Blood and mucus mixed with feces
Nature of lesion	Suppurative due to diffusible toxins	Necrotic due to proteolytic ferment
Depth of ulcer	Shallow	Deep
Margin of ulcer	Uniform, clear-cut (sharp)	Ragged and undermined
Intervening mucosa	Inflamed	Normal
Type of necrosis (cellular level)	Karyolysis (Ghost cell and ring nucleus)	Pyknotic (Pyknotic body and mouse eaten cell)
Liver abscess	Rare	Common
Cellular response	Polymorphonuclear	Mononuclear

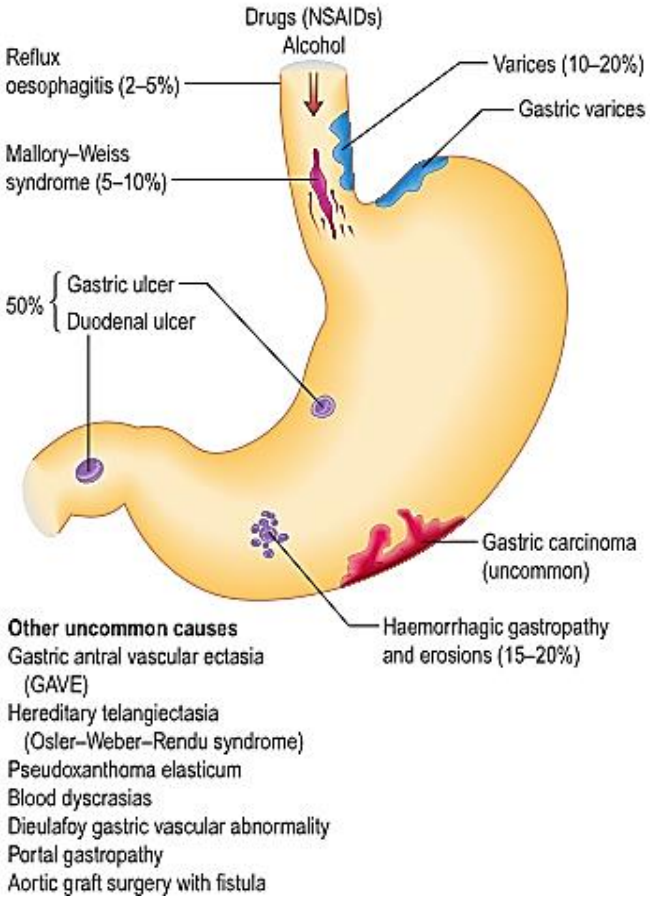
GIT BLEEDING

UPPER GIT BLEEDING

- This is bleeding from the upper gastrointestinal tract proximal to the ligament of Treitz which anatomically separates the duodenum from the jejunum.
- Mortality is 10% and usually results from complications of underlying disease rather than from exsanguination.
- The risk of re-bleeding is low if bleeding occurred more than 48 hours before presentation.

ETIOLOGY

- Peptic ulcer disease (50%) (*H. pylori* and NSAIDs)-ulcer erosion into blood vessel. Commonly posterior duodenal ulcer.
- Gastroesophageal varices (15%) (either due to cirrhosis or schistosomiasis)
- Mallory-Weiss tear (5%) following severe vomiting
- Gastroesophageal reflux disease
- Drugs: Aspirin and NSAIDs
- Inflammation:
  - Esophagitis (25%)
  - Gastritis (25%)
  - Erosive gastritis (in HIV patients consider CMV, HSV, candida)
  - Duodenitis (15%)
- Gastric cancer (5%)
- Gastric vascular ectasia
- Cameron's ulcer
- Dieulafoy's lesion (submucosal artery)
- Aortoenteric fistula
- Hemobilia (mixture of blood and bile due to surgical and non-surgical trauma)



CLINICAL FEATURES

- History:
  - Nausea
  - Retching prior to hematesis (Mallory-Weiss tear)
  - Hematemesis (bright red blood or "coffee ground" emesis due to stasis of blood in the stomach)
  - Dyspepsia
  - Abdominal pain
  - Melena: dark tar like stool (as little as 50ml of blood in the GIT can cause melena)
  - Hematochezia (from rapid upper GI bleeding or massive bleeding with shock)
  - Orthostasis (orthostatic hypotension)
  - Chronic slow upper GI bleeding can present with occult blood positive brown stool and chronic iron deficiency anemia.
  - General features: nausea, epigastric pain, syncope, lightheadedness, dizziness, fatigue
  - History of alcohol use are usually found among those with variceal hemorrhage, esophagitis, and Mallory-Weiss tear
  - History of NSAID use (peptic ulcer)
  - History of prior abdominal aortic graft (aortoenteric fistula)
  - History of chronic GERD (esophagitis)
  - History of weight loss/iron deficiency (malignancy)
- Physical examination
  - Melena or hematochezia
  - Pallor
  - Hypotension and orthostatic hypotension (>10-point rise in pulse when the patient goes from the supine to the standing or sitting position or >20-point drop in systolic blood pressure on change in position)- there should be at least a minute in between the position change and the measurement of pulse and blood pressure to allow time for the normal autonomic discharge to accommodate to the position change. Orthostasis indicates a 15 to 20% blood loss.
  - Tachycardia
  - Stigmata of chronic liver disease (spider angioma, ascites, jaundice)

DIAGNOSIS AND INVESTIGATIONS

- First determine if the bleed is acute or chronic.
  - Ask about the number of bleeding episodes, most recent episode, abdominal pain, weight loss, use of ASA, NSAIDs, alcohol, cirrhosis, risk factors of schistosomiasis.
  - If the bleed is acute, first evaluate hemodynamic stability. Check blood pressure and heart rate. Ask about lightheadedness, syncope, dizziness. Check for orthostatic vital signs, they will be positive in patients with significant blood loss.
  - Do a rectal exam to look for bright red blood or melena.
- Investigations:
  - Full blood count: chronic or subacute bleeding leads to anemia but hemoglobin concentration may be normal after sudden, major bleeding until hemodilution occurs. Thrombocytopenia may be a clue to the presence of Hypersplenism in chronic liver.
  - Stool for occult blood
  - Urea, electrolytes and creatinine: this may show evidence of renal failure. The blood urea rises as the absorbed products of luminal blood are metabolized by the liver, an elevated blood urea with normal creatinine concentration implies severe bleeding.
  - Liver enzymes: for chronic liver disease
  - PT/PTT/INR for coagulopathy
  - Cross-matching- at least 2 units of blood should be cross-matched.
  - NG tube lavage: useful if positive (red blood, coffee grounds), if negative (clear or bilious), does not exclude upper GIT bleeding. 10% of Upper GIT bleeding cases have a negative lavage.
    - If you pull out fresh blood (acute and active upper GI bleed)
    - If you pull out coffee ground like material (recent upper GI bleed)
    - If you pull out non-blood bilious material (this does not exclude an upper GI bleed, the bleed may be lower)
  - *H. pylori* testing: perform on all patients with ulcers. (Stool for *H. Pylori*)
  - Endoscopy: perform after stabilization and resuscitation, often done <12 hours from admission. Diagnostic, prognostic and therapeutic.

MANAGEMENT

- Stabilization:
  - Oxygen given by facemask
  - Nil per oral, consider an NG tube and place two large-bore IVs.
  - If the patient is in shock, treat with aggressive IV fluids (normal saline or Ringer's lactate) and cross-matched blood with a hematocrit goal of 25-30% or above in older patients and in those who may have coronary artery disease. (if you suspect esophageal variceal bleed, start normal saline cautiously)
  - Cross match blood and administer packed red blood cells if needed.
  - In the presence of active bleeding and platelets <50 000/μL or if there is known impaired function (uremia, aspirin), transfuse platelets or desmopressin. With active bleeding, increased PT time, and INR> 1.5 transfuse fresh frozen plasma (FFP).
  - Place a Foley catheter to closely monitor urine output, decreased urine output is a sign of hypoperfusion and bleeding.
  - Hourly measurement of pulse, blood pressure and urine output.
- Medical therapy:
  - Give high dose oral proton pump inhibitors twice daily upon presentation. (Omeprazole 40mg BD)
  - Initiate an IV proton pump inhibitor drip (8mg/h for 72 hours) if esophagogastroduodenoscopy (EGD) suggests a high risk of re-bleeding (i.e. active bleeding, visible vessel, adherent clot). This reduces the relative risk of bleeding by 50%.
  - IV octreotide for suspected variceal hemorrhage continue for 3 days if verified by EGD. This is meant to decrease portal hypertension.
  - Correct any coagulopathies, consider giving vitamin K if signs of liver disease. For severe bleeding give vitamin K 5mg IV stat.
  - Propranolol is a non-selective beta blocker that used in the long-term management of portal hypertension to decrease the frequency of bleeding. Everyone with varices from portal hypertension and cirrhosis should be on a beta-blocker.
  - Broad-spectrum antibiotics in patients with suspected liver disease.
- Endoscopy: should be carried out after adequate resuscitation, ideally within 24 hours and will yield a diagnosis in 80% of cases.
  - Patients can be effectively treated with banding (band ligation for varices), thermal coagulation (heater probe) sclerosant, epinephrine and/or

electrocautery. Predictors of re-bleeding include significant comorbidities, size of lesion and high risk stigmata (visible vessel, adherent clot).

- Refractory or recurrent upper GIT bleeding:
  - Esophageal balloon tamponade (Minnesota or Sengstaken-Blakemore tubes) for varices as a bridge to TIPS (transjugular intrahepatic portosystemic shunting)- a catheter is placed into the jugular vein and guided radiographically through the liver to form a shunt between the systemic circulation in the hepatic vein and the portal circulation through the portal vein. TIPS has largely replaced the need to surgically place the shunt. The most common, long-term complication of TIPS is worsening of hepatic encephalopathy.
  - Angiogram with intra-arterial embolization or surgery for refractory non-variceal bleeding

Management of acute gastrointestinal bleeding

- History and examination. Note co-morbidity
- Monitor the pulse and blood pressure half-hourly
- Take blood for haemoglobin, urea, electrolytes, liver biochemistry, coagulation screen, group and cross-matching (2 units initially)
- Establish intravenous access – 2 large bore i.v. cannulae
- Give blood transfusion/colloid if necessary. Indications for blood transfusion are:
  a. SHOCK (pallor, cold nose, systolic BP below 100 mmHg, pulse >100 b.p.m.)
  b. Haemoglobin <100 g/L in patients with recent or active bleeding
- Oxygen therapy
- Urgent endoscopy in shocked patients/liver disease
- Continue to monitor pulse and BP
- Re-endoscope for continued bleeding/hypovolaemia
- Surgery if bleeding persists

- *H. pylori* eradication: for all peptic ulcer causing upper GIT bleeding with (*H. pylori* testing).
- Surgery is indicated when endoscopic hemostasis fails to stop active bleeding and if re-bleeding occurs on one occasion in an elderly or frail patient or twice in a younger fitter patient. If available, angiographic embolization is an effective alternative to surgery in frail patients.

Risk Assessment in Patients with UGIB

	Low	Moderate	High
History	Age < 60.	Age < 60.	Age > 60, comorbidities, onset while in hospital.
Exam	SBP > 100, HR < 100.	SBP > 100, HR > 100.	SBP < 100, HR > 100.
EGD	Small, clean-based ulcer; erosions; no lesion found.	Ulcer with pigmented spot or adherent clot.	Active bleeding, varices, ulcer > 2 cm, visible vessel.
Rebleed risk	< 5%.	10–30%.	40–50%.
Triage	Ward/home.	Ward.	ICU.

The choice of operation depends on the site and diagnosis of the bleeding lesion.

- *Discharge: The patient's age, diagnosis on endoscopy, co-morbidity and the presence or absence of shock and the availability of support in the community should be taken into consideration. In general, all patients who are hemodynamically stable and have no stigmata of recent hemorrhage on endoscopy can be discharged from hospital within 24 hours. All shocked patients and patients with co-morbidity need longer inpatient observation.*

LOWER GASTROINTESTINAL BLEEDING

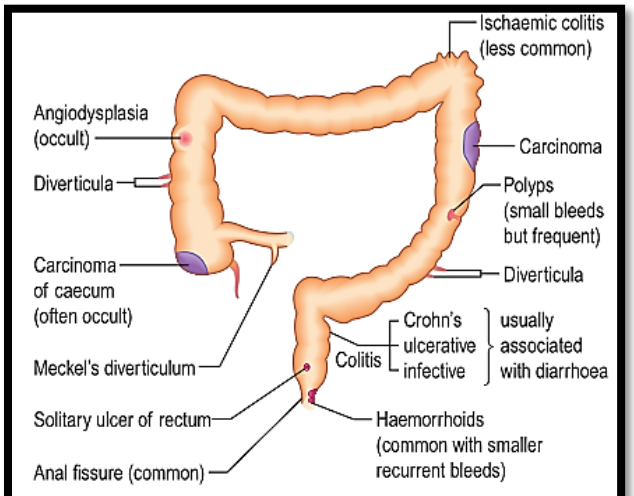
- This is bleeding from a source distal to the ligament of Treitz.
- More 95% of cases are from a colonic source and more than 85% are self-limited.
- It may be due to hemorrhage from the colon, anal canal or small bowel.
- It useful to distinguish those patients who present with profuse, acute bleeding from those who present with chronic or subacute bleeding of less severity.

ETIOLOGY

- Diverticulosis (40%)
  - Diverticular disease
  - Meckel's disease
- Angiodysplasia
- Vascular ectasia
- Neoplasm (carcinoma)
- Fissure
- Inflammatory bowel disease
- Ischemic colitis
- Hemorrhoids
- Infectious e.g. hookworms
- Postpolypectomy
- NSAID ulcers
- Radiation colitis
- Rectal varices
- Solitary rectal ulcer syndrome

Causes of lower gastrointestinal bleeding

Severe acute	
• Diverticular disease • Angiodysplasia • Ischaemia	• Meckel's diverticulum • Inflammatory bowel disease (rarely)
Moderate, chronic/subacute	
• Fissure • Haemorrhoids • Inflammatory bowel disease • Carcinoma	• Large polyps • Angiodysplasia • Radiation enteritis • Solitary rectal ulcer



Causes of lower gastrointestinal bleeding.
The sites shown are illustrative – many of the lesions can be seen in other parts of the colon.

CLINICAL FEATURES

- Symptoms:
  - Usually asymptomatic but may present with abdominal cramps and to a less extent pain.
  - Orthostasis is seen in severe cases.
- Signs:
  - Hematochezia (bright red blood, maroon stool)
  - Melena
  - Pallor, chronic bleeding tends to present with anemia (iron deficiency)
  - Abdominal distension with mild tenderness
  - Hypotension and Tachycardia

DIAGNOSIS AND INVESTIGATIONS

- Demographics and history
  - Age group: distinguish elderly, asymptomatic patients (diverticular/vascular ectasias) from young patients who present with pain (infectious, inflammatory).
  - Description of first blood seen by patient: bright red indicates a distal or rapid proximal source, black or marron blood points to a more proximal source.
  - Rectal examination
- Investigations:
  - Full blood count: chronic or subacute bleeding leads to anemia but hemoglobin concentration may be normal after sudden, major bleeding until hemodiluation occurs. Thrombocytopenia may be a clue to the presence of hypersplenism in chronic liver.
  - Stool for occult blood
  - Stool microscopy, cultures and sensitivity if infection is suspected.
  - Urea, electrolytes and creatinine: this may show evidence of renal failure. The blood urea rises as the absorbed products of luminal blood are metabolized by the liver, an elevated blood urea with normal creatinine concentration implies severe bleeding.
  - Liver enzymes: for chronic liver disease
  - PT/PTT/INR for coagulopathy
  - Cross-matching- at least 2 units of blood should be cross-matched.
  - Anoscopy to exclude an anal source
  - Mild to moderate bleeding: consider nasogastric lavage. Urgent colonic purge (over 4-6 hours then colonoscopy)
  - Massive bleeding
    - Endoscopy to rule out upper GI bleeding.
    - Technetium-labelled RBC scan and/or mesenteric angiography: if >6 units of blood are transfused, consider surgical intervention.
    - Minimum bleeding rates: tagged RBC scan, 0.1-0.5ml/min, mesenteric angiogram, 1.0 ml/min
  - Diagnostic colonoscopy: typically performed 12-48 hours after presentation and stabilization.
  - Proctoscopy for anorectal disease particularly hemorrhoids
  - Flexible sigmoidoscopy or colonoscopy for IBD, cancer, ischemic colitis, diverticular disease, angiodysplasia

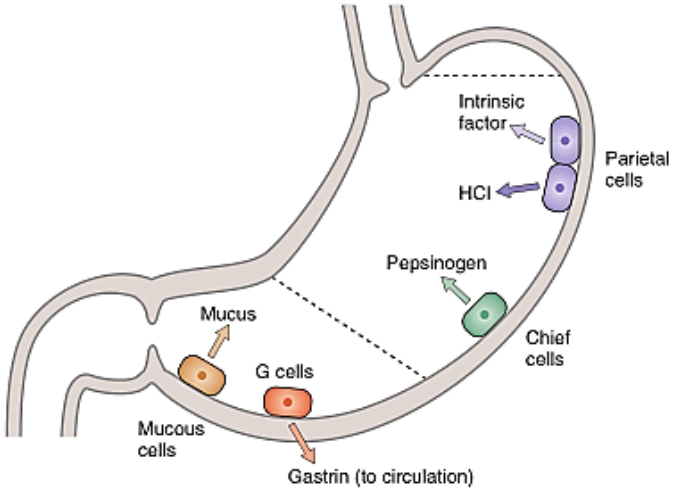
- Angiography- vascular abnormality (angiodysplasia): the yield of angiography is low so it is a test of last resort
- If gastroscopy, colonoscopy and duodenal biopsy have not revealed the cause, investigation of the small bowel is necessary. Capsule endoscopy is the diagnostic investigation of choice but currently has no therapeutic ability. (A capsule with a camera is swallowed and it takes pictures along the GIT)

MANAGEMENT

- Stabilization:
  - Oxygen given by facemask
  - Nil per oral, consider an NG tube and place two large-bore IVs.
  - If the patient is in shock, treat with aggressive IV fluids (normal saline or Ringer's lactate) and cross-matched blood with a hematocrit goal of 25-30% or above in older patients and in those who may have coronary artery disease. (if you suspect esophageal variceal bleed, start normal saline cautiously)
  - Cross match blood and administer packed red blood cells if needed.
  - In the presence of active bleeding and platelets <50 000/μL or if there is known impaired function (uremia, aspirin), transfuse platelets or desmopressin. With active bleeding, increased PT time, and INR> 1.5 transfuse fresh frozen plasma (FFP).
  - Place a Foley catheter to closely monitor urine output, decreased urine output is a sign of hypoperfusion and bleeding.
  - Hourly measurement of pulse, blood pressure and urine output.
- Medical therapy: H2 receptor antagonists and PPIs have no role in the treatment of lower GI bleeding. Discontinue ASA and NSAIDs. Oral iron is given to treat anemia.
- Urgent therapeutic colonoscopy:
  - Large volume purge >6L, cautery or injection of epinephrine or clipping.
  - Colonoscopy is technically challenging with brisk Lower GI bleeding (urgent colonic purge requires sedation; visualization is often poor)
- Mesenteric angiography/embolization: the intervention of choice for brisk lower GI bleeding. Associated with 80-90% cessation rates for those with diverticular or vascular ectasia etiology though 50% experience re-bleeding.
- Surgery: indicated with active lower GI bleeding involve >4-6 units of blood in 24 hours or >10 units in total. If the site is well localized, consider hemicolectomy, otherwise perform total abdominal colectomy.

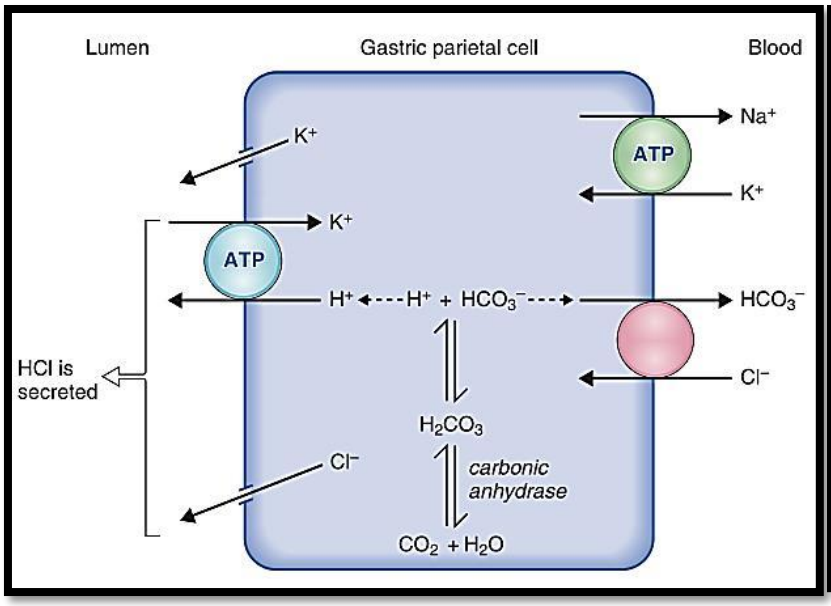
THE STOMACH AND DUODENUM

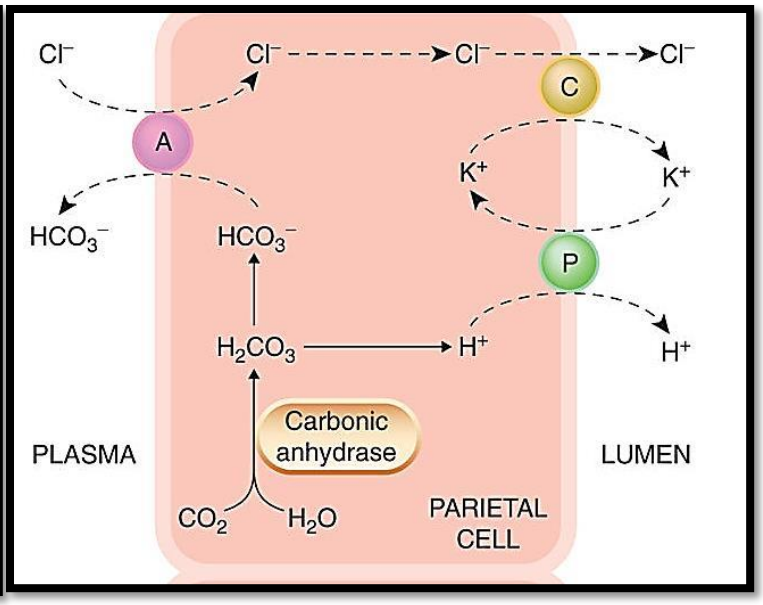
- The stomach is a muscular pouch continuous from the esophagus (the cardia) to the pylorus.
- It consists of the cardia, an upper region (the fundus, under the left diaphragm), the mid-region or body and the antrum, which extends to the pylorus.
  - The cardia is lined by mucin-secreting foveolar cells that form shallow glands.
  - The fundus contains parietal cells and chief cells.
  - The body also contains parietal and chief cells.
  - The antrum contains G-cells and D-cells.
  - The pylorus has a sphincter separating the stomach from the duodenum.



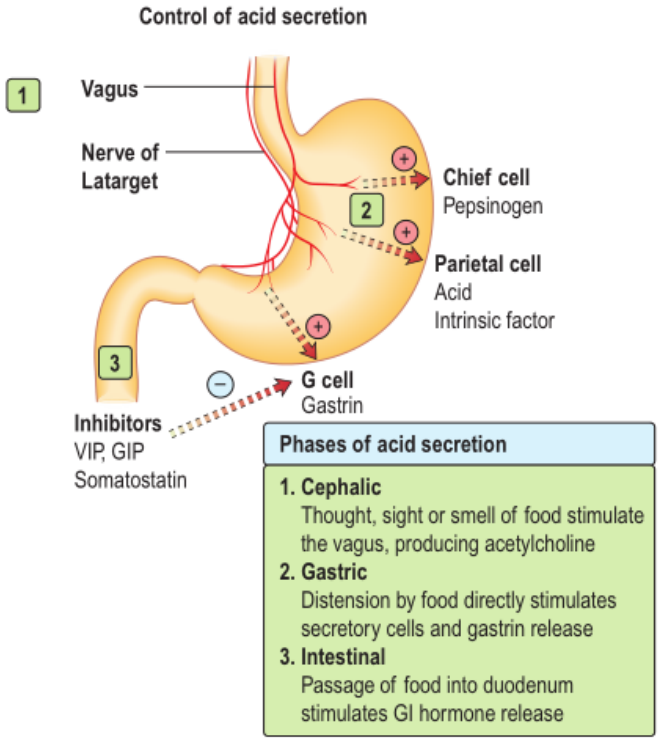
- It serves as a reservoir where food can be retained (Stomach capacity=1500-3000ml) and broken up before being actively expelled into the proximal small intestine.
- The stomach is innervated by the vagus nerve.
- The smooth muscle of the wall of the stomach has 3 layers:
  - Outer longitudinal
  - Inner circular
  - Innermost oblique
- There are 2 sphincters, the gastro-esophageal sphincter and the pyloric sphincter.
- The pyloric sphincter is largely made up of a thickening of the circular muscle layer and controls the exit of gastric contents into the duodenum.
- The duodenum has outer longitudinal and inner smooth muscle layers, it is C-shaped and the pancreas sites in the concavity. It terminates at the duodenojejunal flexure where it joins the duodenum.
- The mucosal lining of the stomach can stretch in size with feeding. The greater curvature of the undistended stomach has thick fold or rugae.
- The mucosa of the upper 2/3 of the stomach contains:
  - Parietal cells which secrete hydrochloric acid and intrinsic factor.
  - Chief cells these secrete pepsinogen (which initiates proteolysis)

- There is a color change at the junction between the body and the antrum of the stomach that can be seen macroscopically and confirmed by measuring surface pH.
- The antral mucosa contains
  - G- cells which secretes gastrin which stimulates acid production. There are 2 major forms of gastrin G17 and G34, depending on the number of amino acid residues. G17 is the major form found in the antrum.
  - D-cells which secrete somatostatin, a suppressant of acid secretion.
  - Mucus secreting cells which produce mucus and bicarbonate. The mucus is made of glycoproteins called mucins.
- The wall of the stomach also contains enterochromaffin cells which produce histamine that promotes acid secretion.
- The 'mucosal barrier' made up of the plasma membrane of mucosal cells and the mucus layer protects the gastric epithelium from damage by acid and for example, alcohol, aspirin, NSAIDs and bile salts. Prostaglandins stimulate secretion of mucus and their synthesis is inhibited by aspirin and NSAIDs which inhibit cyclo-oxygenase
- The duodenal mucosa has villi like the rest of the small bowel and also contains Brunner's glands that secrete alkaline mucus. This along with pancreatic and biliary secretions, helps to neutralize the acid secretion from the stomach when it reaches the duodenum.
- Gastric acid secretion:
  - The apical membrane contains H^+-K^+ ATPase as well as Chloride channels.
  - The basolateral membrane contains Na^+-K^+ ATPase and Cl^-—HCO^-_3 exchanger
  - The parietal cell also contains the enzyme carbonic anhydrate.
  - Carbon dioxide in the cell reacts with water in the presence of carbonic anhydrase to form carbonic acid which dissociates into hydrogen and bicarbonate ions.
  - The hydrogen ions are secreted along with chloride ions into the lumen of the stomach while the bicarbonate is absorbed into the blood.
  - At the apical membrane hydrogen ions are exchanged for potassium ions.
  - Potassium ions leave via a potassium channel found on the apical membrane.
  - At the basolateral side of the cells chloride is exchanged for bicarbonate ions (Responsible for the alkaline tide observed in gastric venous blood after a meal)





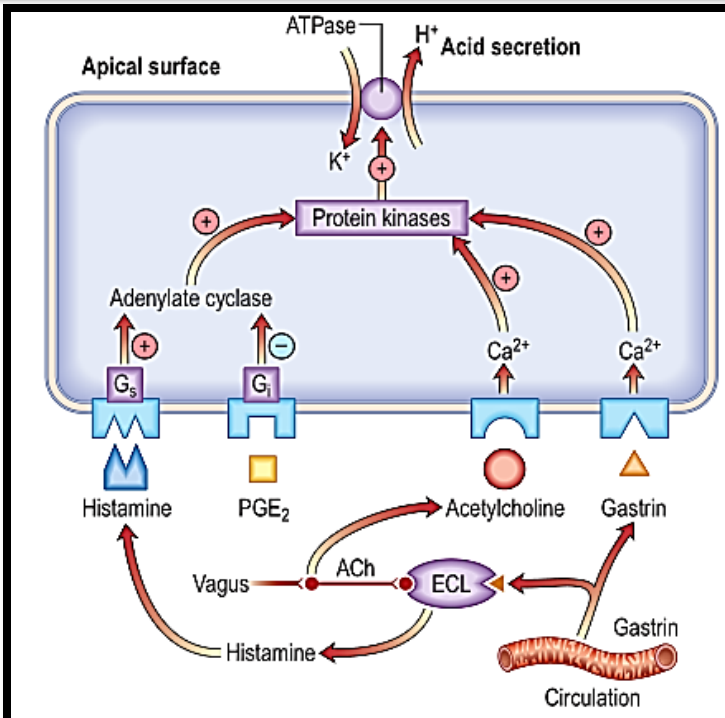
- Acid is not essential for digestion but does prevent some food-born infectious. It is under neural and hormonal control and both stimulate acid secretion through the direct action of histamine on the parietal cell. Acetylcholine and gastrin also release histamine via the enterochromaffin cells.
- Somatostatin inhibits both histamine and gastrin release therefore acid secretion.
- Other major functions are:
  - Reservoir for food
  - Emulsification of fat and mixing of gastric contents
  - Secretion of intrinsic factor
  - Absorption (of only minimal importance)



- Gastric emptying depends on many factors. There are osmoreceptors in the duodenal mucosa that control gastric emptying by local reflexes and the release of gut hormones. In particular, intraduodenal fat delays gastric emptying by negative feedback through duodenal receptors.

GASTRITIS

- This is inflammation of the gastric mucosa (although the term is often used loosely by endoscopists to describe 'redness').
- Note the word gastritis is not synonymous with dyspepsia or gastric erythema seen during endoscopy.
- In gastritis there is a disruption of mucous layer, stimulation of acid secretion and decreased production of bicarbonate which eventually cause direct damage to the epithelium.
- It is classified into:
  - Acute gastritis
  - Chronic gastritis



(a) Control of acid secretion. **(b)** Mechanisms involved in acid secretion: Histamine stimulates Gs via the H2 receptors and acts via cyclic AMP; prostaglandin E2 activates the Gi protein and *inhibits* acid secretion; acetylcholine (ACh) acts via the vagus M3 receptors; ACh also acts via the ECL cell; gastrin acts via the gastrin receptor, increasing the intracellular free calcium, and also via the ECL cell stimulating histamine. Gs and Gi, stimulating and inhibiting G-proteins; ECL, enterochromaffin cells.

ACUTE GASTRITIS

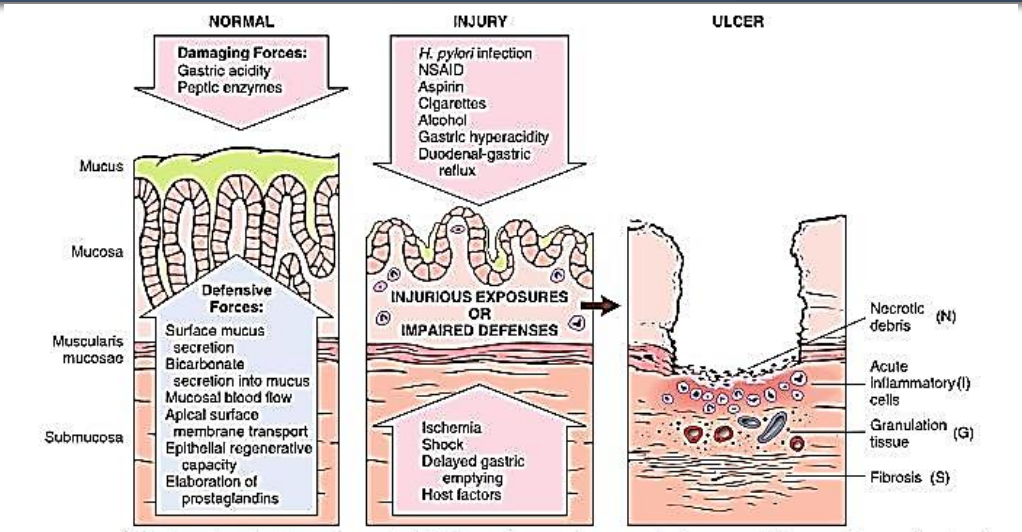
- This is commonly caused by *Helicobacter pylori*.
- Other causes:
  - Drugs e.g. ASA, NSAIDs
  - Alcohol in high doses
  - Severe stress
  - Other infections e.g. virus (CMV, Herpes simplex), mycobacterium and syphilis
- Patients are usually asymptomatic but at times may present with sudden onset of epigastric pain, nausea & vomiting (with or without diarrhea), upper GIT bleeding (melena and hematesis), indigestion with neutrophilic infiltration, edema and hyperemia of the gastric mucosa.
- If not treated, H. pylori gastritis may progress to one of the chronic gastritis. No specific treatment of acute gastritis is indicated. Removal of the offending agents may be adequate.

CHRONIC GASTRITIS

- This is defined as a histological demonstration of lymphocytic and plasma cell infiltration of gastric mucosa.
- Course: Superficial gastritis is followed by atrophic gastritis (characterized by distortion and destruction of gastric glands) progressing to gastric atrophy (with loss of gastric glands) which then undergo intestinal metaplasia (replacement of gastric mucosal cells by intestinal cells) and finally progressing to gastric carcinoma.
- Chronic gastritis is classified into 3 types:
  - Type A (autoimmune) gastritis (chronic fundal gastritis)
    - The inflammation is limited to the gastric fundus and body with antral sparing.
    - Associated with pernicious anemia, with circulating autoantibodies to parietal cells (AKA Autoimmune gastritis)
  - Type B (bacterial) gastritis (chronic antral gastritis)
    - It is the more common type
    - It commonly involves the antrum and mostly associated with *H. pylori infection*. However, the inflammation may progress to involve the gastric fundus and body causing pangastritis usually after 15-20 years.
    - Histology improves with eradication of *H. pylori*.
  - Type C (chemical) gastritis
    - Is due to repeated injury with bile reflux (duodenal-gastric reflex) or chronic ingestion of NSAIDs
- Most chronic gastritis is asymptomatic.
- Treatment:
  - Lifelong parenteral Vitamin B12 is recommended for patients with pernicious anemia.
  - There is no need to treat *H. pylori* unless there is ulcer or MALT Lymphoma.

PEPTIC ULCER DISEASE

- A peptic ulcer is a break in the superficial cells (Mucosal surface) penetrating down to the muscularis mucosa (found in the submucosa) of either the stomach or the duodenum.
- An erosion by contrast are superficial breaks in the mucosa alone.
  - Recall the layers of the GIT include: mucosa, submucosa, muscularis and serosa
- Peptic ulcers are caused by discrete tissue destruction caused by acid and pepsin.
- Most duodenal ulcers are found in the duodenal cap, the surrounding mucosa appears inflamed, hemorrhagic or friable (duodenitis).
- Gastric ulcers are most commonly seen on the lesser curve near the incisura but can be found in any part of the stomach.
- Duodenal ulcers affect approximately 10% of the adult population and are 2 to 3 times more common than gastric ulcers.
- Peptic ulcer disease occurs more commonly in males than females. They are common in adults between 25 and 64 years.
- About 90-100% of all duodenal ulcers and 75-85% of gastric ulcers are associated with *H. pylori* infection.
- Ulcers occur when there is an imbalance between the protective forces of the GIT and aggressive ones.
  - Protective forces:
    - Surface mucus
    - Presence of bicarbonate
    - Rapid epithelial regeneration
    - Normal mucosal blood flow
    - Normal mucosal prostaglandin secretion
  - Aggressive forces:
    - H. pylori
    - NSAIDs
    - Corticosteroids
    - ASA
    - Smoking
    - Alcohol
    - Psychological stress
    - Zollinger-Ellison syndrome



Mechanisms of gastric injury and protection. This diagram illustrates the progression from more mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrotic debris *(N)*, inflammation *(I)*, and granulation tissue *(G)*; a fibrotic scar *(S)*, which develops over time, is present only in chronic lesions.

ETIOLOGY

- *H. pylori*
  - This is a slow-growing spiral Gram-negative flagellate urease-producing bacterium.
  - It is acquired through fecal-oral or oral-oral route
  - It colonizes the mucous layer in the gastric antrum but is also found in the duodenum in areas of gastric metaplasia.
  - It is found in greatest numbers under the mucous layer in gastric pits, where it adheres specifically to gastric epithelial cells.
  - It is protected from gastric acid by the juxtamucosal mucous layer which traps bicarbonate secreted by antral cells and ammonia produced by bacterial urease.
  - Mechanisms by which H. pylori damages mucosa:
    - Induction of IL-8 which recruits neutrophils
    - Production of urease which cleaves urea to ammonia and carbon dioxide creating a buffer against the HCL.
    - Enhancement of gastric acid secretion and impairment of duodenal bicarbonate production
    - Adheres to surface epithelial cells and secretes phospholipase, adhesins, platelet activating factors and protease enzymes (catalase, lipase)
    - Production of a passive urea transporter (VacA) that causes cell injury (vacuolization)

  - CagA (cytotoxic-associated protein) and VacA (vacuolating toxin) genes have also been implicated in the development of ulcers.
- NSAIDs, ASA, Corticosteroids: these drugs inhibit prostaglandin synthesis which leads to decreased mucus production, bicarbonate secretion and an impaired blood flow. It commonly causes gastric ulcers as opposed to duodenal ulcers.
- Alcohol and smoking
- Uremia and radiation therapy
- Severe burns (Curling ulcer)- hypovolemia and dehydration leads to decreased blood supply and so acid that infiltrates into the mucosa is not carried away.
- Cushing ulcer- increased intracranial pressure and increased stimulation of Vagus nerve leads to increased acid production. This is seen with head injury.
- Sever physiological Stress

CLINICAL FEATURES

- Manifestation is dependent on ulcer location and patient age.
- Course is usually chronic and recurrent.
- Pain is the most common symptom it is described as burning, gnawing or felt as hunger often localized to epigastrium and relieved by food or antacids.
- Gastric ulcers:
  - Symptoms often do not follow a consistent pattern, especially when ulcer is located in pyloric channel where symptoms of obstruction may predominate (bloating, nausea, vomiting due to edema and scarring).
- Duodenal ulcers:
  - Pain tends to be consistent usually absent when patient wakes up but appears in the morning, and relieved by food but recurs again 2-3 hours after a meal.
  - Pain may be severe enough to awaken patient at night.
- Note: the relationship of the pain to food is variable and on the whole not helpful in diagnosis. The pain of a duodenal ulcer classically occurs at night (as well as during the day) and is worse when the patient is hungry but this is not reliable. The pain of both gastric and duodenal ulcers may be relieved by antacids.
- Nausea may accompany the pain, vomiting is infrequent but can relieve the pain. Anorexia and weight loss may occur particularly with gastric ulcers. Persistent and severe pain suggests complications such as penetration into other organs.
  - Duodenal ulcer pain that becomes constant is no longer relieve by food or antacids or radiates to the back or to either upper quadrant may signal penetration of the ulcer to the pancreas.

  - Duodenal ulcer pain accentuated rather than relieved by food and/or accompanied by vomiting often indicates gastric outlet obstruction
  - Abrupt severe or generalized abdominal pain is characteristic of free ulcer perforation into the peritoneal cavity.
- Back pain suggests a penetrating posterior ulcer.
- Severe ulceration can occasionally be symptomless, as many who present with acute ulcer bleeding or perforation have no preceding ulcer symptoms.
- Physical findings:
  - Epigastric tenderness
  - Signs of peritonitis may be found in ulcer perforation
  - Succussion splash is often detected in gastric outlet obstruction

	Duodenal ulcer	Gastric ulcer
Age	Uncommon before 16 years	May develop in children as young as 5 years but peak incidence is later than duodenal ulcer
Relation of pain to food/antacids	Pain is relieved by food or antacids	Pain aggravated by ingestion of food
Relation of pain to food timing	The pain characteristically comes 2 to 3 hours after ingestions of food (hunger pain)	The pain comes within 30 minutes of ingestion of food
Nausea and vomiting	Not common	Common
Weight loss	Uncommon	Common because of fear to eat
Perforation	More common	Less common
Bleeding	Less common	More common

INVESTIGATIONS

- Endoscopy: this is the most sensitive and specific method for the diagnosis of PUD.
  - Direct visualization and photographic documentation of the ulcer is possible
  - Permits mucosal biopsy for detection of *H. pylori* infection
  - Provides baseline reference for the assessment of ulcer healing
- *H. pylori* tests: stop Proton pump inhibitors 2 week before.
  - ^{13}C-Urea breath test- simple, rapid, useful for early follow up, false negative with recent therapy. The measurement of $^{13}CO_2$ in the breath after ingestion of ^{13}C urea requires as mass spectrometer. The test is sensitive (90%) and specific (96%) but the sensitivity can be improved by insuring the patient has

not taken antibiotics in the 4 weeks prior and proton pump inhibitors in the 2 weeks before the test.

- Stool antigen test: it is 97.6% sensitive and 96% specific.

- Barium studies (Barium meal and Barium follow through): sensitivity of this investigation to detect ulcers ranges from 70-90%.
- Full blood count may show iron deficiency anemia.

MANAGEMENT

- Remove any offending drug
- Stop smoking.
- Avoid coffee, and foods that cause or aggravate their symptoms
- Drugs:
  - For indigestion/dyspepsia, to relieve symptoms given then between meals and at bedtime:
    - Magnesium trisilicate compound 250-500mg to chew PRN.
    - Aluminium hydroxide 500mg-1g to chew PRN
  - For acid reflux: Omeprazole 20mg PO daily BD.
  - No single agent is effective for eradication of H. pylori hence a combination of multiple drugs is essential. Proton pump inhibitors are added to antibiotics
    - Triple therapy:
      - Omeprazole 20mg BD (or 40mg OD), Clarithromycin 250mg or 500 mg BD and Metronidazole/Amoxicillin 500mg BD/1g BD for 14 days.
      - Omeprazole 20mg BD (or 40 mg OD), Metronidazole 400mg TDS, Amoxicillin 500mg TDS
      - Omeprazole 20 mg BD (or 40 mg OD), Metronidazole 400mg (or Tinidazole 500mg) BD and Clarithromycin 500mg BD for 14 days.
    - Quadruple therapy: Bismuth subsalicylate 2 tabs QID, Omeprazole 20mg BD, Metronidazole 400mg TDS, Tetracycline 500mg QID
      - This is used for eradication failures
- Surgical treatment is indicated for:
  - Perforation
  - Obstruction not responding to medical therapy
  - Uncontrolled/recurrent bleeding
  - Suspected malignancy
  - Symptoms refractory to medical management

COMPLICATIONS

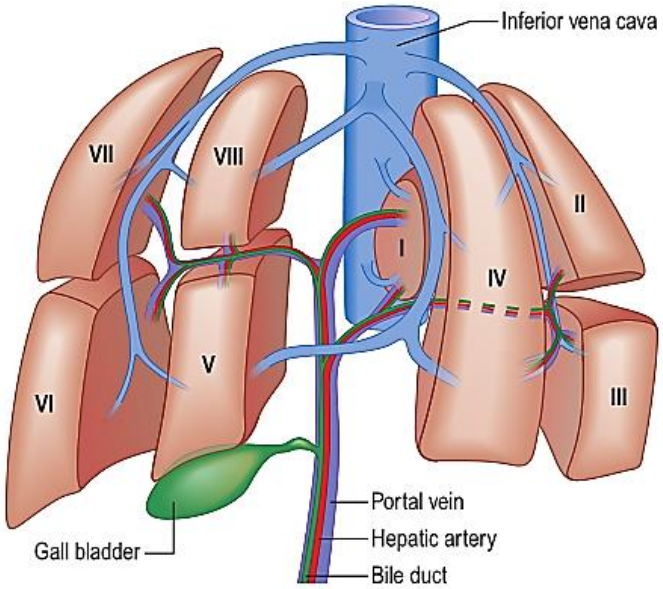
- Hemorrhage
- Anemia
- Penetration to other organs e.g. pancreas, liver
- Perforation
- Gastric outlet obstruction, Pyloric stenosis
- Stomach cancer

CHAPTER 8: LIVER AND BILIARY DISEASE

LIVER AND BILIARY TRACT DISEASE

THE LIVER

- In many countries, alcohol is the major cause of liver disease, followed by hepatitis C virus infection.
- Hepatitis B virus is still a significant factor but widespread vaccination will reduce its prevalence.
- Non-alcoholic fatty liver disease is associated with the metabolic syndrome and is increasing in affluent (wealthy) countries.
- Imaging techniques enable the liver, biliary tree and pancreas to be visualized with precision, resulting in earlier diagnosis.
- The liver is one of the largest internal organ (1.2-1.5kg) and is situated in the right hypochondrium.
- A functional division into the larger right lobe (containing caudate and quadrate lobes) and the left lobe is made by the middle hepatic vein.
- The liver is further subdivided into 8 segments by divisions of the right middle and left hepatic veins. Each segment has its own portal pedicle permitting individual segment resection at surgery.
- The hepatic blood supply constitutes 25% of the resting cardiac output and is delivered via two main vessels, entering via the liver hilum (portal hepatis):
  - Hepatic artery: A branch of the coeliac axis, supplied 25% of the hepatic blood flow. The hepatic artery auto-regulates flow ensuring a constant total blood flow.



Segmental anatomy of the liver, showing the eight hepatic segments. I, caudate lobe; II–IV the left hemiliver; V–VIII the right hemiliver.

- Portal vein: drain most of the GIT and spleen. It supplies 75% of hepatic blood flow. The normal portal pressure is 5-8mmHg, flow increases after meals

- Blood from these vessels is distributed to the segments and flows into the sinusoids via the portal tracts. Blood leaves the sinusoids, entering branches of the hepatic vein which joint into 3 main branches before entering the inferior vena cava.
- The caudate lobe is an autonomous segment as it receives an independent blood supply from the portal vein and hepatic artery and its hepatic vein drains directly into the inferior vena cava.
- Lymph, formed mainly in the perisinusoidal space is collected in lymphatics which are present in the portal tracts. These small lymphatics enter larger vessels which eventually drain into the hepatic ducts.
- The acinus is the functional hepatic unit. It consists of parenchyma supplied by the smallest portal tract containing portal vein radicles, hepatic arterioles and bile ductules.
- The hepatocytes near this triad (zone 1) are well supplied with oxygenated blood and are more resistant to damage than the cells near the terminal hepatic (central veins (zone 3).
- The sinusoids lack a basement membrane and are loosely surrounded by specialist fenestrated endothelial cells and Kupffer cells (phagocytic cells).

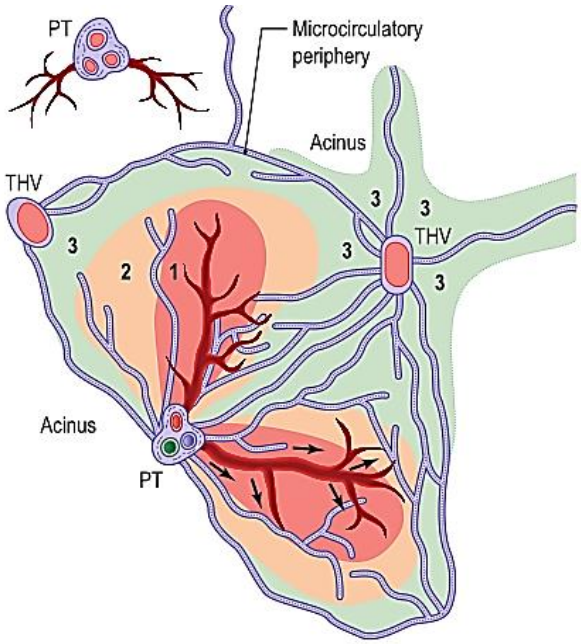


Diagram of an acinus. *Zones 1, 2 and 3* represent areas supplied by blood, with zone 1 being best oxygenated. *Zone 3* is supplied by blood remote from afferent vessels and is in the microcirculatory periphery of the acinus. The perivascular area (star-shaped green area around THV) is formed by the most peripheral parts of zone 3 of several adjacent acini and is the least well oxygenated. THV, terminal hepatic venule; PT, portal triad.

- Sinusoids are separated by plates of liver cells (hepatocytes). The subendothelial space between the sinusoids and hepatocytes is the space of Disse, which contains a matrix of basement membrane constituents and stellate cells.
- Stellate cells store retinoids in their resting state and contain the intermediate filament, desmin. When activate (to Myofibroblast) they are contractile and probably regulate sinusoidal blood flow.

- Endothelin and nitric oxide play a major role in modulating stellate cell contractility.
- Activated stellate cells produce signal proteins for synthesis or inhibition of degradation of extracellular matrix components, including collagen as well as cytokines and chemotactic signals.
- Functions of the liver include:
  - Protein metabolism
    - Synthesis and storage: all serum proteins (albumin and fibrinogen except gamma-globulins are synthesized by the liver).
    - It also synthesizes other proteins such as transferrin, ceruloplasmin, acute-phase reactive protein, alpha-1 antitrypsin and alpha-fetoprotein as well as clotting factors: fibrinogen, prothrombin, V, VII, IX, X and XII, proteins C, S and anti-thrombin as well as proteins of complement system.
  - Carbohydrate metabolism: gluconeogenesis, glycolysis, glycogenesis, glycogenolysis
  - Lipid metabolism: synthesis and transport of lipids via lipoproteins.
  - Storage of vitamins: A, D, B_{12}, K, folate and other minerals such as iron in ferritin & hemosiderin, and copper
  - Synthesis and secretion of bile
  - Detoxification and inactivation of endogenous and exogenous substances
  - Immunological function: complement proteins.

LIVER DISEASE

- Liver disease is classified according to duration:
  - Acute: <6 months
  - Chronic: >6 months

SYMPTOMS AND SIGNS OF LIVER DISEASE

1. Signs of cirrhosis (i.e. signs of liver dysfunction): Jaundice, Spider naevi, gynecomastia, loss of body hair, palmar erythema, Asterixis, easy bruising and testicular atrophy
2. Signs of portal hypertension: splenomegaly, ascites, caput medussae (distended abdominal veins)

- Note: cirrhosis will present with both signs of cirrhosis & portal hypertension whereas schistosomiasis will present only with signs of portal hypertension.

SYMPTOMS OF LIVER DISEASE

ACUTE LIVER DISEASE

- This may be asymptomatic and anicteric (without jaundice).
- Symptomatic disease which is often viral, produces generalized symptoms of malaise, anorexia and fever. Jaundice may appear as the illness progresses.

CHRONIC LIVER DISEASE

- Patients may be asymptomatic or complain of nonspecific symptoms, particularly fatigue.
- Specific symptoms include:
  - Right hypochondrial pain due to liver distension
  - Abdominal distension due to ascites
  - Ankle swelling due to fluid retention
  - Hematemesis and melena from GIT hemorrhage
  - Pruritus due to cholestasis-this is often an early symptom of primary biliary cirrhosis.
  - Breast swelling (gynecomastia), loss of libido and amenorrhea- due to endocrine dysfunction (increased estrogen in the body because most of it is not broken down by the liver).

SIGNS OF LIVER DISEASE

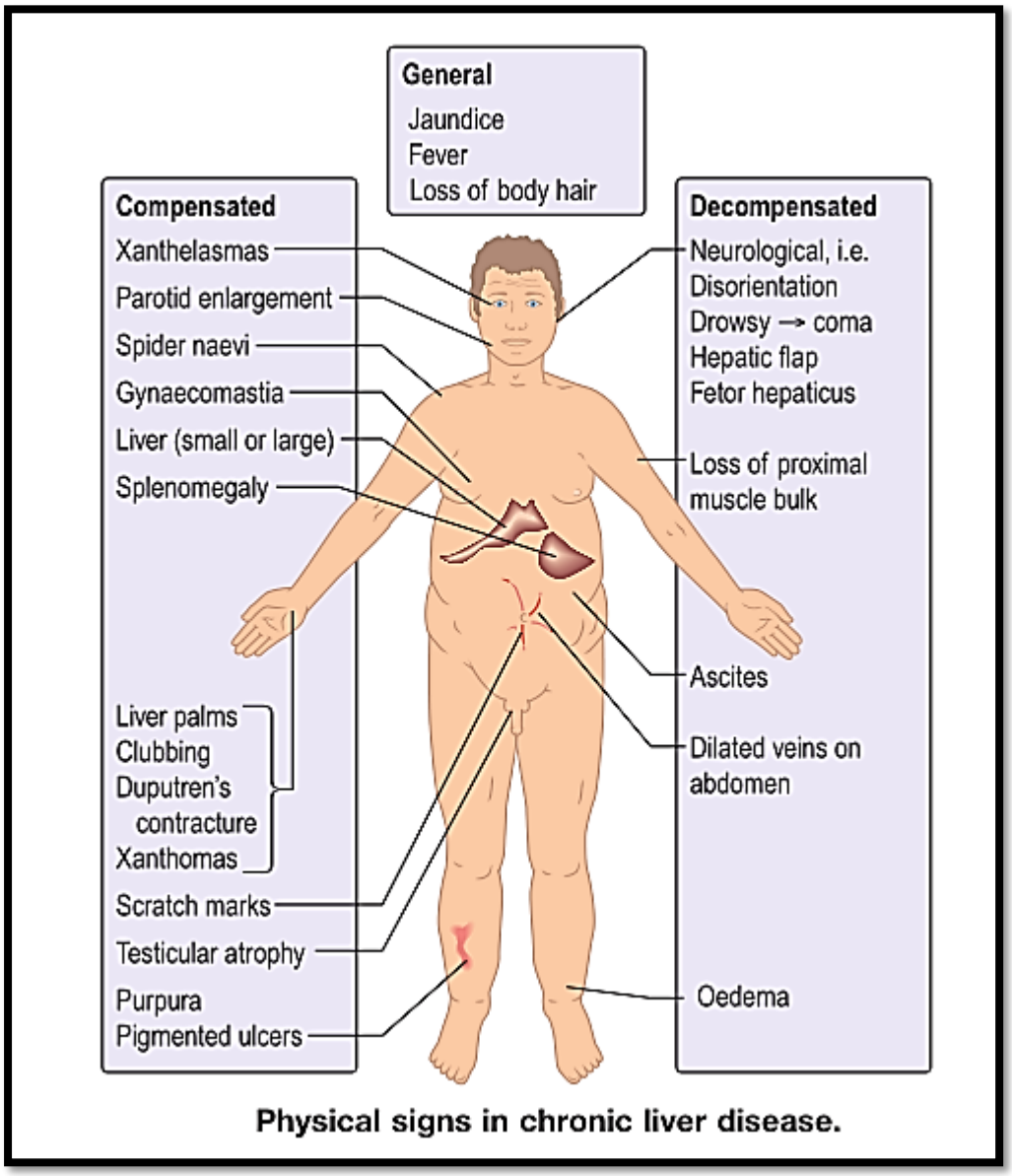
ACUTE LIVER DISEASE

- There may be few signs apart from jaundice and an enlarged liver.
- Jaundice is a yellow coloration of the skin and mucous membranes and is best seen in the conjunctivae and sclerae.
- In the cholestatic phase of the illness, pale stools and dark urine are present.
- Spider naevi and palmar erythema usually indicated chronic disease but they can occur in severe acute disease.

CHRONIC LIVER DISEASE

- The physical signs include:
  - Skin
    - The chest and upper body may show spider naevi. These are telangiectasia (widened venules) that consist of a central arteriole with radiating small vessels. They are found in the distribution of the superior vena cava (i.e. above the nipple line)- commonly more than five is taken as diagnostic. They are also found in pregnancy.
    - In hemochromatosis the skin may have a slate-grey appearance.
    - The hands may show palmar erythema, which is a nonspecific change indicative of hyper-dynamic circulation, i.e. it is also seen in pregnancy, thyrotoxicosis or rheumatoid arthritis.
    - Clubbing occasionally occurs and a Dupuytren's contracture is often seen in alcoholic cirrhosis.
    - Xanthomas (cholesterol deposits) are seen in the palmar creases or above the eye in primary biliary cirrhosis.
  - Abdomen:
    - Initially hepatomegaly will be followed by a small liver in well-established cirrhosis.
    - Splenomegaly is seen with portal hypertension.
  - Endocrine system:
    - Gynecomastia (usually unilateral) and testicular atrophy may be found in males. The cause of gynecomastia is complex but it is probably related to altered estrogen metabolism or to treatment with spironolactone.

- In decompensated cirrhosis, additional signs include:
  - Neurological (Hepatic encephalopathy) i.e. disorientation, drowsy➔ coma, hepatic flap, fetor hepaticus (also known as breath of the dead or hepatic fetor, a condition seen in portal hypertension where portosystemic shunting allows thiols to pass directly into the lungs, the breath becomes strong and musty)
  - Ascites
  - Edema
  - Loss of proximal muscle bulk
  - Dilated veins on abdomen



Physical signs in chronic liver disease.

- Sometimes the physical examination is sometimes normal in patients with advanced chronic liver disease.
- Additional signs of acute and chronic liver disease include:
  - Hepatomegaly: a smooth tender liver is seen in hepatitis and with extrahepatic obstruction but a knobby irregular liver suggests metastases.
  - Splenomegaly: indicates portal hypertension in patients when signs of chronic liver disease are present. The spleen can also be "tipped" occasionally in viral hepatitis.
  - Ascites: this is found in cirrhosis but can also be due to carcinoma (particularly ovarian) and many other causes.
- A palpable gall bladder occurs with a carcinoma of the pancreas obstructing the bile duct.
- Generalized lymphadenopathy suggests a lymphoma.
- Cold sores are seen with a herpes simplex virus hepatitis.

EXAMINATION OF THE LIVER

- Size: normal size is 12cm. Upper border defined by percussion which is normally at the 5th intercostal space and lower border below the costal margin in the midclavicular space.
- Edge: regular or irregular
- Surface: smooth or nodular
- Consistency- hard or soft or firm
- Pulsatile or not
- Bruit- present or not and position
- If a mass is identified within the liver, define its margins, is it fluctuant?

LABORATORY EVALUATION

- These tests used to determine the following: if the liver disease is primary or secondary, due to parenchymal or extrahepatic biliary obstruction and how progressed the disease has become.
- Due to large reserve, test may be normal in early liver disease
- Liver synthetic function tests: Albumin, bilirubin, PT/PTT
  - Albumin: this is a marker for liver protein synthesis. It decreases in chronic liver disease.
  - Bilirubin: This is a product of heme metabolism in liver. Direct/conjugated bilirubin is high in obstruction. Indirect/unconjugated bilirubin is high in hemolysis and decreased conjugation by the liver.
  - Prothrombin time (PT): depends on synthesis of coagulation factors. Increased levels found in severe acute injury or chronic injury. Best guide to the prognosis in acute hepatitis. Because of its short half-life, it is a sensitive indicator of both acute and chronic liver disease. Vitamin K deficiency should be excluded as the cause of a prolonged PT by giving an intravenous bolus (10mg) of vitamin K.
    - This is the time taken by blood to clot after adding tissue thromboplastin to it.
    - Normal prothrombin time= 11-16s.
    - It is a marker of the extrinsic pathway.
    - Since PT varies in different laboratories depending upon the thromboplastin used in the assay, the international normalized ratio (INR) was developed to standardize anticoagulation with coumarin derivatives but is very variable in liver disease.
  - Partial thromboplastin time/activated partial thromboplastin time: this is the time taken for blood to clot after adding an activator such as phospholipid along with calcium to it.
    - Normal PTT = 40s
    - It is a marker of the intrinsic pathway.
- Inflammatory/injury tests (liver enzymes): AST/ ALT
  - These are intracellular enzymes released secondary to necrosis/inflammation.
  - AST is primarily a mitochondrial enzyme (80%, 20% in cytoplasm)
  - ALT is a cytosol enzyme more specific to the liver so that a rise only occurs with liver disease.

  - ALT is more specific for the liver than AST (also found in heart, skeletal muscles, brain and kidney).
  - ALT> AST more likely viral hepatitis or fatty liver.
  - AST: ALT > 2.1 suggests alcoholic hepatitis
  - Increased LDH suggests ischemic or toxic hepatitis.
- Alkaline phosphatase: Enzyme bound in hepatic canicular and sinusoidal membrane. Also in bone and intestines. If from liver GGT (Gamma glutamyl transferase, a microsomal enzyme present in the liver and many other tissues) will also be increased. High alkaline phosphatase is seen in biliary obstruction or intrahepatic cholestasis.
- Viral markers: can be used to detect multiple viral diseases especially hepatitis viruses.
- Urine tests- for bilirubin and urobilinogen
- Alpha 1 antitrypsin- a deficiency of this enzyme can produce cirrhosis
- Alpha fetoprotein- this is normally produced by the fetal liver, its reappearance in increasing and high concentrations in adults indicates hepatocellular carcinoma. Increased concentrations in pregnancy in blood and amniotic fluid suggests fetal neural tube defects. Blood levels are also slightly raised with regenerative liver tissue in patients with hepatitis, chronic liver disease and also in teratomas.
- Imaging technique- to define gross anatomy
  - Ultrasound
  - Abdominal X-ray
  - Upper GI endoscopy
  - CT scan
  - MRI
- Liver biopsy- for histology

PATTERNS OF LIVER INJURY

- Hepatocellular: marked increase in AST and ALT +/- increased bilirubin (indirect ++) in severe forms. AST and ALT >1, 000 is indicative of severe viral hepatitis, acetaminophen toxicity or ischemic hepatitis
- Cholestasis: increased alkaline phosphatase and direct bilirubin +/- mild increases in AST and ALT
- Jaundice: a clinical sign when bilirubin levels are high >2.5 mg/dl, if hyperbilirubinemia is conjugated, should see increase in urine bilirubin.

- Fulminant liver failure: high AST/ALT, alkaline phosphatase, bilirubin, PT with hepatic encephalopathy

TYPES OF LIVER INJURY

Pre-haptic causes	Hepatic causes	Post-hepatic (biliary origin)
• Falciparum malaria • Hemolytic uremic syndrome • Sepsis • Pneumococcal pneumonia • Sickle cell disease	• Viral hepatitis • Alcoholic hepatitis • Vascular hepatitis • Toxin-induced hepatitis • Genetic causes of liver disease: ➢ Hemochromatosis ➢ Wilson's disease	• Primary biliary cirrhosis

HEPATITIS

- This is inflammation of the liver due to viral, toxic, pharmacologic or immune mediated damage to the liver.
- Hepatocellular necrosis and inflammatory cell infiltration of the liver are common pathologic features.
- There are 2 types of hepatitis:
  - Acute hepatitis: lasts for about 6 months or less.
  - Chronic hepatitis: sustained inflammatory response for over 6 months.

HEPATITIS

- Ranges from asymptomatic to fulminant liver failure.
- When encephalopathy is seen within 8 weeks the prognosis is poor.

ETIOLOGY

- Viral: hepatitis A, E, G, EBV and CMV viruses. (note even B, C, and D have the propensity to cause acute hepatitis but most often cause chronic hepatitis)
- Toxins: amanita phylloides in mushroom poisoning, carbon tetrachloride.
- Drugs: acetaminophen, Isoniazide, halothane, chlorpromazine, erythromycin, heavy alcohol intake.
- Others: Wilson's disease, herbs.

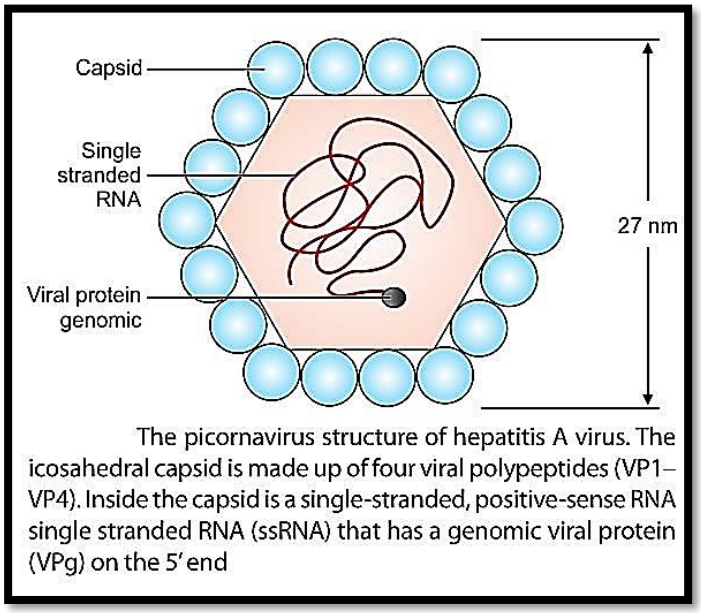
VIRAL HEPATITIS

- Viral hepatitis is the most common form of acute hepatitis.
- Viral hepatitis can be self-limiting or can progress to fibrosis, cirrhosis or liver cancer.
- Most of viral hepatitis cases are caused by one of the following:
  - Hepatitis A (HAV) virus (infectious hepatitis)
  - Hepatitis B (HBV) virus (serum hepatitis)
  - Hepatitis C (HCV) virus (was the most common cause of post-transfusion hepatitis)
  - Hepatitis D (HDV) virus (defective virus dependent on co infection with HBV)
  - Hepatitis E virus (HEV) (enterically transmitted hepatitis)
- Note: acute viral hepatitis is caused by hepatitis viruses HAV, HEV and HGV (non A, non B virus) all of which are RNA viruses (remember HBV, HCV and HDV have propensity to cause acute viral hepatitis but are more associated with chronic hepatitis, HBV is a DNA virus).

- HDV is an incomplete RNA virus and requires the presence of HBV to cause infection, thus it causes hepatitis when HDV infection occurs at the same time as HBV infection (HDV co-infection) or in patients with chronic hepatitis B infection (super infection- it may present as an acute infection superimposed on a chronic infection).
  - Superinfection is much more severe than co-infection.
- Type A and E are typically caused by ingestion of contaminated food or water.
- Hepatitis B, C and D usually occur as a result of parenteral contact with infected body fluids.
- Clinical features:
  - Swelling and tenderness of the liver
  - Jaundice, fever, nausea, vomiting, anorexia and dark urine.
  - Transaminase, alkaline phosphatase levels increase.

HEPATITIS A

- This is a non-enveloped (naked) single stranded positive sense linear RNA virus with icosahedral symmetry belonging to the picornavirus family.
- Although it was first provisionally classified as enterovirus 72. It is now assigned to the genus hepatovirus.
- It has only one known serotype.
- The Virus resists inactivation and is stable at -20°C with low pH.
- Its genome is divided into 3 coding regions:
  - P1 region which encodes structural proteins.
  - P2 and P3 which encodes non-structural proteins.



The picornavirus structure of hepatitis A virus. The icosahedral capsid is made up of four viral polypeptides (VP1–VP4). Inside the capsid is a single-stranded, positive-sense RNA single stranded RNA (ssRNA) that has a genomic viral protein (VPg) on the 5′ end

PATHOGENESIS

- It is transmitted via the fecal-oral route.
  - The largest known modern epidemic of HAV was from consumption of contaminated seafood as well following consumption of contaminated lettuce, ice slush beverages, frozen strawberries and salad food items.
  - The virus is hardy, surviving on human hands and inanimate objects (fomites).

- Incubation period is 2-6 weeks (on average 30 days).
- HAV is ingested and probably enters the bloodstream (viremia) through the oropharynx or the epithelial lining of the intestines to reach its target, the parenchymal cells of the liver.
  - It interacts with α-macroglobulin receptors on target cells (liver cells and a few other cell types on enteric mucosa).
- The response to replication in the liver is followed by lymphoid infiltration, necrosis of the liver parenchymal cell and proliferation of Kupffer cells.
- The virus is produced in these cells and is released into bile and from the stool.
- The virus is shed in large quantity into the stool approximately 10 days (1-2 weeks) before symptoms of jaundice appear or antibody can be detected.
- There is no chronic carrier stage. Except in rare instances of acute hepatic necrosis, the infection is cleared and the liver damage is reversed.

CLINICAL FEATURES

- Disease in children is generally milder than in adults and is usually asymptomatic.
- The clinical disease has 2 stages:
  - Prodromal or preicteric stage: onset may be acute with fever, malaise, anorexia, nausea, arthralgia (joint pain), myalgia, upper respiratory symptoms, vomiting and liver tenderness. Patients will have aversion to smell of food and cigarette with mild fever and flu-like symptoms.
  - Icteric or jaundice stage: 1-2 weeks dark urine and pale stool is common in cholestasis, jaundice, mild pruritus (itch) and slight liver enlargement (hepatomegaly +/- splenomegaly), lymphadenopathy (less likely to occur if patient is <30 years) and tenderness (right upper quadrant pain).
    - The hyperbilirubinemia is due to both conjugated and unconjugated bilirubin. Damage to the bile ductules causes conjugated bile to leak into the blood while damage to the hepatocytes renders conjugation in the liver inefficient resulting in a rise in unconjugated bilirubin.
- Recovery is slow over a period of 4-6 weeks.

INVESTIGATIONS

Note: to convert mg/dl to µmol/L multiply by 17.1

- Liver enzymes: damage to hepatocytes causes release of intracellular enzymes like AST and ALT. Normal levels range between 0-35U/L. In acute hepatitis. They often rise to 20 fold or more. In viral hepatitis ALT rises more than AST.
- Serum bilirubin usually peaks after transaminase levels but usually remains less than 10mg/dl. Normal levels range between 0.3 and 1mg/dl (5.1-17.1 µmol/L). When levels go above 2.5-3.0mg/dl (42.8-51.3 µmol/L) jaundice appears (Called icteric hepatitis).
- Alkaline phosphatase: may be increased by about 3 fold except in cholestatic hepatitis, in which the increment is very much higher.
- Full blood count: leucopenia with atypical lymphocytes (relative lymphocytosis) is common.
- Serology: Diagnosis requires the presence of serum HAV IgM.
  - IgM antibodies present for 3-6 months after onset of symptoms.
  - IgG is not diagnostic. IgG is an indication of recovery or immunization (vaccination).
  - IgG confers lifelong immunity.

TREATMENT

- Alcohol should be avoided until serum transaminases normalize.
- Supportive:
  - Rest to limit fatigue
  - Maintain hydration
  - Adequate dietary intake (adequate nutrition)
  - Vitamin supplementation has no proven value but vitamin K can be given if there is prolonged cholestasis.
  - Metoclopramide (plasil) for nausea.
    - More than 60kg: 10mg PO daily in 3 divided doses (when administered by slow intravenous injection to be given over at least 3 minutes)
    - Less than 60kg: 500micrograms/kg PO daily in 3 divided doses (when given as slow intravenous injection to be given over at least 3 minutes)
- Admission:
  - Patients with severe nausea and vomiting
  - Patients with deteriorating liver function, especially those with encephalopathy or prolonged prothrombin time.

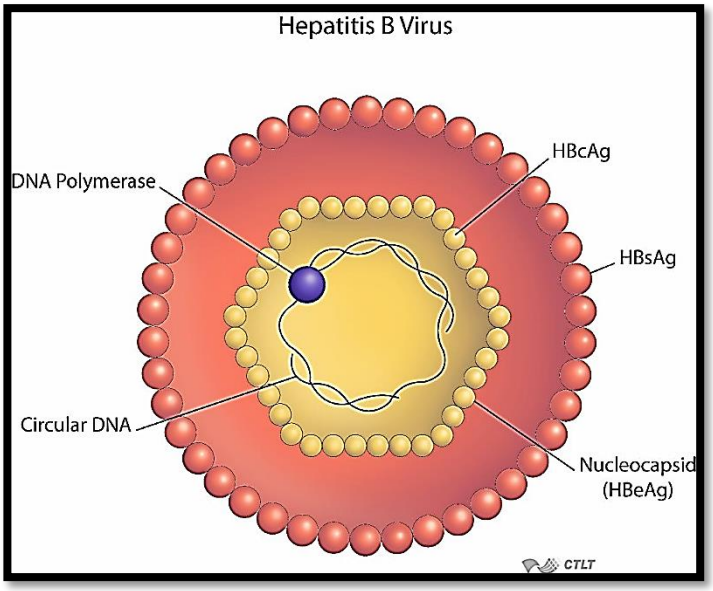
- In general, HAV may be regarded as non-infectious after 2-3 weeks.
- It usually resolves in 2-6 weeks.

PROPHYLAXIS

- Good hygiene.
- For close contracts of HAV infected people:
  - Immune serum globulin (IgG) as soon as possible but no later than 6 weeks after exposure. Manufactured immune serum globulin (ISG) is protective if given before or during incubation period of disease. When clinical symptoms have appeared ISG administration is not indicated as the person is already producing antibodies. ISG should be administered to household and intimate contacts of hepatitis A patient, those in contact with food handled by HAV infected people.
  - Active immunization: Formalin-killed HAV grown in human cells. Induces antibody titers similar to those of wild type virus Infection. Two doses are given at 6 and 12 months apart.

HEPATITIS B

- This is the most widespread and most important type of viral hepatitis. It can cause both acute and chronic disease.
- It infects the liver and to a lesser extent the kidneys and pancreas of only humans and chimpanzees.
- HBV is an encapsulated DNA virus with circular double stranded DNA belonging to the Hepadnaviridae family.
- The nucleocapsid encloses the viral genome consisting of 2 linear strands of DNA held in circular configuration. 1 strand (the plus strand) is incomplete so that DNA appears partially double stranded and partially single stranded. Viral DNA polymerase is associated with the plus strand. It has both DNA-Dependent polymerase as well as RNA dependent reverse transcriptase functions.



- Although it is a DNA virus, it encodes a reverse transcriptase and replicates through an RNA intermediate. This polymerase can repair the gap in the plus strand and render the genome fully double stranded.
- The complete HBV consists of several antigenetically distinct components including:
  - a surface coat (Hepatitis B surface antigen- HBsAg) and
  - a core of circular DNA, DNA polymerase, hepatitis B core antigen (HBcAg) and hepatitis B envelope antigen (HBeAg)
- The HBsAg is expressed on the surface of the virion. It is encoded by the S region of DNA. The body's immune response produces antibodies against these antigens. Antibodies against HBsAg are called anti-HBs.
  - HBsAg appears 1-2 weeks (late to 11-12 weeks) after exposure and persists for 1-6 weeks (even 5 months) in acute hepatitis B.
  - In chronic patients/carriers HBsAg persists many years.
  - HBsAg can be found in body fluids: saliva, urine, semen, tears, sweat and breast milk.
  - It has 10 subtypes with the major being adr, adw, ayr and ayw.

  - Anti-HBs appear after HBsAg disappear several weeks (or months) anti-HBs the protective antibody, can persist for many years.
- The HBcAg is expressed on the core. HBcAg can be found in the nuclei of liver cells, no free HBcAg in serum. HBcAG is the marker of replication of HBV.
  - The stage in which both HBsAg and Anti HBs levels are equal in blood and so they both cannot be detected is called the window period (Anti-HBc is then used).
  - Anti-HBc IgM is a marker of acute infection and acute attack of chronic infection of HBV.
  - Anti-HBc IgG is a marker of past infection, high titer means low levels of replication of HBV, it is important in disease resolution. It does not develop in response to vaccine.
- The HBeAg is a soluble non-particulate nucleocapsid protein. It is a reliable indicator of active replication of HBV. Anti-HBe is a marker of reduced infectivity. If it exists long, it may be a marker of integration of HBV into the liver cells.

- The main antigens that induce antibodies include HBsAg, HBcAg and HBeAg.
- With the exception of HBcAg all other antigens and antibodies together with the viral DNA polymerase can be detected in the blood at various times after infection and are referred to as "markers"
  - HBcAg is readily detectably only in the hepatocyte nuclei.
- HBsAg stimulates protective antibodies and is a marker for current infection
- HBcAg localized within the liver cells indicates acute infection, anti-HBcAg persists for life and is a marker of past infection.
  - Anti-HBc IgM is a marker of acute infection and acute attack of chronic infection of HBV
  - Anti-HBc IgG is a marker of past infection. High titers indicate low levels of replication
- HBeAg is a marker of active replication and infectivity.
  - Anti-HBe is a marker of reduced infectivity

PATHOGENESIS

- Transmissions occurs parenterally via blood, saliva, menstrual and vaginal discharges, semen and breast milk as well as through sexual contact. It can also occur perinatally from mother to child.
  - HBV is found in highest concentrations in blood and in lower concentrations in other body fluids (e.g. semen, vaginal secretion and wound exudates)
- The incubation period is 6weeks to 6 months.
- The factors determining the clinical manifestations of acute hepatitis B are largely unknown however some appear to involve immunologic response of host (cell mediated and humoral immunity)
- Antibody to HBsAg is protective and associated with resolution of disease.
- Defects in cellular immunity results in high incidence of chronic infection.
- Chronic infection leads to progressive fibrosis and cirrhosis.
- HBV infection may not cause hepatitis but may lead to carrier state.
- There are 2 types of carriers:
  - Super carriers: they have HBeAg, high titers of HBsAg and DNA polymerase in their blood. HBV may also be demonstrated in blood. Very minute amount of serum or blood can transmit infection.
  - Simple carriers: these are more common types of carriers who have low titer of HBsAg in blood with negative HBeAg, HBV and DNA polymerase. They transmit the infection only when large volumes of blood are transferred as in blood transfusion.

CLINICAL MANIFESTATION

ACUTE INFECTION

- Preicteric phase: long incubation (1-6 months) and an insidious onset. Symptoms include arthralgia, urticaria, fever, malaise, anorexia, vomiting, abdominal discomfort, chills, joint pain, cholestasis in some patients (clay-colored stool).
  - Arthritis and urticarial may be present particularly in HBV which are attributed to immune complex deposition.
- Icteric phase: jaundice, dark urine, pale stool. Right upper quadrant pain, hepato ± splenomegaly
- Convalescent (recovery) phase: 90-95% of adults with acute HBV recover within 1-2 months of onset and eliminate the virus from the body within about 6 months, remaining immune thereafter.

CHRONIC INFECTION

- 1-10% remain chronically infected.
- There may be asymptomatic carriers or may progress to recurrent or chronic liver disease or cirrhosis.
- A few of them develop hepatocellular carcinoma after many decades.
- Fulminant hepatitis leading to liver necrosis and death develops in less than 1% of the cases.

DIAGNOSIS

- Liver enzymes: increase in AST and ALT. Normal range between 0 to 35U/L. In acute hepatitis, they often rise to 20 fold or more. The rise in ALT is greater than that in AST.
- Serum bilirubin: normal levels between 0.3 to 1mg/dl when levels go above 2.5-3.0mg/dl jaundice appears (called icteric hepatitis)
- Alkaline phosphatase: may increase about 3 fold except in cholestatic hepatitis when rise is much higher.
- Full blood count: leucopenia with atypical lymphocytes (relative lymphocytosis) is common.
- Serodiagnosis: Serodiagnosis involves antigen/antibody detection.
  - Diagnosis of HBV
    - Antigens
      - HBsAg- First marker to appear (2-6 weeks), usually cleared within 3 months. It may persist in some patients for 6 months to one year without complications. Its clearance from the blood precedes the appearance of anti-HBs antibody with a time gap in between (known as the window period) during which the only evidence of HBV infection may be anti-HBc antibody.
      - HBeAg- indicates HBV replication and high chance of infectivity to others
    - Antibodies
      - Anti HBs antibody- confers long term immunity
      - Anti HBc- IgM indicates recent infection, IgG indicates remote infection, do not provide immunity.
      - Anti HBe- active infection, do not provide immunity.

- Incubation: HBs Ag and HBeAg present and neither is detectable (=infective)
- Acute infection: HBs Ag, HBc IgM, HBc IgG, HBe Ag (=infective), ↑↑ LFTs
- Chronic infection: HBs Ag, HBc IgG, ↑LFTs. Sometimes HBe Ag (=infective), HBc IgM (acute insult)
- Recovered: Hbs Ag, HBc IgG
- Vaccinated: HBs Ig

TREATMENT

- For acute infection there is no specific medication. Treatment is supportive (high caloric diet is desirable).
- HBV antibodies may be administered with a week of exposure and to newborn infants with HBs Ag positive mothers.
- Acute infection:
  - Alcohol should be avoided until serum transaminases normalize.
  - Supportive:
    - Rest to limit fatigue
    - Maintain hydration
    - Adequate dietary intake (adequate nutrition)
    - Vitamin supplementation has no proven value but vitamin K can be given if there is prolonged cholestasis.
    - Metoclopramide (plasil) for nausea.
      - More than 60kg: 10mg PO daily in 3 divided doses (when administered by slow intravenous injection to be given over at least 3 minutes)
      - Less than 60kg: 500micrograms/kg PO daily in 3 divided doses (when given as slow intravenous injection to be given over at least 3 minutes)
  - Admission:
    - Patients with severe nausea and vomiting
    - Patients with deteriorating liver function, especially those with encephalopathy or prolonged prothrombin time.
  - Lamivudine (3TC), tenofovir (TDF/TAF), or entecavir can be used if acute liver failure develops in acute HBV.

- Chronic infection:
  - Advice and support:
    - Avoid alcohol
    - Prevent transmission: avoid unprotected sex and toothbrush sharing
  - Monitoring for complications:
    - Hepatocellular carcinoma screening: 6 monthly Ultrasound and AFP in hepatitis B cirrhosis
    - Cirrhosis detection: 2-yearly
    - Varices detection: 3 yearly
  - Medication
    - Overview
      - Start treatment if LFTs changes, HBV DNA rises or cirrhosis develops
      - Rarely cures but lower complications risk
      - Aims for seroconversion from HBe Ag positive to negative and HBe Ab negative to positive
    - Options
      - Lamivudine, Tenofovir or entecavir: PO once-daily until 6 months after seroconversion
      - Peginterferon alpha 2a, subcutaneous once weekly for 48weeks.

PROPHYLAXIS

- HBV vaccine
  - Contains Recombinant inactive HBsAg
  - Indications: sexual and household contacts, children of affected mothers, men who have sex with men, HIV positive individuals, healthcare workers, and those with chronic liver disease.
  - Efficacy ranges from 80-100%
  - Duration of immunity 20 or more years
  - Immunologic memory established following vaccination
  - Dose of HBV vaccine: 3 dose series (0, 1, 6 months) or for the new vaccines 1 month apart.
    - 2.5µg for <11 years (when mother is HBsAg negative)
    - 5 µg for 11-19 year and children <11 years born to HBsAg positive mother
    - 10 µg for immunocompetent adults.

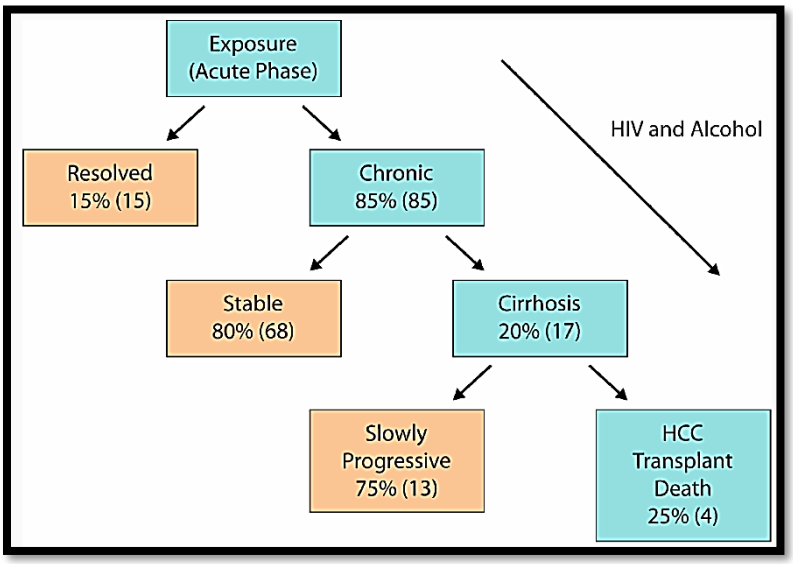
- Post-exposure prophylaxis within 48hours, even if already immunized. May be given to healthcare workers, babes or sexual contacts. Add HBV Ig (HBIG) if non-immune.

HEPATITIS C

- HCV resembles Flaviviruses in structure and organization.
- It is a linear single stranded positive sense RNA genome enclosed within an envelope, carrying glycoprotein spikes and E1 + E2 envelope glycoproteins.
- It consists of 6 genotypes.
- It replicates in liver cells, lymphocytes and monocytes.
- The virus mutates rapidly (error prone RNA polymerase) and it also down regulates stimulatory receptors on NK cells as well as increasing inhibitory receptors on NK and CD8+ killer cells.
- In addition to this the virus produces TGF-beta which blocks activation of T-cells and inhibits production of IFN-gamma.
- HCV disease is mainly immune mediated. Cytokines cause inflammation in HCV infection.
- There is no cure for hepatitis C.
- Transmission is through:
  - Intravenous drug uses
  - Contaminated equipment
  - Perinatal
  - Sexual
  - Blood transfusions and other blood products although blood is now routinely checked for HCV

CLINICAL FEATURES

- Incubation period is 15 to 60 days.
- HCV causes 3 type:
  - Acute hepatitis with resolution of infection and recovery in 15% of cases.
  - Chronic hepatitis infection with possible progression to disease much later in life-85%
  - Severe rapid progression to cirrhosis in 20% patients- many patients develop cirrhosis and are at high risk of hepatocellular carcinoma (25%) decades later.



DIAGNOSIS

- 60-70% of persons newly infected with HCV typically are usually asymptomatic or have a mild clinical illness.
- HCV RNA can be detected in blood within 1-3 weeks after exposure.
- The average time for exposure to antibody to HCV (anti-HCV) seroconversion is 8-9 weeks. Anti-HCV can be detected in more than 97% of persons by 6 months after exposure.

TREATMENT AND PROPHYLAXIS

- Screening of blood and blood products prior to transfusion.
- No specific active or passive immunizing agent is available.
- Treatment:
  - Recombinant interferon-alpha alone or with ribavirin
  - Goals in treatment of chronic HCV infection
    - Achieve sustained eradication of HCV: persistent absence of HCV RNA in serum 6 months or more after completing antiviral treatment.
    - Preventing progression to cirrhosis, hepatocellular carcinoma (HCC) and decompensated liver disease requiring liver transplantation.

HEPATITIS D

- This is also known as a delta virus. It is a single stranded negative sense circular RNA virus structurally unrelated to the other hepatitis viruses.
- HDV is an incomplete virus that requires the helper of HBV to replicate and only occurs among people infected with HBV.

PATHOGENESIS

- Its mode of transmission is the same as HBV. It is spread through blood, semen and vaginal secretion. It can replicate and cause disease only in people with active HBV infections.
- The virus uses HBsAg for transmission and assembly.
- Replication of HDV is complex and unique.
- Transcription and replication of HDV occurs in the nucleus using host cell RNA polymerase.
- Types of infection:
  - Co-infection: HDV + HBV are transmitted together at the same time.
  - Super-infection: HBV infection and then HDV infection. No association with hepatocellular carcinoma.

DIAGNOSIS

- Detecting presence of Delta antigens and antibodies (ELISA and radioimmunoassay).

TREATMENT AND PROPHYLAXIS

- No specific treatment
- Vaccination against HBV covers HDV infection

HEPATITIS E

- This is a spherical non-enveloped single stranded positive sense RNA virus belonging to the genus Hepevirus.
- HEV usually results in an acute infection. It does not lead to a chronic infection.
- It is transmitted through fecal oral route and outbreaks are usually associated with contaminated water supplies in countries with poor sanitation.
- Symptoms similar to HAV: abdominal pain, anorexia, dark urine, fever, hepatomegaly, nausea, vomiting, malaise and jaundice.

- HEV infection is especially serious in pregnant women and during pregnancy may cause a high rate of abortion, intrauterine death and increased perinatal mortality in babies born to women with fulminant hepatitis.

DIAGNOSIS

- Serology
  - IgM or IgG in serum (mainly IgM because there is no chronic stage)
- PCR for HEV RNA

TREATMENT AND PROPHYLAXIS

- No specific treatment
- ISG (immune serum globulin) does not provide any protection
- Safe hygiene measures reduce risks of transmission (washing with soap)
- Good sanitation

HEPATITIS G

- Resembles HCV (flavivirus), enveloped positive sense RNA.
- Transmitted through blood and blood products
- Role in human disease is currently uncertain but it is associated with chronic hepatitis disease.
- HGV and HIV infection may prolong survival of AIDS patient HGV may inhibit HIV replication.
- HGV frequently results in chronic viremia.
- May be associated with acute, fulminant and chronic hepatitis.
- It often subsides after several years and anti HG env antibody develops.
- Diagnosis:
  - PCR to detect HGV
  - Immunoassay to detect anti-HG env antibodies (Serum HGV RNA indicate viremia and anti-HG env is associated with recovery).

FEATURE	HAV	HBV	HCV	HDV	HEV
FAMILY	Picornavirus (Hepatovirus) (naked)	Hepadnavirus (encapsulate)	Flavivirus (Enveloped)	Delta virus (naked)	Hepevirus (naked)
GENOME	SS (+) RNA linear	Circular dsDNA	SS (+) RNA linear	SS (-) RNA circular	SS (+) RNA
ONSET	Acute	Often insidious	Insidious	Acute on chronic	Acute
AGE PREFERENCE	Children, young adults	Any age	Any age but more common in adults	Any age	Children, young adults
TRANSMISSION	Fecal oral	Parenteral	Parenteral	Parenteral	Fecal oral
SEVERITY	Mild	Often severe	Variable	Often severe with superinfection	Mild, but severe in pregnancy
PROGNOSIS	Generally good	Worse with age, debility	Moderate	Worse with age, debility	Fair
CHRONICITY	None	Occasional (5 to 10%)	Frequent (65-85%)	Occasional	None
PROPHYLAXIS	Immunoglobulin/ HAV vaccine	Standard Ig, HBIg, HB vaccine	None	Protection against HBV	None
CARRIER	None	0.1 to 30%	Exists but prevalence unknown	None	None

COMPLICATIONS

(1) Cholestatic hepatitis

- Occurs mostly with HAV and HEV infection
- Self-limited
- Pruritus is a common symptom
- Marked conjugated hyperbilirubinemia presenting with dark urine and pale stool
- Increased alkaline phosphatase

(2) Fulminant hepatitis

- About 1% cases
- Defined as the onset of encephalopathy occurring within 8 weeks in a patient with acute liver disease
- Associated with massive hepatocellular necrosis
- Commonly follows HAV, HBV (usually superinfection of HBV infection by HDV), HCV and HEV (in pregnancy)

(3) Chronic hepatitis

- Occurs in HBV and HCV infection
- Manifests with persistently increased AST and ALT for over 6 months
- Slowly resolving HBV infection may persist for 6-12 months with eventual complete resolution
- Persistent HBV infection (persistence of HBsAg) without evidence of liver damage resulting in asymptomatic or 'healthy' HBV carriers.

HEPATITIS DUE TO OTHER INFECTIOUS AGENTS

- Abnormal liver biochemistry is frequently found in a number of acute infections. The abnormalities are usually mild and have no clinical significance.
- Infectious mononucleosis: This is due to Epstein-Barr virus (EBV). Mild jaundice associated with minor abnormalities of liver biochemistry is extremely common but 'clinical' hepatitis is rare. Hepatic histological changes occur within 5 days of onset, the sinusoids and portal tracts are infiltrated with large mononuclear cells but the liver architecture is preserved. A Paul-Bunnell or Mono-spot test is usually positive, and atypical lymphocytes are present in the peripheral blood. Treatment is symptomatic.
- Cytomegalovirus (CMV): This can cause acute hepatitis, usually a glandular fever type syndrome in healthy individuals but is more severe in those with an impaired immune response. Only the latter need treatment with valganciclovir or ganciclovir. CMV DNA is positive in blood; CMV IgM is also positive but there are false-positive reactions. The liver biopsy shows intranuclear inclusions and giant cells.
- Herpes simplex: Very occasionally the herpes simplex virus causes a generalized acute infection, particularly in the immunosuppressed and occasionally in pregnancy. Aminotransferases are usually massively elevated. Liver biopsy shows extensive necrosis. Acyclovir is used for treatment.
- Toxoplasmosis: The clinical picture is similar to infectious mononucleosis, with abnormal liver biochemistry but Paul-Bunnell test is negative.
- Yellow fever: This viral infection is carried by the mosquito *Aedes aegypti* and can cause acute hepatic necrosis. There is no specific treatment.

AUTOIMMUNE HEPATITIS

- Autoimmune hepatitis is most frequent in women
- It has 2 types
  - Type 1: associated with other autoimmune disease e.g. pernicious anemia, thyroiditis, coeliac disease and Coomb's positive hemolytic anemia.
  - Type 2: not associated with other autoimmune diseases

- Pathogenesis unknown but though to occur in genetically predisposed people in response to environmental agents e.g. a virus that causes a sequence of T cell mediated events against liver antigens, producing a progressive necroinflammatory process which results in fibrosis and cirrhosis.
- Clinical features:
  - 2 peak presentations
  - In peri- and post-menopausal group, patients may be asymptomatic or present with fatigue, the disease being discovered by abnormalities in liver biochemistry or because of signs of chronic liver disease on routine examination.
  - In teens and early 20s the disease (often type II) presents as an acute hepatitis with jaundice and very high aminotransferases which do not improve with time. Clinical features in this age group: hepatosplenomegaly, cutaneous striae, acne, hirsutes, bruises and sometimes ascites.
  - An ill patient can also have features of autoimmune disease with a fever, migratory polyarthritis, glomerulonephritis, pleurisy, pulmonary infiltration or lung fibrosis.
  - There are rare overlap syndromes with primary biliary cirrhosis and primary sclerosing cholangitis existing concomitantly or developing consecutively
- Investigations:
  - Liver biochemistry: high serum aminotransferases with lesser elevations in the ALP and bilirubin. Serum gamma-globulins are high, frequently twice normal particularly the IgG.
  - Blood:
    - Mild normochromic normocytic anemia with thrombocytopenia and leucopenia even before portal hypertension and splenomegaly.
    - Prothrombin time is often high
  - Autoantibodies:
    - Type 1: anti-nuclear (ANA), Anti-smooth muscle (anti-actin), soluble liver antigen (anti SLA/LP)
    - Type 2: anti-liver/Kidney microsomal (anti-LKM1). The main target is cytochrome P450 2D6 (CYP2D6) on liver cell plasma membranes.
  - Liver biopsy: shows changes of chronic hepatitis. The amount of interface hepatitis is

variable, but tends to be high in untreated patients. Lymphoid follicles are less often seen than in HCV, and plasma cell infiltration is frequent. 1/3 of patients have cirrhosis at presentation.

- Treatment:
  - Steroids:
    - Budesonide 3mg BD or TDS (has fewer side effects than prednisolone) or
    - Prednisolone 30mg daily for at least 2 weeks followed by a slow reduction and a maintenance dose of 10-15mg daily
    - Response to steroids forms part of the diagnostic criteria for autoimmune hepatitis. 80% of cases remit with steroids and azathioprine.
  - Azathioprine should be added 1-2mg/kg daily, as a steroid sparing agent and in some patients as sole long-term maintenance therapy. Levels of thiopurine methyltransferase should be obtained.
  - Mycophenolate, cyclosporine and tacrolimus have been used in resistant cases.
  - Liver transplantation is performed if treatment fails, although the disease may recur. Hepatocellular carcinoma occurs less frequently than with viral-induced cirrhosis.

DRUG INDUCED CHRONIC HEPATITIS

- Several drugs can cause a chronic hepatitis which clinically bears many similarities to autoimmune hepatitis.
- Patients are often female, present with jaundice and hepatomegaly, have raised serum aminotransferases and globulin levels and LE cells and anti-LKM1 antibodies may be detected
- Improvement follows drug withdrawal but exacerbations can occur with drug reintroduction.
- Isoniazid, amiodarone and methotrexate can lead to chronic histological changes.
- With rare exceptions patients with pre-existing chronic liver disease are not more susceptible to drug injury.
- Chronic alcoholic liver disease can occasionally have histological appearances more like a chronic hepatitis.

ALCOHOL AND THE LIVER

- Alcohol abuse is the most common cause of liver disease.
- Patients at risk include those exceeding the critical intake threshold (80g/day in men and 20g/day in women), females, blacks, those with poor nutritional status, and those with HBV or HCV infection.
- 3 major pathologic lesions resulting from alcohol abuse and appearing as stages/spectrum of the disease are:
  - Fatty liver (Alcoholic Steatosis)
  - Acute Alcoholic hepatitis
  - Alcoholic (Laennee's) Cirrhosis
- Note: Alcoholic hepatitis is not a prerequisite to alcoholic cirrhosis.

ALCOHOLIC FATTY LIVER

- Patients may be asymptomatic or present with
  - Right upper quadrant (RUQ) pain
  - Incidentally discovered as tender hepatomegaly
  - Jaundice is rare, transaminases are mildly elevated (<5times normal)
- There is completely reversible on cessation of alcohol.

ALCOHOLIC HEPATITIS

- This is severe and prognostically ominous lesion and characterized by the following pathologic triads:
  - Mallory bodies (intracellular eosinophilic aggregates of cytokeratins) usually seen near or around nuclei.
  - Infiltration by polymorpnuclear leukocytes
  - A network of interlobular connective tissue surrounding hepatocytes and central veins (spider fibrosis)

CLINICAL MANIFESTATION

- Symptoms: Fever, Weight loss, anorexia, nausea, vomiting and abdominal pain (RUQ pain) are common presenting symptoms.
- Signs:
  - Hepatomegaly is found in 80% and splenomegaly is often present.
  - Jaundice, spider angioma/telangiectasia, parotid enlargement gynecomastia, loss of body hair, Dupuytren's contractures and palmar erythema, and testicular atrophy.
- Ascites and encephalopathy may be present and indicate severe disease.
- Full blood count strikingly elevated white blood cells (leukocytosis).

- Transaminases modestly increased (200-400IU/L).
- The ratio of AST to ALT frequently exceeds one in contrast to viral hepatitis in which the ratio is approximately one.
  - AST: ALT ratio >2:1
- Prolonged prothrombin time, hypoalbuminemia and hyperglobulinemia may be found.
- Alcoholic hepatitis can reverse with cessation of alcohol but more commonly progresses to cirrhosis.

ALCOHOLIC CIRRHOSIS

- Patients may be asymptomatic or may present with anorexia, fatigue and decreased libido.
- There is associated increased risk of variceal hemorrhage.

DIFFERENTIAL DIAGNOSIS

- Nonalcoholic fatty liver disease
- Non-alcoholic steatoheatitis
- Autoimmune hepatitis
- Viral hepatitis
- Hemochromatosis
- Alpha-1 antitrypsin deficiency
- Wilson's disease
- Toxic or drug induced hepatitis

DIAGNOSIS AND INVESTIGATIONS

- History of habitual alcohol consumption.
- Alcoholic steatosis:
  - Modest elevation of AST>ALT in a 2:1 ratio,
  - Liver biopsy shows small (microvesicular) and large (macrovesicular) fat droplets in the cytoplasm
- Alcoholic hepatitis:
  - Marked leukocytosis
  - Modest elevation of AST>ALT in a 2:1 ratio
  - Markedly elevated serum bilirubin
  - Liver biopsy shows steatosis, hepatocellular necrosis, Mallory bodies (eosinophilic hyaline deposits), ballooned hepatocytes and lobular PMN inflammatory infiltrate.
- Alcoholic cirrhosis:
  - Liver biopsy shows micro- or macronodular cirrhosis and perivenular fibrosis that is not usually seen in other types of cirrhosis.

TREATMENT

- Stop alcohol
- Alcoholic steatosis: can resolve with abstinence and improved nutrition.
- Alcoholic hepatitis:
  - Corticosteroids: improve survival when discriminant function (DF) is >32 and there are no contraindications (active GI bleeding, active infection, serum creatinine >2.3)

    - DF is a function of PT/INR and total bilirubin
    - DF= [4.6 x (patient's PT-control PT)] + serum bilirubin
    - A DF >32 predicts 1-month mortality as high as 50%.
    - If severe injury with hepatic encephalopathy patients can be treated with steroids for one month with taper.
  - Other therapies under study: Medium-chain triglycerides and pentoxifylline. Pentoxifylline has anti-TNF effects but s less effective than corticosteroids when DF is >32.
  - Long term therapy: antioxidants, S-adenosylmethionine (SAMe), silymarin, Vitamins A and E.
- Alcoholic cirrhosis: hepatic function can significantly improve with abstinence and improved nutrition
- Liver transplant is often precluded by active or recent alcohol abuse or use. Recidivism rates are high. Most transplant centers require at least 6 months of documented abstinence prior to listing for liver transplant.

NONALCOHOLIC FATTY LIVER DISEASE

- The spectrum of disease ranges from benign steatosis (Fatty liver) to steatohepatitis (hepatic inflammation).
- Disease is generally benign and indolent but can progress to cirrhosis in 15-20%.
- Nonalcoholic fatty liver disease is the third most common cause of abnormal LFTs in adult outpatients after medication and alcohol.
- Risk factors:
  - Female gender
  - Age> 45 years
  - Body mass index (BMI)>30
  - AST/ALT >1
  - Type 2 DM

CLINICAL FEATURES

- Patients are asymptomatic in >50% of cases, Symptoms:
  - Fatigue, malaise and to a lesser extent RUQ fullness or pain
- Signs:
  - Hepatomegaly is common but examination may be limited in the obese
  - Stigmata of chronic liver disease.

DIFFERENTIAL DIAGNOSIS

- Alcoholic liver disease
- Nutrition: TPN, kwashiorkor, rapid weight loss
- Drugs: Estrogens, corticosteroids, chloroquine
- Metabolic: Wilson's disease, abetalipoproteinemia
- Iatrogenic: weight reduction surgery with jejunoileal bypass, gastroplasty or small bowel resection.

DIAGNOSIS

- Diagnosis as follows:
  - Exclude causes of liver disease, specifically alcoholic liver disease
  - Aminotransmiases:
    - Typically, ALT>AST (x2-4) (vs alcoholic liver disease in which AST>ALT), poor correlation with the presence and extent of inflammation
    - Normal AST and ALT cannot exclude non-alcoholic fatty liver disease.
  - BMI is an independent predictor of the degree of hepatocellular fatty infiltration.
  - Ultrasound or CT scan
  - Liver biopsy is the gold standard. The grade of inflammation and stage of fibrosis predict disease course and response to therapeutic intervention.

TREATMENT

- Gradual weight loss. Rapid weight loss may increase inflammation and fibrosis.
- Treat hyperlipidemia and diabetes
- No FDA-approved therapy is available
- Therapeutic agents under study include metformin, rosiglitazone, urosodeoxycholic acid and vitamin E.

METABOLIC LIVER DISEASE

HEREDITARY HEMOCHROMATOSIS

- This is an autosomal-recessive disease.
- It is associated with a major mutation on the short arm of chromosome 6, the HFE genes.
- Patients have a normal life expectancy if there is no cirrhosis and the patient is adherent to treatment. Survival is lower if the patient has cirrhosis at the time of diagnosis.
- Cirrhosis with Hereditary hemochromatosis (HH) carries a high risk of hepatocellular carcinoma (200 times that of the control population).
- The condition results in decreased hepcidin synthesis resulting in increased iron absorption and increased release from erythrophagocytosis (iron levels 10 times normal).
- It results in damage to the liver, joints, anterior pituitary, pancreas, heart and thyroid.

CLINICAL FEATURES

- Symptom onset usually in middle-age for men, but 10 years later and less likely in women.
- 10-25% are often asymptomatic.
- Symptoms: arthritis (Pseudogout), skin color change, Right upper quadrant pain, symptoms of chronic liver disease (fatigue, anorexia, muscle wasting), loss of libido, impotence and dysmenorrhea, heart failure, DM.
- Signs: hepatomegaly, skin hyperpigmentation (bronze skin), stigmata of chronic liver disease, hypogonadism
- Clinical features can be remembered using A-J mnemonic:
  - A- anterior pituitary damage (hypogonadism- loss of libido, impotence, and dysmenorrhea)
  - B-bone disease: osteoporosis
  - C-chronic liver disease: hepatomegaly, cirrhosis, fatigue, anorexia, muscle wasting. Liver disease later contributes to hypogonadism
  - D-dilated or restrictive cardiomyopathy
  - E-excess iron
  - F-fatigue
  - G-grey skin - though initially may be bronze
  - H- hypothyroidism

- I-insulin decrease: Diabetes mellitus
- J-joint pain, Arthritis (Pseudogout)- due to chondrocalcinosis. Especially affects 2nd/3rd metacarpophalangeal and Proximal interphalangeal joints

DIAGNOSIS

- Iron studies:
  - Increased ferritin, increased iron, and decreased total iron binding capacity (TIBC).
  - Recall: TIBC is a proximal measure of transferrin and is decreased as most is already bound.
  - Rule out other causes of increased ferritin: inflammation (CRP), alcoholism, metabolic syndrome (BP, BM, lipids, glucose), anemia.
  - Transferrin saturation (TSAT)=$\frac{Iron}{TIBC} \times 100$
  - TSAT>45% is seen in HH and may also be raised in asymptomatic carriers.
  - If TSAT>45% and ferritin is elevated, hereditary hemochromatosis is suggested check HFE genotype.
  - A TSAT<45% and normal ferritin exclude hereditary hemochromatosis.
- HFE genotyping:
  - Homozygote is diagnostic only if (1) age <40 years, (2) ferritin <1000 and (3) transaminases are normal. Otherwise, confirmation with liver biopsy is necessary.
  - If positive, screen first degree relatives
  - If negative but suspicion remains high, consider liver MRI and/or liver biopsy to assess iron content and fibrosis.
- Liver biopsy: the best means of making a definitive diagnosis, a hepatic Prussian blue stain with iron index >1.9 is diagnostic. Also used for disease staging (influences prognosis: hepatocellular carcinoma screening is needed if the patient is cirrhotic).
- Bloods:
  - Liver function tests
  - Glucose
  - Thyroid function tests
- Imaging:
  - Liver MRI
  - Joint X-ray
  - DEXA
  - ECG

- ECHO

DIFFERENTIAL DIAGNOSIS

- Chronic liver disease: HBV, HCV, alcoholic liver disease, non-alcoholic fatty liver disease, Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis.
- Secondary iron overload disease: Homozygous alpha thalassemia, multiple previous blood transfusions.

MANAGEMENT

- Conservative treatment if normal serum ferritin and asymptomatic:
  - Lifestyle changes: avoid iron and vitamin C supplements, minimize alcohol.
  - Annual monitoring with serum ferritin and transferrin saturation
  - Hepatitis A and B vaccination.
- Iron reduction if increased serum ferritin or symptomatic:
  - Remove 1 unit (approximately 450ml) per week until ferritin is mildly low, then maintain with less frequent venesection e.g. 1 unit every 3-6 month for life. Note that this may lead to falsely low HbA1c levels.
  - Second line: iron chelation with desferrioxamine
- Screen first degree family members
- In the setting of cirrhosis, screen for hepatocellular carcinoma.
- Liver transplantation for those with decompensation.

COMPLICATIONS AND PROGNOSIS

- Normal life expectancy if no cirrhosis or diabetes at diagnosis.
- Complications:
  - Cardiomyopathy (dilated or restrictive cardiomyopathy)
  - Joint disease (chondrocalcinosis, degenerative arthritis, Pseudogout)
  - Diabetes mellitus
  - Hepatocellular carcinoma
  - Increased incidence of bacterial infection (especially *Vibrio*, *Yersinia* and *Listeria* spp)

ALPHA-1 ANTITRYPSIN DEFICENCY

- Alpha-1 antitrypsin is a serine protease inhibitor which is synthesized in the liver and controls inflammatory cascades. It protects tissues from protease-related degradation.
- In the lung, alpha 1 antitrypsin inhibits neutrophil elastase preventing breakdown of elastin and thus maintaining lung elasticity.
- The alpha -1 antitrypsin gene on chromosome 14 has 3 possible alleles:
  - M (medium)
  - S (slow)
  - Z (very slow)
- The deficiency has an autosomal-codominant transmission with the Z allele being most commonly deficient.
- Healthy individuals have an MM genotype (aka PiMM) while symptomatic individuals are usually ZZ (aka PiZZ)
- Those with MS and MZ genotypes are just carriers, while SS and SZ genotypes may cause a mild clinical picture.
- There is a high incidence of hepatocellular carcinoma in those with cirrhosis. A high prevalence of HBV and HCV markers suggests synergistic liver injury.

CLINICAL FEATURES

- Neonatal cholestasis, neonatal jaundice, occult cirrhosis, shortness of breath/dyspnea on exertion, panniculitis (inflammation of the panniculus adiposus-a layer of fat underneath the skin producing tender swellings on the thighs and breasts).
- Usually presents as early-onset COPD (age 30-50) especially if they are smokers.
- Liver disease is less common. Presents as hepatitis, cirrhosis and/or liver failure
- Examination reveals:
  - Signs of cirrhosis: spider angiomata, palmar erythema, gynecomastia
    - Abnormal alpha 1 anti-trypsin accumulates in the hepatocyte endoplasmic reticulum causing cell damage.
  - Panacinar Emphysema: clubbing, barrel chest
- Consider alpha 1 antitrypsin deficiency in any adult who presents with chronic hepatitis or cirrhosis of unclear etiology.
- Alpha 1 antitrypsin deficiency is associated with bilateral basilar pulmonary emphysema.

DIAGNOSIS

- Serum alpha-1 antitrypsin concentration: for screening, alpha-1 antitrypsin is an acute phase reactant. False positive may be obtained with inflammation (even if PiZZ)
- Serum alpha 1 antitrypsin phenotyping: the screening and diagnostic test of choice. Genotype is only needed if phenotype does not match the clinical picture.
- Screen family members
- COPDs and liver tests:
  - Chest X-ray
  - Pancreatic function tests
  - Liver function tests
  - Liver ultrasound
  - Liver biopsy: characteristic eosinophilic alpha-1 antitrypsin globules are seen in the endoplasmic reticulum of periportal hepatocytes

MANAGEMENT

- COPD:
  - Manage as usual with smoking cessation, flu and pneumococcal vaccines and stepwise medical therapy
  - Alpha-1 antitrypsin augmentation therapy: consider pooled alpha-antitrypsin from human plasma for those with at least moderate COPD. However, not recommended due to lack of strong evidence for survival benefit.
- Liver disease:
  - Prevention and monitoring for all: Hep A and B vaccine plus LFT +/- coagulation monitoring.
  - If liver disease alcohol cessation, monitoring alpha-fetoprotein and consider transplantation in liver failure.

WILSON'S DISEASE (PROGRESSIVE HEPATOLENTICULAR DEGENERATION)

- This is an uncommon autosomal recessive disease.
- It usually presents between ages 3 and 40 and is associated with mutations in the WD gene on chromosome 13.
- Decreased biliary copper excretion results in toxic copper deposition in tissues.
- Dietary copper is normally absorbed from the stomach and upper small intestine. Copper is transported to the liver loosely bound to albumin where it is incorporated into apoceruloplasmin forming ceruloplasmin a glycoprotein synthesized in the liver and secreted into the blood.
- The remaining copper is normally excreted in the bile and excreted in feces.
- Copper then deposits in various organs including the liver, basal ganglia of the brain and the cornea.

CLINICAL FEATURES

- Symptoms:
  - Presents with abnormal behavior, personality change, psychosis, tremor, dyskinesia, athropathy (Pseudogout) and jaundice.
  - Clinical presentation may be acute, subacute or chronic.
  - Organ involvement (in descending order of frequency): Hepatic, neurologic, psychiatric, hematologic, renal (Fanconi's syndrome), other (ophthalmologic, cardiac, skeletal, endocrinologic, dermatologic)
  - The mean age at onset of hepatic symptoms is 8-12 years.
- Signs:
  - Exam reveals Kayser-Fleischer rings (a greenish-brown ring on the outer edge of the cornea which is a diagnostic sign of hepatolenticular degeneration and deposition of copper in the Descemet's membrane of the cornea), icterus, slowed mentation, hypophonia and tremor
  - Clinical stigmata of cirrhosis are associated with chronic disease.

Characteristics of Wilson's disease–

ABCD

Asterixis
Basal ganglia deterioration
Ceruloplasmin ↓
Cirrhosis
Copper ↑
Carcinoma (hepatocellular)
Choreiform movements
Dementia

DIAGNOSIS

- Suspect Wilson's disease in patients 3-40 years of age with unexplained LFTs or liver disease associated with neurologic or psychiatric changes, Kayser-Fleischer rings, hemolytic anemia and a positive family history.

- Liver biochemistry:
  - Low Alkaline phosphatase
  - Marked hyperbilirubinemia
  - Modest aminotransaminase elevation (AST>ALT)
- Ceruloplasmin (CP): typically, low in Wilson's disease but a low CP is both insensitive (15% have normal CP, since CP is an acute phase reactant) and nonspecific (CP is also low in nephrotic syndrome, protein-losing enteropathy and malabsorption).
- Urinary copper excretion: high if symptomatic (100-1000 μg/24 hours, level may indicate disease severity). Normal excretion is <40 μg/24 hours.
- Liver biopsy: shows high hepatic copper concentration (>250 μg/g) may also be seen in primary biliary cirrhosis, primary sclerosing cholangitis, fibrosis or cirrhosis.
- Other: Serum copper concentration, slit lamp examination.

TREATMENT

- D-penicillamine: improvement lags 6-12 months following treatment, maintenance is typically required.
- Other: trientine, zinc, ammonium
- Liver transplantation: for acute hepatic or medically refractory Wilson's disease, reverses metabolic defect and induces copper excretion.

JAUNDICE

- Jaundice (icterus) is detectable clinically when the serum bilirubin is more than 3mg/dl (50 micromol/L).
  - In neonates it is more than 5mg/dl (85 micromol/L)

METABOLISM OF BILIRUBIN

- Bilirubin is as a result of hemolysis of RBCs.
- Recall, RBCs have the pigment hemoglobin which consists of Heme (with iron) and the globin part.
- RBCs after 120 days are broken down in the reticuloendothelial system (spleen) by macrophages.
- Hemoglobin is broken down to the heme part and the globin part.
  - The globin part is broken down to amino acids that are recycled.
  - The heme part is broken down by heme oxygenase to oxy-heme (a closed tetrapyrrolic ring with iron)
  - Oxy-heme is further converted by heme reductase to biliverdin (an open tetrapyrrolic ring without iron)
  - The iron removed from the heme binds to transferrin and is transported to the liver to be stored where it binds to ferritin.
  - Biliverdin is converted by biliverdin reductase to bilirubin
- Bilirubin is toxic to tissue therefore; it is transported to the liver as it binds to albumin.
- Bilirubin is taken up by hepatocytes at their sinusoidal surface. This uptake is very rapid.
- In the hepatocytes bilirubin is bound to cytoplasmic proteins: ligandins and Z protein.
  - Ligandins are a group of enzymes that represent 2% of cytosolic proteins
  - Z proteins bind fatty acids.
  - The primary function of these proteins is that of avoiding the reflux of free bilirubin into the blood because the time lapse between uptake of bilirubin and conjugation is relatively long.
- In the hepatocytes bilirubin is conjugated as it is bound to glucuronic acid. Conjugated bilirubin is also called Direct bilirubin, while unconjugated bilirubin is called indirect bilirubin. The enzyme important for glucuronidation is Glucuronyl transferase.
- Conjugated bilirubin is then secreted into bile which is stored and concentrated in the gall bladder.

- Bile is then secreted into the first part of the duodenum from the common bile duct.
- In the intestines bilirubin is deconjugated by bacterial/intestinal enzyme Beta-glucuronidase to form free bilirubin.
- Bilirubin is converted by bacterial dehydrogenase to urobilinogen (a colorless substance)
- The bulk of urobilinogen, bilirubin and urobilin is excreted in feces (by conversion to stercobilinogen and stercobilin which gives feces their characteristic orange-yellow color).
- Small amounts of bilirubin and urobilinogen are reabsorbed into the blood stream.
- The reabsorbed urobilinogen is excreted in the urine (about 4mg/day).
- Urobilinogen is converted to urobilin (orange-yellow pigment) by dehydrogenase

CLASSIFICATION OF JAUNDICE

- Jaundice is divided into 3 categories, depending on which part of the physiological mechanism the pathology affects:
  - Pre-hepatic/ Hemolytic jaundice:
    - Increased bilirubin load for the liver cells.
    - The pathology is occurring prior to the liver due to either an intrinsic defect of RBCs or Extrinsic causes external to RBCs.
  - Hepatic/ hepatocellular:
    - The pathology is located within the liver due to disease of parenchymal cells of liver.
  - Post-hepatic/ Cholestatic/obstructive/surgical jaundice:
    - The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage.

PRE-HEPATIC/ HEMOLYTIC JAUNDICE

- Increased breakdown of red cells leads to an increase in production of bilirubin.
  - Red blood cells have a life span of 120 days; they are broken down by the macrophages of the reticuloendothelial system (especially in the spleen)
  - Hemoglobin is split into a globin part and a heme part.
  - The globin part is a protein that is broken down to amino acids that are recycled.
  - The heme part is broken down to iron and protoporphyrin
  - The iron is recycled and stored
  - The protoporphyrin is broken down to unconjugated bilirubin

which then binds to serum albumin and is transported to the liver. In the liver bilirubin is conjugated and deposited into the bile canaliculi and eventually stored in bile in the gall bladder.

- The bile from the gall bladder is excreted into the duodenum following a meal and the conjugated bilirubin is converted by intestinal bacterial normal flora into urobilinogen (which makes stool brown) and some is partially reabsorbed and filtered by the kidneys (making urine yellow).

- The resulting jaundice from excessive breakdown of RBCs is mild (serum bilirubin of 4-6mg/dl or 68-102micromol/L) as the normal liver can handle the increased bilirubin derived from excess hemolysis.
- Unconjugated bilirubin is not water soluble and therefore does not pass into urine, hence the term "acholuric jaundice".
- Urinary urobilinogen is increased (due to increased hemolysis and production of conjugated bilirubin excreted in bile).
- The causes of hemolytic jaundice are those of hemolytic anemia.
  - Inherited:
    - Red cell membrane defects (membranopathies): hereditary spherocytosis, hereditary elliptocytosis
    - Hemoglobin abnormalities (hemoglobinopathies): thalassemia, sickle cell disease
    - Metabolic defects (enzymopathies): glucose-6 phosphate dehydrogenase deficiency, pyruvate kinase deficiency, pyrimidine kinase deficiency
  - Acquired: Immune (autoimmune, transfusion reactions), drug induced (e.g. sulphonamides, penicillins), non-immune (systemic disease e.g. renal and liver failure, malaria)
- The clinical features depend on the cause:
  - Anemia
  - Jaundice
  - Splenomegaly
  - Gallstones (there is an increased risk for pigmented bilirubin gallstones)
  - Leg ulcers may be seen (especially with Sickle cell disease).
- Urine is dark because of increase urine urobilinogen.
- Investigations show features of hemolysis.

  - There is increased level of unconjugated bilirubin but normal serum ALP, transferases and albumin.
  - Serum haptoglobulins are low
  - In urine there is increased urine urobilinogen but no bilirubin.
- The differential diagnosis is from other forms of jaundice.

INTRAHEPATIC JAUNDICE

- It can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug induced hepatitis and alcoholic liver disease.
- Cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood.
- Other causes include primary biliary cirrhosis leading to increase in plasma conjugated bilirubin because there is impairment of excretion of conjugated bilirubin into bile
- Thus intrahepatic jaundice can be further divided into:
  a. Unconjugated
  b. Conjugated

UNCONJUGATED

GILBERT'S SYNDROME

- This is due to mildly low UDP-glucuronosyl transferase (UGT) activity. It is an autosomal recessive disease.
- It is characterized by increase in serum unconjugated bilirubin.
- It is asymptomatic and is usually detected as an incidental finding of a slightly raised bilirubin on a routine check, all other liver biochemistry is normal and there are no signs of liver disease.
- Jaundice may manifest during stress (e.g. severe infection) but otherwise it is not clinically significant.
- The reticulocyte count is normal, excluding hemolysis and no treatment is necessary.

CRIGLER-NAJJAR SYNDROME

- Divided into 2 types:
  - Type 1 (autosomal recessive)- absolute deficiency of UGT
  - Type 2 (autosomal dominant)- decreased UGT
- Liver histology is normal but there is increased unconjugated serum bilirubin.
- It manifests as kernicterus and is usually fatal.
- Transplantation is the only effective treatment.

CONJUGATED

DUBIN JOHNSON AND ROTOR SYNDROME

- Dubin-johnson is a deficiency of bilirubin canicular transport

protein, it is an autosomal recessive disorder.

- There is increased conjugated bilirubin (due to lack of regulation of bilirubin transport)
- It presents with a dark liver (owning to melanin deposition) but is also otherwise not clinically significant.
- Rotor syndrome is similar to Dubin-Johnson syndrome but the liver lacks dark discoloration.

- Other causes of intrahepatic jaundice are due to hepatitis, that cause parenchymal damage:
  - Alcoholic hepatitis
  - Nonalcoholic hepatitis
    - Infectious:
      - Viral hepatitis: HAV, HBV, HDV, HCV, CMV, EBV, Yellow fever virus
      - Non-viral: *Toxoplasma gondii*, *Coxiella burnetti* (Q fever), *Leptospira icterohaemorrhagiae*
    - Autoimmune hepatitis
    - Drugs: paracetamol, methyldopa, isoniazid, ketoconazole, nitrofurantoin
    - Wilson's disease: defect in metabolism of copper
    - Inflammatory bowel disease- ulcerative colitis
    - Poisons: amanita phylloides (mushrooms), aflatoxin, carbon tetrachloride

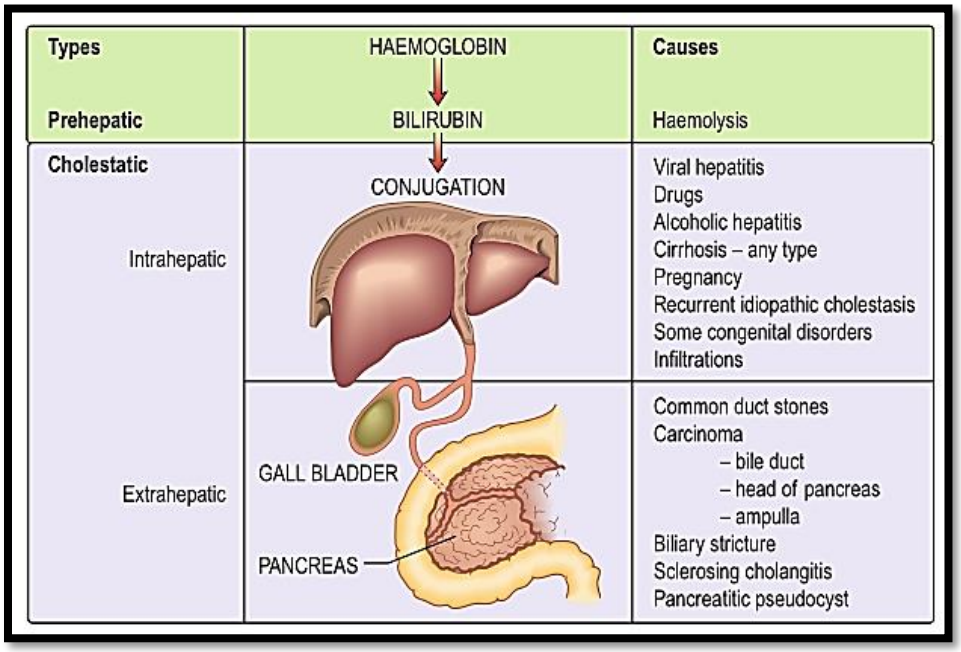
POST-HEPATIC (OBSTRUCTIVE) JAUNDICE

- This is caused by an interruption to the drainage of bile containing conjugated bilirubin in the biliary system.
- The most common causes are gallstones in the common bile duct, pancreatic carcinoma of the head of the pancreas, liver flukes.
- Other causes include: stricture to the common bile duct, biliary atresia, cholangiocarcinoma, pancreatitis, cholestasis of pregnancy and pancreatic pseudocysts.
- In complete obstruction of the bile duct, no urobilinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that it is converted to urobilinogen by micro-organisms, with the urobilinogen partly being absorbed from the intestine into the general circulation and then excreted into the urine.
- In this case, presence of bilirubin (conjugated) in the urine without urine-urobilinogen suggests

obstructive jaundice, either intra-hepatic of post-hepatic.

- Intra-hepatic: occurs due to failure of bile secretion due to either inhibition of the sodium/potassium ATPase pump on the basolateral membranes, decreased fluidity of the sinusoidal plasma membrane, disruption of the microfilaments responsible for canalicular tone and damage to the tight junction. in addition, inflammatory change in ductular cells interferes with bile flow.
- Extra-hepatic: due to large duct obstruction of bile flow at any point in the biliary tract distal to the bile canaliculi.

- Clinically in both types, there is jaundice with pale stools and dark urine and the serum bilirubin is conjugated.
- This type of jaundice presents also with pruritus due to increased plasma bile acids, hypercholesterolemia and Xanthomas.
- Steatorrhea is also present and is due to malabsorption of fat soluble vitamins.
- However, intrahepatic and extrahepatic cholestatic jaundice must be differentiated as their clinical management is entirely different.
- The presence of pale stool and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments.
- However, although pale stools and dark urine are a feature of biliary obstruction, they can occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstructive from hepatic causes of jaundice.



PHYSIOLOGICAL JAUNDICE OF THE NEWBORN

- Newborn liver has low conjugation ability due to low UGT and so there is increase serum unconjugated bilirubin.
- Unconjugated bilirubin is fat soluble and can deposit in the basal ganglia (kernicterus) leading to neurological deficits and death.
- Treatment is phototherapy (makes unconjugated bilirubin more water soluble).

FUNCTION TEST	PRE-HEPATIC JAUNDICE	INTRAHEPATIC JAUNDICE	POST-HEPATIC JAUNNDICE
Total bilirubin	Normal/ increased	Increased	Increased
Conjugated bilirubin	Normal	Increased	Increased
Unconjugated bilirubin	Normal/increased	Increased	Normal
Urobilinogen	Normal/increased	Decreased	Decreased/negative
Urine color	Normal	Dark (urobilinogen + conjugated bilirubin)	Dark (conjugated bilirubin)
Stool color	Normal	Slight pale	Pale
Alkaline phosphatase levels	Normal	Increased	Increased
ALT and AST levels	Normal	Increased	Normal/slightly increased
Conjugated bilirubin in urine	Not present	Present	Present
Large spleen	Present	Present	Absent

DIFFERENTIAL DIAGNOSIS OF JAUNDICE

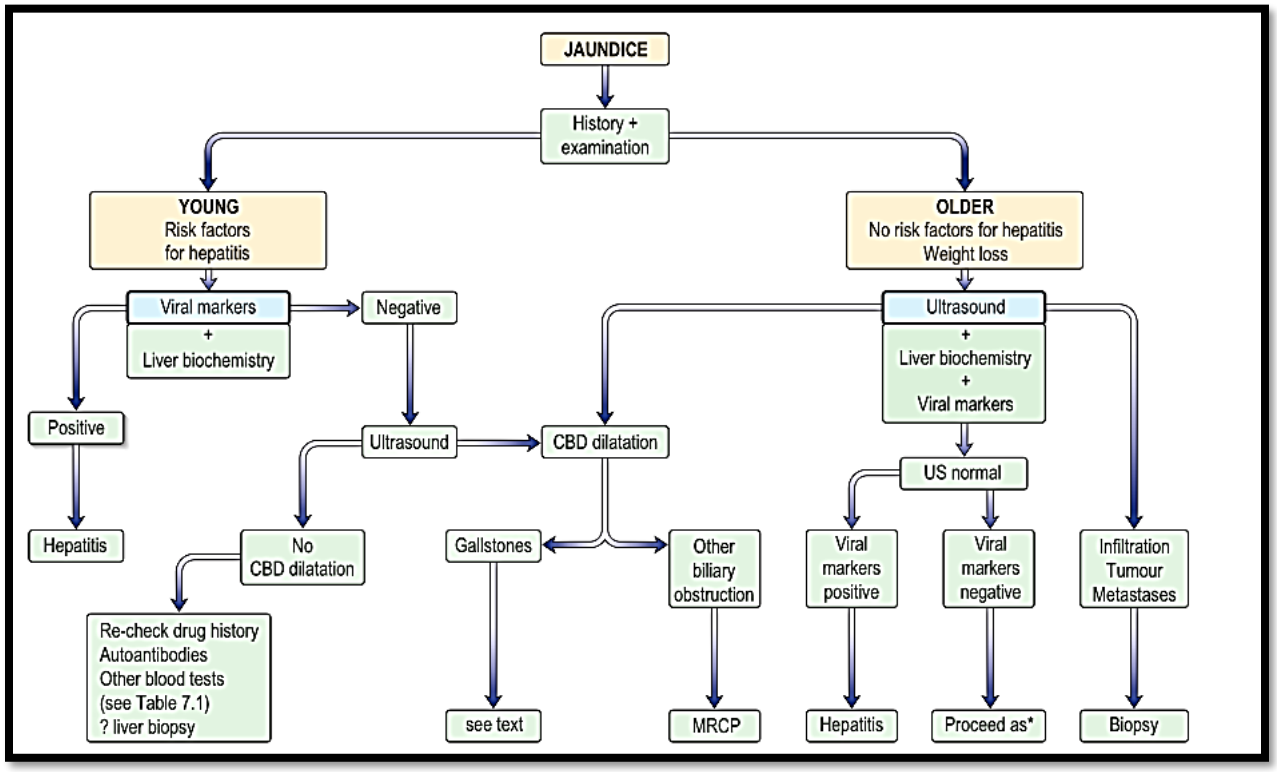
- The history often gives a clue to the diagnosis.
- Certain causes of jaundice are more likely in particular categories of people e.g. a young person is more likely to have hepatitis, so questions should be asked about drug and alcohol use and sexual behavior. An elderly person with gross weight loss is more likely to have a carcinoma.
- All patients may complain of malaise. Abdominal pain occurs in patients with biliary obstruction by gallstones and sometimes with an enlarged liver there is pain resulting from distension of the capsule.
- Questions should be appropriate to the particular situation:
  - Country of origin: HBV infection is increased in many parts of the world
  - Duration of illness: a history of jaundice with prolonged weight loss in an older patient suggest malignancy. A short history with a prodromal illness of malaise points towards hepatitis.

- Recent outbreak of jaundice: HAV
- Recent consumption of shellfish: HAV
- Men having sex with men: HBV
- Female sex workers: HBV
- Blood transfusion or infusion of pooled blood products: HBV and HCV
- Alcohol consumption
- Drugs taken (in previous 2-3 months): many drugs cause jaundice
- Travel: HAV, HEV
- Recent anesthetic: Halothane and occasionally isoflurane and sevoflurane.
- Family history: Gilbert's disease
- Recent surgery on the biliary tract or for carcinoma
- Environment: HEV, exposure to chemicals and people at risk for leptospirosis.
- Fevers or rigors: suggestive of cholangitis or possibly a liver abscess, infections (malaria).

INVESTIGATIONS

- Jaundice is not itself a diagnosis and the cause should always be sought.
- Investigations include:
  - Blood investigations:
    - Liver enzymes: AST and ALT (extent of liver damage)
    - Serum ALP: demonstrates extrahepatic obstruction
    - Serum albumin: usually low
    - Prothrombin time
    - Hepatitis profile
    - Peripheral smear
    - Full blood count: leukocytosis (indicating infections), leucopenia often occurs. In viral hepatitis, while abnormal mononuclear cells suggest infectious mononucleosis and a monospot test should be performed
    - Hepatitis profile
    - Others: anti-mitochondrial antibody (AMA) for primary biliary cirrhosis, HIV status.
  - Imaging
    - Abdominal ultrasound: to exclude an extrahepatic obstruction.
      - Ultrasound demonstrates the size of the bile ducts (which are dilated in extrahepatic obstruction), level of obstruction, cause of obstruction (tumors, gallstones).

APPROACH OF THE JAUNDICE PATIENT



MANAGEMENT

- Dependent on the cause

FULMINANT HEPATIC FAILURE

- This is severe hepatic failure in which encephalopathy develops in under 2 weeks in a patient with a previously normal liver (occasionally in some patients with previous liver damage e.g. D virus superinfection in a previous carrier of HBsAg, Budd-Chiari syndrome or Wilson's disease).
- Cases which evolve at a slower pace (2-12 weeks) are called subacute or subfulminant hepatic failure.
- This is a rare but life-threatening syndrome that is due to acute hepatitis from many causes.
- Most cases are due to viral hepatitis but paracetamol overdose is common.

Causes of fulminant hepatic failure

Viruses
- A, B, (D), E

Other viruses

Drugs (examples)
- Analgesics (e.g. paracetamol)
- Monoamine oxidase inhibitors
- Halogenated anaesthetics
- Antituberculosis (e.g. isoniazid)
- Antiepileptic (e.g. valproate)
- 'Social' drugs (e.g. 'Ecstasy')

Toxins
- *Amanita* poisoning
- Halohydrocarbons

Miscellaneous
- Wilson's disease
- Acute fatty liver of pregnancy
- Reye's syndrome
- Budd–Chiari syndrome
- Autoimmune hepatitis

- Histologically, there is multiacinar necrosis involving a substantial part of the liver. Severe fatty change is seen in pregnancy, Reye's syndrome or following tetracycline administration intravenously.

CLINICAL FEATURES

- Examination shows a jaundiced patient with a small liver and signs of hepatic encephalopathy.
- The mental state varies from slight drowsiness, confusion and disorientation (grades I and II) to unresponsive coma (grade IV) with convulsions.
- Fetor hepaticus is common but ascites and splenomegaly are rare.
- Fever, vomiting, hypotension and hypoglycemia occur.
- Neurological examination shows spasticity and hyperreflexia; plantar responses remain flexor until late.
- Cerebral edema develops in 80% of patients with fulminant hepatic failure but is far less common with subacute failure and its consequences of intracranial hypertension and brain herniation account for about 25% of the causes of death.
- Other complications: bacterial and fungal infections, gastrointestinal bleeding, respiratory arrest, kidney failure (Hepatorenal syndrome and acute tubular necrosis) and pancreatitis.

INVESTIGATIONS

- Blood:
  - Serum bilirubin: hyperbilirubinemia
  - Serum aminotransferases: high serum aminotransferases. Aminotransferases are not useful indicators of the course of the disease as they tend to fall along with the albumin with progressive liver damage.
  - Coagulation factors: low, including prothrombin and factor V
- Imagining:
  - Ultrasound: to define liver size and indicate underlying pathology
  - EEG can be helpful in grading encephalopathy

MANAGEMENT

- No specific treatment
- Transfer to specialized unit if:
  - INR >3.0
  - Presence of hepatic encephalopathy
  - Hypotension after resuscitation with fluid
  - Metabolic acidosis
  - Prothrombin time (seconds) > interval (hours) from overdose (paracetamol cases)
- For signs of increased intracranial pressure give 20% mannitol (1g/kg bodyweight) infused intravenously, this dose may need to be repeated.
- Dexamethasone is of no value
- Hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, and hypocalcemia should be anticipated and corrected with 10% dextrose infusion (checked by 2hourly dipstick testing), potassium, calcium, phosphate and magnesium supplements.
- Hyponatremia should be corrected with hypertonic saline.
- Coagulopathy is managed with intravenous vitamin K, platelets, blood or fresh frozen plasma.
- Hemorrhage may be a problem and patients are given a proton pump inhibitor (PPI) to prevent gastrointestinal bleeding.
- Prophylaxis against bacterial and fungal infection is routine as infection is a frequent cause of death and may preclude liver transplantation.
- Suspected infection should be treated immediately with suitable antibiotics.
- Renal and respiratory failure should be treated as necessary.

- Liver transplantation has been a major advance for patients with fulminant hepatic failure. It is difficult to judge the timing or the necessity for transplantation.

CHRONIC LIVER DISEASE AND LIVER CIRRHOSIS

- Chronic liver diseases include:
  - Chronic hepatitis
  - Liver cirrhosis
  - Hepatocellular carcinoma (hepatoma)

CHRONIC HEPATITIS

- This is a hepatic inflammatory process that fails to resolve after 6 months.

ETIOLOGY

- Infectious: Viral (HBV, HCV, HDV)
- Non-infectious
  - Drug induced hepatitis (e.g. methyldopa, isoniazid, ketoconazole, nitrofurantoin)
  - Hereditary: Wilson's disease
  - Autoimmune disorders
  - Others:
    - Inflammatory bowel disease- ulcerative colitis
    - Alcohol (rarely)
  - Idiopathic causes

PATHOLOGY

- Chronic inflammatory cells infiltrates comprising of lymphocytes, plasma cells and sometimes lymphoid follicles are usually present in the portal tracts.
- The amount of inflammation varies from mild to severe.
- The overall severity of the hepatitis is judged by the degree of hepatitis and inflammation (grading) and the severity of the fibrosis or cirrhosis (staging).
- In chronic viral hepatitis there are various scoring systems e.g. Knodell scoring system (histological activity index) uses the sum of 4 factors (periportal or bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation and fibrosis). The Lshak score stages fibrosis from 0 (none) to 6 (cirrhosis). The METAVIR system has 4 stages. Scoring systems are used for drug trials and for assessing progression of disease, but are descriptions of architectural changes and no quantitative measures of fibrosis.

- Liver changes seen include:
  - Loss of definition of the portal/periportal limiting plate (interface hepatitis) damage is due to apoptosis rather than necrosis
  - Lobular change, focal lytic necrosis, apoptosis and focal inflammation
  - Confluent necrosis
  - Fibrosis which may be mild, bridging (across portal tracts) or severe cirrhosis.

PATHOLOGICAL CLASSIFICATION

- Chronic persistent hepatitis- inflammatory activity is confined to portal areas.
- Chronic lobular hepatitis-
  - Inflammatory activity and necrosis are scattered throughout the lobule.
  - Limiting plates of periportal hepatocytes are intact and no periportal
- Chronic active hepatitis-
  - Inflammatory activity in portal areas spills out into the lobule (periportal hepatitis, piecemeal necrosis) in association with necrosis and fibrosis
  - Though to have a significant risk for progression to cirrhosis and hepatic failure.

CHRONIC VIRAL HEPATITIS

- Chronic viral hepatitis is the principal cause of chronic liver disease, cirrhosis and hepatocellular carcinoma.
- It Complicates about 1% of acute hepatitis B (young, immunocompetent) and 85-90% of acute hepatitis C will develop chronic hepatitis.
- About 20% of the later will develop cirrhosis in 10-20 years.
- Subjects with either HBV or HCV infection have greater risk of developing hepatocellular carcinoma.
- Treatment:
  - Can suppress hepatic inflammatory activity in 30-40%.
  - Hepatitis B- therapy is indicated for patients positive for HBsAg and HBcAg (high replicative phase). Treat with interferon alpha and lamivudine or Tenofovir and Lamivudine (TDF + 3TC).
    - Note only give TDF when creatinine clearance >50.
  - Hepatitis C can be treated with interferon alpha and ribavirin

LIVER CIRRHOSIS

- Cirrhosis results from necrosis of liver cells followed by fibrosis and nodule formation.
- It is the common pathway of many liver diseases that cause hepatocellular injury and lead to fibrosis and nodular regeneration.
- Reversal may occur with treatment of some chronic liver diseases (e.g. HBV, HCV)
- The liver architecture is diffusely abnormal and this interferes with liver blood flow and function. This derangement produces the clinical features of portal hypertension and impaired liver cell function.
- Common causes of cirrhosis include:
  - Alcohol
  - Viral infection: HBV, HDV, HCV
  - Non-alcoholic fatty liver disease
- Other causes include:
  - Biliary cirrhosis: primary and secondary.
  - Autoimmune hepatitis
  - Hereditary hemochromatosis
  - Hepatic venous congestion
  - Budd-Chiari syndrome
  - Wilson's disease
  - Drugs e.g. methotrexate, amiodarone, nitrofurantoin
  - Sarcoidosis
  - Hypervitaminosis A
  - α–antitrypsin deficiency
  - Cystic fibrosis
  - Galactosaemia
  - Glycogen storage disease
  - Veno-occlusive disease
  - Idiopathic (cryptogenic)
  - other viruses
- Young patients with cirrhosis must be investigated to exclude treatable causes (e.g. Wilson's disease).

PATHOGENESIS

- Chronic injury to the liver results in inflammation, necrosis and eventually fibrosis.
- Fibrosis is initiated by activation of the stellate cells.
- Kupffer cells, damaged hepatocytes and activated platelets are probably involved.
- In the space of Disse, the normal matrix is replaced by collagens, predominantly type 1 and 3 and fibronectin.
- Subendothelial fibrosis leads to loss of the endothelial fenestrations (openings) and this impairs liver function.
- Collagenases (matrix metalloproteinases, MMPs) are able to degrade this collagen but are inhibited by tissue inhibitors of metalloproteinases (TIMPs) which are increased in human liver fibrosis.
- There is accumulating evidence that liver fibrosis is reversible, particularly when inflammation is reduced on a long-term basis e.g. by suppressing or eliminating viruses.

PATHOLOGY

- 3 types of cirrhosis have been described which give clues to the underlying cause:
  - Micronodular cirrhosis: regenerating nodules are usually less than 3mm in size and the liver is involved uniformly. This type is often caused by ongoing alcohol damage or biliary tract disease.
  - Macronodular cirrhosis: The nodules are of variable size and normal acini may be seen within the larger nodules. This type is often seen following chronic viral hepatitis.
  - Mixed: small and large nodules is sometimes seen.

CLINICAL FEATURES

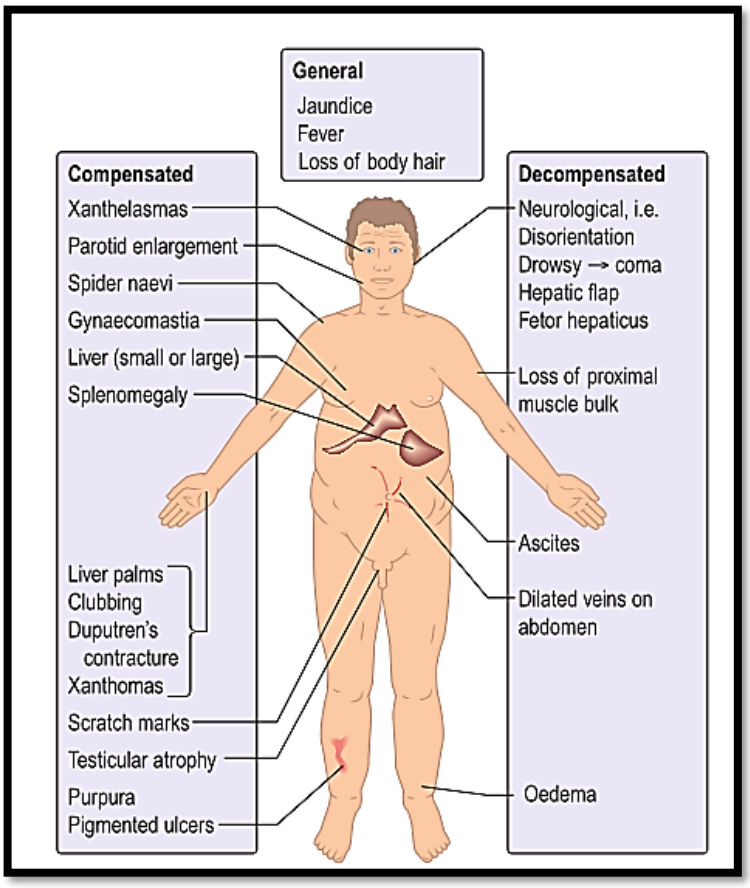
SYMPTOMS

- Patients may be asymptomatic or complain of nonspecific symptoms, particularly fatigue, anorexia, muscles wasting, loss of libido, impotence, dysmenorrhea, gynecomastia.
- Decompensation is associated with:
  - Confusion and drowsiness due to neuropsychiatric complications (portosystemic/hepatic encephalopathy)
  - Abdominal distention due to ascites
  - Hematemesis and melena from gastrointestinal hemorrhage

- Ankle swelling due to fluid retention
- Pruritus due to cholestasis- this is often an early symptom of primary biliary cirrhosis
- Platypnea (dyspnea induced by sitting upright and relived by recumbence) and orthodeoxia (Low PaO_2 when sitting upright that is relieved by recumbence).

SIGNS

- Confusion, drowsiness and coma
- Hepatic flap/ asterixis
- Fetor hepaticus (breath of death): in portal hypertension there is portosystemic shunting which allows thiols to pass directly into the lungs. The breath smells like rotten eggs and garlic.
- Bilateral Parotid enlargement
- Skin:
  - The chest and upper body may show spider naevi. These are Telangiectases that consist of a central arteriole with radiating small vessels. They are found in the distribution of the superior vena cava (i.e. above nipple line)- commonly more than 5 is taken as diagnostic. They are also found in pregnancy.
  - Caput medusae
  - In hemochromatosis the skin may have a slate-grey appearance.
  - The hands may show palmar erythema which is non-specific change indicative of a hyperdynamic circulation, it is also seen in pregnancy, thyrotoxicosis or rheumatoid arthritis.
  - Clubbing occasionally occurs and a Dupuytren's contracture is often seen in alcoholic cirrhosis. As well as Terry's nails (white, obscure nails)



  - Xanthomas (cholesterol deposits) are seen in the palmar creases or above the eyes in primary biliary cirrhosis.
- Abdomen: initial hepatomegaly will be followed by a small liver in well-established cirrhosis, splenomegaly is seen with portal hypertension.
- Endocrine:
  - Gynecomastia (occasionally unilateral) and testicular atrophy may be found in males. The cause of gynecomastia is complex but it is probably related to altered estrogen metabolism or to treatment with spironolactone.
  - In decompensated cirrhosis there are additional signs.

INVESTIGATIONS

- These are performed to assess the severity and type of liver disease.

SEVERITY

- FBC: indicates thrombocytopenia (splenic sequestration)
- Liver function:
  - Serum albumin: there is low albumin due to decreased synthetic function. outlook is poor with albumin level below 28g/L.
  - Prothrombin time: this is prolonged corresponding with the severity of the liver disease (decreased coagulation factors)
  - INR is elevated
- Liver biochemistry: these can be normal depending on severity of cirrhosis. In most cases there may be a slight elevation in serum ALP, GGT (cholestasis) and serum aminotransferases. In decompensated cirrhosis all biochemistry is deranged.
- Serum bilirubin: hyperbilirubinemia
- Serum electrolytes: low sodium indicates severe liver disease due to defect in free water clearance or to excess diuretic therapy.
- Serum creatinine: an elevated concentration >130 μmol/L is a marker of worse prognosis.
- Serum alpha fetoprotein: if >200ng/ml is strongly suggestive of the presence of a hepatocellular carcinoma.

- The Modified Child-Pugh classification is used in scoring cirrhosis to provide a 1 year, 5 year and 10 year survival:

SCORE	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin time (seconds over normal)	<4	4-6	>6

Add above scores for your patient for survival figures below

Grade (scores)	% survival		
	1 year	5 years	10 years
Child's A (<7)	82	45	25
Child's B (7-9)	62	20	7
Child's C (10+)	42	20	0

TYPE

- Viral markers
- Serum autoantibodies and immunoglobulins
- Iron indices and ferritin
- Copper, ceruloplasmin
- Alpha-1 antitrypsin
- Note: Serum copper and serum alpha-1 antitrypsin should be measured in young cirrhotics. Total iron-binding capacity (TIBC) and ferritin should be measured to exclude hereditary haemochromatosis, genetic markers are also available

IMAGING

- Ultrasound: can demonstrated changes in size and shape of the liver. Fatty change and fibrosis produce a diffuse increased echogenicity. In established cirrhosis there may be marginal nodularity of the liver surface and distortion of the arterial vascular architecture. The patency of the portal and hepatic veins can be evaluated. It is also useful in detecting HCC. Elastography is being used in diagnosis and follow-up to avoid liver biopsy.
- Endoscopy: performed for the detection and treatment of varices and portal hypertensive gastropathy. Colonoscopy is occasionally performed for colopathy.

- CT scan: shows hepatosplenomegaly and dilated collaterals are seen in chronic liver disease. Arterial phase-contrast enhanced scans are useful in the detection of HCC.
- MRI scan: this is useful in the diagnosis of both malignant and benign tumors such as hemangiomas. MR angiography can demonstrate the vascular anatomy and MR cholangiography the biliary tree.

LIVER BIOPSY

- This is the gold-standard. It confirms the type and severity of liver disease.
- The core of liver often fragments and sampling errors may occur in macronodular cirrhosis.

MANAGEMENT

- Management is that of complications seen in decompensated cirrhosis.
- Patients should have 6 monthly ultrasounds and serum AFP to detect the early development of a HCC.
- Treatment of the underlying cause may arrest or occasionally reverse cirrhotic changes.
- Patients with compensated cirrhosis should lead a normal life. The only dietary restriction is to reduce salt intake.
- Aspirin, Iron supplements (except in iron deficiency), NSAIDs, benzodiazepines should be avoided.
- Minimize narcotics and limit acetaminophen to <2g/day
- Alcohol should be avoided although if the cirrhosis is not due to alcohol and not due to viral hepatitis, small amounts not taken on a regular basis are probably not harmful.
- Administer pneumococcal and influenza vaccines
- Prophylactic measures:
  - Primary prophylaxis: HAV and HBV vaccination, nonselective Beta blockers for documented esophageal varices
  - Secondary prophylaxis: Antibiotics for spontaneous bacterial peritonitis (SBP), esophageal variceal banding or nonselective beta-blockers +/- long acting nitrates. Patients typically show low adherence/tolerance to beta-blockers/nitrates

- Liver transplant
  - Indications:
    - Acute liver disease: patients with fulminant hepatic failure of any cause including acute viral hepatitis
    - Chronic liver disease: the indications of transplantation are usually for complications of cirrhosis, no longer responsive to therapy. Extrahepatic complications of cirrhosis, even with preserved liver function such as hepatopulmonary syndrome (shunting in the lung leading to hypoxia) and porto-pulmonary hypertension can be reversed by liver transplantation.
      - Primary biliary cirrhosis
      - Chronic HBV if HBV DNA negative
      - Chronic hepatitis C
      - Autoimmune hepatitis
      - Alcoholic liver disease
      - Primary metabolic disorders: Wilson's disease, hereditary hemochromatosis
      - Others: primary sclerosing cholangitis, Polycystic liver disease, NASH and metabolic diseases in which the defect is in the liver e.g. primary oxaluria
  - Contraindications:
    - Absolute:
      - Active sepsis outside the hepatobiliary tree,
      - Malignancy outside the liver,
      - Liver metastases (except neuroendocrine) and
      - If the patient is not psychologically committed.
    - Relative: mainly anatomical considerations that would make surgery more difficult, such as extensive splanchnic venous thrombosis. With exceptions patients aged 70 years or over are not usually transplanted. In hepatocellular carcinoma the recurrence rate is high unless there are fewer than 3 small (<3cm) lesions or a solitary nodule of <5cm.

COURSE AND PROGNOSIS

- Extremely variable and depends on many factors, including the etiology and presence of complications.
- Presence of complications usually worsens the prognosis.
- In general, 5-year survival is about 50% but this also varies depending on the etiology and stage at which the diagnosis was made.

- Poor indicators in cirrhosis:
  - Clinical:
    - Persistent jaundice
    - Failure to respond to therapy
    - Ascites
    - Hemorrhage from varices, particularly with poor liver function
    - Neuropsychiatric complications developing with progressive liver failure
    - Small liver
    - Persistent hypotension
    - Etiology (e.g. alcoholic cirrhosis if the patient continues drinking)
  - Blood tests:
    - Low albumin (<28g/L)
    - Low serum sodium (<125mmol/L)
    - Prolonged prothrombin time >6s above normal value
    - Raised creatinine >130μmol/L

COMPLICATIONS AND EFFECTS OF CIRRHOSIS

- These include:
  - Hepatic encephalopathy (portosystemic encephalopathy)
  - Hepatopulmonary syndrome
  - Porto-pulmonary hypertension
  - Portal hypotension and gastrointestinal hemorrhage
  - Ascites
  - Bacteremia, infections and spontaneous bacterial peritonitis
  - Renal failure (Hepatorenal syndrome)
  - Primary hepatocellular carcinoma

HEPATIC ENCEPHALOPATHY (PORTOSYSTEMIC ENCEPHALOPATHY/ HEPATIC COMA)

- This is a chronic neuropsychiatric syndrome due to cirrhosis.
- It manifests in 2 forms:
  - Acute hepatic encephalopathy:
    - Occurs in the setting of fulminant hepatitis (within 2 weeks)
    - Cerebral edema plays a more important role
    - Mortality rate is very high
  - Chronic hepatic encephalopathy:
    - Occurs in chronic liver disease
    - Often reversible
- Hepatic encephalopathy can occur in portal hypertensive patients due to spontaneous 'shunting' or in those with surgical or TIPS shunts (Transjugular intrahepatic portocaval shunt).
- Encephalopathy is potentially reversible.
- Neuropsychiatric changes in the setting of liver disease constitute hepatic encephalopathy until proven otherwise.

PATHOGENESIS

- The mechanism is unknown but several factors are involved.
- The hepatocellular dysfunction and portosystemic shunt leads to inadequate removal of nitrogenous compounds and toxins ingested or produced in the gastrointestinal tract getting access to the brain and causing hepatic encephalopathy.
- Many 'toxic' substances may be causative factors namely:
  - Ammonia (very well-known and studied)
  - Short chain Fatty acids
  - Mercaptans- a cause of fetor hepaticus in Chronic liver disease
  - Accumulation of false neurotransmitters (octopamine) or activation of the GABA (gamma aminobutyric acid) inhibitory neurotransmitter system.
- Increased blood levels of aromatic amino acids (tyrosine and phenylalanine) and reduced branched amino acids (valine, leucine and isoleucine) also occurs.
- Ammonia has a major role, ammonia-induced alteration of brain neurotransmitter balance-especially at the astrocyte-neuron interface is the leading pathophysiological mechanism.
  - Ammonia is absorbed by astrocytes and is converted to glutamine. Glutamine increases intracellular osmotic pressure causing swelling and cerebral edema.

- Ammonia is produced by intestinal bacterial breaking down protein.
- Predisposing factors/triggers to hepatic encephalopathy:
  - High dietary protein
  - Gastrointestinal hemorrhage
  - Constipation/ileus
  - Alkalosis
  - Infection including spontaneous bacterial peritonitis
  - Fluid and electrolyte disturbance due to diuretic therapy
    - Hypovolemia
    - Dehydration
    - Hypokalemia
  - Paracentesis
  - Azotemia
  - Hypoxia
  - Hypoglycemia
  - Drugs e.g. any CNS depressant (narcotics, benzodiazepines, anticholinergics)
  - Porstosystemic shunt operations, TIPS (Transjugular intrahepatic portocaval shunt)
  - Any surgical procedure
  - Progressive liver damage
  - Development of hepatocellular carcinoma
  - Non-compliance with hepatic encephalopathy treatment

CLINICAL FEATURES

- Acutely the patient becomes increasingly drowsy and comatose.
- Chronically there is disorder of personality, mood and intellect with a reversal of normal sleep rhythm
- These changes may fluctuate and a history from a relative must be obtained.
- The patient is:
  - Irritable
  - Confused
  - Disoriented
  - Slow slurred speech
- General features:
  - Nausea
  - Vomiting

  - Weakness
  - Coma occurs as the encephalopathy becomes more marked but there is always hyperreflexia and increasing tone.
  - Convulsions are so very rare that other causes must be looked for
- Signs include:
  - Fetor hepaticus (breath of death)
  - Course flapping tremor when the hands are outstretched and the wrist is hyperextended (asterixis)
  - Constructional apraxia with the patient being unable to write or draw e.g. a five-pointed star
  - Decreased mental function: can be assessed by using the serial-sevens test.
- The manifestation depends on the stage/grade of hepatic encephalopathy.

STAGE	CLINICAL MANIFESTATION
I	Mildly altered mental status: apathy, restlessness, reversal of sleep rhythm, slowed intellect, impaired computing ability, impaired handwriting
II	Disorientation, drowsiness lethargy, and Asterixis
III	Stupor (arousable) and Upper motor neuron signs (hyperreflexia and extensor plantar responses, increase in tone),
IV	Coma

DIAGNOSIS

- Diagnosis is clinical.
- Routine liver biochemistry merely confirms the presence of liver disease not the presence of encephalopathy.

MANAGEMENT

- Identify and remove the possible precipitating cause, such as drugs with cerebral depressant properties, constipation or electrolyte imbalance due to over-diuresis.
  - Triggers: High dietary protein, Gastrointestinal hemorrhage, Constipation, Alkalosis, Infection including spontaneous bacterial peritonitis, Fluid and electrolyte disturbance (hypokalemia) due to diuretic therapy (hypovolemia), Paracentesis, Azotemia, Drugs e.g. any CNS depressant, Porstosystemic shunt operations, TIPS (Transjugular intrahepatic portocaval shunt), Any surgical procedure, Progressive liver damage, and Development of hepatocellular carcinoma

- Reduce and eliminate substrates for the generation of nitrogenous compound:
  - Maintain nutrition with adequate calories, given if necessary via a fine-bore nasogastric tube, and do not restrict protein for more than 48h.
  - Restrict dietary protein
    - For non-comatose patients restriction of protein to 40-60g/day
    - For patients in coma, no protein should be given
  - Cleanse the bowel with enema in patients with gastrointestinal hemorrhage
    - Give purgatives and enemas to empty the bowels of nitrogenous substances.
    - Oral/NG tube or rectally administered lactulose (adverse effects include dehydration and hypokalemia).
    - Lactulose (10-30ml TDS) is an osmotic purgative that reduces the colonic pH and limits ammonia absorption.
    - Lactilol (beta-galactoside sorbital 30g daily) is metabolized by colonic bacteria and is comparable in efficacy to lactulose.
    - Lactose can be given to patient deficient for lactase.
    - Lactulose, lactilol and lactose are all fermented by bacterial to organic acids and reduce stool pH. The hydrogen ion produced traps ammonia in the colon and changes it to non-diffusable ammonium (NH^+_4) ions.
    - Additionally, the laxative effect increases excretion of ammonia.
  - Increase protein in the diet to the limit of tolerance as the encephalopathy improves.
- Reduce colonic bacteria that generate ammonia.
  - Give antibiotics. Rifaximin is main unabsorbed and well tolerated long term and prevents further episodes of hepatic encephalopathy.
  - Metronidazole 200mg QID is also effective in the acute situation (adverse effect: neuropathy)
  - Neomycin should be avoided (adverse effects: ototoxicity and renal toxicity)
  - Stop or reduce diuretic therapy
- Treat any infection.
- Give intravenous fluids as necessary (beware of too much sodium).
- Zinc, short-term protein restriction, branched-chain amino acids-enriched diet should be instituted.

HEPATOPULMONARY SYNDROME

- This is characterized by abnormal arterial oxygenation in a patient with cirrhosis and/or portal hypertension
- Pathogenesis is thought to be due to intrapulmonary vasodilation leading to impaired oxygen transfer that improves with 100% Oxygen. There is no evidence of primary pulmonary disease.
- Clinical features:
  - Range from subclinical abnormalities in gas exchange to profound hypoxemia causing dyspnea at rest.
  - The patient may have features of cirrhosis with spider naevi and clubbing as well as cyanosis.
  - Most patients have no respiratory symptoms but with more severe disease patients are breathless on standing.
- Transthoracic ECHO shows intrapulmonary shunting and arterial blood gasses confirm the arterial oxygen desaturation.
- It is a functional disorder that reverses with liver transplantation.

PORTO-PULMONARY HYPERTENSION

- This must be distinguished from hepatopulmonary syndrome as in this group there is pulmonary hypertension.
- It occurs in 1-2% of patients with cirrhosis related to portal hypertension.
- It may respond to medical therapy.
- Severe pulmonary hypertension is a contraindication for liver transplantation.

PORTAL HYPERTENSION

- The portal vein is formed by the union of the superior mesenteric and splenic veins.
- The pressure within it is normally 5-8mmHg with only a small gradient across the liver to the hepatic vein in which blood is returned to the heart via the inferior vena cava.
- Portal hypertension can be classified as:
  - Prehepatic: due to blockage of the portal vein before the liver. This is due to portal vein thrombosis.
  - Intrahepatic: due to distortion of the liver architecture which can be:
    - Presinusoidal: Increased resistance to portal blood flow into the liver (e.g. in schistosomiasis due to periportal fibrosis and perisinusoidal portal HTN) or
    - Sinusoidal: The resistance is in the sinusoids of the liver. It is the commonest cause (e.g. found in cirrhosis i.e. alcoholic.)
    - Post-sinusoidal: increased resistance to hepatic venous outflow from the liver causes include veno-occlusive disease, Budd-Chiari syndrome
  - Post-hepatic: due to venous blockage outside the liver (rare) e.g. right heart failure, constrictive pericarditis and IVC obstruction

Causes of portal hypertension

Prehepatic
- Portal vein thrombosis

Intrahepatic
- Presinusoidal
  - Schistosomiasis; sarcoidosis
  - Primary biliary cirrhosis
- Sinusoidal
  - Cirrhosis (e.g. alcoholic)
  - Partial nodular transformation
- Post-sinusoidal
  - Veno-occlusive disease
  - Budd–Chiari syndrome

Post-hepatic
- Right heart failure (rare)
- Constrictive pericarditis
- IVC obstruction

- As portal pressure rises above 10-12mmHg, the compliant venous system dilates and collaterals occur within the venous system.
- The main sites of the collaterals are at the gastro-esophageal junction, rectum, left renal vein, diaphragm, retroperitoneum, and the anterior abdominal wall via the umbilical vein.
- The collaterals at the gastro-esophageal junction (varices) are superficial in position and tend to rupture.
- Portosystemic anastomoses at other sites seldom give rise to symptoms. Rectal varices are found frequently (30%) if carefully looked for and can be differentiated from hemorrhoids which are lower in the anal canal.

CLINICAL FEATURES

- Often asymptomatic and only clinical evidence of portal hypertension is splenomegaly.
- Clinical features of chronic liver disease are usually present.
- Presenting features include:
  - Hematemesis or melena from rupture of gastroesophageal varices or portal hypertensive gastropathy
  - Ascites
  - Encephalopathy
  - Breathlessness due to porto-pulmonary hypertension or hepatopulmonary syndrome (rare)

VARICEAL HEMORRHAGE

- 90% of patients with cirrhosis will develop gastro-esophageal varices over 10 years but only one third of these will bleed from them.
- Bleeding is likely to occur with large varices, red signs on varices (diagnosed at endoscopy) and in severe liver disease.
- It may present with painless hematemesis, melena, hematochezia.

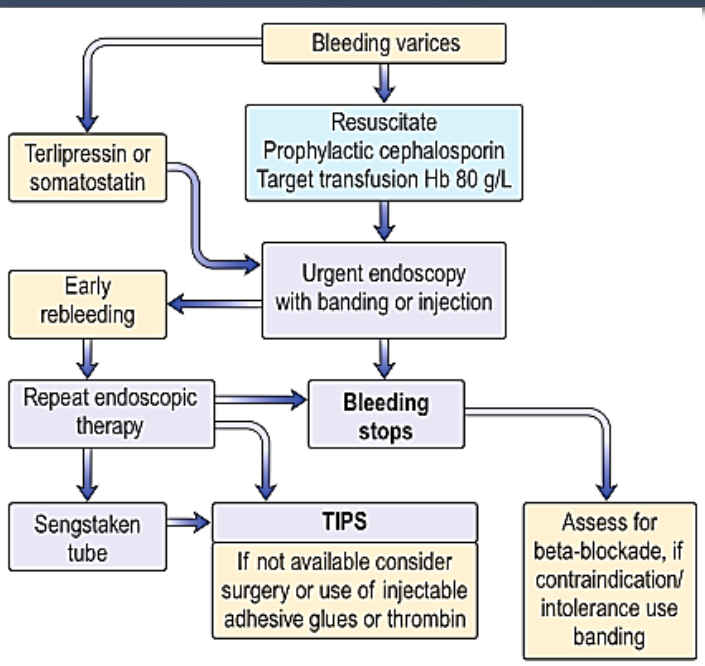
MANAGEMENT

- Depends on the speed and volume of bleeding.
- Management can be divided into:

- Active bleeding episode
- Prevention of re-bleeding
- Prophylactic measures to prevent the first hemorrhage

ACTIVE BLEEDING EPISODE

- Nurse in high dependency/intensive care nursing.
- Stabilization and resuscitation:
  - Assess the general condition of the patient-pulse and blood pressure.
  - Nil per oral, consider an NG tube and place two large-bore IVs. Obtain blood for grouping and crossmatching, hemoglobin, PT/INR, urea, electrolytes, creatinine, liver biochemistry and blood cultures.



Management of gastrointestinal haemorrhage due to oesophageal varices. TIPS, transjugular intrahepatic portosystemic shunt.

  - Cross match blood and administer packed red blood cells if needed.
  - If the patient is in shock, treat with aggressive IV fluids (normal saline), start it cautiously, prompt correction but not over correction of hypovolemia is necessary in patients with cirrhosis as their baroreceptor reflexes are diminished. Restore blood volume with plasma expanders or if possible blood transfusions. Target hemoglobin only needs to be 8g/dl as this lessens the likelihood of early rebleeding.
  - In the presence of active bleeding and platelets <50 000/μL or if there is known impaired function (uremia, aspirin), transfuse platelets or desmopressin. With active bleeding, increased PT time, and INR> 1.5 transfuse fresh frozen plasma (FFP).
  - Oxygen given by facemask
  - Place a Foley catheter to closely monitor urine output, decreased urine output is a sign of hypoperfusion and bleeding.
  - Hourly measurement of pulse, blood pressure and urine output.
- Ascitic tap
- Monitor for alcohol withdrawal. Give thiamine IV
- Start prophylactic antibiotics- third-generation cephalosporins e.g. cefotaxime. These treat and prevent infection and early rebleeding and reduce mortality.

- Give PPI as it lessens the risk of *C. difficile* infection. Sucralfate 1g QID can reduce esophageal ulceration following endoscopic therapy.
- Medical therapy:
  - Vasocontrictor therapy: to control bleeding while waiting for endoscopy. The main aim is to restrict portal inflow by splanchnic arterial constriction
    - Somatostatin (or octreotide) reduces splanchnic blood pressure when given intravenously. An infusion of 250-500 μg/hour appears to reduce bleeding but has no effect on mortality. It should be used if there are contraindications to terlipressin. It has few side effects.
    - Vasopressin (terlipressin) with nitroglycerin help to minimize systemic vasoconstriction.
      - Terlipressin is the only vasoconstrictor shown to reduce mortality. The dose is 2mg 6 hourly, reducing to 1mg 4-hourly after 48 hours if a prolonged dosage regimen is used. It should not be given to patients with ischemic heart disease. The patient will complain of abdominal colic, will defecate and have facial pallor owing to the generalized vasoconstriction.

- Urgent endoscopy to confirm the diagnosis of varices. It also excludes bleeding from other sites e.g. gastric ulceration or portal hypertensive (or congestive) gastropathy. The latter term is used for chronic gastric congestion, punctate erythema and gastric erosions. It is a source of bleeding but varices may or may not be present. Propranolol is the best treatment for this gastropathy.
- Balloon tamponade (with Four-lumen Sengstaken-Blakemore balloon tube)- compressing bleeding varices temporarily. It should be left in place for no more than 12 hours and removed in the endoscopy room prior to the endoscopic procedure. The tube is passed into the stomach and the gastric balloon is inflated with air and pulled back. It should be positioned in close apposition to the gastroesophageal junction to prevent the cephalad variceal blood flow to the bleeding point. The esophageal balloon should be inflated only if bleeding is not controlled by the gastric balloon alone.
- Endoscopic therapy include injection of sclerosing agent and/or band ligation of varices
  - The use of repeated courses of banding at 2 weekly intervals leads to obliteration of varices. This markedly reduces rebleeding most instances

occurring before the varices have been fully obliterated. Banding is superior to sclerotherapy and should be used combined with beta blockers.

- Although a reduction in bleeding episodes occurs, the effect on survival is controversial and probably small. Complications include esophageal ulceration, mediastinitis and rarely strictures.

- Refractory or recurrent upper GIT bleeding:
  - Esophageal balloon tamponade (Minnesota or Sengstaken-Blakemore tubes) for varices as a bridge to TIPS (transjugular intrahepatic portosystemic shunting)- a catheter is placed into the jugular vein and guided radiographically through the liver to form a shunt between the systemic circulation in the hepatic vein and the portal circulation through the portal vein. TIPS has largely replaced the need to surgically place the shunt. The most common, long-term complication of TIPS is worsening of hepatic encephalopathy.
  - Angiogram with intra-arterial embolization or surgery for refractory non-variceal bleeding
- Surgery: portosystemic shunt
- Prevention of variceal hemorrhage:
  - Non-selective beta-blockers (propranolol and nadolol): in a dose sufficient to reduce resting pulse rate by 25% has been shown to decrease portal pressure. Portal inflow is reduced by 2 mechanisms: by decreased in cardiac output (beta 1) and blockade of beta 2 vasodilator receptors on the splanchnic arteries leaving an unopposed vasoconstrictor effect. This decreases the frequency of rebleeding and is as effective as sclerotherapy and ligation as it also prevents bleeding from portal hypertensive gastropathy. It is the treatment of first choice combined with endoscopic ligation but a substantial number of patients either have contraindications or are intolerant of beta-blockers.
  - Mononitrates (isosorbide mononitrate) decrease portal blood flow and pressure

ASCITES

- This is fluid within the peritoneal cavity and is a common complication of cirrhosis.
- The pathogenesis of ascites in liver disease is secondary to renal sodium and water retention.
- Implicated factors:
  - Sodium and water retention: this is due to peripheral vasodilation and consequent reduction in the effective blood volume caused by portal hypertension. Nitric oxide and other substances (e.g. atrial natriuretic peptide and prostaglandins) act as vasodilators. The reduction in effective blood volume activates the Renin-angiotensin aldosterone system.
  - Portal hypertension: increased local hydrostatic pressure leads to increased hepatic and splanchnic production of lymph and transudation of fluid into the peritoneal cavity.
  - Low serum albumin: as a consequence of poor synthetic liver function may further contribute to ascites by reduction in plasma oncotic pressure.

Causes of ascites divided according to the type of ascitic fluid

Straw-coloured
- Malignancy (most common cause)
- Cirrhosis
- Infective
  - Tuberculosis
  - Following intra-abdominal perforation – any bacterium may be found (e.g. *E. coli*)
  - Spontaneous in cirrhosis
- Hepatic vein obstruction (Budd–Chiari syndrome) protein level high in fluid
- Chronic pancreatitis
- Congestive cardiac failure
- Constrictive pericarditis
- Meigs' syndrome (ovarian tumour)
- Hypoproteinaemia (e.g. nephrotic syndrome)

Chylous
- Obstruction of main lymphatic duct (e.g. by carcinoma) – chylomicrons are present
- Cirrhosis

Haemorrhagic
- Malignancy
- Ruptured ectopic pregnancy
- Abdominal trauma
- Acute pancreatitis

CLINICAL FEATURES

- Mild generalized abdominal pain and discomfort but if more severe should raise the suspicion of spontaneous bacterial peritonitis.
- Respiratory distress accompanies tense ascites, and also causes difficulty in eating.

- The presence of fluid is confirmed by demonstrating shifting dullness. It is clinically detectable when larger than 500ml. Subclinical ascites can be detected by ultrasound examination.
- Many patients also have peripheral edema.
- A pleural effusion (usually on the right side) may infrequently be found and arises from the passage of ascitic fluid through congenital diaphragmatic defects.

INVESTIGATIONS

- A diagnostic aspiration of 10-20ml of fluid should be obtained and the following performed:
  - Cell count: a neutrophil count above 250 cells/mm^3 is indicative of an underlying (usually spontaneous) bacterial peritonitis.
  - Gram stain and culture: for bacteria and acid-fast bacilli
  - Protein: a high serum ascites albumin gradient (SAAG criteria) of >1.1g/dL suggests portal hypertension and a low gradient <1.1g/dL is associated with abnormalities of the peritoneum e.g. inflammation, infection, neoplasia.
  - Cytology for malignant cells
  - Amylase- to exclude pancreatic ascites

MANAGEMENT

- Check serum electrolytes, creatinine and eGFR at the start and every other day, weigh patient and measure urinary output daily
- Bed rest to promote diuresis
- Salt restriction to less than 2g/day
- Fluid restriction if serum sodium level is below 120mEq/L
- Drugs that may contain significant amounts of sodium (up to 50mmol daily) e.g. antacids, antibiotics (especially penicillins and cephalosporins) and effervescent tablets. Sodium retaining drugs (NSAIDs, corticosteroids) should be avoided
- The maximum rate at which ascites can be mobilized is 500-700ml in 24 hours.
- The diuretic of first choice is spironolactone starting at 100mg daily. Chronic administration produces gynecomastia. Eplerenone 25mg OD does not cause gynecomastia.
- Spironolactone can be increased gradually to 400mg daily providing there is no hyperkalemia.
- Spironolactone is an aldosterone antagonist is often effective when given with loop diuretics. A loop diuretic such as furosemide 20-40mg or bumetanide 0.5mg or 1mg can be added is response is poor.

  - Side effects of loop diuretics: hyponatremia, hypokalemia and volume depletion
- Diuresis should be monitored because vigorous diuresis leads to hypovolemia and hypokalemia and precipitate hepatic encephalopathy. The goal of diuresis should be dependent on the extent of edema and be monitored by daily body weight measurement i.e.
  - Decrease weight by 0.5-0.7kg/day if no peripheral edema
  - Decrease weight by 1kg/day if peripheral edema is present
- Diuretics should be temporarily discontinued if a rise in serum creatinine level occurs representing over-diuresis and hypovolemia or if there is hyperkalemia or the development of pre-coma.
- Refractory ascites: persistent tense ascites despite maximal diuretic therapy (Spironolactone 400mg/d, Furosemide 160mg/d) or if azotemia develops (creatinine >2mg/dl) while the patients is receiving submaximal doses.
  - It occurs in 10% of ascites of chronic liver disease (CLD) origin.
  - Repeated large volume paracentesis (with IV albumin replacement if available) should be done
    - The main complication is hypovolemia and renal dysfunction (post-paracentesis circulatory dysfunction) as the ascites reaccumulates at the expense of the circulating volume, this is more likely with >5L removal and worse liver function. In patients with normal renal function and without hyponatremia this is overcome by infusing albumin (8g/L of ascitic fluid removed).
    - In practice up to 20L can be removed over 4-6 hours with albumin infusion.
  - Surgical treatment: Portal systemic shunt
  - Liver transplantation

COMPLICATIONS OF ASCITES

- Spontaneous bacterial peritonitis
- Hepatopulmonary syndrome
- Hepatorenal syndrome
- Rupture of the umbilicus

SPONTANEOUS BACTERIAL PERITONITIS

- This is a complication of ascites and in turn increases the risk of hepatorenal syndrome.
- This is usually due to *enterobacteriacae* e.g. *E.coli*, *Klebsiella*, *enterococci* or *pneumococci*.
- It is due to portal hypertension which causes a weakened gut mucosal defence and infection of ascitic fluid usually with *E. coli*.
- The condition should be suspected in any patient with ascites who clinically deteriorates.
- Spontaneous bacterial peritonitis may be asymptomatic or may present with:
  - Fever
  - Abdominal pain/tenderness
  - Vomiting
- Diagnosis is suspected when ascitic polyymorphonuclear cell count is >250/µL.
- It is confirmed by ascitic fluid culture.
- Management:
  - Antibiotics (third generation cephalosporins e.g. cefotaxime or Ceftazidime for 5-7 days) modified on the basis of culture.
  - If severe consider lifelong prophylactic antibiotics (with oral fluoroquinolones).
  - Indications: previous history of SBP, patient admitted with gastrointestinal hemorrhage, ascitic protein less than 1g/dl and candidates of liver transplant
    - Co-trimoxazole 960mg/day for 5 days (Monday-Friday)
    - Ciprofloxacin- 750mg OD weekly
    - Norfloxacin- 400mg/day
  - Refer for possible liver transplant.

HEPATORENAL SYNDROME

- This is functional renal failure in the presence of cirrhosis.
- It accounts for 25% of AKI in cirrhosis patients.
- It can also be defined as kidney failure without known causes in the presence of severe liver disease, the latter defined as ascitic cirrhosis or acute liver failure.
- A diagnosis is made after prerenal causes of renal failure are excluded.
- The urine output is low with a low urinary sodium concentration (<10mg/l), a maintained capacity to concentrate urine (i.e. tubular function is intact) and almost normal renal histology.
- There are normal urinary sediments and azotemia occurs often with disproportionately high levels of blood urea nitrogen and creatinine.
- Two- month mortality rate from hepatorenal syndrome is 90% (prognosis is grave with a 10-14 days median survival rate)

PATHOPHYSIOLOGY

- Hepatorenal syndrome occurs typically in a patient with advanced cirrhosis, portal hypertension with jaundice and ascites.
- Vigorous diuresis, NSAIDs, diarrhea, paracentesis without volume expansion, variceal bleeding and sepsis (spontaneous bacterial peritonitis) may predispose to hepatorenal syndrome.
- The initiating factor is thought to be extreme peripheral vasodilation, possibly due to nitric oxide leading to an extreme decrease in effective blood volume and hypotension.
- The Renin-angiotensin response leads to regional vasoconstriction (cortical vasoconstriction), causing renal hypoperfusion.
- There is an increased preglomerular vascular resistance causing the blood flow to be directed away from the renal cortex. This leads to a reduced glomerular filtration rate and plasma renin remains high.
- Salt and water retention occur with reabsorption of sodium from the renal tubules.
- There is also a decrease in cardiac output inappropriate to the degree of systemic vasodilation which further exacerbates the hemodynamic abnormalities.

MANAGEMENT

- Identify and treat precipitants
- Discontinue diuretics
- Volume expansion to rule out volume depletion: 1.5L IV normal saline or 5% IV albumin. If serum creatinine is decreased suspect another diagnosis.
- Restrict sodium to <2g/day if serum Na <125mEq/L the restrict fluids to <1.5 L/day
- Treat infection
- Low dose vasopressin, octreotide or norepinephrine may be given.
  - Terlipressin a splanchnic vasoconstrictor plus human albumin solution can be given.
- Liver transplantation is the accepted management. Renal failure from hepatorenal syndrome reverses with liver transplant.

LIVER TUMORS

- Tumors of the liver can either be:
  - Primary: these may be benign or malignant, but the most common are malignant.
  - Secondary (metastatic): these are the most common liver tumors, particularly from the gastrointestinal tract (From the distribution of the portal blood supply), breast or bronchus.

PRIMARY BENIGN TUMORS

- The most common benign tumor is a hemangioma. It is usually small and single but can be multiple and large.
  - Hemagiomas are usually found incidentally on ultrasound, CT or MRI and have characteristic appearances. They require no treatment.
- Hepatic adenomas are associated with oral contraceptives. They can present with abdominal pain or intraperitoneal bleeding.
  - Resection is only required for symptomatic patients, those with tumors >5cm diameter or in those in whom discontinuation of oral contraception does not result in shrinkage of the tumor.
  - Immunohistochemical characteristics are helpful in indicating malignant potential which is far more common in men

PRIMARY MALIGNANT TUMORS

HEPATOCELLULAR CARCINOMA (HEPATOMA)

- Hepatocellular carcinoma (HCC) is the 5th most common cancer worldwide.
- Males are affected more than females (4:1 to 8:1).

ETOLOGY

- Carriers of HBV and HCV have extremely high risk of developing HCC.
  - Cirrhosis is present in approximately 80% of patients with HBV.
  - The development of HCC is related to the integration of viral HBV DNA into the genome of the host hepatocyte and degree of viral replication (>10 000 copies/ ml)
  - The risk of HCC is higher in HCV than HBV (even higher with both HBV and HCV) despite no viral integration.
  - Unlike HBV infection, cirrhosis is always present in HIV infection.

- Primary liver cancer is also associated with other forms of cirrhosis including:
  - Alcoholic cirrhosis
  - Non-alcoholic fatty liver disease associated cirrhosis
  - Hemochromatosis
- Other etiological factors:
  - Aflatoxin (a metabolite of a fungus found in groundnuts)
  - Androgenic steroids
  - Contraceptive pill (weak association)

PATHOLOGY

- The tumor is either single or occurs as multiple nodules throughout the liver.
- Histologically it consists of cells resembling hepatocytes.
- It can metastasize via the hepatic or portal veins to the lymph nodes, bones and lungs.

CLINCAL FEATURES

- Common symptoms & findings: Weight loss, anorexia, fever, an ache in the right hypochrondrium, abdominal mass and ascites.
  - The rapid development of these features in a cirrhotic patient is suggestive of HCC.
- On examination an enlarged irregular tender liver may be felt. Sometimes HCC is found without symptoms in cirrhotics.
- Unusual manifestations: bloody ascites, tumor emboli, jaundice, gynecomastia, hepatic bruit or friction rub, metabolic effect (erythrocytosis, hypercholesterolemia, hypoglycemia, hypercalcemia, acquired porphyria)

INVESTIGATIONS

- Serum alpha-fetoprotein: may be raised but normal in at least 1/3 of patients.
- Ultrasound scan: shows filling defects in 90% of cases
- Enhanced CT scans: identifies HCC but it is difficult to confirm diagnosis in lesions <1cm
- MRI: helps further delineate lesions.



Hepatocellular carcinoma. (a) CT showing cirrhosis with a hepatocellular carcinoma. **(b)** T2-weighted MRI of the liver following gadolinium contrast showing a hepatocellular carcinoma.

- Tumor biopsy under ultrasonic guidance is used for diagnosis but is employed less frequent as imaging techniques show characteristic appearances (hypervascularity of the nodule and lack of portal vein wash out) and because seeding along the biopsy tract can occur.

TREATMENT AND PROGNOSIS

- Surgical resection of isolated lesions <5cm diameter or up to 3 lesions <3cm diameter is associated with a median survival of 5 years although the remaining liver remains at risk of further recurrence.
- **Liver transplantation** offers the only opportunity for cure for patients with a small primary but is limited often by the underlying causes of hepatitis and cirrhosis.
- **Conventional chemotherapy** and **radiotherapy** are unsuccessful but transarterial embolization or radiofrequency ablation in patients with small primaries as above and adequate liver function prolongs survival though less successful than surgery.
- Antiangiogenic compounds are being evaluated: sorafenib prolongs survival in patients with non-resectable tumors to 10 months.

PREVENTION

- Widespread vaccination against HBV
- Alcohol abstinence

CHOLANGIOCARCINOMA

- These are increasing in incidence and can be extrahepatic or intrahepatic.
- Intrahepatic adenocarcinomas arising from the bile ducts account for approximately 10% of primary tumors. They are not associated with cirrhosis or hepatitis.
- In the Far East, they may be associated with infection with *Clonorchis sinensis* or *Opisthorchis viverrini*.
- Clinical features are similar to primary HCC except that jaundice is frequent with hilar tumors and cholangitis is more frequent.
- Surgical resection is rarely possible and patients usually die within 6 months.
- Transplantation is contraindicated outside of specialized protocols.

SECONDARY LIVER TUMORS

- The most common liver tumors are secondary (metastatic) tumor.
- They spread from the gastrointestinal tract (from the distribution of the portal blood supply), breast or bronchus.
- They are usually multiple.

CLINICAL FEATURES

- Clinical features are variable but usually include weight loss, malaise, upper abdominal pain and hepatomegaly with or without jaundice.

DIAGNOSIS

- Ultrasound is the primary investigation, with CT or MRI to define metastases and look for a primary.
- The serum alkaline phosphatase is almost invariable raised.

TREATMENT

- This will depend on the site of the primary and the burden of liver metastases.
- The best results are obtained in colorectal cancer in patients with few hepatic metastases.
- If the primary tumor is removed and hepatic resection is performed, reasonable survival rates are possible.
- Chemotherapy is used, particularly with breast cancer.
- Radiofrequency ablation of the metastases is an alternative to surgery.
- Thermal and cryotherapy is also used.

BUDD-CHIARI SYNDROME

- There is obstruction to the venous outflow of the liver owning to occlusion of the hepatic vein.
- Cause is unknown in 1/3 of patients but specific causes including hypercoagulability states (e.g. paroxysmal nocturnal hemoglobinuria, polycythemia vera) or thrombophilia taking the contraceptive pill, or leukemia.
- Other causes include occlusion of the hepatic vein owing to posterior abdominal wall sarcomas, renal or adrenal tumors, hepatocellular carcinoma, hepatic infections (e.g. hydatid cyst), congenital venous webs, radiotherapy or trauma of the liver.
- The acute form presents with:
  - Abdominal pain
  - Nausea
  - Vomiting
  - Tender hepatomegaly and ascites (a fulminant form occurs particularly in pregnant women)
- In the chronic form there is enlargement of the liver (particularly the caudate lobe), mild jaundice, ascites, a negative hepatojugular reflux, and splenomegaly with portal hypertension.
- Investigations:
  - High protein content in the ascitic fluid
  - Ultrasound, CT or MRI will demonstrate hepatic vein occlusion with diffuse abnormal parenchyma on contrast enhancement
  - Liver biopsy: centrizonal congestion, hemorrhage, fibrosis and cirrhosis
  - Thrombophilia screening is mandatory
- Differential diagnosis:
  - Inferior vena caval obstruction
  - Right sided cardiac failure
  - Constrictive pericarditis
- Treatment:
  - Thrombolytic therapy
  - Ascites should be treated as should any underlying cause e.g. polycythemia.
  - Transjugular intrahepatic portosystemic shunt (TIPS) is the first treatment of choice as caval conmpression does not prejudice theefficacy of TIPS.
  - Liver transplantation is the treatment of choice for chronic Budd-Chiari syndrome and for fulminant form.

- Lifelong anticoagulation is mandatory following TIPS and transplantation.

THE BILIARY SYSTEM AND PANCREAS

- Bile canaliculi form a network between the hepatocytes. These join to form thin bile ductules near the portal tract, which in turn enter the bile ducts in the portal tract.
- These then combine to form the right and left hepatic ducts that leave each liver lobe.
- The hepatic ducts join at the porta hepatis to form the common hepatic duct.
- The cystic duct connects the gall bladder to the lower end of the common hepatic duct.
- The gall bladder lies under the right lobe of the liver and stores and concentrates hepatic bile, its capacity is approximately 50mL.
- The common bile duct is formed at the junction of the cystic and common duct and is 8mm in diameter or less, passing through the head of the pancreas, narrowing at its lower end to pass into the duodenum.
- The common bile duct and pancreatic duct open into the second part of the duodenum most often through a common channel at the ampulla of Vater which contains the muscular sphincter of Oddi.
- This contracts rhythmically and prevents all of the bile from entering the duodenum, by maintaining a higher pressure than the gall bladder in the fasting state.

PANCREATITIS

CHAPTER 9: NEPHROLOGY

RENAL CONDITIONS

- Patients with renal disease may have a variety of different clinical presentations.
- Some have symptoms that are directly referable to the kidney (gross hematuria, flank pain) or to associated external symptoms (edema, hypertension, signs of uremia)
- Many patients, however, are asymptomatic and are noted on routine examination to have an elevated creatinine concentration or an abnormal urinalysis.
- Specific disorders are more likely to be acute or chronic.

URINE EXAMINATION (URINALYSIS)

- Indications:
  - Metabolic disorders (Diabetes and DKA)
  - Renal dysfunction (e.g. nephrotic syndrome, nephritic syndrome)
  - Urinary tract infections
  - Hematuria
- Urine may be assessed both at the bedside (dipstick) and in the laboratory (microscopy, culture, sensitivity and urinary electrolytes).
- Urine for laboratory analysis must be transferred quickly and at the correct temperature otherwise it is becomes a breeding ground for contaminants.

BEDSIDE URINALYSIS

- Always wear gloves whilst handling urine and ensure that the dipsticks are functional and not expired.
- Before beginning the test assess the urine for appearance (color, presence or sediments), smell and consistency.

COLOUR

- Normal urine color is often described as straw, yellow or amber. This color may be altered by medications, food sources or disease.
- Vitamin tablets often result in a bright yellow urine, as does the presence of bilirubin (a bile pigment).
- Red urine may be due to blood, hemoglobin or beetroot.
- Iron supplements may cause a dark brown specimen, as might amounts of urobilin (a chemical produced in the intestines).

- Normal urine is also transparent. Turbid or cloudy urine may result from infection, the presence of blood cells, bacteria or yeast (e.g. Candida).
- Foamy urine may indicate either the presence of glucose or protein.

SMELL

- The normal smell of urine can be described as urinoid.
- Other smells include:
  - Fecal smell: gastrointestinal-bladder fistula.
  - Fruity or sweet smell: diabetic ketoacidosis.
  - Smell of ammonia: alkaline fermentation.
  - Smell of asparagus: eating a lot of asparagus.

CONSISTENCY

- Check for any urine sediments
- Check for any visible blood

- When doing the test ensure the dipstick is completely immersed in the specimen of fresh urine. Withdraw immediately, drawing or gently tapping edge along rim of container to remove excess.
- Take your time. Some of the reactions can take up to 2 minutes to cook.
- Compare the colors with the parameters shown on the urinalysis container.

PARAMATERS OF MEASURED

- These include:
  - Leucocytes (white cell count)
  - Nitrites
  - Proteins
  - pH
  - Blood
  - Specific gravity
  - Ketones
  - Bilirubin
  - Glucose

LEUCOCYTES (WHITE CELL COUNT)

- Determines the presence of whole or lysed white cells in the urine (pyuria) by detecting leucocyte esterase activity.
- A positive leucocyte esterase test correlates well with pyuria. However, the diagnosis may be missed in up to 20% of cases if a negative urinalysis dipstick is used to exclude UTI.
- False positive: contaminated specimen, trichomonas vaginalis, drugs or foods that color the urine red.
- False negative: intercurrent or recent antibiotic therapy (especially gentamicin, tetracycline and cephalosporins), glycosuria,

proteinuria, high specific gravity. Low bacteria count UTI (especially in women)

NITRITES

- Nitrates in the urine are converted to nitrates in the presence of Gram-negative bacteria e.g. *E.coli* and *Klebsiella*.
- A positive nitrate test is a surrogate marker of bacteruria.
- Positive test strongly suggests infection but negative test does not exclude it.
- False negative: drugs or foods that color the urine. Certain bacteria such as *S. saprophyticus*, *acinetobacter* and most *enterococci*.

PROTEIN

- Normal daily protein excretion should not exceed 150mg per day or 10mg/100ml. Proteinuria is defined by production of >150mg/day with nephrotic syndrome producing >3.5g/day.
- Dipstick urinalysis detects proteins and is most sensitive to albumin and less sensitive to Bence-Jones proteins and globulins.
- Trace positive results are equivalent to about 150mg/day (the upper limit)
- Proteinuria may be seen in:
  - Renal disease: nephrotic syndrome, nephritic syndrome, glomerulonephritis, malignant hypertension
  - CVS disease: benign hypertension, congestive cardiac failure
  - Drug intake: aminoglycosides, gold, amphotericin, NSAIDs, sulphonamides, penicillins.
  - Other: fever, cold exposure, stress, pregnancy, shock, severe exercise, orthostatic proteinuria, electric current injury, hypokalemia, Cushing's syndrome
- Note: Bence Jones globulin associated with multiple myeloma, lymphoma and macroglobulinemia is not detected by dipstick.

pH

- Normal urine pH is 5.5-6.5 but it may vary from as low as 4.5 to as high as 8.0. Recall the kidneys play an important role in acid-base balance.
- Causes of high urinary pH (alkali urine):
  - Systemic alkalosis
  - Renal tubular necrosis
  - Fanconi syndrome
  - UTI
  - Drugs: Amphotericin B, carbonic anhydrase inhibitor (acetazolamide), sodium bicarbonate, ASA
  - Stale ammoniacal sample (left standing)

  - Vegetarian diet, low carbohydrate diet or ingestion of citrus fruits
- Causes of low urinary pH (acidic urine):
  - Systemic acidosis
  - Diabetes mellitus
  - Starvation
  - Diarrhea
  - Malabsoprtion
  - High protein diet or fruits such as cranberries

BLOOD

- Dipstick urinalysis is able to detect hemolyzed and non-hemolyzed blood in the urine.
- Hematuria is classified:
  - Microscopic: blood is not visible with the naked eye.
  - Macroscopic
- Blood may be present in the urine following trauma, smoking, infection, inflammation, neoplasia, clotting disorders, renal calculi or strenuous exercise.
- It may also be present with:
  - Urinary tract infections,
  - Damage to glomerulus or tumors which erode the urinary tract,
  - Acute tubular necrosis,
  - Traumatic catheterization
  - Damage caused by passage of kidney stones
  - Contamination from the vagina during menstruation
  - The presence of myoglobin (myoglobinuria) after muscle injury will also cause there the reagent strip to indicate blood.

SPECIFIC GRAVITY

- Urine specific gravity is a measure of the weight of dissolved particles in urine, whereas urine osmolality reflects the number of such particles.
- Normal specific gravity: 1.002-1.035
- Decrease in specific gravity:
  - Inability to concentrate urine or excess hydration
  - Nephrogenic diabetes insipidus, acute glomerulonephritis, pyelonephritis, acute tubular necrosis
- Increase in specific gravity
  - Dehydration (fever, vomiting, diarrhea)
  - SIADH, adrenal insufficiency, pre-renal failure, hyponatremia with edema, liver failure, congestive cardiac faiulure, nephrotic syndrome, dibetes mellitus
- Specific gravity is usually fixed at 1.010 in CKD or acute tubular necrosis as compared to pre-renal acute kidney injury and inappropriate ADH secretion where specific gravity is very high- close to 1.025.

KETONES

- Ketones (acetone, aceto-acetic acid, beta-hydroxybutyric acid) are the end-point of incomplete fat metabolism. They accumulate in plasma and are excreted in urine.
- Ketonuria is seen in:
  - Diabetic ketoacidosis
  - Low carbohydrate (high fat/protein) diet
  - Starvation
  - Alcoholism
  - Eclampsia
  - Hyerthyroidism

BILIRUBIN

- Bilirubin is not present in the urine of normal healthy individuals. The presence of bilirubinuria may be an early indicator of liver disease and occur before the clinical signs of jaundice develop.
- Bilirubin is formed as a by-product of red blood cell degradation in the liver, and then conjugated with the solubilizing sugar, glucoronic acid and excreted in bile. Within the intestine, the bilirubin is converted into stercobilin (excreted in feces) and urobilinogen (excreted by the kidneys).
- Failure of conjugated bilirubin to reach the intestines (e.g. biliary obstruction) will result in bilirubinuria. Note: only conjugated bilirubin can be excreted as bilirubinuria. A positive test for urine bilirubin confirms conjugated hyperbilirubinaemia.
- Raised conjugated bilirubinemia (with bilirubinuria) is associated with hepatocellular disease, cirrhosis, viral and drug induced hepatitis, biliary tract obstruction (e.g. choledocholithiasis), pancreatic causes of obstructive jaundice (e.g. carcinoma of the head of the pancreas) and recurrent idiopathic jaundice of pregnancy.
- False positive: phenothiazines.
- False negative: ascorbic acid (Vitamin C), aged sample (conjugated bilirubin hydrolses to unconjugated bilirubin at room temperature), rifampicin and exposure to UV light (converts bilirubin to biliverdin)

UROBILINOGEN

- Urobilinogen is normally present in the urine in low concentrations (0.2-1.0mg/dl or <17 μmol/L).
- Bilirubin is converted to urobilinogen by intestinal bacteria in the duodenum. Most urobilinogen is excreted in feces or transported back to the liver and converted into bile. The remaining urobilinogen (<1%) is excreted in the urine.
- Urobilinogen is present in increased concentrations in the urine in patients with cirrhosis, infective hepatitis, extravascular

hemolysis, hemolytic anemia, pernicious anemia, malaria and hepatitis secondary to infectious mononucleosis.

- Urobilinogen levels are decreased or absent in obstructive jaundice and elevated in bilirubinuria.

Dipstick urinalysis	Normal	Biliary obstruction	Hepatic disease	Hemolytic disease
Bilirubin	Negative	Positive	Positive	Negative
Urobilinogen	Positive	Negative/decreased	Increased	Increased

GLUCOSE

- Glucose is not normally present in the urine with <0.1% of glucose normally filtered by the glomerulus appears in urine (<130mg/day)
- Glycosuria indicates as rise in serum glucose levels.
- It may be seen in:
  - Diabetes mellitus
  - Renal tubular
  - Pregnancy
  - Drugs: cephalopsorins, penicillins, nitrofurantoin, methyldopa, tetracycline, lithium, carbamazepine, phenothiazines, steroids, and thiazides.

ACUTE KIDNEY INJURY (AKI)

- Acute kidney injury is an abrupt deterioration in parenchymal renal function, which is usually but not invariably, reversible over a period of days or weeks.
- It is a rapid reduction in kidney function over hours to days, as measured by serum urea and creatinine and leading to failure to maintain fluid, electrolyte and acid-base homeostasis.
- In clinical practice such deterioration in renal function is sufficiently severe to results in uremia.
- Acute renal failure is a syndrome characterized by:
  - Rapid decline in glomerular filtration rate (hours to days)
  - Retention of nitrogenous wastes due to failure of excretion
  - Disturbance in extracellular fluid volume and
  - Disturbance in electrolyte and acid base homeostasis.
- The hallmark of acute renal failure is azotemia, often with oliguria
  - Azotemia: increase in nitrogenous waste products in the blood (Blood urea nitrogen and creatinine) without symptoms (GFR is about 20-35% of normal).
  - Uremia implies a deterioration of renal function associated with symptoms (GFR <20% of normal)
  - Oliguria is a condition in which a person does not produce enough urine.
- Oliguria is usually but not invariably, a feature.
- Based on the amount of urine output acute renal failure may be classified as:
  - Anuric: if urine volume is less than 100ml/day
  - Oliguric- if urine volume is less than 400ml/day
  - Non-oliguric- if urine volume is greater than or equal to 400ml/day
- AKI may cause sudden life-threatening biochemical disturbances and is a medical emergency.
- AKI can also be defined as any 1 of the following:
  - Urine output <0.5 ml/kg/hr for 6 hours or 8 hours consecutive in kids
  - Creatinine x 1.5 from baseline in 1 week
  - Creatinine increase greater than 26 µmol/L in 48 hours

Normal urine output= 0.5-1 ml/kg/hr

Normal Creatinine

Male= 53-106 µmol/L (0.6-1.2mg/dl

Female= 44-97 µmol/L (0.5-11mg/dl)

Normal Urea

2.5 to 7.2 mmol/L (7 to 20mg/dl)

Normal BUN

3.6 to 7.1 mmol/L (10 to 20mg/dl)

- Decrease in GFR 25% in children over 7 days

- The distinction between acute and CKD or even acute-on chronic kidney disease cannot be readily apparent in a patient presenting with uremia.
- In view of these difficulties, the Acute Dialysis Quality initiative group proposed the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria utilizing either increases in serum creatinine or decreases in urine output.
- It characterizes 3 levels of renal dysfunction (R, I, F) and 2 outcome measures (L, E). These criteria indicate an increasing degree of renal damage and have a predictive value for mortality. (See the table below for RIFLE classification for acute kidney injury)

Grade	GFR criteria	Urine output
Risk (KDIGO Stage 1)	Serum creatinine x 1.5 baseline or increase >26μmol/L in 48 hours	Urine output <0.5ml/kg/h for 6 hours
Injury (KDIGO Stage 2)	Serum creatinine x 2-2.9 baseline	Urine output <0.5 ml/kg/h for 12 hours
Failure (KDIGO Stage 3)	Serum creatinine x 3 or Serum creatinine >350 μm with an acute rise >40 μmol/L or dialyzed	Urine output <0.3 ml/kg/h for 24 hours or anuria for 12 hours
Loss	Persistent AKI >4 weeks (1 month)	
ESKD (end stage Kidney disease)	Persistent renal failure >3 months	

- Note: KDIGO (Kidney Disease Improving Global Outcome)
- Risk factors for developing AKI
  - Age>75
  - Chronic kidney disease
  - Cardiac failure
  - Peripheral vascular disease
  - Chronic liver disease
  - Diabetes
  - Drugs (especially newly started)
  - Sepsis
  - Poor fluid intake/increased losses
  - History of urinary symptoms

- Signs and symptoms of uremia include:
  - General: Nausea and vomiting, fatigue, weight loss, anorexia (loss of appetite), fetor uremicus (urine like odor of the breath), metallic taste, hiccups, pruritus, uremic frost, muscle cramps, metabolic flap/asterexis
  - Neurologic: encephalopathy (change in mental status, Intellectual clouding, confusion, drowsiness, fits, coma, decreased memory and attention), seizures, neuropathy.
  - Cardiovascular: Pericarditis, hypertension, volume overload, CHF, cardiomyopathy, hyperlipidemia, accelerated atherosclerosis
  - Hematologic: Anemia, and bleeding (due to platelet dysfunction)
  - Metabolic: hyperkalemia, hyperphosphatemia, acidosis, hypocalcemia, secondary hyperparathyroidism, osteodystrophy

CLASSIFICATION OF ACUTE KIDNEY INJURY

- Renal failure results in reduced excretion of nitrogenous waste products, of which urea is the most commonly measured. A raised serum urea concentration (Uremia) is classified as:
  - Pre-renal (40-70%)
  - Renal (10-50%)
  - Post-renal (10-25%)
- More than one category may be present in an individual patient.
- Other causes of altered serum urea and creatinine concentration include:

	Decreased concentration	Increased concentration
Urea	• Low protein intake • Liver failure • Sodium valproate treatment	• Corticosteroid treatment • Tetracycline treatment • Gastrointestinal bleeding
Creatinine	• Low muscle mass	• High muscle mass • Red meat ingestion • Muscle damage (rhabdomyolysis) • Decreased tubular secretion e.g. Cimetidine, trimethoprim therapy

PRE-RENAL UREMIA

- This accounts for nearly 55% of all cases of acute renal kidney.
- It is also known as pre-renal azotemia.
- There is impaired perfusion of the kidneys with blood.
- Usually the kidney is able to maintain glomerular filtration close to normal despite wide variations in renal perfusion pressure and volume status- so called 'autoregulation'. Further depression of renal perfusion leads to a drop in the glomerular filtration and development of pre-renal uremia.
- Renal hypoperfusion leads to a decrease in GFR as an appropriate response to retain Na^+/H_2O. There is no renal cell injury and restoration of perfusion restores function.
- Prolonged hypoperfusion can lead to acute tubular necrosis, thus ischemic AKI is a spectrum from pre-renal to intrinsic AKI, differentiated by presence of renal cell injury.

CAUSES OF PRE-RENAL UREMIA

- This results either from
  - Hypovolemia: hemorrhage, severe diarrhea, severe vomiting, burns dehydration, renal fluid loss (diuretics, osmotic diuresis e.g. diabetes mellitus), hypoadrenalism, third spacing (pancreatitis, peritonitis, trauma, burns, severe hypoalbuminemia).
  - Low cardiac output and hypotension: diseases of myocardium (dilated cardiomyopathy), valves, and pericardium, arrhythmias, tamponade, congestive heart failure, others (pulmonary hypertension, massive pulmonary embolism)
  - Altered renal systemic vascular resistance ratio: systemic vasodilatation (sepsis, anaphylaxis, renal hypoperfusion with impairment of renal autoregulatory response e.g. with NSAIDs, ACE inhibitors. NSAIDs constrict the afferent arterioles while ACEi and ARBs dilate efferent arterioles than afferent arterioles)
  - Vascular disease limiting renal blood flow

CLINICAL FEATURES

- Pre-renal failure is suggested by clinical signs of:
  - Intravascular volume depletion (e.g. orthostatic hypotension, rapid pulse and poor skin turgor).

- Congestive heart failure e.g. raised JVP, S3, dependent edema and pulmonary rales.

DIAGNOSIS

- Careful history is essential:
  - Exposure to nephrotoxins and drugs
  - Anuria may indicate post-renal causes
  - Skin rashes may indicate allergic nephritis
  - Evidence of volume depletion: diarrhea, bleeding
  - Pelvic and per-rectal examination: look for evidence of abortion
  - Ischemia or trauma to the legs or arms may indicate rhabdomyolysis
  - Recent surgical or radiologic procedures
  - Past and present use of medications
  - Family history of renal disease
- Physical examination should be focused to rule out possible differential diagnosis.
- In pre-renal uremia:
  - There is decrease in GFR (due to decreased blood flow), azotemia and oliguria.
  - Urine sodium (<20mmol/L) is low if there is avid (eager) tubular reabsorption, but may be increased by diuretics or dopamine.
  - The urine osmolarity is also >500mOsm/kg also indicating there is no damage to the tubules yet.
  - The urine specific gravity is >1.020
  - The serum BUN: Cr increases (20mg/dl) and is more than 15mg/dl (normal)
    - Recall BUN and Creatinine are both filtered by the glomerulus but only BUN is reabsorbed and creatinine is not.

- In pre-renal uremia because of decreased renal perfusion the renin angiotensin system is activated resulting in release of aldosterone from the adrenal glands causing resorption of sodium and water. Resorption of water will also result in resorption of some filtered BUN, this increased the BUN: Cr ratio.

➢ The fractional excretion sodium (FE_{Na}) i.e. a ratio of sodium clearance to creatinine clearance, is less than 1% indicating there is no damage to the tubules yet. It may remain low in some 'intrinsic' renal disease, including contrast nephropathy and myoglobinuria.

Criteria for distinction between pre-renal and intrinsic causes of renal dysfunction

	Pre-renal	Intrinsic
Urine specific gravity	>1.020	<1.010
Urine osmolality (mOsm/kg)	>500	<350
Urine sodium (mmol/L)	<20	>40
$Fe_{Na} = \frac{U_{Na}}{P_{Na}} + \frac{U_{Cr}}{P_{Cr}} \times 100$	<1%	>1%

FE, fractional excretion; P, plasma; U, urine; Cr, creatinine; Na, sodium.

- Laboratory tests, however are no substitute for clinical assessment. A history of blood or fluid loss, sepsis potentially leading to vasodilatation or of cardiac disease may be helpful.
- Hypotension (especially postural), a weak rapid pulse and a low jugular venous pressure will suggest that the uremia is pre-renal
- In doubtful cases, measurement of central venous pressure is often invaluable, particularly with fluid challenge.

MANAGEMENT

- Treat the underlying cause. There is no specific treatment indicated for AKI, it is just supportive.
- If the pre-renal uremia is a result of hypovolemia and hypotension, prompt replacement with appropriate fluid is essential to correct the problem and prevent development of ischemic renal injury and acute kidney disease.
  - Severe hypovolemia due to hemorrhage should be corrected with packed red blood cells, whereas normal saline is usually appropriate replacement for mild to moderate hemorrhage or plasma loss (e.g. burns, pancreatitis).
  - Urinary and gastrointestinal fluids can vary greatly in composition but are usually hypotonic. Hypotonic solution (e.g. 0.45% saline) are usually recommended as initial replacement in patient with Pre-renal failure due to increased urinary or GI fluid losses, although normal saline may be more appropriate in severe cases.
  - If difficult balance with risk of fluid overload, consider titrating input hourly by matching previous hours output + 25ml/h for insensible losses. If Euvolemic review balance daily over 24 hour period aim to match input to loss + 500ml for insensible loss.
  - Consider fluid boluses if you think the patient is dehydrated and has pre-renal AKI.
    - Fluid challenge if patient dehydrated: give 250-500ml of saline over 30 minutes. Repeat challenge if still dehydrated (give fluids until JVP and systolic BP >100mmHg) caution in patients with cardiac dysfunction
    - Once fluid replete continue fluids at 20ml + Previous hour's urine output per hour
  - For bleeding is still in shock despite 2L crystalloid then cross-match blood and transfuse FFP alongside packed red cells (1:1 ratio) and aim for platelets >100 and fibrinogen >1.

Management box: Pre-renal failure

- Treat underlying cause
- Fluid replacement: Pack red blood cells and normal saline
- Monitoring blood pressure (input/output chart).
- Monitoring serum potassium and acid base status
- Antibiotics to treat sepsis, Antiemetics for vomiting
- Stop Nephrotoxic drugs: NSAIDs, ACEi, ARBs and Diuretics
- Adjust meds to GFR.
- Dialysis

  - Listen to lungs to assess for fluid overload. Signs of fluid overload: increased BP, increased JVP, lung crepitations, peripheral edema, gallop rhythm on cardiac auscultation.
- Since pre-renal and renal uremia may co-exist and fluid challenge in the latter situation may lead to volume overload with pulmonary edema, careful clinical monitoring is vital.
- Blood pressure should be checked regularly and signs of elevated jugular venous pressure and of pulmonary edema sought frequently.
- Central venous pressure monitoring is usually advisable. If the problem relates to cardiac pump insufficiency or occlusion of the renal vasculature, appropriate measures- albeit often unsuccessful need to be taken.
- Serum potassium and acid-base status should be monitored carefully.
- Antibiotics should also be given to treat any infection (Sepsis).
- Give Antiemetics for patients vomiting
- Stop NSAIDs, ACE inhibitors, angiotensin receptor antagonists and Diuretics.
- The role of Furosemide is uncertain. Some advocate it for fluid overload but NICE doesn't and there is no good trial evidence.
- Dialysis can be done in refractory cases.

INTRARENAL/ INTRINSIC UREMIA

- This accounts for nearly 40% of all Acute renal failure cases.

ETIOLOGY

- Causes include:
  - Acute tubular interstitial necrosis (most common cause): can either be ischemic (common) or nephrotoxic
    - Ischemic: prolonged pre-renal
      - Hemorrhage
      - Burns
      - Diarrhea and vomiting, fluid loss from fistulae
      - Pancreatitis, Diuretics
      - Myocardial infarction, Congestive cardiac failure, Endotoxic shock, Snake bite
      - Hepatorenal syndrome
      - Pre-eclampsia and eclampsia
    - Nephrotoxic:
      - Myoglobinemia

- ♦ Hemoglobinemia (due to hemolysis e.g. in Falciparum malaria, 'blackwater fever')
- ♦ Radiological contrast
- ♦ Drugs e.g. aminoglycosides, platinum derivatives, heavy metals, Lithium

➢ Acute Interstitial nephritis (AIN): glomerulonephritis, including rapidly progressive glomerulonephritis (RPGN)
- o Allergic: sulfa, beta lactams, NSAIDs, traditional meds
- o Infection: pyelonephritis
- o Infiltrative: sarcoid, lymphoma, leukemia

➢ Disease of glomeruli or renal microvasculature (renovascular):
- o Renal artery stenosis,
- o Vasculitis, accelerated/malignant hypertension,
- o Cholesterol embolism,
- o Microangiopathy: hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, pre-eclampsia and DIC
- o Crescentic glomerulonephritis

ACUTE TUBUOINTERSTITIAL NECROSIS

- This is the most common cause of AKI.
- This is injury and necrosis of tubular epithelial cells.
- Etiology may be ischemic or nephrotoxic:

➢ Ischemic- decreased blood supply results in necrosis of tubules.
- o Often preceded by pre-renal azotemia (Hypovolemia, low cardiac output, renal vasoconstriction, systemic vasodilatation).
- o Other causes include obstetric complications (abruptio placentae, postpartum hemorrhage).
- o Proximal tubule and medullary segment of the thick ascending limb are particularly susceptible to ischemic damage.

➢ Nephrotoxic- toxic agents result in necrosis of tubules.
- o Proximal tubule is particularly susceptible.
- o Causes include aminoglycosides (most common), heavy metals (e.g. lead and platinum derivative), lithium, myoglobiuria (e.g. from crush injury to muscle, rhabdomyolysis, electric burns), ethylene glycol (associated with oxalate crystals in urine), radiocontrast dye and urate (e.g. tumor lysis syndrome)

- Hydration and allopurinol are used prior to initiation of chemotherapy to decrease risk of urate-induced acute tubular necrosis.

- Necrotic cells plug tubules, obstruction decreases GFR.
  - Brown, granular casts are seen in the urine in 75% of cases.
- Dysfunctional tubular epithelium results in decreased reabsorption of BUN (serum BUN:Cr <15mg/dl), decreased reabsorption of sodium (FENa> 2%) and inability to concentrate urine (urine osm< 350mOsm/kg).

PATHOGENESIS

- Factors implicated in the development of Acute tubulointestitial necrosis include:
  - Intrarenal microvascular vasoconstriction:
    - Vasoconstriction is increased in response to endothelin, adenosine, thromboxane A2, leukotrienes and sympathetic nerve activity.
    - Vasodilation is impaired due to reduced sensitivity in response to nitric oxide, prostaglandins (PGE_2), acetylcholine and bradykinin. There is also increased endothelial and vascular smooth muscle cell structural damage
    - Increased leucocyte-endothalial adhesion, vascular congestion and obstruction, leucocyte activation and inflammation.
  - Tubular cell injury: ischemic injury results in rapid depletion of intracellular ATP stores resulting in cell death by necrosis or apoptosis due to:
    - Entry of calcium into the cells
    - Induction by hypoxia of inducible nitric oxide synthase with increased production of nitric oxide causing cell death
    - Increased production of intracellular proteases such as calpain which causes proteolysis of cytoskeleton protein and cell wall collapse
    - Activation of phospholipase A2 with increased production of free fatty acids particularly arachidonic acid, due to its action on the lipid layer of cell membranes.
    - Cell injury resulting from reperfusion with blood after initial ischemia causing excessive free radical generation.
    - Tubular obstruction by desquamated viable or necrotic cells and casts
    - Loss of cell polarity i.e. integrins located on the basolateral side of the cell are translocated to the apical surface when combined with other desquamated cells forms casts, with tubular obstruction and back leak of tubular fluid.

  - Tubular cellular recovery: tubular cells have the capacity to regenerate rapidly and to reform the disrupted tubular basement membrane, which explains the reversibility of ATN.
- In established ATN, renal blood flow is much reduced, particularly blood flow to the renal cortex. Ischemic tubular damage contributes to a reduction in glomerular filtration by the following mechanisms:
  - Glomerular contraction: reducing the surface area available for filtration due to reflex afferent arteriolar spasm mediated by increased solute delivery to the macula densa. Increased solute delivery is due to impaired sodium absorption in the proximal tubular cells because of loss of cell polarity with mislocalization of the Na/K-ATPase and impaired tight junction integrity, resulting in decreased apical-to-basal transcellular sodium absorption.
  - 'Back leak' of filtrate: in the proximal tubule owing to loss of function of the tubular cells
  - Obstruction of the tubules: by debris shed from ischemic tubular cells, these appear on renal biopsy as flat rather than the normal tall appearance.

COURSE

- Stages: acute kidney injury due to ATN typically occurs in 3 stages: Azotemic, Diuretic and recovery phases. The initial azotemic stage can either be oliguric or non-oliguric type.
- Oliguria is common in the early stages.
- Non-oliguric AKI is usually a result of less severe renal insult.
- Morbidity and mortality are affected by the presence of oliguria:
  - GI bleeding, septicemia, metabolic acidosis and neurologic abnormalities are common in oliguric patients than non-oliguric patients.
  - The mortality rate for oliguric patients is 50% where as that of non-oliguric patients is only 26%.
- Recovery of renal function typically occurs after 7-21 days, although recovery is delayed by continuing sepsis.
- In the recovery phase GFR may remain low while urine output increases sometimes to many liters a day owing to defective tubular reabsorption of filtrates.
- Clinical course is variable and ATN may last for up to 6 weeks even after a relatively short lived initial insult.
- Eventually renal function usually returns to almost normal or normal (except in renal cortical necrosis).

- No treatment is currently available to reduce the duration of ATN once it has occurred.
- The used of IV mannitol, furosemide or 'renal-dose' dopamine (1-5mcg/kg/min) is not supported by controlled trial evidence and none of these treatments is without risk.
- Note: in the polyuric (aka diuretic) phase of kidney injury as the kidney heals from AKI, tubules regenerate but water concentration is last function to return. There may also be increased osmotic load from renal toxin accumulation and this leads to massive polyuria. Treatment is with IV fluids to replace the loss.

CLINICAL FEATURES

- Clinical features:
  - Oliguria with brown, granular casts.
  - Elevated BUN and creatinine.
  - Hyperkalemia (Due to decreased renal excretion, particularly following trauma to muscle and in hemolytic states) with metabolic acidosis (decreased excretion of organic acids).
  - Hyponatremia (due to water overload if patients have continued to drink in the face of oliguria or overenthusiastic fluid replacement with 5% glucose has been carried out)
  - Fluid overload:
    - Pulmonary edema (due to salt and water retention, particularly after inappropriate attempts to initiate diuresis by infusion of normal saline without adequate monitoring of patient's volume status)
    - Orthopnea, Paroxysmal nocturnal dyspnea, peripheral edema
  - Hypocalcemia (due to reduce renal production of 1,25-dihydroxycholecalciferol)
  - Hyperphosphatemia (due to phosphate retention)
  - Signs: Symptoms of uremia
    - Intellectual clouding, confusion, drowsiness, fits, coma,
    - Uremic frost, hiccups, metallic tast
    - Hemorrhagic episodes (Epistaxis and GIT bleeding)
    - Metabolic flap/Asterexis
    - Anorexia, Nausea and vomiting
    - Fatigue
    - Pruritus

  - Severe infection may have initiated the AKI or have complicated it owing to the impaired immune defenses of the uremic patient or ill-considered management such as the insertion and retention of an unnecessary bladder catheter with complicating UTI and bacteremia.
- Reversible but often requires supportive dialysis since electrolyte imbalances can be fatal.
  - Oliguria can persist for 2-3 weeks before recovery, tubular cells (stable cells) take time to reenter the cell cycle and regenerate.
- See management section for details on management.

ACUTE INTERSTITIAL NEPHRITIS

- Drug-induced hypersensitivity involving the interstitium and tubules results in acute renal failure (intrarenal azotemia).
- Causes include NSAIDs, penicillin and diuretics.
- Presents as oliguria, fever and rash days to weeks after starting a drug, eosinophils may be seen in urine.
- Resolves with cessation of drug.
- May progress to renal papillary necrosis.

RENAL PAPILLARY NECROSIS

- Necrosis of renal papillae.
- Presents with gross hematuria and flank pain.
- Causes include:
  - Chronic analgesic abuse (e.g. long term phenacetin or aspirin use)
  - Diabetes mellitus
  - Sickle cell trait or disease
  - Severe acute pyelonephritis

POST-RENAL UREMIA (OBSTRUCTION)

- Accounts for 5% of all acute renal failure cases.
- Uremia results from obstruction of the urinary tract at any point from the calyces to the external urethral orifice (meatus). This results in dilation of the tract above the obstruction. Dilation of the renal pelvis is known as hydronephrosis.

ETIOLOGY

- Causes can be

- Within the lumen: calculus, blood clot, sloughed papilla (diabetes, analgesia abuse, sickle cell disease or trait), schistosomiasis, tumor of renal pelvis or ureter bladder tumor
- Within the wall: pelviuretetic neuromuscular dysfunction (congenital, 10% bilateral), ureteric stricture (TB, especially after treatment, calculus, after surgery), ureterovesical stricture (congenital, ureterocele, calculus, schistosomiasis), congenital megaureter, congenital bladder neck obstruction, neuropathic bladder, urethral stricture (calculus, gonococcal, after instrumentation), congenital urethral valve, pin-hole meatus.
- Pressure from outside: pelviureteric compression (bands, aberrant vessels), tumors, diverticulitis, aortic aneurysm, retroperitoneal fibrosis, accidental ligation of ureter, retrocaval ureter (right sided obstruction), prostatic obstruction (CA prostate, BPH), phimosis.

- Screening for urinary obstruction may present in an acute fashion (if obstruction of a single functioning kidney e.g. a calculus) but typically is of insidious onset.

PATHOPHYSIOLOGY

- Obstruction which may be intra renal i.e. tubules including collecting ducts or extra-renal i.e. renal calyces to uretheral meatus causes a back flow of filtrate and resultant pressure on the glomerulus thus reducing the GFR.
- Lower urinary tract obstruction may be suggested by suprapubic or flank mass or symptoms of bladder dysfunction (e.g. hesitancy, urgency)
- Decreased outflow results in decreased GFR, azotemia and oliguria.
- During early stage of obstruction, increased tubular pressure "forces" BUN into the blood (Serum BUN:Cr ratio >15), tubular function remains intact (FENa <1% and urine osm> 500mOsm/kg)
- With longstanding obstruction, tubular damage ensues, resulting in decreased reabsorption of BUN (serum BUN:Cr ratio <15), decreased reabsorption of sodium (FENa>2%) and inability to concentrate urine (Urine osm <350 mOsm/Kg)

MANAGEMENT

- Management of post-renal ARF requires close collaboration between nephrologist, urologist and radiologist.
- Obstruction of urethra or bladder neck is usually managed initially by transurethral or suprapubic placement of a bladder catheter which provides temporary relief while the obstructing lesion is identified and treated definitively.

- Similarly, ureteric obstruction may be treated initially by percutaneous catheterization of the dilated renal pelvis or ureter.

DIAGNOSTIC APPROACH

- Investigations are aimed at:
  - Determining whether the patient has acute or chronic uremia
  - Determining the cause of uremia i.e. pre-renal, renal or post-renal
  - Determining the underlying cause

ACUTE OR CHRONIC UREMIA

- This depends on:
  - History and Duration of symptoms
  - Examination
  - Previous urinalysis or measurements of renal function
- History:
  - Consider these things for all patients. Remember, Kidney injury in the hospital is often tied into another problem (infection, heart failure, medications).
  - Decreased or no urine output, flank pain, edema, hypertension or discolored urine? Hesitancy, Frequency?
  - Weakness and easy fatigability (from anemia), anorexia, vomiting, diarrhea, mental status changes or seizures and edema?
  - Fever, cough, dysuria? Bleeding (i.e. melena, blood per rectum)? New/changed doses in medications?
  - Does the patient have medical problems that pre-dispose to CKD (i.e. HIV, diabetes, HTN)
- Examination: vital signs (including orthostatics), Tenderness, Prostate exam
- A rapid rate of change of serum urea and creatinine with time suggests an acute process.
- A normochromic normocytic anemia suggests chronic disease but anemia may complicate many diseases that cause AKI owing to a combination of hemolysis, hemorrhage and deficient erythropoietin production.
- Ultrasound assessment of renal echogenicity and size is helpful. Small kidneys of increased echogenicity are diagnostic of a chronic process, although the reverse is not true the kidney may remain normal in size in diabetes and amyloidosis for instance.

- Evidence of renal osteodystrophy (e.g. digital subperiosteal erosions due to hyperparathyroid bone disease) is indicative of CKD

PRE-RENAL, RENAL OR POST RENAL UREMIA

- Bladder outflow obstruction is ruled out by insertion of a urethral catheter or flushing of an existing catheter which should be removed unless a large volume of urine is obtained.
- Absence of upper tract dilation on renal ultrasound will with very rare exceptions rule out urinary tract obstruction.
- The distinction between pre-renal and renal uremia may be difficult.

Criteria for distinction between pre-renal and intrinsic causes of renal dysfunction

	Pre-renal	Intrinsic
Urine specific gravity	>1.020	<1.010
Urine osmolality (mOsm/kg)	>500	<350
Urine sodium (mmol/L)	<20	>40
$Fe_{Na} = \frac{U_{Na}}{P_{Na}} + \frac{U_{Cr}}{P_{Cr}} \times 100$	<1%	>1%

FE, fractional excretion; P, plasma; U, urine; Cr, creatinine; Na, sodium.

INVESTIGATIONS

- Urinalysis and microscopy
  - Urinalysis
    - Trace or no proteinuria with pre-renal and post-renal acute failure
    - Mild to moderate proteinuria with acute tubulointerstitial necrosis.
    - Moderate to severe proteinuria with glomerular diseases.
    - WBCs (pyuria): UTI, Acute interstitial nephritis
    - Blood (hematuria) and protein (albuminuria): Glomerulonephritis, stones, UTI, tumor, trauma. Blood is microscopic in Acute interstitial nephritis.
  - Microscopy
    - RBCs and RBC casts in glomerular disease (glomerulonephritis, Rapid progressive glomerulonephritis)

    - Presence of a few formed elements or hyaline casts is suggestive of prerenal or postrenal failure.
    - Crystal RBCs and WBCs in post-renal failure.
    - Many RBCs may suggest calculi, trauma, infection or tumor
    - Eosinophilia (with Eosinophil casts): occurs in 95% of patients with acute allergic nephritis. Neutrophils may also be seen.
    - Brownish pigmented granular or tubular epithelial cellular casts and many renal epithelia cells are seen in patients with acute tubular necrosis.
  - Urine culture if there are signs of infection.
- Urine chemistry: Urine Sodium: <1% in prerenal, as the kidneys retain their function. >2% in renal causes
- Bloods:
  - Full blood count: decreased Hemoglobin (CKD), increased WBC (infection, eosinophilia in AIN), decreased platelets (hemolytic uremic syndrome, Thrombotic thrombocytopenic purpura)
  - Serum urea, creatinine and electrolytes (Sodium, potassium, chloride, phosphate, calcium, bicarbonate)
  - Liver function test and Liver enzymes: hepatorenal syndrome
    - Serum albumin
    - PT, PTT, INR: DIC in sepsis, altered clotting in CKD.
  - Serum Creatinine Kinase: rhabdomyolysis
  - C reactive protein: infection
  - Arterial blood gasses: metabolic acidosis
  - Blood culture in sepsis
- Radiography/imaging
  - Ultrasound of kidneys: kidney size & shape, and for detecting hydronephrosis (dilated calyces) or hydroureter. It also helps to seen renal calculi and renal vein thrombosis
  - Retrograde pyelography: done when obstructive uropathy is suspected.
  - Abdominal X-ray
  - ECG: increased potassium
  - Chest X-ray: pulmonary edema, systemic disease
  - Abdominal CT
- Renal biopsy
  - Indications
    - Any suspicion of rapid progressive glomerulonephritis
    - Prolonged ATN (not recovered <3 weeks)

- No cause found for AKI.

MANAGEMENT

- General measures:
  - Exclude reversible causes: obstruction should be relieved; infection should be treated.
  - Good nursing and physiotherapy
  - Regular oral toilet and chest physiotherapy
  - Fluid input and output chart
  - Monitoring and maintenance urine output: although the prognostic importance of oliguria is debated, management of non-oliguric patients is easier. Loop diuretics may be useful to convert the oliguric form of ATN to the non-oliguric form. High doses of loop diuretics such as Furosemide (up to 200 to 400mg IV) may promote diuresis in patients who fail to respond to conventional doses.
  - Daily weighing
  - The patient should be confined to bed only if essential
  - Avoid drugs which may cause damage to the kidneys e.g. loop diuretics, beta blockers, ACE inhibitors, ARBs, aminoglycosides (gentamicin, streptomycin), amphotericin B, Penicillins, Sulphonamides, NSAIDs, corticosteroids, and penicillamine
  - Avoid intravenous cannulae, bladder catheters and other invasive devices to avoid infection.
  - Diet:
    - Adequate calorie intake is essential in patients with AKI.
    - Diet should be reduced in protein but contain carbohydrates
    - Routes of administration, in preferred order are enteral by mouth, enteral by NG tube and parenteral. The last of these is however only necessary if vomiting or bowel dysfunction render the enteral route inappropriate.
    - Vitamin supplementation.
- Fluid and electrolyte balance (potassium, phosphate, calcium)
- Management of complications: Pulmonary edema, anemia, sepsis, metabolic acidosis, electrolyte imbalances and GIT bleeding

- Dialysis: dialysis replaces renal function until regeneration and repair takes place to restore renal function. Hemodialysis and peritoneal dialysis appears equally effective for management of AKI.
  - Absolute indications
    - Symptoms or signs of uremic syndrome
    - Refractory hypervolemia
    - Severe hyperkalemia
    - Metabolic acidosis

INDICATIONS OF DIALYSIS

A- acid-base imbalance (Acidosis)

E-electrolyte imbalance (Hyperkalemia)

I- intoxication (methanol, ethylene glycol, lithium, salicylates)

O-overload of volume (pulmonary edema)

U-uremia (pericarditis, encephalopathy, severe bleeding)

EMERGENCY MEASURES

FLUID AND ELECTROLYTE BALANCE

- Twice daily clinical assessment is needed. In general, once the patient is euvolemic.
- Daily fluid intake should equal urine output plus losses from fistulae and from vomiting, plus an allowance of 500ml daily for insensible loss. Febrile patients will require an additional allowance.
- Sodium and potassium intake should be minimized.
- If abnormal loss of fluid occurs e.g. in diarrhea, additional fluid and electrolytes will be required.
- The development of signs of salt and water overload (peripheral edema, basal crackles, elevation of jugular venous pressure) or of hypovolemia should prompt reappraisal of fluid intake.
- Large changes in daily weight reflecting change in fluid balance status should also prompt a reappraisal of volume status.
- Hypervolemia can usually be managed by restriction of salt and water intake and diuretics.

HYPERKALEMIA

- Cardiac (cardiac dysrhythmias i.e. ventricular fibrillation) and neurologic complications may occur if serum potassium level is >6.5mEq/L
- Management:
  - Restrict dietary potassium intake
  - Give calcium gluconate 10ml of 10% solution over 5 minutes
  - Glucose solution 50ml of 50% glucose plus insulin 10 units IV
  - Give potassium binding ion exchange resin (Kayexalate)
  - Dialysis: if medical therapy fails or the patient is very toxic

ECG findings in hyperkalemia

- Peaked T-waves best seen in precordial leads,
- Shortened QT interval
- sometimes ST segment depression
- Widened QRS complex

PULMONARY EDEMA

- Salt and water restriction
- Diuretics (IV furosemide)
- Dialysis or hemofiltration

SEPSIS

- Infections, when detected, should be treated promptly, bearing in mind the need to avoid nephrotoxic drugs and to use drugs with appropriate monitoring and drug levels (e.g. gentamicin, vancomycin).
- Prophylactic antibiotics or barrier nursing is not recommended in all cases.

HYPERPHOSPHATEMIA

- Is usually controlled by restriction of dietary phosphate and by oral aluminium hydroxide or calcium carbonate which reduce gastrointestinal absorption of phosphate.

HYPOCALCEMIA

- Does not usually require treatment.

METABOLIC ACIDOSIS

- Is not treated unless serum bicarbonate concentration fall below 15mmol/L or arterial pH falls below 7.2.
- More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels.
- Patients are monitored for complications of bicarbonate administration e.g. hypervolemia, metabolic alkalosis, hypocalcemia and hypokalemia.

- From a practical point of view most patients requiring sodium bicarbonate need emergency dialysis within days.

ANEMIA

- Blood transfusion if severe or if recovery is delayed

GI BLEEDING

- Regular doses of antacids appear to reduce the incidence of GIT hemorrhage significantly and may be more effective in this regard than H2 antagonists or proton pump inhibitors.

COMPLICATIONS OF ACUTE RENAL FAILURE

- Intravascular overload: may be recognized by weight gain, hypertension, elevated central venous pressure (raise JVP), pulmonary edema.
- Electrolyte disturbances:
  - Hyperkalaemia (serum potassium> 5.5mEq/L): develops as a result of decreased renal excretion combined with tissue necrosis or hemolysis.
  - Hyponatremia (serum sodium <135mEq/L): results from excessive water intake in the face of excretory failure (dilution)
  - Hyperphosphotemia (serum phosphate >5.5mg/dl): results from failure of excretion or tissue necrosis
  - Hypocalcemia (Serum calcium <8.5 mg/dl) results from decreased active Vit-D, hyperphosphatemia or hypoalbuminemia (as necrosis is taking place remember calcium is needed and is used up)
  - Hypercalcemia (Serum calcium> 10.5mg/dl) may occur during the recovery phase following rhabdomyolysis induced acute renal failure.
- Metabolic acidosis (arterial blood pH< 7.35) is associated with sepsis or severe heart failure
- Hyperuricemia: due to decreased uric acid excretion
- Bleeding tendency: may be due to platelet dysfunction and coagulopathy associated with sepsis.
- Seizure: may occur related to uremia
- Chronic renal failure

PROGNOSIS

- Mortality rate among patients with AKI approximates 50. It should be stressed however, that patients usually die from sequelae of the primary illness that induced AKI and not from AKI itself.

- Mortality is affected by severity of the underlying disease and the clinical setting in which acute renal failure occurs. E.g. the mortality of ATN is 60% when it results from surgery or trauma, 30% when it occurs as a complication of medical illnesses, and 10-15% when pregnancy is involved.
- Mortality rates are higher in older debilitated patients and in those with multiple organ failure.
- Patients with no complicating factors who survive an episode of acute renal failure have 90% chance of complete recovery of kidney function.

GLOMERULAR DISEASES

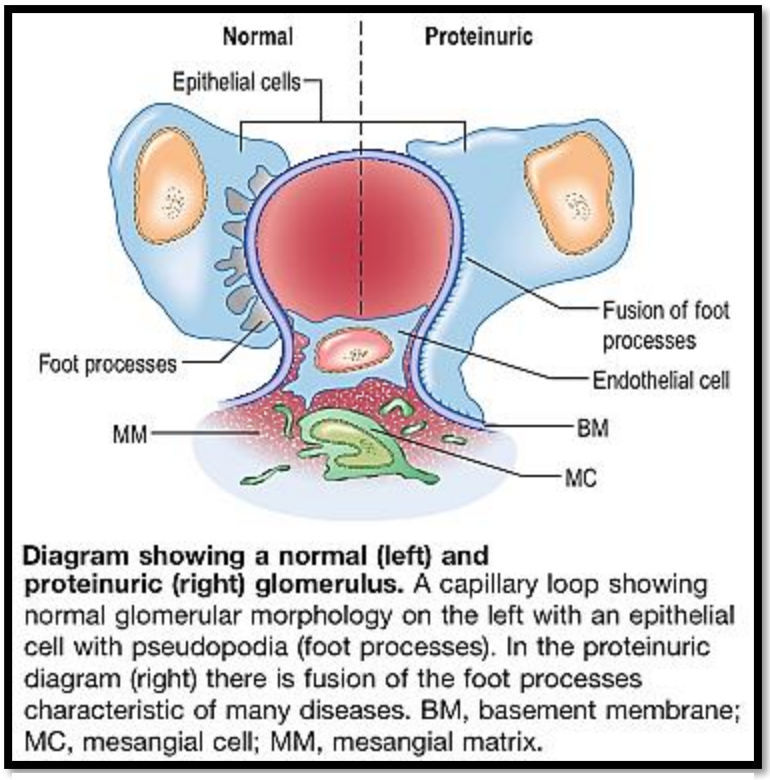


Diagram showing a normal (left) and proteinuric (right) glomerulus. A capillary loop showing normal glomerular morphology on the left with an epithelial cell with pseudopodia (foot processes). In the proteinuric diagram (right) there is fusion of the foot processes characteristic of many diseases. BM, basement membrane; MC, mesangial cell; MM, mesangial matrix.

Figure 48: Filtration membrane

- A glomerulus consists of a collection of capillaries which come from the afferent arteriole and are confined within the urinary space (Bowman's capsule), this is continuous with the proximal tubule.
- The capillaries are partially attached to mesangium, a continuation of the arteriolar wall consisting of mesangial cells and matrix.
- The free wall of glomerular capillaries (across which filtration takes place) consists of basement membrane covered by visceral epithelial cells with individual foot processes and lined by endothelial cells.
- The basement membrane has a normal thickness of 250-300nm.
- The spaces between the foot processes are known as filtration pores they are 20-60nm in diameter. Filtered fluid passes through these pores to reach the urinary space.
- The endothelial cells on the luminal aspect of the basement membrane are fenestrated (diameter 70-100nm)
- The basement membrane is arranged in 3 zones and is composed of type IV collagen and negatively charged proteoglycans (heparin sulphate).
- The glomerular filtration barrier consists of the fenestrated endothelium, the glomerular basement membrane and the terminally differentiated visceral epithelial cells known as podocytes.
- Podocytes dictate the size-selective nature of the filtration barrier.
- Glomerular disease include:
  - Glomerulopathies: there is no evidence of inflammation
  - Glomerulonephritis: inflammation of the glomeruli
- There is an overlap between glomerulopathies and glomerulonephritis.

GLOMERULOPATHIES

- These are the third most common cause of end-stage kidney disease (after diabetes and hypertension).
- Glomerulopathy is a general term for a group of disorders characterized by:
  - Primary immunologically mediated injury to glomeruli, although renal interstitial damage is a regular accompaniment.
  - Bilateral symmetrical involvement of the kidney.
  - Secondary mechanisms of glomerular injury come into play following an initial immune insult such as fibrin deposition, platelet aggregation, neutrophil infiltration and free radical-induced damage.
  - Renal lesions may be part of a generalized disease (e.g. SLE)

PATHOGENESIS

- Glomerulopathies are considered to be an immunologically mediated disorder with involvement of cellular immunity (T-cells, macrophages/ dendritic cells), humoral immunity (antibodies, immune complexes and complement) and inflammatory mediators (cytokines, chemokines and the coagulation cascade).
- The immune response can be directed against known target antigens, particularly when glomerulopathy complicates infections, neoplasms or drugs.
- Primary glomerulopathy may occur in genetically susceptible individuals following an environmental insult.
  - Genes involved HLA-A1, B8, DR2, DR3.
  - Environmental factors: drugs e.g. hydralazine, chemicals e.g. gold, silica, hydrocarbons or infectious agents

PATHOLOGICAL TERMS IN GLOMERULAR DISEASE

- The most commonly used terms are:
  - Focal: some, but not all glomeruli show the lesion.
  - Diffuse (global): most of the glomeruli (>75%) contain the lesion.
  - Segmental: Only a part of the glomerulus is affected (most focal lesions are also segmental e.g. focal segmental glomerulosclerosis)
  - Proliferative: an increase in cell numbers due to hyperplasia of one or more of the resident glomerular cells with or without inflammation.
  - Membrane alterations: capillary wall thickening due to deposition of immune deposits or alterations in basement membrane.
  - Crescent formation: epithelial cell proliferation with mononuclear cell infiltration in Bowman's space.

CLASSIFICATION OF GLOMERULOPATHIES

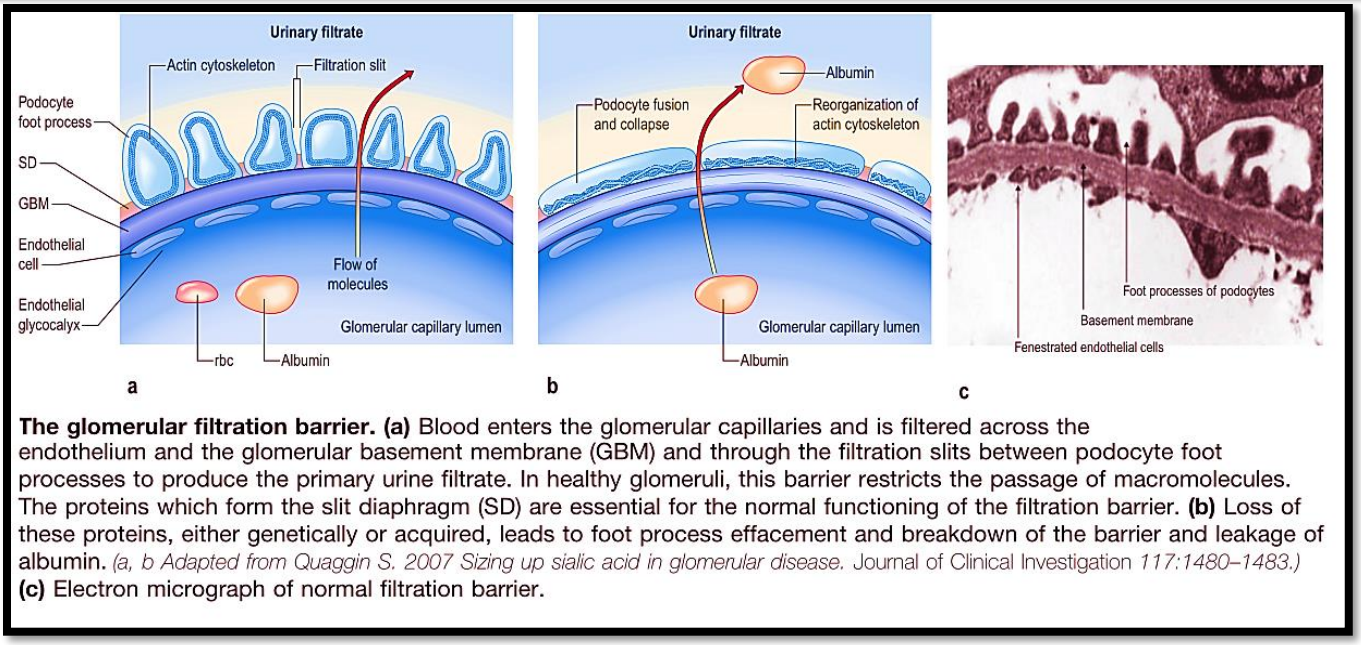
- There is no correlation between histopathological types of glomerulopathies and the clinical features of disease.
- The four major glomerular syndromes include:
  - Nephrotic syndrome- massive proteinuria (>3.5g/day), hypoalbuminaemia, edema, hyperlipidemia and lipiduria.
  - Acute glomerulonephritis (acute nephritic syndrome)- abrupt onset of glomerular hematuria (RBC casts or dysmorphic RBC), non-nephrotic range proteinuria, edema, hypertension and transient renal impairment.
  - Rapidly progressive glomerulonephritis- features of acute nephritis, focal necrosis with or without crescents and rapidly progressive renal failure over weeks.
  - Asymptomatic hematuria, proteinuria or both

NEPHROTIC SYNDROME

- In healthy individuals, urine protein excretion is usually <150mg/day (0.15g/day).
  - 2/3 of these proteins are Tamm-Horsfall proteins (also known as uromodulin is a glycoprotein produced excessively by the renal tubular epithelial cells of the distal loop of Henle).
  - 1/3 are albumin.
- With 24 hours:
  - Albumin Protein loss <30 mg is normal
  - Protein loss between 30-300mg (not detectable on dipstick) is termed microalbuminuria
  - Protein loss between 300-3000mg is termed macroalbuminuria.
  - Protein loss > 3.5g is termed a nephrotic syndrome.

State	Protein loss in 24 hours
Normal	<30 mg
Microalbuminuria	30-300mg
Macroalbuminuria	300-3000mg
Nephrotic syndrome	>3.5g

- Nephrotic syndrome is a clinical complex characterized by:
  - Significant proteinuria of >3.5g per 24h (most important clinical feature).
  - Hypoalbuminemia-pitting edema (lower extremities, periorbital, ascites, pleural effusion) (decreased oncotic pressure).
  - Hypogammaglobinemia- increased risk of infection.
  - Hyperlipidemia and lipiduria (fat casts in urine) and hypercholesterolemia
  - Hypercoagulability- due to loss of anti-thrombin III.
- Proteinuria is a marker of intrinsic kidney disease, including glomerular basement membrane leak or tubule damage.
- Recall the filtration membrane in the kidney consists of:
  - Endothelial cells
  - Basement membrane
  - Epithelial cells with podocytes



The glomerular filtration barrier. (a) Blood enters the glomerular capillaries and is filtered across the endothelium and the glomerular basement membrane (GBM) and through the filtration slits between podocyte foot processes to produce the primary urine filtrate. In healthy glomeruli, this barrier restricts the passage of macromolecules. The proteins which form the slit diaphragm (SD) are essential for the normal functioning of the filtration barrier. **(b)** Loss of these proteins, either genetically or acquired, leads to foot process effacement and breakdown of the barrier and leakage of albumin. *(a, b Adapted from Quaggin S. 2007 Sizing up sialic acid in glomerular disease.* Journal of Clinical Investigation *117:1480–1483.)* **(c)** Electron micrograph of normal filtration barrier.

Figure 49: The glomerular filtration barrier

ETIOLOGY

- Can be divided into
  - Primary nephrotic syndrome
  - Secondary nephrotic syndrome

PRIMARY NEPHROTIC SYNDROME

- Primary glomerulopathies (idiopathic): account for 30-50% of adult nephrotic syndrome.
- These are not a consequence of systemic disease.
- They include:
  - Minimal change disease/nephropathy
  - Focal segmental glomerulosclerosis
  - Membranous glomerulonephritis
  - Membranoproliferative glomerulonephritis

SECONDARY NEPHROTIC SYNDROME

- Multisystem disease: accounts for 50-70% of adult nephrotic syndrome
- Causes include:
  - Endocrine disorders: Diabetes mellitus (diabetic nephropathy)
  - Cardiovascular diseases: Hypertension, Pre-eclampsia
  - Autoimmune: Systemic lupus erythematosus, vasculitis
  - Infiltrative: Amyloidosis, sarcoidosis, myeloma, light chain deposition and fibrillary immunotactoid disease
  - Collagen vascular diseases
  - Infectious: infectious endocarditis, HBV, HCV, HIV, Malaria, EBV, leprosy, syphilis
  - Drugs
  - Neoplasms: leukemias, lymphomas and solid tumors

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

- Clinical features include:
  - Peri-orbital edema which is mostly seen early morning, may also present with a puffy face or generalized edema or scrotal swelling.
    - Differential diagnosis for generalized edema includes: chronic liver disease, Right ventricular heart failure, Adult malnutrition
  - Production of frothy urine (protein in urine)
  - Accelerated atherosclerosis
  - Recurrent infections especially with pneumococcus (due loss of C3b complement)
  - Iron deficiency anemia (loss of transferrin in urine)
  - DVT (hypercoagulable state- loss of antithrombin III and over production of fibrinogen).
  - Note: most patients are normotensive however patients can develop hypertension (from fluid retention, this is much commoner in nephritic syndrome) or hypotension (due to fluid loss from vessels, commoner in kids)

PROTEINURIA

- The mechanism is complex. And occurs partly because of structural damage to glomerular basement membrane leading to an increase in size and number of pores, allowing passage of more and larger molecules.
- Fixed negatively charged components are present in the glomerular capillary wall which repel negatively charged protein molecules. Reduction of this fixed charge occurs in glomerular disease and appears to be a key factor in the genesis of heavy proteinuria.
- The urine produced is froathy due to the presence of proteins.
- Hypercoagulabilty-
  - Is multifactorial: some of the mechanisms are due to loss of anti-thrombin III in the urine, increased fibrinogen production by the liver, increased platelet aggregation.
  - Spontaneous peripheral arterial or venous thrombosis, renal vein thrombosis and pulmonary embolism may occur.
  - Clinical features that suggest acute renal vein thrombosis include sudden onset of flank or abdominal pain, gross hematuria, a left-sided varicocele (the left testicular vein drains into the renal vein), increased proteinuria and an acute decline in GFR.
  - Chronic renal vein thrombosis is usually asymptomatic.
- Loss of transferrin in urine results in iron deficiency anemia.
- Loss of low molecular weight complement and immunoglobulin predisposes patients to infections e.g. pneumococcal infection (especially with loss of complement C3b).

HYPOALBUMINEMIA

- In general, the greater the proteinuria, the lower the serum albumin level.
- The normal dietary protein intake is around 70g daily and the liver can synthesize albumin at a rate of 10-12g daily. How then does a urinary protein loss of the order of 3.5g daily result in hypoproteinemia?
  - There is increased catabolism of reabsorbed albumin in the proximal tubules during nephrotic syndrome even though there is an actual increase in the albumin synthesized. The loss of protein is thus more and only 3.5g is seen in urine causing the liver to fail to match up the synthesis.

- Edema- common sites for edema formation in early stage include: dependent areas, face, peri-orbital areas and scrotum.
  - Hypoalbuminemia (Decrease in oncotic pressure) and primary water and salt retention by kidneys (due to activation of the RAAS as the kidneys are under-perfused) are the postulated mechanisms for edema formation.
  - Edema is initially seen around the eyes because the skin in this area is loosely attached to the underlying tissue so it can easily accommodate fluid by easily expanding.
  - In later stage the edema tends to occur in dependent areas e.g. feet, sacrum, abdomen. There is anasarca (generalized edema). The patient may wake up with a puffy face that goes down as the day progresses due to redistribution of fluid by gravity.

HYPERLIPIDEMIA

- Hyperlipidemia- is believed to be a consequence of increased hepatic lipoprotein synthesis and decreased clearance. Hyperlipidemia may accelerate atherosclerosis and progression of renal disease.
- There is an increase in LDL, IDL and triglycerides but no change or decrease in HDL.
- There is an increase in the LDL/HDL cholesterol ratio.
- Lipids are also passed in urine. Urine may contain fat oval bodies (which are proximal convoluted cells filled with fats).

COMPLICATIONS OF NEPHROTIC SYNDROME

1. Recurrent infections: loss of globulins and low molecular weight complements.
2. Thrombosis: most commonly in renal artery (may present as acute abdomen)
   - Loss of anticoagulant proteins e.g. anti-thrombin III
   - Hyperlipidemia-disturbs platelet membrane as well as endothelium cause platelet activation and aggregation
   - Stasis of blood: since it is concentrated as vascular compartment cannot hold water due to low oncotic pressure caused by hypoproteinemia.
   - Over production of fibrinogen by the liver
3. Iron deficiency anemia: due to loss of transferrin
4. Protein malnutrition
5. Hypocalcemia: Vitamin D deficiency due to enhanced urinary excretion of cholecalciferol-binding protein.

HISTOLOGIC SUBTYPES AND ETIOLOGY

MINIMAL CHANGE DISEASE/NEPHROPATHY

- Most common cause of nephrotic syndrome in children.
- Usually idiopathic or secondary to infection, may be associated with Hodgkin lymphoma (Due to release of cytokines by Reed-Steinburg cells).
  - Many implicated drugs include NSAIDs, Lithium, antibiotics (Cephalosporins, rifampicin, ampicillin), bisphosphonates and sulfasalazine.
  - Atopy is present in 30% of cases and allergic reactions can trigger nephrotic syndrome.
  - Infections e.g. HCV, HIV and TB are rarer causes.
- Normal glomeruli can be seen under light microscopy on H & E stain, lipids may be seen in proximal tubule cells.
- Effacement (flattening) of foot processes is seen on electron microscopy.
  - Recall the glomerular filtration membranes consists of the endothelial cells, basement membrane and the foot processes of the podocytes (epithelial cells).
- No immune complex deposits are seen (negative immunofluorescence (IF))
- Presentation:
  - Selective proteinuria (loss of albumin but not immunoglobulin).
  - Edema is present and in children it may be facial.
- It carries an excellent response to steroids (damage is mediated by cytokines from T-cells) and cytotoxic drugs. It often relapses.
  - High dose corticosteroid therapy with prednisolone 60mg/m^2 daily (up to a maximum of 80mg/day) for a maximum of 4-6 weeks followed by 40 mg/m^2 every other day for a further 4-6 weeks
  - When there is relapse on steroid withdrawal, cyclophosphamide should be added after repeat induction with steroids. A course of cyclophosphamide 1.5-2.0 mg/kg daily is given for 8-12 weeks with concomitant prednisolone 7.5-15 mg/day.
  - Steroid unresponsive patient may also respond to cyclophosphamide. No more than two courses of cyclophosphamide should be prescribed in children because of the risk of side-effects which include azoospermia.
  - An alternative to cyclophosphamide is ciclosporin 3-5mg/kg per day.
- It is often regarded as a condition that does not lead to CKD.

FOCAL SEGMENTAL GLOMERUOSCLEROSIS

- Most common cause of nephrotic syndrome in Hispanics and African Americans.
- All age groups are affected.
- Usually idiopathic, may be associated with HIV, heroin use and sickle cell disease.
- It also recurs in transplanted kidneys, sometimes within days of transplantation, particularly in patients with aggressive renal disease.
- Focal (some glomeruli) and segmental (involving only part of the glomerulus) sclerosis (thickening-deposition of collagen) on H&E stain.
  - Damage tends to occur at junction between the cortex and medulla.
  - Glomerulosclerosis-deposition of collagen
- Effacement of foot process is seen on electron microscopy.
- No immune complex deposits (negative IF).
- Presentation:
  - Massive proteinuria (non-selective)
  - Hematuria
  - Hypertension
  - Renal impairment
- Treatment: steroids, cyclosporine A; cyclophosphamide.
- Poor response to steroids, progresses to chronic renal failure

MEMBRANOUS NEPHROPATHY

- Most common cause of nephrotic syndrome in Caucasian adults. Occurs more in males.
- May present as asymptomatic proteinuria or frank nephrotic syndrome.
- Microscopic hematuria, hypertension and/or renal impairment may accompany the nephrotic syndrome. There is a predilection to clotting (Renal vein thrombosis)
- Usually idiopathic, may be associated with hepatitis B or C, solid tumors, SLE or drugs e.g. NSAIDs and penicillamine
- Thick glomerular basement membrane is seen on H & E.
- Due to immune complex deposition (granular IF), sub-epithelial deposits with 'spike and dome' appearance on EM.
- Treatment: Observation if slow progression. Steroids alternating with either cyclophosphamide or chlorambucil.

- Poor response to steroids, progresses slowly to chronic renal failure. 25% spontaneously remit.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

- This can present with either nephritic or nephrotic syndrome or both.
- Thick glomerular basement membrane on H&E often with 'tram-track' appearance.
- Due to immune complex deposition (granular IF).
- Electron-microscopy shows sub-endothelial deposits
- Divided into 2 types based on location of deposits:
  - Type I- subendothelial, associated with HBV and HCV. Is more often associated with the formation of tram-tracks.
  - Type II (dense deposit disease)- intramembranous associated with C3 nephritic factor (autoantibody that stabilizes C3 convertase, leading to overactivation of complement, inflammation and low levels of circulating C3).
- Treatment:
  - Non-nephrotic: observe
  - Nephrotic or worsening renal function: steroids.
- Poor response to steroids, progresses to chronic renal failure. 50% die within 5 years of renal biopsy.

DISEASE	PRESENTATION	CLINICAL COURSE	PATHOLOGY	TREATMENT
Minimal change disease	• Selective proteinuria (albumin not immunoglobulin) • Edema • Common in children • May be idiopathic or associated with drugs or infection	Responds to steroids but often relapses. Rarely progresses to CKD	• Normal light microscopy • Lipids may be seen in cells of proximal convoluted tubule. • Effacement of foot processes on electron microscopy • Negative immunofluorescence	Steroids
Focal segmental	• Massive proteinuria (non-selective)	Poor response to steroids.	• Focal segmental glomerulosclerosis	Steroids, cyclosporine A;

glomerulosclerosis	• Hematuria • Hypertension • Renal impairment • Common in African Americans and Hispanics • May be idiopathic of associated with infection • Affects all age groups	Progresses to end stage renal disease	• Effacement of foot processes on electron microscopy • Negative immunofluorescence	cyclophosphamide
Membranous nephropathy	• Asymptomatic proteinuria or frank nephrotic syndrome. • Microscopic hematuria • Hypertension • Renal impairment • Clotting (Renal vein thrombosis) • Common among Caucasians • Can be idiopathic or associated with infection	25% spontaneously remit. Slow progression to renal failure	• Thick glomerular basement membrane is seen on H & E. • Due to immune complex deposition (granular IF), sub-epithelial deposits with 'spike and dome' appearance on EM. • Granular Immunofluorescence	Observation if slow progression. Steroids alternating with either cyclophosphamide or chlorambucil.
Membranoproliferative glomerulonephritis	Can present with either nephritic or nephrotic syndrome or both	50% die or progress to end stage renal disease within 5 years of renal biopsy	• Thick glomerular basement membrane on H&E ('tram-track' appearance). • EM shows sub-endothelial deposits • Granular Immunofluorescence	Non-nephrotic: observation Nephrotic or worsening renal function: steroids

DIABETES MELLITUS

- This is one of the common systemic causes of nephrotic syndrome
- High serum glucose leads to non-enzymatic glycosylation of the vascular basement membrane resulting in hyaline arteriolosclerosis (microvascular damage).
- Glomerular efferent arteriole is more affected than the afferent arteriole, leading to high glomerular filtration pressure.
  - Hyperfiltration injury leads to microalbuminuria.
- Eventually progresses to nephrotic syndrome
  - Characterized by sclerosis of the mesangium with formation of Kimmelstiel-Wilson nodules.
- Retinopathy should be present as eyes are usually affected before kidneys.
- It can definitively be diagnosed by biopsy though rarely needed.
- ACE inhibitors slow progression of hyperfiltration induced damage.

SYSTEMIC AMYLOIDOSIS

- Kidney is the most commonly involved organ in systemic amyloidosis.
- Amyloid deposits in the mesangium, resulting in nephrotic syndrome.
- Characterized by apple-green birefringence under polarize light after staining with Congo red.

- Glomerular deposition diseases include: multiple myeloma (in adults), amyloidosis (common because of HIV and infection)

DIAGNOSIS AND INVESTIGATIONS

CONFIRMING SIGNIFICANT PROTEINURIA

- Confirming significant proteinuria
- If protein detected on dipstick rule out benign temporary causes e.g. orthostatic, fever, exercise. Dipstick only detects albumin >100mg/L so in patient with CKD, ACR (Urine albumin to creatinine ratio) is used to screen for proteinuria.
- If persistent, quantify proteinuria and do bloods.
- If nephrotic syndrome is confirmed, renal biopsy may be needed to find or confirm the cause. Not required if specific diagnosis is very likely e.g. minimal change disease in kids.

- If significant proteinuria but not nephrotic just arrange regular review.
- Renal biopsy (if available): to identify the underlying histopathologic abnormality
  - Minimal change disease: account for 80% nephrotic syndrome in children <10 years
  - Focal segmental glomerulosclerosis
  - Membranous glomerulopathy: accounts for 60-70% of nephrotic syndrome in adults.
  - Membranoproliferative glomerulonephritis

INVESTIGATIONS

1. Urinalysis: (To quantify proteinuria)
   - 4+ protein in urine
   - Microscopy, culture and sensitivity to exclude UTIs
   - Look for cell casts
   - Protein electrophoresis
2. 24-hour urine collection (proteins >3.5g/day)- rarely done and instead a spot sample is taken ideally in the morning for ACR or PCR.
3. Urine Albumin-creatinine ratio (ACR):
   - Microalbuminuria: >2.5mg/mmol (men) and >3mg/mmol (women)
   - Proteinuria >30mg/mmol
   - Nephrotic syndrome >250mg/mmol
   - Note: ACR is more sensitive than PCR at lower protein levels (ACR<70 mg/mmol)
4. Urine protein-creatinine ratio (PCR)
   - Proteinuria >45mg/mmol
   - Nephrotic syndrome >300mg/mol
5. Bloods
   - Serum albumin (decreased)
   - Serum cholesterol (increased)
   - Glucose: to rule out diabetes mellitus
   - U and E to assess renal function
   - LFTs: may show other causes of decreased albumin or fluid retention
   - Clotting panel: for clotting abnormalities
   - C-reactive protein: may be elevated in autoimmune disease.
   - Immunological: complement, dsDNA, ANCA, RF
   - Serum Ig and electrophoresis

- Microbiology: Syphilis, HBV, HCV and HIV tests

6. Imaging:
   - Kidney ultrasound is often useful, especially if there is abnormal kidney function. It is needed before biopsy
   - Chest X-ray- for pleural effusions
7. Renal biopsy
   - Microscopy
   - Immunochemical test

MANAGEMENT

- General measures:
  - Control proteinuria
    - Dietary protein restriction: the potential value of dietary protein restriction for reducing proteinuria must be balanced against risk of contributing to malnutrition
    - ACE inhibitors/Angiotensin II receptors antagonists: to decrease proteinuria by decreasing glomerular filtration pressure. (monitor blood pressure and renal function)
    - Controlling hypertension: keeping BP below 130/80 reduces proteinuria
  - Treatment of complications:
    - Edema: should be managed cautiously
      - Moderate salt restriction: usually 1 to 2 g/day
      - Loop diuretics: can be given in higher doses. It is unwise to remove >1.0 kg of edema per day as more aggressive diuresis may precipitate intravascular volume depletion and prerenal azotemia.
      - Start with bendroflumethiazide 5mg daily and add furosemide 40-120mg daily
      - Unresponsive patients require furosemide 40-120 mg daily with addition of amiloride (5mg daily) with serum potassium concentration being monitored regularly.
      - Nephrotic patients may malabsorb diuretics (as well as other drugs) owing to gut mucosal edema and parenteral administration is then required initially.
      - Albumin infusion can be given to patients who are diuretic-resistant as well as oliguric and uremic in absence of severe glomerular damage.

- Sepsis (e.g. Pneumococcal infection): pneumococcal vaccine should be given. There should be early detection and aggressive treatment of infections, rather than long-term antibiotic prophylaxis.
- Thromboembolism: anticoagulation is indicated for patients with deep venous thrombosis, arterial thrombosis and pulmonary embolism. Heparin may not be effective because of urinary loss of anti-thrombin III.
- Hyperlipidemia: may need lipid lowering agents (statins-HMG CoA reductase inhibitors)
- Vitamin D deficiency- Vitamin D supplementation

- Specific treatment of underlying morphologic entity
  - Minimal change disease- steroids
  - Focal segmental glomerulosclerosis: steroids, cyclosporin A; cyclophosphamide.
  - Membranous nephropathy: Observation if slow progression. Steroids alternating with either cyclophosphamide or chlorambucil.
  - Membranoproliferative glomerulonephritis:
    - Non-nephrotic: observe
    - Nephrotic or worsening renal function: steroids

NEPHRITIC SYNDROME

- These are a group of diseases were damage to the glomeruli is mediated by immune complex deposition and inflammatory processes.
- They are characterized by:
  - Sub-nephrotic range proteinuria (<3.5g/day): mild to moderate proteinuria
  - Sudden onset (days to weeks) of acute renal failure
  - Oliguria (<400ml of urine per day) and Azotemia
  - Hypertension, periorbital edema and salt retention.
  - Macroscopic Hematuria (with recurrent red blood cell cast)
  - Pyuria (white blood cells in urine)
  - Presence of urinary sediment.

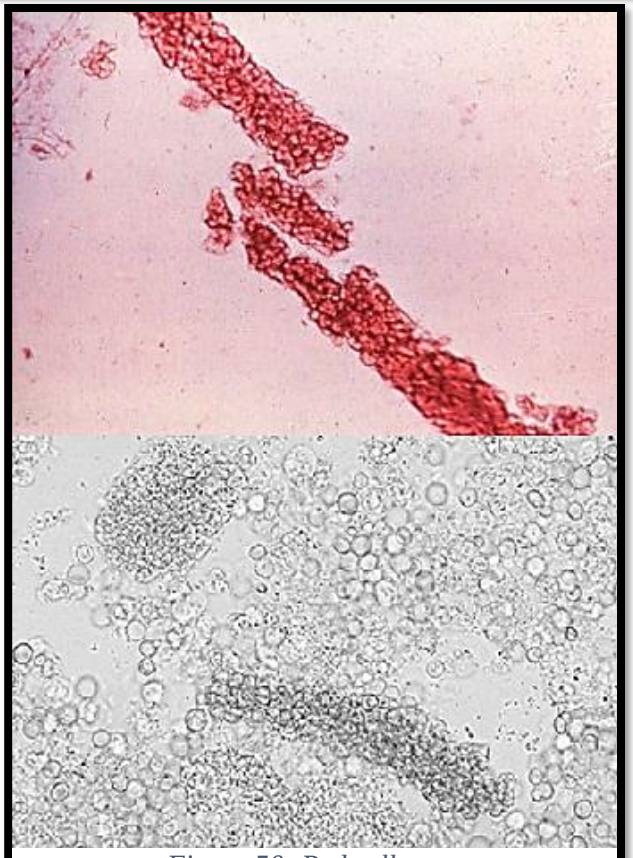


Figure 50: Red cell casts

ETIOLOGY

- Postinfectious glomerulonephritis (including post-streptococcal)
- Subacute bacterial endocarditis
- Lupus nephritis
- Anti-glomerular basement membrane disease
- IgA nephropathy
- ANCA small vessels vasculitis (Wegener's granulomatosis, microscopic polyangitis, Churg-strauss Syndrome)
- Membranoproliferative glomerulonephritis
- Mesangioproliferative glomerulonephritis

DIAGNOSIS AND INVESTIGATIONS

- Definitive diagnosis is by renal biopsy
- If biopsy is not available, use clinical signs/symptoms
- Urinalysis
- Urine microscopy, culture and sensitivity
- U+Es, creatinine

TRATMENT

- Use ACEi if there is component of proteinuria and the creatinine is stable
- Consider corticosteroids therapy or other immunosuppressive agents (although benefit depends on histologic type)
- Specific treatments:
  - Post-streptococcal glomerulonephritis and subacute bacterial endocarditis
    - Supportive care
    - Treat infectious etiologies
  - Others
    - Treat with some combination of steroids, cytotoxic agents and plasmapheresis.

ACUTE GLOMERULONEPHRITIS (ACUTE NEPHRITIC SYNDROME)

- This is a clinical correlate of acute glomerular inflammation.
- The hallmark of nephritic syndrome is glomerular inflammation and bleeding from the glomeruli.
- In its most dramatic form it is characterized by:
  - Sub-nephrotic range proteinuria (<3.5g/day)
  - Sudden onset (days to weeks) of acute renal failure
  - Oliguria (<400ml of urine per day) and Azotemia
  - Hypertension, periorbital edema and salt retention.
  - Macroscopic Hematuria
  - Presence of urinary sediment.

ETIOLOGY

- Acute nephritic syndrome can result from renal-limited primary glomerulopathy or from secondary glomerulopathy complicating systemic disease.
- Immune-complex glomerulonephritis may be:
  - Idiopathic
  - Represent a response to known antigen stimulus (e.g. post infectious glomerulonephritis)
  - Part of a multisystem immune complex disorder (e.g. lupus nephritis, Henoch-Schonlein purpura/Allergic pupura, cryoglobulinemia, bacterial endocarditis).

CLINICAL FEATURES

- Subnephrotic range proteinuria (<3.5g/day)
- Periorbital edema
- Hypertension (due to impaired GFR and salt retention)
- Macroscopic Hematuria: with RBC casts and dysmorphic RBCs in urine.
- Oliguria (<400ml of urine per day)
- Azotemia

LABORATORY TESTS

- Urinalysis: as a result of injury to the glomerular capillary wall, urinalysis typically reveals red blood cell casts, dysmorphic red blood cells, leukocytes and subnephrotic proteinuria of <3.5g/day (nephritic urinary sediment)
- Hematuria is often macroscopic
- Renal function test: elevated serum creatinine
- Serology: immunologic assays suggesting the underlying disease.
- Renal biopsy:
  - Reveals hypercellular inflamed glomeruli
  - Immune-complex deposition activate complement
  - C5a attracts neutrophils which mediate damage

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

- This is the prototypical post-infectious glomerulonephritis and leading cause of acute nephritic syndrome.
- Most cases are sporadic but can also occur as an epidemic.
- Glomerulonephritis develops on average 10 days after pharyngitis or 2 weeks after a skin infection (impetigo) with a nephritogenic strain of *group A beta-hemolytic streptococcus (Carrying M protein virulence factor)*.
- Immunity to these strains is type-specific and long-lasting with repeated infection and nephritis are rare owing to the widespread use of antibiotics.
- Epidemic poststreptococcal glomerulonephritis is most commonly encountered in children of 2 to 6 years of age with pharyngitis during the winter months.
- Poststreptococcal glomerulonephritis in association with cutaneous infection usually occurs in a setting of poor personal hygiene or streptococcal superinfection of another skin disease.
- Nephritic syndrome may occur also after infection with non-strep organisms as well.

CLINICAL PICTURE

- Classical presentation (2-3 weeks after infection):
  - Full-blown nephritic syndrome with oliguric acute renal failure
  - Gross hematuria (red or 'smoky' urine)- cola colored urine.
  - Headache and generalized symptoms such as anorexia, nausea, vomiting and malaise.
  - Swelling of the renal capsule can cause flank or back pain.
- Physical examination:
  - Hypertension
  - Periorbital Edema
  - Hypovolemia
- Usually seen in children but may occur in adults.

LABORATORY FINDINGS

- Urinalysis: as a result of injury to the glomerular capillary wall, urinalysis typically reveals red blood cell casts, dysmorphic red blood cells, leukocytes and subnephrotic proteinuria of <3.5g/day (nephritic urinary sediment).
- Renal function test: the serum creatinine is often mildly elevated at presentation.
- Serology: most patients have circulating antibodies against streptococcal exoenzymes such as ASO, and DNAase.
- Renal biopsy:
  - Hypercellular inflamed glomeruli on H & E.
  - Mediated by immune complex deposition (granular IF)
  - Subepithelial 'humps' on EM

DIAGNOSIS

- Acute poststreptococcal glomerulonephritis is usually diagnosed on clinical and serologic grounds.
- The characteristic lesion is diffuse proliferative glomerulonephritis.

MANAGEMENT

- Eliminating the streptococcal infection with antibiotics.
- Supportive therapy until spontaneous resolution of glomerular inflammation occurs:
  - Bed rest
  - Salt restriction
  - Diuretics to control ECF volume

  - Antihypertensive drugs to control high blood pressure
- Dialysis: some patients may need dialysis.
- Some adults develop rapidly progressive glomelomerulonephritis
  - This is a nephritic syndrome that progresses to renal failure in weeks to months.
  - Renal biopsy is characterized by crescents in Bowman space (H&E) comprised of fibrin and macrophages.

COMPLICATIONS

- Congestive heart failure
- Pulmonary edema
- Acute renal failure
- Severe hypertension with hypertensive encephalopathy

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

- This is a nephritic syndrome that progresses to renal failure in weeks to months.
- Renal biopsy is characterized by crescents in Bowman space (H&E) comprised of fibrin and macrophages.
- Clinical picture and immunofluorescence help resolve etiology

IMMUNOFLUORESCENCE PATTERN	DISEASE	COMMENTS
Linear (anti-basement membrane antibody)	Goodpasture syndrome	Antibody against collagen in glomerular and alveolar basement membrane Presents as hematuria (Renal involvement) and hemoptysis (pulmonary involved) classically in young adult male.
Granular (due to immune complex deposition)	Post-streptococcal glomerulonephritis (most common) or diffuse proliferative glomerulonephritis	Diffuse proliferative glomerulonephritis is due to diffuse antigen-antibody complex deposition usually subendothelial, most common type of renal disease in SLE (lupus nephritis)
Negative IF (pauci-immune)	Wegener granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome	Wegner granulomatosis is associated with c-ANCA- presents with hemoptysis (with history of sinus pathology) and hematuria.

		Miscroscopic polyangiitis associated with p-ANCA. Granulomatous inflammation, eosinophilia, and asthma distinguish Churg-strauss from microscopic polyangiitis

IgA NEPHROPATHY

- IgA immune complex deposition in mesangium of glomeruli.
- Most common nephropathy worldwide.
- Presents during childhood with:
  - Episodic gross or microscopic hematuria with RBC casts usually following mucosal infections.
  - IgA immune complex deposition in mesangium on IF (granular)
- May slowly progress to renal failure.

ALPORT SYNDROME

- Inherited defect in type IV collagen, most commonly X-linked
- Results in thinning and splitting of glomerular basement membrane.
- Presents as isolated hematuria, sensory hearing loss and ocular disturbances.

CHRONIC RENAL FAILURE

- This is progressive and irreversible reduction of the renal function, over a period of more than 3 months.
- It is defined as GFR <60ml/min per 1.73 m^2 for 3months or
- Urinary albumin to creatinine ratio >65mg/mmol or
- Protein creatinine ratio of 100mg/mol
- End-stage renal disease (ESRD) refers to a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy (dialysis or transplantation) in order to avoid life-threatening uremia.
- Recall the difference between uremia (with symptoms) and azotemia (without symptoms)

ETIOLOGIES

- Congenital and inherited disease:
  - Polycystic kidney disease (infantile and adult forms)
  - Medullary cystic disease
  - Tuberous sclerosis
  - Oxalosis
  - Cystinosis
  - Congenital obstructive uropathy
- Glomerular disease
  - Primary glomerulonephritides including focal glomerulosclerosis
  - Secondary glomerular disease:
    - SLE
    - Polyangiitis
    - Wegener's granulomatosis
    - Amyloidosis
    - Diabetic glomerulosclerosis
    - Accelerated hypertension
    - Hemolytic uremic syndrome
    - Thrombotic thrombocytopenic purpura
    - Systemic sclerosis
    - Sickle cells disease
- Vascular disease

- Hypertensive nephrosclerosis (common cause)
- Diabetic nephropathy (common cause)
- Renovascular
- Small and medium-sized vessel vasculitis

- Tubulointerstitial disease
  - Tubulointerstitial nephritis- idiopathic due to drugs (especially nephrotoxic analgesics), immunologically mediated
  - Tuberculosis
  - Schistosomiasis
  - Reflux nephropathy
  - Nephrocalcinosis
  - Multiple myeloma (myeloma kidney)
  - Renal papillary necrosis (diabetes, sickle cell disease and trait, analgesic nephropathy)
  - Chinese herb nephropathy
- Urinary tract obstruction
  - Calculus disease
  - Prostatic disease
  - Pelvic tumors
  - Retroperitoneal fibrosis
  - Schistosomiasis

CLASSIFICATION OF CHRONIC KIDNEY DISEASE

Stage	GFR (ml/min/1.73 m^2)	Description
1	≥90	• No impairment • Normal or increased GFR with other evidence of kidney damage
2	60-89	• Mild impairment • Slight decrease in GFR with other evidence of kidney damage
3	3A 45-59 3B 30-44	• Moderate impairment • Moderate decrease in GFR with or without other evidence of kidney damage
4	15-29	• Severe impairment • Severe decrease in GFR with or without other evidence of kidney damage
5	<15 or on dialysis	• Established kidney failure (End-stage kidney disease)

- Note:
  - Stage 1 and 2 also require the presence of kidney damage (persistent proteinuria or unexplained hematuria, structural disease or glomerulonephritis)
  - The suffix 'P' can be applied on the stage of CKD if the patient has significant proteinuria defined as urinary albumin:creatinine ratio >65mg/mol or protein:creatinine ratio >100mg/mmol

PATHOPHYSIOLOGY

- Uremic manifestations occur mainly due to accumulation of nitrogenous wastes and the reason for accumulation of these wastes is decreased renal excretion and reduced catabolizing capacity of the kidney.
- Most toxins in uremia are by products of proteins and amino acid metabolism, because unlike carbohydrates and fats which are metabolized to carbon dioxide and water which can be excreted through the lungs and skin, byproducts of protein are non-volatile organic acids.

CLINICAL FEATURES

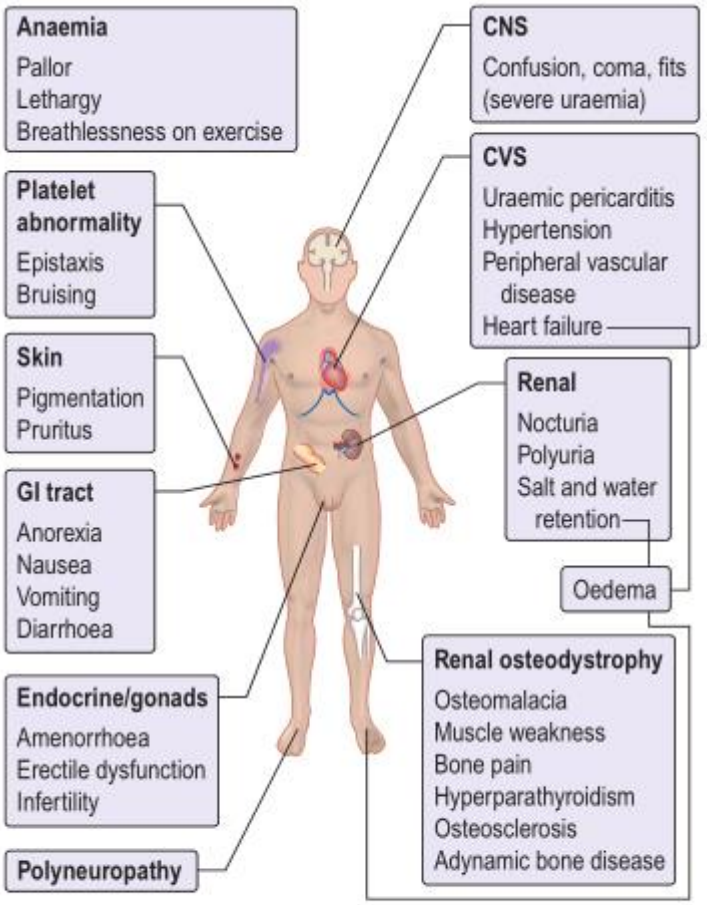
SYMPTOMS

- Early stages of CKD are often completely asymptomatic.
- A rough correlation exists between urea and creatinine concentrations and symptoms.
- Symptoms are common when the serum urea concentration exceeds 40mmol/L but many patients develop uremic symptoms at lower levels of serum urea including:
  - Insomnia
  - Symptoms due to salt and water retention- peripheral or pulmonary edema
  - Symptoms due to anemia
  - Loss of appetite
  - Malaise, loss of energy
  - Nausea, vomiting and diarrhea
  - Nocturia and polyuria due to impaired concentrating ability
  - Amenorrhea in women, erectile dysfunction in men
  - Itching
  - Paresthesia due to polyneuropathy
  - 'Restless legs' syndrome (overwhelming need to frequently alter position of lower limbs)

  - Bone pain due to metabolic bone disease
- In more advanced uremia CKD stage 5 these symptoms become more severe and include:
  - Mental slowing, clouding of consciousness and seizures
  - Myoclonic twitching
- Severe depression of glomerular filtration can result in oliguria. This can occur with either AKI or in terminal stages of CKD. However, even if the GFR is profoundly depressed failure of tubular reabsorption may lead to very high urine volumes, the urine output is therefore not a useful guide to renal function.

SIGNS

- There are few physical signs of uremia per se.
- Findings include:
  - Short status (in patients who have had CKD in childhood)
  - Pallor (due to anemia)
  - Increased photosensitive pigmentation (which may make the patient look misleadingly healthy)
  - Brown discoloration of nails
  - Scratch marks due to uremic pruritus
  - Signs of fluid overload
  - Pericardial friction rub
  - Flow murmurs (mitral regurgitation due to mitral annular calcification, aortic and pulmonary regurgitant murmurs due to volume overload)
  - Glove and stocking peripheral sensory loss (rare)
  - The kidneys are usually impalpable unless grossly enlarged as a result of polycystic disease, obstruction or tumor.
- In addition to these findings, there may be signs of any underlying disease that may have caused the CKD.
  - Cutaneous vasculitic lesions in systemic vasculitides



Symptoms and signs of chronic kidney disease. Oedema may be due to a combination of primary renal salt and water retention and heart failure.

- Retinopathy in diabetes and hypertension
- Evidence of peripheral vascular disease and associated renal artery stenosis
- Evidence of spina bifida or other causes of neurogenic bladder.

COMPLICATIONS

CNS ABNORMALITIES

- Confusion, coma, fits (severe uremia)

CARDIOVASCULAR COMPLICATIONS

- Pericarditis: metabolic toxins are responsible for pericarditis
  - The finding of a multicomponent friction rub strongly supports the diagnosis
  - The pericardial effusion is often hemorrhagic
- Hypertension
  - Is the most common complication of end stage renal disease
  - It results from fluid overload
  - Sometimes severe form of hypertension may occur
- Congestive heart failure and/or pulmonary edema due to:
  - Volume over load
  - Increased pulmonary capillary permeability
- Peripheral vascular disease

HEMATOLOGIC ABNORMALITIES

- Normocytic normochromic anemia: which may be severe (Hb 4-6g/dl) and caused by
  - Decreased synthesis of erythropoietin (the most important factor)
  - Toxins suppressing bone marrow function
  - Bone marrow fibrosis secondary to hyperparathyroidism
  - Hematinic deficiency- iron, vitamin B12, folate
  - Blood loss (mainly GI blood loss)-occult gastrointestinal bleeding, blood sampling, blood loss during hemodialysis or because platelet dysfunction.
  - Decreased life span of RBC (increased red-cell destruction)
  - Abnormal red-cell membranes causing increased osmotic fragility
  - ACE inhibitors (may cause anemia in CKD, probably by interfering with the control of endogenous erythropoietin release).

  - Red-cell survival is reduced in CKD. Increased red-cell destruction may occur during hemodialysis owing to mechanical, oxidant and thermal damage.
- Bleeding tendency: attributed to platelet dysfunction
  - Patients may manifest with bleeding and easily bruiseability.
  - GI bleeding
  - Intracranial hemorrhage
- Susceptibility to infection
  - Change in leukocyte formation and function
  - Lymphocytopenia and atrophy of lymphoid tissue

GASTROINTESTINAL ABNORMALITIES

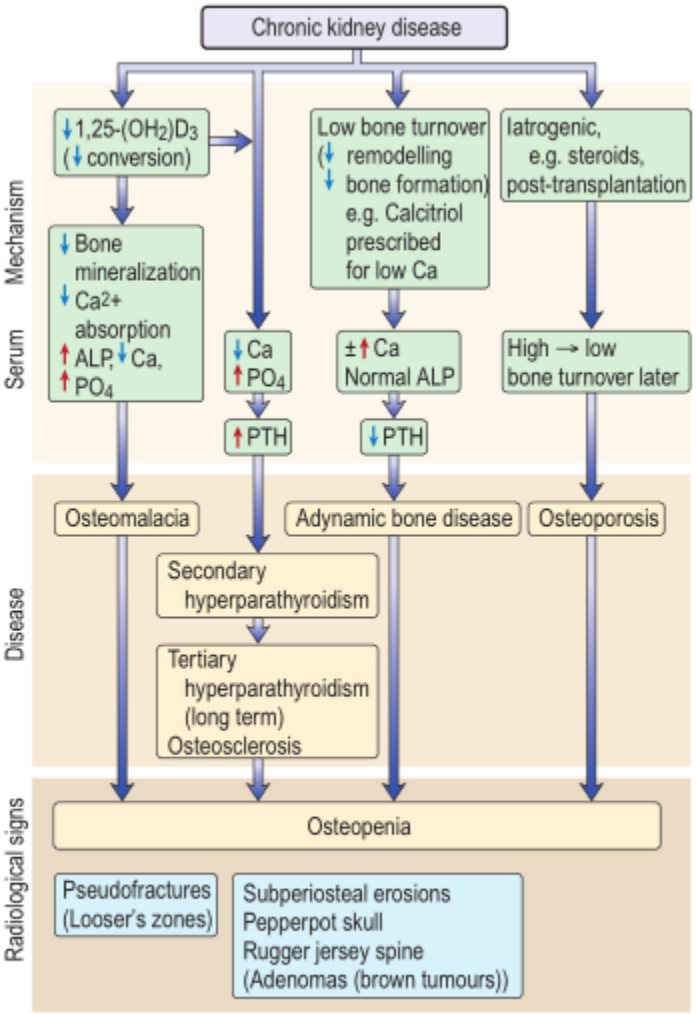
- Decreased gastric emptying
- Increased risk for reflux esophatitis, peptic ulceration, acute pancreatitis, GI bleeding and constipation.

FLUID, ELECTROLYTE AND ACID BASE DISTURBANCES

- Volume expansion and contractions (Edema, dehydration)
  - ECF expansion is isotonic and patient is normonatremic. Hyponatremia will be the consequence of excessive water ingestion.
  - Patients with chronic renal failure also have impaired renal mechanisms for conserving sodium and water. When an extra renal cause for fluid loss is present (e.g. vomiting, diarrhea, sweating, fever) these patients are prone to volume depletion and dehydration
  - In the face of sodium intake patients may retain sodium and water which may lead to congestive heart failure, peripheral edema and ascites.
- Potassium homeostasis:
  - Hyperkalemia occurs when GFR falls below 10ml/min
  - Endogenous factors (e.g. hemolysis, trauma, infection) or exogenous factors (administration of stored blood, potassium containing medications, potassium containing dietary salt substitute) contribute to hyperkalemia.
  - Acidosis: facilitate efflux of potassium from ICF to ECF
  - Drugs: potassium sparing diuretic, ACE inhibitors.
- Metabolic acidosis: common in the advancing stages. Total urinary net daily acid excretion is usually markedly reduced.

RENAL OSTEODYSTROPHY AND METABOLIC BONE DISEASE

- This is due to disturbance in bone phosphate and calcium metabolism.
- Hyperphosphatemia is a feature of advanced renal failure. The serum phosphate concentration rises in patients with a GFR< 20ml/min.
- Total serum calcium in chronic renal failure is often significantly lower than normal. These patients tolerate hypocalcemia quite well, rarely is a patient symptomatic from the decreased calcium concentration. Note that the low serum calcium is attributed to secondary hyperparathyroidism.
- Reduced synthesis of vitamin D during chronic renal disease plays a role in the pathogenesis of hyperparathyroidisim (active vitamin D metabolite is normally produced in the proximal tubule), both directly and through hypocalcemia.
- Bone abnormalities:
  - Renal rickets (osteomalacia)
  - Osteosclerosis: enhanced bone density in the upper and lower margins of vertebrae.
  - Osteitis fibrosa cystica: due to osteoclastic bone resorption (due to hypocalcemia and PTH) of especially terminal phalanges, long bones and distal end of clavicle.



Renal osteodystrophy: pathogenesis and radiological features of renal bone disease. ALP, alkaline phosphatase.

MALIGNANCY

- The incidence of malignancy is raised in patients with CKD and with dialysis. Malignant change can occur in multicystic kidney disease. Lymphomas, primary liver cancer and thyroid cancers can occur.

ENDOCRINE

- Hypogonadism is common
  - In men: decreased plasma testosterone level (erectile dysfuction), impotence and oligospermia
  - In women: Olifomenorrhea/amenorrhea, inability to carry pregnancy to term, hyperprolactinemia (galactorrhea in females as well as males), increased LH levels
- In children: impaired growth hormone secretion
- Abnormal thyroid hormone levels, partly because of altered protein binding. Measurement of TSH is the best way to assess thyroid function. True hypothyroidism occurs with increased frequency in CKD.
- Posterior pituitary gland function is normal in CKD.

METABOLIC ABNORMALITIES

- Gout: due to urate retention. Treatment is complicated by nephrotoxic potential of NSAIDs. Colchicine is useful for the acute attack and allopurinol should be introduced under colchicine cover to prevent further attacks. The dose of allopurinol should be reduced in CKD e.g. 100mg on alternate days.
- Insulin: insulin is catabolized by and to some extent excreted via the kidneys. For this reason, insulin requirements in diabetic patients decreases as CKD progresses. By contrast end-organ resistance to insulin is a feature of advanced CKD resulting in modestly impaired glucose tolerance. Insulin resistance may contribute to hypertension and lipid abnormalities.
- Lipid metabolism abnormalities: correction of lipid abnormalities by e.g. HMG-CoA reductase inhibitor therapy (statins) is used in patients with CKD although without formal proof of survival benefit.
  - Impaired clearance of triglyceride-rich particles
  - Hypercholesterolemia (particularly in advanced CKD)

DERMATOLOGIC ABNORMALITIES

- Pallor due to anemia
- Echymosis, hematoma
- Pruritus and excoriations (due to retention of nitrogenous waste products of protein catabolism or hypercalcemia, hyperphophatemia, and secondary hyperparathyroidism which leads to calcium deposits)
- Yellowish discoloration of skin: urochronmes

- Uremic frost: is seen in advance uremia, it is due to high concentration of urea in the sweat and after evaporat9on of the sweat, a fine white powder can be found on the skin surface.
- Nephrogenic systemic fibrosis: due to Gadolinium-containing contrast agents which are excreted exclusively by the kidney.

DIAGNOSTIC APPROACH

- History:
  - Duration of symptoms
  - Drug ingestion, including NSAIDs, analgesics and other medications and unorthodox treatment such as herbal remedies.
  - Past medical and surgical history:
    - previous chemotherapy, multisystem disease such as SLE, malaria
    - Hypertension
    - Diabetes mellitus
    - Systemic infectious or inflammatory diseases
    - Metabolic diseases
  - Previous occasions on which urinalysis or measurement of urea and creatinine might have been performed e.g. pre-employment or insurance medical examinations, new patient checks.
  - Family history of renal disease.
- Examination
  - Blood pressure
  - Fundoscopy
  - Precordial examination
  - Examination of the abdomen for bruits and palpable renal masses
  - Extremity examination for edema
  - Neurologic examination for the presence of asterixis, muscle weakness and neuropathy.
  - In addition, the evaluation of prostate size in men and potential pelvic masses in women should be undertaken by appropriate physical examination
- Differentiate acute from chronic renal failure
  - Reduced kidney size on ultrasound
  - Longstanding nocturia and pruritus
  - Finding of broad tubular casts on urine analysis
  - Anemia (not always)
  - Renal osteodystrophy

- Identify aggravating factors (acute or chronic)
  - Hypovolemia or hypotension
  - Hypertension
  - Congestive heart failure
  - Sepsis
  - Nephrotoxins
- Evaluation of reversible underlying etiology
  - Malignant hypertension
  - Obstructive uropathy
  - Systemic lupus erythematosis

INVESTIGATIONS

- Diagnostic investigations
  - Urinalysis:
    - Hematuria: may indicate glomerulonephritis, but other sources must be excluded. Hematuria should not be assumed to be due to presence of an indwelling catheter.
    - Proteinuria: if heavy, is strongly suggestive of glomerular disease. Urinary infection may also cause proteinuria.
    - Glycosuria with normal blood glucose is common in CKD
  - Urine culture: including early-morning urine samples for TB
  - Urine microscopy:
    - White cells: indicate active bacterial urinary infection but this is an uncommon cause of CKD, sterile pyuria suggests papillary necrosis or renal TB
    - Eosinophilia: allergic tubulointerstitial nephritis or cholesterol embolization
    - Casts: granular casts are formed from abnormal cells within the tubular lumen and indicate active renal disease. Red cell casts are highly suggestive of glomerulonephritis
    - Red cells in the urine may be from anywhere between the glomerulus and the urethral meatus.
  - Urine biochemistry
    - Urinary electrolytes measurement not helpful in CKD.
    - Urine osmolality: this is a measure of concentrating ability. A low urine osmolality is normal in the presence of a high fluid intake but indicates

renal disease when the kidney should be concentrating urine such as in hypovolemia or hypotension.

- Blood:
  - Urea and creatinine (serial measurements help in determining the severity and chronicity)
  - Calculation of eGFR
  - Full blood count: Eosinophilia suggests vasculitis, allergic tubulointerstitial nephritis or cholesterol embolism.
  - Fragmented red cells and/or thrombocytopenia suggest intravascular hemolysis due to accelerated hypertension, hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.
  - ESR: markedly raised viscosity or ESR suggests myeloma or vasculitis.
  - Test for:
    - Sickle cell disease,
    - Hepatitis B (polyarteritis and membranous nephropathy) and C (cryoglobulinemic renal disease)
    - HIV (HIV-associated renal disease)
    - Antibodies to streptococcal antigens (ASOT): post-streptococcal glomerulonephritis
    - Antibody screening for SLE, scleroderma, wegener's granulomatosis and microscopic polyangitis and Goodpastre's syndrome
- Imaging: Ultrasound of kidney
  - Verifies the presence of 2 symmetric kidneys, provides an estimate of kidney size and rules out renal masses and obstructive uropathy.
  - Symmetric small kidneys support the diagnosis of progressive chronic renal failure with an irreversible component of scarring. The occurrence of normal kidney size suggests the possibility of an acute rather than chronic process. However, in some diseases, chronic renal failure may be present with normal sized or even enlarged e.g. amyloidosis, polycystic kidney diseases, diabetic nephropathy.
- CT and MRI may also be useful in diagnosis.
- Renal biopsy: should be performed in every person with unexplained CKD and normal-sized kidneys, unless there are strong contraindications. If rapidly progressive glomerulonepheitis is possible this investigation must be performed within 24 hours of presentation if at all possible

MANAGEMENT OF CHRONIC RENAL FAILURE

1. Treat reversible causes
   - Hypotension or dehydration
   - Administration of nephrotoxic drugs
   - Urinary tract obstruction
   - Severe hypertension (Goal BP <120/80mmHg)
   - Infection
2. Prevent or slow the progression of renal disease (Renoprotection)
   - ACE inhibitors or angiotensin II receptor blockers slow the progression of chronic renal failure
     - Patients with CKD and proteinuria >1g/24 h
       - ACE inhibitor increasing to maximum dose
       - Add angiotensin receptor antagonist if goals are not achieved (in type 2 diabetes start with angiotensin receptor antagonist)
       - Add diuretic to prevent hyperkalemia and help to control BP
       - Add calcium channel (verapamil or diltiazem) if goals not achieved
   - Blood pressure control: decreases progression of chronic renal failure
   - Target BP:
     - With proteinuria= 125/75mmHg
     - Without proteinuria= 130/85mmHg
   - Additional measures:
     - Statins to lower cholesterol to <4.5mmol/L
     - Stop smoking (three-fold higher rate of deterioration in CKD)
     - Treat diabetes (HBA1c <7%, 53mmol/mol)
     - Normal protein diet (0.8-1g/kg bodyweight): The possible efficacy of dietary protein restriction, in slowing progression of renal diseases, is less clear.
     - Avoid the following drugs:
       - Tetracycline (with the possible exception of doxycycline): due to anti-anabolic effect and tendency to worsen uremia
       - Drugs excreted by kidneys e.g. gentamicin (should only be prescribed when there is no alternative)
       - NSAIDs
       - Potassium sparing agents e.g. spironolactone and amiloride
       - Bardoxolone an antioxidant inflammatory modulator has shown a reduction in GFR in diabetic CKD.

3. Treatment of complications of renal dysfunction
   - Hyperkalemia:
     - Potassium restriction in diet. Stop drugs that cause potassium
     - Protect the heart: 10mls 10% Calcium Gluconate over 10 mins. Effect is temporary but can be repeated after 15 minutes.
     - Push Potassium into cells
       - 50mls 50% Dextrose with 10IU soluble insulin over 15-20 mins. May be given 2-4 hourly as required. Monitor serum glucose and potassium 2-4 hourly
       - 10-20mg Nebulized Salbutamol (or 0.5mg in 100ml of 5% glucose over 15 min-rarely used)
     - Push Potassium out of the body
       - Furosemide 1mg/kg IV (hydrate patient first if dehydrated)
       - Kayexalate (polystyrene sulphonate)/sodium Resonium 15-30g in 50-100ml 20% Sorbitol or with lactulose PO/PR
       - Consider hemodialysis if refractory
   - Hypertension:
     - Salt restriction
     - Diuretics: loop diuretic are recommended for the treatment of hypertension and edema in patients with chronic renal failure. Thiazide diuretics have additive effect when administered with a loop diuretic for refractory edema
     - Antihypertensive drug
   - Volume overload- dietary sodium restriction, diuretic therapy (usually with a loop diuretic given daily)
   - Metabolic acidosis: maintain plasma bicarbonate concentration above 22mEq/L. Give sodium bicarbonate (daily dose of 0.5 to 1 mEq/kg per day)
   - Hyperphosphatemia: dietary phosphate restriction may limit secondary hyperparathyroidism in patients with chronic renal failure. An intake of above 800mg/day may be desirable but can be accomplished only by limiting protein intake.
   - Anemia: blood transfusion (selected patients), recombinant erythropoietin may be given. Target hemoglobin 11-12 g/dl. Failure to respond may be due to iron deficiency (due to hepcidin from the liver produced in response to IL-6), bleeding, malignancy, infection, inflammation or formation of anti-EPO neutralizing antibodies. Intravenous (rather than oral) iron supplements optimize response to EPO treatment by repletion of iron stores.

- Malnutrition:
  - Low protein diet, restrict intake to 0.8 to 1g/kg or high biologic value protein (plant source)
  - Since this level of restriction avoids protein malnutrition and may slow progressive disease. Overall, the diet of most patients with chronic renal failure should provide approximately 30 to 35kcal/kg per day.
- Male Erectile dysfunction: testosterone deficiency should be corrected. The oral phosphodiesterase inhibitors e.g. sildenafil, tadalafill and verdenafil are effective in ESKD and are first line therapy. The use of nitrates is contraindicated to this treatment.

4. Identification and adequate preparation of the patient in whom renal replacement therapy will be required
   - Educate patient
   - Informed choice of renal replacement therapy:
     - Chronic hemodialysis
     - Kidney transplantation

URINARY TRACT INFECTIONS

- UTI is an acute infection of the urinary tract. It is subdivided into 2 general anatomic categories:
  - Lower urinary tract infection: urethritis and cystitis
  - Upper urinary tract infection: acute pyelonephritis, prostatitis, and intrarenal and perinephric abscess
- A UTI can be defined when pathogenic microorganisms are detected in urine, urethra, bladder, kidney or prostate.
- In most instances, growth of more than 10^5 organisms per ml from a properly collected midstream "clean-catch" urine sample indicates infection.
- In symptomatic patients, a smaller number of bacterial 10^2 to 10^4/ml may signify infection.
- In urine specimens obtained by suprapubic aspiration or "in and out" catheterization and in samples from a patient with an indwelling catheter, colony counts of 10^2 to 10^4/ml generally indicate infection.
- Infections that recur after antibiotic therapy can be due to:
  - Persistence of the originally infecting strain (as judged by species, antibiogram, serotype and molecular type) that become evident within 2 weeks of cessation of therapy (Relapse).
  - Reinfection with a new strain that become evident after 2 weeks of cessation of therapy.
- Acute pyelonephritis refers to chronic interstitial nephritis believed to result from bacterial infection of the kidney. It is manifested by calyceal dilation and cortical scarring.

- Bacteriuria: bacteria in urine. May or may not be symptomatic
- Significant bacteriuria: more than 10^5 colony forming units/ml in midstream urine
- UTI: Significant bacteriuria + symptoms
- Complicated UTI: UTI + presence of certain risk factor (renal or urinary tract abnormality, voiding difficulty, decreased kidney function, indwelling catheter, immunosuppression, or virulent organism e.g. *S. aureus*)
- Recurrent UTI: reinfection (new organism) or relapse by same organism (usually within 2 weeks). It has no strict definition but 2-3 per year is a common one.
- Abacterial cystitis: symptoms without bacteria. Sometimes occurs in women.

ACUTE URINARY TRACT INFECTION

- The vast majority of acute symptomatic infections involve young women. Acute symptomatic UTIs are unusual in men under the age of 50.
- The development of asymptomatic bacteriuria is also rare among men under 50 but common among women between 20-50.
- Asymptomatic bacteriuria is more common among elderly men and women with rates as high as 40 to 50%.
- Epidemiologically can be divided into:
  - Community-acquire infections (Non-catheter associated)
  - Nosocomial infections (Catheter-associated)

ETIOLOGY

- Routes of inoculation include:
  - Urethral inoculation: Ascent of bacteria from the bladder may follow and is probably the pathway for most renal parenchymal infections. Whether bladder infection ensues depends on interacting effects of the pathogenicity of the strain, the inoculum size, and the local and systemic host defence mechanisms.
  - Hematogenous spread: pyelonephritis occurs most often in debilitated patient who are either chronically ill or receiving immunosuppressive therapy. Metastatic staphylococcal or candida infections of the kidney may follow bacteremia or fungemia spreading from distant foci of infection in the bone, skin, vasculature or elsewhere.
- Pathogens:
  - *E. coli* (90%)
  - *Staph. saprophyticus*: occurs in sexually active women
  - *Proteus mirabilis*: suggest kidney stones
  - *Enterococcus faecalis*: causes prostatitis
  - *Klebsiella*: usually in catheterized patients
  - *Staph. aureus*: from hematogenous spread
  - STIs: Chlamydia and gonorrhea

Community acquired	Hospital acquired/ catheter associated
• Commonest: ➢ *E coli* (80%) ➢ *S. saprophyticus* (10%) ➢ *Klebsiella pneumoniae* (5%) ➢ Other (5%) • In acute urethral syndrome (STI: *N. gonorrhea, Chlamydia trachomatis, Trichomonas, Candida* and Herpes simplex virus may cause lower UTI)	• *E. coli* (30%) • *Enterococci* (15%) • *Pseudomonas* (10%) • *S. aureus*, yeasts and other *Enterobacteriacea*

RISK FACTORS

- Gender and sexual activity:
  - Females are prone to colonization with colonic gram-negative bacilli because of the urethra's proximity to the anus, its short length (about 4cm) and its termination beneath the labia.
  - Sexual intercourse causes the introduction of bacteria into the bladder and is temporally associated with onset of cystitis, especially in younger women.
  - In men <50 years old and who have no history of heterosexual or homosexual rectal intercourse UTI is exceedingly uncommon and this diagnosis should be questioned in the absence of clear documentation.
  - Lack circumcision has been identified as a risk factor for UTI in both neonates and young men.
- Pregnancy: due to altered urethral smooth muscle function. Bladder catheterization during or after delivery causes additional infections.
- Vesicoureteral reflux:
  - This is defined as reflux of urine from the bladder cavity up into the ureters and sometimes into the renal pelvis.
  - It occurs during voiding or with elevation of pressure in the bladder.
  - It is common among children with anatomic abnormalities of the urinary tract as well as among children with anatomically normal but infected urinary tract (though this disappears with advancing age)
  - Vesicoureteral reflux may promote ascending infection in several ways including increased delivery of bacteria, increased size of inoculum, incomplete bladder emptying.

- Obstruction: tumors, strictures, stones or prostatic hypertrophy result in hydronephrosis. Urinary stasis and impaired host defense greatly increase frequency of UTI.
- Neurogenic bladder dysfunction: spinal cord injury, tabes dorsalis, multiple sclerosis, diabetes, and other diseases.
- Diabetes mellitus: neurogenic bladder disturbance and also do to other immune disorder in diabetes.
- Immunodeficiency: a CD4 count less than 200/μL are at increased risk of both bacteriuria and symptomatic UTI
- Bacterial virulence factors: not all strains of E. coli are equally capable of infecting the intact urinary tract. Bacterial virulence factors markedly influence the likelihood that a give strain once introduced will cause UTI.
- Genetic factors

CLINICAL PRESENTATION

URETHRITIS

- In 30% of women presents with acute dysuria, frequency and pyuria. They have mid-stream urine cultures that show either no growth or insignificant bacterial growth.
- Chlamydial or gonococcal infection should be suspected in women with a gradual onset or illness, no hematuria, no suprapubic pain and more than 7 days of symptoms. The additional history of a recent sex-partner change, especially if the patient's partner has recently had chlamydial or gonococcal urethritis should heighten the suspicions of STI as should the finding of mucopurulent cervicitis.
- Gross hematuria, suprapubic pain, an abrupt onset of illness, a duration of illness of <3 days and a history of UTIs favor the diagnosis of *E. coli* UTI.

CYSTITIS

- Patients with cystitis usually report dysuria, frequency, urgency and suprapubic pain.
- The urine often becomes grossly cloudy and malodorous and it is bloody in about 30% of cases.
- If a genital lesion or a vaginal discharge is evident, then pathogens that may cause urethritis, vaginitis, or cervicitis such *as C. trachomatis, N gonorrhoeae, Trichomonas, Candida* and herpes simplex virus should be considered.

ACUTE PYELONEPHRITIS

- Symptoms of acute pyelonephritis generally develop rapidly over a few hours or a day and include fever, shaking chills, nausea, vomiting and diarrhea.
- Symptoms of cystitis may or may not be present.
- Physical examination:
  - Fever
  - Tachycardia
  - Generalized muscle tenderness
  - Marked tenderness on deep pressure in one or both costovertebral angles or on deep abdominal palpation (Costvertebral/Renal angle tenderness)
- In some patients signs and symptoms of gram-negative sepsis predominate.

CATHETER ASSOCIATED UTI

- Affects at least 10-15% of catheterized hospital patients.
- The risk of infection is about 3 to 5% per day of catheterization.
- Most catheter associated infections cause minimal symptoms and no fever and often resolve after withdrawal of the catheter.
- Gram-negative bacteremia which follows catheter-associated bacteriuria in 1 to 2% of cases, is the most significant recognized complication of catheter-induced UTIs.
- Gram-negative bacteremia which follows catheter-associated bacteriuria in 1-2% of cases is the most significant recognized complications of catheter induced UTIs.

INVESTIGATIONS

- Urinalysis
  - Urinary sediments
  - Nitrites or leukocyte esterase positive
  - Leukocytes are found in urine: >5WBCs/high power field in centrifuged urine or >10WBCs/high power field in unspun urine suggests UTI
  - Microscopic bacteruria: single micro-organism per oil immersion of unspun urine is indicative of a colony growth on culture of more than 10^5 colonies/ml.
  - Gram stain of uretheral discharge may be helpful in patients suspected of having infection that need treatment

- Microscopy, Culture and sensitivity of Urine
  - Definitive means of diagnosis
  - A clean catch, early morning mid-stream urine specimen should be collected
  - The growth of more than 10^5 colonies/ml in the presence of symptoms signifies infection that needs treatment
  - If $<10^5$ CFU/ml but pyuria (>20 WBC/mm^3) it is known as 'sterile pyuria'. Causes include: previously treated UTI, prostatitis, STI, TB, appendicitis, bladder tumor, stones, polycystic kidney disease or drug-induced cystitis.
  - If many different organisms, suspect contaminated sample (i.e. not mid-stream) and repeat midstream urine
- Blood
  - FBC: increased WBC
  - U+ Es, CRP and blood cultures for pyelonephritis
  - Blood glucose to rule out diabetes.
- Radiologic urologic evaluation: to identify some predisposing conditions e.g. urolithiasis, BPH, vesicoureteral reflux.
  - Kidney ultrasound (Obstruction/hydronephrosis)
  - Post-void bladder ultrasound
  - KUB X-ray (kidney ureter bladder X-ray)
  - Intravenous nephrogram

TREATMENT

- Principles:
  - Except in acute uncomplicated cystitis in women, a quantitative urine culture, rapid diagnostic test should be performed to confirm infection before treatment is begun.
  - Factors predisposing to infection e.g. obstruction and calculi should be identified and corrected if possible
  - Relieve of clinical symptoms does not always indicate bacteriologic cure.
  - In general, uncomplicated infections confined to the lower urinary tract respond to short course of therapy while upper tract infections require longer treatment.
- Admission criteria (in acute pyelonephritis):
  - Inability to maintain oral hydration or take medications
  - Concerns about patient compliance
  - Uncertainty about the diagnosis
  - Severe illness with high fevers, pain and marked debility

- Paracetamol +/- NSAIDs for symptom relief.
- Remove catheter if present
- Empiric antibiotic choices:
  - Fluoroquinolones and aminoglycosides achieve higher tissue levels. So these drugs are preferred for empiric treatment.
  - Ampicillin and sulfonamides should NOT be used for empiric therapy because of high rates of resistance among causative uropathogens.
  - All pregnant women should be screened for bacteriuria in the first trimester and should be treated if bacteriuria is demonstrated.
  - Acute uncomplicated Lower UTI in women:
    - Nitrofurantoin (if eGFR>45)
    - Trimethoprim-Sulfamethoxazole (TMP-SMX): 480mg 2 tabs PO BD for 3-5 days
    - Norfloxacin 400mg PO BD or Ciprofloxacin 500mg PO BD for 5-7 days
  - Acute uncomplicated pyelonephritis in women: *E.coli, P. mirabilis, S. saprophyticus*
    - Norfloxacin 400mg PO BD or Ciprofloxacin 500mg PO BD for 7-14 days or
    - Single dose of ceftriaxone 1g or Gentamicin 80mg IV followed by TMP-SMX: 480mg 2 tabs PO BD for 14 days.
  - Complicated UTI in men and women: *E. coli, proteus, Klebsiella, Pseudomonas, Serratia, enterococci, Staphylococci* are common etiologies.
    - Mild to moderate illness, no nausea or vomiting treat as outpatient
    - Norfloxacin 400mg PO BD or Ciprofloxacin 500mg PO BD for 7-14 days
  - Severe illness or possible urosepsis: hospitalization is required
    - Ceftriaxone 1g IV BD or
    - Gentamicin 80mg IV TDS
    - Ampicillin 1g IV QID and then 500mg IV QID
    - IV quinolones such as Ciprofloxacin 200-400mg IV BD can also be used if available.
    - If enterococcus is suspected based upon the Gram stain, Ampicilin (1 to 2g IV 6 hourly) plus gentamicin (1mg/kg 8 hourly or adjusted for renal function)
  - Note: IV medication should be changed to PO as soon as the patient becomes afebrile and then given PO TMP-SMX or Ciprofloxacin or Norfloxacin for 10-21 days

- Parenteral therapy- for hospitalized patients, aminoglycosides (3 to 5mg/kg) OD are cost effective, associated with low toxicity when used for short durations and may provide a therapeutic advantage compared with beta lactams, because of their marked and sustained concentration in renal tissue.

COMPLICATIONS AND PROGNOSIS

- Infectious spread:
  - Pyelonephritis
  - Perinephric or intrarenal abscess
  - Prostatitis
  - Sepsis
- Kidney
  - AKI
  - Hydronephrosis
- Recurrence: 1 in 3 women, usually reinfection (new pathogen)
- Prognosis: symptoms resolve in 3-4 days with an effective antibiotic vs 5-7 days without treatment (or with a resistant organism)

CHAPTER 10: ENDOCRINOLOGY

ENDOCRINE CONDITIONS

THYROID

HYPERTHYROIDISM

HYPOTHYROIDISM

ADRENAL GLAND

ADRENAL GLAND

- The adrenal gland/Supra-renal gland consists of 2 part:
  - Adrenal cortex: which consists of 3 histological layers. All the hormones produced in this layer are derived from cholesterol.
    - Zona Glomerulosa- produces mineralocorticoids such as aldosterone
    - Zone Fasciculata- produces glucocorticoids e.g. cortisol
    - Zona reticularis- produces androgens
  - Adrenal medulla consisting of chromaffin cells (which are derived from the embryonic ectordermal neural crest) and produce catecholamines e.g. epinephrine and norepinephrine
- Common diseases of the adrenal cortex
  - Resulting from excess production of hormones:
    - Cushing's syndrome: excess cortisol production
    - Primary hyperaldosteronism: excess production of aldosterone
  - Resulting from Inadequate production:
    - Addison's disease: inadequate production of cortisol and aldosterone
- Disease of the adrenal medulla
  - Pheochromocytoma: Excess production of catecholamine

CUSHING SYNDROME

- This is a clinical syndrome characterized by excessive concentration of cortisol or other glucocorticoid hormones in the circulation.
- There is a large spectrum of clinical manifestation from subclinical to overt syndrome depending on the duration and the intensity of excess steroid exposure.
- It occurs most often following the therapeutic administration of synthetic steroids or ACTH.
- Spontaneous Cushing's syndrome is rare.

ETIOLOGY

- Causes of Cushing's syndrome are usually subdivided into:
  - Iatrogenic Cushing's syndrome/ Exogenous corticosteroids

- This is the most common cause but is seldom reported.
- Seen in patients receiving long term glucocorticoid treatment for asthma, arthritis and other conditions.
- Both adrenal glands become atrophic (decreased production of ACTH from suppression by exogenous cortisol)

- Ectopic ACTH syndrome (Paraneoplastic ACTH secretion)
  - This is the second most common cause of Cushing's syndrome, but is often not diagnosed.
  - About 1% of patients with small-cell lung cancer have ectopic ACTH syndrome.
  - Small-cell lung carcinoma causes half of all cases of the syndrome.
  - Both adrenals are enlarged.
- Cushing's disease
  - Cushing's disease is pituitary ACTH-dependent Cushing's syndrome.
  - It is five to six times more common than Cushing's syndrome caused by benign and malignant tumors combined.
  - Both adrenal are enlarged.
- Adrenal tumors, hyperplasia or carcinoma
  - Adrenal masses are discovered incidentally at autopsy or by radiographic studies in 1.3 to 8.7 % of adults, more than 99% of whom do not present with symptomatic adrenal disease.
  - The affected adrenal gland is larger while the normal is atrophic, this is due to suppression of ACTH production from excess production from the affected adrenal.

Causes of Cushing's syndrome	
ACTH dependent Cushing's	Non-ACTH dependent Cushing's
• Pituitary-dependent (Cushing's disease) • Ectopic ACTH-producing tumors • ACTH administration	• Adrenal adenomas and carcinomas • Glucocorticoid administration • Alcohol induced pseudo-Cushing's syndrome

CLINICAL FEATURES

- The clinical features of Cushing's syndrome are those of glucocorticoid excess

- Progressive obesity: central obesity with wasting of extremities (muscle is broken down for gluconeogenesis).
- Pigmentation occurs only with ACTH-dependent causes, Purple striae with skin atrophy and easy bruising.
- Cushignoid appearance- Moon face, buffalo hump (cervical fat pad) and supraclavicular fat pads.
- Impaired glucose tolerance or frank diabetes is common, especially in the ectopic ACTH syndrome.
- Hypokalaemia due to the mineralocorticoid activity of cortisol is common with ectopic ACTH secretion.
- Hypertension: common in all causes of Cushing's (Results from the vascular effects of cortisol by upper regulation of alpha 1 receptors on arterioles and sodium retention)
- Oligomenorrhea, hirsutism and acne: due to androgen excess due to stimulation by ACTH.
- Decreased glucose tolerance: results from hepatic gluconeogenesis and decreased peripheral glucose utilization.
- Osteoporosis: due to catabolism of bone.
- Poor wound healing (impaired immune function) and growth retardation.
- Psychiatric disturbance: especially depression, are frequently seen.

PROGRESSIVE OBESITY

- The most common feature of patients with Cushing's syndrome is progressive central/truncal obesity, usually involving the face (moon faces), neck, trunk and abdomen.
  - The "moon face", "buffalo hump" (cervical fat pad) and supraclavicular fat pads contribute to the cushingiod appearance (excess insulin produced because of high glucose levels, excess insulin resulting in storage of fat).
- The extremities are usually spared and may be wasted.

DERMATOLOGICAL FEATURES

- Skin atrophy: the skin usually atrophies, the stratum corneum is thinned and there is loss of subcutaneous fat to a sufficient degree that subcutaneous blood vessels may be seen.
- Easy bruisability: Loss of subcutaneous connective tissue due to the catabolic effects of glucocorticoid results in easy

bruising after minimal, often unremembered injury.

- Striae: purple striae occur as the fragile skin stretches due to the enlarging trunk, breasts and abdomen. The striae appear as wide, reddish-purple streaks and are most common on the abdomen and lower flanks.
  - Cortisol impairs synthesis of collagen so blood vessels are weak and easily rupture forming striae (ruptured blood vessel)
- Fungal infections: cutaneous fungal infections, especially tinea versicolor while some patients have fungal infections of the nails.
- Hyperpigmentation: this is induced by increased ACTH, not cortisol secretion. ACTH has a similar structure to melanocyte-stimulating hormone.
- Hirsutism.

MENSTRUAL IRREGULARITIES

- Menstrual irregularities are common in women and they range from oligomenorrhea, amenorrhea to excess or variable menses.

PROXIMAL MUSCLE WASTING AND WEAKNESS

- Weakness and proximal muscle wasting are common and are induced by the catabolic effects of excess glucocorticoid on skeletal muscle.
- Many patients cannot rise from a squatting position without assistance and patients with more severe disease may be unable to climb stairs or get up from a deep chair.
- The catabolic effects of cortisol are amplified by physical inactivity.
- Hypokalemia, due to increased mineralocorticoid activity, can accentuate the weakness in patients with severe hypercortisolism.

BONE LOSS

- Osteoporosis is common in patients with Cushing' syndrome.
- It is caused by decreased intestinal calcium absorption, decreased bone formation, increased bone resorption, and decreased renal calcium reabsorption.
- It can be demonstrated by densitometry of the lumbar vertebrae even in young patients.
- Pathologic fractures may occur, often resulting in severe skeletal pain.

NEUROPYSCHOLOGICAL CHANGES AND COGNITION

- Symptoms of psychiatric disease occur in over one-half of patients with Cushing's syndrome of any etiology.

- The most common psychologic symptoms are:
  - Emotional lability
  - Agitated depression
  - Irritability
  - Anxiety
  - Panic attacks
  - Mild paranoia

INFECTION AND IMMUNE FUNCTION

- Glucocorticoids inhibit immune function, thereby contributing to an increased frequency of infections.
- The mechanism by which glucocorticoid excess predisposes to infection is poorly understood.
- One mechanisms may be a fall in circulating CD4 cells and decline in natural killer-cell activity.
- Another mechanism is cortisol inhibits phospholipase A2 essential to produce chemical mediators of inflammation.
- Perhaps the major effect is that glucocorticoids inhibit the synthesis of almost all cytokines.

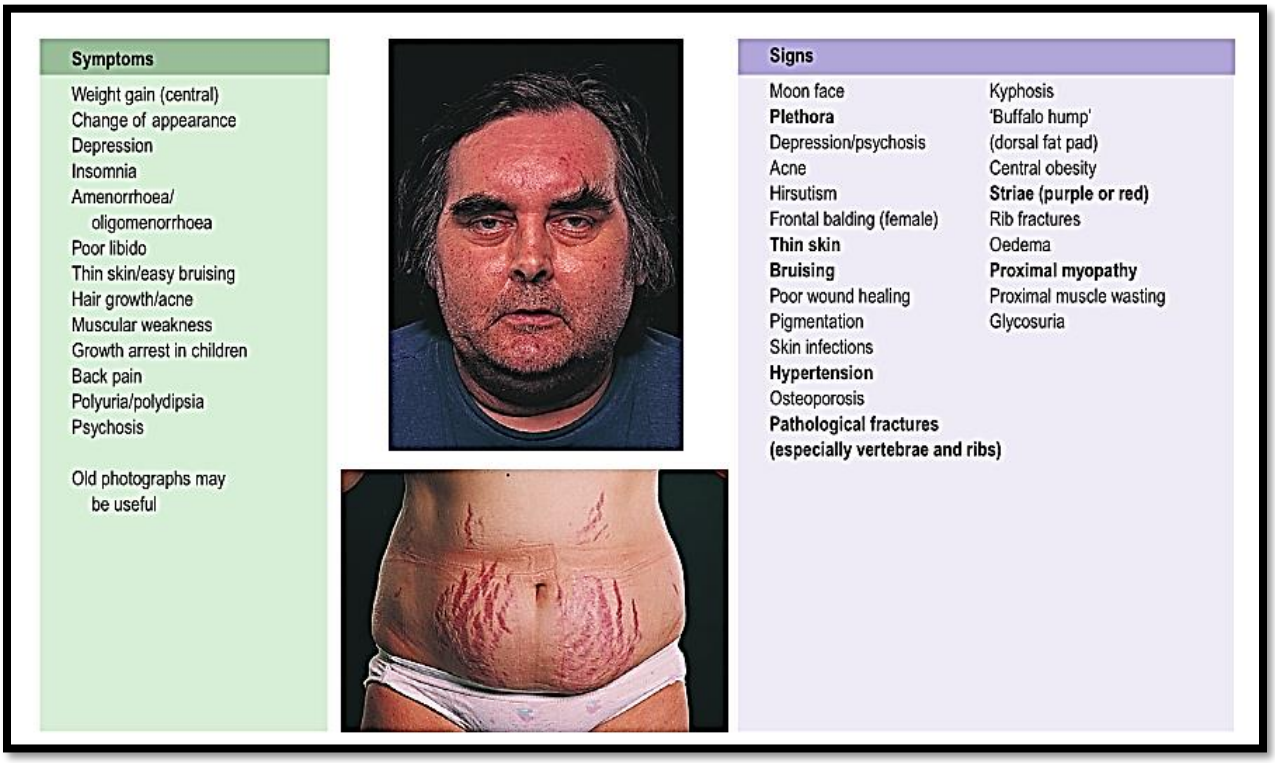
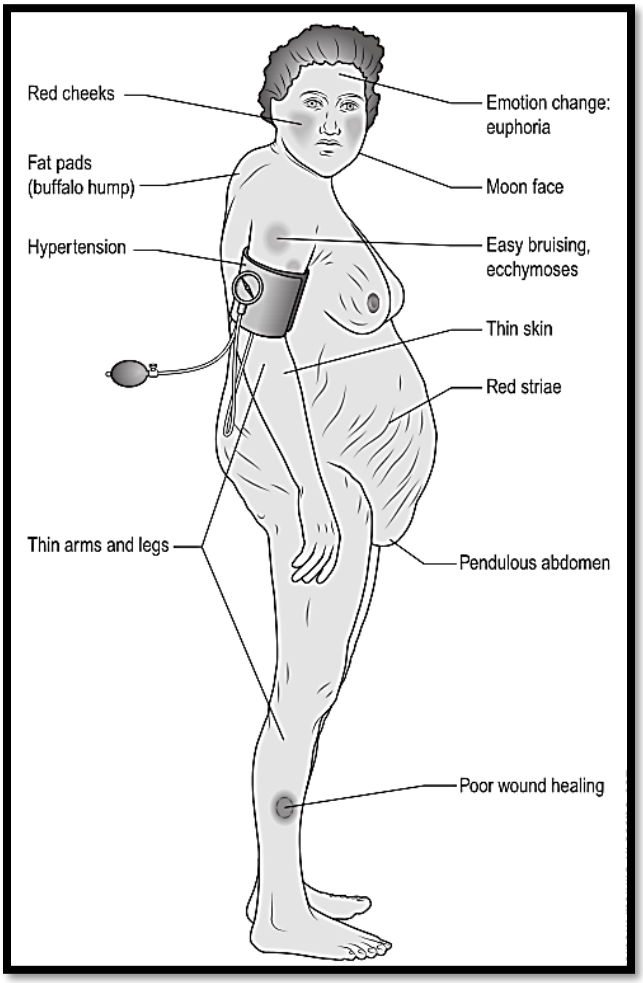


Figure 51: Signs and symptoms of Cushing's syndrome



DIAGNOSIS

- There are 2 phases:
  - Confirmation
  - Differential diagnosis of the cause

CONFIRMATION

- Investigations include:
  - 48-hour low-dose dexamethasone test: normal individuals suppress plasma cortisol to less than 50 nmol/L. In Cushing's syndrome there is inability to suppress plasma cortisol levels (although levels may fall substantially in a few cases). This test is highly sensitive (>97%). The overnight dexamethasone test is slightly simpler but has a higher false-positive rate.
  - 24-hour urinary free cortisol measurements: this is simple but non-reliable- repeatedly normal values render the diagnosis most unlikely but some people with Cushing's syndrome have normal values on some collections (approximately 10%)
  - Circadian rhythm: After 48 hours in hospital, cortisol samples are taken at 09:00 hours and 24:00 hours (without warning the patient). Normal subjects show a pronounced circadian variation those with Cushing's syndrome have high midnight cortisol levels (>100 nmol/L) though the 09:00 hours value may be normal. Midnight salivary cortisol collected at home gives the same information more simply where the assay is available.

DIFFERENTIAL DIAGNOSIS OF THE CAUSE

- This can be extremely difficult since all cause can result in clinical identical Cushing's syndrome.
- The classical ectopic ACTH syndrome is distinguished by a short history, pigmentation and weight loss and diabetes and plasma ACTH above 200ng/L.
- Severe hirsutism/virilization suggest an adrenal tumor.
- Radiological tests:
  - Adrenal CT or MRI: adrenal adenomas and carcinomas causing Cushing's syndrome are large and can be detectable by CT scan.
  - Pituitary MRI: a pituitary adenoma may be seen but is usually small and not visible in most cases.
  - CXR: to look for a carcinoma of the bronchus.
- Biochemical tests:
  - Potassium levels: hypokalemia is common with ectopic ACTH secretion. (all diuretics must be stopped)
  - Plasma ACTH level: Low or undetectable levels of ACTH (<10 ng/L) on 2 or more occasions is a reliable indicator of a non-ACTH dependent disease.
  - CRH test: an exaggerated ACTH or cortisol response to exogenous CRH suggest pituitary dependent disease (Cushing's disease).
  - High-dose dexamethasone test: Failure of significant plasma cortisol suppression suggests an ectopic ACTH or adrenal tumor.

TREATMENT

- Untreated Cushing's syndrome has a bad prognosis with death from hypertension, myocardial infarction, infection and heart failure.
- Whatever the underlying cause cortisol secretion should be controlled prior surgery or radiotherapy.
- Treatment of Cushing's disease
  - Transphenoidal removal of the tumor (treatment of choice)
  - External pituitary radiation
  - Medical therapy to reduced ACTH using Bromocriptine
  - Bilateral adrenalectomy
- Treatment of other causes
  - Adrenal adenoma- resection
  - Tumors secreting ACTH ectopically should be removed surgically, otherwise chemotherapy/ radiotherapy should be used.
- **Nelson's syndrome**: this is increased pigmentation (because of

high levels of ACTH) associated with an enlarging pituitary tumor, which occurs in about 20% of cases after bilateral adrenalectomy for Cushing's disease. The syndrome is rare now that adrenalectomy is an uncommon primary treatment and its incidence may be reduced by pituitary radiotherapy soon after adrenalectomy.

- In chronic alcoholics and patients with depression, there may be increased urinary excretion of steroids, absent diurnal variation of plasma steroids and a positive overnight dexamethasone test. This is **pseudo-cushing syndrome**.

SALIENT FEATURES OF CUSHING SYNDROME

HISTORY

- Ask for
  - History of steroid therapy
  - Central weight gain
  - Hirsutism
  - Easy bruising
  - Acne
  - Weakness of muscle
  - Menstrual disturbances
  - Loss of libido
  - Depression, sleep disturbances
  - Back pain as a result of spinal osteoporosis

EXAMINATION

- Moon-like facies, acne, hirsutism and plethora (From telangiectasia)
- Examine the following:
  - The mouth for superimposed thrush.
  - The interscapular area for 'buffalo hump'.
  - Increased fat pads and bulge above supraclavicular fossae (more specific for Cushing syndrome).
  - The abdomen for thinning of skin and purple striae (also seen over the shoulders and thighs): said to be present on almost all patients.
  - The limbs for bruising, wasting of the limbs, weakness of the muscles of the shoulders and hips: get the patient to squat (proximal myopathy).
- Ask the patient whether he or she has back pain and then examine the spine, looking for evidence of osteoporosis and collapse of vertebra, kyphoscoliosis.
- Measure the blood pressure.
- Tell the examiner you would like to:
  - Test the urine for glucose
  - Check visual fields (for pituitary tumor)
  - Examine the fundus for optic atrophy, papilloedema, signs

of hypertensive or diabetic retinopathy.

- Comment on signs of asthma, rheumatoid arthritis, SLE, fibrosing alveolitis (as these are conditions that are treated with long-term steroids).
- Note: Hirsutism is not common in Cushing syndrome cause by exogenous steroids because they suppress adrenal androgen secretion.

HYPERALDOSTERONISM

- Recall the distal convoluted tube has two types of cells that respond differently to aldosterone.
  - The principle cell: increase the re-absorption of sodium and secretion of potassium
  - The alpha-intercalated cells: increase the excretion of hydrogen ions.
- Presentation:
  - Hypernatremia
  - Hypokalemia (Due to excretion of potassium)
  - Metabolic alkalosis (Due to excretion of hydrogen ion)
  - Hypertension (re-absorption of sodium and water)

PRIMARY HYPERALDOSTERONISM

- Most commonly due to adrenal adenoma
- Sporadic hyperplasia and carcinoma are less common causes.
- Characterized by high aldosterone and low renin (increased blood volume)

SECONDARY HYPERALDOSTERONISM

- Activation of renin-angiotensin system (e.g. renovascular hypertension in fibromuscular dysplasia of renal artery or atherosclerosis of the renal artery)

- Characterized by high aldosterone and high renin

ADDISONS DISEASE (ADRENAL INSUFFICIENCY)

- In Addison's disease there is destruction of the entire adrenal cortex leading to hypofunctioning of the adrenal cortex.
- Endocrine disorder is also known as Adrenal insufficiency.
- Glucocorticoid, mineralocorticoid and sex steroid production are all reduced.
- Addison's disease occurs when 90% of the adrenal cortex is destroyed.

HORMONE	FUNCTION
MINERALOCORTICOIDS (Zona Glomerulosa)	• Electrolyte and fluid balance • Increases sodium and water retention • Regulated by renin and angiotensin
GLUCOCORTICOIDS (Zona fasciculata)	• Carbohydrate, lipid & fat metabolism • Increases blood glucose levels & gluconeogenesis. • Increases protein breakdown • Inhibits protein synthesis
SEX STEROIDS (Zona reticularis)	• Low synthesis in adrenals compared to gonads • Virilising hormones may be secreted

- Adrenal insufficiency can be divided into 2 types:
    - Acute adrenal insufficiency
    - Chronic adrenal insufficiency

ACUTE ADRENAL INSUFFICIENCY

- Waterhouse-Friderichsen syndrome
    - Infection with *Neisseria meningitidis* (classically seen especially in children) other infections include *Pseudomonas, pneumococci, H. influenza*
    - The pathogenesis is unclear but believed to be endotoxin induced vascular injury (massive hemorrhage) with associated disseminated intravascular coagulation (DIC), this results in bilateral necrosis of the adrenal glands.

- Sudden withdrawal of long term corticosteroid treatment
  - xInability of atrophic adrenals to produce glucocorticoids
- Stress with underlying chronic adrenal insufficiency
  - Acute adrenal crises on limited physiological reserves

CHRONIC ADRENAL INSUFFICIENCY

- Is divided into
  - Primary adrenal insufficiency: Addison's disease
  - Secondary adrenal insufficiency: progressive destruction of adrenals
    - Tuberculosis: caseous necrosis of adrenal cortex
    - Autoimmune adrenalitis: associated with pernicious anemia, thyroiditis, IDDM
    - AIDS
    - Metastatic disease: especially lung carcinomas
    - Systemic amyloidosis
    - Fungal infection
    - Hemochromatosis
    - Sarcoidosis

CLINICAL FEATURES

- Insidious onset
  - Progressive weakness and fatigability
  - Non-specific complaints (anorexia, nausea/vomiting, weight loss)
- Primary adrenal disease: hyperpigmentation (due to increased ACTH).
- Hyperkalemia and hyponatremia.
- Hypotension (volume depletion-hypovolemia) and dehydration
- Hypoglycemia
- Sexual dysfunction
- Adrenal crisis:
  - Infections: trauma, surgery-> intractable vomiting, abdominal pain, hypotension, vascular collapse, death.
- In Addison's deficiency the heart is small.

INVESTIGATIONS

SINGLE CORTISOL MEASUREMENTS

- Of little value although a random cortisol below 100nmol/L is highly suggestive and levels above 550nmol/L makes the diagnosis unlikely.

SHORT ACTH STIMULAION TEST (SHORT SYNACTHEN TEST)

- Absent or impaired response is seen.

ELECTROLYTES AND UREA

- Classically show hyponatraemia, hyperkalemia and high urea.

BLOOD GLUCOSE

- Blood glucose may be low with symptomatic hypoglycemia

- Adrenal antibodies may be present in many cases of autoimmune adrenalitis.

TREATMENT

- Hormone replacement.
- Address the cause (secondary adrenal insufficiency).
- For primary adrenal insufficiency (Addisons disease)- long term treatment with replacement glucocorticoid and mineralocorticoid is required.

SALIENT FEATURES

HISTORY

- Ask for:
  - Dizziness, syncope
  - Skin pigmentation (ask if the patient has been sitting in the sun)
  - Ask questions regarding fatigue, weakness, apathy, anorexia, nausea, vomiting, weight loss and abdominal pain
  - Depression

EXAMINATION

- The striking abnormality is hyperpigmentation
- Examine for hyperpigmentation, typically localized to palmar creases and knuckles:
  - Hand: compare the creases with your own
  - Mouth and lips for pigmentation

- Areas not usually covered by clothing: nipples, areas irritated by belts, straps, collars or rings.
- Look for vitiligo
- Tell the examiner that you would like to investigate as follows:
  - BP, in particular for postural hypotension
  - Looking for sparse axillary and pubic hair
  - The abdomen for adrenal scar (if the scar is pigmented, think of Nelson syndrome and examine field defects)
- If you suspect Addison's disease, tell the examiner that you would like do a short ACTH stimulation test.

PHEOCHROMOCYTOMA

- Tumor of chromaffin cells of adrenal medulla.
- Presents with Episodic hypertension, headaches, palpitations, tachycardia and sweating
- Diagnosed by increased metanephrines and increased 24-hour urine metanephrines and vanillin mandelic acid (VMA).
- Treatment is surgical excision.
  - Before surgery give the patient phenoxynenzamine (irreversible blocker of alpha receptor) to prevent hypertension from surge of epinephrine and norepinephrine
- Rules of 10s
  - 10% bilateral
  - 10% familial
  - 10% malignant (90% benign)
  - 10% located outside of adrenal medulla (e.g. bladder wall)

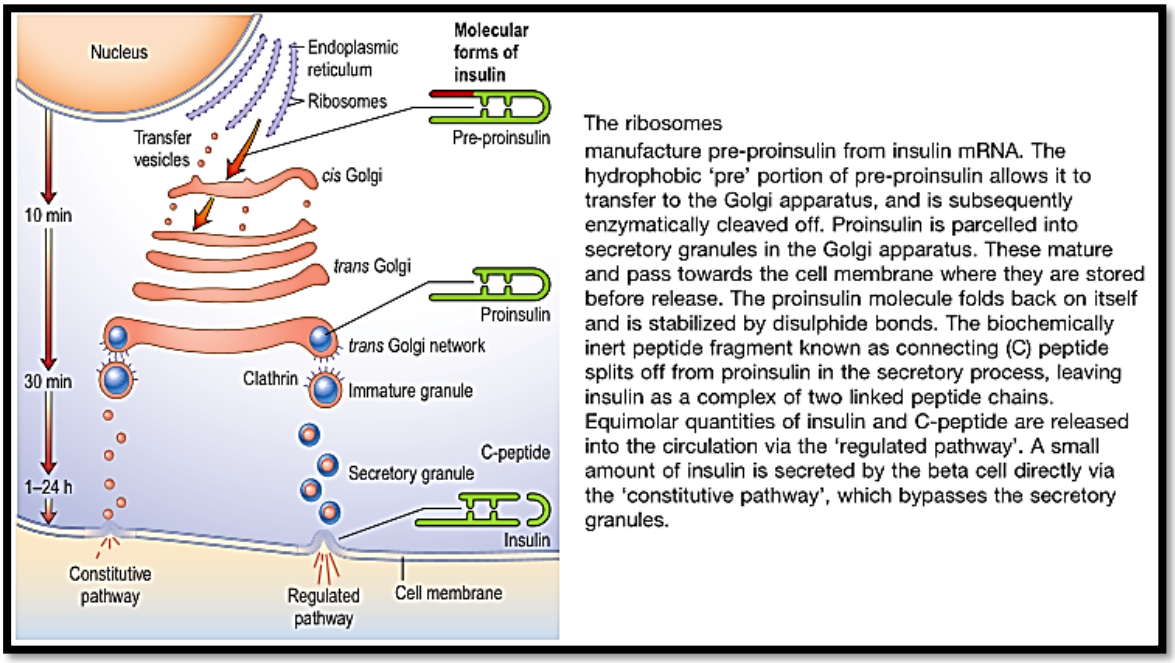
PANCREAS AND DIABETES MELLITUS

- Diabetes is a metabolic disorder of carbohydrate metabolism characterized by persistent hyperglycemia due to either insulin deficiency or resistance.
  - Blood glucose levels are closely regulated in health and rarely stray outside the range of 3.5-8.0 mmol/L (63-144mg/dl) despite the varying demands of food, fasting and exercise.
  - Normal Fasting blood sugar= 3.5-5.5 mmol/l (63-100mg/dl)
  - Normal Random Blood sugar= 4.4-7.8 mmol/l (70-144mg/dl)
    - Note: a random blood sugar between 7.8-11.1 mmol/l is considered pre-diabetic.
- Diabetes is a syndrome of chronic hyperglycemia due to absolute insulin deficiency (Type 1), relative insulin deficiency (Type 2), resistance or both.
- For diagnosis of diabetes mellitus
  - Fasting blood sugar ≥7 mmol/l (126 mg/dl)
  - RBS ≥ 11.1 mmol/L (200mg/dl)
  - 2-hour postprandial plasma glucose ≥ 11.1 mmol/L (200mg/dl) after a glucose load of 75g (during oral glucose tolerance test)
  - HBA1c >6.5% (48mmol/mol)

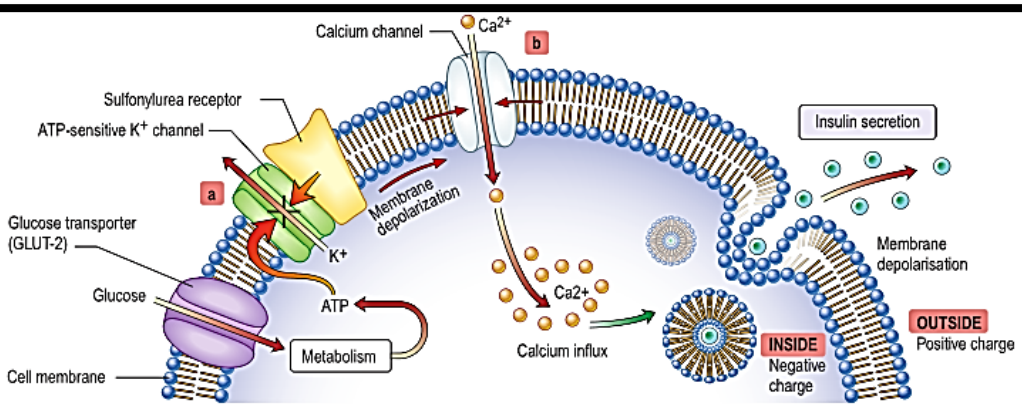
To change mg/dl to mmol/l divide by the factor 18

- Diabetes is usually irreversible and although patients can lead a reasonable lifestyle, its late complications result in reduced life expectancy and major health costs.
- These include macrovascular disease leading to an increased prevalence of coronary artery disease, peripheral vascular disease, stroke and microvascular damage causing diabetic retinopathy and nephropathy. Neuropathy is another major complication.
- Recall:
  - Insulin is coded for on chromosome 11 and is synthesized in the beta cells of the pancreatic islets.
  - The synthesis, intracellular processing and secretion of insulin by the beta cells is typical of the way that the body produces and manipulates many peptide hormones.
  - Synthesis: Preproinsulin is modified into proinsulin which has its C peptide chain cleaved to become insulin (A and B chains) which is packed into granules along with free peptides.

- Mechanism of secretion: glucose from the GI tract activates GLUT2 receptors of beta cells this increases ATP in the cells which closes the ATP-gated potassium channel to prevent efflux of potassium leading to depolarization, increased calcium entry and insulin granule exocytosis.
- After secretion, insulin enters the portal circulation and is carried to the liver, its prime target organ. About 50% of secreted insulin is extracted and degraded in the liver, the residue is broken down by the kidneys.
- C-peptide is only partially extracted by the liver hence provides a useful index of the rate of insulin secretion however, it is degraded by the kidneys.
- Cell membranes are not inherently permeable to glucose. A family of specialized glucose transporter (GLUT) proteins carry glucose through the membrane into cells
    - GLUT-1: enable basal non-insulin stimulated glucose uptake into many cells.
    - GLUT-2: transports glucose into beta cells, a prerequisite for glucose sensing. Also found in renal tubules and hepatocytes. Works in both directions.
    - GLUT-3: enables non-insulin mediated glucose uptake into brain neurons and placenta
    - GLUT-4: enables much of the peripheral action of insulin. It is the channel through which glucose is take into muscle and adipose tissue cells following stimulation of the insulin receptor.
- Some cells such as neurons, placenta cells and cells of the cornea do not require insulin for the uptake of glucose.
- Insulin receptor has 4 subunits (two alpha on the periphery and two beta transmembrane).



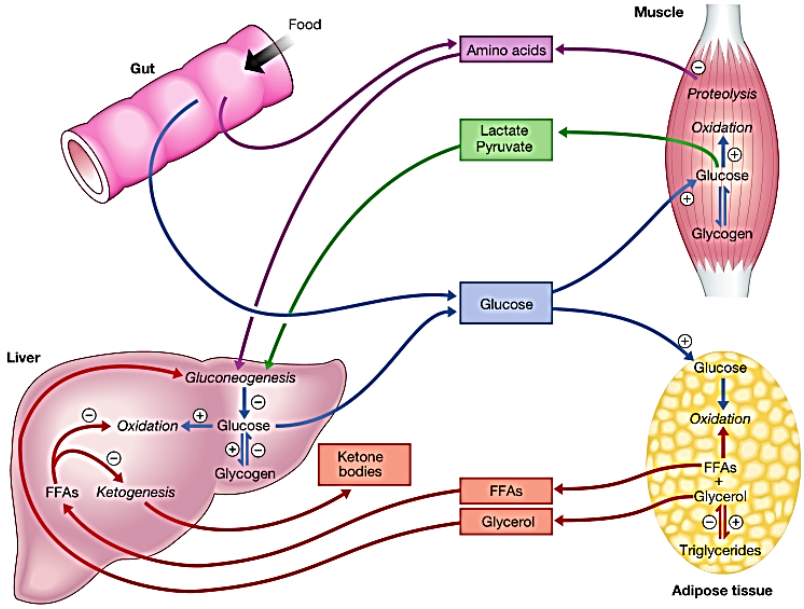
The ribosomes manufacture pre-proinsulin from insulin mRNA. The hydrophobic 'pre' portion of pre-proinsulin allows it to transfer to the Golgi apparatus, and is subsequently enzymatically cleaved off. Proinsulin is parcelled into secretory granules in the Golgi apparatus. These mature and pass towards the cell membrane where they are stored before release. The proinsulin molecule folds back on itself and is stabilized by disulphide bonds. The biochemically inert peptide fragment known as connecting (C) peptide splits off from proinsulin in the secretory process, leaving insulin as a complex of two linked peptide chains. Equimolar quantities of insulin and C-peptide are released into the circulation via the 'regulated pathway'. A small amount of insulin is secreted by the beta cell directly via the 'constitutive pathway', which bypasses the secretory granules.



Local forces regulating insulin secretion from beta cells. Glucose enters the beta cell via the GLUT-2 transporter protein, which is closely associated with the glycolytic enzyme glucokinase. Metabolism of glucose within the beta cell generates ATP. ATP closes potassium channels in the cell membrane **(a)**. If a sulfonylurea binds to its receptor, this also closes potassium channels. Closure of potassium channels predisposes to cell membrane depolarization, allowing calcium ions to enter the cell via calcium channels in the cell membrane **(b)**. The rise in intracellular calcium triggers activation of calcium-dependent phospholipid protein kinase which, via intermediary phosphorylation steps, leads to fusion of the insulin-containing granules with the cell membrane and exocytosis of the insulin-rich granule contents. Similar mechanisms produce hormone-granule secretion in many other endocrine cells.

- Recall also that insulin works on predominantly the liver, skeletal muscle and adipose tissue.
  - Inhibits gluconeogenesis
  - Increases the uptake and utilization of glucose by muscles
  - Inhibits lipolysis and by doing so prevents ketogenesis

- Enhances uptake of amino acids into muscles for protein synthesis and inhibition of proteolysis



Increase	Decrease
Carbohydrate metabolism	
Glucose transport (muscle, adipose tissue)	Gluconeogenesis
Glucose phosphorylation	Glycogenolysis
Glycogen synthesis	
Glycolysis	
Pyruvate dehydrogenase activity	
Pentose phosphate shunt	
Lipid metabolism	
Triglyceride synthesis	Lipolysis
Fatty acid synthesis (liver)	Lipoprotein lipase (muscle)
Lipoprotein lipase activity (adipose tissue)	Ketogenesis
	Fatty acid oxidation (liver)
Protein metabolism	
Amino acid transport	Protein degradation
Protein synthesis	

- Diabetes is classified as:
  - Primary (idiopathic) diabetes
    - Type 1 DM: has an immune pathogenesis and is characterized by severe/absolute insulin deficiency.
    - Type 2 DM: results from a combination of insulin resistance and a relative insulin deficiency.
  - Secondary diabetes
    - Diseases of the exocrine pancreas: Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis.
    - Endocrinopathies: acromegaly, Cushing's syndrome, Phaechromocytoma, Somatostatinoma, Aldosteronoma
    - Drugs: Nicotinic acid (niacin), beta blockers, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, phenytoin, protease inhibitors, immunosuppressive (glucocorticoids, ciclosporin, Tacrolimus), Antipsychotic (clozapine, olanzapine)
    - Infectious: congenital rubella, Cytomegalovirus
    - Genetic disorders: Down's syndrome, Huntington's chorea, Myotonic dystrophy, Turner's syndrome

- Other specific types include: maturity onset diabetes of the young (MODY), type A insulin resistance, Drug induced diabetes mellitus e.g. with beta blocker, oral contraceptive, glucocorticoids etc.
- Gestation diabetes mellitus (GDM): occurs when diabetes onsets during pregnancy and resolves with delivery. These patients are at higher risk of developing DM at a later date.

TYPE 1 DIABETES MELLITUS

- This was formerly known as insulin-dependent DM. It accounts for 10% of the cases.
- It usually occurs in childhood or early adulthood (age less than 30).
- This is due to beta-cell destruction, with absolute deficiency of insulin, which is of multifactorial causes such as:
  - Genetic predisposition
  - Viral infection: injury is due to molecular mimicry between trigger antigen (virus) and beta cell antigen e.g. coxsackie virus antigen and that of glutamic acid decarboxylase (GAD) found within the beta-cell have a similar chemical structure, so that the antibodies produced to fight the foreign antigen of the virus also cross react with antigens of self-tissue bearing GAD hence destroying it.
  - Autoimmune attacks (type IV hypersensitivity)
- It may be immune mediated or idiopathic.
- They require insulin for survival and develop ketoacidosis when patients are not on adequate insulin therapy. Oral hypoglycemic agents will not be effective to lower the blood glucose level.

PATHOGENESIS

- The disease is progressive going through phases of antibody production, then phase of impaired glucose tolerance followed by an abnormal fasting blood sugar and finally culminating in an abnormal fasting blood sugar with ketonemia.

HONEYMOON PERIOD

- In young people who are diagnosed for the first time to have overt DM, the DM may have been precipitated by acute metabolic stressful condition (such as infection or pregnancy).

- In such circumstances, the increased metabolic demand for insulin, may lead to a relative insulin deficiency and patients become symptomatic and may need exogenous insulin to control their symptoms.
- With they return to baseline metabolic demands, when the stressful event abates, the pancreatic reserve may be adequate to maintain normal or near-normal blood glucose. Such patients may undergo a period of transient "cure" during which time they may not require exogenous insulin to control their blood glucose level. Because of this, such patients are said to be in a "HONEYMOON" period.
- This unfortunately is transient and the patients will be needing insulin again when the progressive destruction of beta-cells leads to absolute insulin deficiency.

CLINICAL FEATURES

- It usually occurs in childhood or early adulthood (age less than 30).
- Patients are usually thin.
- Onset tends to be more sudden.
- Signs and symptoms include:
  - Polyuria (due to osmotic diuresis induced by hyperglycemia)
  - Polydypsia (increased feeling of thirst and drinking excess water/fluid due to increased blood osmolality)
  - Polyphagia (feeling hunger, a need to eat several times a day)
  - Calorie loss, generalized weakness and weight loss
  - Visual blurring from lens swelling due to increased osmolality
  - Oral and genital thrush
  - Muscle cramps
  - Lethargy
  - Lipoatrophy from insulin use
- They require insulin for survival and develop ketoacidosis when patients are not on adequate insulin therapy.
- This accounts for 10% of cases of DM.
- Oral hypoglycemic agents will not be effect to lower the blood glucose level.
- Mainstay treatment is insulin.

TYPE 2 DIABETES MELLITUS

- This was formerly known as non-insulin dependent diabetes mellitus.
- It usually occurs in people older than 40 years of age.
- Most (about 60%) of the patients are obese.
- Type 2 DM occurs with intact beta islet cell function but there is peripheral tissue resistance to insulin.
- There may be some decrease in insulin production or a hyperinsulin state.
- These patients are not prone to develop ketoacidosis but may develop it under conditions of stress.
- Patients do not require insulin for survival at least in the earlier phase of diagnosis but may need it later on as the disease progresses.
- The blood sugar level can be corrected by oral hypoglycemic agents.

PATHOGENESIS

- In type 2 DM insulin resistance plays a central role in the pathogenesis.
- In obesity, increased production of non-esterified fatty acids, leads to resistant of peripheral organs to insulin which leads to increased gluconeogenesis in the liver and decreased peripheral uptake and utilization of glucose by muscles.
- Initially there is hypersecretion of insulin by the beta cells to overcome the insulin resistance but later on the beta cells fail to respond to the level resistance. The beta cell number is then decreased and amyloid is deposited in islets.
- Genetic association has been seen in the developments of type 2 DM:
  - Concordance among identical twins is up to 100%.
  - Concordance among fraternal twins is 20%
  - Familial aggregation history is common and up to 50% of siblings and 33% of children of diabetics develop diabetes
- Environment factors:
  - Obesity
  - Physical inactivity
  - Diet
- Natural history includes:
  - Stage 1: insulin resistance: increased glucose and non-esterified fatty acids
  - Stage 2: increased insulin secretion: compensatory hyperinsulinemia
  - Stage 3: impaired glucose tolerance
  - Stage 4: overt type 2 diabetes

CLINICAL FEATURES

- Clinical features:
  - Insidious and subtle onset
  - Polydipsia and polyuria
  - Polyphagia
  - Visual blurring from lens swelling due to increased osmolality
  - Oral and genital thrush
  - Muscle cramps
  - Lethargy. This may be the only symptom initially
  - Neuro: peripheral neuropathy (found in 50% of type 2 at diagnosis), postural hypotension due to autonomic dysregulation, Romberg's positive (loss of balance when eyes are closed while standing with feet together due to loss of proprioception) from dorsal column disease
  - Eyes: xanthelasma, retinopathy, ophthalmoplegia from mononeuritis multiplex
  - Legs: ulcers, necrobiosis lipoidica
  - Lipoatrophy from insulin use
- Some patients may be asymptomatic mainly type 2 patients and GDM.
- Diagnosis is made incidentally during routine medical checkup. ANC follow up etc. therefore it is advisable to screen patient for DM if the following risk factors are present:
  - Obesity (BMI>25kg/m^2)
  - First degree relative with DM
  - History of Gestational DM (GDM) or delivered a baby weighing more than 4kg
  - Hypertensive
  - Hyperlipidemia
  - History of impaired fasting glucose or impaired glucose tolerance on prior testing

DIAGNOSIS

- Symptoms of diabetes plus one of the following:
  - Fasting plasma glucose > 7 mmol/L (126mg/dl)
  - Random blood glucose concentration ≥11.1 mmol/L (200mg/dl)
  - 2-hour postprandial plasma glucose >11.1 mmol/L (200mg/dl) after a glucose load of 75g in 300ml water (during oral glucose tolerance test)
  - HBA1c >6.5% (48mmol/mol)

- Note: these criteria should be confirmed by repeat tests on a different day.
- Keep in mind:
  - Random is defined as without regard to time since the last meal.
  - Fasting is defined as no caloric intake for the last 8 hours.
  - Oral glucose tolerance test: blood glucose is measured after ingestion of 75g anhydrous of glucose dissolved in water.
  - The patient is said to have impaired glucose tolerance (IGT) if the fasting plasma glucose is between 7-11mmol/L.
  - During an oral glucose tolerance test, the patient is asked to fast the night before (for at least 8 hours). The next morning the blood glucose is monitored and glucose is administered as the blood glucose level is checked and recorded after 30 minutes and after 2 hours.

INVESTIGATIONS

- Diagnostic
  - Plasma glucose: Random blood sugar and Fasting blood sugar
  - Oral glucose tolerance test
- Supportive:
  - Urinalysis: for proteins, glucose and ketones (recall ketones can also be seen during starvation, dehydration and not just DKA)
  - Full blood count: to rule out infections and anemia
  - Urea and electrolytes: to check renal function
  - Liver biochemistry: to check liver function
  - Lipid profile (Triglycerides, cholesterol, HDL, LDL): diabetes is associated with dyslipidemia and arteriosclerosis
  - Hemoglobin A1C (HbA1c) this is a measure of an individual's prevailing blood glucose concentration over several weeks (3 months). An HBA1c >6.5% (48mmol/mol) would be considered diagnostic of diabetes, whereas a level of 5.7-6.4% (39-46mmol/mol) would denote increased risk of diabetes.

SOMOGYI PHENOMENON/ REBOUND EFFECT

- A low blood glucose in the late evening causes a rebound effect in the body leading to hyperglycemia in the early morning.
- This occur when the evening dose of insulin is too high, causing hypoglycemia in the early morning hours, resulting in the release of counter-regulatory hormones (epinephrine and glucagon) to counteract this insulin-induced hypoglycemia.
- The patient then has high blood glucose and ketones in the morning.
- The treatment is to actually lower the bedtime insulin dose and not to raise it.

DAWN PHENOMENON

- It is similar to the somogyi effect in that people experience hyperglycemia in the morning (3am to 8am) but for reasons that differ.
- It results from a rise in early morning blood sugar levels which are triggered by declining levels of insulin and an increase in growth hormone.
- Testing blood sugar levels at 3am and again in the morning can help distinguish between the somogyi and dawn phenomenon.
  - Blood sugar that is low at 3am indicates somogyi effect while high or normal blood sugar at that time suggests the dawn phenomenon.

MANAGEMENT

- Goal:
  - Acceptable RBS <11.1mmol/L (200mg/dl)
  - Ideal RBS <8.9mmol/L (160mg/dl)
  - Acceptable FBS < 7.2 mmol/L (130mg/dl)
  - Ideal FBS <5.6mmol/L (100mg/dl)
- Management includes:
  - Non-pharmacological therapy
  - Pharmacological therapy

NON-PHARMACOLOGICAL THERAPY

- Diet therapy
  - Stop alcohol
  - The diet should be low in sugar (though not sugar free), high in starchy carbohydrates (especially foods with a low glycemic index i.e. slower absorption), high in fiber and low in fat (especially saturated fat).

  - Diet should include 60-65% carbohydrates, 25- 35% fat and 10-20% protein
  - Decrease cholesterol intake
  - Avoid simple sugars e.g. sugar, soft drinks, honey and other sweets
  - High fiber diet such as vegetables slow the absorption of digested food in the form of simple sugars
  - Fresh fruit e.g. watermelon and lemon can be taken freely as opposed to oranges and bananas that must be taken with caution.
  - Dividing meal into 4 to 6 equal parts may help in achieving stability in some cases
- Exercise:
  - Regular 20-30 minutes, aerobic exercise such as jogging, walking, swimming etc. 3-4 days is recommended.
  - Note patients on insulin treatment should be cautious to avoid hypoglycemia. (counsel on signs of hypoglycemia and advise patients to move around with sweets)
- Weight:
  - Maintain BMI of 20 and 25.
- Educate patient on diabetes, treatment plan, alcohol intake, smoking, exercise, proper foot care, complications of diabetes, insulin injection technique, self-glucose monitoring and signs & symptoms of hypoglycemia + first aid management.

PHARMACOLOGICAL THERAPY

- Treat infections if any.

INSULIN

- Insulins derived from beef (bovine) or pig (porcine) pancreas have been replaced in most countries by biosynthetic human insulin (through genetic engineering).
- The duration of action of short-acting, unmodified insulin ('soluble' or 'regular' insulin) which is a clear solution, can be extended by addition of protamine and zinc at neutral pH (isophane or NPH insulin) or excess zinc ions (lente insulins). These modified 'depot' insulins are cloudy preparations.
- Types include: rapid acting, short-acting, intermediate-acting, long-acting and very long-acting.
  - Rapid acting (insulin analogues: lispro, aspart, glulisine): onset= less than 30 mins, peak= 30 mins-2hrs 30 mins, duration= 3hrs-4hrs 30 mins.

        - These enter the circulation more rapidly than human soluble insulin and also disappear more rapidly.
    - Short acting (neutral, soluble, regular): onset is 30min to 1 hour, peak is 1-4 hours and duration is 4-8 hours
        - Short acting insulins are used for pre-meal injection in multiple dose regimens, for continuous intravenous infusion in labor or during medical emergencies e.g. diabetic ketoacidosis and in patients using insulin pumps. It can be administered IV, IM or SC
        - Human insulin is absorbed slowly, reaching a peak of 60-90 minutes after subcutaneous injection and its action tends to persist after meals predisposing to hypoglycemia.
    - Intermediate acting: used for ambulatory long term control of sugar level. Given not more than twice a day. Route of administration is limited to SC.
        - Isophane (peak 6-8h and duration 16-24h)
        - Biphasic (peak 4-6h and duration 12-20h)
        - Semilente (peak 5-7h and duration 12-18h)
    - Long acting (lente, ultralente and PZI): onset:1-2 hours, peak 6-12h & 12-30hrs duration.
        - These have their structure modified to delay absorption or to prolong their duration of action.
- Inhaled insulin was withdrawn from the market in 2007 on grounds of limited clinical demand, although lung cancer was also observed.
- Insulin pumps are now being used to achieve better glucose control and to improve lifestyles
- Type 1 DM patients must be started on insulin at the time of diagnosis.
- Daily insulin requirements 0.3-0.5 unit/kg/day (25 units/day).
    - Current regimen uses soluble insulin and lente. A multiple injection regimen with short-acting and longer acting insulin at night is appropriate for most younger patients.
    - 2 subcutaneous injections are given before breakfast and at dinner.
    - 2/3 of total insulin requirement is given in the morning (alternatively 70% can be used)
        - 2/3 of this being lente
        - 1/3 of this being soluble insulin
    - 1/3 of total insulin requirement is given at dinner (alternatively 30% can be used)
        - 2/3 of this being lente and 1/3 of this being soluble insulin or

        - 50% lente and 50% soluble insulin
    - Example if daily requirements is 30IU/day
        - Morning= 2/3 x 30IU= 20IU (2/3 is lente-13IU and 1/3 is soluble insulin-7U)
        - Evening= 1/3 x 30IU= 10IU (2/3 is lente-6IU and 1/3 is soluble insulin 4IU)
- Monitoring
    - Daily blood glucose: before all meals and at bedtime. Ask patient to record reading.
    - Glycosylated hemoglobin level reflecting diabetic control for the past 2-3 months, should be check every 3 months.
    - Watch for hypoglycemia: all patients should have parenteral glucagon available in case of seizure or coma secondary to low blood sugar.
    - Watch for "honeymoon" period.

Guide to adjusting insulin dosage according to blood glucose test results

	Blood glucose persistently too high	Blood glucose persistently too low
Before breakfast	Increase evening long-acting insulin	Reduce evening long-acting insulin
Before lunch	Increase morning short-acting insulin	Reduce morning short-acting insulin or increase mid-morning snack
Before evening meal	Increase morning long-acting insulin or lunch short-acting insulin	Reduce morning long-acting insulin or lunch short-acting insulin or increase mid-afternoon snack
Before bed	Increase evening short-acting insulin	Reduce evening short-acting insulin

- Adjust dose to keep blood sugar levels between 6-8 mmol/L. Changes to insulin should be done by 0.5IU
- Principles of insulin treatment:
    - Injections:
        - The needles used are very fine and sharp Even though most injections are virtually painless, patients are understandably apprehensive and treatment begins with a lesson in injection technique.
        - Insulin is usually administered by a pen injection device but can be drawn up from a vial into special plastic insulin syringes marked in units (100U in 1ml).
        - Injections are given into the fat below the skin on the abdomen, thighs or upper arm and the needle is usually inserted to its full length.
        - Slim adults and children usually use a 31 gauge 6mm needle and fatter adults a 30gauge 8 mm needle.

- Both reusable and disposable pen devices are available together with a range of devices to aid injection.
- The injection site used should be changed regularly to prevent areas of lipohypertrophy (fatty lumps)
- The rate of insulin absorption depends on local subcutaneous blood flow and is accelerated by exercise, local massage or a warm environment.
- Absorption is more rapid from the abdomen than from the arm and slowest from the thigh. All these factors can influence the shape of the insulin profile.

➢ Complications of insulin therapy

- At injection site:
  - Shallow injections result in intradermal insulin delivery and painful, reddened lesions or even scarring.
  - Injection site abscesses occur but are extremely rare
  - Local allergic responses sometimes occur early in therapy but usually resolve spontaneously
  - Generalized allergic responses are exceptionally rare
  - Fatty lumps known as lipohypertrophy may occur as the result of overuse of a single injection site with any type of insulin (atrophy or hypertrophy)
- Insulin resistance especially with obese patients. Insulin resistance may also be associated with antibodies directed against the insulin receptor especially in patients reported with acanthosis nigricans (dark velvety skin especially in skin folds e.g. armpits).
- Weight gain: Many patients show weight gain on insulin therapy, especially if the insulin dose is increased inappropriately, but this can to some extent be overcome by emphasis on the need for diet and exercise, plus addition of metformin. Patients who are in poor control when insulin is started tend to gain (or regain) most weight.
- Hypoglycemia

ORAL HYPOGLYCEMICS

- Used for type 2 diabetics:

Drug	Comment	Dosage
Sulfonylureas Effectiveness of sulfonylureas declines up to 10% annually as the failure of beta cell function progresses	MOA: Stimulate pancreatic beta cells to secrete insulin.	Glyburide (Glibenclamide/Daonil) 2.5 to 20mg PO Glipizide 5 to 20mg PO Glyburide is more likely to result in glycemic control when used once a day than glipizide. Glyburide should be used twice a day if dosing 20mg/day total is required.
Metformin Side effects: lactic acidosis (rare). Risk is minimized if metformin is avoided in patients with renal disease, CHF or pulmonary disease.	Reduces blood glucose levels by improving hepatic and peripheral tissue sensitivity to insulin without affecting secretion of insulin. Used as monotherapy or in combination with above. Hypoglycemia not a problem with metformin	Initial dosage: 500mg PO daily until initial nausea and anorexia are tolerated and then increase to 500 mg BD Dosage can be increased by 500mg weekly to maximum dose of 250mg if reasonable control is not achieved. Use with or after food may lessen the GI side effects
Alpha glycosidase inhibitors In general this group of drugs is less effective than other classes	Reduce absorption of carbohydrates thus reduce postprandial hyperglycemia. Can be used as monotherapy or in combination with insulin or sulfonylureas.	Acarbose 25mg with evening meal, may increase to a maximum dose of 50-100 in weeks.
Thiazolidinediones Side effects: idiosyncratic hepatocellular injury	Reduce insulin resistance and increase peripheral glucose utilization	Pioglitazone 15-45mg/day in a single daily dose Rosiglitazone 2-8 mg total dose given once or in 2 divided doses

- The 2 main classes of drugs used in Zambia are Sulfonylureas and biguanides.
  - Sulfonylureas
    - Glibenclamide initially can be given orally OD or in two divided doses. Usual dose is 5mg orally daily taken before breakfast up to a maximum of 20mg in divided doses before food, depending on the patient's response. Doses above 20mg will not result in any improvement in glucose control.
    - Chlopropamide 250mg PO OD taken with breakfast. Dosage may be adjusted to a maximum of 500mg depending on the patients response
    - Sulfonylureas can be given together with biguanides.
  - Biguanides
    - This is preferred drug in obese patients in addition to dietary control and exercise. It may also be added in patients who have reached the maximum dose of a sulfonylurea without achieving control of blood sugar levels.
    - Metformin 500mg PO BD or TDS daily or 850mg PO BD or TDS with or after food. Maximum dose is 2.55g daily in doses.
  - NOTE: dosage increments in oral antidiabetic drugs should be gradual i.e. at 1 to 2 week intervals.
  - Withdrawal of oral (sulfonylureas and biguanides) drugs should be commenced only after the insulin therapy has been initiated. In some patients, metformin and insulin combination can be given.
- Use of insulin in type 2 DM:
  - Insulin is usually added to an oral agent when glycemic control is suboptimal at maximal doses of oral medications.
  - An intermediate-acting agent is used starting with a low dose and increasing as needed for glycemic control (such as 5 to 10 U of NPH increasing as needed)
  - Adding NPH at bedtime is generally more efficacious than using it during the day.
  - If using only insulin, start with an AM (morning) injection. The dose can be increased by 5U every 3 to 7 days until adequate control is achieved.
  - If early morning hyperglycemia is a problem, intermediate acting insulin can be given twice daily as a split dose.

PATIENT FOLLOW UP

- Points of emphasis:
  - Symptoms of hyper or hypoglycemia
  - Weight
  - Blood pressure
  - Visual acuity (+ fundoscopy), examine the eyes for cataracts and other opacities
  - Examine oral cavity
  - Examine feet
  - Examine injection site
  - Lab tests: blood or urine sugar and urine albumin or protein

COMPLICATIONS

- These can be classified as:
  - Acute:
    - Hypoglycemia
    - Diabetic ketoacidosis
    - Hyperglycemic hyperosmolar state (Non-ketotic hyperosmolar coma)
  - Chronic: due mainly to non-enzymatic glycosylation as well as osmotic damage
    - High levels of glucose are taken in by cells which do not require insulin for glucose uptake e.g. neurons. These cells have the enzyme aldose reductase which converts excess glucose to sorbitol which causes damage to these cells.
    - Retinopathy
    - Neuropathy
    - Nephropathy
    - Diabetic foot ulcer

ACUTE COMPLICATIONS

HYPOGLYCEMIA

- This is caused by overdose of insulin or hypoglycemic agents, missing of meal, strenuous exercise.
- Clinical manifestation:
  - Early: one may feel the effects of sympathetic stimulation such as cold sweat, tremor, hunger or palpitations
  - Late: if early symptoms are neglected then symptoms of the effect of hypoglycemia on the brain such as dizziness, blurring, headache, nightmares and coma may occur
- Management:
  - Any patient with diabetes losing consciousness should always be considered hypoglycemic until proven otherwise by blood sugar determination and should be managed by rapid IV administration of glucose or PO/ NG tube administration of any concentrated sugar solution.
  - Prolonged unconsciousness requires continuous 10% IV glucose administration.

DIABETIC KETOACIDOSIS

- Diabetic ketoacidosis (DKA) is a medical emergency principally associated with diabetes type 1 (due to insulin deficiency) although it has also been recently reported to be associated with diabetes type 2 (due to a relative insulin deficiency).
- It is an acute severe manifestation of insulin deficiency.
- DKA is an acute metabolic crisis in patients with diabetes characterized by:
  - Hyperglycemia (Blood glucose >11 mmol/L (200mg/dl))
  - Metabolic ketoacidosis (venous bicarbonate <15mmol/L and/or venous pH <7.3)
  - Hypotension and features of dehydration
  - Hyperketonemia (>3mmol/L) and ketonuria (more than 2+ on standard urine sticks)
- Precipitating factors include:
  - Infection (30%)
  - Poor compliance with insulin or discontinuation of insulin (poor diabetic control)- 15%

  - Dehydration
  - Stressful conditions such as trauma, surgery, MI or of emotional crisis
  - Excessive alcohol ingestion
  - It can occur in a patient who is not known to be diabetic i.e. the presenting complaint (10%)
- There is no obvious cause in about 40% of episodes.
- The majority of cases reaching the hospital could have been prevented by earlier diagnosis, better communication between patient and doctor and better patient education.
- The most common error of management is for patients to reduce or omit insulin because they feel unable to eat, owing to nausea or vomiting.
- DKA presents at any age although there is a well-defined peak at puberty.

PATHOPHYSIOLOGY

- Any event that decreases insulin availability or causes stress that increases insulin demand leads to severe insulin deficiency and the effect of counter regulatory hormones such as glucagon, cortisol, epinephrine and growth hormone to become overwhelming.
  - Insulin deficiency is a necessary precondition since only a modest elevation in insulin levels is sufficient to inhibit hepatic ketogenesis and stable patients do not readily develop ketoacidosis when insulin is withdrawn.
  - Other factors include counter-regulatory hormone excess and fluid depletion.
  - The combination of insulin deficiency with excess of its hormonal antagonist leads to the parallel processes seen in DKA.
- The biochemical changes include:
  - Increased production of glucose by the liver (gluconeogenesis) and increased glycogen degradation to glucose (glycogenolysis)
  - Decreased glucose uptake and utilization by muscles (because of lack of insulin)
  - Rising glucose levels lead to an osmotic diuresis, loss of fluid and electrolytes and dehydration. Plasma osmolality rises and renal perfusion falls.
  - Lipolysis: enhanced breakdown of free fatty acids (beta-oxidation) and subsequent ketogenesis in mitochondria. This increases blood levels of ketone bodies such as acetoacetic acid, beta-hydroxybutyric acid, and acetone resulting in metabolic acidosis (decrease in pH and bicarbonates). Accumulation of ketone bodies causes metabolic acidosis.

  - The above biochemical processes result in significant hyperglycemia and ketoacidosis which are responsible for the clinical manifestations of DKA.
- The excess ketones are excreted in urine but also appear in the breath, producing a distinctive smell similar to that of acetone.
- Respiratory compensation for the acidosis leads to hyperventilation, graphically described as 'air hunger' (Kussmaul's respiration).
- As the pH falls below 7.0, pH dependent enzyme systems in many cells function less effectively. Untreated severe ketoacidosis is invariably fatal.

SEVERITY

- According to pH:
  - <7.3: Mild
  - <7.2: Moderate
  - <7.1: Severe
- One of more of the following suggests severe DKA.
  - Clinical
    - Pulse >100b/min or <60b/min
    - Systolic BP <90mmHg
    - Glasgow coma Score <12
    - Oxygen saturation <92% on air (if normal respiratory function)
  - Blood
    - Blood ketones >6 mmol/L
    - Bicarbonate <12 mmol/L
    - Venous/Arterial pH <7.1
    - Hypokalemia on admission <3.5mmol/L

CLINICAL FEATURES

- Mental status changes: some patients are mentally alert at presentation but drowsiness, lethargy and confusion may evolve into coma (5%) with severe DKA.
- Dehydration: dry tongue and buccal mucosa, poor skin turgor, hypotension but with an increase in heart rate. (due to osmotic diuresis)
- Polydipsia, polyuria and nocturia
- Kussmaul respiration: deep and fast breathing resulting from metabolic acidosis. Hyperventilation becomes less marked in very severe acidosis owing to respiratory depression.
- Acetone ("fruity") odour of breath due to acetone

- Nausea and vomiting (due to gastroparesis and attempt to remove H^+) with frequent abdominal pain (this may even be confused with surgical acute abdomen)
- Leg cramps
- Weight loss
- Weakness (which may be extreme –prostration)
- Hypothermia
- Sign of infection which may precipitate DKA (pyrexia in late stages)
- A history of diabetes (unless first presentation)
- Cerebral edema: an extremely serious complication of DKA especially in children.

DIAGNOSIS

- Diagnosis (requires all 3)
  - Random blood sugar (capillary glucose): hyperglycemia (>11mmol/l) or a known diabetic
  - Urine dipstick for ketones: hyperketonuria (2+ ketones) or serum Ketone (≥3+ or >6mmol/L)
  - Arterial blood gas analysis: can diagnose metabolic acidosis which is indicated by low serum bicarbonate (<15mmol/L) or low blood pH (<7.35)
  - Other investigations
    - Urea and creatinine: raised
    - Serum potassium:
      - Hyperkalemia (>5.5 mmol/L) (In early stages due to H-K exchanger on RBCs to offset the acidosis)
      - Hypokalemia (<3.5mmol/L) (due to osmotic diuresis as well as hyperaldosteronism)
    - Serum sodium: tends to be low because of dilution as the osmotic effect of hyperglycemia increases ECF volume
    - Serum osmolality is high
    - Increased anion gap
    - Increased WBC
    - CXR, urine culture and sensitivity, blood cultures should also be done to identify an infectious process.

MANAGEMENT

- Management should be carried out in a high dependency area (preferably the ICU).
- Principles:
  - Assess, send blood to the lab, set up IV infusion
  - Fluid, electrolyte and acid-base balance
  - Insulin replacement and glucose stabilization
  - Potassium
  - Antibiotics (or treatment of underlying cause)

Management mnemonic: "SIPA"

S-solutions, I-insulin, P-potassium, A-antibiotics

Anion gap: This is the measurement of the interval between the sum of "routinely measured" cations minus the sum of the "routinely measured anions in the blood.

The anion gap= $(Na^+ + K^+) – (Cl^- + HCO_3^-)$

The anion gap can be normal (16 ± 4mEq/l if the calculation employs potassium and 12 ± 4mEq/L if the calculation does not employ potassium), high or low

The test is commonly performed in patients who present with altered mental status, unknown exposures, acute renal failure and acute illnesses.

A high anion gap indicates metabolic acidosis.

A low anion gap is relatively rare but may occur from the presence of abnormal positively charged proteins, as in multiple myeloma.

- Fluid replacement: normal saline and 5% Dextrose are used
  - Given through large bore cannula.
  - Average loss of water is 5-7 liters with a sodium loss of 500mmol. Normally 6-8L should be given in the first 24 hours.
  - If systolic blood press (SBP) <90mmHg give 500ml of normal saline over 15mins and repeat if required (Give 1L in 30 minutes)
  - If/when SBP> 90 give 1L in 1 hour then 1 liter in 2 hours, then 1L in 4 hours then 1 liter in 8 hours.
  - When the serum glucose level falls to <14mmol/L (13.9mmol/L) change the IV fluid to 5% Dextrose-saline to prevent hypoglycemia
  - If sodium level more than 150mmol/L give half strength (hypotonic) saline.
  - Carefully monitor the urine output
- Insulin
  - Soluble insulin IV 0.1 U/Kg/h (5-10 units/hour) by infusion.
    - 50 short/rapid acting insulin in bag with normal saline made up to 50ml. If glucose remains high (>7) after 2 hours, increase dose.
    - Alternatively, 6IU SC every hour (8IU) for obese- this is what is used
  - Note: soluble insulin given as an IV bolus is rapidly destroyed within a few minutes. IV insulin must always be given as a continuous infusion.
  - When blood sugar levels reach 10-14 mmol/L (13.9) reduce to 0.05 units/kg/h (2-4 units/hour) or titrate against blood glucose level.
  - When patient is able to take oral feeds give soluble insulin 2-3 times before meals
  - Alternative:
    - 20 units IM stat followed by 5-10 units IM hourly until blood sugar is 14mmol/l.
    - When blood glucose is 10-14mmol/L give 8 units 4 hourly subcutaneously until the patient is able to take oral feeds.
    - When patient is taking food orally, change to soluble subcutaneously twice or three times before meals.

Investigations:

- Blood glucose:
  - Measure baseline and hourly for 8 hours initially
  - Aim for fall 3-6 mmol/L (55-110mg/dl) per hour
- Urea and electrolytes
  - Do at baseline and hourly until 6 hours, then 12 hours and 24 hours
- Full blood count
- Creatinine- at 0, 6, 12, 24 hours
- Blood gases- at 0, 2 and 6 hours
- Bicarbonate- at 0, 1, 2, 3, 6, 12, 24 hours.

  - For blood glucose measure baseline and hourly initially. Aim for fall of 3-6mmol/L (55-110mg/dl) per hour.
- Potassium (KCL)
  - Add dosage below to each 1L of infused fluid
    - If plasma K <5.5mmol/L do not include potassium chloride in the first bag of fluids. Dehydration may cause AKI so that should be treated first.
    - If plasma K <3.5mmol/L, add 40mmol KCL
    - If plasma K 3.5-5.5mmol/L, add 20mmol KCL
  - Insulin therapy leads to uptake of potassium by the cells with a consequent fall in plasma potassium levels. Potassium is therefore given as soon as insulin is started.
- Antibiotics: broad spectrum antibiotics e.g. Ceftriaxone 1g IV BD
- Sodium bicarbonate: 600ml of 1.4% or 100ml of 8.4% in large cannulated vein if pH<7.0
- Once stable and able to eat and drink normally, transfer the patient to 4 times daily subcutaneous insulin regimen.
- Sliding-scale regimens are unnecessary and may even delay the establishment of stable blood glucose.
- Other management measures:
  - Bladder catheter if no urine passed in 2 hours or 3 hours of hydration.
  - Nasogastric tube if drowsy.
  - Give subcutaneous prophylactic LMW heparin
  - Other investigations:
    - Blood and urine culture
    - Cardiac enzyme
    - CXR
    - ECG (monitor if electrolyte problems or severe DKA)

PROBLEMS OF MANAGEMENT

- Hypotension: this may lead to renal shutdown. Plasma expanders (or whole blood) are therefore given if the systolic blood pressure is below 80mmHg. A central venous pressure line is useful in this situation. A bladder catheter is inserted if no urine is produced within 2 hours, but routine catheterization is not necessary.
- Coma: The usual principles apply. It is essential to pass a nasogastric tube to prevent aspiration, since gastric stasis is common and carries the risk of aspiration pneumonia if a drowsy patient vomits.
- Cerebral edema: this is a rare, but serious complication and has mostly been reported in children or young adults such as 8.4% bicarbonate may sometimes be responsible. The mortality is high.
- Hypothermia: severe hypothermia with a core temperature below 33°C may occur and can be overlooked unless a rectal temperature is taken with a low-reading thermometer.
- Late complications: these include pneumonia and deep-vein thrombosis (DVT prophylaxis is essential) and occur especially in the comatose or elderly patient.
- Complications of therapy: these include hypoglycemia and hypokalemia, due to loss of potassium in the urine from osmotic diuresis. Overenthusiatic fluid replacement may precipitate pulmonary edema in the very young or the very old. Hyperchloraemic acidosis may develop in the course of treatment since patients have lost a large variety of negatively charged electrolytes, which are replaced with chloride. The kidneys usually correct this spontaneously within a few days.

HYPERGLYCEMIC HYPEROSMOLAR STATE

- Previously called non-ketotic hyperosmolar coma.
- This is a condition, in which severe hyperglycemia develops without significant ketosis, it is a metabolic emergency characteristic of uncontrolled type 2 diabetes.
- Patients present in middle or later life, often with previously undiagnosed diabetes.
- Common precipitating factors:
  - Consumption of glucose-rich fluids
  - Concurrent medication such as thiazide diuretics or steroids
  - Intercurrent illness such as myocardial infarction, stroke, pneumonia, sepsis etc.

- The hyperosmolar hyperglycemic state and ketoacidosis represent 2 ends of a spectrum rather than 2 distinct disorder.
- The biochemical differences may partly be explained as follows:
  - Age: the extreme dehydration characteristic of hyperosmolar hyperglycemic state may be related to age. Old people experience thirst less acutely and more readily become dehydrated. In addition, the mild renal impairment associated with age result in increased urinary losses of fluid and electrolytes.
  - The degree of insulin deficiency: this is less severe in the hyperosmolar hyperglycemic state. Endogenous insulin levels are sufficient to inhibit hepatic ketogenesis, but insufficient to inhibit hepatic glucose production.

PATHOPHYSIOLOGY

- Increase in glucose leads to osmotic shift out of the cells resulting in intracellular dehydration.
- No ketoacidosis due to basal insulin which is sufficient to stop ketogenesis, but not to reduce glucose.
- Usually it is seen in old patients and is the first presentation of diabetes.
- It can be precipitated by illness and dehydration.
- In rare cases mixed HHS and DKA states can occur reflecting some degree of insulin deficiency.

CLINICAL FEATURES

- Symptoms:
  - Such patients present with several weeks history of polyuria, weight loss and diminished oral fluid intake that is followed by mental confusion, lethargy, stupor or coma (10%).
    - Onset over several days: generalized weakness, leg cramps, visual impairment.
  - Impairment of consciousness is directly related to the degree of hyperosmolality.
- Physical examination:
  - Patients have extreme dehydration, hypotension, tachycardia and altered state of consciousness or coma. The dehydration is caused by a hyperglycemia induced osmotic diuresis, when it is not matched by adequate fluid intake.
  - Signs of underlying infection.

DIAGNOSIS

- Diagnostic criteria:
  - Glucose >30 mmol/L
  - Serum Osmolality >320 mOsm/kg
  - No significant ketosis: less than 3+ on urine or <3 mmol/L
  - Other tests:
    - Bloods: FBC, CRP, U&Es
    - Septic screen if infection is suspected
    - ECG
    - Arterial blood gases: should be normal

MANAGEMENT

- Treatment involves:
  - Fluid replacement: administration of IV fluids. Rehydrate with normal saline, slower than DKA (older population). The standard fluid for replacement is normal saline. Avoid 0.45% saline, rapid dilution of the blood may cause more cerebral damage than a few hours of exposure to hypernatremia.
    - Frequently required 6-10 liters.
    - 1L in 30 minutes
    - 1L in 1 hour
    - 1L in 2 hours
    - 1L in 4 hours
    - 1L in 8 hours
  - Bringing down the sugar rapidly by using rapidly acting insulin preparations
    - Give insulin after 1 hour at half the rate of DKA as HHS is highly insulin sensitive.
    - Insulin is not needed if glucose dropping with fluids along. Glucose should drop by 3 mmol/hr.
    - It is sometimes useful to infuse insulin at a rate of 3 U/hour for the first 2-3 hours, increasing to 6U/hour if glucose is falling too slowly.
    - When glucose is less than 14mmol/L check for random blood sugar every 2 hours and use 5% dextrose saline.
  - Identifying and treating the precipitating factor:
  - Monitor fluid balance, glucose and U&Es. Correct electrolytes if needed
  - DVT prophylaxis
    - Low molecular weight heparin should be given to counter the increased risk of thromboembolic complications associated with this condition.

COMPLICATIOSN

- Cerebral edema
- Pulmonary embolism
- Ischemia: MI, stroke
- Much higher mortality (>10%) than DKA, in part reflecting patients' underlying poor health.

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

- These are due mainly to non-enzymatic glycosylation as well as osmotic damage.
- They are a result of poor glycemic control.
- Multiple organs are affected due to macro-microangiopathy include:
  - Diabetic retinopathy
  - Diabetic neuropathy
  - Diabetic nephropathy
  - Diabetic foot

DIABETIC RETINOPATHY

- This is one of the commonest chronic complications (30%) and one of the leading causes of blindness in developed countries.
- It is a retinal disease due to diabetic microvascular damage.
- Diabetes also causes increased risk of cataracts and glaucoma.
- Symptoms include:
  - Difficulty of reading
  - Blurring of vision
  - Floaters
  - Shadowing which may later on progress to total blindness (in advanced stages).
- Signs: seen on fundoscopy or ideally, retinal photograph
  - Microaneurysns: earliest sign. Small red dots.
  - Dot and blot hemorrhages from aneurysm rupture.
  - Hard exudates: lipid and protein leak from vessels.
  - Cotton wool spots: retinal nerve fiber ischemia
  - Venous beading (dilation) and loops: retinal ischemia
  - Intraretinal microvascular abnormalities (IRMA): redomelled capillary beds.

- Classification:
  - Non-proliferative retinopathy (NPDR): formerly divided into 'background retinopathy'-microaneurysms and hard exudates only- and pre-proliferative retinopathy-everything else.
    - "Mild" if there are only microaneurysms,
    - "Severe" if there is 4-quadrant hemorrhage/aneurysms, ≥2 quadrant venous bleeding or ≥1 quadrant IRMA
    - "Intermediate" for anything in-between
  - Proliferative retinopathy:
    - Defined by presence of neovascularization
    - Vitreous hemorrhage. May cause symptoms such as floaters, flashes and sudden painless loss of vision.
    - Tractional retinal detachment: appears as 'tented' retina.
  - Macular edema:
    - Appears as blurring of retinal layers
    - Present with gradual blurring of vision
    - Can occur in NPDR and PDR
    - Commonest cause of vision loss in diabetes.
- Management:
  - Glucose and BP control
  - Laser therapy
  - Vitrectomy if there is vitreous hemorrhage persisting >6 months or tractional retinal detachment.
  - Aspirin 100mg/day prevents further occlusion of small capillaries
  - Surgery: viterotomy removes blood clots and fibrosis that obstruct vision

DIABETIC NEUROPATHY

- Symptoms include:
  - Burning sensation
  - Numbness
  - 'Pins and needles'
  - Constipation or nocturnal diarrhea
  - Impotence
  - Foot ulcer

- Classification:
  - Polyneuropathy: is the commonest neuropathy, characterized by distal symmetrical predominant sensory impairment which manifests with tingling sensations, numbness, burning sensation etc.
  - Radiculopathy: characterized by neurogenic pain, it is often self-limiting.
  - Amyotropy: atrophy of proximal muscles mainly around the hip girdle
  - Autonomic neuropathy (dysregulation): Postural hypotension, GI manifestations (gustatory sweating, gastroparesis, nocturnal diarrhea), Genitourinary manifestations (neuropathic bladder, erectile dysfunction-impotence)
  - Mononeuropathy: paralysis of a specific nerve or nerves e.g. diplopia due to third and sixth nerve palsies.
- Management:
  - Symptomatic treatment: pain control
  - Diarrhea control
  - Treatment of impotence.
  - Painful neuropathy: TCAs are 1st line. Gabapentin or Carbamazeppine are 2nd line

DIABETIC NEPHROPATHY

- This is a common complication in diabetes.
- Clinical features:
  - Periorbital edema (eye or facial puffiness), pedal edema, anasarca
  - Anemia, uremia and osteodystrophy in patients with end stage renal disease
- Lab findings:
  - Progression from micro albuminuria to macroalbuminuria
- Management:
  - Tight blood pressure control
  - ACE inhibitors: decreases the progression of renal disease
  - Renal transplantation or dialysis in End stage renal disease

DIABETIC FOOT

- Symptoms include: numbness and burning, aching pain, swelling, darkening, abscess and cold extremity.
- Mechanisms involved include:
  - Neuropathy: loss of pain sensation exposes to injury and loss of sweating results in dry skin that is susceptible to injury.

- Vascular: poor blood supply to the foot causes decreased healing of wound poor recovery from secondary infection.
- Abnormal pressure loading: due to neuropathy (Charcot's joints) or anatomical deformity of the feet. Since the foot is not in a normal anatomic position it is exposed to abnormal load and pressure sores develop.

- Foot care should be an essential part of diabetes care:
  - Put on comfortable shoe
  - Check for pebbles in shoe and do not walk barefoot (wear comfortable and spacious shoes)
  - Examine the foot daily to detect problems earlier
  - Wash and dry and oil the feet
  - Take caution during nail cutting
  - Treat athletes' foot or any other foot infection as early as possible
  - Remove corn
  - Do not use hot water to wash the feet
  - Stop smoking

CHAPTER 11: NEUROLOGY

NEUROLOGY

NERVOUS SYSTEM EXAMINATION

- The examination is best done in the sitting position except meningeal signs which require the lying position and coordination/ Gate/ Balance which require the patient to stand.
- In severely ill patients, the nervous system exam can be completed in the lying position.
- Always perform the neurological exam systematically so that you do not omit anything.
- Note any deficits and the anatomic site of the neurologic lesion.
- It is traditional to start rostrally and proximally and to work caudally and distally.
- Always report all of the nervous system examination
  - General examination
  - Mental status/Higher centers
  - Cranial nerves
  - Meningeal signs
  - Upper limb examination and Lower limb examination
    - Inspection and posture
    - Tone
    - Reflexes
    - Power
    - Sensation
    - Coordination/ gate/ balance

SUMMARY OF THE NEUROLOGICAL EXAMINATION
Conscious level and cognitive function (determined during history taking)

- Is the patient's conscious level clouded?
- Is the history given accurately, concisely and with insight? Or is the patient concrete, circumlocutory or vague?
- Is the patient neatly dressed and well cared for?
- Is the patient's behaviour normal?
- Is the patient aphasic or dysarthric?

Vision

- Acuity: For each eye, using normal refractive correction, test ability to read small and large print, or use Snellen chart if available. If this fails, test counting of fingers, perception of light.
- Visual fields: Test all four quadrants for each eye individually.
- Fundi: Check for papilloedema, optic atrophy, retinopathy.
- Pupils: Check equality and consensual and direct reactions to light and accommodation (Moving object towards eye).

Eye movements

- Test both eyes together in 'H' pattern for range of movement and diplopia.
- Test both eyes together in '+' pattern for smooth pursuit and nystagmus.

Remainder of cranial nerves

- Nerve V: Pinprick on left and right in ophthalmic, maxillary and mandibular distributions; clenching of teeth; jaw jerk.
- Nerve VII: Appearance and symmetry; screwing up eyes against pressure, forcing lips closed against pressure, blink reflexes.
- Nerve VIII: Hear whispered numbers in each ear/rubbing fingers.
- Nerves IX and X: Ask patient to say 'ah' and observe palate.
- Nerve XI: Ask patient to shrug shoulders and move head to either side and flex against resistance while you observe sternomastoids.
- Nerve XII: Inspect tongue. Ask patient to protrude tongue and press against inside of cheek on either side.

Limbs and trunk

- *Inspection* for wasting, fasciculation, skin lesions.
- *Posture* of outstretched arms with wrists pronated and supinated, looking for drift, tremor, abnormal movements.
- *Tone* at wrist, elbows, knees and ankles, ankle clonus.
- *Power* of proximal, axial and distal muscles on both sides.
- *Reflexes:* Deep tendon reflexes of biceps, supinator, triceps, fingers, quadriceps, gastrocnemius; plantar responses.
- *Sensation:* Test pinprick distally to proximally up arms and legs medially and laterally; and up trunk bilaterally, anteriorly and posteriorly. Vibration sense or joint position sense at little finger, great toe (moving proximally if failed).
- *Co-ordination:* Finger-nose test; rapid alternating movements; heel-shin test.

Gait and stance

- Observe walking pattern.
- Standing still with feet together and eyes closed.
- Walking heel to toe.
- Jumping and hopping.

- Before starting the examination
  - Introduce yourself to the patient.
  - Explain the examination and ask for their consent to carry it out.
  - Ensure that they are comfortable.

GENERAL EXAMINTION

- Begin the examination from the foot-end of the bed.
- Examine the patient and look for:
  - Build
  - Nourishment
  - Orientation to time place and person
  - Handedness- right or left
  - Jaundice- Hepatic encephalopathy and Wilson disease
  - Pallor- Vitamin B12 deficiency
- Examine the facial appearance and note:
  - Mask-like facies in Parkinsonnism.
  - Drooping eyes and sleepy appearance in myasthenia gravis.
  - Risus sardonicus in tetanus.
  - Facial asymmetry in 7th nerve palsy.
- Examine the spine to rule out disc prolapse and spina bifida.
- Examine the extremities to look for presence of thickened nerves (leprosy)
- Look out for neurocutanoeus markers:
  - Café au lait spots (neurofibromatosis)
  - Painful rashes in herpes zoster
  - Hypopigmented patches in leprosy
  - Adenoma sebaceum and ash leaf macules in tuberous scelorosis.
  - Facial naevus in Sturge Weber syndrome

HIGHER CENTERS

- Observe the patient for:
  - Physical appearance
  - Posture
  - Grooming
  - Eye contact with examiner
- For the internal doctor, you should at very least observe the level of consciousness and orientation.

- Level of consciousness: this is the state of awareness of one's self and his surroundings.
  - In extremely ill patients consciousness can be quantified with the Glasgow Coma Scale (GCS). This is the sum of Eye, Verbal and motor responses as below:

Value	Eye (Out of 4)	Verbal response (out of 5)	Motor response (out of 6)
6			Obeys commands
5		Oriented & converses (gives name, place and date)	Localizes to pain (brings hand above clavicle to stimulus on head/neck)
4	Opens eyes spontaneously	Disoriented but Converses (communicates coherently)	Withdraws from pain (bends arm at elbow rapidly but features not predominantly abnormal)
3	Opens to verbal command (sound)	Inappropriate response (intelligible single words)	Decorticate/ Abnormal flexion (Bends arms at elbow rapidly but features clearly predominantly abnormal)
2	Opens to pain	Inappropriate sounds (only moans/groans)	Decerebrate/ Extension (Extends arms at elbow)
1	No response	No response	No response

  - Interpretation
    - Normal state- score 15
    - Mild head injury- Score 13 to 15
    - Moderate head injury- Score 9 to 12
    - Severe head injury= less than 8

- Orientation: check to see if the patient is oriented to person, place and time. Do they know who they are (their name, age, date of birth), where they are (city, hospital, floor) and when it is (year, month, day, time).
  - Alert: patient is awake, aware and responsive to stimuli
  - Clouding of consciousness: mild form of altered status where patient has inattention and reduced wakefulness.
  - Confusion: there is disorientation and difficult in following commands
  - Lethargy (drowsy): patient can be aroused by moderate stimuli and then patient drifts back to sleep.
  - Obtundation: lowered interest in surrounding, slower responses to stimuli and more than normal sleep with drowsiness in between sleep state.
  - Stupor: vigorous and repeated stimuli is required to awake the patient and returns to unresponsive state after removal of stimuli
  - Coma: it is a state of deep stupor where the patient is unarousable and unresponsive
  - Delirium: acute state of confusion and agitation.
- Affect and mood:
  - Affect is the patient's immediate expression of emotion. The affect may be broad, restricted, labile or flat. Affect is inappropriate when there is dissonance between his experience and immediate reaction.
  - Mood is the sustained emotional makeup of the patient's personality.
- Speech: do they have dyarthria, expressive aphasia (Broca aphasia), or receptive aphasia (Wernicke's aphasia)?
  - Sensory (Wernicke's aphasia): failure to comprehend verbal or written messages but speech output is normal
  - Motor (Broca's aphasia): comprehension is normal but speech is non-fluent
  - Conduction Aphasia: intact auditory comprehension but repetition of words is lost.
  - Global aphasia: there is complete derangement of speech. Patients can neither read nor write.
  - Dysarthria: it is a motor speech disorder due to impaired movements of muscles of speech.
- Language:
  - Comprehension: it is the ability to understand, it is assessed by asking simple yes or no questions, or by asking patient to point out at things that you instruct.

- Repetition: it is tested by making the patient repeat the sentence: No If's and's or but's
- Naming: ask the patient to name common and unusual objects.
- Word fluency: ask the patient to say as many words possible in a given category in a fixed period.
- Reading: ask the patient to read out loud and listen for error. Make the patient do things written in command.

- Memory: This is the mental capacity or faculty to retaining and reviving facts, events and impression or of recalling or recognizing previous experiences. It can be immediate recall, short term memory or long term memory.
  - Immediate recall: it can be tested by asking to read newspaper or random sentences and then repeat it without looking.
  - Short term: it can be tested by asking the patient to learn the names of 4 unrelated objects, a short sentence and an address and then recall the information 3-5 minutes later.
  - Long term memory: it can be tested by asking the patient to recall personal or social events e.g. the past presidents of the country, birthdays, distant public events etc.
- Apraxia and constitutional inability
  - Apraxia is the inability to perform previously learnt motor skills. It is tested by asking the patient to use an imaginary scissor, cigarette, pen etc.
  - Constitutional inability is the loss of ability to generate drawing or to manipulate block designs from verbal command or visual reproduction.
- Intelligence: it is the ability to quickly and successfully apply previous knowledge to a new situation and to use reason in solving practical problems. It can be tested by making the patient do:
  - Simple arithmetic problems
  - Simple puzzles
  - Test vocabulary
- Mini-Mental state examination: it is a 30-point questionnaire to measure cognitive impairment. The components include
  - Orientation
  - Registration (Immediate- registering 3 words and recent-recalling 3 words 5 minutes later)
  - Attention and calculation (serial 7s, spell "world" backwards)
  - Language (naming, repetition, comprehension)
  - Complex commands

- Visuospatial ability (Copy of design)

Parameter	Detail and Score
Orientation	• What is the date (day of week, day of month, month, season and year)- 1 point for each correct answer-Maximum of 5 points • Where are we? (State, Country, City/Town, Hospital, floor?)- 1 point for each correct answer)- Maximum of 5 points
Registration	• Name 3 objects and repeat them- 3 points (Maximum=3)
Attention and calculation	• Serial 7s (Subtract 7 from 100 and continue subtracting 7 from each answer) or spell "World" backward- Maximum 5 points
Recall	• Name the 3 objects above 5 minutes later (Maximum= 3 points)
Language	• Naming: name a pen and a clock (2 points) • Repetition: Say "No If's ands or buts" (1 point) • Verbal comprehension (3 step command): Take a pencil in your hand, put in your left hand and put it on the floor (3 points) • Written comprehension: Read the statement written on a piece of paper and do what it says: "close your eyes" (1 point) • Writing: Write a sentence (1 point) • Visuospatial skills: Draw two intersecting pentagons (1 point)

- Results:
  - Maximum score= 30
  - Score >24 is normal
  - Score <24 suggests dementia

CRANIAL NERVES

- The examination of the cranial nerves can be summarized as follows:
  - CN I: smell
  - CN II: Visual acuity, visual field and ocular fundi
  - CN II, III: pupillary reactions
  - CN III, IV, VI: extraocular movements
  - CN V: corneal reflexes, facial sensation and jaw movements.
  - CN VII: Facial movements
  - CN VIII: hearing
  - CN IX, X: swallowing and rise of the palate, gag reflex
  - CN V, VII, X, XII voice and speech
  - CN XI: shoulder and neck movements
  - CN XII: tongue symmetry and position

- CN I (Olfactory): smell is tested with non-irritant and familiar odors. First make sure that each nasal passage is open by compressing one side of the nose and asking the patient to sniff through the other. It is important to ask the patient to close the eyes during the test to prevent visual identification of the substance.
  - Substances with pungent odor must not be used as noxious stimuli is detected by sensory fibers of the trigeminal cranial nerve.
  - To examine olfactory nerve each nostril must be tested separately. Ask the patient to close one nostril, as well as both eyes while they smell and identify the substance with the other nostril, repeat the same on the opposite side.
  - Bottle containing essence of familiar smell (vanilla, coffee, pepper mint) must be tested separately.
  - Ask if the patient smells anything and if so what.
  - Anosmia entails loss of smell of taste and is seen in: nasal disease, tumors, head trauma, aging, use of cocaine, congenital anomalies, meningitis and smoking.
  - This test is often omitted during a brief bedside exam.

- CN II (optic)
  - The optic nerve is tested through: Pupillary reflexes, Visual acuity, Visual fields, Color vision, and fundoscopy.
  - Ask the patient to look straight and inspect the pupil for size, shape and alignment as you compare one side with the other
  - Pupillary light reflex
    - Ask the patient to look straight during examination. Shine the light at a lateral angle and not directing in front of the eye.
    - Direct light reflex: shine torch into one eye and look for immediate constriction of pupil in the same eye.
    - Consensual light reflex: shine torch into one eye and look for immediate constriction of pupil in the opposite eye. (perform a swinging motion of the tourch)
  - Swinging light test: may reveal a relative afferent pupillary defect (Marcus-Gunn pupil).
    - Swing the light back and forth between the eyes. Normally the pupil will constrict with one eye, dilate a little as the light passes over the nose and constrict again with the other eye. Thus you get constrict-constrict-constrict-constrict.

- When one eye doesn't see as well, the pupils don't constrict quite as well. In fact, the pupils appear to dilate a little when you hop over to the bad eye with the flashlight. Thus you get constrict-dilate-constrict- dilate.

➢ Check for the accommodation reflex (constriction and convergence)
- Ask patient to look at an object then bring it closer to their face.
- Avoid standing in front of the patient stand on the side and ask the patient to look forward.

➢ Test visual acuity with Snellen chart (far vision) at 6m (20 feet)
- Ask the patient to remove the glasses or contact lenses while testing visual acuity.
- Each eye must be tested separately.
- Make the patient stand at a distance of 6m from the chart and ask the patient to close one eye and read the chart from the other eye, the lowest possible line on the chart must be read.
- For illiterate patients tumbling E chart is used, where the patient is supposed to identify the direction the letter E is facing.
- Visual acuity is expressed as a fraction. Normal visual acuity is 6/6. Numerator indicates distance from the chart, denominator indicates the distance at which a person with normal eye sight read the same line the patient correctly read.
- If the patient is unable to read at 6m:
  - Move closer (3m)
  - If still unable- move closer again (1m)
  - If still unable- assess ability to count fingers
  - If still unable- assess ability to detect moving hand
  - If still unable- assess light perception
- For near vision the Jaeger's chart is used. The card is held at a distance of 36 cm from the patient's eye. The card must be adequates illuminated. Ask the patient to read the smallest possible line on the chart and record the J value of the line J1 corresponds to 6/6 vision.

➢ Visual fields (Each quadrant one eye at a time) with fingers moving test.
- Visual field is the total portion of space in which objects are visible in the peripheral vision as you focus your eyes on a central point.
- Normal visual field is 100 degrees temporal, 60 degrees nasal, 60 degrees superior and 75 degrees inferior.
- The examiner must have normal visual field to conduct the test.

- Examiner and patient must be seated facing each other at a distance of 1 meter.
- To test patient's left eye, ask the patient to close his right eye with his right hand and to gaze into the examiner's right eye.
- The examiner must close his left eye with his left hand.
- To test vision, the examiner stretches his hands and brings the index finger from periphery of each quadrant (superior, inferior, temporal and nasal) towards the center.
- Patient is asked to say 'yes' when he visualizes the finger.
- In normal acuity both the examiner and the patient visualizes the finger at the same time.

➢ Assess color vision using ishihara chart
➢ Perform fundoscopy to rule out papilledema, optic nerve atrophy, macular haemorrhage, pappilitis etc.

- CN III, IV, VI (Oculomotor, Trochlear, Abducens): have patient keep their head still and follow with their eyes as you trace an 'H' 1m away. Test smooth pursuit and nystagmus by tracing an "H" and a '+'.
  ➢ Note any ptosis (oculomotor lesion)
  ➢ Note any restriction of eye movement
  ➢ Note any nystagumus (stroke, head injury, antiepileptic drugs- phenytoin, high refractive errors, bilateral cataract)
  ➢ Check for the corneal reflex: Ask the patient to look into distance, touch the cornea and conjunctival margin with a wisp of cotton. Normally there will be bilateral blinking. Reflex is lost in lesion of reflex arc and parietal lobe.

- CN V (Trigeminal): Check sensation to light touch and pin prick in all 3 branches of the trigeminal nerve on both sides of the face. If the patient is sedated or comatose, touch cotton to the corneal surface to illicit bilateral blink corneal reflex. Palpate masseter and temporalis muscles as patient clenches teeth to assess motor function.
  ➢ Test for light touch sensation using a wisp of cotton. Ask the patient to close their eyes and say yes each time the examiner touches any part of their face. (ensure first you show them how it feels with their eyes open first before you begin the test).

- Test the motor aspect of the trigeminal nerve. Inspect for wasting of the temporal and masseter on both sides of the face as the patient clenches their teeth
  - To test for the temporalis and masseter muscles ask the patient to clench the teeth and then palpate for muscles above the angle of the mandible. They must stand out equally on both sides. Test the strength of the muscle by making the patient move his/her jaw sidewards as the examiner resists the movements with the palm.
  - To test for the pterygoids ask the patient to hold the mouth open and then attempt to close if forcefully. Normally the examiner will not be able to close the mouth. Unilateral weakness of pterygoids causes jaw to deviate to towards the paralysed side on attempting to open the mouth.
  - Jaw jerk: Ask the patient to open the mouth slightly. Place your finger on the chin of the patient (below lower lip) and then tap it lightly with a tendon hammer. Normally there is slight closure of the mouth. It is exaggerated in pseudobulbar palsy.

- CN VII (Facial):
  - Inspect for facial asymmetry (unilateral weakness) while conversing with the patient, symmetry is maintained in bilateral facial nerve palsy.
  - Observe the blinking and closure of eye, the eyelid on affected side may close just a trace later than the opposite
  - Observe the nasolabial folds, it is lost on the affected side. There will be drooping of eyes on affected side and movements of mouth may be restricted while speaking.
  - Check for movement of upper face:
    - Ask patient to raise the eyebrows, look up and wrinkle the forehead. Inspect for asymmetry or loss of wrinkling.
    - Ask patient to close the eyes tightly. Look for incomplete closure of eyelids on the affected side. Try to force open each eye, eye on the affect side can be opened forcefully.
  - Check for movement of lower face:
    - Ask the patient to smile or show teeth. In case of unilateral palsy the angle of mouth is drawn to the healthy side.
    - Ask the patient to inflate mouth and blow out against closed moth.

- Palpate each cheek by tapping it. Air easily escapes when tapped on affected side.

➢ You can also check taste with various solutions: 'Sweet' with sugar, 'salt' with salt, 'sour' with citric acid and 'bitter' with quinine.Check movement of the lower face by having the patient smile, bare teeth and hold air in the cheeks while you tap on them.

- CN VIII (Vestibulocochlear):
  - ➢ Inspect for presence of any hearing aid, examine the pinna and look for scars and sinuses. Examine the external auditory meatus and the tympanic membrane for any abnormalities.
  - ➢ Test hearing with Ticking clock or Whispering testing:
    - Occlude one ear of the patient by rubbing fingers near the ear and whisper as softly as possible in the other ear letters and numeral.
    - Whispering should be done at a distance of 60cm from the ear.
    - Ask the patient to repeat the letters, if there is abnormal result perform Rinne's and Weber's test.
  - ➢ Rinne's Test: This is done to compare air conduction with bone conduction in same ear. Strike a tuning fork and place the foot piece/base of the tuning fork on the mastoid process and ask the patient to say "now" when he/she stops hearing. When the patient says "now" take the tuning fork and keep its vibrating blades near the external auditory meatus on the same side.
    - Normal: the patient continues to hear the sound when the tuning fork is removed from mastoid process and kept near external auditory meatus. This is because air conduction is better than bone conduction.
    - Rinne's positive: Air conduction is better than bone condition. It is seen in normal hearing and sensorineural hearing loss.
    - Rinne's negative: Bone conduction is better than air conduction. It is seen in conductive deafness and mixed hearing loss.
    - Rinne's false negative: it is seen in severe unilateral sensorineural hearing loss. Here bone conduction is heard longer due to transmission through the skull to the other ear.
  - ➢ Weber's Test: Keep vibrating tuning fork on the center of the forehead or vertex of the patient. Ask the patient if the sound can be heard equally in both ears or better in one ear
    - Normal: sound is heard equally in both ear.

        - Abnormal: sound is lateralized to affected ear in conductive deafness and lateralized to better ear in sensorineural deafness.
    - Schwabach's test: the test, the patient's bone conduction is compared to that of the examiner presuming the examiner has normal hearing. Keep the footplate of the vibrating tuning fork over the mastoid bone of the patient and when the patient stops hearing the tuning fork it is placed on the examiner's mastoid process. In absolute bone conduction (ABC) test, the same procedure is done with occluded external auditory meatus of both the patient and examiner
        - Normal: patient and examiner hears for same duration.
        - Conduction deafness: patient hears for longer duration than examiner
        - Neurosensory deafness: examiner hears for longer duration than patient
    - Check the vestibular function at the end of the neuro exam during the coordination, gait and balance assessment with the Romberg test, and heel to toe walking. You can perform horizontal head impulse test.
        - Make the patient get seated and relaxed, approach the patient from front. Instruct the patient to keep the head loose and gaze at examiner's eyes, hold the head from both the sides and rotate it to the sides (20 degrees rotation from center).
        - Normally the patient's eye deviate to the left as the head is moved to the right and vice versa. In CNS involvement when the head is rotated towards a vestibular lesion there will be corrective gaze shift.

- CN XI (glossopharyngeal): Test for motor function by having patient stick their tongue out. Test for taste on the posterior part of the tongue and gag reflex.

- CN X (Vagus): as the patient says 'ah', confirm soft palate elevates and the uvula stays midline.

- CN XI (Spinal Accessory):
    - From behind, look for atrophy or fasciculations in the trapezius muscles, and compare one side with the other.
    - Ask the patient to shrug both shoulders upward against your hands.
    - Note the strength and contraction of the trapezii.
    - Injury to spinal accessory nerve will manifest as dropping shoulders.

- Ask the patient to turn his or her head to each side against your hand. Observe the contraction of the opposite sternocleidomastoid and note the force of the movement against your hand.
- A supine patient with bilateral weakness of the sternocleidomastoids has difficulty raising the head off the pillow.

- CN XII (hypoglossal)
  - Listen to the articulation of the patient's words.
  - Inspect the patient's tongue as it lies on the floor of the mouth. Look for any atrophy or fasciculations (fine, flickering, irregular movements in small groups of muscle fibers)
  - Then, with the patient's tongue protruded, look for asymmetry, atrophy or deviation from the midline.
  - Ask the patient to move the tongue from side to side and note the symmetry of movement.
  - In ambiguous cases, ask the patient to push the tongue against the inside of each cheek in turn as you palpate externally for strength.
  - In a unilateral cortical lesion, the protruded tongue deviates transiently in a direction away from the side of the cortical lesion.

SIGNS OF MENINGEAL IRRITATION

- Neck stiffness: passively but gently flex the patient's neck to see if they can touch the chest without pain.
- Kernig's sign: with the patient supine on the bed passively extend the patient's knee on either side when the hip is fully flexed and look for patient spasm.
- Brudzinski's sign: when forced flexion of the neck elicits a reflex flexion of the hips.

UPPER LIMB EXAMINATION

INSPECTION

- Inspect the upper limbs and comment on:
  - Symmetry of muscles
  - Wasting of muscles
  - Hypertrophy of muscles
  - Contractures
  - Fasciculations: these are fine, intermittent and involuntary contractions of muscles that occur spontaneously
  - Abnormal movements
- Note the distribution of wasting or hypertrophy, whether unilateral or bilateral, predominantly proximal or distal or both.

PALPATION

INITIAL PALPATION

- Palpate the muscles and feel for consistency.
- Check for muscle bulk and tenderness.
- If the muscles are atrophied, it may feel flabby.
- If the muscles are hypertrophied, may feel firm and resilient.
- In pseudohypertrophy there will be woody consistency.



TONE

- Tone is the resistance offered by muscles when moved passively through its range of movements. It refers to the tension present in relaxed muscle.
- Before beginning with the examination make sure that the patient is relaxed, comfortable and not in any pain (enquire if they are in pain- if so, always examine that limb last).
- Tone can be tested by moving a part through its range of movements.
- To examine the tone of muscles of the upper limb, the examiner must support the patient's elbow in one hand, and hold the patient's hand with the other hand.
- Move it passively by flexing and extending at the elbow, supinating and pronating at the wrist.
- Feel the tension in the muscles as you move them.
- Raise the patient's hand and elbow and allow it to fall on the bed.
  - In a normotonic patient there will be checking movement to prevent the limb from falling.
  - In hypotonia the limb falls to the bed without any resistance.
- Rigidity is a state of hypertonia where the tone is uniformly increased in both agonist and antagonist group of muscles.
- Spasticity is a state of hypertonia affecting both agonist and antagonist group of muscles, but tone is higher in one of the group of muscles.
  - In clasp knife spasticity: on passively flexing a joint there will be initial increase in resistance and on further pressure there is rapid decrease in resistance giving a movement like a clasp knife.
  - In lead pipe rigidity: there is uniform resistance to passive movement through the whole range of movement

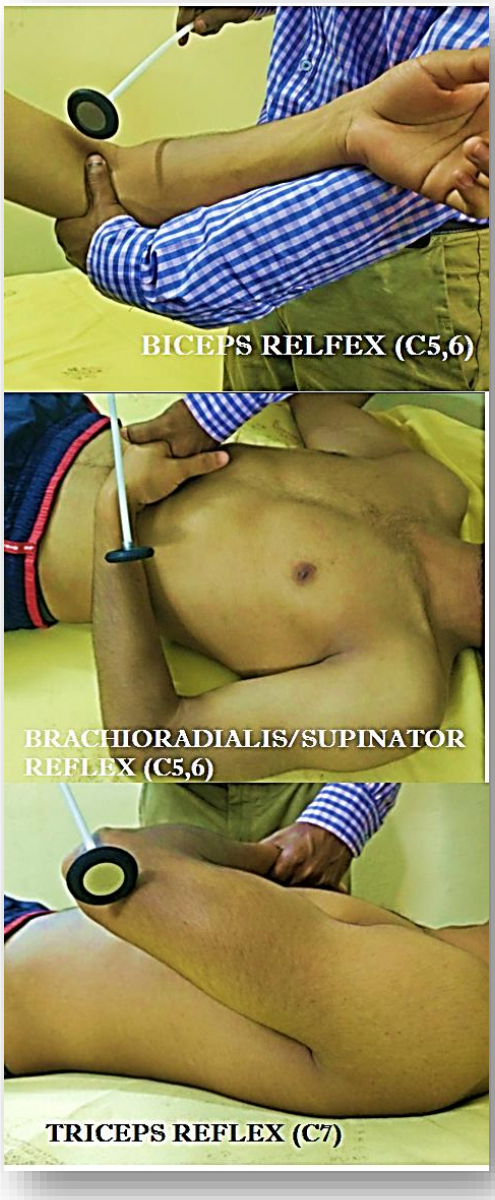
CHECKING FOR MUSCLE TONE



- In cog wheel rigidity: there is a combination of lead pipe rigidity and tremors where the resistance offered is interrupted by tremors which present as jerky resistance

REFLEXES

BICEPS REFLEX (C5-C6)



- Make the patient sit with the forearms resting on their thigh or support it by resting it on your forearm.
- Keep the patient's elbow midway between flexion and extension.
- Place you thumb over biceps tendon (located at the medial aspect of elbow joint) and tap it with a tendon hammer.
- Normally there will be slight flexion at the elbow (look at the bicep muscle for contraction).

BRACHIORADIALIS/SUPINATOR RELFEX (C5-C6)

- Support the patient's hand or make it rest on the patient
- Slightly flex the elbow and wrist must be halfway between pronation and supination.
- Identify the brachioradialis tendon which inserts at the base of the styloid process of the radius.
- Strike the tendon directly with the hammer.
- Normal reflex-
  - Supination at wrist
  - Slight flexion of forearm
  - Slight flexion of fingers
- While eliciting supinator reflex if there is absence of contraction of brachioradialis and if the only response present is finger flexion and elbow extension, it is called an inverted supinator reflex.

TRICEPS REFLEX (C7)

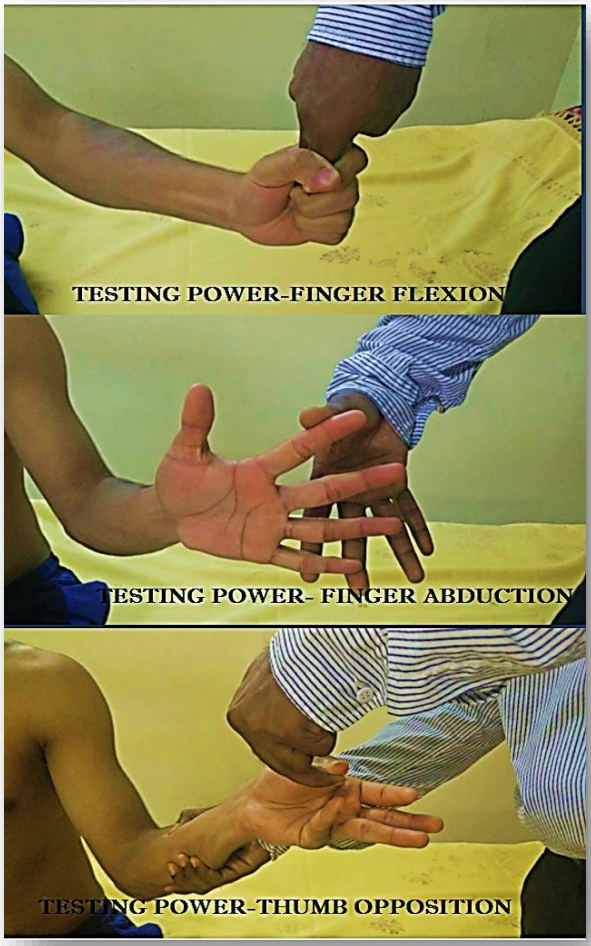
- Support the patient's forearm with one hand.
- Identify the triceps tendon at its insertion.
- Normally, there is extension at elbow joint.

POWER

- Power of a muscle is tested by instructing the patient to resist the examiner's forceful movements or to move a body part against examiner's resistance.
- While examining an individual muscle careful positioning must be done to prevent use of accessory muscles.
- Grading of power:
  - Grade 0- No contraction
  - Grade 1- Flickering movements
  - Grade 2- Active movement with gravity eliminated
  - Grade 3- Active movement against gravity
  - Grade 4- Active movement against gravity and resistance
  - Grade 5- Normal power
- Muscles tested:
  - Deltoid (C5)- abduction of shoulder
    - Ask the patient to raise the arm by the side. Examiner must provide resistance at the elbow.
  - Biceps (C5-C6)- flexion at the elbow
    - Patient should flex the elbow with forearm supinated.
      Examiner must provide resistance at the wrist.
  - Triceps (C7)-extension of elbow
    - Patient should extend the elbow with forearm supinated.
    - Examiner must provide resistance at the wrist.
  - Serratus Anterior (C5, 6, 7)- Scapula protraction
    - Make the patient bring both the hands anteriorly and push them against a wall. In case of paralysis there will be winging of the scapula.
  - External carpi radialis longus (C6)- wrist extension
    - Provide support at the forearm.
    - Make the patient extend their wrist while the examiner resists the movements a the dorsum of hand.



- Supinator (C6, 7)
  - Hold the patient's hand in a handshake and ask the patient to supinate as you resist the action.
- Muscles of the hand
  - Finger flexion (C8): make the patient hold the examiner's fingers by making a fist. Ask them to not let go while the examiner tries to pull the finger out. Normally the examiner cannot remove the fingers.
  - Finger abduction (T1): make the patient abduct the fingers. Examiner must compress them back while the patient tries to resist it
  - Thumb opposition (C8-T1)- make the patient touch the little finger with the thumb (opposition). Examiner mist provide resistance at the thumb.

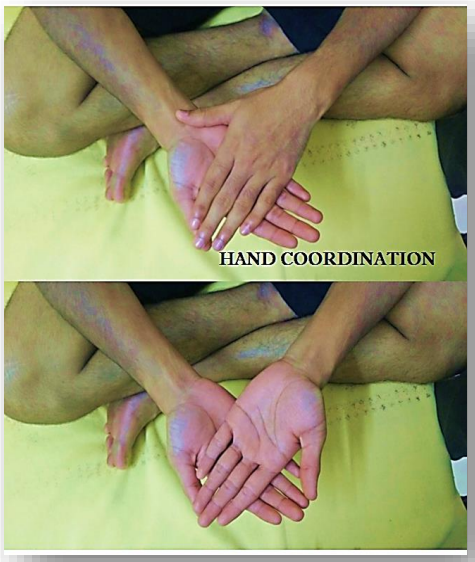


SENSATION

- Temperature (small fibers/ spinothalamic pathway): use cold metal (usually not done)
- Light touch (moderately myelinated fibers/ combined pathways) use finger or cotton and ask patient to tell you when the feeling the touch. The patient should close their eyes when this is done however the examiner should first show the patient should feel with their eyes open. Follow the dermatomes.
- Pinprick (small fibers/spinothalamic pathway): use a pin, start distal and move proximally. The patient should close their eyes when this is done however the examiner should first show the patient should feel with their eyes open. Follow the dermatomes.
- Joint position sense (large myelinated fibers/ dorsal column pathway) test a finger and toe on each limb. Move it up or down and asking the patient to tell you which direction you moved it. (first show the patient the movement with their eyes open). Hold the sides of the finger or toe to avoid giving the patient a clue about the direction of movement.

- Vibration sense (large myelinated fibers/ dorsal column pathway) use a vibrating tuning fork placed over bony prominences. With the patient's eyes closed ask them to tell you when they cannot feel the vibrations as you stop the tuning fork from vibrating.
- Two-point discrimination: normally 2mm separation can be recognized as separate stimuli on the finger tips, but only 1cm separation on the bottoms of the toes.

COORDINATION (CEREEBELLAR INJURY)



- Finger to nose test: ask the patient to touch his nose and then the tip of your finger, held at arm's length in front of the patient's face using their index finger. (move your finger sideways as the patient is doing this)
- Ask the patient to do rapid alternating movements of supination and pronation of hands. (Patients with cerebellar lesions will be unable to perform the test- this is known as Dysdiadochokinesia)

LOWER LIMB EXAMINATION

INSPECTION

- Inspect the lower limbs and comment on:
  - Symmetry of muscles
  - Wasting of muscles
  - Hypertrophy of muscles
  - Contractures
  - Fasciculations: these are fine, intermittent and involuntary contractions of muscles that occur spontaneously
  - Abnormal movements
- Note the distribution of wasting or hypertrophy, whether unilateral or bilateral, predominantly proximal or distal or both.

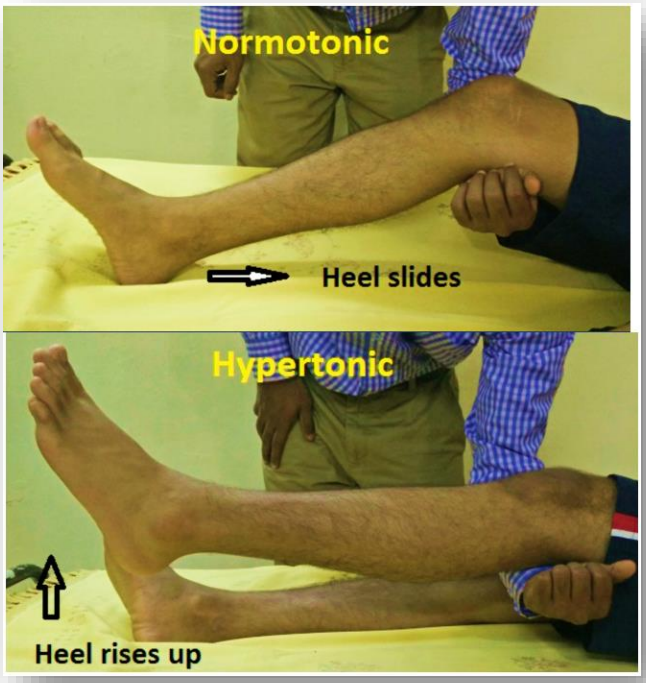
PALPATION

INITIAL PALPATION

- Palpate the muscles and feel for consistency.
- Check for muscle bulk and tenderness.
- If the muscles are atrophied, it may feel flabby.
- If the muscles are hypertrophied, may feel firm and resilient.
- In pseudohypertrophy there will be woody consistency.

TONE

- Tone is the resistance offered by muscles when moved passively through its range of movements. It refers to the tension present in relaxed muscle.
- Before beginning with the examination make sure that the patient is relaxed, comfortable and not in pain (enquire if they are in any pain- if so always examine that limb last).
- Inspect and palpate the muscle to get a general idea of tone.
- Tone can be tested by moving a part through its range of movements.
- To examine the tone of the lower limb make the patient lie in a supine position and ask the patient to relax the lower limbs.
- Keep your hand under the patient's knee and quickly lift it off the table.
  - In a normotonic patient- heel slides up the table
  - In hypotonia- limb is hyperextensible and feels flabby
  - In hypertonia- heel rises off the table



REFLEXES

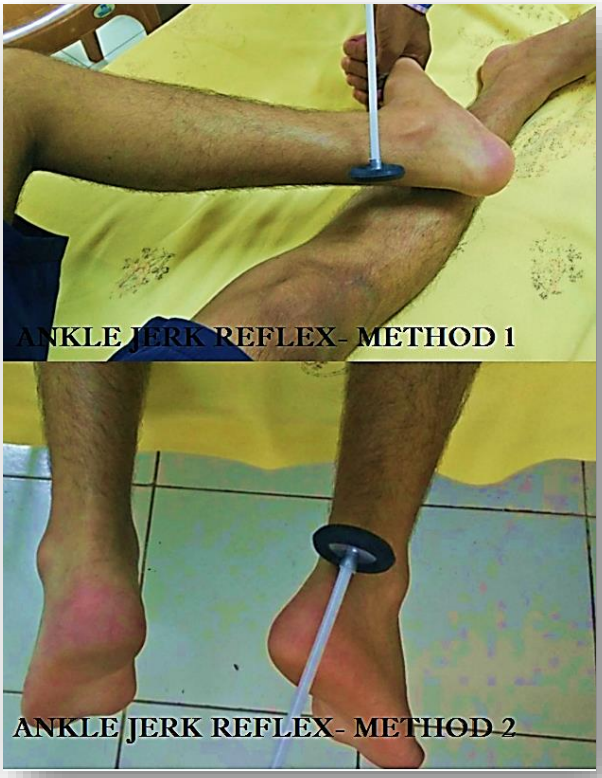
- Grading:
  - Absent
  - 1- present (As a normal ankle jerk)
  - 2- brisk (as a normal knee jerk)
  - 3- very brisk
  - 4- clonus

KNEE JERK (L3 & L5)



- Make the patient lie in a supine position or in the sitting position with the knees swinging by the side of the bed.
- If the patient is in the supine position, slightly flex the knee by lifting it with your forearm.
- Strike the patellar tendon located at the lower aspect of the patella directly with the tendon hammer.
- Normally there will be extension of the knee with contraction of quadriceps muscle (look at the quadriceps muscles and watch out for contraction).

ANKLE JERK (S1, 2)



- There are 2 methods to do this
- Method 1:
  - Make the patient lie in the supine position with the knees slightly flexed.
  - Gently dorsiflex the foot and strike on the Achilles tendon.
- Method 2:
  - Make the patient kneel on a chair with knees resting against the back of the chair and the feet must be out of the chair.
  - Dorsiflex the foot slightly and tap on the Achilles tendon.
- Normally there will be plantar flexion at the ankle joint due to contraction of gastrocnemius muscle.

ANKLE CLONUS



- Clonus is rhythmic sustained involuntary muscular contraction and relaxation caused by sudden passive stretch of muscles and tendon. It can be elicited at the ankle and patella.
- Support the patient's lower limb at the knee.
- Dorsifelex and partially evert the foot with sustained pressure (do not leave the pressure after dorsiflexion).
- Ankle clonus is felt as repeated dorsiflexion and plantar flexion at the ankle joint.

- **NOTE:** If the knee jerk and ankle reflex cannot be elicited, make the patient do the Jendrassik manoeuver (Reinforcement) and repeat the examination.
  - Ask the patient to make a fist in both the hands and interlock the fingers in a hook like form.
  - Instruct the patient to clench their teeth and pull the hands apart while keeping the fingers locked. Immediately elicit the reflex.


Jendrassik manoeuver (reinforcement)

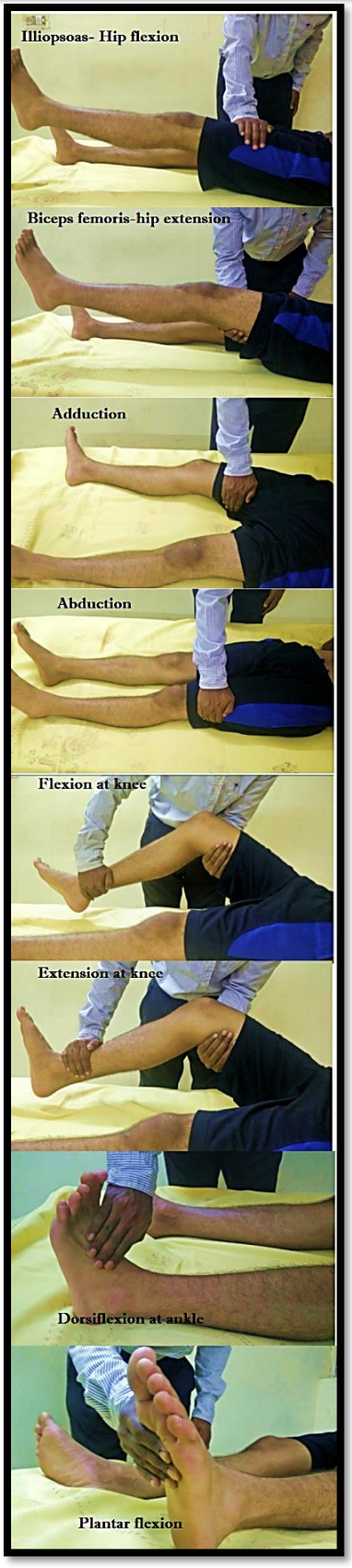
PLANTAR/BABINSKI REFLEX (L5, S1,2)


Plantar/ Babinski reflex

- Make the patient lie in supine position.
- Fix the foot by holding at the ankle joint.
- Strike the lateral part of the sole with a blunt object.
- The strike must begin just above the heel moving upwards and then curve inwards (medially) from little toe to the great toe.
- Normal response (Babinski negative): plantar flexion of great toe, flexion and adduction of other toes, inversion of foot.
- Babinski positive: dorsiflexion of great toe, abduction (fanning) of other toes, dorsiflexion of ankle. It is seen in pyramidal tract lesions, meningitis, multiple sclerosis, poliomyelitis, stroke.

POWER

- Power of a muscle is tested by instructing the patient to resist the examiner's forceful movements or to move a body part against examiner's resistance.
- While examining an individual muscle careful positioning must be done to prevent use of accessory muscles.
- Grading of power:
  - Grade 0- No contraction
  - Grade 1- Flickering movements
  - Grade 2- Active movement with gravity eliminated
  - Grade 3- Active movement against gravity
  - Grade 4- Active movement against gravity and resistance
  - Grade 5- Normal power
- Muscles tested:
  - Illiopsoas (L2, L3): hip flexion
    - Ask the patient to lie down and raise the legs straight while the examiner provides resistance at the anterior aspect of the thigh.
  - Biceps femoris (L5, S2): Hip extension
    - Make the patient lie down. The examiner must place a hand under the leg and provide resistance as the patient pushes the leg down.
  - Adduction of hip (L2, L3, L4)
    - Adductor (brevis, longus, magnus): examiner must place hands on inner aspects of thigh and provide resistance as the patient tires to bring both thighs together.
  - Abduction of hip (Gluteus maximus and minimus L4, 5, S1)
    - Examiner must place hands on outer aspect of thigh and provide resistance as the patient tries to move the thighs apart.
  - Flexion at knee (Hamstrings S1, S2)
    - Provide support at the thighs with one hand and resistance at the ankle with another hand as patient tries to flex the knee.



- Extension at knee (Quadriceps L3, L4)
  - Provide support at the thigh with one hand and resistance at the shin as the patient tries to extend the knee.
- Dorsiflexion at ankle (Tibialis anterior L4, 5)
  - Provide resistance at the dorsum of the ankle as the patient tries to pull the foot upwards.
- Plantar flexion (Grastrocnemius S1, S2)
  - Provide resistance at the bottom of the foot as the patient tries to push down.

SENSATION

- Temperature (small fibers/ spinothalamic pathway): use cold metal (usually not done)
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- Two-point discrimination: normally 2mm separation can be recognized as separate stimuli on the finger tips, but only 1cm separation on the bottoms of the toes.

COORDINATION

HEEL TO SHIN



- Ask the patient to run heel of one leg from the knee, down the shin to the ankle of the other leg. Repeat it many times.

GAIT AND STANCE

- Balance/ Stance: Test with the Romberg's test
  - Standing with feet firmly together, have the patient close his or her eyes and see if balance worsens (do they sway or fall).
- Ask the patient to walk a short distance away from you and towards you.
- Ask the patient to walk back on heels and then on their toes
- Abnormal gait patterns include:
  - Hemiplegic gait (Circumduction gait): it is seen in patients with unilateral weakness (hemiparesis). The affected arm is flexed, adducted and internal rotated, leg is extended with plantar flexion of foot and toes. While walking, the patient drags the affected leg in a semicircle (circumduction)
  - Ataxic gait (cerebellar gait): it is seen in patients with cerebellar lesion. The gait is similar to that of a person under influence of alcohol. Patient walks with a broad base and staggering movements. Heel to toe (tandem) walking will not be possible. When made to stand, the patient sways back and forth and from side to side.
  - Festinant gait (Parkinsonian/shuffling gait): It is seen in patients with Parkinson's disease. The patient assumes stooped posture (head and neck bent forward with flexed knees and upper extremities). Patient walks with typical rapid, short little steps as if trying to catch gravity (festination).
  - Sensory ataxic gait (stomping gait): it occurs in patients with loss of proprioception (dorsal column lesion). Due to loss of position sense the patient cannot assess where the feet are and hence will lift the leg very high and hit the ground forcefully. There is exacerbation of this gait in dark as the patient cannot see.

- Steppage gait (neuropathic/equine gait): It is seen in patients with foot drop. The patient tries to lift the leg high while walking to prevent the foot from dragging on the floor.
- Waddling gait (Myopathic/Trendelenburg gait): It is caused due to weakness of proximal muscles of pelvic girdle. When the patient walks the pelvis on contralateral side drops downwards. To overcome the weakness, the patient moves upper body and lower leg forwards. Patient walks like a drunk broad base. It is seen in patients with muscular dystrophy.
- Choreiform gait (hyperkinetic gait): it is seen in patient with Syndeham's chorea and Huntington's chorea. The patient walks with irregular, involuntary and jerky movements of extremities.

- Ending the examination:
  - Thank the patient
  - Cover the patient
  - Summarize findings, offer an impression and some relevant investigations.

SEIZURES AND EPILEPSY

- The word "Seizure" comes from the Latin word "sacire" meaning "to take possession of".
- A seizure can be defined as abnormal paroxysmal firing of the cerebral neurons.
  - A Convulsion is the outward manifestation of a seizure.
- A seizure may be subtle or dramatic and are often sudden in onset with or without an aura.
- Depending on the distribution of discharge manifestation seizures can be classified as (newer classification):
  - Motor (e.g. automatisms, clonic, tonic movements)
  - Non-motor:
    - Sensory,
    - Autonomic or
    - Psychiatric.
- It may be difficult at times to differentiate a seizure from syncope and it is important to obtain a complete history from any individual who witnessed the event.
  - Generally, patients with syncope will not complain of significant postictal symptoms (symptoms after the seizure including disorientation, sleepiness, and muscle aches)
- Epilepsy- is a syndrome characterized by recurrent (2 or more) unprovoked seizure attacks due to a chronic, underlying process in the brain.
- Epilepsy is age-dependent being highest at the extremes of life, most cases starting before the age of 20 and after the age of 60.
- A person with a single seizure or recurrent seizures due to correctable or avoidable circumstances does not necessarily have epilepsy.
- A seizure often has 3 distinct phases:
  - Aura: involves alterations in taste, smell, visual perception (flashing lights), hearing and emotional state (strange gut feeling), Deja vu. This is a partial seizure that is followed by a larger event. It is common in temporal seizures and uncommon in generalized seizures.
  - Ictus: this is the seizure.
  - Postictal: these are events after the seizure, the person experiences drowsiness and confusion. This is the period in which the brain recovers from the insult it has experienced.

ETIOLOGY

- Causes of seizures can be remembered by the mnemonic "VITAMINS":
  - V-vascular (Stroke, bleed, arteriovenous malformations)
  - I- infection (meningitis, abscess, encephalitis): encephalitis, toxoplasmosis, cerebral malaria, neurological cysticercosis.
  - T- trauma (especially penetrating): depressed skull fracture, intracranial hemorrhage and prolonged post traumatic coma are associated with risk of having seizure disorder. Seizure within 30 days of traumatic brain injury aren't classified as epilepsy and conversely seizures occurring many years later are often not related to injury.
  - A- autoimmune (CNS vasculitis)
  - M- metabolic (hyponatremia, hypocalcemia, hypomagnesemia, hypoglycemia, hypoxia, drug overdose/withdrawal, uremia)
  - I-idiopathic (account for the majority)
  - N-neoplasms: metastatic or primary brain tumors.
  - pSyschiatric
- Other causes include:
  - Genetic factor: family history
  - Perinatal cause: perinatal asphyxia, birth trauma, perinatal infection
  - Inflammatory causes: systemic lupus erythematous
  - Degenerative disease: alzheimer's disease
  - Drugs: Theophylline, cocaine, Lidocaine
  - Developmental: Cerebral palsy, Down syndrome

CLASSIFICATION OF SEIZURES

- Seizures can either be classified as:
  - Partial/focal seizures:
    - Simple partial seizures (with motor, sensory, autonomic or psychic signs)
    - Complex (dyscognitive) partial seizures
    - Partial seizures with secondary generalization
  - Generalized seizures:
    - Tonic-clonic (grand mal)
    - Absence (petit mal)
    - Tonic
    - Myoclonic
    - Atonic
  - Unclassified: neonatal seizures and infantile spasms

PARTIAL (FOCAL) SEIZURES

- This is caused by electrical discharge restricted to a limited part of the cortex of one cerebral hemisphere.
- These type of seizures often suggest an underlying structural disease.
- These arise from localized regions of the brain (involve one hemisphere of the brain).
- They can either be:
  - Simple partial seizures: when consciousness is not impaired e.g. one limb jerking (a Jacksonian seizure)
  - Complex: when consciousness is lost e.g. a temporal lobe seizure.
  - Partial with secondary generalization.
- The patient will often complain of involuntary jerking of a finger or hand.

SIMPLE PARTIAL SEIZURES

- These are partial seizures in which consciousness is not impaired.
- Manifestation can be motor, sensory, autonomic or psychiatric.
  - Motor manifestation is usually focal clonic or tonic movement of angle of mouth, finger or thumbs.
  - This seizure activity may spread over one side of the body (Jacksonian march) to involve larger body part (e.g. the convulsive activity can start in the face, move to ipsilateral arm and then to the leg).
  - The visible spread of activity of the seizure is called the march of a seizure. Local temporal paralysis of the limbs affected sometimes follows-Todd's paralysis.
  - With some frontal seizures, conjugate gaze deviates away from the epileptic focus and the head turns (adversive seizure)
  - The rest of manifestations include transient sensory abnormalities, flushing and sweating, pallor or odd feelings.

COMPLEX (DYSCOGNITIVE)PARTIAL SEIZURES (TEMPORAL LOBE SEIZURES)

- These are focal seizures accompanied by impairment of consciousness.
- They usually arise in the temporal lobe (60%).
- The person is unable to respond appropriately to visual or verbal commands during the seizure and has impaired recollection or awareness of ictal phase.

- The seizure frequently begins with an aura, which may manifest with rising epigastric sensation and nausea, fear, hallucination (e.g. olfactory, visual-micropsia or macropsia, auditory or gustatory) and complex illusions (e.g. having experienced a new event, Déjà vu or jamais vu).
- Start of ictal phase is often a sudden behavioral arrest or motionless stare. There may be complete or partial loss of awareness of surroundings lasting for 1-2 minutes on average (as opposed to 10 seconds in absence seizures)
- This is often accompanied by automatism, which is involuntary automatic behavior (repeated complex activities like chewing, lip smacking, "picking movement" of the hands, and display of emotions).
- Post-ictal confusion and transition to full recovery may take minutes to hours.

PARTIAL SEIZURE WITH SECONDARY GENERALIZATION

- These are focal seizures which evolve into generalized seizures. These are usually tonic-clonic type and difficult to differentiate from primary generalized tonic-clonic seizure.
- Note: this is the only time a generalized seizure can have an aura.

TABLE 11.1: PARTIAL SEIZURES

SEIZURE TYPE	FEATURES
TEMPORAL LOBE	• Autonomic symptoms: rising sensation or pain in the abdomen, vomiting, flushing, pallor, altered heart rate • Altered 'higher' functions: déjà or jamais vu, amnesia, altered emotions, delusions, hallucinations (including smell or taste), dysphasia (also post-ictal) • Motor symptoms: complex movements e.g. singing, driving, undressing- and automatisms e.g. lip smacking, fumbling
FRONTAL LOBE	• Often affects motor complex, causing abnormal movements-e.g. eye and head movements, peddling movements-or motor arrest. • Onset and timing: usually short, quick onset with rapid recovery. Can be night and come in clusters. • Jacksonian march: tingling spreading from one area to another e.g. from the hand up to the face • Speech symptoms: vocalisations, dysphasia, speech arrest • Behavioral changes • Recovery usually rapid but post-ictal phase can feature weakness (Todd's palsy)
BENIGN ROLANDIC EPILEPSY	• Commonest epilepsy syndrome in children especially aged 5-10 years. • Starts around the central sulcus (Rolandic Fisssure) which divides the frontal and parietal lobes. • Nocturnal seizures: facial twitches including eye flickering and lip smacking, aphasia, salivation • No true post-ictal phase but may feel a little weak or have altered sensation • Occasionally can progress to Generalized tonic-clonic seizure.
PARIETAL LOBE	• Often affects somatosensory cortex causing abnormal sensations such as tingling or numbness • Motor symptoms if it spreads to pre-central gyrus
OCCIPITAL LOBE	• Affects the visual cortex causing visual symptoms such as shapes and /or flashes • Shapes are often more colorful and circular than migraine.

GENERALIZED SEIZURES

- These occur because of abnormal electrical discharge from both cerebral hemispheres simultaneously, without any detectable focal onset.
- They are always associated with loss of consciousness or awareness.

GENERALIZED TONIC-CLONIC SEIZURE (GRAND MAL/ MOTOR)

- This is the most common type of seizure.
- Typically seen in genetic epilepsy syndrome and in seizures arising from metabolic abnormalities (e.g. hyponatremia, alcohol withdrawal, medications, CNS infections).
- Seizure usually begins abruptly without warning (no aura or focal manifestations).
- Ictal phase:
  - Begins with tonic contraction (stiffening) of muscles throughout the body which is responsible for loud moan or cry (due to tonic contraction of the muscles of respiration and the larynx)
  - Tonic posturing, respiration is impaired and the patient falls to the ground and there may be tongue biting due to tonic contraction of the jaw muscles.
  - After 10-20 seconds the tonic phase evolves to a clonic phase characterized by bilateral jerking clonic movement involving the whole body. This lasts for another 1 minute as they reduce in frequency.
- Post-ictal phase:
  - Unresponsiveness, muscle flaccidity, excessive salivation and frothing of saliva which may cause stridorous breathing and partial airway obstruction.
  - Bladder or bowel incontinence may occur at this point.
  - Patients gradually regain consciousness over minutes to hours and during this transition there is typically a period of postictal confusion, headache, muscle ache and fatigue that can last for many hours.

Tonic- a contracted muscle

Clonic: referring to clonus, having spasmodic contractions

ABSENCE SEIZURES (PETIT MAL/NONMOTOR)

- It is characterized by sudden and brief lapses (<10s) of consciousness without loss of postural control.
- The seizure typically lasts for only few seconds; consciousness returns as sudden as it was lost.

- It usually manifests with blank staring and they may have also subtle motor manifestations like blinking of the eyes, chewing movements.
- There is no post-ictal confusion.
- The seizure may occur as many as hundreds of times per day.
- It is usually detected by unexplained daydreaming and decline in school performance.
- Typical absence attacks are never due to acquired lesions such as tumors- they are a manifestation of primary generalized epilepsy.
- It usually begins in childhood (4-8 years) and it often has a good prognosis with 60-70% of such patients having spontaneous remission during adolescence.
- Children with absence seizures may go on to develop generalized convulsive seizures.
- It is often characterized by 3Hz spike and slow-wave complexes on EEG.
- Absence seizures are often confused with the complex partial seizures of temporal lobe epilepsy.

TONIC SEIZURES

- Tonic seizures consist of stiffening of the body, not followed by jerking.

MYOCLONIC SEIZURES

- These are characterized by sudden and brief muscle contraction that may involve one part of the body or the entire body.
- There is sudden jerk of bilateral limbs (usually arms), face, or trunk. It may lead to a fall. They can be single or multiple and may occur on waking.
- A normal common physiologic form of myoclonus is sudden jerking movement observed while falling asleep (Hypnic jerk).
- Pathologic myoclonus is most commonly seen with metabolic disorders (especially uremia), degenerative diseases of CNS or anoxic brain injury.
- They are usually not epileptic.

ATONIC (AKINETIC) SEIZURES

- Characterized by sudden loss of postural muscle tone, lasting 1 to 2 seconds.
- Consciousness is briefly impaired.
- It usually manifests as a head drop or nodding movement, while a longer seizure may cause the patient to collapse.
- Primarily seen with inherited forms of childhood epilepsy.

TRIGEERS

- Decreased sleep
- Alcohol
- Fever
- Flickering or flashing lights
- Drugs or drug withdrawal

DIAGNOSTIC APPROACH/EVALUATION

- The patient's history and physical examination can aid in the determination of whether or not a seizure or some other transient event was responsible for the patient's symptoms.
- History should include:
  - History of the event (Before, during and after)
    - Presence of any prodromal symptoms (differentital aura from presyncopal prodrome)
    - Description of seizure by reliable observer (convulsion, automatism vs brief syncopal blackout and pallor)
    - Post ictal symptoms (Post-ictal confusion and headache vs rapid recovery in syncope)
    - Urinary incontinence, myalgia and tongue bite or oral lacerations are clues to the proper diagnosis
  - History of suggesting cause and risk factors (triggers):
    - Febrile convulsion (history of high grade fever)
    - CNS infection (current/ previous)
    - Head injury
    - Stroke
    - Developmental abnormality
    - HIV status
    - Family history
    - Social history (like alcohol abuse, recent travel, not sleeping under a mosquito net (malaria), sleep deprivation, prolonged standing)
    - Diet (pork intake and generally electrolyte intake)
  - Past medical history: Previous seizures
  - Medications

- Physical examination: features that should be looked for include:
  - Skin for evidence of neurofibromatosis
  - Organomegaly: metabolic storage disease
  - CVS/ Carotid artery: stroke
  - Complete neurological exam

INVESTIGATIONS

ELECTROENCEPHALOGRAPHY (EEG)

- This is the most useful test in diagnosis of seizure disorder.
- It should be performed while the patient is asleep and awake.
- Abnormal EEG supports the diagnosis of seizure and may give information about the type of seizure.
- Abnormal EEG is not adequate for diagnosis of seizure and normal EEG can be found in epileptics.

NEUROIMAGING

- Preferably MRI: may help to see any space occupying lesion in the brain.
- A CT scan of the head can also be used.
- MRI and CT scans are indicated to rule out a structural lesion as the cause of the seizure

OTHER ROUTING LABORATORY ASSESSMENT

- Full blood count: to rule out infections
- Urinalysis
- Serum glucose: rule out hypoglycemia
- Liver function test
- Renal function test
- Electrolytes: hyponatremia, hypocalcemia and hypomagnesemia
- Blood arterial gases: to rule out hypoxia
- Lumbar puncture: when infection or inflammatory disease is a concern
- Toxicological screening

DIFFERENTIAL DIAGNOSIS FOR SEIZURE

- Syncope
- Psychogenic seizure (hysteric conversion)
- Transient ischemic attack
- Migraine

COMPLICATIONS

- Status epilepticus
- Accidents
- Hypoxic brain damage
- Mental retardation and impairment of intellectual function
- Sudden death
- Psychosocial (social stigma)

MANAGEMENT

EMERGENCY MEASURES

- The first step in the treatment of any acutely seizing patient is to secure the airway, breathing and circulation.
  - Airway- ensure the airway is patent, suction any secretions, During the seizure place the patient on the side with a mouth gag to prevent them from biting their tongue.
  - Breathing- ensure the patient is breathing
  - C-gain venous access
  - Monitor vitals.
  - During the ictal phase immobilize the main large joints
- Most seizures last only minutes and end spontaneously. A prolonged seizure (>5 min) or repeated seizures may be treated with rectal diazepam, IV lorazepam or buccal midazolam.
  - 5-10mg IV diazepam
- Once this is achieved the next step is to simultaneously evaluate and treat any precipitating cause of seizure. If a reversible cause is identified, it should be treated aggressively.
- The goal is:
  - Complete control of seizure
  - Prevent development of complications and socioeconomic consequences
- Management includes:
  - Treatment of underlying condition: metabolic causes (hypoglycemia, hyponatremia or drug intoxication) should be corrected. Structural CNS lesions like tumors may be removed surgically.
  - Avoidance of precipitating factor: maintain normal sleep schedule, avoid taking excess alcohol, reduce stresses using physical exercise, meditation or counseling.

  - Suppression or control of recurrent seizure: Antiepileptic drug therapy
- If the patient continues to seize manage as status epilepticus.
- In patients with first-time seizure, anticonvulsant therapy should be started only if the patient has an abnormal neurologic exam, presented with status epilepticus, has a strong family history of seizure or has an abnormal EEG. Otherwise first-time seizures are generally not treated with long term anticonvulsant therapy.
- Anti-epileptic drugs can be started if:
  - There are recurrent seizures of unknown cause
  - Single seizure due to:
    - Identified CNS lesion (tumor, infection, trauma)
    - With abnormal neurologic exam
    - Presenting as status epilepticus
    - With post-ictal Todd's paralysis
    - With strong family history of seizure disorder
    - With abnormal EEG
- Anticonvulsant therapy is not often initiated in patients with a single, unprovoked convulsion, a normal neurologic examination and a normal neuroimaging study and EEG unless they experience a second seizure.

ANTIEPILEPTIC DRUGS

- Principles in the introduction of antiepileptic drugs:
  - Introduce antiepileptic drugs at low dose and slowly titrate upwards until the seizures are controlled or side effects become unacceptable.
  - Aim for monotherapy- 70% of patients will have seizure control with a single drug.
  - If seizures are not controlled with first antiepileptic drugs, gradually introduce second agent and then slowly withdraw the first drug. If still not seizure free then combination therapy is required.
  - Epilepsy is one of the few disorder where non-generic ('brand name') prescribing is justified to ensure consistent drug levels.
  - Routine monitoring of drug levels is not needed and should be reserved for assessing compliance and toxicity. Measuring sodium valproate levels is rarely useful as levels fluctuate widely.
  - There are interactions between antiepileptic drugs (and with other medications) e.g. between sodium valproate and lamotrigine. New generation drugs have fewer interactions.
  - Phenytoin is no longer considered as a first line antiepileptic drug. It is used principally in emergency control of seizures (status epilepticus)

Seizure type	Drug of choice
Partial seizure ➢ Simple ➢ Complex ➢ With secondary generalization	First line: Carbamazepine and phenytoin Alternative: Valproic acid and Lamotrigine • Therapy may be stopped if the patient has been free of seizures for 2-3 years.
Generalized tonic-clonic seizure	First line: Valproic acid and lamotrigine Alternative: carbamazepine, phenobarbitone or phenytoin
Absence seizures	First line: Valproic acid, Ethosuximide Second line: lamotrigine, clonazepam
Atypical absence, myoclonic, atonic	First line: valproic acid Second line: Lamotrigin, clonazepam, Topiramate

- Carbamazepine
  - Dose: 100-200mg PO BD and gradually increase the dosage by 200mg Every week until the best response is achieved or maximum dose of 1600mg daily.
  - Side effects:
    - Aplastic anemia
    - Dizziness, drowsiness
    - Skin rash
    - Transient diplopia
- Valproic acid: can be used for all types of epilepsy
  - Dose: 600mg PO OD/BD then increased in steps of 150-300g every 3 days, maintenance 1-2g daily.
  - Side effects:
    - Menstrual disturbance
    - Extrapyramidal disorders
    - Aggression
    - Anemia
    - Confusion, confusion, nystagmus
    - Transient hair loss (regrowth may be curly)
    - Weight again
- Lamotrigin
  - Dose 25mg PO OD daily for 14 days, then increase to 50mg OD daily for further 14 days then increased in steps of up to 100mg every 7-14 days. Maintenance 100-200mg daily in 1-2 divided doses, increased necessary up to 500mg daily, dose titration should be repeated if restarting after internal of more than 5 days
  - Side effects:
    - Blurred vision, nystagmus, diplopia
    - Anemia
    - Exacerbation of Parkinson's disease
    - Rash
    - Tremor
- Phenytoin
  - Dose 100mg BD or TDS which may be gradually increased to a maximum of 200mg PO TDS (i.e. 600mg daily)
  - Side effects:
    - CNS: nystagmus

- Gingival hyperplasia
- Coarsening of facial features
- Toxic hepatitis and liver damage

STATUS EPILEPTICUS

- This is a seizure lasting more than 5 minutes (used to be 30-35 minutes) or 2 or more seizures without recovery of consciousness between them over a similar period. It is a medical emergency.
- Any seizure lasting more than 5 minutes is unlikely to remit spontaneously and carries the risk of permanent neuronal injury.
- It usually occurs in known epileptics but can be a presenting complaint.
- The longer the duration of status, the greater the risk of permanent cerebral damage.
- Rhabdomyolysis may lead to acute kidney injury in convulsive status epilepticus.
- Not all status is convulsive. In absence status, for example status is non-convulsive- the patient is in a continuous, distant, stuporose state. Focal status also occurs.
- Epilepsia partialis continua is continuous seizure activity in one part of the body such as finger or a limb without loss of consciousness. This is often due to cortical neoplasm or in the elderly a cortical infarct.
- Status epilepticus can be precipitated or caused by:
  - Non-compliance with antiepileptic drugs
  - CNS infections: encephalitis
  - Metabolic derangement: electrolyte imbalance, altered glucose
  - Alcohol
  - Withdrawal
  - Tumors
  - Trauma
  - Stroke
  - Refractory epilepsy

CLINICAL FEATURES

- Generalized status epilepticus is obvious when the patient is having convulsions, however after 30-35 minutes of uninterrupted seizure, the signs may become increasingly subtle.
- Seizures are often tonic-clonic with fever and sweats.

- Patients may have mild clonic movement of only fingers or fine, rapid movements of the eyes.
- Can also be non-convulsive, characterized by confusion, altered mental status, odd behavior and derealization.

COMPLICATIONS OF STATUS EPILEPTICUS

- Aspiration
- Hypoxia (death may result from cerebral hypoxia)
- Metabolic acidosis
- Hypotension
- Hyperthermia
- Rhabdomyolysis and associated myoglobinuria (acute kidney injury)
- Multiple physical injuries including vertebral bone fracture
- Irreversible neuronal injury

TREATMENT

- ABCs
  - Keep airway patent and maintain breathing
  - Administer oxygen, monitor ECG, BP
  - Secure IV line and take blood for Labs: Draw labs for metabolic abnormalities e.g. glucose, electrolytes (sodium, potassium, chloride, bicarbonate, calcium), drug screen, anticonvulsant levels
- Pharmacologic:
  - Administer thiamine (vitamin B1) and glucose
    - Thiamine: 25-100mg PO OD for mild deficiency or 200-300mg PO daily in divided doses. (Intravenous administration should be by infusion over 30 minutes)
    - Glucose: 10-25g (20-50ml 50% solution or 40-100ml of 25% IV)
  - Benzodiazepines are first line anticonvulsants for status epilepticus (Early status- up to 30 mins).
    - Give lorazepam IV 4mg slow bolus (3 seconds). Repeat once after 10 min if necessary (beware of respiratory arrest) or
    - Give Diazepam IV 5-10mg IV. Repeat once after 10 min if necessary
  - If seizure continues (Established Status 30-90mins):
    - Give phenytoin: 15-20 mg/kg IV diluted to 10mg/ml in saline into a large vein at 50mg/min (ECG monitoring required) or

- Fosphenytoin: this is a pro-drug of phenytoin and can be given faster than phenytoin. Doses are expressed in phenytoin equivalents (PE): Fosphenytoin 1.5mg=1mg phenytoin. Give 15mg/kg (PE) fosphenytoin (15mg x 1.5=21.5 mg) diluted to 10mg/ml in saline at 50-100mg (PE)/min

- If seizure persists, the next step is to give a second loading dose of phenytoin or fosphenytoin using an additional 5-10mg/kg IV load or move directly to the next step.
- If seizure continues, the next step is to administer phenobarbital, or valproate
  - Phenobarbital 10mg/kg IV diluted 1 in 10 in water for injection at <100 mg/min or
  - Valproate IV 25mg/kg
- If patient is still seizing, then general anesthesia is needed (Refractory status-over 90mins)
  - Only in intensive care setting, intubation and ventilation usually required
  - Profofol bolus 2mg/kg, repeat followed by continuous infusion of 5-10mg/kg/hr
  - Thiopentone and midazolam infusions may also be used
  - Continuous EEG monitoring used to assess efficacy of treatment- aim for EEG burst suppression pattern
  - Reinstate previous anti-epileptic medication via NG tube
  - Establish diagnosis: CT or MRI may reveal an underlying cause
  - Remember: 25% of apparent status turns out to be pseudostatus.

INFECTIONS OF THE CNS

MENINGITIS

- This is inflammation of the leptomeninges (the pia and arachnoid matter).

CLASSIFICATION

- Based on etiology:
  - Infectious
    - Bacterial meningitis: *Neisseria meningitidis*, *Streptococcus pneumoniae (accounts for 70% of acute bacterial meningitis outside the neonatal period)*, *Staphylococcus aureus*, Group B *Streptococcus*, *Listeria monocytogenes*, Gram-negative bacilli e.g. *E. coli*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Hemopilus influenza B (Hib)*-although cases are now rare due to immunization, and *Pseudomonas aeruginosa*.
    - Viral meningitis (Aseptic meningitis): Enteroviruses (ECHO, Coxsackie), Arboviruses, Polio virus (mainly eradicated worldwide), Mumps virus, herpes simplex, Human immunodeficiency virus (HIV), Epstein-Barr virus, Cytomegalovirus (CMV), measles, varicella zoster virus (VZV), Adenovirus, Influenza A, parainfluenza, rabies and rubella virus.
    - Fungal meningitis: *Cryptococcus neoformans*, *Candida albican*, *Coccidiodes immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*.
    - Parasitic: Plasmodium (malaria)
  - Non-infectious: malignant meningitis, intrathecal drugs and blood following subarachnoid hemorrhage.
- Based on onset:
  - Acute meningitis: usually caused by typical bacterial causes of meningitis. It has a sudden onset.
  - Chronic meningitis: it is usually caused atypical bacterial causes of meningitis e.g. TB, Secondary syphilis and fungi e.g. *Cryptococcus*, *Coccidiodes*, *Histoplasma*, *Blastomyces*. It may also be caused by non-infectious causes such as CNS or metastatic neoplasms, leukemia, lymphoma, vasculitis, sarcoid and subarachnoid/subdural bleeds. Symptoms last from weeks to months with persistent CSF pleocytosis- WBCs in CSF (usually lymphocytic).

BACTERIA MENINGITIS

- Bacterial meningitis is the most common form of suppurative CNS infection.
- Bacterial meningitis is fatal unless treated.
- Micro-organisms reach the meninges either by:
  - Droplet infection through the upper airways: e.g. *Neisseria meningitidis*
  - Direct extension from ears (otitis media), nasopharynx (sinusitis), cranial injury or congenital meningeal defect.
  - By bloodstream spread (hematogenous spread).
- Immunocompromised patients are at risk of infection by unusual organisms.
- In acute bacterial meningitis the pia-arachnoid is congested with polymorphs. A layer of pus forms. This may organize to form adhesions causing cranial nerve palsies and hydrocephalus.
- In chronic infection (e.g. TB) the brain is covered in a viscous grey-green exudate with numerous meningeal tubercles. Adhesions are invariable.
- Cerebral edema occurs in any bacterial meningitis.

ETIOLOGICAL AGENTS

- The causes of bacterial meningitis vary with age:
  - Infants (<1 year): *E. coli, Group B streptococcus, Listeria monocytogenes* are the commonest causative agents.
  - Young children/toddler (age 1-6 years): *Haemophilus influenza, Meningococcus* account for more than 50% of cases.
  - Adolescents and Adults: *Meningococcus*, *Pneumococcus* are the commonest etiologies
  - Immunocompromised and cancer patients: *Listeria, Staphylococcus, Pseudomonas aeruginosa* etc.

CLINICAL FEATURES

- Incubation period for meningococcal meningitis may range from 1-10 days however most clinical manifestation occurs within 2-4 days.
- It may manifest as an acute fulminant illness that progresses rapidly in few hours or as a subacute infection that progressively worsens over several days.

- Meningitis triad: Seen in over 90% of patients.
  - Neck stiffness (pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion)
  - Headache
  - Fever
- Alteration in mental state occurs in over 75% of patients and can vary from drowsiness, lethargy to coma (loss of consciousness).
- Photophobia (avoiding light), Nausea and vomiting (projectile) are common symptoms.
- Seizures can occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20-40% of patients.
- In acute bacterial infection there is usually intense malaise, fever, rigors, severe headache, photophobia and vomiting developing within hours or minutes.
- In meningococcal meningitis of sudden onset with severe course, patients develop diffuse erythematous maculopapular rash which rapidly becomes petechial, purpural or bullous lesions.
  - The petechiae are found on the trunk, lower extremities, in the mucous membrane and the conjunctiva and occasionally on the palms and soles.
  - Meningococcemia may be associated with vascular collapse (Waterhouse-Friderichsen syndrome)
- Meningeal signs:
  - Neck stiffness: when head is flexed passively
  - Kerning's sign: elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed, attempts to passively extend the knee elicit pain when meningeal irritation is present. (with hip and knee flexed, pain limits passive extension of the knee).
  - Brudzinski's sign: upon passively flexing the head, one notices flexion of both legs at the knees.
  - Cranial nerve abnormalities may occur (facial nerve palsy, oculomotor nerve palsy and occasional deafness).
- **Note: the classic meningeal signs may not be seen in infants, older people and patients in coma.** The sensitivity of the Kernig's and Brudzinski's sign are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

- Clinical clues:
  - Petechial rash- Meningococcal infection
  - Skull fracture, ear disease, congenital CNS lesion- pneumococcal infection
  - Immunocompromised patients- HIV opportunistic infection
  - Rash or pleuritic pain- Enterovirus infection
  - Recent travel- malaria
  - Occupational (work in drains, canals, polluted water, recreational swimming): leptospirosis. **Features: myalgia, conjunctivitis, jaundice**

DIAGNOSIS AND INVESTIGATIONS

- Principle of diagnosis:
  - History and Physical examination
  - Investigate possible source of infection (pneumonia, otitis media, sinusitis, head injury)
  - CSF analysis and identification of the organism from CSF and blood (culture, PCR etc.)
- Investigations:
  - Lumbar puncture and CSF analysis is done if there are no clinical suspicion of a mass lesion. If the is a suspected mass lesion an immediate CT scan must be performed because coning of the cerebellar tonsils may follow LP.
    - CSF Microscopy, Culture and Sensitivity: Stains used include Gram Stain (For Gram-positive intracellular diploccoci- pneumococcus, Gram-negative cocci-meningococcus), Ziehl-Neelsen stain (AFB stain for TB), India ink (for fungi)
    - CSF biochemistry
    - CSF PCR
  - Full blood count (with differential count), Serum glucose and Blood cultures
  - RPR for Syphilis and RDT for malaria
  - Chest and skull X-ray when appropriate.
  - CT scan/MRI (rule of space occupying lesion)

Feature	Normal	Bacterial meningitis	Viral meningitis	Tuberculous meningitis
Pressure	50-250mm of water	Normal/increased	Normal	Normal/increased
Appearance	Crystal clear	Turbid	Clear	Cob-web appearance
Cell count/ microliter	<10 RBCs <5 WBCs	Several thousands (1000-5000 polymorphs)	Several hundreds (10-2000 lymphocytes)	Several hundreds (50-5000 lymphocytes)
Cell type	None	Granulocytes (Polymorphs)	Lymphocytes	Lymphocytes and monocytes
Glucose	2/3 to ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose	Normal > ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose
Protein	0.2-0.4 g/l	Increased (>120mg/dl) 0.5-2.0g/l	Normal (0.4-0.8g/L)	Increased (>120 mg/dl) 0.5-3.0g/l
Lactate dehydrogenase		>3.5mmol/L	<3.5 mmol/L	>3.5mmol/L

DIFFERENTIAL DIAGNOSIS

- It may be difficult to distinguish between the sudden headache of subarachnoid hemorrhage, migraine and acute meningitis.
- Meningitis should be considered seriously in anyone with headache and fever and in any sudden headache.
- Neck stiffness should be looked for- it may not be obvious.
- Chronic meningitis sometimes resembles an intracranial mass lesion with headache, epilepsy and focal signs.
- Cerebral malaria can mimic bacterial meningitis.

MANAGEMENT

EMPIRICAL ANTIBIOTIC THERAPY

- Antibiotics should be initiated immediately before the result of the CSF gram stain and culture are known as bacterial meningitis is a medical emergency.
- Antibiotics should be given intravenously at higher doses:
  - In adults without underlying disease: Ceftriaxone 2 g IV BID plus Ampicillin 2g IV QID for 2 weeks.
    - Crystalline Penicillin 3-4 million IU, IV every 4 hours plus Chloramphenicol 1g IV QID (50-100mg/kg 6 hourly) are alternative antibiotics.
    - Ampicilin 100-200mg/kg IV QID (6 hourly)
  - Patient with ENT infection or head injury: Ceftriaxone 2g IV BID and Vancomycin 1g IV BID + treatment of the underlying cause.
  - Hospital acquired infection: Ceftriaxone 2g IV BID plus Vancomycin 1g IV BID plus Gentamycin (80mg TDS)
  - Immunodeficient patients: Ceftriaxone 2g IV BID plus Vancomycin 1g IV BID plus Ampicillin (2g IV QID)
- Intravenous antibiotics should be put in place for the first 72 hours or for as long as the patient is unconscious and then changed to the oral form. Treatment should generally be continued for at least 1 week after the fever subsides and the CSF returns towards normal.

SPECIFIC ANTIBIOTIC THERAPY

- *N. meningitidis*: Even though Ceftriaxone or Cefotaxim provide adequate empirical coverage, Penicillin G remains the drug of choice (Crystalline Penicillin 3-4 million IU, IV every 4 hours for 7-10 days)
- *Pneumococcal meningitis*: antibiotic therapy initiated with cephalosporins plus vancomycin (Ceftriaxone 2g IV BID and Vancomycin 1g IV BID for 2 weeks)
- *H. Influenza*: Ceftriaxone 2g IV BID for 1-14 days may be enough. Chloramphenicol 1gm IV QID may be an alternative antibiotic for patients who may not afford ceftriaxone.
- *TB*: antituberculous drugs- Rifampicin, Isoniazid and pyrazinamide- for at least 9 months. Ethambutol should be avoided because of its eye complications. Adjuvant corticosteroids e.g. prednisolone 60mg for 3 weeks are now recommended (often tapered off)

Organism	Antibiotic	Alternative (e.g. allergy)
Unknown pyogenic	Cefotaxime	Benzylpenicillin and chloramphenicol
Meningococcus	Benzylpenicillin	Cefotaxime
Pneumococcus	Cefotaxime	Penicillin
Haemophilus	Cefotaxime	Chloramphenicol

Age Group	Common Microorganisms	Empiric Antibiotics—First Choice[a,b]	Severe Penicillin Allergy
Adults 18–50 years of age	*S. pneumoniae, N. meningitidis.*	Ceftriaxone/cefotaxime +/– vancomycin.[c]	Chloramphenicol + vancomycin.[c]
Adults > 50 years of age	*S. pneumoniae, Listeria monocytogenes,* gram-⊖ bacilli.	Ceftriaxone/cefotaxime + ampicillin +/– vancomycin.[c]	Chloramphenicol (*N. meningitidis*) + TMP-SMX (*Listeria*) + vancomycin.[c]
Impaired cellular immunity (or alcohol abuse)	*S. pneumoniae, L. monocytogenes,* gram-⊖ bacilli (*Pseudomonas*).	Ceftazidime + ampicillin +/– vancomycin.[c]	TMP-SMX + vancomycin.[c]
Post-neurosurgery or post–head trauma	*S. pneumoniae, S. aureus,* gram-⊖ bacilli (including *Pseudomonas*).	Ceftazidime + vancomycin (for possible MRSA).	Aztreonam or ciprofloxacin + vancomycin.

[a] May add steroids (dexamethasone 10 mg q 6 h × 2–4 days) for patients who present with acute community-acquired meningitis that is likely to have been caused by *S. pneumoniae.*

[b] Doses for meningitis are higher than those for other indications: ceftriaxone 2 g IV q 12 h, cefotaxime 2 g IV q 4 h, vancomycin 1 g IV q 12 h or 500–750 mg IV q 6 h, ampicillin 2 g IV q 4 h, or ceftazidime 2 g IV q 8 h.

[c] In areas where penicillin-resistant pneumococcus is prevalent, vancomycin should be included in the regimen.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 1251.

GENERAL MEASURES AND ADJUNCT THERAPY

- Resuscitate and give O_2.
- Regulate water and electrolyte balance.
- Treat increased intracranial pressure:
  - Elevation of the patients' head to 30-45º
  - Intubation and hyperventilation (till $PaCO_2$ is lowered to 25-30mmHg)
  - Mannitol IV infusion: 20% mannitol IV 5ml/kg over 300 minutes and a corticosteroid 4 hourly (e.g. prednisolone 1mg/kg, dexamethasone 0.15mg/kg or hydrocortisone 4mg/kg).
- Steroids:
  - Dexamethasone: when imitated before antibiotic therapy reduces the number of unfavorable outcomes e.g. death and neurologic complications. It is

advantageous in children predominantly with meningitis due to *H. influenza* and *Pneumoniae*.

  - Dose: 10mg IV 15-20 minutes before the first dose of antibiotics and 4 mg IV QID for 4 days.

- Patients with meningococcal meningitis should be isolated.
- Thromboembolism prophylaxis.

COMPLICATIONS

- Brain edema
- Hydrocephalus
- Brain abscess
- Septic vein thrombosis
- Hearing impairment
- Fulminant meningococcal sepsis: Waterhouse-Friedrichsen syndrome, a clinical condition resulting from hemorrhagic necrosis of the adrenal gland, with multi-organ failure. Patients are hypotensive or in shock. DIC with skin and mucosal purpura and bleedings are commonly associated features.

CHEMOPROPHYLAXIS

- In case of *N. meningitides*, all close contacts to the patient should be given chemoprophylaxis with:
  - Rifampicin 600mg PO BID for 2 days in adults and 10mg/kg PO BID for children >1 year
  - Ciprofloxacin 750mg PO stat can be given as an alternative for adults.
- MenC, a meningococcal C conjungated vaccine is part of many countries' immunization programme and often given to case contacts.
- A combined A and C meningococcal vaccine can be given to people in endemic regions e.g. Africa and Asia. A quadrivalent ACWY vaccine for specific events e.g. the Hajj and Umrah in mecca can be given.
  - Note: there is no vaccine for Group B.
- A polyvalent pneumococcal vaccine as well as HiB (*Haemophilus influenzae*) vaccine is given routinely in childhood.

VIRAL MENINGITIS

- Viral meningitis is almost always benign, self-limiting condition lasting 4-10 days.
- Headache may follow for some months. There are no serious sequelae unless an encephalitis is present.
- In viral meningitis there is a predominantly lymphocytic inflammatory CSF reaction without pus formation, Polymorphs or adhesions. There is little or no cerebral edema unless encephalitis develops.

ETIOLOGY

- It is commonly caused by:
  - Enteroviruses: Coxsackie, echovirus
  - Herpes simplex, HSV (type 2 more commonly causes meningitis than HSV 1)
  - Mumps
  - Measles
  - Poliomyelitis
  - HIV
  - Epstein-Barr virus (EBV)

CLINICAL FEATURES

- Meningitis triad: headache, neck stiffness and fever. Photophobia and vomiting are often present.
- In viral meningitis there are less prominent meningitic signs.
- It is benign, self-limiting lasting 4-10 days.
- Headache may follow for some months.

DIAGNOSIS AND INVESTIGATIONS

- Principle of diagnosis:
  - History and Physical examination
  - Investigate possible source of infection (pneumonia, otitis media, sinusitis, head injury)
  - CSF analysis and identification of the organism from CSF and blood (culture, PCR etc.)

- Investigations:
  - Lumbar puncture and CSF analysis is done if there are no clinical suspicion of a mass lesion. If the is a suspected mass lesion an immediate CT scan must be performed because coning of the cerebellar tonsils may follow LP.
    - CSF Microscopy, Culture and Sensitivity: Stains used include Gram Stain (For Gram-positive intracellular diploccoci- pneumococcus, Gram-negative cocci-meningococcus), Ziehl-Neelsen stain (AFB stain for TB), India ink (for fungi)
    - CSF biochemistry
    - CSF PCR
  - Full blood count (with differential count), Serum glucose and Blood cultures
  - RPR for Syphilis and RDT for malaria
  - Chest and skull X-ray when appropriate
  - CT scan and MRI to rule of space occupying lesion

Feature	Normal	Bacterial meningitis	Viral meningitis	Tuberculous meningitis
Pressure	50-250mm of water	Normal/increased	Normal	Normal/increased
Appearance	Crystal clear	Turbid	Clear	Cob-web appearance
Cell count/ microliter	<10 RBCs <5 WBCs	Several thousands (1000-5000 polymorphs)	Several hundreds (10-2000 lymphocytes)	Several hundreds (50-5000 lymphocytes)
Cell type	None	Granulocytes (Polymorphs)	Lymphocytes	Lymphocytes and monocytes
Glucose	2/3 to ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose	Normal > ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose
Protein	0.2-0.4 g/l	Increased (>120mg/dl) 0.5-2.0g/l	Normal (0.4-0.8g/L)	Increased (>120 mg/dl) 0.5-3.0g/l
Lactate dehydrogenase		>3.5mmol/L	<3.5 mmol/L	>3.5mmol/L

MANAGEMENT

- Self-limiting.
- Supportive therapy:
  - Check viral signs, restrict fluid and give antipyretics
  - Treat seizures and/or give prophylactic therapy
- Antiviral therapy can be given:
  - IV acyclovir (10mg/kg TDS for 14-21 days)
  - Gancyclovir (5 mg/kg BID) or Foscarnet (60mg/kg TDS) are especially recommended for CMV infections.

CHRONIC MENINGITIS

- *Tuberculous meningitis* (TBM) and *cryptococcal meningitis* commence typically with vague headache, lassitude, anorexia and vomiting.
  - Out of 39 known Cryptococcal species only 2 cause disease *C. neoformans neoformans* and *C. neoformans gatti*
  - Cryptococcus can also cause pulmonary, cutaneous and disseminated forms of illness.
  - The neoformans variant dominates in AIDS patients. It can be isolated from the environment although it is most often found in pigeon excreta. Growth from soil appears to be enhanced by certain nitrogenous compounds like creatinine in pigeon droppings
  - Birds are not infected although their crop is heavily infested
- Acute meningitis can occur but is unusual.
- Meningitic signs often take some weeks to develop.
- Drowsiness, focal signs (e.g. diploplia, papilloedema, hemiparesis) and seizures are common.
- Syphilis, sarcoidosis and Behçet's (a rare disorder causing inflammation of blood vessels) also cause chronic meningitis.
- In some cases, the organism is never identified.

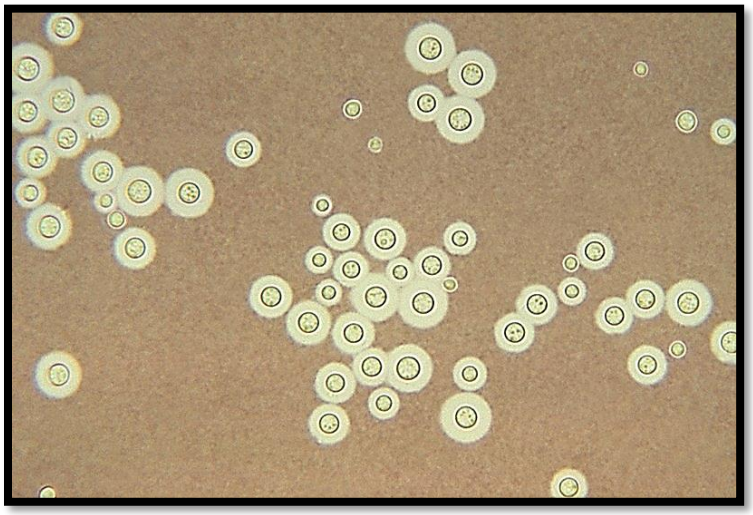


Figure 52: Cryptococcus neoformans (India Ink)

- Investigations are the same as those of Bacterial meningitis.
  - Prompt Lumbar puncture with measurement of CSF opening pressure (which is usually high in Cryptococcal meningitis) and rapid CSF cryptococcal antigen (CSF CrAg) assay or rapid serum Cryptococcal antigen is the preferred diagnostic approach for C. meningitis.
    - Note: Serum CAT (Cryptococcal antigen test) remains positive for months after therapy even when CSF smears are negative.
  - Fungal culture remains the gold standard for confirmation of the diagnosis of initial Cryptococcal disease, confirmation of relapses or cases refractory to treatment and adequate response to treatment.
  - Brain imaging, usually with MRI, may show meningeal enhancement, hydrocephalus and tuberculomas although it may remain normal.
- Treatment:
  - TB: Rifampicin, Isoniazide and Pyrazinamide for 12 months.

MANAGEMENT OF CRYPTOCOCCAL MENINGITIS

- Management is divided into 3 phases:
  - Induction: this is for 14 days (at least 10 days)
    - The drug of choice is amphotericin B combined with fluconazole or flucytosine.
    - Flucytosine has been associated with increased risk of bone marrow toxicity and clinical research showed no increased benefit when compared to amphotericin B and fluconazole.
    - In settings where amphotericin B is not available, regimens containing fluconazole combined with flucytosine or high dose fluconazole monotherapy are alternatives.
    - Amphotericin B 0.7mg/kg slow infusion over 4 hours + Fluconazole 800mg PO daily, to be given over 10-14 days or
    - Amphotericin B 0.7mg/kg slow infusion over 4 hours + Flucytosine 100mg/kg/day every 6 hours
    - Amphotericin B daily dosage should not exceed 1mg/kg for adults or children.

- Note: fluconazole is also effective for Cryptococcus infection, but should not be used as monotherapy particularly in the initial period of treatment.

➢ Consolidation: This is for 8-10 weeks
- Oral fluconazole is the recommended option.
- Oral fluconazole 400-800mg/day for at least 8-10 weeks.

➢ Maintenance (Secondary prophylaxis): variable
- Oral fluconazole is the recommended option
- Long-term maintenance for HIV positive individuals: Oral fluconazole 200mg/day until CD4 count >200 for at least 6 months. It may be reasonable to stop prophylaxis if the CD4 count increase to more than 100-200 for more than 6 months in response to antiretroviral.
- Repeat LP until symptoms resolve in patients with coma or other signs of elevated ICP.

Types of Amphotericin B

1. Amphotericin B Lipid complex (ABLC)
2. Liposomal Amphotericin B (L-AB)
3. Amphotericin B colloidal dispersion (ABCD)

Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/management	Induction phase (2 weeks) Options	Consolidation phase (8 weeks) Options	Maintenance/secondary prophylaxis
Amphotericin B ± flucytosine	Available	a. Amphotericin 0.7-1 mg/kg/day + Flucytosine 100mg/kg/day b. Amphotericin 0.7 mg/kg/day + fluconazole 800mg/day	Fluconazole 400-800mg/day	Fluconazole 200mg daily
Amphotericin B	Not available for full 2 weeks induction period	Amphotericin 0.7-1mg/kg/day short course (5-7 days) + fluconazole 800mg/day (2 weeks)	Fluconazole 800mg/day	
Amphotericin B not available	Not available	a. Amphotericin 1200 mg/day ± Flucytosine 100mg/kg/day b. Fluconazole 1200mg/day alone	Fluconazole 800mg/day	

- In HIV patients initiation of ART should be delayed due to high risk of IRIS. It should be delayed until there is evidence of a sustained clinical response to anti-fungal therapy and
  - After 2-4 weeks of induction and consolidation treatment with amphotericin B containing regimens combined with flucytosine or fluconazole or
  - After 4-6 weeks of induction and consolidation treatment with high dose oral fluconazole regimen.

Side effects of Amphotericin B:

- Arrhythmias
- Renal dysfunction
- Hypokalemia
- Hypomagnesemia
- Abnormal liver disorder
- Thrombocytopenia and anemia

- Pre-requisites to treatment
  - Always check LFTs, U&Es, Creatinine and FBC before starting patient on antifungals.
    - Serum potassium and creatinine should be checked twice weekly, especially in the second week of amphotericin B administration
    - Hemoglobin should be checked weekly
  - Careful attention to fluid monitoring of intake and output and daily weight
  - Pre-emptive hydration and electrolyte supplementation
    - 1 liter of normal saline solution with 1 ampoule (20 mmol) of KCL over 2-4 hours before each controlled infusion of amphotericin B (with 1 L of 5% dextrose) and one to two 8mEq KCL tablets orally twice daily.
    - An additional one 8 mEq KCL tablet twice daily may be added during the second week.
    - If available magnesium supplementation should be provided (two 250mg tables of magnesium trisillicate BD)
    - Potassium replacement should not be given in patients with pre-existing renal impairment or hyperkalemia.
    - If saline is unavailable then other intravenous rehydration solutions that contain potassium can be used e.g. Darrow's or Ringer's lactate solutions.
    - A test dose of amphotericin B is not recommended.
  - Also given an antiemetic (Promethazine) and steroid (hydrocortisone) as premedication
  - Management
    - If significant hypokalemia (Potassium <3.3 mmol/L) increase potassium supplementation to 2 KCL ampoules (40mmol) or one or two 8mEq KCL tables TDS. Monitor potassium daily.
    - If hypokalemia remains uncorrected, double magnesium oral supplementation.
    - If creatinine increased by more than 2 fold from baseline value either temporary omission of an amphotericin B dose or increase pre-hyrdration to 1 L 8 hourly. Once improved, restart at 0.7mg/kg/day and consider alternate day amphotericin B.
    - If creatinine remains elevated discontinue amphotericin B and continue with fluconazole at 1200mg/day. Monitor creatinine daily.

MALIGNANT MENINGITIS

- Malignant cells can cause subacute or chronic non-infective meningitis process.
- A meningitic syndrome, cranial nerve lesions, paraparesis and root lesions are seen often in confusing and fluctuating patterns.
- The CSF cell count is raised, with high protein and low glucose.
- Treatment with intrathecal cytotoxic agents is rarely helpful.

ENCEPHALITIS

- This is acute inflammation of brain parenchyma; it is usually viral.
- In viral encephalitis fever (90%) and meningism are usual but in contrast to meningitis the clinical picture is dominated by brain parenchyma inflammation.
- Personality and behavioral change is a common early manifestation which progresses to a reduced level of consciousness and even coma.
- Seizure (focal and generalized) are very common and focal neurological deficits e.g. speech disturbance often occurs (especially in herpes simplex encephalitis).

VIRAL ENCEPHALITIS

- This is inflammation of the brain parenchyma, with or without involvement of the meninges, caused by virus.
- The spinal cord and/or nerve roots may also be rarely involved.

ETIOLOGY

- Common: Arboviruses, Enteroviruses, HSV-1, Mumps
- Less common: CMV, EBV, HIV, Measles, VZV, Human Herpes viruses 6 and 7
- Rare: Adenoviruses, Influenza A, Parainfluenza, Rabies, Rubella, Flaviviruses (Japanese encephalitis, West Nile virus, Tick-borne encephalitis)

CLINICAL FEATURES

- Acute febrile illness with evidence of meningeal involvement (meningeal signs)
- Altered level of consciousness (ranging from lethargy to coma)
- Abnormal mental state (hallucinations, agitation, personality change, behavioral disorder, psychosis)
- Evidence of either focal or diffuse neurologic signs or symptoms.
- Focal or generalized seizures occur in more than 50% of cases.
- Most common focal findings are aphasia, ataxia, hemiparesis (with hyperactive tendon reflexes), involuntary movements and cranial nerve deficits.

INVESTIGATIONS

- CSF examination:
  - Check for increased intracranial pressure first
  - Characteristic profile is undistinguishable from viral meningitis and consists of lymphocytic pleocytosis (95%), elevated protein, normal glucose level.
- CSF culture, usually negative (especially in HSV 1 infections)
- Viral detection by CSF PCR (if available) is highly sensitive for several viruses such as HSV and VZV. However, a false negative result may occur within the first 48hours after symptom onset.
- Serology (blood and CSF) is also helpful.
- MRI shows areas of inflammation and swelling generally in the temporal lobes in HSV encephalitis. Raised intracranial pressure and midline shift may occur leading to coning.
  - MRI, CT and EEG are done to exclude alternative diagnoses and assist in differentiation between focal and diffuse encephalitic processes.
- EEG shows periodic sharp and slow wave complexes.
- Brain biopsy is rarely required since the advent of MRI and PCR.

TREATMENT

- Supportive therapy (usually in ICU)
  - Check vital signs, restrict fluid, and give antipyretics.
  - Treat seizures and/or give prophylactic therapy (high risk for seizures).
- Medication:
  - Suspected HSV and VZV encephalitis is treated immediately with IV acyclovir (10mg/kg TDS for 14-21 days) even before investigation results.
  - Gangicyclovir (5mg/kg BID) or Foscarnet (60mg/kg TDS) are especially recommended for CMV infections.
- Early treatment significantly reduces both mortality and long term neurological damage in survivors.
- Seizures are treated with anticonvulsants.
- Occasionally decompressive craniectomy is required to prevent coning but coma confers a poor prognosis.
- Long term complications:
  - Memory impairment
  - Personality change
  - Epilepsy

POST-INFECTIOUS ENCEPHALOMYELITIS

- Acute disseminated encephalomyelitis (ADEM) follows many infections (e.g. measles, mycoplasma, mumps and rubella) and rarely follows immunization after 1-2 weeks.
- There is a monophasic illness with multifocal brain, brainstem and often spinal cord inflammatory lesions in white matter with demyelination.
- ADEM is caused by an immune mediated host response to infection and occurs principally in children and young adults.
- Mild cases recover completely. Survivors often have permanent brain damage.
- Treatment is supportive with steroids and anticonvulsants.

AUTOIMMUNE ENCEPHALITIS

- Autoantibodies directed against neuronal epitopes cause a subacute encephalitis illness- limbic encephalitis or panecephalitis.
  - Limbic encephalitis presents over weeks or months with memory impairment, confusion, psychiatric disturbance and seizures (usually temporal lobe seizures reflecting involvement of the hippocampus and mesial temporal lobes)
- Paraneoplastic limbic encephalitis (PLE):
  - Seen particularly with small cell lung cancer and testicular tumors associated with a variety of antibodies including anti-Hu and anti-Ma2.
  - Antibodies can be detected in 60% of cases.
  - MRI usually shows a hippocampal high signal.
  - PLE precedes the diagnosis of cancer in most cases and should prompt investigation to identify the tumor.
- Voltage gated potassium channel (VGKC) limbic encephalitis:
  - VGKC antibodies (which can be tested for) produce a variety of disorders including limbic encephalitis, characteristic faciobrachial dystonic seizures, neuromyotonia and peripheral nerve hyperexcitability syndromes.
  - This usually occurs in patients older than 50 but is rarely associated with cancer (thymoma)
- AntiNMDA receptor antibody panecephalitis:
  - Presents as limbic encephalitis followed by coma and often status epilepticus.
  - Orofacial dyskinesias are characteristic.
  - Usually younger patients, some have ovarian teratomas.

- **Patients may respond to immunotherapy-IV immunoglobulin or plasma exchange initially followed by steroids, rituximab or cyclophosphamide. PLE responds less well to treatment.**

CEREBROVASCULAR DISEASE

- This is defined as a syndrome of an abrupt onset of non-convulsive, focal neurologic deficit resulting from sudden interruption of the blood supply to parts of the brain lasting 24 hours or longer.
- Avoid using the vague term 'cerebrovascular accident' as it is vague can mean one of many presentations.

CLASSIFICATION

- Can be classified according to:
  - Duration
  - Etiology

CLASSIFICATION BASED ON DURATION

- This includes:
  - Transient ischemic attack (TIA): focal neurologic deficit lasting less than 24 hours confined to an area of the brain perfused by specific artery. Neurologic deficit resolves in less than 24 hours. In a majority of cases they resolve within an hour.
  - Reversible ischemic neurologic deficit (RIND): sudden onset focal neurologic deficit which lasts for more than 24 hours but the neurologic deficit recovers/resolves.
  - Stroke in evolution: a focal neurologic deficit, the degree of which is progressing over a couple of hours or days.
  - Complete stroke: sudden onset of focal neurologic deficit, in which the deficit neither improves nor gets worse over time. It is often associated with infarction of part of the brain. It can either be ischemic or hemorrhagic.

C LASSIFICATION ACCORDING TO ETIOLOGY

- There are 2 main types:
  - Ischemic stroke (80-90% in developed countries): due to
    - Embolic
    - Thrombotic
  - Hemorrhagic stroke (10-20% in developed countries but is higher in developing countries): associated with unrecognized or poorly controlled hypertension. Includes:
    - Primary intracranial hemorrhage (PICH): intraparenchymal or intraventricular

- Subarachnoid hemorrhage (SAH)

- The nature of the focal neurologic deficit caused by strokes depends on the vascular territory involved and the region of the brain supplied.

EPIDEMIOLOGY AND RISK FACTORS

- In developed countries stroke is the third most common cause of death (behind coronary heart disease and cancer) and the leading cause of adult disability worldwide.
- Stroke rates are higher in Asian and Black African populations than in Caucasians.
- Stroke risk increases with age but ¼ of all strokes occur before the age of 65.
- The death rate following stroke is 20-25%.
- Risk factors:
  - Non-modifiable:
    - Increasing age
    - Male gender
    - Race: Blacks and Asians
  - Modifiable:
    - Cardiovascular: Hypertension, Congestive heart failure, Myocardial infarction, Atrial fibrillation, Hyperlipidemia, rheumatic heart disease, sick cell anemia
    - Coagulation abnormalities:
      - Thrombophilia-Ischemic,
      - Coagulopathy (warfarin, liver disease)-Hemorrhagic
    - Endocrine: Diabetes
    - HIV
    - Lifestyle: Smoking, Acute alcohol abuse
    - Combined contraceptive pill
    - Inflammatory and congenital: vasculitis (SLE, Takayasu Arteritis), Homocystinuria, amyloid angiopathy, mitochondrial disease, syphilis
- Stroke should be considered as a medical emergency, as it affects vital functions of an individual.

DIFFERENTIAL DIAGNOSIS

- Space occupying lesion (neoplasm or infectious-sepsis, encephalitis)
- Trauma (subdural or epidural hematoma)
- Toxins (including medications)
- Hypo/hyperglycemia
- Electrolyte abnormalities (e.g. hypo/hypernatremia)
- Migraine
- Seizures especially Todd's palsy
- Syncope
- Old strokes with intercurrent illnesses

ISCHEMIC STROKE

- This is the more common type of stroke (80-90%). It is caused by occlusion of arterial blood flow to the brain.
- It usually occurs in elderly patients except in cases of sickle cell anemia or rheumatic heart disease.
- Mortality rate is low in the first week (10-20%) however, many patients die of complications in the first 1-2 months.
- Complications include: aspiration pneumonia, septic decubitus ulcers and DVT.

ETIOLOGIES

- Embolic:
  - Occurs when an extracranial thrombus dislodges and embolizes to and occludes one of the large intracranial arteries.
  - Emboli most common arise from atherosclerotic plaques, atrial fibrillation, rheumatic heart disease or endocarditis.
  - Paradoxical emboli can arise from right to left shunting of venous thrombi and emboli across an atrial septal defect.
  - Embolism usually occurs suddenly when the patient is awake, most often early in the morning, giving maximum deficit at onset.
- Thrombotic: usually related to atherosclerosis.
  - Thrombosis often occurs during sleep hour or present upon arising from bed progressing in a stepwise fashion.
  - Thrombotic strokes are associated with previous transient ischemic attacks.

CLINICAL FEATURES

- The most common clinical features are hemiparalysis, aphasia and coma.
- Clinical features of ischemic stroke are variable depending on the artery and part of the brain affected:
  - Anterior cerebral artery: hemiplegia (legs affected more than arms), confusion, urinary incontinence, primitive reflexes
  - Ophthalmic artery: ipsilateral monocular vision loss (amaurosis fugax)
  - Middle cerebral artery (most common)- hemiplegia (face/arm affected more than arms), hemianesthesia, aphasia (if dominant hemisphere)
  - Posterior cerebral artery- thalamic syndromes with contralateral hemisensory disturbances.
  - Cerebellum- vertigo, nystagmus, nausea, vomiting, ipsilateral incoordination
  - Brain stem- double vision, vertigo, nausea, vomiting and cranial nerve deficits
  - Lacunar (involving internal capsule)- pure hemiplegia
- Physical examination should include:
  - Cardiovascular system looking out for rhythm, murmurs, carotid and subclavian bruits as well as signs of peripheral emboli such as Janeway lesions or splinter hemorrhage.
  - A complete and thorough neurological examination.

INVESTIGATIONS

- Diagnostic:
  - Imaging:
    - Urgent non-contrast head CT scan (if available- will help distinguish ischemic from hemorrhagic stroke). MRI is best for characterizing the location and size of ischemic strokes.
    - ECG: for arrhythmias (atrial fibrillation and flutter), myocardial infarction
    - Also consider a transesophageal echocardiograph for cardiac sources of emboli
    - Also consider Doppler ultrasound, CTA or MRA of the extracranial carotid arteries to evaluate for significant stenosis (>70%)
  - Blood work should include
    - HIV test
    - Creatinine
    - Lipid profile

- Serum glucose and electrolytes (to rule out electrolyte imbalance or hypoglycemia)
- PT/PTT if you are considering a hemorrhagic stroke as you want to reverse coagulopathies

MANAGEMENT

- General management:
  - Airway maintenance: Keep the head of the bed elevated to prevent aspiration.
  - Fluid management (Normal saline). AVOID GLUCOSE AS IT IS NEUROTOXIC
  - Close monitoring of blood pressure and correction of both hyper- and hypotension.
  - Control of body temperature: fever occurs in 44% of patient with acute stroke due to stroke or infections.
  - 4-6 hourly bed turning to prevent decubitus ulcers.
  - After 48 hours start physical therapy. It is very important in stroke management. It should be started early and continued for at least 2-3 months.
  - Lifestyle modification: improving diet, increased exercise, cessation of smoking and drinking. No driving for 1 month.
- Specific management (drugs)
  - Consider thrombolysis with tPA (tissue plasminogen activator)/alteplase (if available) if onset of symptoms is within 3 hours, there is a large deficit and there is no evidence of hemorrhage or other contraindications to lysis (INR >1.7, thrombocytopenia, uncontrolled hypertension SBP>185 and prior intracranial hemorrhage). We usually do not perform lysis in our setting
  - Start ASA 150mg daily for 30 days (only if hemorrhage stroke is ruled out by CT).
  - BP should not be lowered in the first 48 hours unless it is very severe (systolic blood pressure> 200 or diastolic pressure> 120) after 48 hours, lower blood pressure slowly. Short acting antihypertensive drugs are preferred.
  - Start statin (simvastatin 20mg)
  - Start ranitidine or proton pump inhibitor to prevent stress ulcers (Cushing's ulcer).
  - Start subcutaneous heparin to prevent DVT (if hemorrhagic bleed has been ruled out).

- Watch out for signs of cerebral edema/elevated ICP (usually peaks at 3-4 days post stroke), if evidence of elevated ICP (like declining GCS or papilledema) start mannitol.
  - 20% mannitol, intravenously 5ml/kg over 20 minutes and corticosteroid intravenously or intramuscularly 4 hourly (e.g. prednisolone 1mg/kg or hydrocortisone 4mg/kg)

HEMORRHAGIC STROKE

- This is less common (10-20%) but more severe.
- It usually occurs in elderly patients or middle aged patients with severe hypertension.
- Patients often present with coma, headache and/or vomiting. Otherwise symptoms are similar to ischemic stroke.
- Almost 50% mortality in first week.
- Hemorrhagic strokes occur suddenly while the patient is awake, patients may be physically active or staining, it progresses within minutes to hours.

ETIOLOGY

- Primary intracerebral hemorrhage (PICH): usually associated with hypertension and sometimes coagulopathy.
- Subarachnoid hemorrhage (SAH): ruptured aneurysm, arteriovenous malformation, vasculitis, trauma.

CLINICAL FEATURES

- Primary intracerebral hemorrhage: sudden impairment in level of consciousness, vomiting +/- headache, may see progressive focal neurologic deficit depending on site of bleeding.
- Subarachnoid hemorrhage: severe headache, nausea and vomiting. Often described as 'thunderclap'. Can see nuchal rigidity (blood is a meningeal irritant), impairment in level of consciousness.

INVESTIGATIONS

- Diagnostic:
  - Imaging:
    - Urgent non-contrast head CT scan (if available- will help distinguish ischemic from hemorrhagic stroke)
    - ECG: for arrhythmias, myocardial infarction
    - Also consider a transesophageal echocardiograph
  - Blood work should include
    - PT/PTT for coagulopathies
    - HIV test
    - Creatinine
    - Lipid profile
    - Serum glucose, urea and electrolytes (to rule out electrolyte imbalance or hypoglycemia)

MANAGEMENT

- General management:
  - Airway maintenance: Keep the head of the bed elevated to prevent aspiration.
  - Fluid management (Normal saline). AVOID GLUCOSE AS IT IS NEUROTOXIC
  - Close monitoring of blood pressure and correction of both hyper- and hypotension.
  - Control of body temperature: fever occurs in 44% of patient with acute stroke due to stroke or infections.
  - 4-6 hourly bed turning to prevent decubitus ulcers.
  - After 48 hours start physical therapy. It is very important in stroke management. It should be started early and continued for at least 2-3 months.
- Specific management:
  - Blood pressure control with goal of systolic blood pressure 140-160mmHg (diastolic <110mmHg) to prevent further bleeding.
    - Drugs used include hydralazine (if diastolic >110mmHg) and nifedipine (if diastolic <110mmHg)
  - Ranitidine to prevent stress ulcer.
  - Consider nimodipine (a calcium channel blocker) and phenytoin if you suspect SAH as they decrease the risk of vasospasm and seizure in these patients.

FEATURE	ISCHEMIC STROKE	HEMORRHAGIC STROKE
Frequency	80-90%	10-20%
Etiology	• Embolic: atherosclerotic plaque, atrial fibrillation, rheumatic heart disease and endocarditis • Thrombotic: atherosclerosis	• Primary intracerebral hemorrhage: Hypertension and coagulopathy • Subarachnoid hemorrhage: Ruptured aneurysm, trauma
Onset of symptoms	• Embolic: sudden, occurs when patient is awake early in the morning. Maximum deficit at onset. Not associated with TIA (warning sign) • Thrombotic: occurs in a stepwise fashion, occurs during sleep hour and presents upon waking up. Associated with TIAs	• Occur suddenly while patient is awake. • Patients may be physically active or straining. • It progresses within minutes to hours.
Common Clinical features	Hemiparalysis, apahasia and coma. Others depend on blood vessel involved.	Coma, headache and/or vomiting. Otherwise symptoms similar to ischemic stroke. • Primary intracerebral hemorrhage: sudden impairment in level of consciousness, vomiting, headache and progressive focal neurologic deficit depending on blood vessel involved. • Subarachnoid hemorrhage: severe headache (thunderclap), nausea and vomiting, impaired level of consciousness and nuchal rigidity
CT SCAN	• Embolic: Decreased density • Thrombotic: Decreased density	• Primary intracerebral hemorrhage: increased density • Subarachnoid hemorrhage: usually abnormal
LP	• Embolic: usually clear • Thrombotic: usually clear	• Primary intracerebral hemorrhage: usually bloody • Subarachnoid hemorrhage: invariably blood

SYNCOPE

- Syncope (a faint) is a sudden transient loss of consciousness and postural tone mostly due to global cerebral hypoperfusion.
- A faint is characterized by a rapid onset, short duration and spontaneous recovery.
- Syncope may occur suddenly, without warning, or may be preceded by symptoms of faintness ("pre-syncope").
- These include lightheadedness, "dizziness" without true vertigo, a feeling of warmth, diaphoresis (sweating), nausea and visual blurring occasionally proceeding to blindness.
- Pre-syncopal symptoms vary in duration and may increase in severity until loss of consciousness occurs or may resolve prior to loss of consciousness if the cerebral ischemia is corrected.
- Syncope may occur as a single event or may be recurrent.
- Recurrent, unexplained syncope, particularly in an individual with structural heart disease is associated with a high risk of death.
- The differentials of syncope include:
  - Seizure: a sudden, uncontrolled electrical disturbance in the brain.
  - Transient ischemic attack
  - Hysterical fainting: the attack is usually unattended by an outward display of anxiety. Lack of change in pulse and blood pressure or color of skin and mucous membranes distinguishes it from the vasodepressor.
- The distinction between a fit (seizure), a faint (syncope) or another type of attack is primarily clinical and dependent on history and an eyewitness account.
- Mistaking a syncopal loss of consciousness for a seizure is the most frequent error made in differential diagnosis.
- The simple faint that over half the population experiences at some time (particularly in childhood, in youth or in pregnancy) is due to sudden reflex bradycardia with vasodilation of both peripheral and splanchnic vasculature (neurocardiogenic or vasovagal syncope)

PRECIPITANTS

- Prolonged standing
- Fear
- Venesection
- Pain
- Syncope almost never occurs in the recumbent posture.

PATHOPHYSIOLOGY

- Syncope results from a sudden impairment of brain metabolism usually brought about by hypotension with reduction of cerebral blood flow.
- Several mechanisms sub-serve circulatory adjustments to the upright posture.
- Approximately ¾ of the systemic blood volume is contained in the venous bed and any interference in venous return may lead to a reduction in cardiac output.
- Cerebral blood flow may still be maintained as long as systemic arterial vasoconstriction occurs, but when this adjustment fails, serious hypotension, with resultant cerebral under-perfusion to less than half of normal, results in syncope.
- Normally, the pooling of blood in the lower parts of the body is prevented by:
  - Pressor reflexes that induce constriction of peripheral arterioles and venules.
  - Reflex acceleration of the heart by means of aortic and carotid reflexes.
  - Improvement of venous return to the heart by activity of the muscle of the limbs.

STAGES OF SYNCOPE

- They include:
  - Prodromal/Presyncope: usually brief. Dizziness and light-headed feeling often with nausea, sweating, feeling of heat and visual grey-out.
  - Blackout: usually lie still but jerking and twitching movements can occur and are sometimes mistaken for a convulsion. Appearance is pale. Incontinence of urine or faeces can occur and is not a good discriminator between seizure and syncope.
  - Recovery: is rapid, usually seconds but may be followed by a feeling of general fatigue (as opposed to post-ictal drowsiness and confusion following a seizure).

CAUSES OF SYNCOPE

- Transient cerebral hypoperfusion is usually due to one of three mechanisms:
  1. Cardiogenic syncope
  2. Neurogenic syncope (Reflex syncope)
  3. Orthostatic hypotension

Loss of consciousness without global cerebral hypoperfusion (Nonsyncopal causes):

- Epilepsy: complex partial or generalized seizures
- Metabolic disorders: hypoglycemia, hypoxia and hypercapnia
- Drugs: medical or recreational

CARDIOGENIC SYNCOPE

- Cardiac syncope results from a sudden reduction in cardiac output caused most commonly by a cardiac arrhythmia.
- Cardiogenic syncope has no warning signs and can occur in any position (including lying flat). The patient may have had palpitations and chest pain at the time or recently.
- Cardiogenic syncope usually lasts seconds to minutes, with no incontinence. The patient may look pale during and after. They may also have a few clonic jerks. Recovery is quick.
- Heart rate between 30 and 180 beats/min do not reduce cerebral blood flow, especially if the person is in the supine position.
- As the heart rate decreases, ventricular filling time and stroke volume increase to maintain normal cardiac output.
- At rates greater than 180 beats/min, ventricular filling time is inadequate to maintain adequate stroke volume.
- Upright posture, cerebrovascular disease, anemia, loss of atrioventricular synchrony and coronary, myocardial or valvular disease all reduce the tolerance to alterations in rate.
- Causes of cardiogenic syncope include
  - Cardiac arrhythmias
    - Bradyarrhythmias
      - Sinus bradycardia, sinoatrial block, sinus arrest, sick-sinus syndrome (especially in sepsis), Atrioventricular block (especially 2^o type 2 or 3^o resulting in syncope and presyncope may be called Stokes-Adams attacks).
      - May cause syncope if the escape pacemaker rate is insufficient to maintain cardiac output.
      - Syncope may occur abruptly without presyncopal symptoms and recur several times daily.

- Patients with sick sinus syndrome may have sinus pauses (> 3s) and those with syncope due to high degree AV block (Stokes-Adams-Morgagni syndrome) may have evidence of conduction system disease (e.g. prolonged PR interval bundle branch block).
- Drugs such as Digoxin, beta adrenergic receptor antagonists, calcium channel blockers and many antiarrhythmic drugs may suppress SA node impulse generation or slow AV nodal conduction.

- Tachyarrhythmias
  - This is usually preceded by palpitation or lightheadedness but may occur abruptly with no warning symptoms.
  - Supraventricular tachycardia is unlikely to cause syncope unless with structural cardiac disease such as Wolf-parkinson-white syndrome, cerebrovascular disease, disorder of vascular tone or blood volume or a rapid ventricular rate.
  - Atrial fibrillation associated with the Wolff-Parkinson-White syndrome.
  - Atrial flutter with 1:1 atrioventricular conduction.
  - Ventricular tachycardia. Patients with aortic valvular stenosis and hypertrophic obstructive cardiomyopathy are also at risk for ventricular tachycardia.
  - Drugs (such as certain antiarrhythmics and erythromycin) and electrolyte disorders (i.e. hypokalemia, hypocalcemia, hypomagnesemia) can prolong QT interval and predispose to torsades de pointes.

➢ Structural causes
- Valve disease, especially severe aortic stenosis
- Cardiomyopathy especially hypertrophic cardiomyopathy
- Other cardiac disease: MI, Pericardial disease (Pericardial constriction or tamponade), atrial myxoma (tumor), congenital heart disease
- Extracardiac: Pulmonary embolism, Pulmonary hypertension, Aortic dissection.

NEUROGENIC SYNCOPE (REFLEX SYNCOPE)

- Mainly due to reflex increase in vasovagal stimulation. It results from reflex drop in heart rate and peripheral vascular resistance.
- During onset, patients can be standing or sitting (but not lying flat), they may have presyncope (nausea, pallor, sweating, visual field narrow). During the event patients may have myoclonic jerks and even urinary incontinence. Duration is brief with quick recovery.
- This type of syncope is usually recurrent and commonly precipitated by a hot or crowded environment, alcohol, extreme fatigue, severe pain, hunger, prolonged standing, emotional and stressful situations.
- These are the common faints that many normal persons may experience, accounting for approximately half of all episodes of syncope.
- Causes include:
  - Vasovagal syncope (neurocardiogenic/simple/uncomplicated syncope or common faint):
    - Commonest cause of transient loss of consciousness
    - Often due to orthostatic stress: long-standing, hot weather, and/or reduced fluid intake
    - May also be caused by emotional stress: pain, emotion, blood, needles.
    - 3 Ps suggestive of vasovagal syncope: Postural, Provocation, Prodrome.
  - Carotid sinus hypersensitivity (Carotid sinus syncope): Altered heart rate and blood pressure due to hypersensitive baroreceptors. Syncope on minimal stimulus of the neck e.g. shaving, tight shirt collar.
  - Situational syncope: vasovagal syncope due to a specific physical trigger.
    - Cough
    - Postprandial
    - Micturition
    - Defecation
    - Valsalva
    - Deglutition
    - Exercise (though syncope during exercise most often indicates cardiac pathology)
  - Glossopharyngeal neuralgia

ORTHOSTATIC (POSTURAL) HYPOTENSION

- This is seen in patient that have just stood up. There is a fall in blood pressure greater than 20 mmHg systolic or 10 mmHg diastolic.
- It is typically tested by checking BP while lying or sitting then 1 minute after standing.
- Syncope or presyncopal symptoms occur on standing. It is worse in the morning.
- This type of syncope may cause 'coat hanger pain' across neck and shoulders due to neck muscle hypoperfusion.
- Causes include:
  - Drug (especially antihypertensive or vasodilator drugs, antianginals, antiarrhythmics, sedatives, antidepressants-TCAs)
  - Peripheral neuropathy (diabetic, alcoholic, nutritional, amyloid)
  - Idiopathic postural hypotension
  - Multisystem atrophies
  - Physical deconditioning
  - Decreased blood volume (hypovolemia): Diarrhea, burns, hemorrhage, diuresis, adrenal insufficiency, Ruptured ectopic pregnancy, Abdominal aortic aneurysm.
  - Decrease in peripheral resistance: autonomic dysfunction (diabetes mellitus, Parkinson's, multiple system atrophy, amyloidosis), Addison disease, pheochromocytoma

Mechanism	Suggestive Features
Orthostatic hypotension	History of presyncope upon standing; advanced age; a drop in BP (SBP by 20 mmHg or DBP by 10 mmHg) upon standing.
Medication-related	Diuretics, antihypertensives, polypharmacy.
Autonomic insufficiency	Shy-Drager syndrome or multiple system atrophy.
Neurally mediated (**vasovagal,** vasomotor, neurocardiogenic, situational)	Preceded by nausea, flushing, diaphoresis, and tachycardia. Autonomic symptoms often persist upon awakening. Occurrence during emotional stress or pain, or in specific situations (e.g., while coughing, micturating, or defecating).
Carotid sinus hypersensitivity	A specific type of neurally mediated syncope seen in older patients, classically provoked by neck stretching (e.g., while shaving or while looking over the shoulder when driving a car in reverse).
Cardiac arrhythmia (tachyarrhythmia, bradyarrhythmia)	No premonitory symptoms or residual symptoms upon awakening; history of cardiovascular disease.
Valvular heart disease (aortic stenosis, pulmonic stenosis)	Characteristic murmur on exam.
Myocardial ischemia/infarction	Associated chest pain.
Hypertrophic obstructive cardiomyopathy (HOCM)	Characteristic murmur on exam.
Aortic dissection	Chest pain radiating to the back; differential pulses in upper extremities.
PE	Pleurisy; dyspnea; history of venous thromboembolism.
Atrial myxoma	Tumor plop on auscultation.
Migraine	Subsequent headache.
Vertebrobasilar insufficiency (VBI)	Tinnitus, dysarthria, diplopia; focal neurologic findings. It is very unusual to have VBI as a cause of syncope without other brain stem findings.
Seizures	Postictal state.
Psychiatric	Signs and symptoms of psychiatric disease.

TYPES OF SYNCOPE

- They include:
  - Neurocardiogenic/Vasovagal syncope: This is due to sudden reflexive bradycardia with vasodilation of peripheral and splanchnic vasculature. It is seen in childhood, youth and pregnancy.
  - Cardiac syncope (Stokes-Adams attacks): these are potentially serious and often treatable. There is little to no warning. Cardiac arrhythmias e.g. due to heart block or left ventricular outflow tract obstruction may be the cause, syncope during exercise is often cardiac in origin.
  - Micturition syncope: Occurs during micturition in men, particularly at night.
  - Cough syncope: occurs when venous return to the heart is obstructed by bouts of severe coughing. Also occasionally seen with laughter.
  - Postural hypotension: can cause syncope and occurs in elderly in autonomic neuropathy with some drugs e.g. antihypertensive.
  - Carotid sinus syncope: due to a vagal response caused by pressure over the carotid sinus baroreceptors in the neck e.g. due to a tight collar.
  - Convulsive syncope: collapsing in a propped up position following a syncope results in a delayed restoration of cerebral blood and may result in a secondary anoxic seizure following syncope.

INVESTIGATIONS

- Blood tests:
  - Full blood count (anemia)
  - Serum glucose
  - U&Es + Creatinine
  - HIV
  - RPR (for syphilis)
  - Liver function tests
  - Lipid profile
  - Clotting profile
- Imaging:
  - Chest X-ray
  - 12-lead ECG: to identify heart block, pre-excitation or long QT syndrome.
  - Echocardiography
  - CT and MRI of the head are rarely indicated unless there was concomitant head trauma.
  - EEG is useful only when seizures are suspected.

- Tilt table testing is sometimes diagnostic, but has low sensitivity.
  - Patients with suspected neurocardiogenic (vasovagal) syncope should be investigated by tilt testing.
  - The patient is secured to a table which is tilted to $+60^{o}$ to the vertical for ≥45 minutes. The ECG and blood pressure are monitored throughout. If neither symptoms nor signs develop, isoprenaline may be slowly infused or glyceryl trinitrate inhaled and the tilt repeated.
  - A positive test results in hypotension, sometimes bradycardia and presyncope/syncope and supports the diagnosis of neurocardiogenic syncope.
  - If symptoms and signs appear, placing the patient flat can quickly reverse them.
  - The effect of treatment can be evaluated by repeating the tilt test, but it is not always reproducible. The overall sensitivity, specificity and reproducibility is low.

APPROACH TO THE PATIENT

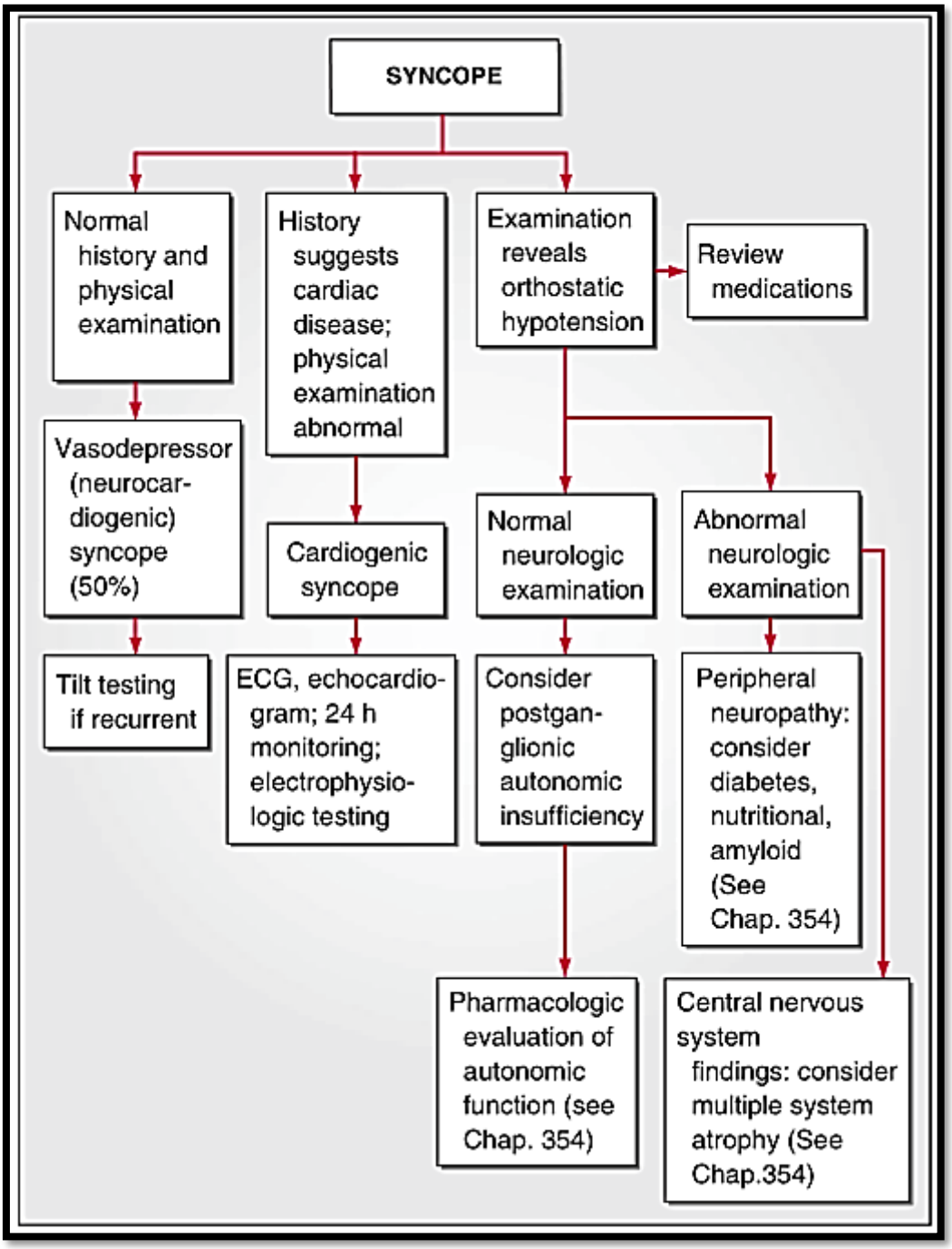


Figure 53: Approach to a syncope patient

MANAGEMENT

- Management is dependent on the underlying cause.
- Provide first aid and general advice to patients who have fainted:
  - Lay the fainted individual on a flat surface
  - Remove any ties, necklaces, shoes or anything strangulating the patient.
  - Check blood sugar, vitals and pupillary response to light
  - Elevate the legs above the head level
  - When patient recovers take a history, full physical examination and order investigations to determine underlying cause.
    - History focuses on: (use the mnemonic BAD BALANCE)
      - What happened Before, After and During the episode
      - B-Banged their head? Any associated head injury?
      - A-Arrhythmic symptoms: palpitations, chest pain?
      - L-Loss of consciousness or do they remember the fall?
      - A- Alcohol: have they been drinking?
      - N-New medication?
      - C-Collateral history (from an observer)
      - E- Ever happened before?
  - In cases of benign causes, reassure the patient and advise them to avoid triggers.
  - Give general advice to patient on maneuver to prevent fainting:
    - Educate the patient on the warning signs that precede a syncopal attack.
    - Avoid tight clothing around the neck
    - Avoid standing fixed in one place for too long, if individual is standing in one place for too long they should repeated squeeze their toes and hands. As well as move their legs about.
    - If they feel dizzy they should lay down flat with legs in the air (on chair or against the wall), or sit down and tuck their head in-between their knees.
    - Avoid hypoglycemia for extending periods and always keep hydrated
- Hospitalize if risk factors for cardiac syncope are present or if syncope is suspected to be 2^{o} to arrhythmic or obstructive/low cardiac output, as patients with cardiogenic syncope are at increased risk of sudden death.

HEADACHE

- Headache is defined as pain located in the head, neck or jaw.
- This is the commonest complaint in medical practice.
- It results from distention, stretching, inflammation or destruction of pain sensitive cranial structures. These pain sensitive structures are the scalp, dura, sinuses, paranasal sinuses, falx cerebri, middle meningeal arteries, proximal segments of large pial arteries, eyes, teeth and cranial nerves V, IX and X. The brain parenchyma is not pain sensitive.
- A pain (sensory stimuli) from these structures is conveyed to the brain either via trigeminal nerve (CN V), Glossopharyngeal (CN IX) or first three cervical sensory roots.
- All patients presenting with headache merit a detailed history and neurologic evaluation (including fundoscopy exam for papilledema).

CLASSIFICATION

- Headache can be pathophysiologically classified into:
  - Primary Headache syndromes
    - Migraine headache
    - Cluster headache
    - Tension headache
    - Miscellaneous (orgasmic, hangover)
  - Secondary headache disorders (usually due to life-threatening and/or treatable causes)
    - Traction-inflammation headache
      - Cranial arteritis e.g. temporal arteritis
      - Meningitis
      - Brain tumor
      - Increased/decreased ICP: intracranial hemorrhage
    - Cranial neuralgia
    - Extracranial lesions
      - Paranasal sinusitis
      - Dental problems
      - Ear problems
      - Ocular problems e.g. glaucoma
      - Cervical problems

PRIMARY HEADACHE SYNDROMES

- These can be classified as
  - Migraine headache
  - Cluster headache
  - Tension headache
  - Miscellaneous (orgasmic, hangover)

MIGRAINE HEADACHE

- This is the commonest cause of episodic headache (90%).
- Its onset is before 40 years (in childhood or young adult life) and affects women (15-20%) more than males (5-10%).
- 90% of patients have a strong family history (genetic link).
- Some environmental triggers have also been liked such as emotional stress/depression, altered sleep pattern/sleep deprivation, Menses/Oral contraceptives, Alcohol intake (especially red wine), caffeine withdrawal, various foods (e.g. chocolates, nuts, aged cheese, monosodium glutamate, meals containing nitrates), hunger, perfumes and even after minor head injury.
- Episodes of headache are associated with sensory sensitivity such as light, sound or movement and sometimes with nausea and vomiting.
- Severity varies greatly among individuals.
- Migraine is usually high impact with inability to function normally during episodes.
- Headache frequency in migraine varies from an occasional inconvenience to frequent headaches severely impacting quality of life and may transform into chronic daily headache.

MECHANISMS

- Genetic factors play a part in causing the neuronal hyperexcitability that is probably the biological basis of migraine.
- The pathophysiology of migraine is now thought to have a primarily neurogenic rather than vascular basis.
- Spreading cortical depression- a wave of neuronal depolarization followed by depressed activity spreading slowly anteriorly across the cerebral cortex from the occipital region- is thought to be the basis of the migraine aura.
- Activation of trigeminal pain neurons is the basis of the headache.
- The innervation of the large intracranial vessels and dura by first division of the trigeminal nerve is known as the trigeminovascular system.

- Release of calcitonin gene-related peptide (CGRP), substance P and other vasoactive peptides including 5-HT by activated trigeminovascular neurons causes painful meningeal inflammation and vasodilation.
- Peripheral and central sensitization of trigeminal neurons and brainstem pain pathways makes otherwise innocuous sensory stimuli (such as CSF pulsation and head movement) painful and light and sound perceived as uncomfortable.

CLINICAL FEATURES

- Benign, recurrent headaches that classically produce unilateral (in a few cases can be bilateral), retro-orbital, throbbing or pulsating pain lasting 4-72 hours often accompanied by nausea, vomiting, and photophobia.
  - They may sometimes be associated with anorexia and phonophobia/sonophobia (dislike and avoidance of loud sounds or noises)
- Severity may range from moderate to severe.
- Migraines are exacerbated by physical activity.
- Patients often report improvement with resting in a dark, quiet room or by sleep and exhilaration, sumatriptan and pregnancy.
- They can be associated with or without a visual aura.
- Subtypes include:
  - Common migraine (Migraine without aura)
    - This is the commonest variation of migraine headache.
    - No focal neurological disturbance precedes the recurrent headache.
    - It starts around puberty with increasing prevalence into the 4th decade.
  - Classic migraine (Migraine with aura-20%):
    - It is associated with aura consisting of sensory, motor or visual symptoms. Most common symptoms reported are visual which include scotomas (a small area in the field of vision where someone cannot see i.e. blind spots) and/or hallucinations.
      - The pathognomic aura for classic migraine is the scintillating scotoma.
      - Fortification spectra/teichopsia are also seen. (these are complicated images e.g. zig-zag lines that can float in the vision during a migraine)
      - Visual auras are also described as stars, sparks and flashes of light.
      - They may evolve into hemianopia or tunnel vision.

- Positive sensory symptoms (mainly tingling), dysphasia and rarely loss of motor function may also occur and may occur successively within the same episode of aura following the visual symptoms.
- The aura usually evolves over 5-20 minutes with symptoms changing as the wave of spreading neuronal depression moves across the surface of the cortex. It rarely lasts longer than 60 minutes and followed immediately by the headache phase.

♦ Focal neurologic symptoms usually occur during the headache rather than as a prodrome.

♦ Classic migraine has 5 phases

- Prodromal phase: characterized by lassitude (a state where a person does not want to do anything), irritability, difficulty in concentrating.
- Aura phase: patients with aura often report visual complaints, vertigo, aphasia or other neurological deficit before the onset of the headache.
- Headache phase: characteristic migraine headache
- Headache termination: usually occurs within 24 hours
- Post-headache phase: feeling fatigued, sleepiness and irritability.

➢ Complicated migraine

♦ Migraine associated with dramatic transient neurological deficit or a migraine attack that leaves a persisting residual neurological deficit.

➢ Other types of migraines include:

♦ Migraine equivalent: focal neurologic symptoms without the classic complaints of headache, nausea and vomiting.

♦ Basilar migraines: migraine headaches associated with symptoms consistent with brain-stem involvement (vertigo, diplopia, ataxia or dysarthria).

♦ Hemiplegic migraines: rare autosomal dominant disorders which causes hemiparesis, and/or coma and headache with recovery within 24 hours. Some patients have permanent cerebellar signs as it is allelic with episodic ataxia.

♦ Ophthalmologic migraines: unilateral CN III palsy and pupillary abnormality

DIAGNOSIS

- Based on the history, with a focus on the exact character of the headache as well as the presence of a strong family history.
- Headache lasting 4 hours to 3 days (untreated) with:

At least 2 of:	At least 1 of:
• Unilateral pain (may become holocranial later in attack) • Throbbing type pain • Moderate to severe in intensity • Motion sensitivity (headache made worse with head movement or physical activity)	• Nausea/vomiting • Photophobia/phonophobia • Normal examination and no other cause of headache

TREATMENT

- Remove inciting agent when possible.
  - ➢ Explanation
  - ➢ Avoidance of trigger factors and lifestyle modification where possible
- Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as aspirin, paracetamol (preferably in a soluble or dispersible form) or a NSAID is often effective, concomitant antiemetic treatment may be required.
- If treatment with an analgesic is inadequate an attack may be treated with a specific antimigraine compound such as 5HT 1- receptor agonists (‘triptans’).
- Acute/abortive treatment of migraine:
  - ➢ NSAIDs: for mild to moderate attacks and are most effect when take early.
    - ASA-900mg
    - Paracetamol- 1g
    - Ibuprofen-250-500mg
    - Side effects: dyspepsia and GI irritation
  - ➢ 5-hydroxytryptophan-1 Agonists: these are serotonin agonists that decrease substance P release at trigeminovascular junction. They are used to relief acute attack
    - Non selective- Ergot preparations (ergotamine and dihydro-ergotamine)
      - ♦ Dose: initial dose 1-2mg oral/sublingual/rectal and repeat and repeat every hour if there is no relief of headache to a maximum of 6-8mg over 24 hours.

- ♦ Route of administration: oral, sublingual, rectal, nasal and parental. Parenteral forms are used for rapid relief.
- ♦ Side effects: nausea, vomiting, chest discomfort, peripheral ischemia and even angina. Excess use may lead to rebound headache and dependency.
- ♦ Contraindications: patients with vascular diseases like coronary heart disease

- Selective- Triptans (Naratriptan, Ritatriptan, Sumatriptan and Zolmitriptan)
  - ♦ Sumatriptan- Single 6mg Subcutaneous dose is effective in 70-80% of patients

- Dopamine agonist: used as adjunct therapy, can act as antiemetic.

- Prophylactic treatment:
  - Medical therapy:
    - This is indicated if patient has 3 or more attacks per month.
    - Drugs: Beta-blockers (slow release propranolol 80-160mg daily), Tricyclic antidepressants (amitriptyline-10mg increasing weekly in 10mg steps to 50-60mg) and calcium channel blockers (verapamil), valproic acid (800mg).
    - Start with low dose and gradually increase if there is no adequate response.
  - Biofeedback therapy: it is simple and cost effective. It lessens migraine attacks by helping patients deal more effectively with stress.

SECONDARY HEADACHE DISORDERS

- Traction-inflammation headache
  - Cranial arteritis
  - Meningitis
  - Brain tumor
  - Increasaed/decreased ICP
- Cranial neuralgia
- Extracranial lesions
  - Paranasal sinusitis
  - Dental problems
  - Ear problems
  - Occular problems
  - Cervical problems

IMPAIRMENT OF CONSCIOUSNESS AND COMA

- Structural, metabolic or toxic insult of diffuse nature to cerebral hemispheres, reticular activating system found in brain stem and corticothalamic connections results in alteration of conscious level of different degree
  - Drowsiness: a state of reduced consciousness characterized by easy arousal that can be maintained only for brief period of time.
  - Stupor: is a sleep like unarousability from which the patient can be awakened by vigorous stimuli.
  - Coma: is severe degree of reduce consciousness (alertness and responsiveness) from which the patient cannot be aroused.
  - Vegetative state: is characterized by the patient's unawareness of self or external stimuli. Autonomic functions are relatively well maintained and a sleep-wake cycle exists. The patient cannot interact with others in a meaningful fashion. The patient can survive with medical and nursing support.
  - Brain death: this is a state in which there has been cessation of cerebral blood flow, as a result there is global loss of brain function while respiration is maintained by artificial means and the heart continues to pump.

ETIOLOGY

Diseases that cause no focal neurologic deficit or lateralizing neurologic signs (patient have diffuse bilateral hemispheric impairment with normal brain stem function)		• Metabolic disturbances: hepatic encephalopathy, hypoglycemia, diabetic ketoacidosis, electrolyte imbalances (hyponatremia, hypernatremia, hyperkalemia, hypocalcemia), hypoxia, hypercapnia etc. • Intoxication: alcohol, sedative drugs, opiates • Severe systemic or CNS infection: meningitis, encephalitis, cerebral malaria, cerebral abscess • Post-seizure state: status epilepticus • Hypertensive encephalopathy, eclampsia • Severe hyper or hypothermia • Head trauma: brain concussion
Diseases that cause focal neurologic deficit (Disorders affect the reticular activating system)	Supratentorial (hemispheric lesions)	• Epidural or subdural hematoma • Intraparenchymal hemorrhage (hemispherical hemorrhage) • Large ischemic infarction • Tumor, abscess, trauma
	Infratentorial	• Pontine or cerebellar hematoma • Basilar artery thrombosis • Ischemic cerebellar infarction • Tumor, abscess

APPROACH TO A PATIENT IN COMA

- Complete and rapid assessment of the patient is critical for optimal care

ASSESSMENT AND MAINTENANCE OF VITAL FUNCTION

- This is the initial step
- Maintain the airways and ensure adequate breathing (ABC of life)
- Maintain circulation

ESTABLISHMENT OF CAUSE OF COMA

- This is done by taking a careful history, doing rapid but thorough physical examination and investigations.

HISTORY

- Look for diseases like diabetes, hypertension, cirrhosis, chronic renal diseases, malignancies, and other disease e.g. CNS infections.
- History of medications: legal or illicit drugs (sedative, hypnotics, narcotics) and history of drug and alcohol abuse.
- Circumstances and rapidity with which changes in mental status developed:
  - Sudden onset indicating vascular causes
  - Gradual onset indicating metabolic and infectious causes
  - Fluctuations suggest subdural hematoma
- Recent patient complaints preceding loss of consciousness: Medical and neurological symptoms (fever suggesting infection, polyuria and polydipsia indicating DKA)
- Details regarding the site where the patient was found e.g. the presence of empty drug vials or evidence of fall or trauma.

PHYSICAL EXAMINATION

- Vital signs: Extremes of BP, pulse or temperature and abnormal patterns of breathing.
  - Fever: systemic or CNS infection or neurogenic fever
  - Tachypnea- pulmonary infections or acidosis
  - Hypertension- hypertensive encephalopathy
- Head and neck: evidence of trauma and presence of meningism.
- Skin: look for signs of trauma or injection.
- General examination: looking for evidences of systemic illnesses like cirrhosis, chronic renal failure, meningococcemia etc.

NEUROLOGICAL EXAMIANTION

- Level of consciousness: Glasgow coma scale

Score	Eye opening	Verbal (best response)	Motor (best motor response)
6			Obeys commands
5		Oriented	Localizes pain
4	Spontaneous	Confused	Flexion & Withdrawal from pain
3	To verbal stimulus	Inappropriate words	Abnormal arm flexion to pain (Decorticate)
2	To pain	Unintelligible words	Abnormal arm extension to pain (Decerebrate)
1	None	None	None

- Brain stem reflexes:
  - Pupillary light response: Should be examined with a bright, diffuse light. Note size, shape, symmetry and reaction to light in both eyes.
    - Normally reactive and round pupils of midsize (2.5 to 5mm) essentially exclude midbrain damage
    - Enlarged (>6mm) and unreactive pupil on one side signifies a compression or stretching of the 3rd cranial nerve from the effects of a mass above
    - Bilateral dilated and unreactive pupils indicate severe midbrain damage, usually from compression by a mass.
    - Bilaterally small (1 to 2.5mm) and reactive pupils (not pinpoint) are seen in metabolic encephalopathies or deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage
    - Very small but reactive pupils (<1 mm)/pinpoint pupils characterize narcotic or barbiturate overdoses but also occur with extensive pontine hemorrhage
  - Ocular movements: before maneuvers of the eye, elevate the lids and note the resting position and spontaneous movements of the eyeballs.
    - Lid tone is tested by lifting the eyelids and noting their resistance to opening and speed of closure. Resistance to opening the eyelid suggest hysteric conversion. Easy eyelid opening with slow closure indicates severe coma.
    - Midline deviation suggests frontal/pontine damage
    - Dysconjugate gaze (abduction or adduction) suggest cranial nerve abnormalities.
    - Spontaneous eye movements roving, dipping, bobbing suggest damages being at different sites
    - The eyes look towards a hemispheric lesions and away from a brainstem lesion.
    - Occulocephalic reflex: this is elicited by moving head from side to side or vertically with eyes held open. In comatose patient with intact brainstem:
      - If the eyeballs move to the opposite direction of the head movement brainstem function is intact (“doll’s eyes” movement is positive)

        - If the eyeballs move to the same direction of the head movement there is brainstem dysfunction.
    - Caloric (occulovestibular) reflex: this test is performed by irrigating the ear with ice (cold) to stimulate the vestibular apparatus. In patients with intact brain stem the eyes move to the irrigated ear
- Corneal reflex: This test assesses the integrity of dorsal midbrain and pontine. It is lost if the reflex connections between the fifth (afferent) and the seventh (efferent) cranial nerves within the pons are damaged.
- Respiration: Abnormalities of respiratory pattern can help in coma diagnosis but are of less localizing value in comparison to other brainstem signs
    - Shallow, slow but regular breathing: suggests metabolic or drug depression
    - Cheyne Stokes respiration (irregular breathing with short breaths gradually increasing to deep breaths then reducing again until breathing appears to stop): signifies bihemispherical damage or metabolic suppression and commonly accompanies light coma.
    - Rapid deep (Kussmaul) breathing: usually implies metabolic acidosis but may also occur with pontomesencephalic lesions and severe pneumonia
    - Agonal gasps: reflects bilateral lower brainstem damage and are indicators of severe brain damage and a near death situation

- Motor function/response: Assess posture of the patient, tone, response to painful stimuli and presence of asterixis. Asymmetric motor responses have localizing value.
    - Quadriparesis and flaccidity: suggest pontine or medullary damage
    - Decorticate posturing: flexion of the elbows and the wrists with supination of the arms and extension of the legs, suggests severe bilateral or unilateral hemispheric or diencephalic lesion (damage above the midbrain)
    - Decerebrate posturing: extension of elbows and the wrist with pronation of the forearm and extension of the legs, indicates damage to the brainstem (midbrain or pontine compromise)
    - Spontaneous activities: if the patient is yawning, swallowing, coughing or moaning the coma is not deep
    - Abnormal body movement: Seizures, myoclonus may suggest the cause of the coma is status epilepticus, uremia etc.

INVESTIGATIONS

- Blood:
  - Full blood count
  - Serum glucose
  - Renal function tests
  - Liver function tests
  - Electrolytes
  - Blood Culture
  - Arterial blood gasses
- Urine analysis
- Lumbar puncture and CSF examination: should be done unless if there is increased intracranial pressure. Exclude infections and subarachnoid hemorrhage
- EEG, CT/MRI of head if available to rule out SOL and other causes

- Psychogenic coma (hysteric coma): patient often has history of psychiatric illness and non-physiologic response on physical examination.
  - Resistance to having the eyelids open (the patient resists eyelid opening when the examiner tries to open it)
  - Failure of the patient's arm, when held by the examiner over the patient's face to fall up on the face when released by the examiner
  - Nystagmus when the ear is irrigated with colder water.
  - Aversive head and eye movement

MANAGEMENT

- This is ideally started with the initial assessment to identify the etiology.
- Initial therapy (ABCs): maintaining an adequate airway, optimal ventilation and maintaining adequate perfusion (blood pressure)
  - Immobilization of the neck if there is a possibility of a cervical fracture
  - Endotracheal intubation is often indicated to protect the airway
  - Blood samples for: FBC, electrolytes, glucose, Renal function tests, Liver function tests etc. should be obtained
  - Intravenous thiamine: 100mg IV with 50% glucose solution is given. This treatment is given if hypoglycemia is even remote possibility, and thiamine is given with glucose in order to avoid eliciting Wernicke disease in malnourished.
  - Naloxone (0.4mg) should be administered in case of opiate intoxication
  - Flumazenil can be given if benzodiazepine or haptic coma is suspected
- Care given:
  - Monitor vital signs
  - Nurse while propped up (appropriate position) with 4 hourly turning
  - Provide adequate ventilation, oxygenation and warmth
  - Catheterized and insert an NT tube (NG tube feeds)
- Manage the primary cause of the coma

PARKINSON DISEASE

BULBAR AND PSEUDOBULBAR PALSY

- The 'bulb' refers to the medulla and bulbar palsy is dysfunction of the cranial nerves 9 to 12 (hypoglossal, Vagus, accessory and glossopharyngeal)- whose nuclei lie within it.
- It presents with dysphonia, dysarthria and/or dysphagia.

Bulbar palsy	Pseusdobulbar palsy
• Lower motor neuron lesion of the medulla (nuclei) or cranial nerve fibers. • Causes: ➢ Brain stem stroke or tumor ➢ MND especially progressive bulbar palsy ➢ Guillain Barre ➢ Myasthenia gravis ➢ Central pontine myelinolysis ➢ Iatrogenic: surgery, radiotherapy • Distinguishing features: ➢ Fasciculating tongue which may sit in one side of the mouth	• Upper motor neuron lesions of the corticobulbar tract. Commoner than bulbar palsy • Causes: ➢ Stoke e.g. of the bilateral internal capsule ➢ Multiple sclerosis ➢ Progressive supranuclear palsy ➢ MND ➢ Tumors higher in the brainstem ➢ Syphilis • Distinguishing features: ➢ Bilateral defects ➢ Paralyzed tongue with Donald duck speech ➢ Also non-bulbar symptoms- as corticobulbar tract supplies all

	motor cranial nerves- including hyper-reflexia (jaw jerk, gag) and facial paralysis ➢ Emotional lability

CHAPTER 12: INFECTIOUS DISEASES

INFECTIOUS DISEASES

PARASITIC INFECTIONS: MALARIA

MALARIA

- Malaria is a protozoal infection of the genus plasmodium.
- Human malaria is usually caused by one of four species of the genus Plasmodium: *P. falciparum*, *P. vivax*, *P. ovale, P. malariae*.
- *P. knowlesi* is also another simian plasmodium specie.
- The majority of malaria infection in Africa (and Zambia) is caused by *P. falciparum* while *P. vivax* infection is more commonly seen in Central America, the Middle East and India.
- P. falciparum can be associated with severe morbidity and symptoms can progress to coma or death very rapidly.
- The risk of severe disease is highest among non-immune individuals, asplenic individuals, children less than 5 and pregnant women.
- Malaria is transmitted by the bite of an infected female *anopheles* mosquitoes.
  - Autochthonous malaria can result if a mosquito feeds on a malaria-infected individual and transmits the infection by biting someone else.
- It also be transmitted in contaminated blood transfusions. It has occasionally been seen in

injecting drug users sharing needles and as a hospital-acquired infection related to contaminated equipment.

- Malaria is characterized by paroxysms of chills, fever and sweating and may lead to anemia and splenomegaly.

LIFE CYCLE

- The female mosquito becomes infected after taking a blood meal containing gametocytes, the sexual form of the malarial parasite.
- The developmental cycle in the mid-gut of the mosquito usually takes 7-20 days (Depending on temperature), culminating in infective sporozoites migrating to the insect's salivary glands.
  - In the mid-gut the gametocytes fuse to form a zygote which matures to a ookinete and eventually an oocyst which ruptures and gives off sporozoites.
- The sporozoites are inoculated into a new human host and those which are not destroyed by the immune response are rapidly taken up by the liver within 30 minutes.
- In the liver they multiply inside hepatocytes forming pre-erythrocytic schizonts which contain thousands of merozoites; this is pre-erythrocytic (or hepatic) sporogeny.
- After a few days (6-16 days), the infected hepatocytes rupture, releasing merozoites into the blood from where they are rapidly taken up by erythrocytes (48-72 hours).
  - In the case of *P. vivax* and *P. ovale*, a few parasites remain dormant in the liver as hypnozoites. These may reactivate at any time subsequently causing relapsing infection.
  - In species which lack hypnozoites i.e. *P. knowlesi, P. falciparum and P. malariae* recurrence of infection occurs from persistent blood stages of malaria parasite this is term recrudescence.
- Inside the red cells, some parasites again multiply changing from merozoite to trophozoite to erythrocytic schizont and finally appearing as 8-24 new merozoites.
- The erythrocyte ruptures releasing the merozoites to infect further cells.
  - Each cycle takes about 48hours in *P. falciparum, P. vivax and P. ovale* and about 72 hours in *P. malariae*.
  - *P. vivax* and *P. ovale* mainly attack reticulocytes and young erythrocytes, while *P. malariae* tends to attack older cells.

- *P. falciparum* will parasitize any stage of erythrocyte.

- A few merozoites do not develop into trophozoites but into gametocytes (microgametes and macrogametes). These are not released from the red cells until taken up by a feeding mosquito to complete the life cycle.

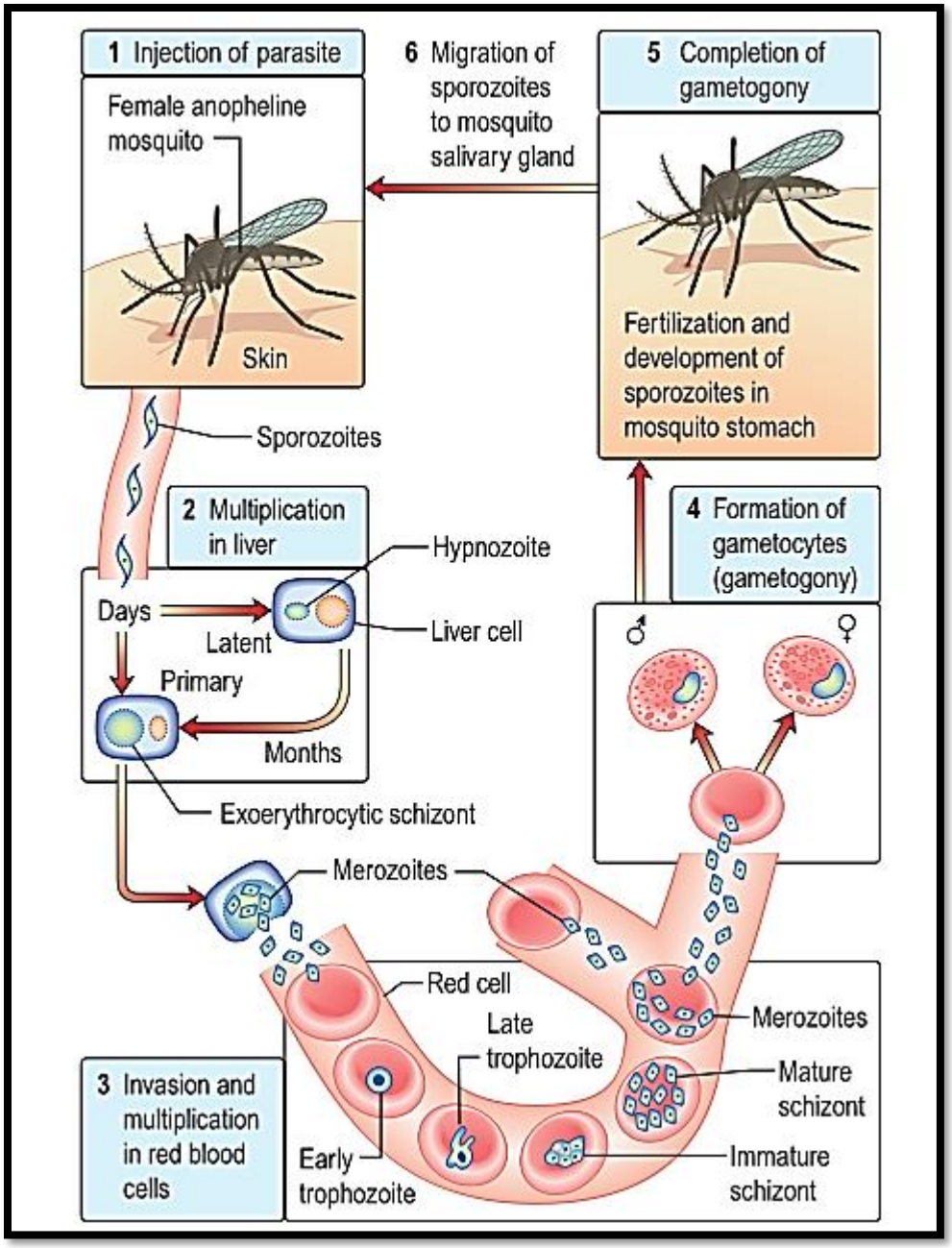


Figure 54: Life cycle of Malaria (Adapted from Kumar and Clark)

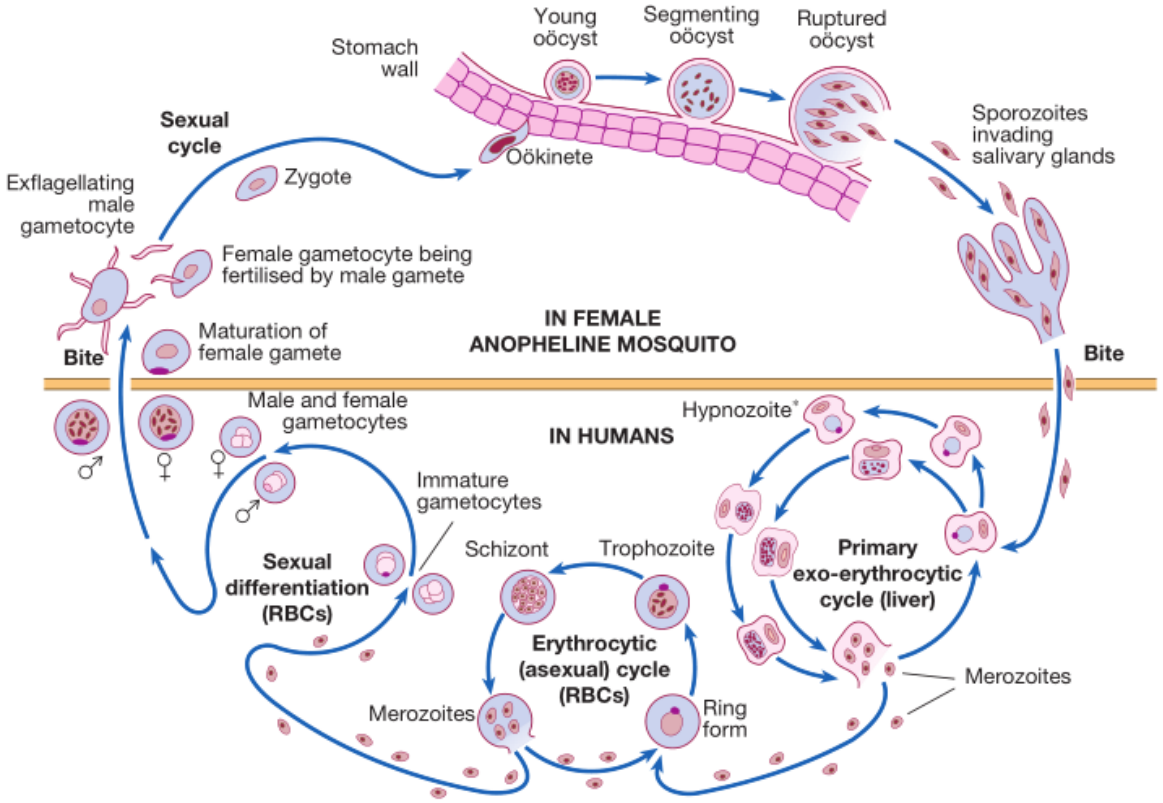


Figure 55: Life cycle of Malaria

PATHOGENESIS

- Red cells infected with malaria are prone to hemolysis.
  - ➢ *P. falciparum* invades red cells at all ages
  - ➢ *P. vivax* and *P. ovale* invade reticulocytes
  - ➢ *P. malariae* invades older red blood cells
- The anemia seen in malaria is multifactorial.
  - ➢ Causes include: hemolysis of infected red cells, Hemolysis of non-infected red cells (blackwater fever), Dyserythropoiesis, Splenomegaly & sequestration and folate depletion.
  - ➢ Death of non-infected cells, bone marrow suppression and hypoglycemia due to high parasite burden cause severe anemia leading to hypoxia and metabolic acidosis
- In *P. falciparum* malaria, red cells containing schizonts adhere to the lining of capillaries in the brain, kidneys, gut, liver and other organs e.g. placenta by formation of 'Knob' protein. They also form 'rosettes' and rouleaux with uninfected red cells.

- There is accumulation of mature parasites in capillary and post capillary venules including brain, muscle, kidneys and kidneys. This leads to tissue hypoxia and contributes to the metabolic acidosis.
- There is a significant increase in a number of pro-inflammatory cytokine factors in particular TNF. There is a clear relationship between their concentration and the severity of illness seen. The mechanisms of damage are likely to include direct effects on cellular metabolism and stimulation of the release of other toxins. It is also thought the cytokine factors release act to up regulate cytoadherence of cells contributing to the sequestration process and its consequences.
- Certain genetic traits also confer some immunity to malaria.
- People who lack the Duffy antigen on the red cell membrane (a common finding in West Africa) are not susceptible to infection with *P. vivax*.
- Iron deficiency may also have some protective effect.
- *P. falciparum* does not grow well in red cells that contain hemoglobin F, C or especially S. Hemoglobin S heterozygotes (AS) are protected against the lethal complications of malaria.
- The spleen appears to play a role in controlling infection and splenectomized people are at risk of overwhelming malaria. Some individuals appear to have a genetic predisposition for developing cerebral malaria following infection with *P. falciparum*.
- Pregnant women are especially susceptible to severe disease.

CLINICAL FEATURES

- Normal incubation period is 10-21 days but can be longer.
  - This is because symptoms of malarial infection develop only with the erythrocytic stage thus patients may remain asymptomatic after being bitten by an infected mosquito.
- The most common symptom is fever, although malaria may present initially with general malaise, myalgias, headache, nausea, vomiting, abdominal pain or diarrhea.
- At first the fever may be continual or erratic: the classical tertian (*P. falciparum*, *P. ovale* & *P. vivax*) or quartan fever (*P. malariae*) only appears after some days. The temperature often reaches 41 degrees and is accompanied by rigors (chills) and drenching sweats.

- Classically malaria manifests in regular paroxysms of high grade fever, chills and rigor occurring every 2 days in P. vivax and P. ovale and every 3 days in P. malariae but irregularly in P. falciparum.
- Malarial febrile paroxysms (which are due to rupture of schizonts and release of pyrogens) typically have 3 stages:
  - The "cold stage" the patient feels intensely cold and has shivering. This lasts 30 minutes to 1 hour. IT is characterized by vasoconstriction of vessels and the temperature rises rapidly.
  - The "hot stage" the patient feels hot and uncomfortable and becomes delirious. This stages lasts for 2-6 hours.
  - The "sweating stage" patient will have profuse sweating and become very much exhausted.

P. VIVAX AND P. OVALE INFECTION

- The illness is usually relatively mild (although *P. vivax* can occasionally cause severe disease).
- The illness starts with several days of continued fever before the development of classical bouts of fever on alternate days. Fever starts with a rigor. The patient feels cold and the temperature rises to about 40 degrees Celsius, after 30 minutes, the hot or flush phase begins and lasts several hours giving way to profuse perspiration and a gradual fall in temperature.
- The cycle is repeated 48 hours later.
- Gradually the spleen and liver enlarge and may become tender.
- Anemia develops slowly.
- Spontaneous recovery usually occurs within 2-6 weeks, but hypnozoites in the liver can cause relapses for many years after infection.
- Repeated infections often cause chronic ill health due to anemia and hyperactive splenomegaly.

P. MALARIAE INFECTION

- This also causes a relatively mild illness but tends to run a more chronic course.
- Bouts of fever appear every third day.
- Parasitaemia may persist for years, with or without symptoms.
- In children it is associated with glomerulonephritis and nephrotic syndrome.

P. FALCIPARUM INFECTION

- This is the most dangerous of the malarias and patients are either 'killed or cured'.
- The onset is often insidious with malaise, headache and vomiting. Cough and mild diarrhea are also common.
- Jaundice is common due to hemolysis and hepatic dysfunction. The liver and spleen enlarge and may become tender. Anemia develops rapidly as does thrombocytopenia.
- It may also cause serious complications and the vast majority of malaria deaths are due to *P. falciparum*.
- Mature P. falciparum parasites (schizonts) bind to vascular endothelium leading to capillary obstruction and ischemia. If left untreated this can lead to hypoglycemia, cerebral malaria, nephritis, renal failure and pulmonary edema.
- Features of severe malaria:
  - CNS:
    - Cerebral malaria (coma-unarousable for more than 30 minutes, convulsion= 3 seizures in 24 hours only attributed to malaria)
    - Cranial nerve palsies
    - Opisthotonus (trunk is in position like in tetanus)
    - Disconjugate gaze due to cranial nerve palsy
    - Malaria retinopathy with Roth's spot
  - Respiratory
    - Tachypnea
    - Acute respiratory distress syndrome due to pulmonary edema
    - Secondary bacterial pneumonia
  - Cardiovascular
    - Shock ('algid malaria')
    - Cardiac failure
    - Dysrhythmias with quinine
  - Gastrointestinal/Liver
    - Diarrhea
    - Jaundice (bilirubin >50 micromol/L), tender liver edge with hepatitis
    - Splenic rupture
  - Renal
    - Hemoglobinuria (blackwater fever)
    - Oliguria and acute renal failure
    - Uremia (Serum creatinine> 250 micromol/L) (Acute tubular necrosis)
  - Blood
    - Severe anemia (<6g/dl) (hemolysis and dyserythropoiesis)
    - Thrombocytopenia
    - Disseminated intravascular coagulation (DIC)

- Bleeding e.g. retinal hemorrhages

➢ Metabolic
- Hypoglycemia (<2mmol/L- particularly in children)
- Metabolic acidosis (blood pH< 7.25)

➢ Others: Gram-negative septicemia, hyperpyrexia

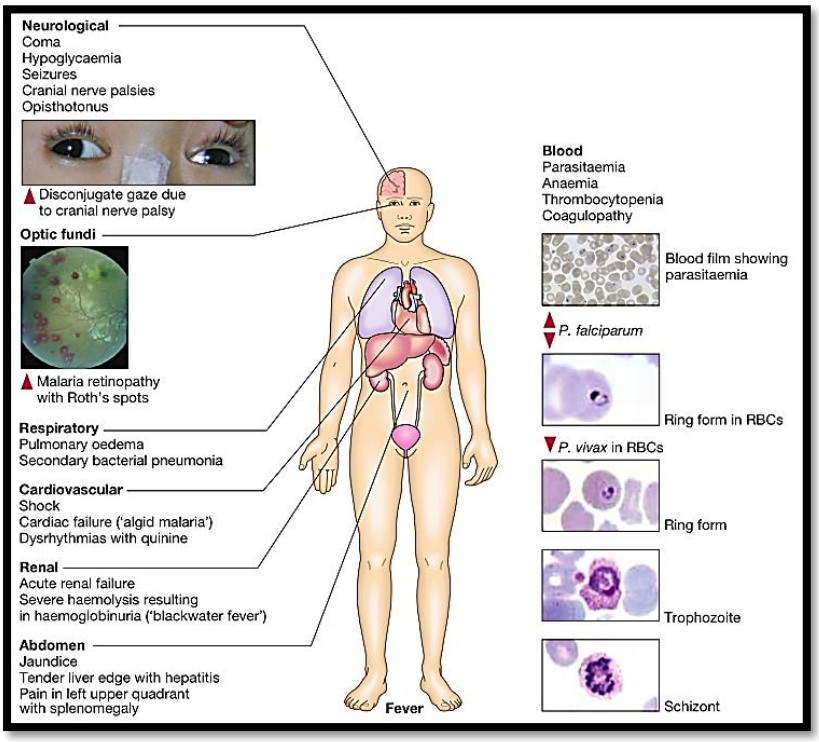


Figure 56: Severe Malaria (Image adapted from Kumar and Clark Clinical Medicine)

- Patients can deteriorate rapidly and children in particular progress from reasonable heath to coma and death within hours.
- A high parasitaemia (>1% of red cells infected) is an indicator of severe disease, although patients with apparently low parasite levels may also develop complications.

UNCOMPLICATED MALARA

- Prodromal symptoms are usually non-specific and are often characterized by intermittent febrile illness.
- Fever is the most common symptom. Headache, aching joints, back pain, nausea and vomiting and general discomfort usually accompany the fever.
- The patient may not present with fever but may have had a recent history of fever. This is due to the natural malaria cycle.
- A history of fever during the previous 2 days along with other symptoms of malaria is a critical basis for suspecting malaria.
- It is equally important to note that fever is a common symptom for other infections besides malaria such as ear infections, measles and pneumonia. Malaria has been nicknamed "the great imitator" because of this.
- The possibility of other infection, either co-existing with malaria or as the sore cause of fever, should always be borne in mind in arriving at the diagnosis. It is therefore important to carry out a differential diagnosis.
- In children the onset of malaria may be characterized, in the early stages, only by symptoms like poor appetite, fever, restlessness, cough, diarrhea, malaise and loss of interest in the surroundings.

SEVERE MANIFESTATIONS AND COMPLICATIONS OF MALARIA

(1) Cerebral malaria (more than 2 convulsions- generalized tonic clonic in 24 hours or unarousable coma/altered level of consciousness for more than 30 minutes attributed only to malaria)

(2) Acute pulmonary edema & respiratory distress

(3) Shock ('Algid malaria'): cold moist skin, low blood pressure (SBP<80mmHg), Increased capillary refill time, collapse

(4) Acute renal failure (oliguria of <400ml/24 hours), blackwater fever

(5) Severe anemia (Hb<6 g/dl or Hct <15%)- normocytic normochromic

(6) Spontaneous bleeding and coagulopathy

(7) Hyperpyrexia (Temperature >39^{o}C)

(8) Hypoglycemia (blood glucose <2.2 mmol/L): due to parasites consuming glucose, catabolic state increases glucose demand of the host, anorexia associated with the illness, drugs e.g. qunine

(9) Metabolic acidosis (pH <7.25 or Bicarbonate <15mmol/L)
(10) Hyperparasitemia (>5% of erythrocytes affect by plasmodium or >100 000 plasmodium/μL)

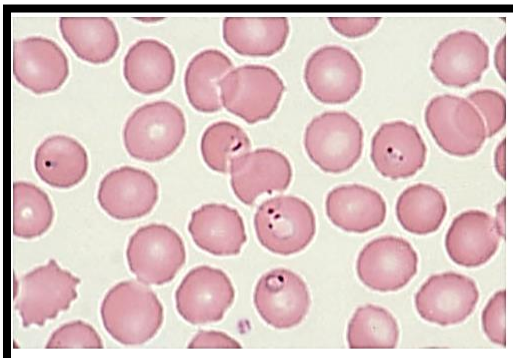
TROPICAL SPLENOMEGALY SYNDROME (HYPERACTIVE MALARIAL SPLENOMEGALY)

- This is a syndrome resulting from an abnormal immunologic response to repeated infection. It is seen in some residents of malaria endemic areas.
- It is characterized by:
  - Huge spleen (>10cm below the lower costal margin) with or without hepatomegaly
  - Hypersplenism (anemia, pancytopenia)
  - Marked elevation of serum IgM and anti-malarial antibody
  - Hepatic sinusoidal lymphocytes
  - Peripheral B-cell lymphocytosis
- Clinical features:
  - Abdominal mass or dragging sensation in the left upper quadrant and sometimes abdominal pain
  - Anemia and sometimes pancytopenia (susceptibility to infection)
  - The parasite may not be detected in peripheral blood film.
- Treatment:
  - Antimalarial prophylaxis for a long time, usually for the duration of malaria exposure
  - Drugs commonly used are chloroquine (in areas not resistant) or mefloquine.
    - Mefloquine 250mg PO per week
    - Doxycycline 100mg PO daily (not to be used in children <8 years and during pregnancy)
  - The enlarged spleen and liver usually regress over a period of months with effective antimalarial prophylaxis
  - Splenectomy is only indicated for those with failure of antimalarial prophylaxis at least given 6 months.

DIAGNOSIS

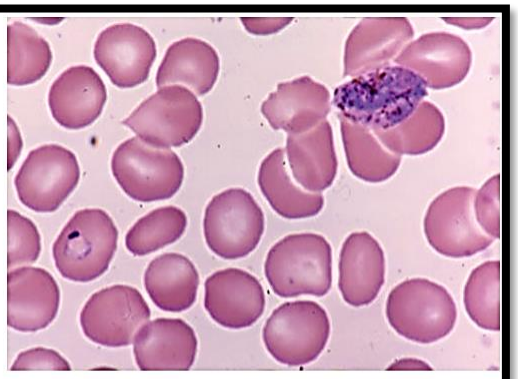
- Malaria should be considered in the differential diagnosis of anyone who presents with a febrile illness in or having recently left, a malarious area.
- Diagnosis is usually made by identifying parasites on a Giemsa-stained thick or thin blood film (Malaria parasite slide- MPS)
  - Thick slide (not methanol fixed, RBC are lysed during

staining, parasites are seen free from RBC): used to confirms the diagnosis.
  - Thin slide (methanol fixed, you can see intact RBC with parasites inside it) it confirms the diagnosis, identifies the species and even quantifies the parasite load.
  - At least 3 films should be examined before malaria is declared unlikely.
  - First smear is positive in 95% of the cases.
  - Because of the cyclical nature of the parasitemia, smear should be taken every 6-12 hours for 48 hours.
- Rapid antigen detection tests are available for near-patient use.
  - They detect the P. falciparum histidine-rich protein 2 (HRP2), these tests do not detect other species of plasmodium and so should be used in parallel with blood film examination.
- Serological tests are of no diagnostic value.
- Other labs:
  - Full blood count (Anemia, thrombocytopenia)
  - AST & ALT (may be raised)
  - U & Es, Creatinine
  - Serum bilirubin
  - Serum glucose
  - Peripheral morphology- normocytic normochromic anemia (low or normal WBC)
  - Serum LDH
  - Clotting panel (DIC)
- Further investigations include a lumbar puncture, may be needed to exclude bacterial infection.
- DNA detection (PCR) is used mainly in research and is useful for determining whether a patient has a recrudescence of the same malaria parasite or a re-infection with a new parasite.



Falciparum malaria on a thin blood smear.

Young signet-ring-shaped parasites are seen for all species of *Plasmodium*, but only *P. falciparum* shows multiple parasites within a single RBC. (Reproduced, with permission, from Lichtman MA et al. *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005.)



Vivax malaria on a thin blood smear.

Blood smear of *Plasmodium vivax* showing both a ring form and a female gametocyte. (Reproduced, with permission, from Lichtman MA et al. *Lichtman's Atlas of Hematology*. New York: McGraw-Hill, 2007: Figure III.A.20.)

MANAGEMENT

Uncomplicated malaria	• Artemisin based combination therapy (ACT) is the recommended oral treatment for uncomplicated falciparum malaria worldwide. • Co-artemether (CoArtem) contains artemether (20mg) and lumefantrine (120mg) and is given as 4 tablets at 0, 8, 24, 36, 48 and 60 hours (first and second tablet taken 8 hours in between then 16 hours after then 12 hourly). • Side effects of Coartem: dizziness, fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache and rash. • Alternatives are quinine by mouth (600mg of quinine salt PO TDS for 5-7 days), together with or followed by either doxycycline (100mg PO OD for 7 days) or clindamycin (450mg 3 times daily for 7 days). • Side effects of quinine: Cinchonism (tinnitus, hearing loss, dizziness, tremor, nausea, restlessness, blurring) and hypoglycemia (most common side effect) • Doxycycline should not be used in pregnancy and artemether should be avoided in early pregnancy. In first trimester use quinine whilst in the second and third trimester Artemisin based combination therapy can be used (though guidelines advocate for quinine). • P. malariae, P. vivax and P. ovale respond to chloroquine. It is given as 600mg PO initial dose followed by 300mg after 6, 24 and 48 hours.

	• Following successful treatment of P. vivax or P. ovale malaria, it is necessary to give a 2 to 3 week course of primaquine (15mg daily) to eradicate the hepatic hypnozoites and prevent relapse. This drug can precipitate hemolysis in patients with G6PD deficiency.
Complicated malaria	• Severe malaria indicated by the presence of any of the complications discussed above, or a parasite count above 1% in a non-immune patient • Intravenous artesunate is more effective than intravenous quinine and should be used where available. Absorption from intramuscular injection is less reliable than from intravenous injection. • If intravenous administration is not possible, Artesunate may be given intramuscularly into the anterior thigh. • Give 2.4mg/kg IV at 0, 12 and 24 hours. If patient does not improve then once daily. However, as soon as the patient has recovered sufficiently to swallow tablets, commence full course of recommended ACT such as Artemether plus Lumefantrine. • Intensive care facilities may be needed, including mechanical ventilation and dialysis • Severe anemia may require transfusion • Careful monitoring of fluid balance: both pulmonary edema and pre-renal failure are common. • Quinine can also be used and is started with a loading dose infusion of 20mg/kg diluted in 10ml of 5% or 10% dextrose over 4 hours up to a maximum of 1.4g followed by a maintenance dose of 10mg/kg quinine given as 4-infusions 2-3 times daily up to a maximum of 700mg per dose until the patient can take drugs orally, then oral quinine 10mg/kg 8 hourly to complete 7-day course of treatment. • By intramuscular injection, quinine 10mg/kg diluted in saline or water for injection (to a concentration of 60-100mg salt/ml), repeated after 4 hours and then 8 hourly. A loading dose is not recommended by this route. • Hypoglycemia can be induced both by the infection itself and by quinine treatment. It is also associated with arrhythmias. • Superadded bacterial infection is common • Quinine is sometimes used in combination with tetracycline or clindamycin, doxycycline in places where there is reduced sensitivity to Quinine. In Zambia, quinine sensitivity is still very high and there is no justification for using the combination. • In very heavy infections (parasitemia> 10%) there may be a role for exchange transfusion, if the facilities are available.

SUMMARY OF MANAGEMENT

- Take and record a confirmatory history
- Do a confirmatory clinical assessment including body temperature.
- Make a differential diagnosis on clinical basis.
- Do a lumbar puncture if there is need to exclude meningitis
- Prepare a thick and thin blood smear (collect blood in a purple bottle)
- Do a full blood count
- Decide on treatment and method of administration
- Keep treatment, follow-up and referral records. Record treatment failures and adverse events
- Give oral, subcutaneous, intravenous or intramuscular medications
- Decided on need for referral
- Supportive therapy:
  - Bring down fever (cold sponges, paracetamol)
  - Monitoring and correction of fluid and electrolyte balance
    - Check input and output
    - Ensure adequate fluid intake
  - Correct management of anemia
    - Transfusion
  - Management of hypoglycemia
    - Administer glucose IV or PO and encourage early PO intake of food.
  - Management of any other complications

MANAGEMENT OF COMPLICATIONS

- Cerebral malaria (coma):
  - Maintain airway, intubate if necessary
  - Position the patient on his/her sides or nurse while propped up.
  - 2 hourly turning to avoid bed sores
  - Exclude other treatable causes of coma e.g. hypoglycemia, bacterial meningitis
  - Catheterize the patient and monitor input- output
  - Monitor blood glucose regularly
  - Ensure adequate nutrition, insert an NG tube
  - Avoid fluid overload

- Avoid harmful ancillary treatments such as corticosteroids, heparin and adrenaline

- Convulsions:
  - Maintain airway
  - Treat promptly with diazepam injection
  - Exclude other treatable causes of coma e.g. hypoglycemia, bacterial meningitis
  - Monitor blood glucose regularly
  - Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation.
  - Intravenous antimicrobial agents and oxygen should be administered and pulmonary toilet should be undertaken.
- Acute pulmonary edema:
  - Nurse at 45^{o}
  - Give oxygen (high flow-3-5L of 100% oxygen)
  - Venesect 250ml of blood
  - Give diuretics (loop diuretics 60-80mg Furosemide)
  - Intubate if necessary and Positive-pressure ventilation should be started early if immediate measures fail
- Aspiration pneumonia:
  - Give parenteral antimicrobials
  - Change position
  - Physiotherapy
  - Give oxygen
- Hypoglycemia:
  - An initial slow injection of 50% dextrose (0.5g/kg i.e. 20-50ml of 50% Dextrose or 40-100ml of 25% dextrose) should be followed by an infusion of 10% dextrose (0.10 g/kg per hour)
  - Regular checking blood glucose (1, 2 or 4 hourly)
- Severe anemia:
  - Transfuse whole blood or packed cells.
- Acute renal failure:
  - Exclude pre-renal causes
  - Rehydrate the patient however if the level of BUN or creatinine rises despite adequate rehydration, fluid administration should be restricted to prevent volume overload.
  - Dialysis can be performed.

  - For blackwater fever: give antimalarials, intravenous fluids and dialysis if indicated
- Spontaneous bleeding and coagulopathy:
  - Transfuse screened fresh whole blood or cryoprecipitate/fresh frozen plasma and platelets.
  - Give Vitamin K injection
- Shock ("algid malaria)
  - Suspect Gram-negative septicemia
  - Take blood culture
  - Give parenteral antimicrobials
  - Correct hemodynamic disturbances
- Hyperpyrexia:
  - Tepid sponging, fanning, cooling blanket
  - Antipyretic drug (paracetamol)
- Hyperparasetemia: consider exchange or partial exchange transfusion, manual or hemophoresis (e.g. >10% of circulating erythrocytes parasite in non-immune patient with severe disease)
- Metabolic acidosis:
  - Exclude or treat hypoglycemia, hypovolemia and gram-negative septicemia
  - Fluid resuscitation
  - Give oxygen

- Note: hypoglycemia or gram negative septicemia should be suspected when the condition of any patient suddenly deteriorates for no obvious reason during antimalarial treatment. Systemic *Salmonella* infections are common complications among African children with falciparum malaria.

Coma (cerebral malaria)
- Maintain airway
- Nurse on side
- Exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis)
- Avoid harmful ancillary treatments such as corticosteroids, heparin and adrenaline (epinephrine)
- Intubate if necessary

Hyperpyrexia
- Tepid sponging, fanning, cooling blanket
- Antipyretic drug (paracetamol)

Convulsions
- Maintain airway
- Treat promptly with diazepam or paraldehyde injection

Hypoglycaemia
- Measure blood glucose
- Give 50% dextrose injection followed by 10% dextrose infusion (glucagon may be ineffective)

Severe anaemia (packed cell volume < 15%)
- Transfuse fresh whole blood or packed cells if pathogen screening of donor blood is available

Acute pulmonary oedema
- Nurse at 45°, give oxygen, venesect 250 mL of blood, give diuretic, stop intravenous fluids
- Intubate and add PEEP/CPAP (p. 193) in life-threatening hypoxaemia
- Haemofilter

Acute renal failure
- Exclude pre-renal causes
- Fluid resuscitation if appropriate
- Peritoneal dialysis (haemofiltration or haemodialysis if available)

Spontaneous bleeding and coagulopathy
- Transfuse screened fresh whole blood (cryoprecipitate/fresh frozen plasma and platelets if available)
- Vitamin K injection

Metabolic acidosis
- Exclude or treat hypoglycaemia, hypovolaemia and Gram-negative septicaemia
- Fluid resuscitation
- Give oxygen

Shock ('algid malaria')
- Suspect Gram-negative septicaemia
- Take blood cultures
- Give parenteral antimicrobials
- Correct haemodynamic disturbances

Aspiration pneumonia
- Give parenteral antimicrobial drugs
- Change position
- Physiotherapy
- Give oxygen

Hyperparasitaemia
- Consider exchange or partial exchange transfusion, manual or haemophoresis (e.g. > 10% of circulating erythrocytes parasitised in non-immune patient with severe disease)

Specific therapy
- Intravenous artesunate
- Mefloquine should be avoided due to increased risk of post-malaria neurological syndrome

PREVENTION AND CONTROL

- Treatment, vector eradication and personal protection from vector bites e.g. insecticide (permethrin) treated nets, spraying of the house (indoor residual spraying), mosquito repellants, health education.
- Vitamin A supplementation and immunization in children.
- Prophylaxis in sickle cell anemia and post splenectomy used Pyrimethamine 25mg once weekly.
- Non-immune travelers to malarious areas should take antimalarial prophylaxis, although this is never 100% effective.
- Zambia has no prophylaxis policy for visitors. Recommendations are provided from their country of origin. Some countries e.g. UK are using Mefloquine. Sulphadoxine/ Pyrimethamine (Fansidar) is not recommended for this purpose.
- The use of other drugs like amodiaquine, dapsone-pyramethamine (maloprim) and mefloquine for prophylaxis needs further evaluation and is not therefore recommended.

SCHISTOSOMIASIS

- These are a group of diseases caused by the trematode (blood fluke) of genus *Schistosoma* affecting mainly the gastrointestinal and genitourinary organs.
- Schistosomiasis in man is caused by 5 species
  - *S. mansoni*- found in Africa even in Zambia (affects the gastrointestinal system i.e. Intestinal schistosomiasis)
  - *S. haematobium*- also found in African including Zambia (affects the genitourinary system i.e. urinary schistosomiasis/Bilharziasis)
  - *S. japonicum*- found in South-east Asia
  - *S. makongi*- found in South East Asia (Makongi valley, Laos, Cambodia)
  - *S. intercalatum*- endemic in Congo basin
- *S. mansoni, S. haematobium* and *S. japonicum* are common causes of schistosomiasis.

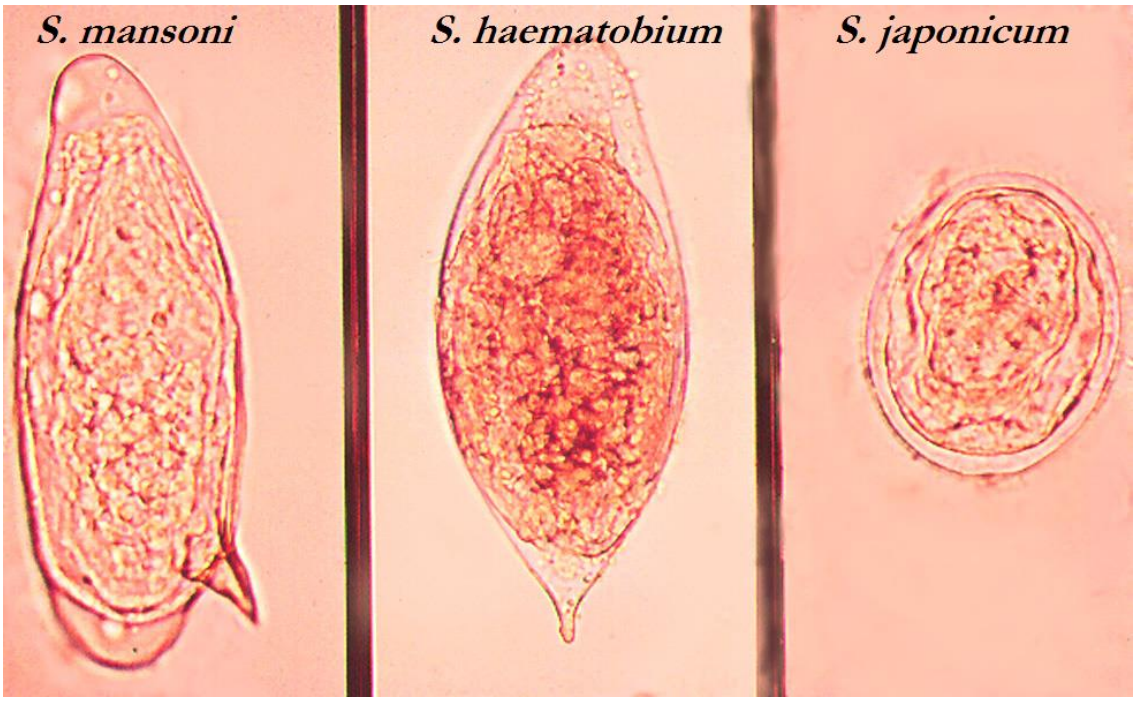


Figure 57: Schistosoma Eggs: note S. haematobium has a Terminal spine (Mnemonic: remember the "T" for haematobium helps you remember that it has a terminal spine), S. mansoni has a lateral spine while S. japonicum is round

- Recall in contrast to other trematodes which are hermaphrodites (which have both sexes), adult schistosomes exist as separate sexes but live attached to each other. The female resides in a groove in the male, the gynecophoric canal ("Schist") where he continuously fertilizes her eggs.

- Man is the definitive host where sexual reproduction takes place after cercarial entry by skin penetration and snail are intermediate hosts in which asexual regeneration continues.
- The life cycle is as follows:
  - Fork-tailed free-swimming Cercariae released by snail into water from snail infects humans and penetrates the skin (this causes itching and dermatitis-swimmer's itch)
  - Cercariae lose their tails during penetration and become shistosomulae (larvae) as they enter the blood and are carried via the veins into the arterial circulation. They also migrate through the pulmonary vessels.
  - Those that enter the superior mesenteric artery pass into the portal circulation and reach the liver where they mature into adult flukes.
  - *S. mansoni* and *S. japonicum* adults migrate against the portal flow to reside in the mesenteric venules.
  - *S. haematobium* adults reach the bladder veins through the venous plexus between the rectum and the bladder.
  - In their definitive venous sites the female lays fertilized eggs which penetrate the vascular endothelium and enter the gut or bladder lumen respectively.
  - The eggs are excreted in the stools or urine and must enter fresh water to hatch.
  - Once hatched, the ciliated larvae (miracidia) penetrate snails and undergo further development and multiplication to produce many cercariae.
  - Each species of Schistosoma has a specific snail host i.e.
    - *S. mansoni*- Biomphalaria species
    - *S. haematobium*- Bulinus species
    - *S. japonicum*- Onchomelania species
  - Cercariae leave the snails enter fresh water and complete the cycle by penetrating human skin.

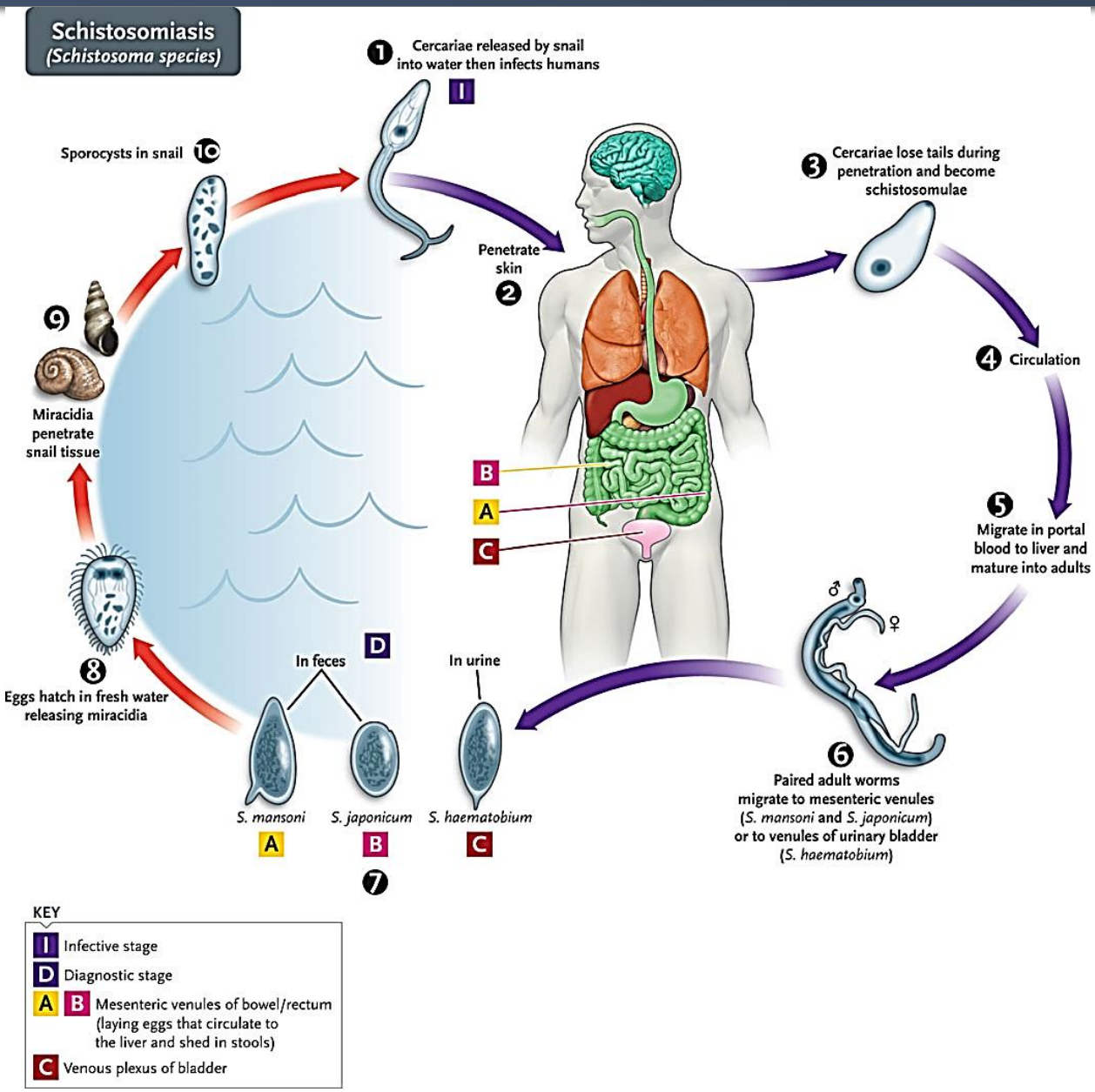


Figure 58: Life-cycle of Schistosomiasis

CLINICAL MANISFESTATIONS

- *S. haematobium* is responsible for urinary schistosomiasis while the other species cause intestinal schistosomiasis.
- Intestinal schistosomiasis affects the large bowel, liver, distal colon and rectum.
- Manifestations are dependent on the stages of infection.
- Urinary schistosomiasis affects the bladder and urinary tract.
- The first 2 stages are the same for all species of Shistosoma.

STAGE 1: SWIMMER'S ITCH (STAGE OF INVASION

- This is the first clinical sign of acute infection appearance 24-48hours after exposure.
- It is characterized by itching at sites of cercarial entry (commonly known as Swimmer's itch)
- It is seen in new comers and not common in indigenous people.

STAGE 2: ACUTE STAGE (TOXEMIA STAGE/KATAYAMA SYNDROME)

- This is an early allergic manifestation to egg deposition (3-10 weeks) in response to massive antigenic stimulus of eggs and include:
  - Fever
  - Headache
  - Chills
  - Myalgias, Malaise
  - Profuse diarrhea
  - Nausea and vomiting
  - Patients may have generalized lymphadenopathy, hepatosplenomegaly, urticarial and leukocytosis with marked eosinophilia.
- Severity depends on intensity of infection and tends to be mild in indigenous population. It is most common with *S. Japonicum*.

STAGE 3 & 4 (CHRONIC STAGE)

- Occurs 3 months to several years later, coincides with deposition of eggs in the tissues.
- Clinical picture represents the effect of the pathologic lesions caused by the eggs on the urinary and gastrointestinal systems.
- Urinary schistosomiasis:
  - Deposition of eggs in the wall of the urinary bladder induces the formation of pseudo tubercles and epithelial hyperplasia with subsequent fibrosis and calcification causing dribbling, incontinence, frequency, dysuria and hematuria.
  - Chronic infection leads to obstructive uropathy, hydronephrosis, Chronic pyelonephritis, renal failure and contraction of the bladder as well as bladder squamous cell carcinoma.
  - In rare instances gonads, CNS (brain, spinal cord), lungs and endocrine organs can be involved.

- Intestinal schistosomiasis:
  - The disease is very light and symptom-less for months and then presenting with recurrent diarrhea with blood and lethargy.
  - They may have intestinal polyps and progressive fibrosis of the intestinal wall leading to formation of strictures but intestinal obstruction is very rare.
  - Granulomatous hepatitis followed by progressive peri-portal fibrosis (also called pipe-stem fibrosis) may develop resulting in portal hypertension with associated splenomegaly, ascites and esophageal varices that occasionally may bleed.

DIAGNOSIS AND INVESTIGATIONS

- Clinical diagnosis:
  - Urinary schistosomiasis
    - Urinalysis: blood
    - Cystoscopy- demonstrate fibrosis and calcification of the bladder
    - Bladder biopsy and histology demonstrates ova in biopsy sample
    - Radiological
      - Plain abdominal X-ray may detect calcification of bladder
      - Ultrasound of kidneys and ureter
      - Intravenous pyelogram to see the presence of obstructive uropathy
  - Intestinal Schistosomiasis
    - Sigmoidoscopy and rectal snip identifies lesions and ova of the parasite
    - Ultrasound of the liver and spleen to demonstrate peri-portal fibrosis and spleen enlargement
    - Liver biopsy
- Laboratory diagnosis
  - Full blood count: marked eosinophilia
  - Identification of characteristic ova in stool or urine by
    - Direct smear method: it is easy but light infection can be missed.
    - Sedimentation/concentration method
    - In rectal snip/bladder biopsy sample: if it cannot be detected in the stool or urine
  - Seroimmunological diagnosis lacks specificity (Serology is positive after 3 months)

TREATMENT

- Praziquantel single oral dose
  - *S. mansoni* and *S. haematobium*= 40mg/kg Orally once
  - *S. japonicum*= 60mg/kg orally once

PREVENTION

- Environmental sanitation: avoidance of pollution of surface water
  - Provision of latrine and sanitary waste disposal
  - Prevention of human contact with infected water
  - Provision of safe and adequate water
  - Protective clothing when contact is unavoidable
  - Health education to reduce contact with infected water bodies
- Elimination of the disease in the reservoir by chemotherapy
  - Case finding and treatment and mass (community) drug administration in selected populations.
- Snail control
  - Physical control- alteration of habitat e.g. removal of vegetation, drainage of swamps etc.
  - Chemical control (moluscicide) Yurimin, Frescon, “Enodd” (phytholacca dedocandra)
  - Biological control- Fish or other snails that feed on vector snails

VIRAL INFECTIONS

HUMAN IMMUNE DEFICIENCY VIRUS AND AIDS (RETROVIRUS)

- HIV belongs to the lentivirus group of the retrovirus family.
- There are two types:
  - HIV-1: most frequently occurring strain globally. It is more aggressive than HIV-2. It has several groups and subtypes
    - M group: comprises of 9 subtypes i.e. A, B, C, D, F, G, H, J, K as well as growing numbers of major circulating recombinant forms (CRFs) e.g. AE, AG etc.
    - O group (Outliers): relatively rare seen in Cameron and Gambia
    - N group (reported only in Cameroon)
    - In Africa more than 75% of strains recovered to date have been subtypes A, C and D with C being the most common
    - Europe and America: Subtype B is the predominant strain
    - Asia: recombinant forms such as AE account for the infections in South East Asia while subtypes C is prevalent in India. Subtype B is also seen in Asia
  - HIV-2: almost entirely confined to West Africa. It has only 40% structural homology with HIV-1 and although it is associated with immunosuppression and AIDS, appears to take a more indolent course than HIV-1.
- Many drugs that are used in HIV-1 are ineffective in HIV-2.
- Retroviruses are characterized by the possession of the enzyme reverse transcriptase which allows viral RNA to be transcribed into DNA and thence incorporated into the host cell genome.
- Reverse transcription is an error-prone process with a significant rate of mis-incorporation of bases. This combined with a high rate of viral turnover, leads to considerable genetic variation and a diversity of viral subtypes.

TRANSMISSION

- Despite the fact that HIV can be isolated from a wide range of body fluids and tissues, the majority of infections are transmitted via semen, cervical secretions and blood.
  - Sexual intercourse-90% (vaginal and anal): passage of HIV appears to more efficient from men to women and to the receptive partner in anal intercourse, than vice versa.

- Anal sex appears to be the sexual practice that carries the highest risk of transmitting HIV. The reason being rectal mucosa is thin and fragile and there are susceptible cells (Langerhans' cells) in rectal mucosa.
- Vaginal sex is also an effective form of transmission.
- Presence of other STIs like syphilis, Gonorrhea increases the risk of infection by several folds as the quantity of virus in seminal or vaginal fluid significantly increases and the number of infected monocytes is high around the genital area in patients with STIs.
- Oral sex may have some risk however there are no reports so far attributable to oral sex.

➢ Mother to child 30-45% (transplacental, perinatal, breast-feeding): vertical transmission is associated with advanced disease in the mother, maternal viral load, prolonged and premature rupture of membranes and chorioamnionitis. Transmission can occur in utero, although the majority of infections take place perinatally. Breast-feeding (mixed feeding practices) has been shown to double the risk of vertical transmission.
  - Pregnancy -10% before the 3rd trimester
  - Labor and delivery- 70% late pregnancy and during labor
  - Breast feeding- 10-15%

➢ Contaminated blood, blood products and organ denotation (risk has reduced due to screening using antibody and p24 antigen testing to identify donors in the window period)

➢ Contaminated needles (intravenous drug misuse, infections, needle-stick injuries)

- There is no evidence that HIV is spread by social or house-hold contact or by blood-sucking insects such as mosquitoes and bed bugs.

MORPHOLOGY

- HIV is a spherical shaped virus.
- It is a positive-sense RNA virus. In the nucleocapsid there are 2 identical strands of positive sense RNA (retroviruses are diploid).
- The genome organization is similar for all retroviruses. They have the following genes: gag, pol and env which encode structural proteins:

➢ Gag gene (group specific antigen): determines the core and shell of the virus (capsid proteins)

  - It encodes for p25 (capsid protein), p7p9 (core nucleocapsid protein) and P17 (matrix protein)
- Pol gene endcodes: Reverse transcriptase, integrase, protease and endonuclease
- Env gene: determines the synthesis of envelope glycoprotein GP 160 which is cleaved into GP120 and GP 41

- It is an enveloped virus and has many small spikes which consist of 2 important glycoproteins gp41 and gp120 which play an important role when the virus attaches to its host cells.
  - gp120 binds CD4 receptors on CD4+ T-lymphocytes, microglial cells, monocytes, macrophages, follicular dendritic cells (in spleen and lymph nodes) or Langerhans' cells.
  - gp41 helps in the ultimate fusion of the viral membrane to the host cells. (this is the target of certain drugs such as fusion inhibitors)
- Matrix protein (p17) stabilizes the envelope proteins.
- The viral capsid (core) is composed of p24 proteins.
  - p24 is a relatively stable protein that is not associated with entry and fusion.
  - Antibodies against p24 (anti-p24 antibodies) are not protective.
  - Antibodies and p24 protein in blood are diagnostic.
- Also found in the capsid are the enzymes
  - Reverse transcriptase (which is a characteristic of retroviruses)
  - Integrase
  - Protease

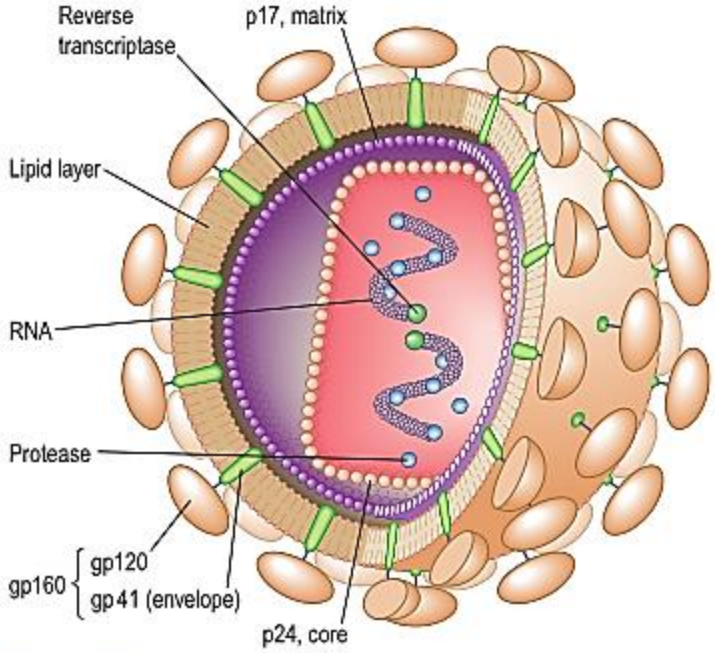
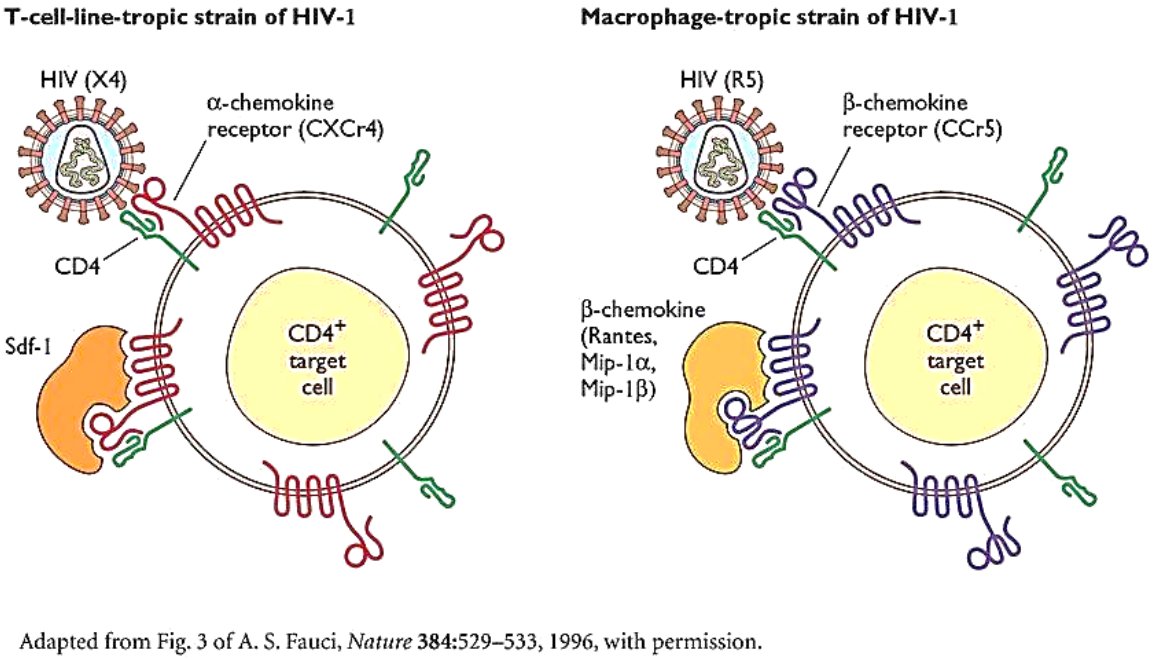


Figure 4.41 Structure of HIV. Two molecules of single-stranded RNA are shown within the nucleus. The reverse transcriptase polymerase converts viral RNA into DNA (a characteristic of retroviruses). The protease includes integrase (p32 and p10). The p24 (core protein) levels can be used to monitor HIV disease. p17 is the matrix protein; gp120 is the outer envelope glycoprotein which binds to cell surface CD4 molecules; gp41, a transmembrane protein, influences infectivity and cell fusion capacity.

- HIV attaches via gp120 to the CD4 surface receptors and undergoes a conformational change and expresses 2 more active sites.
- Depending upon the target cell, different receptors are expressed:
  - On macrophages, monocytes, microglial, dendritic cells and Langerhan's cells chemokine co-receptor 5 (CCR5) is expressed.
  - T-helper cells express CXCR-4.
- Once primary glycoproteins (gp120) and co-receptors bind, gp 41 causes fusion of the HIV with the host cells. (gp41 is a fusion molecule).

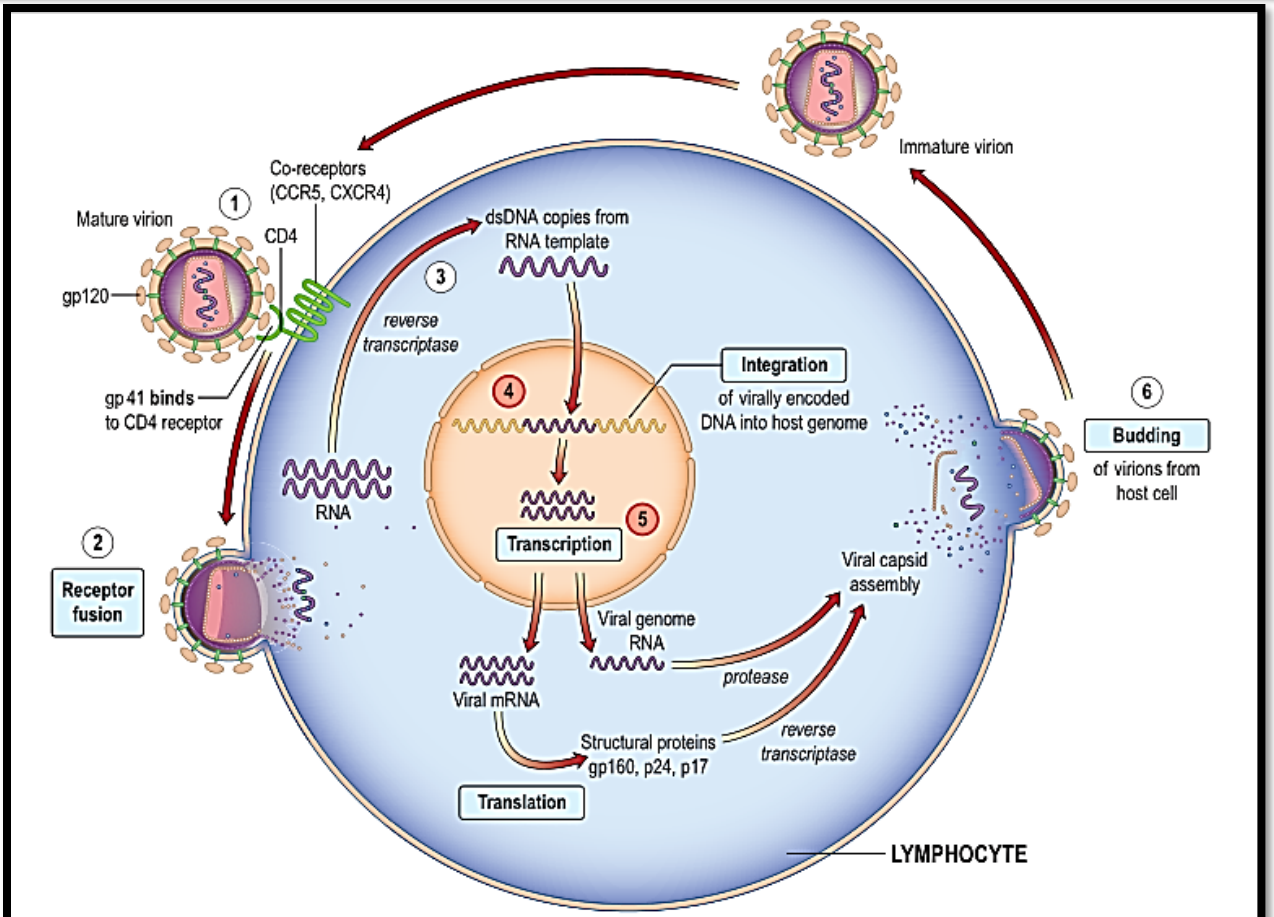


Adapted from Fig. 3 of A. S. Fauci, *Nature* **384**:529–533, 1996, with permission.

- Complete Lack of CCR5 receptors (due to a homozygous mutation) is associated with immunity to HIV.
- In heterozygous mutation the progression of HIV is slow.

LIFE CYCLE

- Attachment/binding and fusion of the virus to the host cells: the receptor and co-receptors of CD4 cells interact with HIV's gp 120 and gp 41 proteins during entry into a cell.
- Uncoating: of the viral capsid and release of viral RNA into the cytoplasm of the host cell.
- Reverse transcription: viral RNA is converted into double stranded DNA by reverse transcriptase enzyme
- Translocation: viral DNA is imported to cell nucleus
- Integration: of proviral DNA to host-cell DNA
- Cellular activation causes transcription (copying): of HIV back to RNA
  - Some RNA translated to HIV proteins
  - Other RNA moved to cell membrane
- Viral assembly: HIV assembled under cell membrane and buds from cell
- Maturation: viral proteases enzymes cleave longer proteins into important viral proteins and help to convert immature viral particle into infectious HIV.



HIV entry and replication in CD4 T lymphocytes. (1) Binding: the virus binds to host CD4 receptor molecules via the envelope glycoprotein gp 120 and co-receptors CCR5 and CXCR4. (2) Fusion: a subsequent conformational change results in the fusion between gp41 and the cell membrane. (3) Reverse transcription: entry of the viral capsid is followed by the uncoating of the RNA. DNA copies are made from both RNA templates. DNA polymerase from the host cell leads to formation of dsDNA. (4) Integration: in the nucleus, virally encoded DNA is inserted into the host genome. (5) Transcription: regulatory proteins control transcription (an RNA molecule is now synthesized from the DNA template). (6) Budding: the virus is reassembled in the cytoplasm and budded out from the host cell.

PATHOGENESIS

- CD4 positive T-lymphocytes play central role in the defense mechanism of the body against infection.
- They mainly coordinate the cell mediated immune system and also assist the antibody mediated immune system.
- HIV virus has special affinity to CD4 T-cells and infects them leading to a progressive decline of T-helper cells (profound immunodeficiency).
- The pathogenetic mechanism of HIV disease is multi-factorial and multiphasic and it differs in different stage of disease. Depletion of CD4 cells is due to
  - HIV- mediated direct cytopathicity (single cell killing)- infected CD4 cells die
  - HIV- mediated syncytia formation
  - Defect in CD4 T-cell regeneration in relation to the rate of destruction.
  - Maintenance of homeostasis of total T-lymphocytes (decreased CD4, increased CD8)
  - HIV specific immune response (killing of virally infected and innocent cells)
  - Autoimmune mechanism
  - Programmed cell death (apoptosis)
- HIV is a unique infection in that, though the body reacts by producing antibodies to destroy the virus, the virus is not cleared, except partially in the early period of infection.
- A chronic infection is established and it persists with varying degrees of viral replication.
- Viral replication is continuous in all stages (Early infection, during the long period of clinical latency and in advanced stage). There is no virological latency.
- HIV evades the immune system because:
  - High level of viral mutation- HIV has an extraordinary ability to mutate.
  - Large pool of latently infected cells that cannot be eliminated by viral-specific Cytotoxic T-lymphocytes.
  - Virus homes in lymphoid organs while antibody is in circulation. HIV seeds itself in areas of the body where sufficient antibodies might not reach e.g. the central nervous system.
  - Exhaustion of CD8 T-cells by excessive antigen stimulation
  - HIV attacks CD-4 T-cell which are central to both humeral and cell-mediated immunity

HIV PROGRESSION

- Include:
  - Rapid progressors (15%): develop OIs very quickly and die within 2-3 years.
  - Normal progressors (80%): remain health for 6-8 years before they start having overt clinical manifestations.
  - Long term survivors: patients who remain alive for 10-15 years after initial infection. In most the disease might have progressed and there may be evidences of immunodeficiency.
  - Long term-non progressors: these have been infection with HIV for more than 10 years. Their CD4 count may be in the normal range and they may remain clinically stable for several years.
- Factors affecting progression include:
  - Immune response
    - High CD8 slow progression
    - Low CD8 rapid decline
  - Viral type: HIV 2 slow course
  - Concomitant conditions: malnutrition hastens the progression of HIV, chronic infectious conditions e.g. TB also hasten the progression.

CLINICAL MANIFESTATIONS OF HIV INFECTION

SEROCONVERSION ILLNESS

- Seroconversion (the time it takes the body to make antibodies against the HIV virus, it varies in individuals and generally takes 3-12 weeks)
  - Lymphadenopathy
  - Pharyngitis
  - Systemic: fever, malaise
  - Pain: myalgia, headache
  - GI symptoms: anorexia, nausea, vomiting, diarrhea
  - Maculopapular rash
  - Lasts 1-2 weeks

PRESENTATIONS BY SYSTEM

NEUROLOGICAL

- Toxoplasma encephalitis: protozoal infection. Focal neurological signs
- Cryptococcal meningitis: fungal infection. Causes insidious, chronic meningitis usually without stiff neck
- Primary cerebral lymphoma

- Progressive multifocal leukoencephalopathy (PML): JC virus infection
- HIV dementia: neurological decline in multiple domains, in the absence of other infection
- HIV peripheral neuropathy

EYE

- CMV retinitis (Mozzarella pizza sign on fundoscopy)

RESPIRATORY

- *Pneumocystis jiroveci* pneumonia (PJP or PCP), fungal infection causes dry cough, sweats, SOB and desaturation on exertion but no chest signs
- Other fungal infections: Aspergillus, Cryptococcus, Histoplasma
- TB: pulmonary TB or atypical and disseminated forms such as miliary TB and TB meningitis
- Strep and Staph pneumonia
- CMV

MOUTH

- Oral and esophageal candidiasis
- Oral hairy leukoplakia: non-malignant white growths on lateral tongue due to EBV
- HSV and aphthous mouth ulcers

GIT

- Cryptosporidiosis: Protozoa. Chronic diarrhea
- CMV colitis
- HIV wasting syndrome: Unexplained weight loss >10%
- Mycobacterium avium complex (MAC): GI, Lung, or disseminated
- Fungal: Cryptococcus, Histoplasma
- Other bacteria: Salmonella, Shigella
- Hepatitis B and C

SKIN

- Kaposi's sarcoma: due to human herpes virus 8. Purple papules on the face, mouth, back, lower limbs or genitalia. Can also affect GI and respiratory tract
- Multi-dermatomal zoster (Shingles)
- Recalcitrant psoriasis

CANCER

- B-cell lymphoma, EBV related
- Cervical and anal cancers. HPV-related
- Lung cancer
- Head and neck cancers

INFECTIONS BY CD4 LEVEL

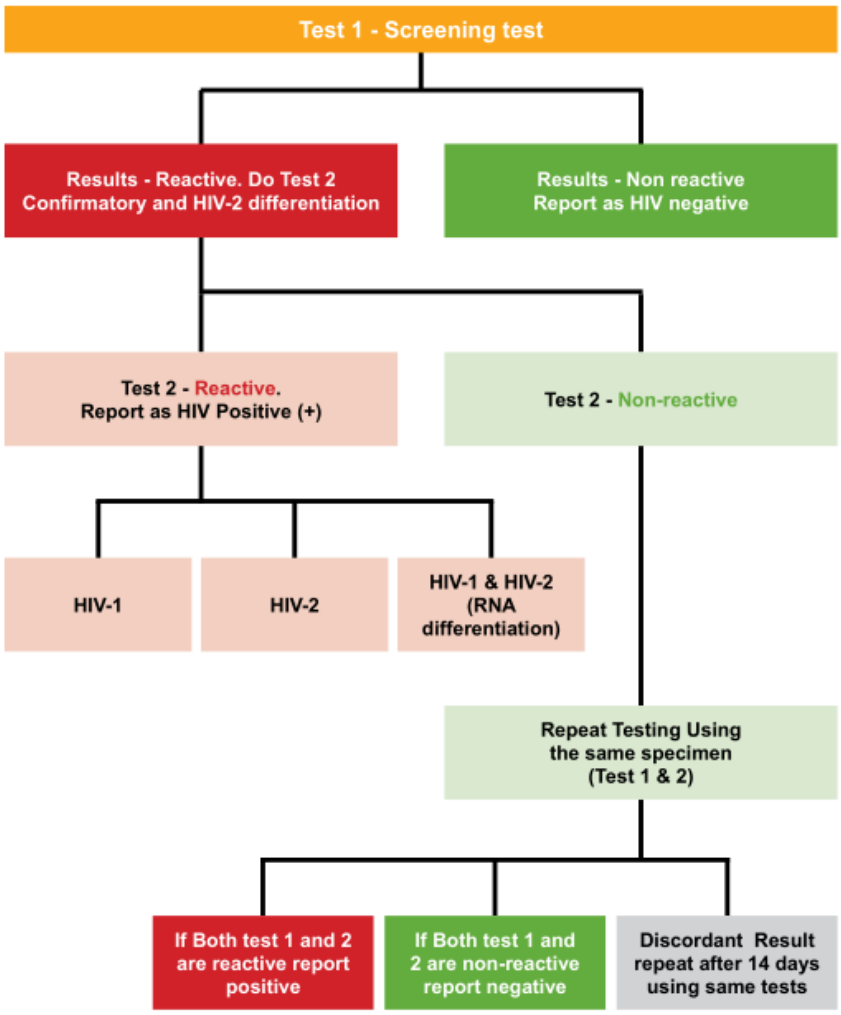
- 200-500: TB, Candida, VZV, Kaposi's, other pneumonias
- 100-200: PCP, histoplasmosis, PML
- 50-100: atypical TB, CMV retinitis/colitis, toxoplasmosis, cryptosporidiosis, Cryptococcal meningitis
- <50: MAC

DIAGNOSIS

- Serologic tests:
  - HIV antibody tests: detect antibodies formed by the immune system against HIV
    - ELISA: used to be standard screening test for HIV
      - Tests for a number of antibody proteins
      - A very sensitive (99.5%) but not very specific
      - A positive result needs to be confirmed by Western blot for confirmation.
      - The test needs skilled personnel, takes several hours
    - Western blot: is an excellent confirmatory test
      - It has high specificity but relatively poor sensitivity
      - It should not be used for screening purpose
    - Rapid HIV antibody tests:
      - Rapid tests have reasonable good sensitivity and specificity (>99%)
      - Easy logistically, do not need continuous water or electric supply
      - Can be done by less skilled personnel and the interpretation of results is easy.
      - Test result can be available in <30 minutes.

Note: When the first test is non-reactive then the client can receive the negative HIV result. When both tests are reactive the final HIV result is positive. If one test is reactive and the other is non-reactive, then a third test known as a tiebreaker is performed. The tie-breaker determines the final result- if the tiebreaker is reactive then the final HIV result is positive, if the tiebreaker is non-reactive then the final HIV result is negative.

Screening test- determin test
Conformation test- unigold test
Tie breaker test- bioline test



- HIV antigen assays (Tests)
  - P24 antigen capture assay: this test detects p24 viral protein in the blood of HIV infected individuals. This viral protein can be detected during early infection, before seroconversion. Thus this test is used to detect blood donors during the window period.

- DNA PCR: Viral replication
  - Extremely sensitive test can detect 1-10 copies of HIV proviral DNA per ml of blood.
  - Uses PCR technology to amplify proviral DNA
  - This test is costly and needs sophisticated instruments and highly skilled professional
  - It is highly sensitive and the chance of false positive is high hence it should not be used for making initial diagnosis of HIV infection
  - It is used for
    - Making early diagnosis of HIV in HIV exposed infants as serology tests are unable to diagnose HIV till the infant is 18 months old.
    - To diagnose or confirm virologic failure in patients who are not responding to ART
    - When there is indeterminate serology
- CD4 T cell count
  - This is an indicator of the level of immune suppression that a patient with HIV has.
  - The average CD4 count of a normal person is in the range of 1000-1200/mm^3.
  - In patients with HIV CD4 count drops by an average of 50-100 cells per year
  - It should not be used to make a diagnosis of HIV.
  - CD4 count no longer used in deciding on initiation of ART as all HIV positive patients are started on ART immediately
  - CD4 may be used to follow the progress of a patient on ART however, viral load is a more important measure.
  - It should be done 3 to 6 monthly.
  - CD4 count may be variable depending on circumstances:
    - Diurnal variation: high evening, low at midnight
    - Intercurrent infection, use of steroids and stress could affect CD4 count.
- Additional tests:
  - Viral load
  - Hepatitis Panel (especially B and C)
  - Full blood count and ESR

  - AST and ALT
  - Serum creatinine
  - Syphilis serology: RPR
  - AFB chest X-ray where possible
  - Stool examination for parasites
  - Malaria blood slide
  - Pregnancy test for women in child bearing age
- Serum HIV combined antibody + P24 antigen test to screen, to confirm with Western blot. 50% detectable within 1 month of infection and nearly all by 6 months.
- If positive screen for TB, PCP (CXR shows bilateral interstitial infiltrates), hepatitis A-C, syphilis, toxoplasma (Contrast-enhancing lesions on CT/MRI brain), CMV, Cryptococcal (Cryptococcal antigen test on CSF and serum)
- Genotype testing to guide drug treatment
- Pregnancy test for women
- Baseline bloods: FBC, U&Es, LFT, Lipids, Glucose

STAGING OF HIV

- WHO stages HIV as:
  - Stage 1: Asymptomatic
  - Stage 2: Minor symptoms
  - Stage 3: Moderate symptoms
  - Stage 4: AIDS defining illness
- CDC staging is by CD4 count
  - Stage 1: CD4 >500
  - Stage 2: CD4 200-500
  - Stage 3: CD4<200 (or stage 3-defining opportunistic infection)

WHO STAGING

STAGE 1

- Asymptomatic
- Persistent generalized lymphadenopathy (presence of lymph node> 1cm in 2 extra inguinal sites and persisting for more than 3 months)

STAGE 2

- Unexplained moderate weight loss (<10% of body weight)
- Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Minor mucocutaneous manifestations/pruritic pupular eruption (seborrheic dermatitis, fungal nail infections, recurrent oral ulcerations, angular chelitis)
- Herpes zoster within the past 5 years (single dermatome)

STAGE 3

- Unexplained severe weight loss (>10% of body weight)
- Unexplained chronic diarrhea longer than 1 month
- Unexplained prolonged fever >1 month
- Oral hairy leukoplakia
- Persistent oral candidiasis
- Pulmonary TB
- Severe bacterial infection (pneumonia, pyomyositis, empyema, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (<8g/dl), neutropenia <500/mm^3 and or chronic thrombocytopenia (<50 000/mm^3)
- AIDS-related complex is an associated term describing weight loss, fever diarrhea, minor infections, occurring before AIDS criteria are met

STAGE 4

- HIV wasting syndrome
- AIDS defining conditions: note the term Acquired immunodeficiency syndrome (AIDS) was traditionally used to describe a CD4 count <200 or the presence of AIDS defining illness.
  - The term AIDS is now less used in clinical practice. This partly reflects the huge decline in AIDS (due to cART) but also the possible stigma surrounding the term. More practically it is more useful to refer to specific CD4 counts, viral load and infection history to give a picture of someone's clinical condition than the non-specific "AIDS".
  - Advanced or Late-stage HIV may be useful alternative terms to 'AIDS'
- Pneumocystis jiroverci pneumonia
- CNS toxoplasmosis
- Cryptosporidosis or Isosporiasis related watery diarrhea >1 month

- Extrapulmonary cryptococcosis
- CMV disease of an organ other than liver, spleen, or lymph nodes e.g. CMV retinitis
- Chronic HSV- orolabial, genital anorectal lasting for more than 1 month
- Any disseminated endemic mycosis (e.g. Histoplasmosis, coccidiodomycosis)
- Esophageal candidiasis (involving esophagus, trachea, bronchi or lungs)
- Recurrent bacterial pneumonia
- Recurrent septicemia
- Disseminated atypical mycobacterium
- Extrapumonary TB
- Lymphoma (cerebral or B-cell Non-Hodgkin's lymphoma)
- Invasive cervical carcinoma
- Kaposi's sarcoma
- HIV encephalopathy
- Symptomatic HIV associated neuropathy

MANAGEMENT OF HIV

- Lifestyle and preventative:
  - Counselling to prevent high-risk sexual behavior
  - Lifelong condom use traditionally recommended but good evidence that those with undetectable viral load cannot transmit even during condomless sex.
  - Specific methods are available for reproduction in serodiscordant couples e.g. IUI with sperm washing, IVF with ICSI
  - Assistance with partner notification and contact tracing
  - Vaccines: hepatitis A and B, annual flu, pneumococcal vaccine, HPV. Avoid live vaccine if CD4 <200 (VZV, MMR, BCG and oral and intranasal vaccines, yellow fever)

- Combination antiretroviral therapy (cART)/High active ART (HAART):
  - Treatment is now initiated for all patients found positive regardless of CD4 count, WHO clinical stage, pregnancy status or AIDS-related illness.
  - Triple therapy: (2 x NRTI) + (NNRTI or Protease inhibitor or integrase inhibitor)
    - Currently preferred regimen (2020): TDF (or TAF[c]) + XTC[d] (3TC or FTC) + DTG[e]
    - Alternative regimen:
      - TDF (or TAF[e]) + XTC[d] + EFV_{400}[a]
      - ABC + 3TC + DTG[*]
      - ABC + 3TC + EFV
      - ABC + 3TC + NVP
    - Past recommended first line(TLE): TDF + (3TC or FTC) + (EFV or NVP)
    - Second line:
      - AZT + 3TC (or FTC) + LPV-r (or ATV-r)
  - Indications for changing from first line to second line:
    - Clinical failure
    - Immunologic failure
    - Virological failure

- EFV_{400}[a] is the lower dose of EFV-400mg/day and is preferred ARV agent in HIV/TB patients on TB treatment
- TAF[c] is tenofovir alafenamide. Avoid in pregnancy and HIV/TB patients on Rifampicin (currently not recommended)
- XTC[d]: can either be 3TC or FTC. FTC is not available as a single drug and is expected to be part of the fixed dose combination TAF + FTC + DTG
- DTG[e]: Dolutegravir to be given to ART naïve adolescents and adults. For HIV/TB patients on Rifampicin and cannot tolerate EFV_{400} increase the frequency of DTG to 50mg BD instead of the usual 50mg OD where single tablet is available
- DTG[*]: ABC + 3TC + DTG can be used as an alternative for those with renal insufficiency or where TAF is not available and EFV is not tolerated

1. AZT/3TC/LPV/r is preferred second line regimen for patients failing Tenofovir based first line.
2. Lamivudine (3TC) or Emtricitabine (FTC) are continued in the second line regimen because their resistance mutations decrease viral replication capacity, increase the HIV susceptibility to Tenofovir (TDF) and AZT
3. For women who have had exposure to sdNVP without tail coverage with 7 days of AZT + 3TC within the last 12 months (for PMTCT), do not use a Nevirapine or Efavirenz containing regimen, use LPV/r. If unsure whether tail coverage for sdNVP was provided then use LPV/r
4. Stavudine (d4T) is associated with long term toxicity and should only be used in the second line if AZT cannot be taken
5. TDF mutations can increase HIV susceptibility to AZT and may increase AZT efficacy, while TDF may maintain some activity
6. If unable to tolerate LPV/r then refer to HIV Specialist.

1. Lamivudine (3TC) or emtricitabine (FTC) are continued in the second line regimen because their resistance mutations decrease viral replication capacity. increase the susceptibility to Tenofovir (TDF) and AZT.
2 If unable to tolerate LPV/r then refer to HIV Specialist for additional options
3 For women who have had exposure to Nevirapine within 6 months for PMTCT, do not use a Nevirapine containing regimen.
4 3TC resistance reduce efficacy of ABC, therefore, Didanosine (ddI) will be substituted for 3TC.
5. D4T should only be used in doses of 30mg to avoid adverse effects and toxicity.

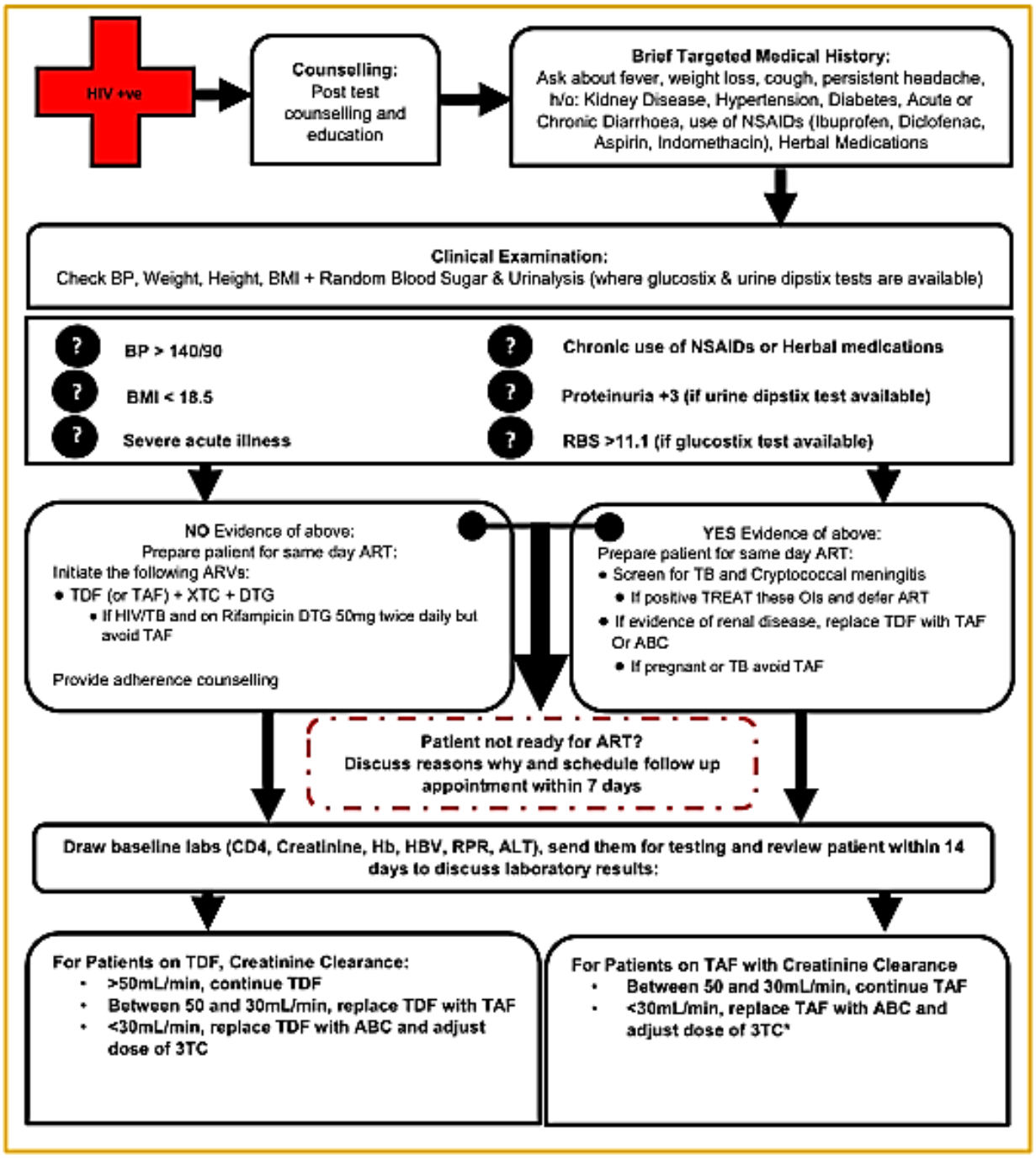
- Visit 1 (enrollment/initiate ART based on patient readiness)
  - Complete history and examination
  - Screen for TB and other OIs
  - WHO clinical staging
  - Initiate CTX if eligible (CD4 <350 cells/μL or stage I, II or IV or pregnant)
  - Initiate TB prophylaxis if TB screening is negative if not initiated
  - Adherence counseling
  - Urinalysis
  - Lab tests: Full blood count, CD4 count, ALT, Creatinine (Calculate Cr clearance), ALT, HBsAg (if not vaccinated), Pregnancy test (adolescent or woman or reproductive age), syphilis test (adolescent or adult), cholesterol and triglycerides (especially if starting PI), HPV test or visual inspection with acetic acid in sexually active adolescent or woman.

- Visit 2 (1-2 weeks later initiate ART if not initiated on visit 1)
  - Target history and examination
  - Screen for TB, cryptococcus and PCP
  - Review CTX adherence (if already started)
  - Initiate CTX (if eligible and not initiated at enrollment)
  - Initiate TB prophylaxis if TB screening is negative if not initiated
  - Review lab test result.
  - Initiate ART if not imitated
  - Lab tests: Urinalysis, sputum AFB smear/geneXpert MTB RIF in individuals with a positive screening, serum Cryptococcal antigen test for adolescents and adults with CD4 count< 100cells/µL.
- Visit 3 (2-4 weeks from enrollement, initiate ART if not imitated)
  - Targeted history and examination
  - Screen for TB and other OIs
  - Review CTX adherence
  - Initiate TB prophylaxis if TB screening is negative if not initiated
  - Initiate ART if not started in the last 2 visits
  - Adherence counselling
  - Lab tests: urinalysis, sputum AFB, serum Cryptococcal antigen test for adolescents and adults with CD4 count< 100cells/µL.

Creatinine clearance= $\frac{(140-age)\times Weight\ (kg)\times(constant)}{Serum\ creatinine\ (in\ micromol/L)}$

Constant= 1.23 for males and 1.04 for women.

- If creatinine clearance >50ml/min you can use TDF
- If creatinine clearance between 30 to 50 ml/min replace TDF with TAF
- If creatinine clearance <30ml/min replace TDF with ABC and adjust dose of 3TC
- Note: if evidence of renal disease replace TDF with TAF or ABC. Avoid TAF in pregnant women or TB patients on Rifampicin, also increase DTG to 50mg BD.


HIV +ve
Counselling:
Post test counselling and education
Brief Targeted Medical History:
Ask about fever, weight loss, cough, persistent headache, h/o: Kidney Disease, Hypertension, Diabetes, Acute or Chronic Diarrhoea, use of NSAIDs (Ibuprofen, Diclofenac, Aspirin, Indomethacin), Herbal Medications
Clinical Examination:
Check BP, Weight, Height, BMI + Random Blood Sugar & Urinalysis (where glucostix & urine dipstix tests are available)
BP > 140/90
BMI < 18.5
Severe acute illness
Chronic use of NSAIDs or Herbal medications
Proteinuria +3 (if urine dipstix test available)
RBS >11.1 (if glucostix test available)
NO Evidence of above:
Prepare patient for same day ART:
Initiate the following ARVs:
• TDF (or TAF) + XTC + DTG
• If HIV/TB and on Rifampicin DTG 50mg twice daily but avoid TAF
Provide adherence counselling
YES Evidence of above:
Prepare patient for same day ART:
• Screen for TB and Cryptococcal meningitis
• If positive TREAT these OIs and defer ART
• If evidence of renal disease, replace TDF with TAF Or ABC
• If pregnant or TB avoid TAF
Patient not ready for ART?
Discuss reasons why and schedule follow up appointment within 7 days
Draw baseline labs (CD4, Creatinine, Hb, HBV, RPR, ALT), send them for testing and review patient within 14 days to discuss laboratory results:
For Patients on TDF, Creatinine Clearance:
• >50mL/min, continue TDF
• Between 50 and 30mL/min, replace TDF with TAF
• <30mL/min, replace TDF with ABC and adjust dose of 3TC
For Patients on TAF with Creatinine Clearance
• Between 50 and 30mL/min, continue TAF
• <30mL/min, replace TAF with ABC and adjust dose of 3TC*

- Treat co-infection
  - Active TB: 4FDCs. Overlapping toxicities and drug interactions make TB-HIV co-treatment difficult, but if CD4 <350 (and especially <100), treat TB then initiate HAART after 2 weeks of treatment.
  - Latent TB: 6 months isoniazid and pyridoxine
  - Hepatitis C: combination direct-acting antiviral, paying attention to drug interaction.
- Prophylactic antibiotics:
  - Co-trimoxazole for PCP and toxoplasma if CD4 <200.
  - Azithromycin for MAC if CD4 <50

TREATMENT FAILURE

- Treatment failure can be:
  - Clinical: Treatment failure should be considered when clinical symptoms appear whilst on therapy that is suggestive of deteriorating status.
  - Immunological: treatment failure is indicated by a drop of CD4 values to below pre-treatment levels or 50% from the peak value on treatment or perisistant CD4 levels below 50 cells/mm^3 after 12 months on therapy. Note: patients initiating at very low CD4 may not be able to mount an adequate CD4 recovery in this case viral load is indicated.
  - Virologic: plasma HIV viral load >400 copies/ml after 6 months on therapy.
- Patients who appear to be failing on treatment while viral load is undetectable should be considered to have undiagnosed opportunistic infection or other concomitant illness.
- It should not be concluded on the basis of clinical criteria, that an ARV regimen is failing until there has been a reasonable trial of 1st line therapy lasting at least 6 months, adherence has been assessed and optimized, intercurrent OIs have been treated and resolved and IRIS has been excluded.
- Clinical events that occur before the first 6 months of therapy are excluded from this definition because they often represent immune reconstitution inflammatory syndroems related to pre-existing conditions.
- Factors leading to treatment failure:
  - Poor adherence to treatment
  - Prior exposure to antiretroviral treatment with development of resistance
  - Primary viral resistance (infected with resistant HIV strain)
  - Inadequate drug absorption

- Suboptimal dosing (e.g. sharing dose because of side effets)
- Inadequate or inconsistent drug therapy
- Drug interactions

Management of Treatment Failure (Salvage Therapy)

Reason for failure	Action	What to do
Poor compliance within 8-16 weeks of therapy	Review reasons for poor compliance and counsel accordingly.	Continue with same combination or simplify dosing.
Poor compliance > 16 weeks of therapy	Consider changing therapy. Review reasons for poor compliance.	Change two drugs.
Treatment failure	Change therapy.	Use drugs not used in previous regimen preferably new classes.
Adverse drug reaction	Check drug –drug interactions. Stop the drugs if continuation is of no benefit to the patient.	Change the offending drug.
Depression	Psychosocial support	Refer to appropriate care provider

PROGNOSTIC FACTORS

- CD4 count: measures the degree of immune compromise and predicts the risk of opportunistic infections
- HIV viral load: measures HIV replication rate, gauges the efficacy of anti-retrovirals and predicts CD4 count decline.

ANTIRETROVIRAL DRUGS

- Selection of the appropriate combination is based on:
  - Avoiding the use of 2 agents of the same nucleoside analogue
  - Avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus
  - Patient factors such as disease symptoms and concurrent illnesses
  - Impact of drug interactions
  - Ease of adherence to the regimen
- The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality and to improve quality of life.
- Common side effects of antivirals: GI upset (diarrhea, vomiting, hepatitis especially with Nevirapine), Skin (mild rash, in rare cases hypersensitivity or SJS/TEN), Metabolic (lipodystrophy- fat reduction peripherally i.e. head and limbs but gain central it is seen with NRTIs and PIs; diabetes and dyslipidemia especially with PIs but possible with all)

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

- These are prodrugs (chain terminators). They use non-specific kinases to be activated (and so carry a risk of bone marrow suppression).
- They are used with protease inhibitors (PIs) in HAART.
- Drugs:
  - Zidovudine (azidothymidine)- (AZT)
  - Tenofovir (TDF)
  - Abacavir (ABC)
  - Lamivudine (3TC)
  - Emtricitabine (FTC)
  - Stavudine (D4T)
  - Didanosine (DDI)
- Mechanism of action: NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose) which all lack a 3’ hydroxyl group. Once they enter cells, they are phosphorylated by cellular enzymes to the corresponding triphosphate analog which is preferentially incorporated into the viral DNA by reverse transcriptase. Because the 3’ hydroxyl group is not present, a 3’5’ phophodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed and DNA chain elongation is terminated.

- Resistance occurs by mutations (multiple) in the gene (pol gene) that codes for reverse transcriptase, integrase and aspartate protease.
- Not complete cross-resistance between NRTIs. Mutations confers a high degree of resistance to lamivudine and emtricitabine but more importabtly restores sensitivity to zidovudine and tenofovir.
- Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine and adenosine), concomitant use of agents with the same analog target is contraindicated (e.g. Zidovudine and stavudine are both analogs of thymidine and should not be used together)
- Common combinations
  - First line combinations
    - Lamivudine/tenofovir (3TC/TDF)
    - Emtricitabine/tenofovir (FTC/TDF)
    - Abacavir/Lamivudine (ABC/3TC)
  - Second line combination: Lamivudine/ zidovudine (3TC/ AZT)
  - Others: didanosine, stavudine

Drug	Comment	Side effect
Zidovudine (AZT)	• Prototype drug • Pyrimidine analogue (thymidine) • Both stavudine and ribavirin are activated by the same intracellular pathway and should not be given with AZT	• Myleosuppression (bone marrow suppression)/hematotoxicity- this is the major and dose limting side effect, patients may require blood transfusion before initiating therapy ➢ Anemia ➢ Neutropenia • Headache, asthenia (Extreme fatigue), myalgia, myopathy, peripheral neuropathy
Tenofovir (TDF)	• It is an adenosine analog. • The drug should not be used with didanosine (DDI) due to drug interactions • Tenofovir decreases the concentrations of the PI atazanavir such that atazanavir must be boosted with ritonavir if these agents are given concurrently	• Renal failure • GIT compliaints: nausea and bloating • Osteoporosis
Lamivudine (3TC)	• Inhibits the reverse transcriptase in both HIV and HBV. It does not affect	• Least toxic of NRTIs and least potent

	mitochondrial DNA synthesis or bone marrow precursor cells resulting in less toxicity.	• Has some GI effects and neutropenia
Zalcitabine (DDC)	• Do not combine DDI and DDC because of pancreatitis as a side effect	• Peripheral neuropathy (major and dose limiting) • GI distress, pancreatitis, neutropenia, rash
Abacavir (ABC)	• It is a guanosine analogue	• GI distress, headache, and dizziness. 5% show hypersensitivity reactions to drug • Myocardial infarction
Didanosine (DDI)	• This is a precursor for both adenine and guanine	• Pancreatitis (major and dose limiting) • Peripheral neuropathy, hyperuricemia, liver dysfunction
Emtricitabine (FTC)	• This is a derivative of lamivudine and inhibits both HIV and HBV reverse transcriptase. • It is more active than lamivudine	• Headache, diarrhea, nausea and rash • It may also cause hyperpigmentation of soles and palms.
Stavudine (D4T)	• Thymine analogue • Should not be used with AZT as it would compete for phosphorylation and site of action on the DND provirus	• Peripheral neuropathy (major and dose-limiting) • Myelosuppression <zidovudine

NON-NUCLESIDE REVERSE TRANSCRIPTASE INHIBITORS

- These do not require activation by cellular enzymes to inhibit reverse transcriptase inhibitor. (they are not prodrugs, no risk of myelosuppresion)
- They are additive or synergistic with NRTIs
- Drugs:
  - Efavirenz (EFV)
    - Can disrupt sleep cycle (insomnia and "dysphoric dreams"-nightmares) and cause psychosis
    - Avoid in pregnant women
  - Nevirapine (NVP)
    - A single dose of NVP given at the time of delivery will decrease vertical transmission of HIV by 50%.

- Primary side effects: Rash and increased liver function tests (hepatotoxicity) as well as Stevens-Johnson syndrome and Toxic epidermal necrolysis
- It is an inducer of cytochrome P450 3A4 and so shows drug interactions (i.e. with warfarin)

PROTEASE INHIBITORS

- Mechanism of action
  - Aspartate protease (pol gene encoded) is a viral enzyme that cleaves precursor polypeptides in HIV buds to form the proteins of the mature virus core
  - Enzyme contains a dipeptide structure not seen in mammalian proteins. PIs bind to this dipeptide inhibiting the enzyme
  - Resistance occurs via specific point mutations in pol gene such that there is not complete cross-resistance between different PIs
- These drugs are combined with NNRTIs as second line e.g. AZT, 3TC, LPV/r
- Drugs:
  - Lopinavir/ritonavir (LPV/r): due to poor bioavailability it is boosted with ritonavir
  - Saquinavir (SQV): one of the least toxic and has low oral bioavailabity and so is also boosted with low dose ritonavir
  - Ritonavir (RTV): no longer used as a single PI but used as a booster of other PIs
  - Indinavir (IDV): combined with ritonavir nearly always in combination regiemns with 2 NRTIs

  - Atazanavir (ATV)
  - Darunavir (DRV)
- Side effects:
  - Crystalluria (indinavir)
  - Syndrome of disordered lipid and carbohydrate metabolism with central adiposity and insulin resistance (less with atazanavir)
  - Gall stones (atazanavir)
  - Kidney stones (indanavir)
  - Major drug interactions (Ritonavir works on cytochrome P450)
    - Rifampicin
    - Digoxin (use lower dose of digoxin dose)
    - Oral contraceptives: use higher dose contraceptives



Figure 59: Accumulation of fat at the base of the neck in a patient receiving a PI

FUSION INHIBITORS

- Drugs:
  - Enfuvirtide (fusion inhibitor)
  - Maraviroc (Entry inhibitor-CCR5 inhibitor)

INTEGRASE INHIBITORS

- Inhibit intergrase preventing integration of viral genome into host genome
- Drugs:
  - Dolutegravir
  - Raltegravir
- Cross-resistance between raltegravir and elvitegravir can occur although dolutegravir has limited cross-resistance to other integrase inhibitors.
- Side effects: nausea, diarrhea are most common as drugs are well tolerated.

ARV drug	Common associated toxicity	Recommended ARV substitute
ABC	Hypersensitivity reaction	TAF, or TDF (if normal creatinine clearance or if child >= 30Kg), or AZT (if child <25 Kg)
ATV-r	Hyperbilirubinaemia,	DRV-r, LPV-r
AZT***	Severe anaemia or neutropenia, severe gastrointestinal intolerance, lactic acidosis	TDF or ABC (if on 1st line ART regimen; rule out failure before substitution) TAF Consult next level if on 2nd line
DTG	Insomnia, anxiety, depression, weight gain** and hypersensitivity reactions	EFV-400, ATV-r or LPV-r or DRV-r
EFV	Severe or persistent CNS side effects	DTG, ATV-r or LPV-r or DRV-r
LPV-r	Persistent diarrhoea, hyperlipidaemia	DTG if naïve RAL if in children,
NVP (or EFV)	Rash, Stevens Johnson Syndrome, hepatitis	DTG, ATV-r or LPV-r
RAL	Rash and hypersensitivity reaction	DTG, ATV-r or LPV-r
TAF	Gastrointestinal symptoms, headache	Rarely causes significant side toxicities, if occurs consult expert advice
TDF	Renal toxicity (renal tubular dysfunction)	ABC or TAF

PRE-EXPOSURE PROPHYLAXIS (PrEP)

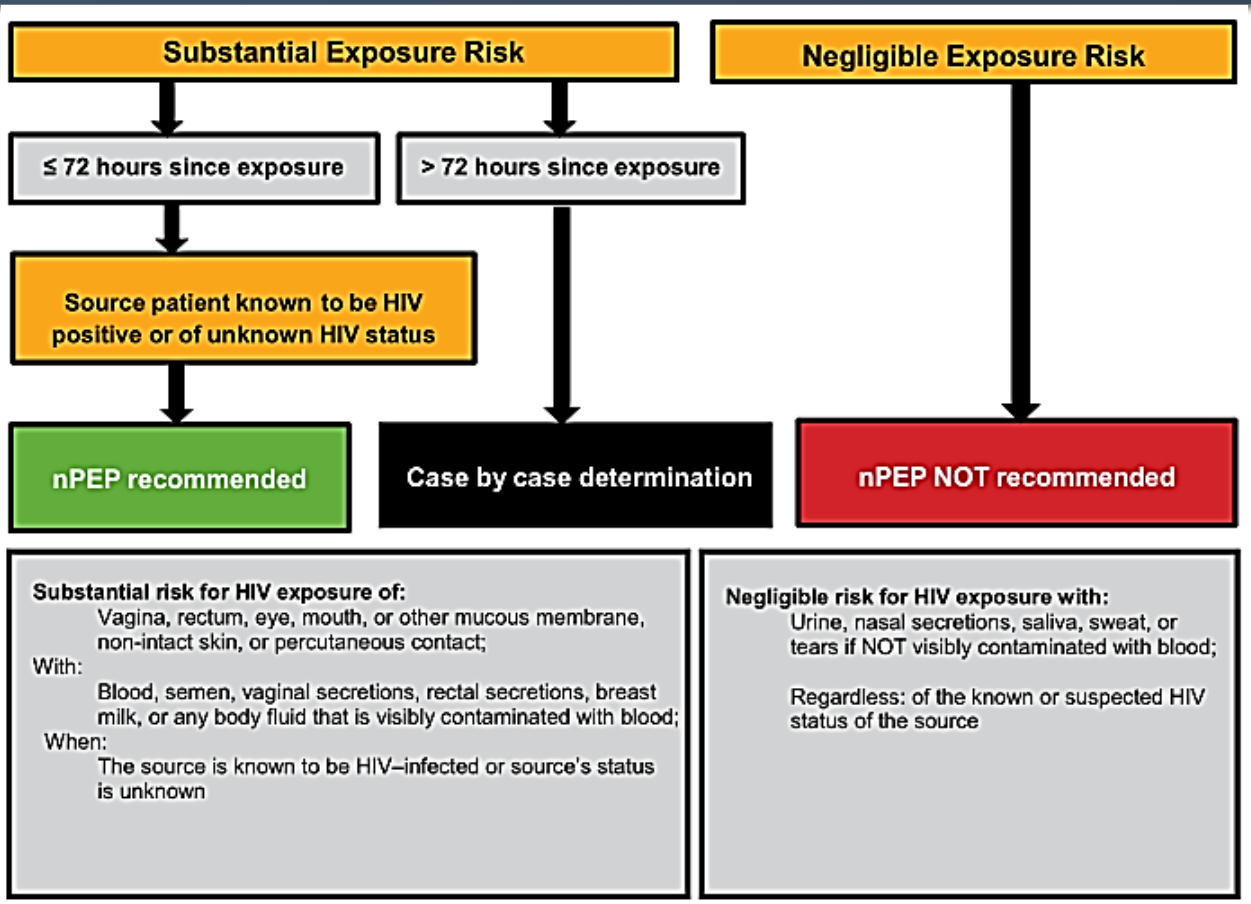
- PrEP is used as a preventive measure of HIV transmission in people at substantial risk of HIV acquisition.
- Eligibility criteria:
  - No suspicion of acute HIV infection
  - Test HIV negative
  - Perceives to be at substantial risk of HIV acquisition and willing to be adherent
  - Able to attend regular 3 month reviews and HIV testing
  - Able to concomitantly apply other methods such as barriers to prevent the transmission of other STIs
  - Willing to stop taking PrEP when no longer eligible
  - People at high risk: engaging in 1 or more of the following in last 6 months
    - Vaginal/anal intercourse without condomes with more than 1 partner
    - Sexually active with a partner who is known positive or at substantial risk of being HIV positive
    - Sexually active with an HIV positive partner who is not on effective treatment (ART for <6 months or not virally suppressed)
    - History of STI

  - History of PEP use
  - Sharing injection material or equipment
- ARVs are used for oral PrEP and PEP
- Oral PrEP containing Tenofovr disoproxil fumarate (TDF) or alternatively Tenofovir alafenamide (TAF) with with either Emtricitabine (FTC) or Lamivudine (3TC) should be offered as an additional prevention choice for people at substantial risk of HIV acquisition as part of combination HIV prevention approaches.
- Drugs used:
  - TDF + XTC (emtricitabine FTC or lamivudine 3TC) is safe in pregnancy and during breastfeeding. It is also active against hepatitis B infection thus discontinuation of this combination requires close monitoring in those infected with hepatitis B due to concern of rebound viremia
  - TAF + FTC can be used in patients with a Creatinine clearance between 30 and 50ml/min, though TAG is not currently recommended for use in patients with TB or pregnancy.
- Persons with osteopenia/Osteomalacia/osteoporosis may be at risk of bone loss associated with TDF therefore TAF would be recommended in such population
- TDF should not be co-administered with other nephrotoxic drugs e.g. aminoglycosides.
- Standard TB medication or oral contraceptives do not interact with PrEP drugs and there is no need for dose adjustments.
- PrEP clients must be routinely test for HIV infection and ART offered immediately if the PrEP user seroconverts.
- PrEP should be taken a minimum of 7 days in men and 21 days in women to achieve maximal protection from HIV acquisition before engaging in high risk sexual exposure and must be continued as long as risky exposure persists or one remains negative.
- PrEP should be discontinued after 4 weeks of elimination of the risky exposure.
- Note: PrEP alone is not 100% effective at preventing HIV and clients need to be counselled that they should use other prevention methods as well.

Activity	Timing of Visit
Confirmation of HIV-negative status	Initial visit, month 1, and then every 3 months
Adherence Counselling	Every visit
Side effects	Every visit
Creatinine Clearance Test	Initial visit, month 1, 2, then every 3 months for the first year, then annually
ALT	Every 3 months for first year, then annually
STI Screening	Every visit
PrEP Drug Dispensation	Initial visit, month 1, and then every 3 months
Behavioral sexual risk reduction counselling	Every visit

POST-EXPOSURE PROPHYLAXIS (PEP)

- This is the use of ART to prevent HIV transmission.
- There is no risk of transmission when the skin is intact.
- Factors associated with increased risk:
  - Deep injury
  - Visible blood on the device that caused the injury
  - Injury with a large bore needle from artery or vein
  - Unsuppressed HIV viral load in source patient
  - Body fluids and materials that pose risk of HIV transmission are amniotic fluid, cerebrospinal fluid, human breast milk, pericardial fluid, peritoneal fluid, pleural fluid, saliva in association with dentistry, synovial fluid, unfixed human tisues and organs, vaginal secretions, semen, any other visibly blood stained fluid and fluid from burns or skin lesion.
- Management:
  - Immediately after exposure
    - Clean the site: wash skin wounds with soap and running water. Do not squeeze, allow wound to freely bleed. If the exposed area is an eye or mucous membrane, flush with copious amounts of clean water. Do not use bleach or other caustic agents/disinfectants to clean the skin
  - Contact incharge or supervisor
  - Consult medical officer to determine the need for PEP based on the risk of transmission and risks and benefits of taking (or not taking) ART



Risk category	ART	Duration
No risk: intact skin	Not recommended	
Medium risk: invasive injury, no blood visible on needle High risk: large volume of blood/fluid, known HIV-infected patient, large bore needle, deep extensive injury Penetrative sexual abuse	Preferred: TDF or TAF + XTC + DTG Alternative: TDF or TAF + XTC + DRV-r TDF or TAF + XTC + LPV-r TDF or TAF + XTC + ATV-r AZT + 3TC + LPV-r (children < 20kg) AZT + 3TC + DTG (children ≥ 20kg) TAF + FTC + DTG (children ≥ 25kg)	28 days

Clients on PEP should have an HIV test before starting PEP, 6 weeks and at 3 months. While on PEP, the client should be reviewed and offered appropriate laboratory investigations

SYSTEMIC MANIFESTATIONS OF HIV INFECTION

- These include:
  - Neurological manifestations (second most common)
    - Directly related to HIV
    - Secondary to immunodeficiency
      - Opportunistic infections (AIDS defining)
      - Opportunistic malignancies (AIDS defining)
    - ART related
  - Respiratory manifestations (most common)
    - Opportunistic infections (AIDS defining)
    - Opportunistic malignancies (AIDS defining)
  - Gastrointestinal manifestations
    - Oral candidiasis
    - Oral hairy leukoplakia
    - Diarrhea
      - Persistent cryptosporidiosis (AIDS defining)
      - Chronic diarrhea of unknown cause (HIV enteropathy)
    - Weight loss of unknown causes
    - Infection with *Salmonella*, *Shigella*, *Campylobacter*, Hepatitis B infection, Hepatitis C infection
  - Dermatological
    - Kaposi's sarcoma (AIDS defining)
    - Severe/recalcitrant seborrheic dermatitis
    - Multidermatomal/Recurrent herpes zoster
  - Oncology (Opportunistic malignancies)
    - Kaposi's sarcoma
    - Lymphomas
    - Cervical cancer

HIV-associated indicator conditions

Respiratory

Tuberculosis; pneumocystis[a]; bacterial pneumonia; aspergillosis.

Neurology

Cerebral toxoplasmosis[a]; primary cerebral lymphoma[a]; cryptococcal meningitis[a]; progressive multifocal leucoencephalopathy[a]; aseptic meningitis/encephalitis; cerebral abscess; space-occupying lesion of unknown cause; Guillain–Barré syndrome; transverse myelitis; peripheral neuropathy; dementia.

Dermatology

Kaposi's sarcoma[a]; severe/recalcitrant seborrhoeic dermatitis; severe/recalcitrant psoriasis; multidermatomal/recurrent herpes zoster.

Gastroenterology

Persistent cryptosporidiosis[a]; oral candidiasis; oral hairy leukoplakia; chronic diarrhoea of unknown cause; weight loss of unknown cause; *Salmonella*; *Shigella*; *Campylobacter*; hepatitis B infection; hepatitis C infection.

Oncology

Non-Hodgkin's lymphoma[a]; anal cancer; anal intraepithelial dysplasia; lung cancer; seminoma; head and neck cancer; Hodgkin's lymphoma; Castleman's disease.

Gynaecology

Cervical cancer[a]; vaginal intraepithelial neoplasia; cervical intraepithelial neoplasia, grade 2 or above.

Haematology

Any unexplained blood dyscrasia including thrombocytopenia, neutropenia and lymphopenia.

Opthalmology

Cytomegalovirus retinitis[a]; infective retinal diseases including herpesviruses and toxoplasma; any unexplained retinopathy.

ENT

Lymphadenopathy of unknown cause; chronic parotitis; lymphoepithelial parotid cysts.

Other

Mononucleosis-like syndrome (primary HIV infection); pyrexia of unknown origin; any lymphadenopathy of unknown cause; any sexually transmitted infection.

[a]*AIDS-defining condition.*

- Opportunistic infections are infections that develop as a result of HIV-inflicted damage to the immune system. They are the leading cause of morbidity and mortality in HIV infected persons. Most opportunistic infections and complications of HIV develop when the CD4 count drops below 200cell/ml.
- Opportunistic malignancies are neoplastic conditions which tend to occur more frequently in patients with underlying immunodeficiency.

NEUROLOGICAL MANIFESTATIONS

- This is the second commonly affected organ system by HIV next to the respiratory system.
- Neurological manifestations can occur at any stage of HV.
- All lelves of the neuro-axis are involved.
- Clinical manifestations are variable and include:
  - Directly related to HIV
    - Aseptic meningitis
    - AIDS dementia complex: Acute demyelinating distal polyneuropathy (AIDP), monouritis multiplex (MNM) and Distal sensory polyneuropathy (DSPN)
    - Myelopathy
    - Peripheral neuropathy
    - Myopathy
    - Vasculitis
  - Secondary to immunodeficiency
    - Opportunistic infections
      - CNS toxoplasmosis
      - Cryptococcal meningitis
      - Tuberculous meningitis/Tuberculoma
      - Progressive multifocal leucoencephalipathy
      - CMV polyradiculopathy/Encepalitis
    - Opportunistic malignancies: Primary CNS lymphoma
  - ART related
    - Peripheral neuropathy: didanosine (DDI) and stavudine (D4T)
    - Myopathy: zidovudine (AZT)
    - Psychiatric manifestations (psychosis): Efavirenz (EFV)

NEUROLOGIC MANIFESTATIONS DIRECTLY RELATED TO HIV

ASEPTIC MENINGITIS

- This may occur at any time in the course of HIV infection, most commonly at the time of acute HIV infection.
- It becomes increasingly rare following the development of AIDS.
- Patients experience a syndrome of:
  - Headache
  - Photophobia
  - Sometimes: Frank-encephalitis and cranial nerve involvement (Commonly VII cranial nerve is affect)
- CSF findings:
  - Lymphocyte pleocytosis 10-100 cells/μL
  - Increased protein level
  - Normal glucose level
- Diagnosis of HIV: HIV serology may be negative if it occurs during the primary HIV infection. To confirm the diagnosis of HIV p24 antigen or DNA PCR may be done or repeat serology after few weeks.
- The syndrome usually resolves spontaneously within 2-4 weeks.

AIDS DEMENTIA COMPLEX

- This may be the first AIDS defining illness in up to 5-10%. It is a major cause of dementia in young people.
- A major feature of this entity is the development of dementia which is defined as a decline in cognitive ability, motor and behavioral dysfunction.
- Triad:
  - Cognitive dysfunction
  - Motor dysfunction
  - Behavioral dysfunction

	Cognition	Behavior	Motor
Early	Inability to concentrate	Altered personality	
Middle	Mental slowing Forgetfulness	Social withdrawal	Poor coordination
Late	Global dementia	Apathy	Paraparesis

- Diagnosis:
  - Neuropsychological tests
  - Mini-mental test
  - It is often a diagnosis of exclusion
- Treatment:
  - Antiretroviral therapy especially with those that penetrate the CNS (zidovudine, Stavudine, abacavir and nevirapine)
  - Supportive care

PERIPHERAL NEUROPATHY

- Occurs in 1/3 of patients with AIDS.
- Types:
  - Mononeuropathy e.g. Bell's palsy
  - Mononuritis multiplex
  - Distal sensory peripheral polyneuropathy (DSPN)
- DSPN: is the most common, it presents with symmetric bilateral painful burning sensation, paresthesia and tingling of the feet and lower extremities.
- Diagnosis:
  - Clinical
  - Nerve condution study
  - Exclsion of other causes
- Treatment: Symptomatic treatment and discontinuation or changing the drug causing it when symptoms are severe.

OPPORTUNISTIC INFECTIONS

CNS TOXOPLASMOSIS

- This is caused by the protozoa *Toxoplasma gondii*.
- It is a zoonotic infection and cats are the definite host and excrete the oocysts in their feces and can be transmitted from animal to humans.
- *T. gondii* cysts are also found in under-cooked meat.
- This is the second most common cause of secondary CNS infection in patients with AIDS.
- It is generally a late complication of HIV infection and usually occurs when the CD4 cell count is less than 100/mm^3.
- It is though to represent a reactivation syndrome of prior infection
- Clincal features:
  - Onset- subacute

- Fever, headache, hemiparesis, seizures and altered mental status
- Focal neurological signs (90%)
- Encephalitis picture (10%)- confusion or common and become more toxic
- Commonly affected areas- basal ganglia, brain stem and cerebellum
- Extracranial manifestations:
  - Chorioretinitis
  - Myocarditis
  - Pneumonitis (lung)

- Diagnosis:
  - Clincial: history and physical examination
  - Neuroimaging (CT/MRI):
    - Multiple ring enchancing lesions are seen in 90% of patients with mass effect and edema. (A solitary lesion on MRI makes the diagnosis unlikely)
    - Preferential location: basal ganglia, grey-white junction, white matter
  - Therapeutic trial +/- histology (biopsy)
    - Histology: brain biopsy- in patients with treatment failure (not possible in Zambia)

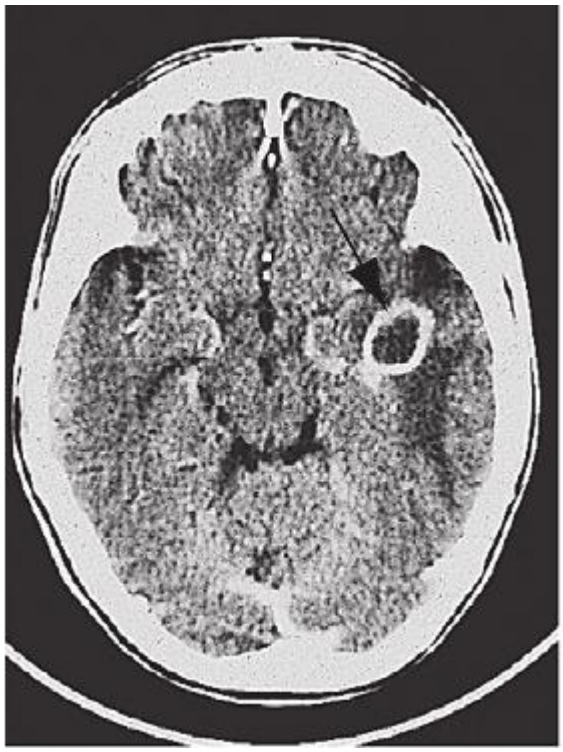


Figure 60: : CT showing a ring enhancing lesion with adjacent edema (Pyogenic cerebral abscess).

- Serologic assays are of limited value, a negative toxoplasma antibody test makes the diagnosis less likely.
- Treatment:
  - Regimen one: Loading dose of pyrimethamine 200mg (loading dose 200mg, then 50mg daily) combined with sulfadiazine (2-4g/day) and folinic acid (10-20mg/day)
  - Regimen two: Fansidar (Pyrimethamine 25mg + Sulfadoxine 500mg) + Folinic acid 10-20mg/day
    - Dose: 525mg (2 tabs) PO BD for 2 days and then 1 tab PO/day, if patient is very critical add Doxycycline 100 PO BD.
  - Regimen 3: Pyrimethamine (loading dose 200mg, then 50mg daily) and Folinic acid 10-20mg/day plus Clindamycin 450mg 8 hourly
  - Note: Clindamycin and pyrimethamine may be used in patients allergic to sulphonamide

- Duration of treatment is 6 weeks or 3 weeks after complete resolution of lesions on CT.
- Continue suppressive therapy for life: Pyrimethamine 25mg/day + Sulfadiazine 2g/day + folinic acid 5-10mg/day.
- HAART should be initiated as soon as the patient is clinically stable, approximately 2 weeks after acute treatment has begun to minimize the risk of IRIS.
- Side effect:
  - Leucopenia (main side effect of treatment). A higher dose of fansidar (2 tab/day) has been found to be associatd with frequent incidence of fatal hemorrhage
  - Check for bleeding tendency such as gum bleeding, epistaxis, hematuria
  - Do FBC once per week
  - To prevent effects give folinic acid 10mg PO
  - If there is bleeding tendency stop fansider and start Doxycycline 100mg PO BD
  - Alternatives:
    - Co-trimoxazole or Clindamycin + Pyrimethamine/Primaquine
    - Azithromycin, Clarithromycin, Doxycycline
- Indications for steroid use:
  - Evidence of marked increased intracranial pressure and altered mentation
  - Dose: administer: dexamethasone 8mg IV stat and then 4mg IV DIQ till the suppressive/maintenance therapy: Fansidar 1 tab per day should be continued. Suppressive therapy (Secondary prophylaxis) can be stopped when the CD4 count is more than 200 for 6 months.

- Prevention: for all with CD4 count <100cells/microliter
  - Use TMP-SMX 2 tablets per day
  - TMP-SMX 2 tablets three times per week
  - Alternatively: Dapson plus pyrimethamine plus folinic acid.
  - Primary prophylaxis can be stopped if CD count> 200cells/ml for more than 3 months following antiretroviral therapy

CRYPTOCOCCAL MENINGITIS

- This is caused by Cryptococcus neoformans which is a yeast-like fungus.
- Pigeon dropping common contain serotypes A or D.
- Infection is acquired through inhalation.
- It is the leading cause of meningitis in patients with AIDS.
- It occurs late in the course of HIV/AIDS when the CD4 count drops below 100.
- Clinical features:
  - Low grade fever, nausea, vomiting, headache
  - Both fever and nuchal rigidity are often mild or lacking
  - Papilledema is seen in 1/3 of patients
  - Neck stiffness, photophoba- meningeal signs (30%)
  - Late manifestations: confusion, altered state of consciousness➔ coma.
  - Extracranial manifestations:
    - Pulmonary or disseminated disease that includes the skin (10%)
    - Cutaneous Cryptococcosis: centrally umbilicated multiple lesions on the face (look very much like Molluscum contagiosum)
    - Pulmonary disease
    - Fungemia
    - Lymphadenopathy
    - The prostate gland may be a reservoir for smoldering infection
- Diagnosis:
  - LP-CSF analysis
    - Opening pressure is high
    - WBC with differential, protein, glucose is normal in 1/3 of patients
    - India Ink- positive in 60-80%
    - CSF cryotptoccal antigen- Positive in 95-99%
    - Cryptococcal culture- Gold standard
- Treatment (See meningitis for details)
  - Induction: Amphotericin B 0.7-1 mg/kg for 2 to 3 weeks with fluconazole 800mg
  - Consolidation: Fluconazole 400mg PO daily for 8-10weeks or until CSF is sterile
  - Maintenance: Fluconazole 200mg PO daily life long
    - Discontinue maintence or secondary prophylaxis when CD4 count >200 for more than 6 months after completion of treatment following patient who are taking HAART

- Adjunct treatment:
  - Management of raised intracranial pressure: if CSF opening pressure- CSF drainage until CSF pressure <200mmHg, repeat LP daily until stable or CSF pressue normalizes.
  - There is no place for dexamethasone

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

- This is due to reactivation of JC virus (John Cunningham virus).
- It is seen in 2-4% of AIDS patients.
- PML is characterized by progressive damage (-pathy) or inflammation of the white matter (leuko-) of the brain (encephalo-) at multiple locations (multiple)
- Clincal presentation:
  - Occurs late in the course of HIV when CD count <100
  - Subacute onset
  - The patient is afebrile, alert without headache
  - Multifocal neurologic deficit
  - Classic triad:
    - Dementia
    - Hemiparesis
    - Hemianopsia
- Diagnosis:
  - CSF is often non-diagnostic.
    - CT shows multifocal, non-contrast enhancing hypodense lesions without mass effect but MRI is more sensitive.
    - Common areas of involvement: cortical white matter of frontal and parietaloccipital lobes. Lesions can occur anywhere
  - Serology: 90% adults are seropositive for JC virus so this is not useful in diagnosis
  - JCV PCR or brain biopsy may help to make diagnosis
- There is no effective treatment but initiation of HAART increases survival.

OPPORTUNISTIC MALIGNANCIES

PRIMARY CNS LYMPOMA

- This occurs late in the coruse of HIV (CD<100)
- Clinical features:
  - Confusion, lethargy, memory loss (57%)
  - Hemiparesis or aphasia (40%)

  - Seizures (14%)
  - Cranial nerve palsy (9%)
  - Headaches only (3%)
  - No fever unless concomitant infection
- Diagnosis
  - CT/MRI: Multiple lesions as frequent or as single lesions (irregular and solid enhancement, subependymal enhacement more specific, variable mass effect. Localization mainly periventricular)
  - CSF: EBV DNA PCR- CSF (85-100% sensitive, 98-100% specific)
  - Histology: diffuse infiltrating, multicentric tumor of B cell lineage with the presence of EBV genome in approximately 100%.
- Treatment:
  - Cytotoxic chemotherapy is not effective
  - Radiotherapy can help some patients
  - Response to steroid variable

SEIZURES

- These are a relatively frequent complication of HIV infection.
- They may be due to opportunistic infections, neoplasms or HIV encephalitis.
- The seizure threshold is often lower than normal in patients with HIV infection owing to the frequent presence of electrolyte abnormalities.
  - CNS infections may cause increased released of ADH (SIADH) with reabsorption of water and a Euvolemic hyponatremia.
- Common causes:
  - CNS toxoplasmosis
  - Primary CNS lymphoma
  - Cryptococcal meningitis
  - HIV encephalopathy
- Treatment:
  - Most of the time patient will have 2 or more seizures suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rapidly correctable cause is found.
  - While phenytoin (100mg PO TDS) remains the initial treatment of choice. Phenobarbital (100mg PO every night) or Valproic acid are aslo alternative.

RESPIRATORY MANIFESTATIONS

- There is a widespread spectrum of pulmonary manifestations.
- Opportunistic infections include:
  - Bacterial: *Stretococcal, H. influenza, gram negative, Staphylococcal*
  - Mycobacterial: *M. tuberculosis, M. kansasi, M. avium intracellularie*
  - Fungal: *PJP, Cryptococcus neoformans, Histoplasmosis, Coccidiodeocomycosis, Aspergillosis*
  - Viral: Cytomegalovirus, Herpes simplex infection
  - Parasitic: *Toxoplasmosis, Strongliodosis*
- Opportunistic malignancies include:
  - Pulmonary Kaposi's sarcoma
  - Non-Hodgkin's lymphoma
- The types of opportunistic infections and malignancies develops depending on the degree of immunosuppression.

CD4 COUNT /mm^3	MANIFESTATIONS
Any CD4 level	• Upper respiratory tract infection (URTI): Sinusitis, Pharyngitis • Acute bronchitis • Bacterial pneumonia • Tuberculosis • Non-Hodgkin's lymphoma
<500	• Bacteria pneumonia • Pulmonary TB
<200	• Pneumocystis jiroverci pneumonia • Cryptococcus neoformans pneumonia • Bacterial pneumonia (associated with bacteremia/sepsis) • Disseminated or extrapulmonary tuberculosis
<100	• Pulmonary Kaposi's sarcoma • Bacterial pneumonia (Gram-negative bacilli and *Staphylococcus aureus* increased) • Toxoplasma pneumonitis
<50	• Disseminated *Histoplasma capsulatum* • Disseminated *Coccidiodes immitis* • Cytomegalovirus pneumonitis • Disseminated *mycobacterium avium complex* • Disseminated mycobacterium (non-tuberculous) • Aspergillus species pneumonia

BACTERIAL PNEUMONIA

- Common etiological agents: *S. pneumoniae.*
- As the degree of immunosuppression worsens pneumonia may be recurrent and associated with sepsis
- Clinical presentation:
  - Abrupt onset fever
  - Cough
  - Production of purulent sputum
  - Dyspnea
  - Pleuritic chest pain
- Recommended investigations:
  - Chest Xray:
    - Pneumonic consolidation
    - Infiltrate
    - Pleural effusions
  - Blood culture
  - FBC: leukocytosis
  - Gram stain of the sputum
  - Sputum culture and sensitivity
- Treatment:
  - Antibiotics: Penicillin (procaine Pen/Crystalline Pen), Amoxicillin, Fluoroquinolones
  - Supplemental oxygen

PNEUMOCYSTIS JIROVECI PNEUMONIA

- This is caused by a fungus Pneumocystis jiroveci.
- It is one of the commonest OIs in industrialized countries however, due to initiation of antiretroviral therapy and use of CTX prophylaxis its incidence has declined.
- 50% of patients experience at least one bout of PCP during the course of their life time.
- It is transmitted from human to human or from environmental reservoirs to human.
- Clinical presentations:

- Indolent course characterized by weeks of vague symptoms prior to presentation or diagnosis.
- Median duration of symptom is 28 days.
- Dyspea and fever are cardinal symptoms
- Cough with scanty sputum in more than 2/3 of cases
- Physical examination reveals: (findings may be minimal, usual findings or pneumonia may not be noted)
  - Respiratory distress +/- cyanosis
  - Little abnormality on chest examination: rhonchi or wheeze may be heard especially in patients wiith some other underlying pulmonary disease; findings of consolidation are usually absent.
  - P. jiroveci appears to be capable of hematogenically spread with seeding of a variety of organ systems as well as causing primary infection of the ear.

- Diagnostic work up:
  - Chest X-ray: could be normal or show diffuse bilateral alveolar/interstitial infiltrates.
  - LD is elevated in more than 90% cases: has a very high negative predictive value i.e. if LDH level is low in a patient the diagnosis of PCP is less likely.
  - Definitive diagnosis- demonstration of the trophozoite or cyst from the organisms in camples obtained from induced sputum in which the yield is 60% or Broncho-alveolar lavage in which the yield is 95%. Staining: Wright-Giemsa, Methenamine silver, Direct IF, PCR.
  - Other tests: Gallium 67 scan, PFT, ABG
- Treatment
  - Antibiotics:
    - Gold standard: Co-trimoxazole IV/PO
    - Dose: 15mg/kg/day (trimethoprim) in 3-4 divided doses (3-4 tabs 480mg QID)
    - Duration of treatment: 21 days (3 weeks)
    - Side effects: rash, fever, leucopenia
    - Response to treatment may not occur until the end of the first week and the patient may get worse during the first few days owing to the inflammatory response resulting from the death of large number of organism in the lungs.
    - Alternatives:

- ♦ Clindamcin 600mg IV 8 hourly or 300-400mg PO 6 hourly + Primaquine 15-30mg base/day x 21 days
- ♦ Pentamidine 4mg/kg/day IV x 21 days
- ♦ Atovaquone 750mg PO BD with meal x 21 days

➢ Adjunct treatment
- ○ Supplemental oxygen
- ○ Steroids: reduce need for mechanical ventilation and mortality in 50%
  - ♦ Start within 72 hours of presentations
  - ♦ Indications: moderate/severe respiratory distress or cyanotic (PaO_2 <70mmHg)
  - ♦ Dose: Prednisolone 40mg PO BD x 5days, 40mg PO daily for 5 days, 20mg PO daily for 11 days

➢ PCP prophylaxis
- ○ Primary prophylaxis:
  - ♦ Recommended for HIV infected persons with evidence of significant immune deficiency
  - ♦ CD4 <200/microliter
  - ♦ HIV associated thrush
  - ♦ Unexplained fever
- ○ Secondary prophylaxis: for patients with prior episode of PCP
- ○ Regimens:
  - ♦ TMP-SMX 2 tablets/day (single strength)
  - ♦ TMP-SMX 2 tables three times a week
- ○ Alternatives
  - ♦ Dapsone 100mg PO daily
  - ♦ Dapsone 50mg PO daily plus pyrimethamine 50mg PO weekly plus folinic acid 25mg PO weekly
  - ♦ Aerosolized pentamidine 300mg monthly via nebulizer
  - ♦ Atovaquone 1500mg daily
- ○ Prevention of PCP may also be beneficial in reducing the risk of having other HIV associated infections such as CNS toxoplasmosis and other bacterial infections.

TUBERCULOSIS

- This is the leading opportunistic infection in developing countries.
- HIV is the most potent factor known to increase risk of progression form M. tuberculosis infection to active disease.
- Clinical presentation depends on degree of immunosuppression.

	Early stage of HIV infection (CD4 >200cells/mm^3)	**Late stage of HIV infection (CD4 <200 cells/mm^3)**
Clinical presentation	Similar to Non-HIV infected with productive cough Pulmonary manifestations dominate	Atypical presentation: Extrapulmonary TB is more common. TB tends to be disseminated (involving different organs like meningitis, pleura, pericardium, lymph nodes etc)
Laboratory diagnosis **sputum smear** **PPD**	• Often positive • Often reactive with >10mm	• Often negative • Often negative or annergic
Chest X-ray	• Typical CXR findgins of TB • Upper lobe and/or bilateral infiltrates • Cavitations • Pulmonary fibrosis	• Atypical CXR findings • CXR may show interstitial infiltrates especially in lower zones with no features of cavitations and fibrosis • Negative CXR can be associated with sputum AFB (+ 12% with pulmonary disease)

- Treatment:
  - When TB and HIV are co-existing TB is more life threatening and it should be treated first and patients should be stabilized.
  - The same combination anti-TB drugs are given based on the treatment category
  - Close follow up of patinets on DOTS is required
  - Complete cure from TB may be achieved in 6 to 8 months.
  - ART can usually be deferred for about 14 days and started as soon as the patient can tolerate anti-TB medication.
- Challenges/Problems in treatment of TB/HIV co-infected patients:
  - Increased morbidity, mortality and high case fatality rate
  - Increased drug toxicity
  - Decreased drug absorption
  - High pill burden which decreases adherence to treatment
  - Drug interaction between anti-TB drugs and ART e.g. TDF/TAF and Rifampicin (TDF has to be substituted for ABC)
- INH preventive therapy:
  - Advised for HIV infected patients
  - Patients should be screened for active TB before they are given preventive therapy
  - INH 300mg/day for 6-9 months
  - Alternatively, Rifampicin for 4 months can be used.

GASTROINTESTINAL MANIFESTATIONS

- These include:
  - Candidiasis
  - Oral hairy leucoplakia
  - Diarrhea

CANDIDIASIS

- This is due to infection with *Candida albicans*.
- It can manifest as:
  - Oral candidiasis
    - Appears as white, chessy exudates, often on an erythematous mucosa (most commonly seen on the soft palate) which gives an erythematous or bleeding surface on scrapping
    - Erythematous form: there is predominantly erythema rather than white patches



Figure 61: Oral candidiasis

  - Esophageal candidiasis
    - Usually coincides with CD4 count of <50/μL
    - Causes substernal pain or a sense of obstruction on swallowing
    - Most lesions occur on the distal third of the esophagus and appears on endoscopy as redness, edema and focal white patches or ulcers.
    - If an HIV infected person has oral thrush and substernal pain on swallowing presumed diagnosis of esophageal candidiasis can be made.
    - Endoscopy is needed to prove the diagnosis but is unnecessary if the patient responds to antifungal therapy



Figure 62: Esophageal candidiasis

    - Linear ulcerations of the esophagus may be seen on barium X-ray.
- Treatment:
  - Oral candidiasis:
    - Nystatin IU/ml suspension 2.5-5ml gargled 5times daily
    - 2% Miconazole oral gel applied 2-3 times daily
    - Amphotericin B lozenges

- Fluconazole 100-200mg PO/day for 7-14 days in severe and persistent cases
- Oral hygiene, discontinue steroids and antibiotics if the patient is taking any.

➢ Esophageal candidiasis: Fluconazole 200mg/day PO (up to 400mg/day) for 14-21 days

ORAL HAIRY LEUCOPLAKIA

- This is characterized by white plaques with vertical ridging on the sides of the tongue.
- Unlike with oral Candida the lesions cannot be peeled off.
- It was first recognized in HIV disease but can rarely occur in other forms of immunosuppression.
- It is thought to be due to co-infection with Epstein-Barr virus.
- Treatment is with acyclovir, ganciclovir or foscarnet.

DIARRHEA IN HIV POSITIVE PATIENTS

- This is a common clinical condition in over 50% of HIV infected patients
- It may be acute or chronic, watery, mucoid or bloody
- It may or may not be associated with fever.
- Spectrum of condition varies with degree of immunodeficiency state.
- Pathogens may be:
  - ➢ Bacterial
  - ➢ Viral
  - ➢ Protozoal
  - ➢ Fungal
  - ➢ Spirochetal
  - ➢ Mycobaterial
  - ➢ Metazoa
  - ➢ Others (malignancies)
- Mechanism of diarrhea:
  - ➢ Adhesion to mucosal surface
  - ➢ Enterotoxin
  - ➢ Entero-invasion
  - ➢ Atrophy of mucosal
- Chronic diarrheas

- This is diarrhea lasting for more than 2 weeks with a single watery bowel motion and/or 3 or more loose stools per day.
- Frequency of diarrhea increases as the CD4 count falls
- With Antiretroviral therapy, incidence of chronic diarrhea decreases
- Protozoa causing chronic diarrhea:
  - *Cryptosporidium parvum*
  - *Isospora belli*
  - *Microsporidium*

- HIV enteropathy (AIDS enteropathy)
  - This is a chronic diarrheal syndrome for which no etiologic agent other than HIV can be identified (Chronic diarrhea of unknown cause).
  - Clinical features
    - Early stage: intermittent self-limiting diarrhea however in advanced stage, persistent life threatening diarrhea
    - Copious amount of stool several times per/day associated with abdominal cramp, nausea and vomiting
    - Significant weight loss (wasting) may occur due to the associated malabsorption
    - Fluid and electrolyte depletion

DIAGNOSTIC INVESTIGATIONS

- Stool microscopy, culture and sensitivity
  - Special stains: Modified AFB stain (Modified ZN stain)
- Intestinal biopsy

TREATMENT

- General treatment of chronic diarrhea
  - Hydration: oral, parenteral with electrolyte replacement
  - Symptomatic treatment: Anti-diarrheal agents
    - Loperamide 2-4mg QID
    - Lomotil 5mg QID
    - Tincture of opium 0.3ml QID
    - Codeine tablets
- Specific treatment
  - Cryptosporidium
    - Nitazoxanide 0.5-1.0g BD or
    - Paromomycin 1g BD + Azithromycin 600mg QID
  - Isospora

  - Cotrimoxazole 2 tabs QID for 10 days then BD for 3 weeks or
  - Pyrimethamine 75mg + Folinic acid 10
  - Chronic suppression (Secondary prevention) Cotrimoxazole 2 tabs/day or pyrimethamine 25mg + folinic acid 5mg QID

STRONGYLOIDIAS

- This is a parasitic infection caused by *Strongyloid stercolaris*.
- It is acquired through skin penetration of its larva form.
- Auto-infection is common
- In its life cycle there is transition via the lungs and settles in the GIT, primarily small intestine free-living or parasitic.
- Usually a mild disease in immunocompetent individuals.
- Disseminated infection common in immune-compromised hosts
- Systemic manifestation may mimic sepsis.
- Clinical manifestations:
  - Immunocompetent: asymptomatic to mild symptoms with occasional severe pruritus. It may manifest with mild diarrhea, epigastric pain.
  - Immunocompromised: large amount of filariform larva are released and may invade
    - GIT tract: causing enteritis with severe diarrhea and malabsorption
    - Lungs: manifest with cough, shortness of breath (Lofflers' pneumonia)
    - CNS, peritoneium and liver may also be invaded
    - Severe systemic symptoms are commonly seen in disseminated infection
    - May be complicated by gram negative sepsis
- Treatment:
  - Ivermectine 200µg 1-2 days
  - Thiabendazole 75mg/kg BD for 3 days
  - Albendazole 400mg/day for 5 days

SKIN MANIFESTATIONS

- 80-90% of HIV patients have skin manifestations.
- The skin problems could be the first organ system to be affected.

Manifestation/ Etiology	Feature	Diagnosis & comments	Treament
BACTERIAL INFECTIONS ASSOCIATED WITH HIV			
Staphylococcus aureus	• Bullous impetigo • Folliculitis • Furuncle • Carbuncle • Cellulitis	• Microscopy, Culture and sensitivity	Topical antibiotics or systemic antibiotics depending on severity of the disease
Syphilis (*Treponema pallidum)*	• Atypical presentation in HIV patients • Primary chancre usually painless can be tender • Latent period befor development of meningovascular syphilis is shorter • Rapidly progresses to tertiary syphilis • Pleomorphic skin lesions reported	• VDRL can be negative due to high titer antibody level • Screening tests- VDRL (Venereal disease research laboratory test), RPR (Rapid plasma reagin) • Specific test- FTA-ABS- fluorescent treponemal antibody absorption	• Benzathine penicillin 2.4 Mega unit IM weekly 3 doses • Penicillin IV 2 to 4 mega unit every 4 hours for 10 to 14 days (with CNS involvement) • Azithromycine + Benzathine penicillin + Amoxicillin • Relapses without re-exposure • Follow up at 1, 2, 3, 6, 9 and 12 months
VIRAL DISEASE ASSOCIATED WITH HIV			
Herpes simplex	• Due to reactivation of latent virus • Usual manifestations are grouped vesicle with erythematous base • Atypical presentation in HIV patients • Chronic non healing deep ulcer • Verrucous erosion	• Clinical • Biopsy • PCR	• Systemic acyclovir 200mg 5x a day 5-10 days • Acyclovir 50mg/kg every 8 hours were absorption is poor

	• Widespread local extension • High incidenc of dissemination • Viremic spread to visceral organs which is life threatening		• Acyclovir 400mg BD in frequent relapse • High frequency of reactivation
Varicella-Zoster virus	• Hemorrhagic necrotic lesion • Chronic verrucous lesion • Multiple dermatormal involvement • Tendency to be generalized • May occur recurrently	• Clinical • Biopsy • PCR	• Primary varicella-acyclovir IV 10mg/kg every 8 hours for 7 to 10 days • Herpes zoster: ➢ Acyclovir 800mg 5x a day for 7-10 days ➢ Famcyclovir 500mg 5x a day for 7 days ➢ Valacyclovir 1g TDS for 7 days
Human papilloma virus	• Warts • Refractory to treatment • Complications are neoplastic changes and increased risk of cervical carcinoma	• Clinical • Biopsy • PCR	• Podophyllin 20% or 5-fluorouracil • Cyrotherapy or excision of big tumors
Molluscum contagiosum (Pox virus)	• Occurs in HIV patients with low CD4 count • Atypical presentations are common • It tends to be generalized • Giant molluscum contagiosum (Umbilicated papules) • Secondary infection	• Clinical • Biopsy • PCR	• Cryosugery or curettage or electrosurgery • Podophyllin or cantridine or 5-fluorouracil

PRURITIC PAPULAR ERUPTION (PPE)

- This is a chronic itchy condition commonly seen in HIV infected patients.
- Symmetrical non-folliclar papules are seen on the trunk and extensors of extremities.
- It is the most common cutaneous manifestations in HIV.
- Diagnosis: Biopsy
- Treatment:
  - Topical: Antipruritic lotion, corticosteroid, oatmeal bath
  - Systemic: Antihistamines, Corticosteroids, Phototherapy, UV-B, UV-A + Psoralen

OPPORTUNISTIC MALIGNANCIES

- These include:
  - Kaposi's sarcoma
  - Lymphoma
  - Cervical cancer

KAPOSI'S SARCOMA

- This is a tumor of vascular and lymphatic endothelium that presents as purplish nodules and plaques on skin and mucosa.
- It was first described by Moritz Kaposi in 1872.
- Immunosuppression increases risk of KS 400-500 times higher than general population.
- The presence of human herpes virus 8 (HHV-8) is found in all types of KS.
- KS has a worldwide distribution. In Africa it occurs largely in the south of the Sahara.
- Prevalence of AIDS-related KS has decreased due to widespread availability of HAART.
- KS associated with other forms of immunosuppression include those with iatrogenic suppression from oral prednisolone or other chronic immunosuppressive therapies as may be given to transplant patients.
- It affects more men than women (2:1 ratio).
- It is the most common cutaneous malignancy in HIV disease.
- This condition carries a variable clinical course ranging from minimal mucocutaneous disease to extensive organ involvement.
- Various visceral organs can also be affected.

- It has several subtypes which have different presentations, epidemiology and prognoses.

ETIOPATHOGENESIS

- KS is formed by abnormal proliferation of vascular endothelial cells.
- Infection with HHV-8 has been associated with the development of KS.
- HHV-8 (human herpes virus-8) is found in KS lesional tissue irrespective of clinical type.
- Transmission of HHV-8: mainly through saliva, organ transplantation, blood transfusion it is even believed to be transmitted sexually.
  - HHV-8 titers 2-3 times higher in saliva than in semen, anorectal or prostate fluid samples.
- HHV-8 is known to encode products that lead to growth dysregulation or evasion of immune surveillance.
  - A virally encoded G protein induces VEGF (vascular derived endothelial growth factor) production, stimulating endothelial growth
  - Cytokines produced by inflammatory cells recruited to the sites of lytic infection also create a local proliferative milieu
  - Other proteins disrupt normal cellular proliferation and prevent apoptosis by inhibiting p53.
- HIV virus Tat protein potentiates the milieu conducive to KS growth.

CLINICAL FEATURES

- Can affect almost any organ system.
- Cutaneous lesions in Kaposi sarcoma are characterized as follows:
  - Cutaneous lesions may occur at any location but typically are concentrated on the lower extremities and the head and neck region.
  - Lesions characterized by brown, pink, red or violaceous macules/patches, papules/plaques, nodules.
  - Nearly all lesions are palpable and non-pruritic
  - Lesions may range in size from several millimeters to several centimeters in diameter.





  - Lesions may assume a brown, pink, red or violaceous color and may be difficult to distinguish in dark-skinned individuals.
  - Lesions may be discrete or confluent and typically appear in a linear, symmetrical distribution, following Langer lines.
  - Mucous membrane involvement is common (palate, gingiva, conjunctiva)
- Lesions may vary depending on the clinical variant.
- Mucous membrane, cutaneous and visceral involvement is common (lymph nodes, GIT and lungs).
- The subtypes of KS include:
  - Classic or sporadic
  - African cutaneous (Endemic)
  - AIDS-associated (Epidemic)
  - Immunosuppressant therapy related (iatrogenic)

CLASSIC KAPOSI SARCOMA

- It is an indolent disease.
- It is seen chiefly in middle-aged men of southern and Eastern European origin.
- It is not associated with HIV.
- Early lesions appear most commonly on the toes or soles as reddish, violaceous or bluish-black macules and patches that spread and coalesce to form nodules or plaques.
- Brawny edema of the affected limb may be present
- Macules or nodules may appear, usually much later on the arms and hands and rarely may extend to the face, ears, trunk, genitalia or oral mucosa.
- Classic KS has a slowly progressive course.

AFRICAN CUTANEOUS (ENDEMIC)

- Endemic in tropical Africa.
- Mostly seen in men between the ages of 20 and 50.
- It is seen in HIV-seronegative persons.
- It has a locally aggressive but systemically indolent course.
- Characterized by nodular, infiltrating, vascular masses on the extremities.

- A particularly severe form, with prominent lymph node and visceral involvement, occurs in pre-pubertal children, the prognosis is poor, with an almost 100% mortality rate within 3 years. (African lymphadenopathic Kaposi sarcoma)
  - An aggressive disease of young patients mainly children under age 10.
  - Lymph node involvement with or without skin lesions.
  - Has an aggressive course, often terminating fatally within 2 years on onset.

AIDS ASSOCIATED KAPOSI SARCOMA (EPIDEMIC)

- KS in patients immunosuppressed by AIDS.
- AIDS-related Kaposi sarcoma, unlike other forms of the disease, tends to have an aggressive clinical course.
- It is the most common presentation of Kaposi sarcoma.
- Cutaneous lesions begin as one or several red to purple-red macules, rapidly progressing to papules, nodules, and plaques.
- There is a predilection for the head, neck, trunk and mucous membranes.
- A fulminant, progressive course with nodal and systemic involvement is expected.
- It may be the presenting manifestation of HIV infection (HIV stage 4).

IMMUNOSUPPRESION-ASSOCIATED KAPOSI SARCOMA

- Occurs in patients on immunosuppressive therapy
- Clinical features may be similar to that of classic KS, however, site of presentation is more variable.
- Removal of immunosuppression may result in regression of the KS.

INTERNAL ORGAN INVOLVEMENT

- Classic KS: GIT is most frequently involved (intestinal blockage and bleeding). Lungs, heart, liver, conjunctiva, adrenal glands, abdominal lymph nodes, and bones may also be affected.
- African cutaneous KS (endemic): frequently accompanied by massive leg edema and frequent bone involvement.
- African lymphadenopathic KS: reported among Bantu children who develop massive lymph node involvement, preceding appearance of skin lesions. The children also develop lesions on the eyelids and conjunctiva.
  - Eye involvement is often associated with swelling of the lacrimal, parotid, and submandibular glands.

- AIDS-associated KS: Lungs (37%), Gastrointestinal tract (50%), and lymph nodes (50%).

DIAGNOSIS

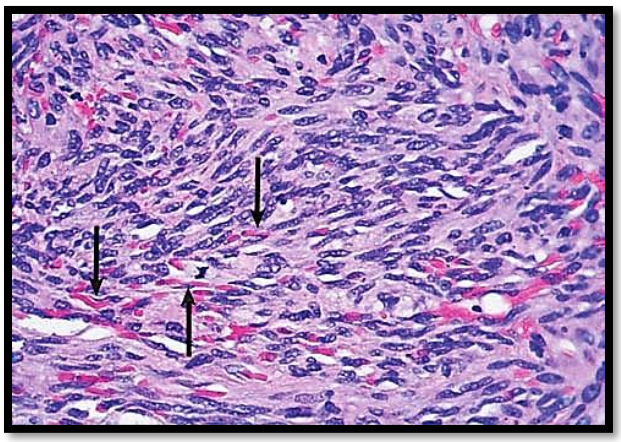
- Skin and oral lesions can be diagnosed by visual examination even though skin biopsy is most accurate to make diagnosis.
- Lung and GI-tract lesions would need endoscopy and biopsy for accuracy.
- Resolution of skin lesions with HAART can give a presumptive diagnosis.
- Testing for HHV-8 is more research than clinically applicable.

DIFFERENTIAL DIAGNOSIS

- Bacillary angiomatosis
- Pyogenic granuloma
- Leukemia cutis
- Cellulitis
- Severe stasis dermatitis
- Small-vessel vasculitis

WORK-UP

- Baseline investigations: Full blood count, Liver enzymes, Urea & electrolytes, Creatinine, RPR (syphilis)
- Skin biopsy
  - Prominent spindle cells
  - Prominent slit-like vascular spaces
  - Extravasated red blood cells
- Immunohistochemistry
- HIV test
- HHV-8 PCR
- CXR/CT-scan
- Endoscopy



TREATMENT

- Topical retinoid (Alitretinoin gel 35-50% response)
- Surgical excision
- Local Radiation (20-70% response)
- Cryotherapy (85% response)
- Laser

- Anti-retroviral therapy for epidemic KS
- Chemotherapy:
  - Liposomal doxorubicin, liposomal daunorubicin
  - Vincristine, Bleomycin, Doxorubicin: 1st line at UTH/CDH
  - Paclitaxel monotherapy: 2nd line agent

COURSE

- Classic KS: Progresses slowly, rare lymph node or visceral involvement. Death occurs years later from unrelated causes.
- African cutaneous KS: Aggressive, early nodal involvement, death from KS expected within 1-2 years.
- AIDS-related KS: although widespread, most patients die of intercurrent infection
- Immunosuppression related KS: removal of immunosuppression may result in resolution of the KS without therapy.

LYMPHOMA

- Lymphomas occur with increased frequency in immunodeficiency states.
- As HIV disease progresses the risk of lymphoma increases.
- The incidence of lymphoma has not shown dramatic decrease even after HAART is being widely used by HIV patients worldwide.
- It is a late manifestation which often occurs when the CD4 count falls below 200/mm^3
- 3 main categories are seen with HIV
  - Grade III or IV immunoblastic lymphoma (60%)
  - Burkitt's lymphoma (20%)-associated with EBV
  - Primary CNS lymphoma
- Treament:
  - In patients with high CD4 count- intensive chemotherapy, low dose chemotherapy in patients with low CD count.
  - Palliative measures to decrease the size of the lesion and associated edema
    - Radiotherapy
    - Glucocorticoides

CERVICAL CANCER

- There is a 5 fold increased risk of developing cervical cancer in women with AIDS.
- It is associated with human papilloma virus infection.
- Invasive carcinoma of the cervix is an AIDS defining illness
- Abnormal PAP smear is seen in 60% of HIV infected women
- Anorectal CA may also be seen in homosexual men

SEXUALLY TRANSMITTED INFECTIONS

- Sexually transmitted infections are a diverse group of infections, caused by different types of microbial agents that are frequently transmitted by sexual contact, and for which sexual transmission is epidemiologically important, are considered sexually transmitted infection.
- "Sexual" includes the full range of heterosexual or homosexual behavior including genital, oral-genital, oral-anal and genital-anal contact.
- At present there are more than 20 known causes of STD. No single STI can be regarded as an isolated problem because multiple infections are common and because the presence of one STI denotes high-risk sexual behavior that is often associated with other more serious infections.
- Most STIs are rarely if ever transmitted by formites, food, flies or causal contact.
- At least one sexual partner is always infected, the apparent exceptions usually can be attributed to prolonged sub-clinical infection in one or both partners. Therefore, risk assessment (including elicitation of a sexual history) and management of sexual partners are of paramount importance.
- Treatment of STIs reduces transmission of HIV.
- STIs can be classified and managed in 3 different ways (approaches)
  - Clinical approach: where one depends on past experience and own knowledge
  - Etiologic approach: where one collects specimens for laboratory identification of causative agent prior to treatment
    - Advantages: accurate diagnosis, accurate treatment proper use of antibiotics (decreases over treatment and antibiotic resistance). It is the better way to diagnose and treat asymptomatic infections.
    - Disadvantages: needs lab support and expertise, expensive (cost may be incurred due to lab tests) and it is time consuming.
  - Syndromic approach: where one identifies on the basis of symptoms and signs and treats to cover the majority of organisms that may cause those symptoms.
    - Advantages: Treatment can be given immediately, mixed infection may exist and may be addressed, there is no need for laboratory diagnosis and the treatment can be given by middle level health professionals. Hence this approach may be a good alternative for in resource limited settings.

- Disadvantages: over treatment with antibiotics, there is risk of creating antibiotic resistance and decreased compliance. There is also increased cost of drugs. Moreover, asymptomatic infection missed.

APPROACH TO MANAGEMENT

- Approach includes:
  - Risk assessment of:
    - Sexual orientation and practice
    - Number of recent and current sexual partners
    - History of STI in the patient
    - Recent history of STI of the partner
    - Sociodemographic and other markers of high risk
  - Clinical assessment: elicitation of information on specific current symptoms and signs of STIs.
  - Laboratory tests: if available, confirmatory diagnostic or screening tests may be then ordered.
  - Comprehensive case management: this is vital approach for controlling STIs. So health care providers should undertake the following measure besides treating individual patients
    - Partner notification and management
    - Condom promotion and supply
    - Health education and risk education counseling
    - Linkage with HIV counseling and testing
    - Follow-up visits for patients with STI

STI SYNDROMES

- These include:
  - Urethral discharge syndrome
  - Vaginal discharge
  - Genital ulcer
  - Genital growth
  - Inguinal bubo
  - Scrotal swelling
  - Lower abdominal pain
  - Neonatal conjunctivitis

URETHRAL DISCHARGE SYNDROME

- Urethral discharge is the most common presenting compliant of men with STI.
- In urethral discharge, exudate is present in the anterior urethra and the discharge (which may be copious or mucoid) is often accompanied by dysuria or urethral discomfort.

ETIOLOGY

- STI-related urethritis is divided into:
  - Gonoccocal urethritis:
    - This is an acute inflammatory condition of the columnar epithelial lining of the urethra.
    - Caused by *Neisseria gonorrhea* (Gram negative intracellular diplococcus)
    - Has a short incubation period (2-3 days)
    - Vast majority of cases present with abundant (copious) and purulent yellowish green discharge.
    - The lip of the meatus may be red and swollen.
    - Tend to produce more severe urinary tract infection symptoms like dysuria, urgency and frequency.
    - The patient may have pharyngitis, proctitis and PID.
    - Disseminated gonococcal infection is associated with 2 syndromes:
      - Fever, malaise, migratory polyarthralgia or polyarthritis, tenosynovitis and painful vesiculopustular skin lesions.
      - Purulent arthritis without skin lesions.
    - Complications:
      - Acute epididymo-orchitis: this is an important complication which is usually unilateral swelling and tenderness of the testis and epididymis.
      - Bilateral epididymo-orchitis may result in sterility.
      - Urethral strictures: this is a late complication occurring in cases which are treated inadequately or not at all. This could occur 10 to 25 years after an infection or in cases of recurrent infection.

- Non-gonoccocal urethritis (NGU):
  - Usually caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum.*
  - Other pathogens include *Mycoplasma genitalium, HSV, Trichomonas vaginalis.*
  - Has a long incubation period (1-3 weeks)
  - It has scanty to moderate, white, mucoid or serous discharge.
  - Although the discharge may be slight and the symptoms mild, they are frequently more marked in the morning when the lips of the meatus are often stuck together with dried secretions.
  - Mild urinary tract infection symptoms.
  - On examination the meatus may be red, with evidence of dried secretion on underwear. Occasionally the onset is more acute, with dysuria, frequency and a copious purulent discharge.
  - Other syndromes include proctitis, epididymitis, and PID. NGU has a known association with postinfectious reactive arthritis.
  - Complications:
    - Epididymitis
    - Urethral stricture
    - Perihepatitis

- The quantity and appearance of the discharge can be used to distinguish accurately gonococcal and non-gonococcal urethritis in about 75-80% of patients who have not urinated recently. It can't of course, be used to diagnose dual infection with *N. gonorrhea* and *C. trachomatis*. Milking of the urethra may be necessary to get a good amount of discharge sample.

INVESTIGATIONS

- Microscopy of urethral discharge stained with methylene blue or Safranin or Gram stain shows pus cells with characteristic intracellular coffee bean shaped diplococci (this is indicative of *N. gonorrhea*)
- Pus cells without intracellular diplococci is indicative of NGU.

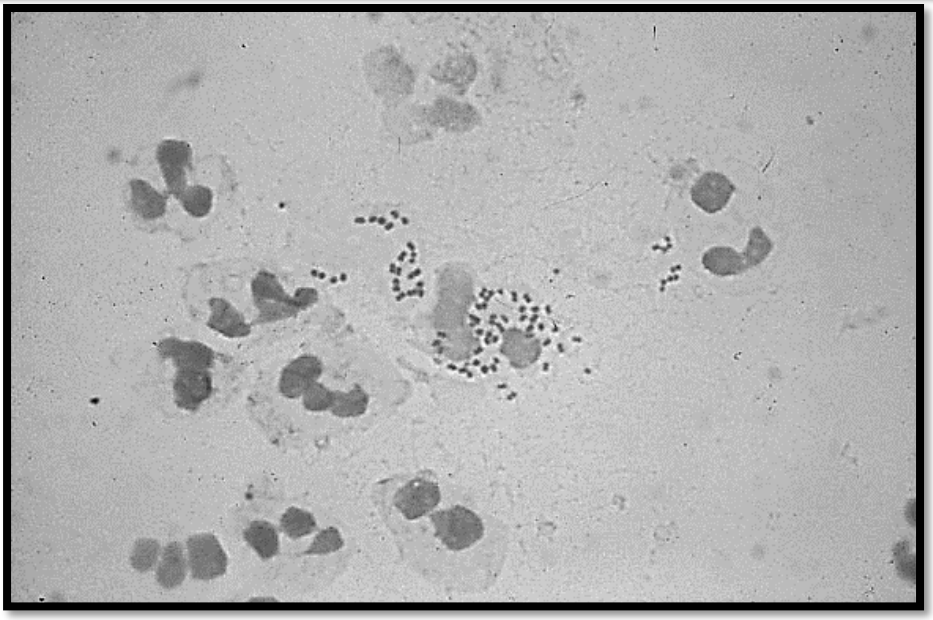


Figure 63: Pus cells with multiple intracellular and extracellular gram negative diplococci of a smear from a urethral discharge indicative of gonococcal urethritis

- Other tests for include:
  - Culture on Thayer-Martin media (Gonococcal urethritis)
  - Nucleic acid amplification test (NAAT)
  - DNA Probe

TREATMENT

- Gonococcal urethritis:
  - Ciprofloxacin 500mg PO stat or
  - Ceftriaxone 250mg IM stat or
  - Spectinomycin 2mg IM stat
- NGU:
  - Doxycycline 100mg PO BID for 7 days or
  - Tetracycline 500mg PO QID for 7 days or
  - Erythromycin 500mg PO QID for 7 days if the patient has contraindication for TTC.
  - Azithromycin 1g PO Stat
- When there is no etiologic diagnosis: Treatment should cover both gonococcal and chlamydial infections (combine the above treatments)
- Persistent urethral discharge one week after treatment consider *Trichomonas vaginalis*, then treatment Metronidazole 2g PO stat.

PREVENTION

- Avoiding multiple sexual partners and unprotected casual sexual intercourse.
- Condom use is advised.

CHAPTER 13: MISCELLANEOUS

MISCELLANEOUS

POISONING

- This is the exposure by ingestion, inhalation or other means of a substance capable of causing harm to the body.
- Clinical features:
  - The patient may present a variety of symptoms ranging from mild to serious ones like loss of consciousness.
- Diagnosis
  - Assess for vitals (Airways, Breathing and Circulation) and:
    - Level of consciousness: GCS
    - Ventilation: pulse oximetry
    - Blood pressure and pulse rate
    - Pupil size and reaction to light
    - Evidence of intravenous drug use
    - A head injury complicating poisoning
    - If the patient is unconscious also check for:
      - Cough and gag reflex: present or absent
      - Temperature: measured with a low-reading rectal thermometer if the ear temperature suggests it is low

Features	Likely poisons
Constricted pupils (miosis)	Opioids, organophosphorus insecticides, nerve agents
Dilated pupils (mydriasis)	Tricyclic antidepressants, amfetamines, cocaine, antimuscarinic drugs
Divergent strabismus	Tricyclic antidepressants
Nystagmus	Carbamazepine, phenytoin
Loss of vision	Methanol, quinine
Papilloedema	Carbon monoxide, methanol
Convulsions	Tricyclic antidepressants, theophylline, opioids, mefenamic acid, isoniazid, amfetamines
Dystonic reactions	Metoclopramide, phenothiazines
Delirium and hallucinations	Amfetamines, antimuscarinic drugs, cannabis, recovery from tricyclic antidepressant poisoning
Hypertonia and hyperreflexia	Tricyclic antidepressants, antimuscarinic drugs
Tinnitus and deafness	Salicylates, quinine
Hyperventilation	Salicylates, phenoxyacetate herbicides, theophylline
Hyperthermia	Ecstasy (MDMA), salicylates
Blisters	Usually occur in comatose patients

MDMA, 3,4-methylenedioxymetamfetamine.

  - History
    - Ascertain as far as possible, the nature and quantity of the poison and when it was taken.
    - In the unconscious patient a history from friends or relatives is helpful.
    - In any patient with an altered level of consciousness, acute poisoning must always be considered in the differential diagnosis.

- Management:
  - Depends on the type of poison taken and the clinical condition of the patient.
  - It is aimed at slowing down, reducing or preventing further absorption of the poison and to counteract the effects of the poison already absorbed.
  - Emergency resuscitation:
    - Obstructed airway
      - Pull the tongue forward
      - Remove denture, foreign bodies (e.g. food) and oral secretion
      - Hold the jaw forward and insert an oropharyngeal airway if possible
      - Put the patient in a semi-prone position with the head down to minimize the risk of inhaling vomit.
    - Inadequate respiration
      - Give continuous oxygen
      - Apply assisted ventilation with an ambu bag or mouth to mouth or intubate and do mouth to tube respiration.
      - Do not use respiratory stimulants as they cause harm
    - Hypotension
      - Keep the patient in a position with his head downwards by elevating the foot of the bed.
      - Gain venous access and send blood for: Urea, electrolytes, creatinine, full blood count, blood sugar, and liver function
      - Administer normal saline intravenously
    - Recurrent fits
      - Control with diazepam 5-10mg intravenously stat. Repeat as necessary
    - Removal of poison from the stomach
  - Gastric emptying carries the risk of the victim inhaling gastric contents. The benefit of the procedure should therefore be weighed against this risk. The procedure should not be performed in the following circumstances:
    - When corrosive substance (e.g. acids, alkalis and petroleum products) have been swallowed.
    - When there is marked hypothermia (less than 30^{o}C)
    - When the amount of poison swallowed is minimal
    - If poison was ingested more than 2 hours earlier (except in the case of poisoning with salicylate, tricyclic anti-depressants and beta blockers).
  - To remove poison from the stomach, two methods may be used:

- Inducing vomiting by giving: Ipecacuanha syrup 30ml followed by a glass of water. Repeat after 20 minutes if necessary.
- Gastirc lavage: if done in an unconscious patient, a cuffed endotracheal tubeshould be passed to prevent aspiration of stomach contents into the lungs.

➢ After vomiting has occurred:

- Activated charcoal: 50mg mixed with 400ml water in a bottle and shaken well. Administer the suspension in a dose of 5ml/kg. Repeat every 4 hours. Total dose of 100g. If necessary
- Magnesium sulphate mixture or magnesium hydroxide mixture, 50ml to avoid constipation.
- Milk, cooking oil or beaten raw egg may also be given in the absence of activated charcoal to delay absorption of the poison.

DRUG	FEATURES	TREATMENT
Aspirin and other salicylates	• Increased rate and depth of respiration • Respiratory alkalosis • Tachypnea, sweating, vomiting, epigastric pain, tinnitus, and deafness.	• Induce emesis with ipecacuanha unless respiration is depressed • Give activated charcoal • If respiration is depressed, do airway-protected gastric lavage • Gastric emptying is effective up to 4 hours after ingestion of poison
Carbon monoxide	• Headache • Exertional dyspnea • Coma • Convulsions • Cardiorespiratory arrest • Metabolic acidosis • Myocardial ischemia • Hypertonia • Extensor plantar responses • Retinal hemorrhages • Papilloedema • Neuropsychiatric features	• Remove patient from further exposure • Give oxygen for several hours • Maintain blood pressure and normal body temperature • To reduce cerebral edema give 20% mannitol IV 5ml/kg body weight over 20 minutes and an IV or IM corticosteroid 4 hourly (prednisolone 1mg/kg or dexamethasone 0.15mg/kg or hydrocortisone 4mg/kg) • Control convulsions or hyperactivity with diazepam 0.1mg/kg by slow intravenous or per rectum
Ethanol	• Emotional lability	• Remove unabsorbed ethanol by gastric lavage or induce emesis with ipecacuanha syrup

	• Impairment of coordination • Visual impairment • Slow reaction time • Slurred speech • Hypoglycemia • Stupor • Hypothermia • Convulsions • Depressed reflexes and respiration	• Give activated charcoal • Maintain adequate airway • Maintain normal body temperature • If patient is hypoglycemic give dextrose 50% followed by 5% IV • May need vitamin B compound if chronic alcohol abuser
Organochlorides	• Convulsions, hyperactivity and tremors • Respiratory depression	• Remove patient from source of poisoning and remove contaminated clothing • Give ipecacuanha syrup • After vomiting give activated charcoal followed by gastric lavage with 2-4 liters water. • Give a laxative such as magnesium hydroxide • Do not give milk, fats or oils as they will increase absorption of poison • Scrub the skin with soap and cold water to remove skin contamination • Give artificial respiration with oxygen if there is respiratory depression • Give diazepam 10mg slow IV or phenobarbitone 100mg IM to control convulsions, hyperactivity or tremors
Organophosphates and carbamate	• Anxiety, restlessness, tiredness, headache • Muscarinic features: nausea, vomiting, abdominal colic, diarrhea, tenesmus, sweating, sweating, hypersalivation, lacrimation and chest tightness. Miosis • Nicotinic signs: fasciculations and flaccid	• Remove patient from source of poisoning and remove contaminated clothing • Establish airway and give artificial respiration if necessary • Remove excess bronchial secretion by suction • Give ipecacuanha syrup or start gastric lavage • Give atropine 2mg IV stat every 3-8 minutes until signs of atropinisation appear (hot dry skin, dry mouth, widely dilated pupils and fast pulse)

	paresis of limb muscles, respiratory muscles and occasionally extraocular muscles.	
Paraffin, petrol and other petroleum products		• Prevent the substance from entering the lungs to avoid damage to tissue • Do not induce vomiting • Do not do gastric lavage • Look out for pulmonary edema and chemical pneumonitis and treat accordingly.
Paracetamol poisoning	• Anorexia, nausea and vomiting • Liver damage result in paracetamol overdose. The damage occurs within a few hours of ingestion	• Keep the patient quiet and warm • Induce emesis with ipecacuanha syrup • Where there is depressed respiration use airway-protected gastric lavage • N-acetylcysteine 20% solution, orally 140mg/kg as a loading dose, followed by 70mg/kg every 4 hours for 3 days it may be necessary to administer through an NGT. • Dextrose 5% intravenously for the first 48 hours • Phytomendione 1-10mg IM if the prothrombin time ratio exceeds 2.0 • Do not force diuresis
Chloroquine poisoning	• Blurred vision • Tinnitus, weakness, hemoglobinuria, oliguria • Low blood pressure, shock • Convulsions, cardiac arrest	• Induce emesis • Stomach wash (air-war protected gastric lavage if respiration is depressed) • Give activated charcoal • Treat symptomatically
Mushroom or other food poisoning	• Abdominal pain • Nausea • Vomiting • Diarrhea • Shock in severe cases	• Symptomatic: ➢ Bed rest ➢ Keep patient warm ➢ Stomach wash using normal saline ➢ Give ORS or IV fluids to re-hydrate ➢ If no improvement refer to specialist
Snake bites	• Pain • Swelling • Tissue necrosis	• Immobilize limb and keep slightly elevated • Administer tetanus toxoid (0.5ml) • IV Dextrose 5% in saline

	• Regional lymph node swelling • Hemorrhagic symptoms, bleeding at wound sites and other parts of the body • Danger signs: drowsiness, slurred speech, excessive oral secretion, difficulty in breathing and neurological signs	• Treat shock • Vitamin K 1-10mg intramuscularly • Anti-snake venom if available • Transfer patient to specialist

ORGANOPHOSPHATE POISONING

- Organophosphorus (OP) insecticides are used widely throughout the world and are a common cause of poisoning, causing thousands of deaths annually, in the developing world.
- Intoxication may follow ingestion, inhalation or dermal absorption.
- Because some are very lipophilic they may be released from fat depots over a period of many days.
- Organophosphorus insecticides inhibit acetylcholinesterase causing accumulation of acetylcholine at central and peripheral cholinergic nerve endings, including neuromuscular junction.
- Many OP insecticides require biotransformation before becoming active and so the features of intoxication may be delayed.
  - Metabolism occurs by oxidation and hydrolysis by esterases and by reaction with glutathione.
- Elimination of OP is mostly in the urine and lesser amounts in feces and expired air.

PATHOPHYSIOLOGY

- OP insecticides form an irreversible bond with acetylcholinesterase (the enzyme responsible for the breakdown of acetylcholine).
- When this enzyme is inhibited there is an accumulation of acetylcholine at central as well as peripheral cholinergic nerve endings.
- This results in overstimulation of both muscarinic and nicotinic receptors resulting in the signs and symptoms seen.
- Recall that:
  - Acetylcholine is found in autonomic ganglia (both sympathetic and parasympathetic ganglia).
  - Terminal postganglionic parasympathetic nerves fibers at the motor endplates of nerves in skeletal muscle as well as some cranial nerves innervating visceral contain acetylcholine.
  - Both muscarinic and nicotinic receptors are widely distributed in the central nervous system as well as all over the body.

CHOLINOCEPTORS	LOCATION	MECHANISM	ACTIONS

Muscarinic, M1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites, in the stomach (oxyntic cells)	Gq coupled protein with formation of IP_3 and DAG, increased intra-cellular calcium	Enhances cognitive processes which may lead to improved memory, increases gastric acid secretion
Muscarinic, M2	Myocardium, and smooth muscle	Gi coupled protein, opening potassium channels, inhibition of adenylyl cyclase	Decreases heart rate, force of contraction of AV conduction.
Muscarinic, M3	Exocrine glands, Vessels (smooth muscle and endothelium), eye (iris circular muscle and ciliary muscle)	Gq coupled protein with formation of IP_3 and DAG, increased intra-cellular calcium	Increased secretions in GIT and lungs, contraction of smooth muscle in walls of GIT & bladder, relaxation of sphincters of GIT & urinary tract, constriction of pupil (miosis) and ciliary muscle (lens broadens for near accommodation)
Muscarinic, M4	CNS neurons, possibly vagal nerve endings	Gi coupled protein, opening potassium channels, inhibition of adenylyl cyclase	-
Muscarinic, M5	Vascular endothelium, especially cerebral vessels, CNS neurons	Gq coupled protein with formation of IP_3 and DAG, increased intra-cellular calcium	Synthesis and release of endothelium-derived relaxation factor (nitric oxide) leading to vasodilation of cerebral vessels

Nicotinic, N_N	Postganglionic neurons, some presynaptic cholinergic terminal	Opening of sodium and potassium channels, depolarization	Transmission of action potential
Nicotinic, N_M	Skeletal muscle neuromascular end plates	Opening of sodium and potassium channels, depolarization	Increase in muscle tone

CLINICAL FEATURES

- Poisoning is characterized by:
  - Anxiety
  - Restlessness
  - Tiredness
  - Headache
- Muscarinic (cholinergic) features such as nausea, vomiting, abdominal colic, diarrhea, tenesmus, sweating, hypersalivation and chest tightness. Miosis may be present.
- Nicotinic effects include muscle fasciculation and flaccid paresis of limb muscles, respiratory muscles and occasionally of extraocular muscles.
  - Respiratory failure will ensue in severe cases and is exacerbated by development of bronchorrhea and pulmonary edema.
- The intermediate symptoms usually become established 2-4 days after exposure when the symptoms and signs of the acute cholinergic syndrome are no longer obvious.
- The characteristic features of the syndrome are weakness of muscles of respiration (Diaphragm, intercostal muscle and accessory muscle including neck muscle) and of proximal muscle.
- Accompanying features often include weakness of muscles innervated by some cranial nerves.
- Delayed polyneuropathy is a rare complication of acute exposure to some OP insecticides not marketed in most countries. It is initiated by phosphorylation and subsequent aging of at least 70% of neuropathy target esterase (NTE) in peripheral nerves.

DIAGNOSIS

- This is confirmed by measuring the erythrocyte cholinesterase activity.
  - This may be decreased to 30-50% in asymptomatic patients, 10-20% in moderate poisoning and <10% in severe poisoning.
- Plasma cholinesterase activity is less specific but may also be depressed.

- Other investigations include:
  - Full blood count
  - Urea and electrolytes to rule out electrolyte disturbances
  - Stool for microscopy, culture and sensitivity to rule out gastroenteritis.

TREATMENT

- Diagnosis
  - Assess for vital signs
  - Ascertain as far as possible, the nature and quantity of the poison and when it was taken.
- Treatment is aimed at slowing down, reducing or preventing further absorption of poison and to counteract the effects of the poison already absorbed.
- ABCs (Resuscitation)
  - Clear and secure the airway: pull the tongue forward, remove dentures/foreign bodies (e.g. food) and oral secretion, hold the jaw forward and insert an oropharyngeal airway if possible.
  - Put the patient in a semi-prone position with head down to minimize the risk of aspiration
  - Suction all secretions and ensure patient is breathing
  - Apply assisted ventilation with an ambu bag
  - Give continuous oxygen.
  - Do not use respiratory stimulants as they cause harm
  - Gain venous access and send blood to the lab.
  - Run IV normal saline
  - Remove the clothes that may be soiled.
- Mild cases require no specific treatment other than the removal of soiled clothing.
- Atropine 2mg IV should be given every 5-10 min until there are signs of atropinisation. The skin becomes flushed and dry, the pupils dilate and bradycardia (fast pulse) is abolished, frequency of administration dependent of severity.
- Symptomatic patients should be give an oxime (pralidoxime, obidoxime or HI-6) to reactivate inhibited acetylcholinesterase.
  - Pralidoxime chloride 30mg/kg by slow IV injection followed by an infusion of pralidoxime mesylate 8-10 mg/kg per hour.

ALCOHOL INTOXICATION AND ALCOHOL WITHDRAW

GOUT

- These are a group of disorders of purine metabolism that are characterized by serum uric acid elevation (hyperuricemia), urate deposits in articular or extra-articular tissues.
- Elevation of serum uric acid alone is not sufficient for the diagnosis of gout, only 10% of patients with hyperuricemia develop gout.

ETIOLOGIC CLASSIFICATION OF HYPERURICEMIA

- Gout syndromes are characterized by either episodic or constant elevation of serum uric acid concentration above 7mg/dl.
- Patients with elevated uric acid are mainly due to:
  - Overproduction (10%): these patients synthesize greater than normal amount of uric acid de novo. They have normal urinary excretion of uric acid (>1000mg/day). Cause can be:
    - Primary: purine pathway enzyme defect
    - Secondary: increased cell turn over or cellular destruction with
      - Alcohol use
      - Hematologic malignancies
      - Chronic hemolysis
      - Cancer chemotherapy (tumor lysis syndrome)
  - Reduced excretion (90%): decreased renal excretion of uric acid (<700mg/dl)
    - Drugs: diuretics, alcohol, Aspirin interfere with tubular handling of urate
    - Renal disease: chronic renal failure, lead nephropathy, inherited disorders
- Conditions associated with gout:
  - Obesity: Serum uric acid level rises with body weight
  - Diabetes mellitus: more common in gout patients
  - Hypertension: is more common in gout patients
  - Hyperlipidemia
  - Atherosclerosis

CLINICAL FEATURES

- Clinical stages of gout include:
  - Asymptomatic hyperuricemia: raised serum uric acid level without any clinical evidences of deposition disease (i.e. arthritis, tophi, nephropathy or uric acid stones)
    - These patients have increased risk for nephrolithiasis or acute obstructive uropathy
  - Acute gouty arthritis: second and primary manifestation of gout.
    - Extremely painful
    - Acute onset arthritis
    - Mostly affects middle aged or elderly men who had sustained asymptomatic hyperuricemia for 20-30 years before first attack.
    - Premenopausal women are not affected (probably due to effect of estrogen on uric acid clearance) however, gout may be seen in postmenopausal women who have hypertension especially.
    - Onset in teens or 20s is unusual and when present is often associated with primary or secondary causes of uric acid overproduction
    - Precipitating events of an acute gouty attack:
      - Dietary excess
      - Trauma
      - Surgery
      - Excessive alcohol ingestion
      - ACTH or glucocorticoid withdrawal
      - Hypouricemic therapy
      - Serious Medical illnesses e.g. myocardial infarction and stroke
    - Presentation:
      - Acute onset of severe, painful and tender joint swelling, affecting the first metatarsophalangeal joint (called podagral)
      - Other affected joint: tarsal joints, ankle and knee.
      - Many attacks occur suddenly at night with rapid evolution of joints with erythema, swelling, tenderness and warmth. Intense joint

inflammation can extend in to the soft tissue and mimic cellulitis or phlebitis
- ♦ Fever can occur in severe attacks.
- ♦ Polyarticular involvement can occur.
- ♦ Acute attacks usually resolve spontaneously in few days (3-10 days) though some can extend over several weeks.
- ♦ The affected joint usually returns to normal between attacks and patients do not have residual symptoms until the next episode

➢ Intercritical gout: this is the third stage of gout. It is asymptomatic after the initial attack. Recurrence of new attacks may occur during this stage. Attacks tend to become polyarticular and more severe over time. Some patients develop chronic inflammatory arthritis without asymptomatic intervals leading to a condition which may resemble rheumatoid arthritis.

➢ Chronic tophaceous gout: develops in untreated patients as the final stage of gout. The tophus is a collection of urate crystal masses surrounded by inflammatory cell and fibrosis. Typical locations for tophaceous deposits include: Pinna of ear, the surfaces of chronically involved joints and subchondral bone as well as extensor surface of the forearm, olecranon and the intrapatellar and Achilles tendons.

➢ Renal complications: may arise at any stage of gout but nephrolithiasis is the only common clinical presentation of renal involvement. Proteinuria and impaired ability to concentrate urine related to urate deposition in the renal interstitium have been described in gout patients.

DIAGNOSIS AND INVESTIGATIONS

- Acute gouty arthritis:
  - ➢ Synovial fluid analysis: the demonstration of urate crystals, especial intracellular crystals, in synovial fluid is diagnostic. Synovial fluid WBC of 10, 000-60 000/µl with predominant neutrophils are common in acute attacks.
  - ➢ Serum uric acid: value often is not helpful in the clinical diagnosis of acute gout. Serum uric acid concentration is normal in about 10% of patients at the time of an acute attack and an elevated serum uric acid is non-specific of acute gout. It can be used to assess the effectiveness of hyouricemic therapy.
- Chronic tophaceous gout
  - ➢ Physical appearance: Tophi are firm movable and superficial located. If they ulcerate a chalky material extrudes.

- Radiologic findings: tophaceous deposits appear as well defined large erosions (punched out erosions) of the subchrondral bone. These erosions are common at the first Metatarsophalangeal joint (MTP) and at the base of the head of phalanges however any joint area can be affected. Typically, gouty erosions have an overhanging edge of subchondral new bone formation.
- Aspiration: tophi can be aspirate and crystals can be demonstrated.

MANAGEMENT

- Asymptomatic: treat underlying cause, no further treatment.
- Acute gouty arthritis: therapy most effective when started early after symptoms begin.
  - Colchicine: This has anti-inflammatory effect and if given early is effective in 85% of patients.
    - Dose: colchicine 0.6mg is given every hour until the relief of symptoms of gastrointestinal toxicity occurs. It may also be given intravenously during acute attack in patients who cannot take PO medication.
  - NSAID: are used in high but quickly tapered doses. Drugs like Aspirin that affect uric acid clearance should be avoided
    - Ibuprofen: 800mg PO TDS
    - Diclofenac: 25-50mg PO TDS
    - Indomethacin: 25-50mg PO TDS
  - Corticosteroids:
    - Prednisolone 30-50mg/day as the initial dose and taper over 5-7 days. Intra-articular injections of steroids can be used to treat acute gout of single joint, particularly when the use of other agents is contraindicated.
  - Drugs that alter serum uric acid concentration (e.g. allopurinol, probenecid) should be avoided during acute attack because of lowering of serum uric acid level induces the release of crystals into joint space and prolong the acute attack
- Intercritical gout: prophylactic treatment with small dose of colchicine (0.6mg OD or BD) or small doses of NSAIDs can be used to prevent new attacks.
- Chronic tophaceous gout: aim is to control hyperuricemia (reduce serum urate level to <5mg/dl)
  - Uricosuric agents: e.g. probenecid, facilitate the renal excretion of uric acid. It can be used in patients who excrete less than 700mg of uric acid daily, who have normal renal function and who have no history of urinary stones.
    - Dose: Probenecid 200mg PO BD increased gradually as needed up to 2g.

- Xanthine oxidase inhibitors: e.g. Allopurinol, competitively inhibit xanthine oxidase. This drug is preferred in patients with urate excretion greater than 1000mg/day, creatinine clearance <30ml/min, tophaceous gout or history of nephrolithiasis.
  - Dose 300mg single morning dose initially and may be increased up to 800mg if needed.
  - Dosage is reduced in the presence of renal failure to avoid toxicity.

OSTEOARTHRITIS

- This is a degenerative bone and joint condition initially involving thinning of the hyaline cartilage until the underlying bone is exposed and becomes damaged due to direct stress.
- It can be:
  - Primary (idiopathic) which is localized or generalized or
  - Secondary which is usually localized.
- Nodal osteoarthritis is a primary osteoarthritis involving the hands.

RISK FACTORS

- Age>50 years
- Nodal OA:
  - Post-menopausal women
  - Family history
- Secondary:
  - Mechanical strain from obesity, trauma or employment
  - Joint disease: inflammatory arthritides
  - Hemochromatosis
  - Osteoporosis reduces the risk

CLINICAL FEATURES

Primary nodal OA	Secondary OA
• Tender, swollen joints with reduce movement • Typically affects the distal interphalangeal joints (DIP), thumb carpometacarpal (CMC) joint, and knees • Muscle wasting • Squaring of hand due to thumb adduction and bone swelling at CMC • Heberden's nodes at the DIP and Bouchard's nodes at the PIP	• Typically affects the knee, hip or spine • Painful joint exacerbated by movement and worse in the evening • Joint gelling- stiffness after resting and instability • Hip OA typically radiates to the groin and buttocks. • Spin OA may compress a nerve and radiate down the leg

INVESTIGATIONS

- Diagnosis can be clinical- especially if patient >45 years old- and does not require radiological evidence.
- X-ray can be useful to exclude other conditions and are needed in younger patients or atypical histories. In osteoarthritis, may see 'LOSS':

  - L-loss of joint space (asymmetrical), reflecting thinning of the cartilage
  - O-osteophytes, reflecting proliferation and ossification of cartilage in unstressed areas
  - S-subchondral sclerosis (thickening)
  - S-Subchondral cysts, reflecting fluid-filled microfractures
- Bloods:
  - CRP/ESR to rule out inflammatory cause.

MANAGEMENT

- Lifestyle and physical therapy:
  - Exercise to improve strength and joint stability
  - Reduce weight
  - Walking aids
  - Physio
- Pharmacological:
  - Regular paracetamol +/- topical NSAID gel (knee or hands only), then move up pain ladder if needed. Paracetamol is traditionally preferred for long-term use over NSAIDs as it is safer but recent research question its efficacy.
  - If adding/switching to NSAIDs PO (standard or coxib) stop topical NSAID and give PPI. Unlike paracetamol, there is good evidence of efficacy.
  - Further option: intra-articular steroid injections, topical capsaicin for hand or knee OA.
  - Glucosamine and chondroitin are not recommended
- Surgical: joint replacement

RHEUMATOID ARTHRITIS

- This is a multisystemic inflammatory disease of unknown cause characterized by persistent inflammatory synovitis usually involving peripheral joints in a symmetrical distribution.
- It is an autoimmune disease in which IgG forms against cartilage and rheumatoid factor (RF)- an IgM antibody forms against that IgG, leading to synovitis.
- This eventually leads to pannus (deposits in the synovial membrane) and joint destruction, the hallmark of the disease.
- Rheumatoid arthritis is much more common in females (3:1).
- The prevalence increases with age. Peak onset around 50 years but any age can be affected.

ETIOLOGY

- Cause remains unknown however genetic and environmental factors (infectious agents) have been implicated.
  - Genetic factors: genetic susceptibility to altered immune response may play a role. The concordance rate among monozygoitic twins is 4 times and first degree relatives of patients with RA have a very high chance of developing RA. HLA-DR4 allogen has been associated with high incidence of RA.
  - Infectious agent: May play a role in triggering an autoimmune reaction. Infectious agents such as rubella, Mycoplasma, CMV and EBV virus may play a role in the pathogenesis

CLINICAL FEATURES

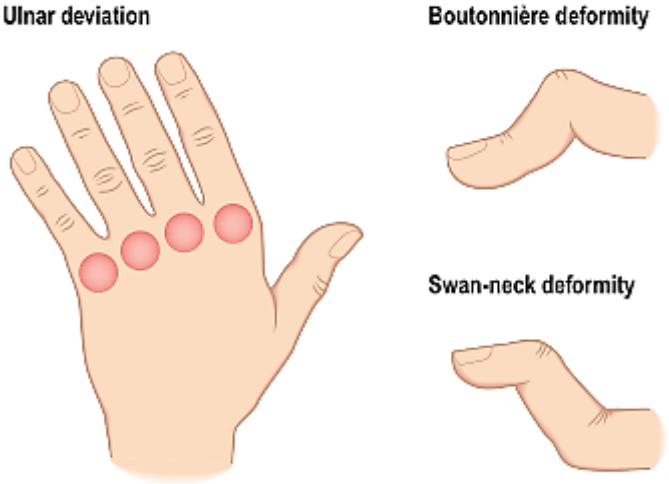
- Onset:
  - Insidious onset: in about 2/3 of patients, RA begins insidiously with prodromal nonspecific symptoms such as fatigue, weight loss, anorexia, generalized body weakness and vague musculoskeletal symptoms, for weeks or months before the occurrence of specific joint symptoms.
  - Acute onset: in about 10% of patients, RA has an acute onset, with rapid development of polyarthritis, associated with constitutional symptoms including fever, lymphadenopathy and splenomegaly.
- Patterns:
  - Typical: Onset of symmetrical polyarthritis over weeks to months, it has a relapsing-remitting course.
  - Rare: persistent large joint monoarthropathy or palindromic RA, a recurrent acute monoarthritis

ARTICULAR (JOINT) MANIFESTATIONS

- Inflammatory features:
  - Swollen, painful and stiff joints.
  - Generalized joint stiffness is often seen after a period of inactivity. Morning stiffness which lasts greater than 1 hour which is a feature of inflammatory arthritis is a common complaint.
  - Bilateral, symmetrical small joint involvement is typical for RA.
  - Commonly joints affected:
    - Wrist joints, metacarpophalangeal joints and proximal interphalangeal joint are often involved. The distal interphalangeal joints are often spared.
      - Wrist joints: synovitis of wrist joint is very common in RA and may lead to limitation of movement, deformity and median nerve entrapment (Carpal tunnel syndrome)
    - The elbow and knee joint are also affected
      - Elbow joint involved may lead to flexion contracture
      - Knee joint is commonly involved with synovial hypertrophy, chronic effusion and frequent ligamentous laxity. Pain and swelling behind the knee may be caused by extension of inflamed synovium in to popliteal space (Baker's cyst)
    - Arthritis of the forefoot, ankles and subtalar joints can produce severe pain with ambulation as well as a number of deformities.
    - Axial involved is limited to cervical spines: atlantoaxial ligament involvement in the cervical spine can lead to instability between C1 and C2 vertebrae and potential neurologic complaints
- Joint deformities: with persistent inflammation, a variety of characteristic joint changes develop due to damage or weakening of ligaments, tendons and joint capsule. They are less common in the age of effective treatment. These include:
  - Z-deformity: radial deviation at the wrist with ulnar deviation of the digits

Carpal tunnel syndrome: this is caused by compression of the median nerve due to reduce size of the osseofibrous carpal tunnel, resulting from inflammation of the flexor retinaculum, arthritic changes in the carpal bones, or inflammation or thickening of the synovial sheaths of the flexor tendons. It leads to pain and paresthesia (tingling, burnng and numbness) in the hand in the area supplied by the median nerve and may also cause atrophy of the thenar muscles in case of severe compression. There is no paresthesia over the thnar eminence skin because this area is supplied by the palmar cutaneous branch of the median nerve

- Swan neck deformity: hyperextension of the Proximal interphalangeal joints with compensatory flexion of distal interphalangeal joint
- Boutonier deformity: flexion contracture of proximal interphalangeal joints and extension of distal interphalangeal joints
- Baker's Cyst (from joint rupture)



EXTRAARTICULAR FEATURES

- Even though not all of them have clinical significance, they may be the major evidence of disease activity and source of morbidity
- Most often the manifestations occur in patients who have high titer of rheumatoid factor and patients who have more severe and established disease.
- Systemic symptoms (constitutional symptoms): fatigue, fever, weight loss.
- Neurological manifestations: the CNS is not directly affected
  - Eye:
    - Keratoconjunctivitis sicca (10-15%) these patients have a secondary form of Sjogren syndrome.
    - Scleritis or episcleritis occur less common but can lead to scleromalacia.
  - Atlantoaxial subluxation: may lead to compression of spinal cord (cervical myelopathy/radiculopathy)
  - Peripheral nerves are affected through entrapment (Carpal tunnel syndrome) or vasculitis related mononuritis multiplex. Tarsal tunnel syndrome may also be seen.
- Cardiovascular
  - Asymptomatic pericarditis (50% of patients on autopsy). It is often associated with pleural effusion
  - Pericardial effusion

  - Atherosclerosis
  - Myocarditis and valvular dysfunction (mitral regurgitation)
  - Rheumatoid vasculitis: this can affect nearly any organ system and is seen in patients with severe RA, and high titers of circulating Rheumatoid factor.
    - Peripheral nerves: distal sensory neuropathy or mononuritis multiplex
    - Skin: cutaneous ulceration, dermal necrosis
    - Digital gangrene
    - Visceral infarction: MI, vasculitis involving the lungs, bowel, liver, spleen, pancreas, kidneys etc.
- Hematological
  - Anemia of chronic disease
  - Methotrexate or sulfasalazine induced folate-deficiency anemia
  - Thrombocytosis
  - Felty's syndrome: chronic RA with splenomegaly and neutropenia with an occasional thrombocytopenia and anemia.
- Lungs:
  - Pleuritis and pleural effusion. The pleural fluid is typically low in glucose.
  - Interstitial pulmonary fibrosis
  - Rheumatoid nodules may appear on the lung, single or multiple
  - Obliterative bronchiolitis: fibrotic and inflammatory narrowing of bronchioles
  - Methotrexate pneumonitis
- Kidneys:
  - Amyloidosis
  - Glomerulonephritis
- Dermatological and mucosal:
  - Sjogren's
  - Raynaud's
  - Rheumatoid nodules (most common feature-20-25%) on elbows and sometimes lungs, meninges and eyes
    - They are firm subcutaneous masses typically found in areas on periarticular structures and on areas exposed to repetitive trauma e.g. extensor surface of the forearm, the olecranon at the elbow, proximal ulna, Achilles tendon and occiput.
  - Pyoderma gangrenosum
  - Erythema nodosum.
- Others: osteoporosis, hypothyroidism and cancer (lymphoma, lung if smoker)

DIAGNOSIS

- History and examination
- Laboratory investigations
  - Bloods
    - Full blood count: normocytic normochromic anemia, leukocytosis and thrombocytosis
    - ESR: raised indicating chronic inflammation
    - Rheumatoid factor: it is an autoantibody against the Fc component of IgG. It is typically present in 60% of patients in the first year and 80% of patients with long standing disease. Note 30-40% of patients with RA may be sero-negative for RF (70% sensitivity)
    - Anti-CCP- anti-cyclic Cetrullinated Peptide (more specific and prognostic)
    - Liver function tests, U + Es for baseline before DMARDs.
  - Imaging: X-ray shows 'LESS'
    - L-loss of joint space
    - E-erosion (high risk of progression)
    - S-soft tissue swelling
    - S-see through bones (Juxta-articular/periarticular osteopenia)
  - Other investigations:
    - Joint aspirate if diagnostic uncertainty of septic arthritis suspected.
    - Urine: may contain blood and/or protein
    - CXR to exclude lung disease.

AMERICAN REVISED CRITERIA FOR CLASSIFICATION OF RA

- 4 out of 7 needed to classify a patient as having RA:
  - Morning stiffness lasting >1 hour
  - Arthritis of 3 or more joint areas
  - Arthritis of hand joints: Wrist, MCP, and PIP
  - Symmetrical arthritis
  - Rheumatoid nodules: subcutaneous nodules over bony prominences
  - Serum rheumatoid factor
  - Radiologic changes: periarticular bony erosion of RA is not excluded
- Patients with 2 or more criteria, the diagnosis of RA is not excluded.

MANAGEMENT

- Goals of therapy:
  - Short term: controlling pain and reducing inflammation without causing undesired side effects.
  - Long term: preservation of joint function and the ability to maintain lifestyle.
- Non-pharmacological
  - Patient education
    - Description of the illness: the chronicity of the disease
    - Rest and exercise
      - Patients should be advised to rest or splint acutely involved joints
      - Exercise is advised to strengthen muscle surrounding involved joints, when the arthritis is resolved.
  - Physiotherapy and occupation therapy to reduce disability
- Pharmacological:
  - First Line treatment
    - NSAIDs are used to control symptoms and signs of local inflammatory process. These agents are rapidly effective in alleviating pain and symptoms but their effect on long term disease progression is minimal
    - Drugs used:
      - Aspirin 900 mg PO TDS
      - Ibuprofen 400mg PO BD
      - Diclofenac 50mg PO BD or TDS
      - Indomethacin
    - Side effects: dyspepsia, PUD, renal dysfunction, bone marrow toxicity
  - Second line treatment: Low dose oral corticosteroids have potent anti-inflammatory but they equally have predictable unwanted side effects.
    - Systemic administration: given in severe progressive articular disease and extra-articular involvement.
      - Dose: start 5-10mg OD in the morning. If patient improves attempt should be made to taper the dose.
    - Local injection: steroids may be injected occasionally to joints which are severely affected
  - Third line treatment: Disease modifying antirheumatic drugs or slow acting antirheumatic drugs (DMARDs)
    - Drugs include: Methotrexate, Gold compounds, D-penicillamine, antimalarials and sulfasalazine

- Methotrexate is the most frequently used DMARD, which is relatively rapid acting
  - Dose: given in an intermittent low dose: 7.5 to 30mg once a week.
- Side effects: GI upset, oral ulcer, liver function abnormalities and insidious liver fibrosis. Administration of folic acid may diminish the frequency of some side effects.
- These are drugs which have no analgesic effect and generally require weeks to month before anti-inflammatory effects are evident. Hence NSAIDs should continue during the administration of DMARDs.
- They have the capacity to alter the course of RA.
- They are used in patients with RA who are not responding to NSAIDs (with or without steroids)
- These drugs may be used singly mostly but they may be prescribed in combinations in patients with bad prognosis or refractory diseases.
- The disease progression is delayed with these drugs and acute phase reactants such as ESR and C-reactive protein frequently decline.

➢ Fourth line: Anti-cytokine agents
- These are biological agents that bind and neutralize TNF. These drugs are effective in controlling signs and symptoms of RA in patients who fail to respond with DMARDs.

➢ Fifth line: immunosuppressive therapy
- These include drugs such as Azathioprine, Cyclosporine, and Cyclophosphamide. They have the same therapeutic effect as DMARDs but they are not more effective than DMARDs. They are prescribed to patients who fail to respond to DMARDs.

- Surgical:
  - ➢ Early: synovectomy may decrease the inflammatory process in joint pain, stiffness and swelling
  - ➢ Late: arthroplasty or total joint replacement may be appropriate to relieve pain or help restore function in structurally deformed joints.

ASSESSMENT OF RESPONSE

- Resolution of symptoms: reduction or disappearance of joint pain, stiffness and swelling.
- Functional status: ability of the patient to perform daily activities and living
- Laboratory: anemia may be corrected and ESR declines

PROGNOSTIC FACTORS

- Poor prognostic factors:
  - Many persistently inflamed joints
  - Poor functional status
  - Low educational status of the patient
  - Rheumatoid factor positivity
  - HLA-DR4 positivity
  - Extra-articular diseases
  - Persistently elevated acute phase reactants (ESR, C-reactive protein)
  - Radiologic evidence of erosion

SYSTEMIC LUPUS ERYTHEMATOSUS

- This is a chronic immune disorder characterized by multisystem involvement and clinical exacerbations and remission.
- Circulating immune complexes and autoantibodies cause tissue damage and organ dysfunction.
- SLE is 8-10 times more common among young women of child bearing age than in men.
- It is common among black women than white women as well as among pregnant women.
- SLE has a familial tendency and the concordance rate among identical twins is 50%.

ETIOLOGY

- No single cause has been identified, a mixture of environmental, genetic factors and hormonal influences have been linked.
  - Environmental factors: UV light, virus (e.g. EBV), smoking, toxins and drugs (isoniazid, hydralazine, chlorpromazine, sulfasalazine, phenytoin, procainamide, carbamazepine etc.)
  - Genetic factors: there is genetic predisposition to SLE. HLA-DR2 and DR3 as well as complement deficiencies (C1q, C2, C4) have been implicated.
  - Autoimmunity: loss of tolerance to autoantigens is central to the pathogenesis
  - Hormonal influence: as the disease is more common in women of child bearing age, estrogen may play a role in the pathogenesis.

PATHOGENESIS

- When cells die by apoptosis, the cellular remnants appear on the cell surface as small blebs which carry self-antigens.
- The antigens include nuclear constituents (e.g. DNA and histones) which are normally hidden from the immune system.
- In people with SLE removal of these blebs by phagocytes is inefficient so that they are transferred to lymphoid tissue where they can be taken up by antigen presenting cells.
- The self-antigens from these blebs can then be presented to T cells which in turn stimulate B-cells to produce autoantibodies directed against these antigens.
- Presence of self-antigens and failure of the immune system to inactivate B cells and T cells which recognize these self-antigens (i.e. a breakdown of tolerance) leads to:
  - Development of autoantibodies that either form circulating complexes or deposit by binding directly to tissues
  - This leads to activation of complement and influx of neutrophils causing inflammation in those tissues.
  - Abnormal cytokine production: increased blood levels of IL-10 and alpha-interferon are particularly closely linked to high activity of inflammation in SLE.

CLINICAL FEATURES

- SLE can affect virtually all organs with a wide range of severity and a relapsing-remitting course.

- Note: Arthralgia and rashes are the most common clinical features while cerebral and renal disease are the most serious problems.
- Systemic symptoms: fatigue (90%), weight loss, lymphadenopathy and fever (50%)
- CNS (60%):
  - Generalized manifestations: severe headache, reactive depression, psychosis (20%), seizures (20%) and cognitive disturbances
  - Focal: focal seizure, hemiparesis, paraparesis, cranial nerve lesions, ataxia, chorea may also be seen
  - Peripheral nerves: some patients may have sensory or sensorimotor neuropathies.
- Cardiovascular (25%):
  - Ischemic heart disease (5 times risk)
  - Hypertension from renal involvement
  - Vasculitis
  - Endocarditis
  - Myocarditis
  - Pericarditis
  - Antiphospholipid syndrome (causes arterial and venous thrombosis)

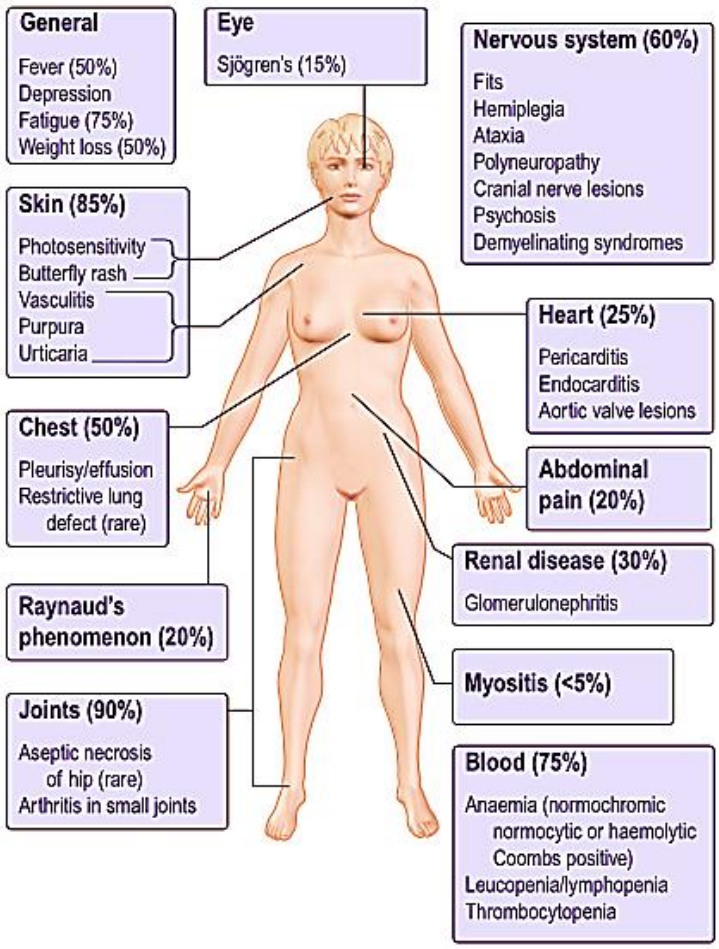


Figure 64: Clinical features of SLE (Adapted from Kumar and Clark Clinical Medicine)

- Blood (75%):
  - Anemia (normochromic normocytic or hemolytic- Coombs positive)
  - Leucopenia/Lymphopenia
  - Thrombocytopenia
- Respiratory system (50%):
  - Interstitial lung disease (fibrosing alveolitis)
  - Pleurisy
  - Pulmonary hemorrhage (causes hemoptysis and anemia)
  - Lupus pneumonitis
- Gastrointestinal (20%):
  - Painless oral and nasal ulcers (30%)
  - Diarrhea and vomiting
  - Dysphagia (10%)
  - Abdominal pain
  - Splenomegaly (10%)
  - Pancreatitis
  - Intestinal vasculitis



Figure 65: Photosensitive malar rash (Butterfly rash) (Image adapted from Kumar and Clark Clinical Medicine)

- Genitourinary (50%): due to deposition of complement and IgG antibodies and influx of neutrophils and lymphocytes.
  - Lupus nephritis (50%): can cause 6 different types of glomerulonephritis from minimal mesangial to advance sclerosis.
  - Can manifest with proteinuria, casts, edema and later on chronic renal failure (uremia)
- Musculoskeletal (90%):
  - Joint/muscle pain
  - Arthritis usually symmetrical, non-erosive polyarthritis with morning stiffness but without swelling.
  - Myalgia, tenosynovitis and tendon rupture
  - Myositis and proximal myopathy
  - Aseptic bone necrosis
- Skin (85%): due to deposition of complement and IgG antibodies and influx of neutrophils and lymphocytes.
  - Malar rash (60%)- Photosensitive malar butterfly rash (facial erythema over the cheeks and nose)
  - Photosensitivity (40%)

  - Discoid rash (20%)
  - Alopecia
  - Raynaud's phenomena (50%)
  - Purpura
  - Urticaria
- Others:
  - Eyes: Keratoconjunctivitis sicca (dry eyes), optic neuritis
  - Recurrent abortions

INVESTIGATIONS

- Blood
  - Full blood count: decreased hemoglobin (due to anemia of chronic disease or Coomb's positive hemolytic anemia), decreased WBC, Decreased platelets
  - ESR: elevated
  - C-reactive protein: may be normal (or raised)
  - U and Es + Creatinine: raised
  - Clotting panel: increased aPTT in antiphospholid syndrome
  - Serology:
    - Antinuclear antibodies/ Antinuclear factor (ANA): are antibodies which bind to elements of the cell nuclear. 95% sensitive (so screen with this first) however they are 50% specific as they are mildly raised in 10% of healthy population
    - Double-stranded DNA (dsDNA) antibody is highly specific for SLE (>90%) but only 60% sensitive. Especially associated with lupus nephritis. Good for monitoring disease activity.
    - Anti-smith (Sm) antibody: highly specific for SLE (>95%) but not sensitive (30%)
    - Anti-Ro and Anti-La antibody: can be seen in SLE, but commoner in Sjogren's syndrome
    - Complements: C3 and C4 are low
- Other tests:
  - Urinalysis: protein, blood, casts (red cells, tubular, granular)
  - Imaging as per symptoms e.g. Chest X-ray if CVS or Respiratory symptoms are present.

DIAGNOSTIC CRITERIA

- 4 out of 17 of SOAP B_2RAI_6N MD, including more than 1 clinical and 1 immune criteria are needed for a diagnosis:
  - Serositis (pleurisy, pericarditis)
  - Oral or nasopharyngeal ulcer
  - Arthritis
  - Leuco-or lympho-Penia
  - Blood disorders (up to 2): hemolytic anemia, decreased platelet count
  - Renal disease: proteinuria or red cell casts
  - Alopecia (non-scarring)
  - Immune markers (up to 6): ANA, dsDNA, anti-Sm Antibodies, Antiphospholipid antibodies, Decreased C3/C4 complements and Coomb's positive
  - Neurocognitive symptoms: seizures or psychosis
  - Malar rash
  - Discoid rash
- Alternatively: a biopsy plus positive glomerulonephritis consistent with SLE plus ANA or dsDNA antibodies is enough to warrant a diagnosis

Diagnostic Criteria for SLE[a]	
	Criteria
Skin/Sunlight	1. Malar rash 2. Discoid rash 3. Photosensitivity
Serosa/mucous membranes	4. Oral ulcers 5. Serositis (pleuritis/pericarditis)
Synovitis	6. Arthritis
Seizures, "S"ychosis	7. Neurologic disease
"S"ellular casts, proteinuria	8. Renal disease (any one of the following): a. > 0.5 g/day proteinuria b. ≥ 3+ dipstick protein c. Cellular casts
"S"ytopenias	9. Hematologic disorders (any one of the following): a. Hemolytic anemia b. Leukopenia (< 4000/mL) c. Lymphopenia (< 1500/mL) d. Thrombocytopenia (< 100,000/mL)
Serologies	10. ⊕ ANA 11. Immunologic abnormalities (any one of the following): a. Antibodies to native DNA b. Anti-Smith antibodies c. Antiphospholipid antibodies: (1) False-⊕ serologic test for syphilis (2) Evidence of anticardiolipin antibodies (3) Evidence of lupus anticoagulant

[a] Four out of 11 are needed for diagnosis.

MANAGEMENT

- If SLE is believed to be due to be drug-induced, stop the drug
- Give Sun-block/Sunscreen lotions
- NSAIDs are used in full anti-inflammatory dose for fever, joint complaints and Serositis
- Hydroxychloroquine (antimalarial medication) if joint/skin symptoms are not controlled by NSAIDs e.g. 400mg/day PO for 6 months and then 200mg/day
- Corticosteroids

  - High dose prednisolone in life-threatening condition, 1mg/kg/day for 6 weeks, then taper. May be combined with other immunosuppressive
  - Low dose prednisolone is of value in chronic disease.
- Cytotoxic drugs e.g. azathioprine and cyclophosphamide sometimes can be used to treat severe refractory features of SLE particularly renal diseases.

Mild disease	Moderate disease	Severe disease
• Skin/joint involvement, oral ulcers, Serositis • NSAIDs • Topical corticosteroids for skin disease • Low-dose systemic corticosteroids (<10mg/day) • Antimalarial medications (i.e. Hydroxychloroquine, good for mild symptoms and skin disease)	• Cytopenias/hemolytic anemia, Serositis, mild pneumonitis, mild myocarditis • Moderately dosed systemic corticosteroids (approximately 0.5mg/kg/day) • Steroid-sparing agents such as azathioprine, methotrexate (good for skin and arthritis) and mycophenolate mofetil.	• Nephritis, severe CNS disease, vasculitis, pulmonary hemorrhage • High dose corticosteroids (≥1 mg/kg/day) • IV cyclophosphamide (proven efficacy for nephritis, less established for other indications • Azathioprine • Mycophenolate mofetil • IVIG (for antibody-mediated cytopenias) • Plasmapheresis (in extreme circumstances)

PROGNOSIS

- Early diagnosis and treatment decreased morbidity and mortality.
- Renal diseases and infectious complications are the major causes of death.
- CNS disease can lead to severe disability.
- Complications are as follows:
  - Accelerated atherosclerosis, CAD
  - Transitional cell carcinoma and hematologic malignancies if the patient received cyclophosphamide
  - Opportunistic infections

METABOLIC DISTURBANCES

HYPERKALEMIA

- Normal potassium ECF concentration= 3.5-5.5 mEq/L
- Hyperkalemia is a serum potassium >5.5 mmol/L
- Causes:
  - Trauma
  - Crush injuries
  - Burns
  - Renal failure
  - Excessive intake of potassium rich food and supplements
  - Metabolic acidosis
  - Addison's disease
  - Diuretic therapy (potassium sparing diuretics)
- Clinical features:
  - Symptoms:
    - Muscle weakness
  - Signs:
    - Ascending paralysis with respiratory failure
    - Cardiac instability, ventricular fibrillation, cardiac arrest
    - May have signs of acute kidney injury or metabolic acidosis
- Investigations:
  - Serum potassium
    - Mild hyperkalemia: 5.5-5.9
    - Moderate hyperkalemia: 6.0-6.5
    - Severe hyperkalemia: >6.5 and ECG changes
  - ECG findings:
    - Bradycardia
    - Flat P waves
    - Increased PR interval
    - AV block
    - Wide QRS complex
    - Tall peaked symmetrical T waves

MANAGEMENT

- Stop source of potassium (Oranges, bananas, ACEI, potassium sparing diuretics, septrin, heparin, NSAIDs, Beta-blockers)

Mild hyperkalemia (5.5-5.9)	Moderate hyperkalemia (6.0-6.5)	Severe hyperkalemia (>6.5)
• Push Potassium out of the body ➢ Furosemide 1mg/kg IV (hydrate patient first if dehydrated) ➢ Kayexalate/sodium Resonium 15-30g in 50-100ml 20% Sorbitol or with lactulose PO/PR ➢ Consider hemodialysis if refractory	• Protect the heart: 10mls 10% Calcium Gluconate over 10 mins. Effect is temporary but can be repeated after 15 minutes. • Push Potassium into cells ➢ 50mls 50% Dextrose with 10IU soluble insulin over 15-20 mins. May be given 2-4 hourly as required. Monitor serum glucose and potassium 2-4 hourly ➢ 10-20mg Nebulized Salbutamol (or 0.5mg in 100ml of 5% glucose over 15 min-rarely used) • Push Potassium out of the body ➢ Furosemide 1mg/kg IV (hydrate patient first if dehydrated) ➢ Kayexalate (polystyrene sulphonate) /sodium Resonium 15-30g in 50-100ml 20% Sorbitol or with lactulose PO/PR • Consider hemodialysis if refractory	• Protect the heart: 10mls 10% Calcium Gluconate over 10 mins. Effect is temporary but can be repeated after 15 minutes. • Push Potassium into cells ➢ 50mls 50% Dextrose with 10IU soluble insulin over 15-20 mins. May be given 2-4 hourly as required. Monitor serum glucose and potassium 2-4 hourly ➢ 10-20mg Nebulized Salbutamol (or 0.5mg in 100ml of 5% glucose over 15 min-rarely used) • Push Potassium out of the body ➢ Furosemide 1mg/kg IV (hydrate patient first if dehydrated) ➢ Kayexalate (polystyrene sulphonate)/sodium Resonium 15-30g in 50-100ml 20% Sorbitol or with lactulose PO/PR ➢ Consider hemodialysis if refractory

HYPOKALEMIA

- This is a serum potassium <3.5, it may be associated with hypomagnesemia and hypocalcemia.
- Causes:
  - GIT losses (NG tube suctioning, vomiting, diarrhea)
  - Renal losses (Renal disease)
  - Metabolic alkalosis
  - Potassium wasting diuretics
  - Cushing's disease (Sodium retention leads to potassium loss)
- Clinical features:
  - Symptoms:
    - Muscle weakness
    - Fatigue
    - Constipation
    - Muscle cramps
  - Signs:
    - Paralytic ileus
    - Ascending paralysis
    - Reduced reflexes
    - Tetany when associated with alkalosis
    - Arrhythmias
- Investigations:
  - Check potassium, other electrolytes and serum pH.
  - ECG
    - Flat or inverted T wave
    - Prominent U wave

MANAGEMENT

- 20mmol KCL in 250-500ml Normal saline over 1 hour. Check Potassium before repeating dose and ECG monitoring.
- Consider 6-12ml (5-10mml/l) 20% $MgSO_4$ or 2ml 50% diluted in 50ml over 1 hour.
- It cardiac arrhythmia or arrest give 2mmol KCL per minute IV for 5mins. Repeat once only if necessary
- Oral Potassium supplements if potassium >3.0.

HYPERNATREMIA

- Normal sodium ECF concentration= 135-145 mEq/L
- This is defined as a serum sodium >150 mmol/L
- Causes:
  - Water loss more than electrolyte
  - GIT losses
  - Renal losses
  - Diabetes insipidus
  - Diabetes mellitus
  - Increase in sodium
    - Hyperaldosteronism
    - Cushing's
    - Excessive saline or Sodium bicarbonate infusion
- Clinical features:
  - Symptoms:
    - Thirst
    - Nausea and vomiting
    - Weakness
    - Malaise
    - Muscle tremor
  - Signs
    - Dry mucous membranes and lips
    - Oliguria
    - Increased temperature and flushed skin
    - Drowsiness
    - Confusion
    - Stupor
    - Coma
    - Convulsions
    - Tremors
    - Ataxia
- Investigations:
  - Serum Sodium
  - Urine Sodium

MANAGEMENT

- Correct water deficit- rehydrate patient if dehydrated
- Stable/asymptomatic patients
  - Take it easy
  - Replace fluids orally
- Unstable/symptomatic patients
  - IV fluids with NS, DNS
  - Avoid 5% dextrose as sodium may drop too fast
  - Rate of lowering serum sodium 0.5-1mmol/hr, aim for 12 mmol/L in 24hours and not more than this.
  - Estimate the effect of 1 liter of any infusion on serum sodium
  - Change in serum Sodium= $\frac{Infusion\ sodium - Serum\ sodium}{Total\ body\ water + 1}$
  - The answer is in mmol/L. The formula helps to calculate the infusion rate so that you do not exceed 1 mmol/min.

HYPONATREMIA

- This is low serum sodium but treatment warranted with severe (<120mmol/L) or acute
- Causes:
  - Hypovolemic
    - GI losses (NG tube suctioning, vomiting, diarrhea)
    - Renal losses
    - Diuretic therapies
  - Euvolemic
    - Hypothyroidism
    - SIADH
    - Adrenal insufficiency (Addison's disease)
  - Hypervolemic
    - Congestive heart failure
    - Cirrhosis
    - Nephrotic syndrome
- Clinical features:
  - Asymptomatic unless severe or acute
  - Abdominal cramps, Nausea, vomiting, pitting edema over the sternum, confusion, seizures, coma
- Investigations:

- Serum sodium
- Urine sodium
- Serum and Urine osmolarity

MANAGEMENT

- CNS manifestations
  - 200ml 5% NaCl over 6 hours. Monitor serum sodium hourly.
  - Aim to increase sodium to 120mmol/l at a rate of 0.5-1.0 mmol/l per hour
  - If no CNS symptoms, do not use hypertonic saline.
  - Once serum sodium is around 120 mmol/L, stop active therapy and restrict fluid intake to approximately 500ml/day.
- Asymptomatic
  - Can use conservative measure like fluid restriction may be enough
- SIADH
  - Restrict fluid intake to 50-60% of estimated maintenance fluid requirements (+/- 1L/day)

HYPERCALCEMIA

- Normal serum calcium: 2-2.5mmol/L
- Corrected serum Calcium >2.65mmol/L
- Causes
  - Hyperparathyroidism
  - Malignancy
  - Sarcoidosis
  - Drugs
  - Vitamin D intoxication especially in renal patients
- Clinical features:
  - Symptoms
    - Polyuria
    - Polydipsia
    - Dysphagia
    - Bone pain
    - Renal colicky
    - Muscle weakness
  - Signs
    - Confusion
    - Hypotonia

  - Dysarthria
  - Coma
  - Seizures
- Investigations
  - Serum Calcium, Urea + Electrolytes, Albumin, Magnesium, phosphate, ALP, serum electrophoresis
  - PTH
  - X-rays
  - ECG
    - Short QT interval
    - Wide QRS complex
    - Flat T waves
    - AV block
    - May have fatal arrhythmias (frequent association with hypokalemia increases risk of arrhythmias)

MANAGEMENT

- Hydrate with normal saline 500ml/hr until urine output >200ml/hr then reduce 100-200ml/hr.
- Furosemide 1mg/kg only when patient has been hydrated or if in cardiac failure
- Hemodialysis or peritoneal dialysis with low calcium dialysate. Hemodialysis is preferred.
- Prednisolone 40mg daily especially for Vitamin D intoxication, sarcoidosis, multiple myeloma, metastasis
- Pamidronate 60-90mg in 500-100ml NS infusion.

CHAPTER 14: RADIOLOGY AND IMAGING

RADIOLOGY

INTEPRETING X-RAYS

CHEST X-RAYS

GENERAL DETAILS

- On all X-rays check the following details:
  - Check patient details: first name, surname, and date of birth.
  - Check orientation, position and side description: left, right, erect, anterior-posterior, posterior-anterior, supine, and prone.
  - Check additional information: inspiration and expiration.
  - Check for rotation: measure the distance from the medial end of each clavicle to the spinous process of the vertebra at the same level, which should be equal.
  - Check adequacy of inspiration: 9 pairs of ribs should be seen posteriorly in order to consider a chest X-ray adequate in terms of inspiration
  - Check exposure: one needs to be able to identify both costophrenic angles and lung apices.
    - On a PA view, the costophrenic recesses are seen on each side as the costophrenic angles
    - The costophrenic angles are formed by the lateral chest wall and the dome of each hemidiaphragm.
    - On a lateral view the costophrenic recesses are seen in the region of the anterior and posterior costophrenic angles formed by the chest wall and the dome of each hemidiaphragm.
- Ideally the chest X-ray is taken in the posterior-anterior (PA) direction at maximum inspiration with the heart close to the X-ray film to minimize magnification with respect to the thorax.
- A lateral may give additional information if the PA is abnormal. The cardiac structures and great vessels can be seen on these X-rays.
- An Anterior posterior (AP) view is only taken in an emergency.

SPECIFIC RADIOLOGICAL CHECK LIST

- Use the ABCDEFGH approach

A- AIRWAY

- Ensure that the trachea is visible and in the midline.
  - Trachea gets pushed away from abnormalities such as pleural effusion or tension pneumothorax.

  - Trachea gets pulled towards abnormality such as atelectasis.
  - Trachea normally narrows at the vocal cords.
  - View the carina, angle should be between 60-100 degrees
  - Beware of things that may increase this angle e.g. left atrial enlargement, lymph node enlargement and left upper lobe atelectasis.
  - Check for tubes, pacemaker wires, lines, foreign bodies.
  - If an endotracheal tube is in place, check the positioning, the distal tip of the tube should be 3-4cm above the carina.
- Check for a widened mediastinum
  - Mass lesions (e.g. tumor, lymph nodes)
  - Inflammation (e.g. mediastinitis, granulomatous inflammation)
  - Trauma and dissection (e.g. hematoma, aneurysm of the major mediastinal vessels)

B- BONES

- Check for fractures, dislocations, subluxation (a partial dislocation), osteoblastic or osteolytic lesions in clavicles, ribs, thoracic cage.
- Check the spine and humerus including osteoarthritic changes.
- At this time also check for soft tissues for subcutaneous air, foreign bodies and surgical clips
- Take caution with nipple shadows, which may mimic intrapulmonary nodules:
  - Compare side to side, if on both sides the "nodules" in question are in the same position, then they are likely to be due to nipple shadows.

C- CARDIAC

- Check heart size and heart borders
  - Appropriate or blunted
  - Thin rim of air around the heart, think of pneumomediastinum
- Check aorta
  - Widening, tortuosity, calcification
- Check valves
  - Calcification, valve replacements
- Check superior vena cava, inferior vena cava, azygos vein
  - Widening, tortuosity

D- DIAPHRAGM

- Right hemidiaphragm
  - Should be higher than the left

    - If much higher, think of effusion, lobar collapse, diaphragmatic paralysis
    - If you cannot see parts of the diaphragm, consider infiltrate or effusion
- If film is taken in erect or upright position you may see free air under the diaphragm if intra-abdominal perforation is present

E- EFFUSIONS

- Effusion
    - Look for blunting of the costophrenic angle
    - Identify the major fissures, if you can see them more obvious than usual, then this could mean that fluid is tracking along the fissure.
- Check out the pleura
    - Thickening, loculations, calcifications and pneumothorax

F- FIELDS (LUNG FIELDS)

- Check for infiltrates
    - Identify the location of infiltrates by use of known radiological phenomena e.g. loss of heart borders or the contour of the diaphragm
    - Remember that right middle lobe abuts the heart, but the right lower lobe does not
    - The lingual abuts the left side of the heart
- Identify the pattern of infiltration
    - Interstitial pattern (reticular) versus alveolar (patchy or nodular) pattern
    - Lobar collapse
    - Look for air bronchograms, tram tracking, nodules, kerley B lines
    - Pay attention to the apices
- Check for granulomas, tumor and pneumothorax

G- GASTRIC AIR BUBBLE

- Check correct position
- Beware of hiatus hernia
- Look for fee air
- Look for bowel loops between diaphragm and liver

H- HILUM

- Check the position and size bilaterally
- Enlarged lymph nodes
- Calcified nodules
- Mass lesions
- Pulmonary arteries, if greater than 1.5cm think about possible causes of enlargement

SILHOUETTE SIGN

- Can localize abnormalities on a PA film without need for a lateral view.

- The loss of clarity of a structure, such as the hemidiaphragm or heart border suggests that there is adjacent soft tissue shadowing such as consolidated lung.
    - The reason is that borders, outlines and edges seen on plain radiographs depend on the presence of two adjacent areas of different density.
    - Roughly speaking, only 4 different densities are detectable on plain films: air, fat, soft tissue and calcium (5 if you include contrast such as barium).
    - If soft tissue densities lie adjacent, then they will not be visible separately (e.g. the left and right ventricles). If, however they are separated by air, the boundaries of both will be seen.

LUNG COLLAPSE

- A collapse usually occurs due to proximal occlusion of a bronchus, causing subsequently a loss of aeration.
- The remaining air is gradually absorbed and the lung loses volume.
- Proximal stenosing bronchogenic carcinoma, mucous plugging, fluid retention in major airways, inhaled foreign body or malposition of an endotracheal tube are the most common reasons for a lung collapse.
- Tracheal displacement or mediastinal sift towards the side of the collapse is often seen.
- Further findings are elevation of the hemidiaphragm, reduce vessel count on the side of the collapse or herniation of the opposite lung across the midline.

CHAPTER 15: COMMON PROCEDURES

COMMON PROCEDURES

PROCEDURE DOCUMENTATION

- Before you begin any procedure, stop and confirm:
  - Consent has been obtained from the patient and the procedure has been explained to the patient.
  - Correct patient
  - Correct procedure and Correct site
  - No contraindications
- After you finish, document the procedure in the patient's file: date, time, procedure, indication, site, technique, quantity and quality of specimen, complications.
- Examples:
  - 25/12/2020-10AM. A lumbar puncture was performed to rule out meningitis: A 20g needle was inserted at L3-L4 using sterile technique. 5ml of clear fluid was removed, normal pressure. A dipstick of the fluid revealed negative leukocyte esterase. No complications occurred.

LUMBAR PUNCTURE (LP)

INDICATIONS

- Diagnostic:
  - Meningitis
  - Sub-arachnoid hemorrhage
  - Demyelinating disorders
- Therapeutic: Cryptococcal meningitis to reduce ICP
  - Patient presents with 2/4 of the following symptoms should have an urgent LP performed:
    (1) Fever (T>38.0^{o}C)
    (2) Headache
    (3) Altered mental status (GCS<14) and
    (4) Neck stiffness/Kernig/Brudzinski's sign (Fever + headache alone are an indication for LP if MPS is negative or patient already treated for malaria)

CONTRAINDICATIONS

- Cardiorespiratory instability
- Increased intracranial pressure due to mass (papilledema, CT scan with mass)
- Skin infection over puncture site
- Bleeding disorders

TECHNIQUE

- Position the patient in either the lateral decubitus or upright sitting position. In both positions the patient's spine should be straight and as flexed as possible with the forehead bent toward the knees. Position is very important for LP.
- Identify the puncture site. Palpate the top of the iliac crest and the vertebral interspace located at the same level (L4- L5). Palpate L3-L4, L4-L5, L5-S1 and mark the interspace that is most open. Note: Conus Medullaris is at L1-L2.
- Sterilize the puncture site around your mark with iodine solution and methylated spirit.
- Using a sterile 20g needle (or spinal needle) and sterile gloves, enter the middle of the interspace. Advance the needle slowly toward the umbilicus and parallel to the ground. There will be some resistance and a give-in as the needle passes through the ligamentum flavum.
- Once CSF is obtained, estimate the opening pressure based on the flow rate. Collect fluid in at least 3 separate red bottles/tubes. Only the 2nd bottle needs to be sterile to be sent for microbiology. Describe the appearance of the fluid in each bottle/Tube.
- Place one drop of CSF on a urine dipstick and record results.
- Send the 1st bottle to chemistry (1ml) for total protein and glucose.
- Send the 2nd bottle (5 ml) to microbiology for gram stain, culture, sensitivity and AFB (if indicated).
- Send the 3rd bottle to hematology for cell count and differential.
- Note: Blood should also be sent for estimation of serum glucose.

COMPLICATIONS

- Post LP headache (common, treat with caffeine)
- Nerve root injury (shooting pains, transient)
- Tonsillar herniation/Spinal hemorrhage (rare but severe)

Feature	Normal	Bacterial meningitis	Viral meningitis	Tuberculous meningitis
Pressure	50-250mm of water	Normal/increased	Normal	Normal/increased
Appearance	Crystal clear	Turbid	Clear	Cob-web appearance
Cell count/ microliter	<10 RBCs <5 WBCs	Several thousands (1000-5000 polymorphs)	Several hundreds (10-2000 lymphocytes)	Several hundreds (50-5000 lymphocytes)
Cell type	None	Granulocytes (Polymorphs)	Lymphocytes	Lymphocytes and monocytes
Glucose	2/3 to ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose	Normal > ½ blood glucose	Decreased (<30mg/dl) < ½ blood glucose
Protein	0.2-0.4 g/l	Increased (>120mg/dl) 0.5-2.0g/l	Normal (0.4-0.8g/L)	Increased (>120 mg/dl) 0.5-3.0g/l
Lactate dehydrogenase		>3.5mmol/L	<3.5 mmol/L	>3.5mmol/L

THORACENTESIS

INDICATIONS

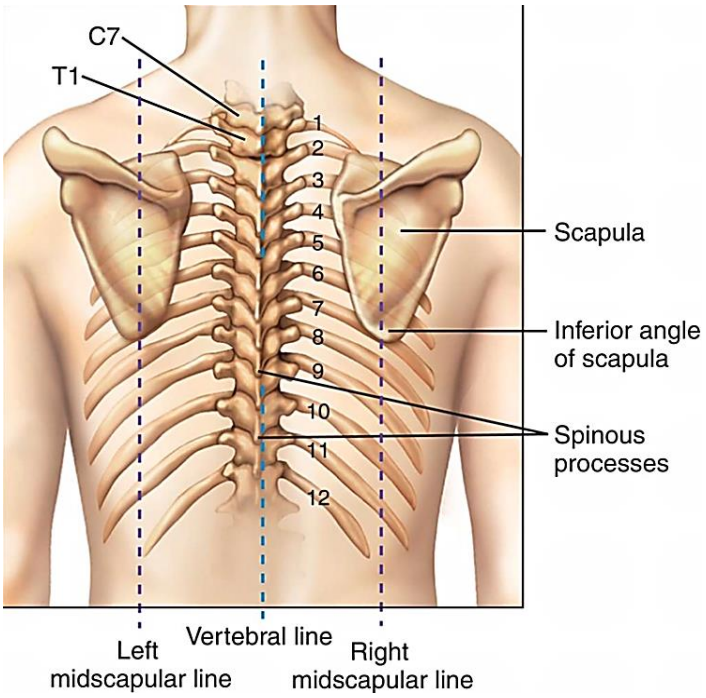
- Diagnostic:
  - Should be performed for any patient with a moderate-large pleural effusion who have not had a previous diagnostic thoracentesis.
- Therapeutic:
  - For patient with respiratory distress due to large pleural effusion
  - Patients with moderate-large exudative effusions.

CONTRAINDICATIONS

- Small pleural effusions (<1cm on lateral decubitus film)
- Bleeding disorders
- Cardiorespiratory instability
- Uncooperative patient
- Skin infection over the puncture site

TECHNIQUE

- Position the patient. Have them sit on the edge of their bed while leaning over a bedside table. The posterior approach reduces risk of lung injury.
- Identify the puncture site by reviewing the chest X-ray and percussing the level of the effusion. Verify the presence and location of the pleural fluid. Mark a puncture site 1-2 intercostal spaces below this level at the midline (in line with the tip of the scapula-Midscapular line). Do not enter below the 8th intercostal space to avoid the abdominal organs. Alternatively, the axillary approach can be used entering at the mid-axillary line between the 7th to 9th intercostal space. Some experts recommend using the intercostal space below the upper limit of the dullness



- Sterilize the puncture site with iodine solution and methylated spirit. Infiltrate using 1% lignocaine.
- Using a sterile 16 or 18g needle attached to a sterile syringe (5 or 10 ml) and sterile gloves, insert the needle at the puncture site above the rib to avoid the neurovascular bundle below the rib. Insert the needle slowly while drawing back on the syringe. Stop inserting the needle when fluid starts to flow.
- Withdraw 5-10ml of fluid into the syringe for a diagnostic tap.
  - Send 1ml to chemistry for total protein and
  - 4-5ml to microbiology for gram stain, culture, sensitivity and AFB (ZN stain).
  - Also send serum for total protein at the same time.
  - Consider sending fluid for cytology if concerned for malignancy.
- For therapeutic tap, remove the needle but leave the plastic cannula in place and attach it to IV tubing and a urine bag. Never drain more than 1 liter at a time to prevent re-expansion edema.
- If more than 1 liter needs to be removed, clamp the IV tubing and wait 4-6 hours before draining another 1 liter. This process can be repeated several times if necessary.

- An urgent CXR should be ordered post procedure if air is aspirated or the patient develops cough, shortness of breath or chest pain.
- Note: patients with empyema or loculated pleural effusion should have chest tubes or surgical drainage.

COMPLICATIONS

- Pneumothorax (common but usually mild, if signs of tension pneumothorax consider immediate needle decompression)
- Hemothorax

Light's Criteria: Exudate if any of the 3 are found		
	Transudate	Exudate
Protein (Pleural/Serum)	≤0.5	>0.5
Lactate dehydrogenase (Pleural/Serum)	≤0.6	>0.6
	Pleural LDH ≤ two thirds of upper limit of serum LDH	Pleural LDH > two-thirds of upper limit of serum LDH
Common causes	• Hypoalbuminemia (Cirrhosis, Nephrotic syndrome) • Congestive heart failure • Constrictive pericarditis • Myxedema (hypothyroidism) • Ovarian tumors producing right sided pleural effusion- Meigs' syndrome	• Infection (Parapneumonic, TB, fungal, empyema) • Esophageal rupture • Pulmonary embolism • Neoplasms • Autoimmune (Systemic lupus erythematosus) • Rheumatoid pleural effusion • Esophageal rupture • Sub-diaphragmatic abscess • Pancreatitis • Uremic pleural effusion • Hemothorax • Chylothorax (thoracic duct injury) • Radiation and drugs

Note: in resource limited setting where LDH is often not available: Total protein effusion >30g/L is often used to indicate an exudate effusion whilst that <30g/L is a transudate

PARACENTESIS

BACKGROUND

- Paracentesis is a procedure in which a needle or catheter is inserted into the peritoneal cavity to obtain ascitic fluid for diagnostic or therapeutic purposes.
- Ascitic fluid may be used to help determine the etiology of ascites as well as to evaluate for infection or presence of cancer.

INDICATIONS

- Diagnostic:
  - Should be performed on any patient with ascites detectable by examination who has not had a previous diagnostic paracentesis. The fluid evaluation helps to determine etiology, differentiate transudative versus exudate, detect the presence of cancerous cells or address other considerations.
  - Suspected spontaneous bacterial peritonitis or secondary bacterial peritonitis.
  - Refractory ascites
- Therapeutic:
  - Only for patients with severe respiratory distress
  - Abdominal pressure or pain secondary to ascites (abdominal compartment syndrome due to massive ascites)

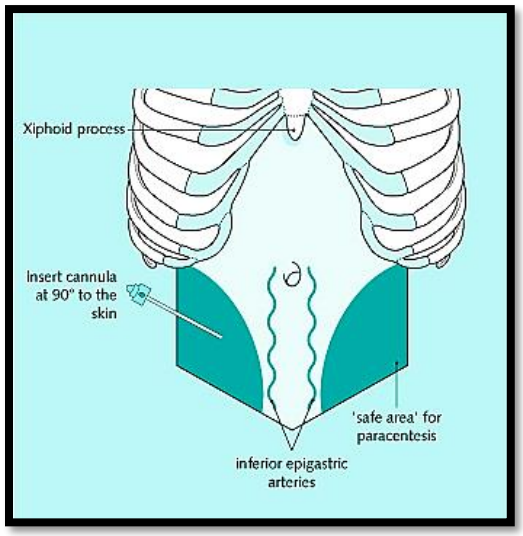
CONTRAINDICATIONS

- Acute abdomen requiring surgery is an ABSOLUTE CONTRAINDICATION
- Skin infection at puncture site
- Pregnancy
- Hypotension
- NOTE: Bleeding disorders (severe thrombocytopenia of $<20 \times 10^3/\mu L$ and coagulopathy with INR>2.0) are generally not a contraindication to paracentesis (relative contraindication)
- Other relative contraindications:
  - Distended urinary bladder
  - Abdominal wall cellulitis
  - Distended bowel
  - Intra-abdominal adhesions

EQUIPEMENT

- Dressing pack and adhesive tap
- Abundant supply of gauze pads
- Iodine/cleaning solution
- Sterile gloves
- 10ml Syringe and 50ml Syringe
- 21 Gauge (green) cannula or Grey cannula
- Urine bag

TEECHNIQUE



- Expose the patient's abdomen fully and percuss out ascitic fluid. Demonstrate shifting dullness and a fluid thrill. Percuss either right or left iliac fossa- this is where the drain will be inserted. Mark the position with a pen if necessary.
- Position the patient either sitting up in bed or lying in the left lateral decubitus position.
- Identify the puncture site. Use either 2 cm below the umbilicus (lower risk of bleeding) or McBurney's point in the left lower quadrant (to prevent cecal perforation). Avoid the lateral border of the rectus abdominis muscle.
- Confirm by percussion that there is fluid at the puncture site. Sterilize the puncture site.
- Using a sterile 22g needle (18g for therapeutic paracentesis) attached to a sterile 5-10ml syringe and sterile gloves, enter the skin at the puncture site while pulling the skin 2cm caudal in relation to the deep tissue (Z-line tract approach). This helps to reduce skin leakage after the procedure. Advance the needle slowly while drawing back on the syringe. Stop advancing the needle when fluid is obtained.
- For diagnostic tap, remove 5-10ml of fluid in the syringe. For therapeutic tap, remove the needle and attach the plastic cannula to IV tubing and a urine bag. Drain 2-6L as necessary to remove the patient's symptoms.
- Send 1ml for chemistry for albumin and total protein. Send blood for albumin at the same time. Send 5ml to microbiology for gram stain, culture and AFB (if indicated) if concerned for Spontaneous bacterial peritonitis, send 1ml to hematology for cell count and differential. Consider sending fluid for cytology if concerned for malignancy.

COMPLICATIONS

- Hemorrhage
- Hypovolemia and Hypotension (if too much fluid withdrawn)
- Renal dysfunction (post-paracentesis circulatory dysfunction) as the ascites re-accumulates at the expense of the circulating volume (this is likely with >5L removal and worse liver function)
  - This is overcome by infusing albumin (8g/L of ascitic fluid removed)
  - In practice up to 20L can be removed over 4-6 hours with albumin infusion.
- Skin leak
- Bowel/Bladder perforation

EVALUATION OF ASCITIC FLUID

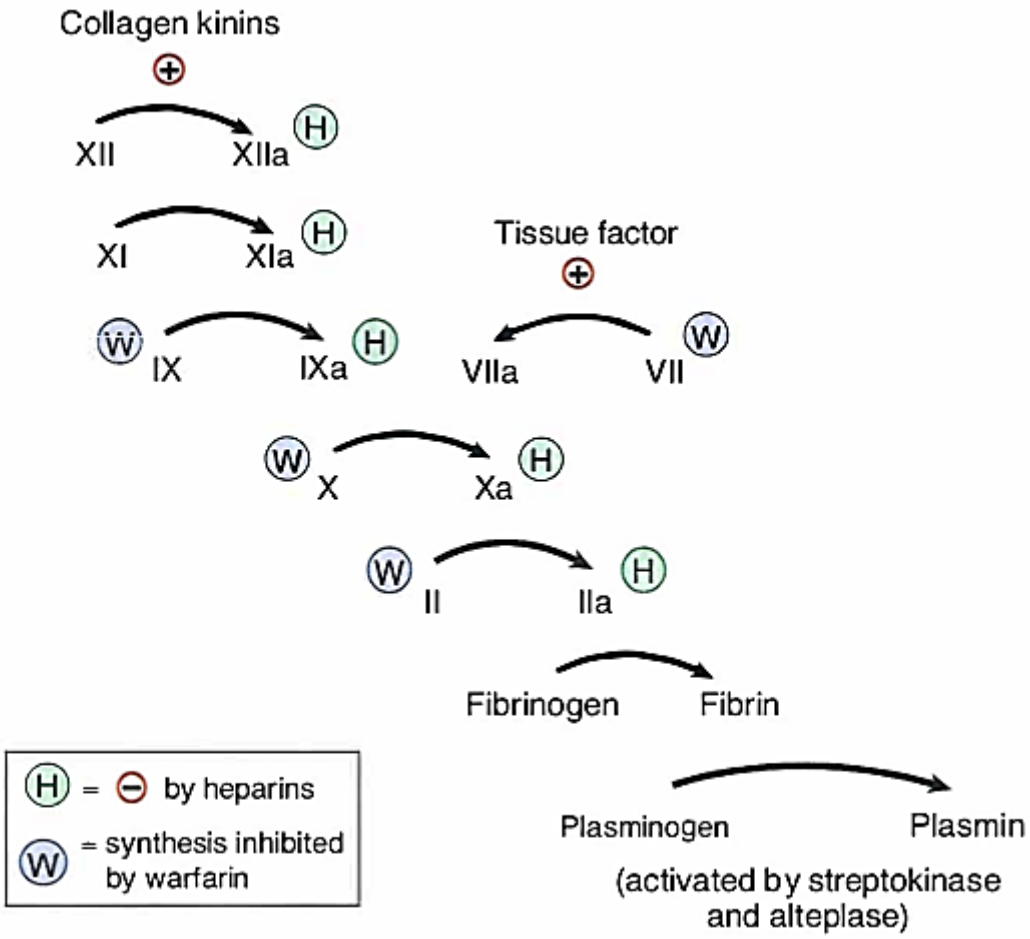
- This is done with Serum-Ascitic Albumin Globulin Ratio (SAAG).
- This helps distinguish transudates from exudates in relation to ascitic fluid.
- SAAG= Serum Albumin Concentration- Ascitic Albumin concentration
- The SAAG correlates directly with portal pressure.
- Transudative ascites occurs when a patient's SAAG is greater than or equal to 1.1g/dl (suspect portal hypertension as the cause of ascites). Causes include:
  - Hepatic cirrhosis
  - Alcoholic hepatitis
  - Fulminant hepatic failure
  - Heart failure (right sided), Tricuspid regurgitation, Constrictive pericarditis
  - Portal vein thrombosis, hepatic veno-occlusive disease, Budd Chiari syndrome
  - Schistosomiasis
- Exudative ascites occurs when patient's SAAG is lower than 1.1g/dl. Causes include:
  - Peritonitis (TB peritonitis)
  - Inflammation of pancreas (pancreatitis) or biliary system
  - Ischemic or obstructed bowel
  - Peritoneal carcinomatosis (peritoneal cancer).
  - Nephrotic syndrome

CHAPTER 16: COMMONLY USED DRUGS

COMMONLY USED DRUGS

ANTICOAGULANTS

- Blood coagulates by transformation of soluble fibrinogen into insoluble fibrin.
- Circulating protein interact in a "cascade" where clotting factors undergo limited proteolysis to become active serine proteases.
- Anticoagulants decrease the formation of fibrin clots
- Oral anticoagulants inhibit the hepatic synthesis of clotting factors II, VII, IX and X in the liver
- The endogenous anticoagulants protein C and protein S cause proteolysis of factors Va and VIIIa.



- Heparin blocks the clotting factors of the intrinsic pathway as such PTT is used to monitor the intrinsic cascade and it increases the PTT
- Warfarin works on the liver not the factors already synthesized. It blocks synthesis of vitamin K dependent clotting factors

Feature	Heparin	Warfarin (Coumadins)
Chemical nature	Large polysaccharide, water soluble	Small molecule lipid soluble derivatives of vitamin K
Kinetics	• Given parenterally (IV, SC), • Hepatic and reticuloendothelial elimination • Half-life=2h (short) • No placental access	• Given orally • 98% protein bound • When given orally it is metabolized by the liver • Half-life- 30+ hours • Placental access (can cause teratogenicity and bleeding in the infant)
Mechanism	Heparin catalyzes the binding of antithrombin III (a serine protease inhibitor) to factors IIa, IXa, X, XIa and XIIa resulting in their rapid inactivation Works in vivo and in vitro	Decreases hepatic synthesis of vitamin K dependent clotting factors (II, VII, IX and X). Coumarins prevent gamma-carboxylation by inhibiting vitamin K epoxide reductase. It has no effect on factors already present. In vivo effects only
Monitoring	Partial thromboplastin time (PTT)	Prothrombin Time (PT), INR (international normalization ratio= $\frac{PT\ od\ the\ patient}{PT\ of\ the\ control}$) INR should be around 1.5-2.5
Antagonist	Protamine sulfate- chemical antagonism, fast onset	Vitamin K (displaces warfarin from epoxide reductase)- increases cofactor synthesis, slow onset, fresh frozen plasma (fast)
Uses	• Rapid anticoagulation (intensive) for thromboses • Emboli • Unstable angina • DIC • Open heart surgery	• Longer-term anticoagulation (controlled) for thromboses • Emboli • Post-MI • Heart valve damage • Atrial arrhythmias etc.

Toxicity	• Bleeding • Osteoporosis • Heparin-induced thrombocytopenia (hypersensitivity type II response, heparin binds to platelet factor 4 leading to opsonization and destruction by the platelets). LMW heparin (Enoxaparin) are less likely to cause heparin induced thrombocytopenia • Hypersensitivity	• Bleeding • Skin necrosis (if low protein C deficiency) • Drug interaction (high plasma protein bound, other drugs that are highly protein bound could potential displace warfarin and cause bleeding e.g. sulphonamides, sulfonylureas, NSAIDs other drugs deal with absorption as a Vitamin K analogue it requires to be emulsified by bile so cholestyramine and cholestipole reduce absorption as they decrease bile) • Teratogenic (bone dysmorphogenesis) • Warfarin is contraindicated in pregnancy.

TEST YOURSELF

TRUE/FALSE QUESTIONS

1. Causes of inappropriate ADH secretion include:
   A. Meningitis
   B. Head injury
   C. Lobar pneumonia
   D. Small cell bronchial carcinoma
   E. Phenothiazine therapy

2. Acute confusion in the elderly is likely to be the result of
   A. Adverse drug reaction
   B. Hypothermia
   C. Bronchopneumonia
   D. Myocardial infarction
   E. Cerebral infarction

3. Common etiologies of adult community acquired bacterial meningitis includes the following except:
   A. Norcardia pneumonia
   B. Neisseria meningitidis
   C. Streptococcus pneumonia
   D. Listeria monocytogenes
   E. Cryptococcal infection

4. Migraine headache is often characterized by the following except:
   A. Being throbbing
   B. Being unilateral
   C. Associated with projectile vomiting
   D. May be associated with visual disturbances

5. The most common cause of meningitis is:
   A. Viral
   B. TB
   C. Bacterial
   D. Malignancy
   E. Fungal

6. Generalized seizure types include:
   A. Localized
   B. Absence
   C. Tonic-Clonic
   D. Myoclonic
   E. Atonic

7. Meningitis may present with the following clinical features:
   A. Fever
   B. Reduced alertness
   C. Photophobia
   D. Headache
   E. Shortness of breath

8. The following might precipitate seizures
   A. Fever
   B. Flickering light
   C. Alcohol
   D. Sleep deprivation
   E. Laughter

9. Paralysis of the fourth cranial nerve produces:
   A. Weakness of the inferior oblique muscle
   B. Pupillary dilation
   C. Impaired downward gaze
   D. Elevation and abduction of the eye
   E. None of the above.

10. With respect to lumbar puncture:
    A. Coagulation is a contraindication
    B. Papilledema is an absolute contraindication
    C. Can be therapeutic by reducing intracranial pressure
    D. The less CSF is removed; the less likely coning is to occur

11. About Parkinsonism
    A. Mainly results from reduction of dopaminergic transmission within the basal ganglia
    B. Intentional tremor and akinesia help in diagnosis
    C. Family history is a risk factor
    D. Neuropsychiatry symptoms might be present

12. Outcome of bacterial meningitis relates to:
    A. Age of the patient
    B. Time of first administration of antibiotics
    C. CSF concentration of antibiotics
    D. Development of antibiotics resistance during therapy

13. A 70-year-old woman complains of sudden onset of weakness of left arm and leg, she also experiences difficulties in speech and loss of vision in one eye. Although these symptoms were frightening, they improved within 10 hours and she was feeling well when she came to the clinic. What is the likely diagnosis?
    A. Patient has a minor stroke
    B. Patient has motor neuron disease
    C. Patient has Parkinson's disease
    D. Patient has Transient ischemic attack

14. Aseptic meningitis may be due to
    A. Viral infection
    B. TB
    C. Partly treated bacterial infection
    D. Lyme disease

15. In a patient presenting with seizures
    A. A screen for toxins may be indicated
    B. Blood sugar is indicated
    C. CSF studies is mandatory in HIV infected (if no contraindication), even in the absence of symptoms or signs suggesting infection
    D. Brain scan might be indicated

16. Differential diagnosis of seizure includes
    A. Migraine
    B. Syncope
    C. Transient ischemic attack
    D. Sleep walking

17. In motor neuron disease
    A. The pathological hallmark is death of lower and upper motor neurons
    B. Dementia is a component of Amyotrophic lateral sclerosis
    C. Ocular motility is a late sign in Amyotrophic lateral sclerosis (ALS)
    D. No treatment arrests the underlying process in ALS

18. Regarding the central nervous system (CNS) in HIV infection
    A. Cytomegalovirus is the most common viral infection
    B. Highly active anti-retroviral therapy significantly improves the survival of patients with progressive multifocal leukoencephalopathy
    C. The target sign on CT is pathognomic for tuberculoma
    D. Gummas are the most frequent features of neurosyphilis

19. The following are true of CNS involvement in AIDS
    A. HIV encephalopathy (HIVE) is the most common cause of neurological disease
    B. Progressive multi-focal leukoencephalopathy is associated with Jacob Creutzfeldt papova virus (JC virus)
    C. CMV encephalitis is easily differentiated from HIVE by its imaging characteristics
    D. Lumbar puncture is contraindicated in evaluating patients with AIDS and CNS involvement

20. In the evaluation of a confused patient, following should be considered
    A. Motor neuron disease
    B. Drug intoxication
    C. Cerebral malaria
    D. Post-seizure event

21. The risk factor for bronchogenic cancer are:
    A. HIV
    B. Asbestos
    C. Radon gas
    D. Cigarette smoking

22. Paraneoplastic manifestations of bronchial carcinoma include:
    A. Cerebellar degeneration
    B. Skin rash and proximal myopathy
    C. Eaton-Lambert syndrome
    D. Bone pain

23. A 68-year-old pub landlord and lifelong smoker is admitted with lethargy and drowsiness. Laboratory tests reveal results consistent with syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and a chest radiograph demonstrates a 3cm right upper lobe mass. He is due to undergo a CT guided biopsy of the mass. What is the histological subtype most likely to be?
    A. Bronchoalveolar cell carcinoma
    B. Squamous cell carcinoma
    C. Pulmonary hamartoma
    D. Small (oat) cell carcinoma

24. The following tumor markers can be used as surrogate for bronchial carcinoma:
    A. CA 125
    B. CA 19-9
    C. Neuron specific Enolase
    D. Placental Alkaline phosphatase

25. The following are contraindications to surgical resection in bronchial carcinoma:
    A. Distant metastases
    B. Pleural effusion (non-malignant)
    C. Bilateral mediastinal lymphadenopathy
    D. Esophageal involvement

26. Pancoast's syndrome
    A. Results from local extension of a tumor growing in the base of the lung
    B. May result in involvement of the 8^{th} cervical and 1^{st} and 2^{nd} thoracic nerves
    C. Often with destruction of 4^{th} and 5^{th} ribs
    D. May result in shoulder pain that characteristically radiates in the ulna distribution of the arm

27. The following primary tumors can metastasis to the lungs:
    A. Melanoma
    B. Salivary gland tumor
    C. Soft tissue sarcoma
    D. Testicular cancer

28. A 60-year-old with congestive cardiac failure due to hypertensive heart disease, who is also epileptic and HIV patient on HAART complains of breast enlargement. Which of the following medications he is currently taking would cause gynecomastia?
    A. Calcium channel blockers
    B. Spironolactone
    C. Efavirenz
    D. Sodium valproate

29. Which of the following statement is true about secondary diabetes?
    A. A patient can be assumed not to be ketosis-prone
    B. A patient is more than 85% likely to have clinical pancreatic exocrine deficiency
    C. Classical diabetic complications do not occur
    D. Thiazide diuretics and beta-blockers can both impair insulin secretion

30. Which of the following statement is true about hypoglycemia?
    A. About 50% of patients who have had type 1 DM for 20 years or more develop 'hypoglycemia awareness'.
    B. Sweating and shaking are always late symptoms of insulin-induced hypoglycemia
    C. Metformin is responsible for as many cases of hypoglycemia as sulfonylureas
    D. The symptoms characteristically come on over hours rather than minutes.

31. Which of the following is true about diabetic retinopathy?
    A. Characteristically causes arterial-venous nipping
    B. Should be referred to an ophthalmologist only if the patient has visual symptoms
    C. Inevitably causes blindness
    D. May cause soft and hard exudates

32. The following will increase secretion of insulin
    A. Ketone bodies
    B. Vagal nerve stimulation
    C. Amino acids
    D. Glucagon

33. The following will decrease secretion of insulin
    A. Glucagon
    B. Alpha-agonist
    C. Cortisol
    D. Thyroxine

34. Complication of insulin include
    A. Lipoatrophy
    B. Lipohypertrophy
    C. Hyperglycemia
    D. Gynecomastia

35. A 30-year-old HIV patient, Pre-HAART, is admitted with weight loss, diarrhea, night sweats and cough. On TB treatment for 4 weeks and recently treated for oral thrush. His BP 80/60, RR 24. Which other clinical signs are suggestive of a possible cause of her low BP?
    A. Clearly audible heart sound
    B. Hyperpigmented palm creases and gums
    C. A pulse of 70/minute with full volume
    D. Normal JVP

36. Features of renal failure may include:
    A. Loss of libido
    B. Hyperparathyroidism
    C. Delirium
    D. Platelet dysfunction

37. A 28-year-old female presents with hematuria, proteinuria 2+, increased BP and mild pedal edema and creatinine 60mmol/L. The doctor suspects a glomerular disease. A urine microscopy was ordered. Which result is highly suggestive of a glomerular disease
    A. RBC casts
    B. Hyaline casts
    C. Muddy brown casts
    D. Epithelial casts

38. The most likely clinical syndromes in the patient in Question 37 above
    A. Nephrotic syndrome
    B. Nephritic syndrome
    C. Rapid progressively
    D. Chronic glomerulonephritis

39. What is the Gold standard for making a definitive diagnosis in the above patient in Question 37?
    A. No need for further evaluation as long as the clinical syndrome is known
    B. Kidney ultrasound
    C. Histological diagnosis
    D. 24-hour urine protein and creatinine

40. In the diagnosis of Acute Kidney injury (AKI), diagnosis is usually based on the following parameters:
    A. Baseline creatinine, latest creatinine and/or urine output
    B. Baseline GFR and latest GFR
    C. A patient with AKI on dialysis is in stage 2
    D. Urine output alone is not sufficient to make a diagnosis of AKI

41. A marathon runner was found fitting after taking 2L of water after a 10Km marathon on a hot sunny day. What is the likely cause of seizures?
    A. Hypernatremia
    B. Dilutional hyponatremia
    C. Pseudohyponatremia
    D. Diabetic ketoacidosis

42. What will be the management of the patient in question 41?
    A. Normal saline
    B. 3% saline
    C. Darrow's
    D. Ringer's lactate

43. Cerebral blood flow is increased by:
    A. Hypercapnia
    B. Hypoxia
    C. Alkalosis
    D. Hypothermia
    E. Polycythemia

44. Recognized features of pseudobulbar palsy include:
    A. Inappropriate laughter
    B. Dysarthria
    C. An absent jaw jerk
    D. Dysphagia
    E. Fluctuating level of consciousness

45. Guillan-Barre' syndrome
    A. Has an acute onset
    B. Is typically associated with normal CSF protein
    C. Presents with periods of loss of consciousness
    D. Is characterized by bilateral motor weakness
    E. Has a recognized association with carcinoma of the lung

46. Myasthenia gravis is characterized by
    A. Dysphagia
    B. Ptosis
    C. Aplastic anemia
    D. HLA antigen DR3
    E. Morning stiffness

47. In the elderly stroke is significantly associated with
    A. High serum cholesterol
    B. Obesity
    C. Polycythemia rubra vera
    D. Myocardial infarction
    E. Atrial fibrillation

48. Infarction in the territory of the anterior cerebral artery
    A. Causes more severe hand then shoulder weakness on the affected side
    B. Produces predominant weakness of the lower limb
    C. Is most frequently seen after SAH after berry aneurysm rupture
    D. Causes transcortical motor aphasia when affecting the dominant hemisphere
    E. Usually occurs as a result of cerebral embolism

49. Characteristics features of occlusion of the left middle cerebral artery include
    A. Hemiplegia with involvement of the leg more than the arm
    B. Paralysis of conjugate gaze towards the left
    C. Deep xanthochromia of CSF
    D. Diplopia
    E. Dementia

50. Cases of SIADH include
    A. Chest infection
    B. Head injury
    C. Chlopropamide
    D. Addison's disease
    E. Liver cirrhosis

51. Which of the following is true about SAH?
    A. It is common among elderly women and very rare in the young
    B. Over 90% of SAH are due to untreated hypertension
    C. Neck stiffness is very rare unless patient has meningitis
    D. The presence of hypotension with tachycardia indicates raised intracranial pressure
    E. Nifedipine treatment is very important in the management

52. Which of the following are true about seizures?
    A. Imipenem may cause seizures and should not be used to treat meningitis
    B. These may occur in poisoning due to tricyclic antidepressants, mefenamic acid or opioids
    C. In Tenia solium infection, focal seizures can occur if cysts are present in the brain
    D. Pre-eclampsia is marked by seizures or coma in addition to other signs
    E. In CKD, mental slowing, clouding of consciousness and rarely seizures may occur

53. Which of the following are true about stroke?
    A. In Zambia, cerebral hemorrhage accounts for more than 30% of acute strokes
    B. In supratentorial strokes with homonymous hemianopia, patient cannot see on the hemiplegic side
    C. Vertigo, vomiting, dysphagia and Horner's syndrome indicate occlusion of the vertebrobasilar circulation
    D. Pinpoint pupils and bilateral upgoing plantars could signal a brainstem stroke
    E. Carotid endarterectomy should be considered for patient with more than 70% stenosis

54. In a patient with AIDS, Cryptococcal meningitis is
    A. The commonest cause of meningitis
    B. Characterized by abrupt onset of the classical features of a bacterial meningitis
    C. Diagnosed by India ink stain of cerebrospinal fluid
    D. Typically associated with negative CSF culture

55. Cryptococcal meningitis
    A. Is caused only by Cryptococcus neoformans neoformans
    B. Is more common than Cryptococcal pneumonia
    C. Characteristically causes leucopenia
    D. Only occurs in the immunosuppressed
    E. Should be treated with ketoconazole

56. Amphotericin B is used in the treatment of
    A. Visceral leishmaniasis
    B. Dermatophyte infections of the nails
    C. Azole resistant oral candida
    D. Primary amoebic meningoencephalitis caused by Naegleria species
    E. Cryptococcal meningitis

57. Common cause of blackouts include:
    A. Drugs
    B. Valvular heart disease
    C. Myocardial infarction
    D. Hypoglycemia
    E. Alcohol ingestion

58. HIV infection is associated with
    A. An RNA retrovirus
    B. Involvement of CD4 lymphocytes
    C. Viral half-life of 1-2 hours in plasma
    D. A better prognosis in the presence of Kaposi's sarcoma

59. In HIV infection
    A. 80% of vertically transmitted infections are transplacental
    B. A child born to an infected mother has a 90% chance of acquiring HIV
    C. Transmission can occur via breast milk
    D. Risk of fetal transmission is unaffected by pre-partum antiviral agents

60. In the diagnosis of HIV infection
    A. ELISA testing has a low false negative rate
    B. Seroconversion invariably occurs in under 4 weeks
    C. Antibody detection tests are particularly helpful in neonates
    D. HIV-RNA is typically detected before anti-HIV antibodies

61. In the classification of HIV infection
    A. Stage 1= acute seroconversion simulating glandular fever
    B. Stage 2= persistent generalized lymphadenopathy
    C. Stage 3= have absolute CD4 count >500/mm^3
    D. Kaposi's sarcoma is stage 3 disease

62. Presenting features of HIV infection include
    A. Hairy leucoplakia
    B. Atypical pneumonia
    C. Thrombocytopenic purpura
    D. Pulmonary tuberculosis

63. Cryptosporidiosis in an HIV positive patient is
    A. An AIDS-defining diagnosis if chronic
    B. Likely to present with painless profuse diarrhea
    C. Likely to self-limiting if the CD4 count is > 200 cells/mm3
    D. Preventable by the use of boiled tap water

64. *Pneumocystis carinii* infection in an HIV positive patient is
    A. The commonest cause of respiratory infection in African patients
    B. Characterized by copious sputum production
    C. Characterized by widespread fine pulmonary crackles
    D. Excluded by the finding of a normal chest X-ray

65. The following have been reported with initiation of HAART;
    A. Immune reconstitution syndrome
    B. Osteonecrosis
    C. Diabetes Mellitus
    D. Lipodystrophy syndrome

66. Side effects of Nucleoside reverse transcription inhibitor include;
    A. Cough
    B. Fever
    C. Insomnia
    D. Liver damage

67. The following are true;
    A. Maraviroc is an antagonist of protease
    B. A Fusion inhibitor is helpful in the treatment of HIV
    C. Raltegravir is an inhibitor of HIV integrase
    D. Stavudine has very few side effect

68. On protease inhibitor;
    A. Should be used with caution in Diabetic Mellitus patient
    B. Should not be used in patient with acute porphyria
    C. Should be used with caution in patient with chronic hepatitis B
    D. Should not be used in AIDS stage

69. About peptic ulcer disease
    A. Gastrinoma should be suspected if there are multiple duodenal ulcers
    B. Alcohol abuse is a risk factor for gastric ulcer
    C. Peptic ulcer disease may lead to acute pancreatitis
    D. Helicobacter pylori infection and NSAIDs are the two most common causes of peptic ulcer disease
    E. Biopsy must be performed in all patients with duodenal ulcer

70. Patients with HIV stage 4 WHO may have the following conditions
    A. Pulmonary tuberculosis
    B. HIV encephalopathy
    C. Esophageal candidiasis
    D. Abdominal TB
    E. Severe anemia

71. Regarding tuberculosis pericardial effusion
    A. Pericardiocentesis is mandatory
    B. Low dose prednisolone given during the first 2 months of treatment
    C. Culture of pericardial fluid is confirmatory
    D. Treatment is given for 12 months
    E. Constrictive pericarditis is not a known complication

72. Signs of hypokalemia on ECG include:
    A. Flattening of T wave
    B. Prolonged QT interval
    C. Tall U waves
    D. J wave
    E. Shortening of PR interval

73. Causes of hyperkalemia include
    A. Addison's disease
    B. Diabetic ketoacidosis
    C. Rhabdomyolysis
    D. Renal puncture
    E. Alkalosis

74. The most effective drug in control of hypertension in an emergency is
    A. Nifedipine
    B. Hydralazine
    C. Sodium nitroprusside
    D. Lasix
    E. Methyldopa

75. Optic neuritis is complication of:
    A. Rifampicin
    B. Isoniazid
    C. Ethambutol
    D. Pyrazinamide
    E. Streptomycin

76. In community acquired pnemonias:
    A. The commonest pathogen is Mycoplasma pneumoniae
    B. Erythromycin is the first-line antibiotic for psittacosis
    C. The serum urea correlates with severity of illness
    D. Ciprofloxacin can be used as a single agent when the organisms is not known
    E. The pneumococcal antigen can be identified in urine

77. Misoprostol is
    A. H2 receptor antagonist
    B. Synthetic prostaglandin analogue
    C. Proton pump inhibitor
    D. NSAID
    E. Antacid

78. Microcytic anemia is a typical finding in:
    A. Folic acid deficiency
    B. Hemolytic anemia
    C. Alcohol abuse
    D. Primary sideroblastic anemia
    E. Iron deficiency

79. Non-infectious causes of diarrhea:
    A. Inflammatory bowel disease
    B. Histoplasmosis
    C. Bechets disease
    D. Clostridium perfringens
    E. Pseudomembranous colitis

80. Causes of chronic liver disease
    A. Alcohol
    B. Methyldopa
    C. Hepatitis B virus
    D. Methotrexate
    E. Idiopathic

81. The following is true of viral hepatitis:
    A. Hepatitis C commonly presents with jaundice
    B. Hepatitis C is fatal particularly in pregnancy
    C. Hepatitis BeAg is a marker of viral replication
    D. Hepatitis A is a risk factor for hepatoma
    E. Hepatitis D occurs only in association with hepatitis C

82. The following are common causes of meningitis
    A. Neisseria meningitidis
    B. Haemophilus influenza
    C. Listeria monocytogenes
    D. Staphylococcus aureus
    E. Gram negative bacilli

83. In the treatment of HIV infection
    A. All useful drugs work via inhibition of reverse transcriptase
    B. Reverse transcriptase inhibitors prevent replication in infected cells
    C. Reverse transcriptase inhibitors prevent spread of infectious virus into uninfected cells
    D. Drug resistant strains of virus have not been recognized
    E. Monotherapy is preferred

84. Recognized features of severe heart failure include
    A. Tiredness
    B. Weight loss
    C. Epigastric pain
    D. Nocturia
    E. Nocturnal cough

85. The pain of Myocardial ischemia
    A. Is typically induced by exercise and relieved by rest
    B. Radiates to the neck and jaw but not to the teeth
    C. Rarely lasts longer than 10 seconds
    D. Is easily distinguished from esophageal pain
    E. Can easily be distinguished from pain arising from acute pancreatitis

86. Jone's major criteria for the diagnosis of rheumatic fever
    A. Migratory polyarthritis
    B. Pancarditis
    C. Chorea
    D. Fever
    E. Subcutaneous nodules

87. Adverse effects of corticosteroid therapy include:
    A. Peptic ulceration
    B. Hypertension
    C. Avascular bone necrosis
    D. Pseudogout
    E. Insomnia

88. The typical features of type B viral hepatitis include:
    A. Incubation period of 1 month
    B. History of exposure to unsafe sex or drug abuse
    C. Prodromal illness with polyarthralgia
    D. Hepatic illness more severe than type A
    E. Absence of progression to chronic hepatitis

89. Typical features of advanced hepatic cirrhosis include
    A. Progressive hepatomegaly
    B. Massive splenomegaly
    C. Peripheral blood macrocytosis
    D. Parotid gland enlargement
    E. Central cyanosis

90. Hepatic encephalopathy in cirrhosis is typically precipitated by:
    A. Infection
    B. Hypokalemia
    C. Abdominal surgery
    D. Gastrointestinal bleeding
    E. Lactulose therapy

91. Hemoptysis is a clinical feature of
    A. Carcinoma of lung
    B. Bronchiectasis
    C. Pulmonary tuberculosis
    D. Primary pulmonary hypertension
    E. Pulmonary embolism

92. A pleural effusion with a protein content 50g/L would be compatible with:
    A. Congestive cardiac failure
    B. Pulmonary infarction
    C. Subphrenic abscess
    D. Pneumonia
    E. Nephrotic syndrome

93. Recognized causes of pyrexia of unknown origin (PUO)
    A. Infective endocarditis
    B. Renal cell carcinoma
    C. Systemic lupus erythematosus
    D. Tuberculosis
    E. Drug fevers

94. The following would help distinguish between a kidney and a spleen in the left upper quadrant
    A. Dull percussion note over the mass
    B. A well localized notched lower margin
    C. Moves with respiration
    D. A ballotable mass
    E. A family history of renal failure

95. The following are classified as high output states:
    A. Hypertension
    B. Sepsis
    C. Hypothyroidism
    D. Pregnancy
    E. Arterial venous malformation

96. Clinical features of raised intracranial pressure:
    A. Tachycardia and hypotension
    B. Dizziness and lightheadedness
    C. Headache aggravated by bending and straining
    D. Behavioral and personality changes
    E. Sixth or third nerve palsies

97. Recurrent headache could be due to
    A. Migraine
    B. Cluster
    C. Glaucoma
    D. Analgesia overdose
    E. Tension headache

98. The definition of epilepsy includes being
    A. Spontaneous
    B. Intermittent
    C. Having abnormal electrical discharge in some part of the brain
    D. Diagnosis is predominantly clinical
    E. A known epileptic and independent observer's description being suggestive of epilepsy

99. Migraine headache is often characterized by following except:
    A. Being throbbing
    B. Being unilateral
    C. Associated with projectile vomiting
    D. Associated with nervous tension
    E. May be associated with visual disturbances

100. CSF protein level is normal in the following types of meningitis?
   A. Viral
   B. TB
   C. Bacterial
   D. Malignant
   E. Septicemia

THIRD YEAR ESSAY QUESTIONS

1. HIV is a very common condition observed in the medical wards at Levy Mwanawasa General hospital. Please answer the following questions:
   a. What do you understand by immune reconstitution syndrome? (5 marks)
   b. What are the central nervous system complications of HIV? (5 marks)
   c. What are the renal complications of HIV? (5 marks)
   d. What are the parameters of monitoring treatment? (5 marks)

2. 34-year-old male businessman present to you with a history of productive cough, evening chills, night sweats, loss of appetite and loss of weight of the past 3 months. He is newly diagnosed RVD with CD4 count of 3 cells/ml. His chest X-ray shows a miliary picture and the safe lab markers are normal.
   a. Which other investigations are you going to order- list 3 (3 marks)
   b. List 5 differentials for the chest X-ray picture (5 marks)
   c. If the diagnosis is Miliary TB, outline the management plan in the above patient (4 marks)
   d. List the common side effects of the antituberculosis- 2 for each (8 marks)

3. In relation to endocrine disorders, please answer the following:
   a. Describe pathophysiology of Diabetic ketoacidosis (5 marks)
   b. What are the causes of Addison's disease (5 marks)?
   c. What are the metabolic abnormalities with primary adrenal insufficiency? (5 marks)
   d. What is a thyroid storm? (5 marks)

4. A 20-year-old female patient presented to emergency unit at Levy Mwanawasa General Hospital with a history of progressive exercise intolerance. She has to use extra pillows in order to get some peaceful sleep but she still wakes up often in the middle of the night in gasps for breath. Professor Njelesani asks you to demonstrate a cardiovascular exam and you on auscultation find a left parasternal diastolic murmur loudest in expiration. Her BP is 110/50. You also find bibasal end-inspiratory fine crackles and sacral edema.
   a. What is your full diagnosis? (5 marks)
   b. What other 'special signs' will you look out for? Name and describe 5 of them (10 marks)

c. What do you expect to see on her chest radiograph? (3 marks)
d. Give one differential for 'bibasal end-inspiratory crackles' (2 marks)

5. In relation to liver cirrhosis:
   a. Please describe Child-purg score in relation to liver cirrhosis? (5 marks)
   b. What are the poor prognostic indicators for liver cirrhosis? (5 marks)
   c. What are the complications related to liver cirrhosis? (5 marks)
   d. What is the pathophysiology of ascites related to liver cirrhosis? (5 marks)

6. In relation to hemato-oncology
   a. What are the clinical features of iron-deficiency anemia? How do you make a diagnosis? (5 marks)
   b. Write short notes on the types of crises related to sickle cell disease? (5 marks)
   c. What are the complications of multiple myeloma? (5 marks)
   d. What are the complications of acute leukemias? (5 marks)

7. A young man is brought into the emergency department with history of vomiting, increased urination and diarrhea of sudden onset after 30 minutes of spraying farm products with unknown insecticides. On examination, he is semi-conscious, frosting from the mouth, miosis and bradycardic with soiled clothing.
   a. What is the most likely diagnosis? (2 marks)
   b. What other signs might he present with? List 4 (4 marks)
   c. Outline the pathophysiology of the above (4 marks)
   d. What samples would you take to confirm diagnosis (4 marks)
   e. Outline principle of management of the above young man (6 marks)

8. A 23-year-old African lady presents to a medical clinic with fatigue, weight loss, anorexia, a photosensitive malar rash, oral ulcers, intermittent polyarthritis and urinalysis reveals proteinuria. Anti-double stranded DNA is strongly positive.
   a. What is the working diagnosis? (6 marks)
   b. Briefly describe the immunopathology in this condition (8 marks)
   c. Briefly describe hematological disorders in this conditions- List at least 3 (3 marks)
   d. Describe briefly the CNS manifestation- at least 3 (3 marks)

9. A 44-year-old coal miner presented with a 3-month history of polyuria and dyspnea on exertion. He had developed a frontal headache the past 6 weeks and was sweating profusely. He had recently noticed tingling in his hand which was worse at night. On systemic enquire he admitted to loss of libido and impotence for 6 years. On examination he has coarse face, macrognathia, 'spade' hand and feet with thick skin. Heart rate is 100/min regular with a BP of 200/100. Neurological examination was grossly normal except for bi-temporal hemianopia and reduced sensation to pin-prick over the thumb, index and ring fingers.
   a. What is the diagnosis? (4 marks)
   b. Give 2 possible causes of polyuria (4 marks)
   c. What is cause of bi-temporal hemianopia (2 marks)
   d. What is the cause of reduced sensation to pin-prick over the thumb, index and ring fingers (4 marks)?
   e. What single test would you use to confirm diagnosis (4 marks)
   f. Give another test that will help in locating the cause of bi-temporal hemianopia? (2 marks)

10. Write short notes on the following
   a. Features of Nephrotic syndrome (5 marks)
   b. Major differences between Nephrotic and Nephritic syndrome (5 marks)
   c. Complication related to chronic renal failure (5 marks)
   d. Hepatorenal syndrome (5 marks)

11. In relation to heart failure, please write short notes on the following include definition, pathophysiology and clinical significance
   a. Pulsus paradoxus
   b. Systolic dysfunction
   c. Paroxysmal nocturnal dyspnea
   d. 'A' waves in relation to raised JVP
   e. Please classify '3 types of Angina' with symptoms

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FIFTH YEAR ESSAY QUESTIONS

1. You have been asked to evaluate a patient in the Department of Obstetrics and gynecology. The consultation reads: "**very urgent, come and manage our patient with suspected acute renal failure**".

   You find that she is 26 years old. She had given birth 10hours earlier by spontaneous vaginal delivery to a mildly asphyxiated baby. She has not passed urine since delivery. The Antenatal card shows she had no medical or gynecological problems. Urinalysis was done twice during antenatal and was reported normal. The midwife tells you that the labor was "very hectic" and patient was difficult during delivery and hence "bled a lot"

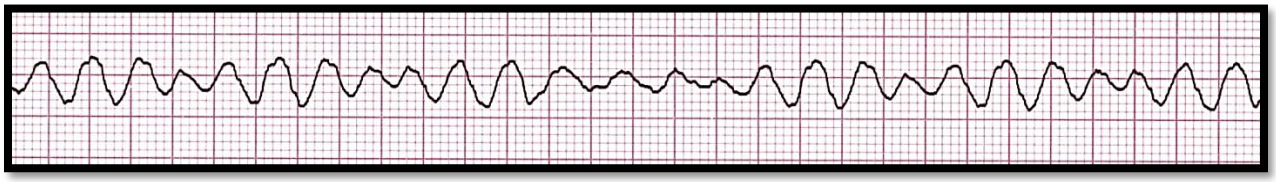
   Examination:
   Drowsy, pulse 142/min, Blood pressure 85/55 mmHg, respiratory rate 29/min.
   CVS-tachycardia, no murmurs, no gallop, RS- clear lung fields, GIT- normal.
   There is no active bleeding per vagina and uterus is well contracted

   Urinalysis
   pH= 5.5
   Specific gravity >1.030
   Amino acids= trace
   Glucose= trace
   Casts=present
   Hemoglobin, RBC, Albumin, White blood cells, nitrites= all negative

   Glucometer random blood sugar= 6, Urea=26
   Urgent bedside ultrasound shows normal kidneys

   (a) What assessment needs to be done on this patient?
   (b) Analyse the findings
   (c) Plan your full management

2. A male patient 45 years old was admitted yesterday to ICU with severe chest pain. He is a known diabetic and hypertensive patient for more than 10 years. Diagnosis of admitting doctor was Unstable angina. Doctor on call was informed that patient suddenly changed his condition after a short episode of breathlessness (though in the morning he appeared to be stable, pain free and not on ventilation). The nurse reported the absence of pulse and unrecordable BP.
   On the monitor attached to the patient the fine oscillations seen.



   (a) What condition is this?
   (b) What is your immediate action?
   (c) If the monitor still shows oscillations and pulse is absent on the carotid arteries what do you do next?
   (d) What is the possible diagnosis?
   (e) How would you manage in post-resuscitation period?

3. A 20-year-old male patient presents to admission ward after being found unconscious at home. The friend accompanying him says that he is a known diabetic on "injections" that are kept in the fridge and that he has been unwell the past 4 days with a febrile illness and is not sure whether he was getting his injections or not.
   Examinations: unconscious (GCS 8/14), moderately wasted, no generalized lymphadenopathy, dehydrated, febrile and has Kaussmaul's respiration.
   You are the attending officer in Phase 5
   Please, fully manage him (all the facilities are there i.e. labs etc.)
   Answer in Bullet form…

4. Daniel comes to the admission ward with complaints of weakness, nausea, fatigability and poor appetite. He is a known HIV positive patient on HAART (AZT,3TC and NVP) for over 2 years. His last CD4 was 200 cell/ml (at baseline was 55 cells/ml). He was recently diagnosed to have sputum positive PTB at the local clinic and started on anti-tuberculosis treatment.
   (a) List two problems Daniel has and justify your answers (2 marks)
   (b) List and justify investigations you would order (9 marks)
   (c) Outline your management plan (9 marks)

5. A 22-year female lady (known cardiac patient) come in with history of weakness, fever, malaise, sweating and painful sores on hands.
   (a) List differential diagnosis? (4 marks)
   (b) Write down the "Dukes criteria" (4 marks)
   (c) What other signs would you look for and give the pathogenesis of the signs (6 marks)
   (d) How would you manage this patient (6 marks)?

6. A 35-year-old Zambian man complains of easy fatigability of long-standing duration. The following are his blood results.
   WBC 5.3 x 10^9/L
   RBC 1.2 x 10^{12}/L
   Hb 4g/dl
   Platelets 20 x 10^9
   Blood glucose 6 mmol/L
   Sodium 137 mmol/L
   Potassium 6.2mmol/L
   Creatinine 1200 μmol/L

   (a) Comment on the results and their significance? (4 marks)
   (b) What is your diagnosis? (4 marks)
   (c) What will be the other clinical features of the patient with such results (6 marks)
   (d) How would you confirm the definitive diagnosis (i.e. investigations and justify)? (11 marks)

7. Mr. Mabvuto Sakala is a 76-year-old male that arrives in AMEU at Levy Mwanawasa General Hospital in an ambulance. As an intern doctor on duty he is brought in your consultation room. He complains of shortness of breath for a week which seem to have gotten worse today. He complains of also a persistent dry cough especially at night.

   He is known to be Diabetic and hypertensive on Losartan 50mg, Amlodipine 10mg and insulin therapy. He has no known drug allergies.
   On assessment- Vitals BP: 218/110mmHg, RR-36b/min, Temp- 37.7, O_2 Sat 95% (Room oxygen), dusky nail beds, skin cool and moist with ankle edema. JVP is 10cm, Apex beat in the 6^{th} intercostal space anterior axillary line with a tachycardia and occasional ectopics. Rales noted right middle lobe and lower lobes bilaterally.

   The following are investigations done on the patient:
   Sodium 135
   Potassium 3.9
   Hb 12.5
   Creatinine 220 μmol/L
   CXR- bilateral pulmonary congestion with enlarged cardiac shadow
   12 lead EKG: sinus tachycardia with occasional PVCS, Old anterior MI

   (a) From the patient's chief complain and your initial assessment, what is the patient's primary problem? (4 marks)
   (b) Describe the pathophysiology of CHF (congestive heart failure) (6 marks)
   (c) What are the signs and symptoms of heart failure in this patient? (2 marks)
   (d) What factors contribute to the patient's heart failure? (4 marks)
   (e) What pharmacologic agents are used to improve performance in patients with CHF? (4 marks)

8. A 65-year-old man present with a 6-week history of cough, progressive shortness of breath and 10kg weight loss. He has 50-pack year smoking history and his family doctor orders a chest X-ray and blood work.

   The CXR shows a left lower lobe mass. His physical is normal. He is otherwise healthy and takes no regular medication

(a) List 4 differentials for above patient (8 marks)
(b) How would you further investigate this man in order to get a pathologist diagnosis- List 5 (5 marks)
(c) If it is Bronchogenic carcinoma, what addition tests are required to properly stage this patient- List 7 (7 marks)

9. Mrs. Banda is a 27-year-old woman (unemployed) who was referred from VCT center after testing HIV positive 3 weeks ago. Her husband recently died from Cryptococcal meningoencephalitis during his hospitalization he tested positive for HIV causing her to pursue testing.

   Her medical history has been unremarkable except being diagnosed with extrapulmonary TB 4 months ago. She declined HIV test at the time of TB diagnosis.

   She is allergic to trimethoprim/Sulfamethoxazole which causes a diffuse erythematous rash. Her physical examination is notable for a thin, well developed woman with no acute distress. Her ENT exam reveals Candida on the tongue and buccal mucosa. Heart, Lung and Abdomen examinations are normal.

   Her Laboratory test
   Hb- 11.7mg/dl
   Platelets 167 000
   HIV positive
   CD4 4 410/μL

   (a) For this patient, what evidence (history, physical examination, and/or laboratory data), support beginning antiretroviral therapy (ART) (4 marks)
   (b) Do you identify any barriers to ARV adherence? List 3. What would you recommend to address these barriers? (6 marks)
   (c) What antiretroviral medication would initiate? (4 marks)
   (d) What toxicities could be associated with the anti-retroviral therapy you chose? 2 for each (6 marks)

10. Mr. Saili is a 74-year-old man who presents to your consultation room with his wife complaining of shortness of breath and fever. His wife did bring records from his last physician that he has Chronic Obstructive Pulmonary Disease (COPD). After evaluation you make a diagnosis of acute exacerbation in COPD.
    (a) What is the mechanism of airflow limitation in COPD? (4 marks)
    (b) What is the role of inflammatory mechanisms in COPD? (4 marks)
    (c) What are the organisms commonly associated with exacerbation of COPD? (4 marks)
    (d) What investigation would you order? (4 marks)
    (e) How would you treat an acute exacerbation? (4 marks)

11. A 20-year-old young lady comes to the hospital complaining of fevers and oral ulcers for a week. She reports having had fevers in the recent past. She says she has no urinary symptoms. She feels tired and has no cardiac symptoms. She also has noticed her hair is thinning out. The registrar suspects she has a connective tissue disease.
    (a) What else would you want to probe for in the history? (5 marks)

    The patient is noted to have rash on her face that looks like a butterfly pattern and she also has joint tenderness in the hands. Your registrar further suggests that this could be Systemic Lupus Erythematosus (SLE).

    (b) List the manifestations used in the criteria to make a diagnosis of SLE. (5 marks)
    (c) What drugs can you use in a patient with SLE? (4 marks)

12. A 40-year-old HIV negative male patient presents to AMEU with four days of Jaundice, upper abdominal pain, nausea, vomiting and headache. He is a patient on sputum positive PTB on treatment for 6 weeks. He is currently on Rifampicin, Isoniazid, Ethambutol and Pyrazinamide. The patient has no other pertinent past medical history and uses no other medications.

    On physical examination, he is alert and oriented with the following vital signs: Blood pressure 113/62mmHg, heart rate 88b/min, respiratory rate 14 breaths/min, pulse oximetry 100% on room air, temperature 37.1 degree Celsius.

His skin is jaundiced but without ecchymoses or petechiae. Eye examination reveals scleral icterus.

Cardiovascular and pulmonary findings are unremarkable. His abdomen is soft, but diffusely tender to palpation without and organomegaly, rebound, guarding or rigidity.

Initial pertinent laboratory results include: AST> 2600 IU/L, ALT>2600 IU/L, total bilirubin >20mg/dl, INR 3.7.

(a) What is the primary problem with this patient? (2 marks)
(b) How would you investigate this patient? List 4 important investigations (4 marks)
(c) How does Isoniazid (INH) cause hepatotoxicity? (6 marks)
(d) How would you manage this patient if it was purely due to INH? (8 marks)

13. Write short notes on:
(a) Diagnosis of Myocardial infarction (5 marks)
(b) Mechanism of diarrhea in Cholera (5 marks)
(c) Symptoms, signs and diagnosis of Organophosphate poisoning (5 marks)
(d) Treatment of organophosphate poisoning (5 marks)

14. The patient is a 41-year-old male who has a longstanding history of hypertension and diabetes and presents with a complaint of pruritus, lethargy, lower extremity edema, nausea and emesis. He denies any other medical illnesses.
On physical examination the patient is well-developed, well-nourished male in moderate distress. Blood pressure 180/110, pulse 80, respirations 24 and he was afebrile. Body weight 76.5kg. ENT exam was remarkable for fundoscopic findings of AV nicking and copper wire changes consistent with hypertensive injury. Cardiac exam had an S1, S2 and S4. The remainder of the exam was remarkable for 2+ lower extremity edema and superficial excoriations of his skin scratching.

Laboratory data

Chemistry		Normal Values	Urinalysis
Sodium	133	136-146 mmol/L	pH 6.0 Specific gravity 1.010 Protein 1+ Glucose negative Acetone negative Occult blood negative Bile negative Waxy casts
Potassium	6.2	3.5-5.3 mmol/L	
Chloride	100	98-108 mmol/L	
Total CO_2	15	23-27 mmol/L	
BUN	170	7-22 mg/dl	
Creatinine	16.0	0.7-1.5 mg/dl	
Glucose	108	70-110 mg/dl	
Calcium	7.2	8.9-10.3 mg/dl	
Phosphorus	10.5	2.6-6.4 mg/dl	
Alkaline Phosphatase	306	30-110 IU/L	
Parathyroid Hormone	895	10-65 pg/ml	
Hemoglobin	8.6	14-17 gm/dl	
Hematocrit	27.4	40-54 %	
Mean cell volume	88	85-95 FL	

24-hour urine protein and creatinine- volume 850ml, protein 600mg/dl and creatinine 180 mg/dl.

Renal ultrasound- Right Kidney 9 x 6.0 cm, Left Kidney 9.2 x 5.8cm

Both kidneys illustrate hyperechogenicity and no hydronephrosis

(a) "Presents with a complaint of pruritus, Lethargy, lower extremity edema, nausea and emesis." What do these symptoms suggest to you? (2 marks)
(b) What are the fundus changes in a hypertensive? (4 marks)
(c) What are the fundus changes of a diabetic? (4 marks)
(d) What does S4 signify? What cardiac findings will you expect to find in a hypertensive? (6 marks)

(e) What is the significance of the finding "superficial excoriations of his skin from scratching"? (2 marks)
(f) Why was a renal ultrasound ordered? (2 marks)

15. A 58-year-old woman comes to a physician's office complaining of feeling lightheaded for past week. She says she can feel her heart racing in her chest. She mentions she has been staying up late for the past few weeks because of her workload at work. The medical history reveals well controlled diabetes mellitus.

Physical examination reveals an anxious woman with pallor and mild diaphoresis. Cardiac examination reveals an irregularly irregular beat. Vital signs are as follows: Temperature: 36.1^{o}C, Respiratory rate 22b/min, Heart rate 142 bpm, BP 118/55mmHg and Glucose 7.7 mmol/L

(a) What is the most likely diagnosis?
(b) What clinical and ECG abnormalities are most commonly associated with this condition?
(c) What is the most appropriate treatment for this condition?
(d) How do Heparin and Warfarin work together to treat this condition?
(e) Why does paradoxical reaction sometimes occur after starting warfarin therapy?

16. A 38-year-old male present to AFC with profuse diarrhea, low grade fever, cough, shortness of breath for 3 days. On examination, BP: 85/40mmHg, HR: 110bpm, Temp 38.9^{o}C, RR: 32/min. CXR: bilateral infiltrates
Part A

Labs: sodium= 140 mmol/L, chloride=110 mmol/L, bicarbonate= 12, pH= 7.30, PCO_2= 20
(a) What is the pH?
(b) What is the primary disorder?
(c) Is there any compensation>
(d) What is the anionic gap and what is the complete diagnosis?

Part B

A 24-year-old female present with right flank pain and hematuria for 2 days' duration

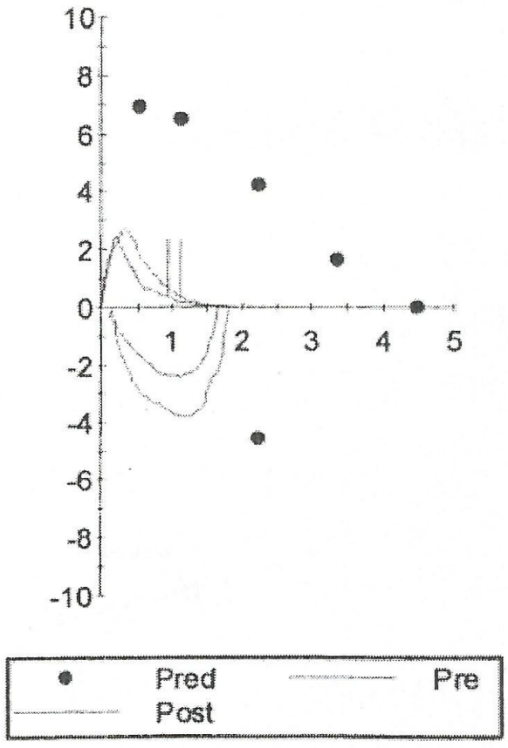
Lab results: Sodium= 138, Chloride= 115, bicarbonate= 12, pH=7.35, Potassium=3.0

(a) What is the pH?
(b) What is the primary disorder?
(c) Is there any compensation?
(d) What is the anionic gap and what is the complete final diagnosis?

17. A 35 year-old previously health man presents with dyspnea, fevers, chills, and night sweats for the past 2 months. He is a non-smoker with no concerning habits or occupational exposures. His pulmonary function tests are as follows:

	Pre-Bronchodilator (BD)		
Test	**Actual**	**Predicted**	**% Predicted**
FVC (L)	1.66	4.48	37
FEV_1 (L)	0.94	3.67	26
FEV_1/FVC (%)	57	82	
RV (L)	1.39	1.66	84
TLC (L)	3.06	5.96	51
RV/TLC (%)	45	29	

His flow volume loops is as follows:



(a) Describe the pattern of the abnormality, if one is present
(b) Grade the severity of the abnormality
(c) Generate a differential diagnosis for the observed abnormality
(d) Outline management of Acute severe asthma

18. A 55-year old male presents with weakness in his legs and shortness of breath. Sodium 142mmol/L, Potassium 2.5 mmol/L, urea 8 mmol/L, Glucose 9.6mmol/L, bicarbonate 35mmol/L
    (a) What is the likely unifying diagnosis?
    (b) What cause is suggested by the data?
    (c) What 3 further investigations would you request?
    (d) Name 5 reasons why this person may have limb weakness

19. A 28-year-old man comes to your office complaining of a 5-day history of nausea, vomiting, diffuse abdominal pain, fever to 101^{o}F and muscle aches. He has lost his appetite, but he is able to tolerate liquids and has no diarrhea. He has not significant medical history of family history and he has not travelled outside the Lusaka. He admits to having 12 different lifetime sexual partners, denies illicit drug use, and he drinks alcohol occasionally but not since this illness began. He takes no medications routinely, but he has been taking acetaminophen, approximately 30 tablets per day for 2 days for fever and body aches since this illness began.

    On Examination his temperature 38.9^{o}C, heart rate 98 bpm and blood pressure 120/74 mmHg. He appears jaundiced, his chest is clear to auscultation and his heart rhythm is regular without murmurs. His liver percusses 12cm and is smooth and slightly tender to palpation. He has no abdominal distention or peripheral edema.
    Laboratory values are significant for a normal full blood count, creatinine 92 μmol/L, Alanine aminotransferase (ALT) 3440 IU/L, aspartate aminotransferase (AST) 2705 IU/L, total bilirubin 24.5mg/dl, direct bilirubin 18.2mg/dl, alkaline phosphatase 349IU/L, serum albumin 3.0g/dl and prothrombin time 14 seconds.

    (a) What is the most likely diagnosis?
    (b) What is the most important immediate diagnostic test?

    In short notes interpret (in terms of progression and infectivity) the hepatitis B profile tests seen below.

20. A 28-year-old man comes to the emergency room complaining of 2 days of abdominal pain and diarrhea. He describes his stools as frequent, with 10 to12 per day, small volume, sometimes with visible blood and mucus and preceded by a sudden urge to defecate. The abdominal pain is crampy, diffuse and moderately severe and it is not relieved with defecation.
    In the past 6 to 8 months he has experienced similar episodes of abdominal pain and loose mucoid stools but the episodes were milder and resolved within 24 to 48 hours. He has no other medical history and takes no medication. He has neither traveled out of Zambia nor had contact with anyone with similar symptoms. He works as an accountant and dose not smoke or drink alcohol. No member of his family has gastrointestinal problems.

    On Examination his temperature is 38^{o}C, heart rate 98bpm, and blood pressure 118/74mmHg. He appears uncomfortable, is diaphoretic and is lying still on the stretcher. His sclerae are anicteric and his oral mucosa is pink and clear without ulceration. His chest is clear and his heart rhythm is regular, without murmurs. His abdomen is soft and mildly distended, with hypoactive bowel sounds and minimal diffuse tenderness but go guarding or rebound tenderness.
    Laboratory studies are significant for a white blood cell (WBC) of 15, 800/mm^3 with 82% polymorphonuclear leukocytes, hemoglobin 10.3g/dl, and platelet count 754, 000/mm^3. The HIV assay is negative. Renal function and liver function tests are normal. A plain film radiograph of the abdomen shows a mildly dilated air-filled colon with a 4.5cm diameter and no pneumoperitoneum or air/fluid levels.

    (a) What is the most likely diagnosis?
    (b) What is your next step?
    (c) How do you distinguish Amoebic dysentery from Shigella dysentery (please answer in table form)?

21. A 30-year-old male patient was admitted to the emergency Room with history of severe epigastric pain. His past medical history is unremarkable. He reports to have been fine, in fact he was from having a copious meal with some wine with his friends. You examined him and found a normal temperature but low blood pressure of 86/55mmHg. He is conscious but in severe pain.
    (a) Discuss the differential diagnosis?

(b) What investigations would you do to confirm it?
(c) How would you classify this condition?
(d) Discuss the pathophysiology and common causes?
(e) Outline your management plan for this patient. Please fully manage him if all the facilities were available.

22. A 35-year-old female teacher presents with 2 weeks' complaint of general fatigue. She had previously been well, her past medical history is unremarkable and thought that it was work related fatigue. When it persisted, she came to see you in the OPD.

You examined her and note that she is stable, not pale nor jaundiced but has generalized lymphadenopathy and splenomegaly. The rest of examination is unremarkable.

You obtain the following lab results:
WBC 98 $x10^9$/L with 90% lymphocytes
Monocyte 1%
Eosinophils 2%
RBC 4.28 x 10^{12}/L
Hb 14.7
Platelet 240 x 10^9/L

(a) What is the possible diagnosis for this patient?
(b) What additional investigations are you going to order to confirm your diagnosis?
(c) List 3 differentials
(d) Outline your management plan

23. A 27-year-old female with SLE is in remission. Last year she had a life-threatening exacerbation of her disease. She is currently well controlled and her treatment consists of azathioprine 75mg/d and prednisolone 5mg/d. She comes for review and now strongly desires to become pregnant.
(a) Discuss the clinical manifestations of SLE
(b) Discuss the pathogenesis of SLE

(c) What investigations do you do in SLE and discuss relevance?
(d) What advice would you give her on her desire to conceive?

24. A 20-year old male presents with a 3-day history of lethargy and generalized malaise. He is confused and looks very unwell. His past medical history is unremarkable and he is HIV negative. On examination, you found a rapid feeble pulse with hypotension and cold extremities. He is tachypnoeic with clear lungs. Abdominal examination is normal.

The following blood tests are obtained:
Blood gasses:
PH: 7.0
Bicarbonate 11mmol/L (22-30)
PCO_2 20mmHg (35-45)

Electrolytes:
Potassium 2.7
Sodium 153
Chloride 124

Creatinine 70μmol/L
Urea: 5.2 mmol/L
Glucose 52mmol/L

(a) What further history would you like to get from the bedside?
(b) Describe the acid-base balance
(c) What is the diagnosis?
(d) What electrolyte abnormalities does the patient have?
(e) What further tests would you order in this patient?
(f) How are you going to manage this patient?

25. A 25-year-old patient was admitted to the Emergency Room with easy fatigability. His past medical history is remarkable for tooth extraction two weeks ago. He also reports history of fever on and off. On examination his temperature is 37.8°C and BP 120/80mmHg. He is pale with tinge of jaundice. His chest is

clear and he has pansystolic murmur at the apex. Abdominal examination reveals splenomegaly. Urinalysis shows red blood cells in urine.

(a) What is your working diagnosis?
(b) What investigations would you do to confirm it?
(c) What criteria is used to diagnose this condition?
(d) Outline your management plan for this patient. Please fully manage him if all the facilities are available.

26. A 54-year-old man presents to his primary care provider with dyspnea and a cough. He is a non-smoker with no relevant occupational exposures.

Lung function test results are as follows:

	Pre-Bronchodilator (BD)			Post-BD Bronchodilator	
Test	Actual	Predicted	% Predicted	Actual	% change
FVC (L)	3.19	4.22	76	4.00	25
FEV1 (L)	2.18	3.39	64	2.83	30
FEV1/FVC (%)	68	80		71	4

(a) Describe the pattern of abnormality, if one is present
(a) Grade the severity of the abnormality
(b) What would be the management of this patient?

27. A 52-year-old woman with heart disease presents with shortness of breath, easy fatigability and swollen feet. She has longstanding hypertension and takes medicine when she feels unwell. She has been taking 2 bottles of wine on weekends for the past 6 years but denies history of smoking. She feels her condition is getting worse and can't now climb stairs at her place. On examination you noticed that her heart rate is 70 beats per minute irregular and her blood pressure is 100/60mmHg. Her JVP is raised, her chest is clear but she has tender hepatomegaly and pitting pedal edema. The doctor makes a diagnosis of heart failure.

(a) List the common causes of heart failure in our settings
(b) What is the pathophysiology of heart failure?
(c) What two investigations would you do to confirm this diagnosis?

(d) Which therapeutic modalities have been shown to improve survival in heart failure?

28. A 23-year-old male patient is brought to the emergency room with history of malaise and headache. Apart from history of palpitations and constipation, his past medical history was apparently unremarkable. His blood pressure on admission was 210/124mmHg. He had hyperpigmented lesions on the trunk. The mini-mental test score was 8/10. Both heart sounds were normal and chest was clear. He had tender liver and pitting edema of lower extremities. Fundal examination revealed grade III retinopathy. Urinalysis shows protein +++ and glucose trace. You obtain the following lab results: Hb 9g/dl, platelets 120 x 10^9/L, Urea 28 mmol/L, Sodium 138 mmol/L, potassium 7.4 mmol/L

(a) Discuss this patients' clinical presentation and lab results
(b) What is the diagnosis?
(c) What further investigations would you order?
(d) Outline your management plan

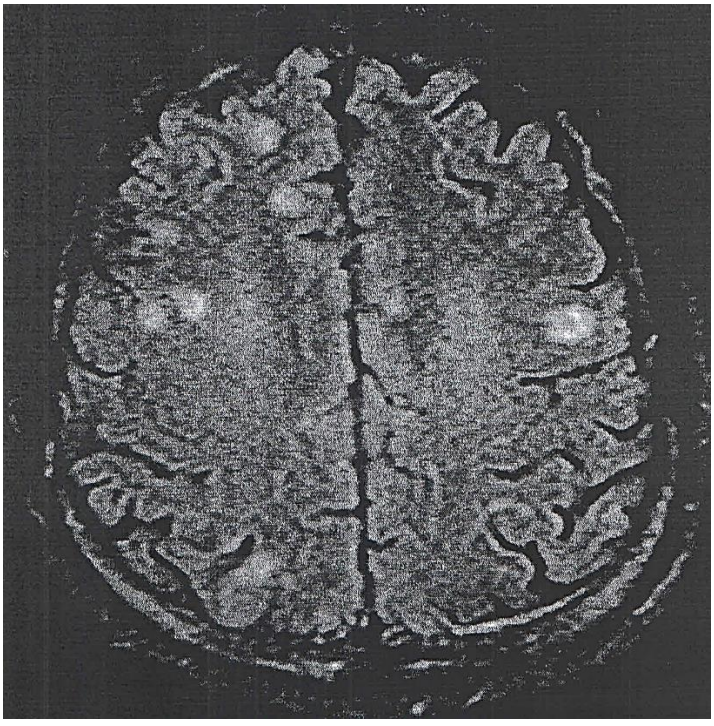
29. Chanda a 24-year-old man is admitted complaining of headaches and confusion. His headache had developed over the past 3 weeks and has become progressively more severe. The headaches are now persistent and diffuse. He has lost 10Kg in weight over 6 months and has recently become increasingly more confused. His speech is slurred. While in AMEU he has a generalized tonic-clonic convulsion.

Examination reveals that he is wasted and weighs 55kg. His temperature is 38.5^{o}C and has oral candidiasis but has no lymphadenopathy. Prior to the fit neurological exam showed him to be disoriented in time place and person with no focal neurological signs. Fundoscopy shows papilledema. The rest of the exam is normal. You order an HIV test and comes out positive for HIV-1.

Investigations:
Hb: 12.2g/dL
WCC: 12.1 X 10^9/L
Platelets: 365 X 10^9/L
K: 3.9 mmol/L
Sodium: 126 mmol/L
Creatinine: 73 umol/L
Urea: 6.2 mmol/L
Serum Glucose: 5.6 mmol/L
CD4: 22 cells/mL
Measured Osmolality: 255 osm/L

(a) What would be the cause of this man's headaches, confusion and fits? (name 3)
(b) What is his HIV WHO clinical stage?
(c) Why is his sodium low and why is he having papilledema?
(d) What further test should you order

A CT was done and the following Image was obtained



(e) What is the most likely diagnosis?
(f) How would you treat this man and include the dosing?

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ANSWERS TO TEST YOURSELF

TRUE/FALSE QUESTIONS

1. Causes of inappropriate ADH secretion include:
   A. Meningitis-True
   B. Head Injury-True
   C. Lobar Pneumonia-True
   D. Small cell bronchial Carcinoma-True
   E. Phenothiazine Therapy-True

2. Acute confusion in the elderly is likely to be the result of
   A. Adverse drug reaction-True
   B. Hypothermia-True
   C. Bronchopneumonia-True
   D. Myocardial infarction-True
   E. Cerebral infarction-True

3. Common etiologies of adult community acquired bacterial meningitis includes the following except:
   A. Norcardia pneumonia-True
   B. Neisseria meningitidis-False
   C. Streptococcus pneumonia-False
   D. Listeria monocytogenes-True
   E. Cryptococcal infection-True

4. Migraine headache is often characterized by the following except:
   A. Being throbbing-False
   B. Being unilateral-False
   C. Associated with projectile vomiting-False
   D. May be associated with visual disturbances-False

5. The most common cause of meningitis is:
   A. Viral-True
   B. TB-True
   C. Bacterial-True
   D. Malignancy-False
   E. Fungal-True

6. Generalized seizure types include:
   A. Localized-False
   B. Absence-True
   C. Tonic-Clonic-True
   D. Myoclonic-True
   E. Atonic-True

7. Meningitis may present with the following clinical features:
   A. Fever-True
   B. Reduced alertness-True
   C. Photophobia-True
   D. Headache-True
   E. Shortness of breath-False

8. The following might precipitate seizures
   A. Fever-True
   B. Flickering light-True
   C. Alcohol-True
   D. Sleep deprivation-True
   E. Laughter-True

9. Paralysis of the fourth cranial nerve produces:
   A. Weakness of the inferior oblique muscle-False
   B. Pupillary dilation-False
   C. Impaired downward gaze-True
   D. Elevation and abduction of the eye-True
   E. None of the above-False

10. With respect to lumbar puncture:
   A. Coagulation is a contraindication-True
   B. Papilledema is an absolute contraindication-True
   C. Can be therapeutic by reducing intracranial pressure-True
   D. The less CSF is removed; the less likely coning is to occur-True

11. About Parkinsonism
    A. Mainly results from reduction of dopaminergic transmission within the basal ganglia-True
    B. Intentional tremor and akinesia help in diagnosis-False
    C. Family history is a risk factor-True
    D. Neuropsychiatry symptoms might be present-True

12. Outcome of bacterial meningitis relates to:
    A. Age of the patient-True
    B. Time of first administration of antibiotics-True
    C. CSF concentration of antibiotics-True
    D. Development of antibiotics resistance during therapy-True

13. A 70-year-old woman complains of sudden onset of weakness of left arm and leg, she also experiences difficulties in speech and loss of vision in one eye. Although these symptoms were frightening, they improved within 10 hours and she was feeling well when she came to the clinic. What is the likely diagnosis?
    A. Patient has a minor stroke-True
    B. Patient has motor neuron disease-False
    C. Patient has Parkinson's disease-False
    D. Patient has Transient ischemic attack-True

14. Aseptic meningitis may be due to
    A. Viral infection-True
    B. TB-True
    C. Partly treated bacterial infection-True
    D. Lyme disease-True

15. In a patient presenting with seizures
    A. A screen for toxins may be indicated-True
    B. Blood sugar is indicated-True
    C. CSF studies is mandatory in HIV infected (if no contraindication), even in the absence of symptoms or signs suggesting infection-True
    D. Brain scan might be indicated-True

16. Differential diagnosis of seizure include
    A. Migraine-True
    B. Syncope-True
    C. Transient ischemic attack-True
    D. Sleep walking-True

17. In motor neuron disease
    A. The pathological hallmark is death of lower and upper motor neurons-True
    B. Dementia is a component of Amyotrophic lateral sclerosis-True
    C. Ocular motility is a late sign in Amyotrophic lateral sclerosis (ALS)-False
    D. No treatment arrests the underlying process in ALS-True

18. Regarding the central nervous system (CNS) in HIV infection
    A. Cytomegalovirus is the most common viral infection-True
    B. Highly active anti-retroviral therapy significantly improves the survival of patients with progressive multifocal leukoencephalopathy-True
    C. The target sign on CT is pathognomic for tuberculoma-True
    D. Gummas are the most frequent features of neurosyphilis-True

19. The following are true of CNS involvement in AIDS
    A. HIV encephalopathy (HIVE) is the most common cause of neurological disease-False
    B. Progressive multi-focal leukoencephalopathy is associated with Jacob Creutzfeldt papova virus (JC virus)-True
    C. CMV encephalitis is easily differentiated from HIVE by its imaging characteristics-False
    D. Lumbar puncture is contraindicated in evaluating patients with AIDS and CNS involvement-False

20. In the evaluation of a confused patient, following should be considered
    A. Motor neuron disease-True
    B. Drug intoxication-True
    C. Cerebral malaria-True
    D. Post-seizure event-True

21. The risk factor for bronchogenic cancer are:
    A. HIV-True
    B. Asbestos-True
    C. Radon Gas-True
    D. Cigarette Smoking-True

22. Paraneoplastic manifestations of bronchial carcinoma include:
    A. Cerebellar Degeneration-True
    B. Skin rash and proximal Myopathy-True
    C. Eaton-Lambert Syndrome-True
    D. Bone Pain-True

23. A 68-year-old pub landlord and lifelong smoker is admitted with lethargy and drowsiness. Laboratory tests reveal results consistent with syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and a chest radiograph demonstrates a 3cm right upper lobe mass. He is due to undergo a CT guided biopsy of the mass. What is the histological subtype most likely to be?
    A. Bronchoalveolar cell Carcinoma-False
    B. Squamous cell Carcinoma-False
    C. Pulmonary Hamartoma-False
    D. Small (oat) cell Carcinoma-True

24. The following tumor markers can be used as surrogate for bronchial carcinoma:
    A. CA 125-False
    B. CA 19-9-False
    C. Neuron specific Enolase-True
    D. Placental Alkaline Phosphatase-False

25. The following are contraindications to surgical resection in bronchial carcinoma:
    A. Distant Metastases-True
    B. Pleural effusion (non-malignant)-False
    C. Bilateral mediastinal Lymphadenopathy-True
    D. Esophageal Involvement-True

26. Pancoast's syndrome
    A. Results from local extension of a tumor growing in the base of the Lung-False
    B. May result in involvement of the 8th cervical and 1st and 2nd thoracic Nerves-True
    C. Often with destruction of 4th and 5th Ribs-False
    D. May result in shoulder pain that characteristically radiates in the ulna distribution of the Arm-True

27. The following primary tumors can metastasis to the lungs:
    A. Melanoma-True
    B. Salivary gland Tumor-True
    C. Soft tissue Sarcoma-True
    D. Testicular Cancer-True

28. A 60-year-old with congestive cardiac failure due to hypertensive heart disease, who is also epileptic and HIV patient on HAART complains of breast enlargement. Which of the following medications he is currently taking would cause gynecomastia?
    A. Calcium channel Blockers-True
    B. Spironolactone- True
    C. Efavirenz-True
    D. Sodium Valproate-True

29. Which of the following statement is true about secondary diabetes?
    A. A patient can be assumed not to be Ketosis-Prone-False
    B. A patient is more than 85% likely to have clinical pancreatic exocrine Deficiency-True
    C. Classical diabetic complications do not occur- False
    D. Thiazide diuretics and beta-blockers can both impair insulin Secretion-True

30. Which of the following statement is true about hypoglycemia?
    A. About 50% of patients who have had type 1 DM for 20 years or more develop 'hypoglycemia awareness'-True
    B. Sweating and shaking are always late symptoms of insulin-induced Hypoglycemia-False
    C. Metformin is responsible for as many cases of hypoglycemia as Sulfonylureas-False
    D. The symptoms characteristically come on over hours rather than Minutes-False

31. Which of the following is true about diabetic retinopathy?
    A. Characteristically causes arterial-venous Nipping-False
    B. Should be referred to an ophthalmologist only if the patient has visual Symptoms-False
    C. Inevitably causes Blindness-False
    D. May cause soft and hard Exudates-True

32. The following will increase secretion of insulin
    A. Ketone bodies- True
    B. Vagal nerve Stimulation-True
    C. Amino Acids-True
    D. Glucagon-False

33. The following will decrease secretion of insulin
    A. Glucagon-True
    B. Alpha-Agonist-True
    C. Cortisol-True
    D. Thyroxine-True

34. Complication of insulin include
    A. Lipoatrophy-True
    B. Lipohypertrophy-True
    C. Hyperglycemia-False
    D. Gynecomastia-False

35. A 30-year-old HIV patient, Pre-HAART, is admitted with weight loss, diarrhea, night sweats and cough. On TB treatment for 4 weeks and recently treated for oral thrush. His BP 80/60, RR 24. Which other clinical signs are suggestive of a possible cause of her low BP?
    A. Clearly audible heart Sound-False
    B. Hyperpigmented palm creases and Gums-True
    C. A pulse of 70/minute with full Volume-False
    D. Normal JVP-False

36. Features of renal failure may include:
    A. Loss of libido- True
    B. Hyperparathyroidism- True
    C. Delirium-True
    D. Platelet Dysfunction-True

37. A 28-year-old female presents with hematuria, proteinuria 2+, increased BP and mild pedal edema and creatinine 60mmol/L. The doctor suspects a glomerular disease. A urine microscopy was ordered. Which result is highly suggestive of a glomerular disease
    A. RBC Casts-True
    B. Hyaline Casts-False
    C. Muddy brown Casts-False
    D. Epithelial Casts-False

38. The most likely clinical syndromes in the patient in Question 37 above
    A. Nephrotic Syndrome-False
    B. Nephritic Syndrome-True
    C. Rapid Progressively-True
    D. Chronic Glomerulonephritis-True

39. What is the Gold standard for making a definitive diagnosis in the above patient in Question 37?
    A. No need for further evaluation as long as the clinical syndrome is Known-False
    B. Kidney Ultrasound-False
    C. Histological Diagnosis-True
    D. 24-hour urine protein and Creatinine-False

40. In the diagnosis of Acute Kidney injury (AKI), diagnosis is usually based on the following parameters:
    A. Baseline creatinine, latest creatinine and/or urine output- True
    B. Baseline GFR and latest GFR-True
    C. A patient with AKI on dialysis is in stage 2- False
    D. Urine output alone is not sufficient to make a diagnosis of AKI-False

41. A marathon runner was found fitting after taking 2L of water after a 10Km marathon on a hot sunny day. What is the likely cause of seizures?
    A. Hypernatremia-False
    B. Dilutional Hyponatremia-True
    C. Pseudohyponatremia-False
    D. Diabetic Ketoacidosis-False

42. What will be the management of the patient in question 41?
    A. Normal Saline-False
    B. 3% Saline-True
    C. Darrow's-False
    D. Ringer's Lactate-False

43. Cerebral blood flow is increased by:
    A. Hypercapnia- True
    B. Hypoxia- False
    C. Alkalosis-False
    D. Hypothermia-False
    E. Polycythemia- False

44. Recognized features of pseudobulbar palsy include:
    A. Inappropriate Laughter-False
    B. Dysarthria-True
    C. An absent jaw Jerk-False
    D. Dysphagia-True
    E. Fluctuating level of Consciousness-False

45. Guillan-Barre' syndrome
    A. Has an acute Onset-False
    B. Is typically associated with normal CSF protein- False
    C. Presents with periods of loss of Consciousness-False
    D. Is characterized by bilateral motor Weakness-True
    E. Has a recognized association with carcinoma of the Lung-False

46. Myasthenia gravis is characterized by
    A. Dysphagia-True
    B. Ptosis-True
    C. Aplastic Anemia-False
    D. HLA antigen DR3-True
    E. Morning Stiffness-False

47. In the elderly stroke is significantly associated with
    A. High serum Cholesterol-True
    B. Obesity-True
    C. Polycythemia rubra vera-True
    D. Myocardial Infarction-True
    E. Atrial Fibrillation-True

48. Infarction in the territory of the anterior cerebral artery
    A. Causes more severe hand then shoulder weakness on the affected Side-False
    B. Produces predominant weakness of the lower Limb-True
    C. Is most frequently seen after SAH after berry aneurysm Rupture-True
    D. Causes transcortical motor aphasia when affecting the dominant Hemisphere-True
    E. Usually occurs as a result of cerebral Embolism-True

49. Characteristics features of occlusion of the left middle cerebral artery include
    A. Hemiplegia with involvement of the leg more than the Arm-False
    B. Paralysis of conjugate gaze towards the Left-True
    C. Deep xanthochromia of CSF-True
    D. Diplopia-False
    E. Dementia-False

50. Causes of SIADH include
    A. Chest Infection-True
    B. Head injury- True
    C. Chlopropamide-True
    D. Addison's Disease-False
    E. Liver Cirrhosis-False

51. Which of the following is true about SAH?
    A. It is common among elderly women and very rare in the Young-True
    B. Over 90% of SAH are due to untreated Hypertension-False
    C. Neck stiffness is very rare unless patient has Meningitis-False
    D. The presence of hypotension with tachycardia indicates raised intracranial Pressure-False
    E. Nifedipine treatment is very important in the Management-True

52. Which of the following are true about seizures?
    A. Imipenem may cause seizures and should not be used to treat Meningitis-True
    B. These may occur in poisoning due to tricyclic antidepressants, mefenamic acid or Opioids-True
    C. In Tenia solium infection, focal seizures can occur if cysts are present in the Brain-True
    D. Pre-eclampsia is marked by seizures or coma in addition to other Signs-False
    E. In CKD, mental slowing, clouding of consciousness and rarely seizures may Occur-True

53. Which of the following are true about stroke?
    A. In Zambia, cerebral hemorrhage accounts for more than 30% of acute Strokes-False
    B. In supratentorial strokes with homonymous hemianopia, patient cannot see on the hemiplegic Side-True
    C. Vertigo, vomiting, dysphagia and Horner's syndrome indicate occlusion of the vertebrobasilar Circulation-True
    D. Pinpoint pupils and bilateral upgoing plantars could signal a brainstem Stroke-False
    E. Carotid endarterectomy should be considered for patient with more than 70% Stenosis-True

54. In a patient with AIDS, Cryptococcal meningitis is
    A. The commonest cause of Meningitis-True
    B. Characterized by abrupt onset of the classical features of a bacterial Meningitis-False
    C. Diagnosed by India ink stain of cerebrospinal Fluid-True
    D. Typically associated with negative CSF culture- False

55. Cryptococcal meningitis
    A. Is caused only by Cryptococcus neoformans neoformans- False
    B. Is more common than Cryptococcal pneumonia- True
    C. Characteristically causes leucopenia- False
    D. Only occurs in the Immunosuppressed-True
    E. Should be treated with Ketoconazole-False

56. Amphotericin B is used in the treatment of
    A. Visceral leishmaniasis- True
    B. Dermatophyte infections of the nails- True
    C. Azole resistant oral Candida-True
    D. Primary amoebic meningoencephalitis caused by Naegleria Species-True
    E. Cryptococcal Meningitis-True

57. Common cause of blackouts include:
    A. Drugs-True
    B. Valvular heart Disease-True
    C. Myocardial Infarction-True
    D. Hypoglycemia-True
    E. Alcohol Ingestion-True

58. HIV infection is associated with
    A. An RNA retrovirus- True
    B. Involvement of CD4 lymphocytes- True
    C. Viral half-life of 1-2 hours in plasma- False
    D. A better prognosis in the presence of Kaposi's sarcoma- False

59. In HIV infection
    A. 80% of vertically transmitted infections are transplacental-False
    B. A child born to an infected mother has a 90% chance of acquiring HIV-False
    C. Transmission can occur via breast Milk-True
    D. Risk of fetal transmission is unaffected by pre-partum antiviral Agents-False

60. In the diagnosis of HIV infection
    A. ELISA testing has a low false negative rate- True
    B. Seroconversion invariably occurs in under 4 Weeks-False
    C. Antibody detection tests are particularly helpful in Neonates-False
    D. HIV-RNA is typically detected before anti-HIV Antibodies-True

61. In the classification of HIV infection
    A. Stage 1= acute seroconversion simulating glandular Fever-True
    B. Stage 2= persistent generalized Lymphadenopathy-False
    C. Stage 3= have absolute CD4 count >500/mm^3-False
    D. Kaposi's sarcoma is stage 3 Disease-False

62. Presenting features of HIV infection include
    A. Hairy Leucoplakia-True
    B. Atypical pneumonia- True
    C. Thrombocytopenic purpura- True
    D. Pulmonary tuberculosis- True

63. Cryptosporidiosis in an HIV positive patient is
    A. An AIDS-defining diagnosis if chronic- True
    B. Likely to present with painless profuse diarrhea- True
    C. Likely to self-limiting if the CD4 count is > 200 cells/mm^3- True
    D. Preventable by the use of boiled tap water- True

64. *Pneumocystis carinii* infection in an HIV positive patient is
    A. The commonest cause of respiratory infection in African Patients-True
    B. Characterized by copious sputum Production-False
    C. Characterized by widespread fine pulmonary Crackles-True
    D. Excluded by the finding of a normal chest X-Ray-False

65. The following have been reported with initiation of HAART;
    A. Immune reconstitution syndrome- True
    B. Osteonecrosis- True
    C. Diabetes Mellitus- True
    D. Lipodystrophy syndrome- True

66. Side effects of Nucleoside reverse transcription inhibitor include;
    A. Cough-False
    B. Fever-False
    C. Insomnia-False
    D. Liver Damage-True

67. The following are true;
    A. Maraviroc is an antagonist of Protease-False
    B. A Fusion inhibitor is helpful in the treatment of HIV-False
    C. Raltegravir is an inhibitor of HIV Integrase-True
    D. Stavudine has very few side effect- False

68. On protease inhibitor;
    A. Should be used with caution in Diabetic Mellitus Patient-True
    B. Should not be used in patient with acute porphyria- True
    C. Should be used with caution in patient with chronic hepatitis B-True
    D. Should not be used in AIDS Stage-False

69. About peptic ulcer disease
    A. Gastrinoma should be suspected if there are multiple duodenal Ulcers-True
    B. Alcohol abuse is a risk factor for gastric Ulcer-True
    C. Peptic ulcer disease may lead to acute Pancreatitis-True
    D. Helicobacter pylori infection and NSAIDs are the two most common causes of peptic ulcer Disease-True
    E. Biopsy must be performed in all patients with duodenal Ulcer-False

70. Patients with HIV stage 4 WHO may have the following conditions
    A. Pulmonary Tuberculosis-True
    B. HIV Encephalopathy-True
    C. Esophageal Candidiasis-True
    D. Abdominal TB-True
    E. Severe Anemia-False

71. Regarding tuberculosis pericardial effusion
    A. Pericardiocentesis is Mandatory-False
    B. Low dose prednisolone given during the first 2 months of Treatment-True
    C. Culture of pericardial fluid is Confirmatory-True
    D. Treatment is given for 12 Months-False
    E. Constrictive pericarditis is not a known Complication-False

72. Signs of hypokalemia on ECG include:
    A. Flattening of T Wave-True
    B. Prolonged QT Interval-True
    C. Tall U Waves-True
    D. J wave -False
    E. Shortening of PR Interval-True

73. Causes of hyperkalemia include
    A. Addison's Disease-True
    B. Diabetic ketoacidosis- True
    C. Rhabdomyolysis-True
    D. Renal Puncture-True
    E. Alkalosis-False

74. The most effective drug in control of hypertension in an emergency is
    A. Nifedipine-False
    B. Hydralazine-True
    C. Sodium Nitroprusside-True
    D. Lasix-False
    E. Methyldopa-False

75. Optic neuritis is complication of:
    A. Rifampicin-False
    B. Isoniazid-False
    C. Ethambutol-True
    D. Pyrazinamide-False
    E. Streptomycin-False

76. In community acquired pnemonias:
    A. The commonest pathogen is *Mycoplasma pneumoniae*-False
    B. Erythromycin is the first-line antibiotic for Psittacosis-False
    C. The serum urea correlates with severity of illness- True
    D. Ciprofloxacin can be used as a single agent when the organisms is not Known-True
    E. The pneumococcal antigen can be identified in Urine-True

77. Misoprostol is
    A. H2 receptor Antagonist-False
    B. Synthetic prostaglandin Analogue-True
    C. Proton pump Inhibitor-False
    D. NSAID-False
    E. Antacid-False

78. Microcytic anemia is a typical finding in:
    A. Folic acid deficiency- False
    B. Hemolytic anemia- False
    C. Alcohol Abuse-False
    D. Primary sideroblastic Anemia-True
    E. Iron Deficiency-True

79. Non-infectious causes of diarrhea:
    A. Inflammatory bowel Disease-True
    B. Histoplasmosis-False
    C. Bechets Disease-True
    D. Clostridium perfringens-False
    E. Pseudomembranous Colitis-True

80. Causes of chronic liver disease
    A. Alcohol- True
    B. Methyldopa-True
    C. Hepatitis B Virus-True
    D. Methotrexate-True
    E. Idiopathic-True

81. The following is true of viral hepatitis:
    A. Hepatitis C commonly presents with Jaundice-True
    B. Hepatitis C is fatal particularly in Pregnancy-True
    C. Hepatitis BeAg is a marker of viral Replication-True
    D. Hepatitis A is a risk factor for hepatoma-False
    E. Hepatitis D occurs only in association with hepatitis C-False

82. The following are common causes of meningitis
    A. Neisseria meningitidis-True
    B. Haemophilus Influenza-True
    C. Listeria monocytogenes-True
    D. Staphylococcus Aureus-True
    E. Gram negative Bacilli-True

83. In the treatment of HIV infection
    A. All useful drugs work via inhibition of reverse transcriptase- False
    B. Reverse transcriptase inhibitors prevent replication in infected Cells-True
    C. Reverse transcriptase inhibitors prevent spread of infectious virus into uninfected Cells-False
    D. Drug resistant strains of virus have not been Recognized-False
    E. Monotherapy is Preferred-False

84. Recognized features of severe heart failure include
    A. Tiredness-True
    B. Weight Loss-True
    C. Epigastric Pain-True
    D. Nocturia-True
    E. Nocturnal Cough-True

85. The pain of Myocardial ischemia
   A. Is typically induced by exercise and relieved by Rest-True
   B. Radiates to the neck and jaw but not to the Teeth-True
   C. Rarely lasts longer than 10 Seconds-False
   D. Is easily distinguished from esophageal Pain-False
   E. Can easily be distinguished from pain arising from acute Pancreatitis-False

86. Jone's major criteria for the diagnosis of rheumatic fever
   A. Migratory Polyarthritis-True
   B. Pancarditis-True
   C. Chorea-True
   D. Fever-False
   E. Subcutaneous Nodules-True

87. Adverse effects of corticosteroid therapy include:
   A. Peptic Ulceration-True
   B. Hypertension-False
   C. Avascular bone Necrosis-True
   D. Pseudogout-True
   E. Insomnia-True

88. The typical features of type B viral hepatitis include:
   A. Incubation period of 1 month- True
   B. History of exposure to unsafe sex or drug Abuse-True
   C. Prodromal illness with polyarthralgia-True
   D. Hepatic illness more severe than type A-True
   E. Absence of progression to chronic Hepatitis-False

89. Typical features of advanced hepatic cirrhosis include
   A. Progressive Hepatomegaly-False
   B. Massive Splenomegaly-True
   C. Peripheral blood macrocytosis-True
   D. Parotid gland Enlargement-True
   E. Central Cyanosis-False

90. Hepatic encephalopathy in cirrhosis is typically precipitated by:
    A. Infection-True
    B. Hypokalemia-True
    C. Abdominal Surgery-True
    D. Gastrointestinal Bleeding-True
    E. Lactulose Therapy-False

91. Hemoptysis is a clinical feature of
    A. Carcinoma of Lung-True
    B. Bronchiectasis-True
    C. Pulmonary Tuberculosis-True
    D. Primary pulmonary Hypertension-True
    E. Pulmonary Embolism-True

92. A pleural effusion with a protein content 50g/L would be compatible with:
    A. Congestive cardiac Failure-False
    B. Pulmonary Infarction-False
    C. Subphrenic Abscess-True
    D. Pneumonia-True
    E. Nephrotic Syndrome-False

93. Recognized causes of pyrexia of unknown origin (PUO)
    A. Infective Endocarditis-True
    B. Renal cell Carcinoma-True
    C. Systemic lupus Erythematosus-True
    D. Tuberculosis-True
    E. Drug Fevers-True

94. The following would help distinguish between a kidney and a spleen in the left upper quadrant
    A. Dull percussion note over the Mass-True
    B. A well localized notched lower Margin-True
    C. Moves with Respiration-True
    D. A ballotable Mass-True
    E. A family history of renal Failure-False

95. The following are classified as high output states:
    A. Hypertension-False
    B. Sepsis-True
    C. Hypothyroidism-False
    D. Pregnancy-True
    E. Arterial venous Malformation-True

96. Clinical features of raised intracranial pressure:
    A. Tachycardia and hypotension-False
    B. Dizziness and lightheadedness-True
    C. Headache aggravated by bending and straining-True
    D. Behavioral and personality changes-True
    E. Sixth or third nerve palsies-True

97. Recurrent headache could be due to
    A. Migraine-True
    B. Cluster-True
    C. Glaucoma-True
    D. Analgesia overdose-False
    E. Tension headache-True

98. The definition of epilepsy includes being
    A. Spontaneous-True
    B. Intermittent-True
    C. Having abnormal electrical discharge in some part of the brain-True
    D. Diagnosis is predominantly clinical-True
    E. A known epileptic and independent observer's description being suggestive of epilepsy-True

99. Migraine headache is often characterized by following except:
    A. Being throbbing-False
    B. Being unilateral-False
    C. Associated with projectile vomiting-False
    D. Associated with nervous tension-True
    E. May be associated with visual disturbances-False

100. CSF protein level is normal in the following types of meningitis?
   A. Viral-True
   B. TB-False
   C. Bacterial-False
   D. Malignant-False
   E. Septicemia-True

THIRD YEAR ESSAY QUESTIONS

1. HIV is a very common condition observed in the medical wards at Levy Mwanawasa General hospital. Please answer the following questions:
   a. What do you understand by immune reconstitution inflammatory syndrome? (5 marks)

      Answer:

      Immune reconstitution inflammatory syndrome is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover, but then responds to previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.

      The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. Not only does this make it more difficult to fight infection it may mean that a level of infection that would normally produce symptoms is instead undetected (subclinical infection) If the CD4 count rapidly increases (Due to effective treatment of HIV) a sudden increase in the inflammatory response produces nonspecific symptoms such as fever and in some cases a worsening of damage to the infected tissue.

      There are 2 common IRIS scenarios. The first is the 'unmasking' of an occult opportunistic infection and the second is the 'paradoxical' symptomatic relapse of a prior infection despite microbiologic treatment success.

   b. What are the central nervous system complications of HIV? (5 marks)

      Answer:

      - Progressive multifocal leukoencephalopathy
      - Unexplained nerve palsy
      - HIV encephalitis
      - Aseptic meningitis
      - CNS lymphoma
      - Immune reconstitution inflammatory syndrome of the CNS (CNS-IRIS)
      - HIV related stroke
      - Acute demyelinating polyneuropathy
      - Peripheral neuropathies

c. What are the renal complications of HIV? (5 marks)

Answer:

- Acute kidney injury
- HIV associated nephropathy
  - Thrombotic microangiopathy
  - HIV related tubulointerstitial injury
  - Immune complex-mediated glomerular disease (nephritic syndrome)
  - Nephrotic syndrome
- Comorbid chronic kidney disease

d. What are the parameters of monitoring treatment? (5 marks)

Answer:

- CD4 count
  - Should be measured at time of diagnosis before commencement of therapy and every 1-3 months after initiating antiretroviral treatment and then every 3-4 months (when CD4 count is above 350 cells for at least 12 months).
  - Measure CD4 if new clinical staging events develop.
- Viral Load
  - Desirable but not entirely essential prior to initiating therapy
  - Viral load should be assessed to confirm clinical or immunological failure where possible prior to switching treatment regimen.
  - By 4 weeks' therapy the viral load should have dropped by at least 1 log10 copies/mL and by 12-24 weeks should be below 50 copies/mL.
  - Once stable on therapy the viral load should be routinely done every 3-4 months.
- Baseline hemoglobin level, white blood cell count, Liver enzyme, Urea & electrolytes, creatinine, blood glucose and lipid profile.
  - This should be assessed before and after initiation of therapy

2. 34-year-old male businessman present to you with a history of productive cough, evening chills, night sweats, loss of appetite and loss of weight of the past 3 months. He is newly diagnosed RVD with CD4 count of 3 cells/ml. His chest X-ray shows a miliary picture and the safe lab markers are normal.
   a. Which other investigations are you going to order- list 3 (3 marks)
      Answer:
   - Erythrocyte sedimentation rate
   - Sputum microscopy with Ziehl-Neelsen stain (Acid-fast bacilli), culture and sensitivity
   - Sputum for GeneXpert

   b. List 5 differentials for the chest X-ray picture (5 marks)
      Answer:
   - Miliary tuberculosis
   - Histoplasmosis
   - Sarcoidosis
   - Pneumoconiosis
   - Pulmonary siderosis
   - Bronchoalveolar carcinoma

   c. If the diagnosis is Miliary TB, outline the management plan in the above patient (4 marks)
      Answer:
   - Assess sensitivity of bacilli to the first line drugs
   - Treatment duration is for 9-12 months.
     - 2 months' intensive phase with Rifampicin, isoniazid, pyrazinamide and ethambutol
     - 7-10 months' continuation phase with rifampicin and isoniazid
   - Give isoniazide with vitamin B6.
   - Since CD4 <50 cell/ml also start antiretroviral treatment immediately.
     - Triple therapy according to current national guidelines.

d. List the common side effects of the antituberculosis drugs- 2 for each (8 marks)

Answer:

- Rifampicin
  - Hepatotoxicity, Acute renal failure
  - Orange/red discoloration of body fluids
  - Stevens-Johnson syndrome
- Isoniazid
  - Hepatotoxicity and jaundice
  - Sideroblastic anemia
  - Peripheral neuropathy
- Pyrazinamide
  - Hepatotoxicity
  - Hyperuricemia and gout
- Ethambutol
  - Optic neuritis
  - Color blindness, loss of visual acuity, peripheral neuritis
  - Thrombocytopenia
- Streptomycin
  - Ototoxicity (hearing impairment)
  - Mild skin rash

3. In relation to endocrine disorders, please answer the following:

a. Describe pathophysiology of Diabetic ketoacidosis (5 marks)

Answer:

This is mainly a complication of type 1 diabetes mellitus but can sometimes also arise in type 2 diabetes mellitus.

Any event that decreases insulin availability or causes stress that increases the insulin demand (e.g. infection, poor compliance with insulin or discontinuation of insulin, dehydration, stress- trauma, surgery or emotional crisis, and excessive alcohol ingestion) will lead to severe insulin deficiency and excessive release of the stress hormones glucagon, cortisol, epinephrine and growth hormone.

This results in:

- Increased production of glucose by the liver and increase glycogen degradation to glucose
- Decreased glucose uptake and utilization

- Lipolysis: enhanced break down of free fatty acids and subsequent ketogenesis. This increases blood levels of ketone bodies such as acetoacetate, beta-hydroxybutyric acid, and acetone resulting in metabolic acidosis.

The above biochemical processes result in significant hyperglycemia and ketoacidosis, which is responsible for the clinical manifestations of diabetic ketoacidosis:

- Volume depletion (dehydration) due to osmotic diuresis- dry tongue and buccal mucosa, poor skin turgor and hypotension
- Kaussmaul's respiration: deep and fast breathing resulting from metabolic acidosis
- Nausea and vomiting with abdominal pain
- Acetone ('fruity') odor of breath: due to acetone
- Mental status changes: lethargy and confusion which may lead to coma in severe DKA
- Cerebral edema: especially in children

b. What are the causes of Addison's disease (5 marks)?

Answer:

- Acute causes:
  - Waterhouse-Friderichsen syndrome- Infection with *Neisseria meningitidis*
  - Sudden withdrawal of long term corticosteroid treatment
- Chronic causes:
  - Primary adrenal insufficiency
  - Chronic
    - Tuberculosis of adrenal cortex
    - AIDS
    - Systemic amyloidosis
    - Hemochromatosis
    - Sarcoidosis
    - Fungal infection
    - Autoimmune adrenalitis

c. What are the metabolic abnormalities with primary adrenal insufficiency? (5 marks)

Answer:

- Hyperkalemia
- Hypercalcemia
- Increased urea
- Hyponatremia
- Hypoglycemia

d. What is a thyroid storm? (5 marks)

Answer:

This is a severe life-threatening form of hyperthyroidism. It is characterized by excessive thyroid hormones in the blood (e.g. from performing a thyroidectomy of a hyperthyroid patient) accompanied with signs and symptoms consistent with thyrotoxicosis:

- Tachycardia, arrhythmias and cardiac failure
- Restlessness
- Fever
- Confusion
- Agitation
- Weakness
- Dyspnea
- Diarrhea
- Shock

It is also known as thyroid crisis.

4. A 20-year-old female patient presented to emergency unit at Levy Mwanawasa General Hospital with a history of progressive exercise intolerance. She has to use extra pillows in order to get some peaceful sleep but she still wakes up often in the middle of the night in gasps for breath. Professor Njelesani asks you to demonstrate a cardiovascular exam and you on auscultation find a left parasternal diastolic murmur loudest in expiration. Her BP is 110/50. You also find bibasal end-inspiratory fine crackles and sacral edema.
   a. What is your full diagnosis? (5 marks)
   b. What other 'special signs' will you look out for? Name and describe 5 of them (10 marks)
   c. What do you expect to see on her chest radiograph? (3 marks)
   d. Give one differential for 'bibasal end-inspiratory crackles' (2 marks)

5. In relation to liver cirrhosis:
   a. Please describe Child-purg score in relation to liver cirrhosis? (5 marks)
   Answer: this is a scoring system in cirrhosis used liver cirrhosis to determine 1 year, 5 years and 10-year survival

SCORE	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
Prothrombin time (Seconds over normal)	<4	4-6	>6

Once the total score is added the survival rates are as follows

Grade (SCORES)	% SURVIVAL		
	1 YEAR	5 YEARS	10 YEARS
<7	82	45	25
7-9	62	20	7
10+	42	20	0

b. What are the poor prognostic indicators for liver cirrhosis? (5 marks)

Answer:

- Blood tests
  - Low albumin (<28g/l)
  - Low serum sodium (<125 mmol/L)
  - Prolonged prothrombin time >6s above normal value
  - Raised creatinine >130µmol/L
- Clinical
  - Persistent jaundice
  - Failure of response to therapy
  - Ascites
  - Hemorrhage from varices particularly with poor liver function
  - Neuropsychiatric complications developing with progressive liver failure
  - Small liver
  - Persistent hypotension
  - Etiology e.g. alcoholic cirrhosis if the patient continues drinking

c. What are the complications related to liver cirrhosis? (5 marks)

Answer:

- Portal hypertension
- Gastrointestinal hemorrhage
- Ascites
- Portosystemic encephalopathy
- Hepatocellular carcinoma
- Bacteremia and infections
- Renal failure

d. What is the pathophysiology of ascites related to liver cirrhosis? (5 marks)

Answer:

Ascites with liver cirrhosis is associated with many factors including:

- Decreased synthetic ability of the liver due to fibrosis of parenchyma: there is a decrease in the synthesis of proteins which contribute to oncotic pressure which opposes hydrostatic pressure (which forces fluid out of the vascular space). In liver cirrhosis there is hyperproteinemia and a resultant decrease in oncotic pressure leading to an imbalance in the starling forces across the blood vessels. The hydrostatic pressure exceeds the oncotic pressure and more fluid leaves the vascular compartment into the interstitium leading to ascites.

- Severe sinusoidal portal hypertension: which results in congestion and an increase in hydrostatic pressure in the venous system leading to transudation of fluid.

8. In relation to hemato-oncology
   a. What are the clinical features of iron-deficiency anemia? How do you make a diagnosis? (5 marks)

   Answers:

- Clinical features:
  - Pica
  - Brittle nails
  - Koilonychia
  - Atrophic glossitis
  - Brittle hair
  - Angular stomatitis
  - Palpitations, lightheadedness, dizziness, headaches, fatigue, tinnitus and syncope
- Diagnosis:
  - Clinical features: History and examination (as above)
  - Full blood count
    - Hemoglobin and red blood cell count- reduced
    - Mean corpuscular volume-reduced (<80fL)
    - Mean corpuscular hemoglobin- reduced (<27 pg)
    - Mean corpuscular hemoglobin concentration- reduced
  - Peripheral smear
    - Hypochromic cells
    - Poikilocytosis
    - Target cells
  - Iron studies
    - Decreased serum iron
    - Decreased ferritin
    - Decreased percentage saturation
    - Increased total iron binding capacity
  - Investigations to establish cause:
    - Stool for occult blood
    - Stool for ova and parasites

- Chest x-ray to exclude pulmonary hemosiderosis
- Upper and lower GI radiologic and endoscopic studies
- Urinalysis for hematuria or hemosiderinuria

b. Write short notes on the types of crises related to sickle cell disease? (5 marks)

Answer:

The crises include:

- Splenic sequestration crisis
  - There is pooling of red cells in the spleen and hypovolemia leading to circulatory collapse.
  - There is severe hemolysis, rapid splenomegaly and a high reticulocyte count.
  - This is common in childhood before multiple infarcts occur that lead to a fibrotic non-functioning spleen.
- Hyper hemolytic crisis
  - This is due to excessive hemolysis of red blood cells.
  - Presents as pre-hepatic jaundice.
- Aplastic crisis
  - This happens following infection with erythrovirus B19 (previously called Parvovirus B19) which invades proliferating erythroid progenitors.
  - There is a rapid fall in hemoglobin with no reticulocytes in the peripheral blood because of the failure of the marrow.
- Vaso-occlusive crisis
  - This is due to vaso-occlusion of the blood vessels as a result of sickling of red blood cells.
  - When this happens in the hands and feet dactylitis ensures. Severe pain can also be felt in other bones such as femur, humerus, vertebrae, ribs, pelvis.
  - One of the feared complications that may arise from a vaso-occlusive crisis in the lungs is acute chest syndrome due to pulmonary infarction. Patient may present with shortness of breath, fever, cough and chest pain.
  - Blockage of splanchnic vasculature results in recurrent abdominal pains.

c. What are the complications of multiple myeloma? (5 marks)

Answer:

- Anemia
- Pancytopenia
- Bleeding disorders- retinal bleeds
- Heart failure

- Bone marrow failure
- Infections
- Spinal cord compression
- Pathological fractures
- Carpal tunnel syndrome
- Nephrotic syndrome
- Chronic kidney disease

d. What are the complications of acute leukemias? (5 marks)

Answer:

- Anemia
- Bone marrow failure
- Pancytopenia
- Bleeding disorders
- Infections

9. A young man is brought into the emergency department with history of vomiting, increased urination and diarrhea of sudden onset after 30 minutes of spraying farm products with unknown insecticides. On examination, he is semi-conscious, frosting from the mouth, miosis and bradycardic with soiled clothing.

a. What is the most likely diagnosis? (2 marks)

Answer: Organophosphate poisoning

b. What other signs might he present with? List 4 (4 marks)

Answer:

- Muscle fasciculation and tremors
- Muscle weakness and Flaccid paralysis of limbs, respiratory and extraocular muscles
- Sweating
- Seizures, with slurred speech

c. Outline the pathophysiology of the above (4 marks)

Answer:

- Organophosphate are absorbed through inhalation as well as the skin. The irreversibly bind and inhibit the enzyme acetylcholinesterase both centrally and peripherally resulting in accumulation of acetylcholine and subsequent overstimulation of muscarinic receptors (resulting in sweating) as well as nicotinic receptors (Resulting in muscle fasciculation, tremor, muscle

weakness and flaccid paralysis) including receptors in central nervous system resulting in seizures with slurred speech

d. What samples would you take to confirm diagnosis (4 marks)

Answer:

- Blood for erythrocyte cholinesterase activity or plasma for cholinesterase activity (this may be decreased to 30-50% in asymptomatic patients, 10-20% in moderate poisoning and <10% in severe poisoning)- This confirms diagnosis of organophosphate poisoning.
- Full blood count
- Urea and electrolytes to rule out electrolyte disturbances
- Stool for microscopy, culture and sensitivity to rule out gastroenteritis

e. Outline principle of management of the above young man (6 marks)

Answer:

- Ensure Airway is patent by suctioning all the secretions
- Ensure patient is breathing and chest is rising (assess for possible need to intubate)
- Obtain venous access and start running fluids (normal saline)
- Change and remove soiled clothing
- Insert a urinary catheter and monitor urine output
- Start Atropine 2mg IV every 3-5 min to reduce increased secretions, rhinorrhea and bronchorrhea
- Give Pralidoxime (to reactivate inhibited acetylcholinesterase)
    - Pralidoxime chloride 30mg/kg slow IV injection followed by an infusion of pralidoxime mesylate 8-10mg/kg per hour.

10. A 23-year-old African lady presents to a medical clinic with fatigue, weight loss, anorexia, a photosensitive malar rash, oral ulcers, intermittent polyarthritis and urinalysis reveals proteinuria. Anti-double stranded DNA is strongly positive.

a. What is the working diagnosis? (6 marks)

Answer: Systemic lupus erythematosus

b. Briefly describe the immunopathology in this condition (8 marks)

c. Briefly describe hematological disorders in this conditions- List at least 3 (3 marks)

d. Describe briefly the CNS manifestation- at least 3 (3 marks)

11. A 44-year-old coal miner presented with a 3-month history of polyuria and dyspnea on exertion. He had developed a frontal headache the past 6 weeks and was sweating profusely. He had recently noticed tingling in his hand which was worse at night. On systemic enquire he admitted to loss of libido and impotence for 6 years. On examination he has coarse face, macrognathia, 'spade' hand and feet with thick skin. Heart rate is 100/min regular with a BP of 200/100. Neurological examination was grossly normal except for bi-temporal hemianopia and reduced sensation to pin-prick over the thumb, index and ring fingers.
    a. What is the diagnosis? (4 marks)
    b. Give 2 possible causes of polyuria (4 marks)
    c. What is cause of bi-temporal hemianopia (2 marks)
    d. What is the cause of reduced sensation to pin-prick over the thumb, index and ring fingers (4 marks)?
    e. What single test would you use to confirm diagnosis (4 marks)
    f. Give another test that will help in locating the cause of bi-temporal hemianopia? (2 marks)

12. Write short notes on the following
    a. Features of Nephrotic syndrome (5 marks)

    Answer:
    - Proteinuria >3.5g/day.
    - Hypoalbuminemia- due to proteinuria.
    - Edema (peri-orbital, generalized edema especially early morning)- due to decreased oncotic pressure
    - Hypercoagulable state- due to loss of anti-thrombin III and overproduction of fibrinogen by the liver.
    - Recurrent infections (with encapsulated organisms)- due to loss of immunoglobulins (hypogammaglobinemia) and low molecular weight complement proteins e.g. C3b.
    - Hyperlipidemia and lipiduria- increased cholesterol, increased low, intermediate & very low density lipoproteins, decreased high density lipoproteins.

b. Major differences between Nephrotic and Nephritic syndrome (5 marks)

Answer:

FEATURE	NEPHROTIC SYNDROME	NEPHRITIC SYNDROME
Proteinuria	> 3.5g/day	<3.5g/ day
Signs and Symptoms	Edema Hypoalbuminemia Hypogammaglobinemia Hypercoagulable states Hyperlipidemia Frothy urine	Hematuria Hypertension Edema Oliguria Azotemia RBC casts in urine
Etiology	Primary: • Minimal change disease • Focal segmental glomerulosclerosis • Membranous nephropathy • Membranoproliferative glomerulonephritis Secondary: • Diabetes mellitus • Hypertension • Collagen vascular disease • Amyloidosis	• Idiopathic • Lupus nephritis • IgA nephropathy • Poststreptococcal glomerulonephritis

c. Complication related to chronic renal failure (5 marks)

Answer:

1. Metabolic acidosis: due to accumulation of organic acids
2. Electrolyte imbalance: hyperkalemia, hypocalcemia, hyperphosphatemia
3. Uremia
4. Cardiovascular:
    - Hypertension: due to fluid overload
    - Congestive heart failure: due to fluid overload
    - Pericarditis: due to accumulation of toxins. Pericardial effusions are often hemorrhagic
5. Hematological:

- Anemia (normocytic normochromic): due to decreased production of erythropoietin
- Bleeding tendency (platelet dysfunction)- GI bleeding, intracranial hemorrhage

6. Pulmonary edema: due to fluid overload and increased pulmonary capillary permeability
7. Endocrine
   - Men: impotence and oligospermia due to decreased levels of plasma testosterone.
   - Women: amenorrhea, inability to carry pregnancy to term
8. Renal osteodystrophy- hyperphosphatemia, hypocalcemia
   - Osteitis fibrosis cystica: due to osteoclastic bone resorption of especially terminal phalanges, long bones and distal end of clavicles
   - Renal rickets (Osteomalacia)
   - Osteosclerosis: enhanced bone density in the upper and lower margins of vertebrae

d. Hepatorenal syndrome (5 marks)

Answer: Hepatorenal syndrome is a condition consisting of rapid deterioration of kidney function in individuals with cirrhosis or fulminant liver failure. Vigorous diuresis, paracentesis and sepsis may predispose to Hepatorenal syndrome. Typically, the kidneys are histologically normal with the capacity of regaining normal function in the event of recovery of liver function. There is severe cortical vasoconstriction.

It is characterized by declining GFR, oliguria, low urine sodium (<10mg/l), normal urinary sediment and azotemia often with disproportionately high levels of blood urea nitrogen and creatinine.

Diagnosis is made after pre-renal causes of renal failure is excluded.

Management includes volume expansion to rule out volume depletion, low dose vasopressin, octreotide or norepinephrine may be given and liver transplantation is the accepted management.

101. In relation to heart failure, please write short notes on the following include definition, pathophysiology and clinical significance

a. Pulsus paradoxus:

Answer:

- This refers to an abnormally large decrease in stroke volume, systolic blood pressure and pulse wave amplitude during inspiration. The normal fall in pressure is less than 10mmHg. In pulsus paradoxus it drops more than 10mmHg.
- It is characteristic of cardiac tamponade and severe airway obstruction (e.g. chronic obstructive pulmonary disorders, asthma, sleep apnea and croup)
- In airway obstruction, it is due to accentuation of change in intrathoracic pressure with respiration. In cardiac tamponade, compression of the right heart prevents the normal increase in flow through the right heart on inspiration, which exaggerates the usual drop in venous return to the left heart and produces a marked fall in BP (>10mmHg fall during inspiration)

b. Systolic dysfunction

Answer:

- Systolic dysfunction denotes heart failure due to reduced ejection fraction and an enlarged ventricular chambers. It can involve either of the ventricle. In left ventricular systolic dysfunction the cardiac output to the systemic circulation is markedly impaired and so this results in a back flow of blood into the pulmonary circuit and resultant signs and symptoms such as dyspnea, paroxysmal nocturnal dyspnea and orthopnea. In right ventricular systolic dysfunction, the cardiac output to the pulmonary vasculature is reduce and there is a backflow into the systemic circuit resulting in ankle edema, sacral edema or generalized edema. Systolic dysfunction is seen in both congestive heart failure and dilated cardiomyopathy.

c. Paroxysmal nocturnal dyspnea

Answer:

- This refers to attacks of severe shortness of breath and coughing generally occurring at night. It usually awakens the person from sleep and may be quite frightening.
- In paroxysmal nocturnal dyspnea fluid shifts from the interstitial tissues of the peripheries into the circulation within 1-2 hours of lying down.

Pulmonary edema follows causing the patient to wake and sit upright, profoundly breathless.

- It is indicative of severe heart failure

d. 'A' waves in relation to raised JVP

Answer:

- The 'a' wave is produce by atrial systole and is increased with right ventricular hypertrophy secondary to pulmonary hypertension or pulmonary stenosis.
- Giant cannon waves occur in complete heart block and ventricular tachycardia.

e. Please classify '3 types of Angina' with symptoms

Answer:

- The 3 types of angina include:
  - Stable angina pectoris
  - Unstable angina pectoris
  - Prinzmetal/vasospastic angina
- Stable angina
  - This is characterized by a short-lasting 'crushing' like chest feeling/ Chest pain (not lasting more than 20 minutes) during exertion. The pain may radiate to the left arm, left jaw, epigastric area and even the back.
  - It is due to a fixed obstruction of one or more of the coronary arteries. The lumen is 70% occluded.
  - Due to the fixed obstruction, the blood supply cannot increase and the heart becomes vulnerable to ischemia whenever there is increased demand such as that produced by physical activity, emotional stress or excitement or any other cause of increased cardiac workload.
  - Ischemia is limited to the subendocardial myocardium
- Unstable angina
  - This is characterized by an unstable coronary atheromatous plaque which can undergo severe acute changes making it highly thrombogenic.
  - The chest pain (not lasting longer than 20 minutes) occurs with increased frequency duration and it can be precipitated by

progressively less effort. The pain may radiate to the left arm, left jaw, epigastric area and even the back.
    - Ischemia initially involves subendocardial myocardium but can be transmural if obstruction is complete
- Prinzmetal angina
    - This is characterized by spastic constriction of the coronary arteries resulting in complete occlusion of blood flow.
    - Symptoms are not associated with exertion or any atheromatous plaque.
    - Ischemia to myocardium is transmural.

FIFTH YEAR ESSAY QUESTIONS

1. You have been asked to evaluate a patient in the Department of Obstetrics and gynecology. The consultation reads: "**very urgent, come and manage our patient with suspected acute renal failure**".

You find that she is 26 years old. She had given birth 10hours earlier by spontaneous vaginal delivery to a mildly asphyxiated baby. She has not passed urine since delivery. The Antenatal card shows she had no medical or gynecological problems. Urinalysis was done twice during antenatal and was reported normal. The midwife tells you that the labor was "very hectic" and patient was difficult during delivery and hence "bled a lot"

Examination:
Drowsy, pulse 142/min, Blood pressure 85/55 mmHg, respiratory rate 29/min.
CVS-tachycardia, no murmurs, no gallop, RS- clear lung fields, GIT- normal.
There is no active bleeding per vagina and uterus is well contracted

Urinalysis
pH= 5.5
Specific gravity >1.030
Amino acids= trace
Glucose= trace
Casts=present
Hemoglobin, RBC, Albumin, White blood cells, nitrites= all negative

Glucometer random blood sugar= 6, Urea=26
Urgent bedside ultrasound shows normal kidneys

(a) What assessment needs to be done on this patient?

Answer:

Blood investigations:

- Full blood count: assess the level of RBCs, WBCs Hemoglobin and platelets
- Cross match
- Liver function tests and liver enzymes to exclude Hepatorenal syndrome
- Serum electrolyte (check potassium levels especially and also calcium, and phosphate)
- Creatinine
- Arterial blood gases for metabolic acidosis

Urine

- Urine chemistry: urine sodium (if <1% indicates prerenal failure, if >2% indicates renal causes)
- Urine microscopy and culture

(b) Analyse the findings

Answer:

The woman is anuric given that she has not passed urine over 10hours (urine output <0.5ml/kg/hr for more than 6 hours- Stage 1 acute kidney injury), in addition she has bleed a lot leading to hypovolemia (and shock) as evidenced by the drowsiness, a systolic blood pressure less than 90mmHg (blood pressure was 85/55mmHg) with a tachycardia of 142b/min. Furthermore, the woman is tachypnic with a respiratory rate of 29/min however, with the chest being clear on auscultation as per examination findings pulmonary edema seems unlikely. From the findings of the urinalysis there is an increase in specific gravity (normal 1.010 to 1.030) indicating there is no intrinsic damage to the nephron, the cast cells may be suggestive of acute tubular necrosis due to the hypoperfusion brought about by the massive blood loss during delivery. Lastly the rise in urea signifies the decrease in the excretory function of blood urea nitrogenous waste and so they tend to accumulate in the blood stream.

Working Diagnosis: Acute tubular necrosis (AKI) 2^{o} Postpartum hemorrhage

(c) Plan your full management

Answer:

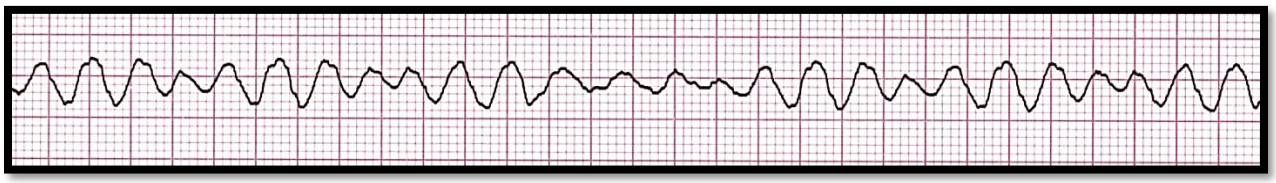
- Cannulate and Catheterize the patient
- Avoid/stop nephrotoxic drugs (beta blockers, ACE inhibitors, ARBs, aminoglycosides-gentamicin, streptomycin, penicillin, NSAIDs or corticosteroids)
- Cross match and transfuse with packed cells (depending on the level of RBC or Hemoglobin)
- Administer intravenous fluids (normal saline) while awaiting blood
  - Fluid challenge as patient is dehydrated. 250-500ml of saline over 30 minutes.
  - Reassess after fluid challenge if still dehydrated (give fluids until JVP visible and systolic BP >100mmHg).

        - Once fluid replete, continue fluids at 20ml + previous hour's urine output/hour
        - If overloaded, consider urgent dialysis.
    - Monitor:
        - Blood pressure
        - Fluid input and output
        - Urine output
        - Daily weighing
        - Electrolytes (especially potassium) and acid base status
        - ECG monitoring
    - If any signs of infection place patient on antibiotics
    - Treat any complications that arise
        - Hyperkalemia
- Protect myocardium: 10ml of 10% Calcium gluconate given in 5 minute. Dose can be repeated after 15 minutes
- Push potassium into cells: 10IU insulin and 50ml of 50% dextrose IV over 10-15mings with regular check of glucose and/or salbutamol 0.5mg in 100ml of 5% glucose over 15 minutes.
- Push Potassium out of cells: polystyrene sulphonate resins: 15g orally TDS with laxatives 30g rectally followed 9hour later by an enema
- Hemodialysis or peritoneal dialysis if above fails
        - Pulmonary edema: IV diuretics (Furosemide)
    - Consult renal unit
    - Dialysis if patient refractory to above management or develops acidosis, Fluid overload (pulmonary edema) refractory to conventional dose of diuretic, electrolyte imbalance (hyperkalemia) and uremia

2. A male patient 45 years old was admitted yesterday to ICU with severe chest pain. He is a known diabetic and hypertensive patient for more than 10 years. Diagnosis of admitting doctor was Unstable angina. Doctor on call was informed that patient suddenly changed his condition after a short episode of breathlessness (though in the morning he appeared to be stable, pain free and

not on ventilation). The nurse reported the absence of pulse and un-recordable BP.

On the monitor attached to the patient the fine oscillations seen.



(a) What condition is this?

Answer: Ventricular fibrillation

(b) What is your immediate action?

Answer:

- Check if patient is unresponsive by shaking him/her and shouting into one ear.
- If no response:
  - Call for help
  - Ensure airway is patent (remove any dentures or foreign bodies, suction secretions)
  - Perform a jaw thrust or chin lift to keep head in "sniffing air in the morning" position
  - Endotracheal intubation and ensure oxygenation
  - Gain venous access and start an intravenous infusion in a large peripheral or central vein
  - Perform chest compression: 30 cardiac compressions with 2 effective breaths (30:2)
  - Attach patient to defibrillator

(c) If the monitor still shows oscillations and pulse is absent on the carotid arteries what do you do next?

Answer: Defibrillation with unsynchronized shock of 150-200J biphasic (or 360 J monophasic) via paddles or self-adhesive pads followed immediately by 2 minutes of cardiopulmonary resuscitation.

(d) What is the possible diagnosis?

Answer: Pulseless ventricular tachycardia

(e) How would you manage in post-resuscitation period?

Answer:

- Ensure patient's airway is patent and patient is breathing.
- Get full history and complete physical examination full neurological and cardiovascular exam
- Monitor vitals: Blood pressure, pulse, O_2 Saturation
- Monitor U+Es, creatinine.
- Do lipid profile, FBC
- Controlled oxygenation and ventilation
- 12-Lead ECG
- Treat precipitating cause:
  - Insulin for the diabetes (monitor blood glucose levels)
  - ASA 75mg PO OD to prevent thrombi formation
  - Antihypertensives (Beta blocker) to control BP
- Temperature control and monitoring, keep temperature between 32-34^{o}C
- Resuscitate if patient when necessary

3. A 20-year-old male patient presents to admission ward after being found unconscious at home. The friend accompanying him says that he is a known diabetic on "injections" that are kept in the fridge and that he has been unwell the past 4 days with a febrile illness and is not sure whether he was getting his injections or not.
   Examinations: unconscious (GCS 8/14), moderately wasted, no generalized lymphadenopathy, dehydrated, febrile and has Kaussmaul's respiration.
   You are the attending officer in Phase 5
   Please, fully manage him (all the facilities are there i.e. labs etc.)
   Answer in Bullet form…
   Answer:

- Admit to high dependency unit or ICU
- Ensure Airway is patent, suction any secretions and ensure patient is breathing
- Keep patient warm.
- Gain venous access with 2 large bore cannulae, send blood for:
  - Full blood count

  - Urea, Electrolytes (Sodium, potassium, bicarbonate, chloride, calcium and magnesium), Creatinine
  - Liver enzymes and liver function tests
  - Serum glucose (also perform a random blood sugar)
  - Serum ketones
  - Arterial blood gases
  - Cross match
- Also send blood and urine cultures as well as perform and chest X-ray
- Catheterize the patient and insert an NGT
- Perform a urinalysis
- Check vitals: (1 hourly for first 8 hours)
  - Blood pressure
  - Temperature
  - Respiratory rate
  - Pulse
  - Oxygen saturation
- Continuous ECG monitoring
- Start fluids normal saline
  - If SBP <90mmHg give 500ml of normal saline in 15 minutes repeat as necessary. Give 1L in 30 minutes
  - If/When SBP >90mmHg give normal saline:
    - 1L in 1 hour
    - 1L in 2 hours
    - 1L in 4 hours
    - 1L in 8 hours
  - When blood sugar <14mmol use 5% dextrose
- Give insulin (0.1IU/kg/hr) as an intravenous infusion. Check random blood sugar (RBS) hourly. When blood glucose between 10-14mmol/L use 0.05IU/Kg/hr
  - When patient becomes conscious and can take oral feeds calculate total insulin usage and give TDS soluble insulin SC for each meal
  - Alternatively, 6IU SC every hour (8IU if obese)
  - Aim for 3-6mmol/L per hour drop of blood glucose from baseline
  - Blood glucose (RBS) should be less than 8.9mmol/L
  - Monitor glucose hourly for first 8 hours
- Check potassium:

  - If >5.5 mmol/L do not give potassium chloride
  - If 3.5-5.5 mmol/L give 20mmol of KCl to second bag of fluids
  - If <3.5mmol/L give 40mmol of KCl to second bag of fluids
- Cover on antibiotics (Ceftriaxone 1g BD)
- Give sodium bicarbonate 600ml of 1.4% or 100ml of 8.4% in large cannulated vein if pH<7.0
- Monitor:
  - For signs of pulmonary edema
  - Urine output (check hourly for first 8 hours)
  - Electrolytes (check at baseline then hourly till 6 hours and then at 12 hours and 24 hours)
  - Glucose (check hourly for first 8 hours)
  - Blood gases (check at 0, 2 and 6 hours)
  - Vitals (check hourly for first 8 hours)
- Take full history after patient gains consciousness, counsel on diabetes management and its complications. Adapt patient's regimen to fit their needs.

4. Daniel comes to the admission ward with complaints of weakness, nausea, fatigability and poor appetite. He is a known HIV positive patient on HAART (AZT, 3TC and NVP) for over 2 years. His last CD4 was 200 cell/ml (at baseline was 55 cells/ml). He was recently diagnosed to have sputum positive PTB at the local clinic and started on anti-tuberculosis treatment.
   (a) List two problems Daniel has and justify your answers (2 marks)
   Answer:

- Treatment failure this is because despite Daniel being on treatment for 2 years he has clinical symptoms that show signs of deteriorating status, a poor rise in CD4 count and the presence of an opportunistic infection.
- Poor compliance and adherence to treatment as justified by the rise of CD4 count from baseline over the past 2 years on treatment coupled with the emergence of pulmonary TB. This may also contribute to the treatment failure. Furthermore, there may be a poor response to treatment probably due to resistance of HIV to the anti-retroviral drugs.
- AZT may have caused bone marrow suppression leading to the decrease in WBC and the onset of PTB.

(b) List and justify investigations you would order (9 marks)

Answer:

- Liver enzymes/Biochemistry: AST and ALT as the anti-TB drugs are hepatotoxic
- Urea, Electrolytes and Creatinine: To assess kidney function before changing Antiretroviral therapy regimen, as well as continuation of anti-TB treatment. Calculate creatinine clearance
- Full blood count to assess WBC (infection) and look out for pancytopenia (RBC and platelets) which may indicate Zidovudine induced bone marrow suppression.
- Viral load: to assess the level of viremia and effectiveness of treatment
- Chest X-ray- to assess for pulmonary involvement as well as rule out any other pulmonary pathologies and for comparison with prior radiographs for any radiological improvement.
- Repeat sputum microscopy, culture and sensitivity to assess effectiveness of the TB therapy
- Lumbar puncture for CSF analysis and biochemistry as well CT scan of the head if possible to rule out CNS opportunistic infections

(c) Outline your management plan (9 marks)

Answer:

- Admit
- Continue Anti-tuberculous treatment-4FDCs (intensive phase for 2 months on Rifampicin, Isoniazid, Pyrazinamide and Ethambutol and Continuation phase for 4 months on Rifampicin and Isoniazid)
- Repeat sputum and Chest X-ray after 14 days of TB treatment

- After patient stabilizes, change anti-retroviral drugs to ABC + 3TC (or FTC) + DTG (avoid TDF since patient is on Rifampicin, increase DTG to 50mg BD)
- Keep hydrated and daily monitoring of urine output
- Monitor Creatinine, Liver function tests weekly
- Counsel patient on treatment adherence, compliance and side-effects of drugs
- Discharge via psychosocial counseling when patient improves and review in clinic after 2 weeks.

5. A 22-year female lady (known cardiac patient) come in with history of weakness, fever, malaise, sweating and painful sores on hands.
   (a) List differential diagnosis? (4 marks)

   Answer:
   - Infective endocarditis
   - Systemic lupus erythematosus
   - Reactive arthritis
   - Disseminated gonococcal infection

   (b) Write down the "Dukes criteria" (4 marks)

   Answer:
   - Major criteria:
     - Positive blood cultures for typical microorganisms from 2 separate blood cultures
     - Positive echocardiogram findings: definitive vegetation, abscess, new partial dehiscence of prosthetic valve, new valvular regurgitation
   - Minor criteria:
     - Predisposition: predisposing heart condition or IV drug abuse
     - Microbiologic evidence: Positive culture but not meeting major criterion (e.g. 1 positive culture)
     - Echocardiogram consistent with IE but not meeting major criterion (i.e. positive echo for other abnormality)
     - Fever greater than 38 degrees Celsius
     - Embolic phenomena: Embolism, CNS hemorrhage, conjunctival hemorrhage, Janeway lesion

- Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots, false positive VDRL test

➢ For diagnosis:
- 2 major
- 1 major plus 3 minor
- 4 minor

(c) What other signs would you look for and give the pathogenesis of the signs (6 marks)

Answer:

➢

(d) How would you manage this patient (6 marks)?

Answer:

➢ Admit patient
➢ Investigate:
- Blood culture
- Echocardiography
- Chest X-ray
- ECG
- Full blood count
- Urinalysis and microscopy
- U/E, LFTs

➢ Bed rest
➢ Antibiotics for 4-6 weeks (IV antibiotics for at least 2 weeks):
- Crystalline penicillin 3-4 million IU IV every 4 hours for 4-6 weeks' plus
- Gentamicin 1mg/kg IV TDS for 2 weeks

➢ Treat any heart failure and arrhythmias than ensue
➢ Refer for Surgery: for debridement, repair or valve replacement if medical therapy fails or complications ensue.

6. A 35-year-old Zambian man complains of easy fatigability of long-standing duration. The following are his blood results.

WBC 5.3 x 10^9/L
RBC 1.2 x 10^{12}/L
Hb 4g/dl

Platelets 20 x 10^9
Blood glucose 6 mmol/L
Sodium 137 mmol/L
Potassium 6.2mmol/L
Creatinine 1200 μmol/L

(a) Comment on the results and their significance? (4 marks)
Answer:
(b) What is your diagnosis? (4 marks)
(c) What will be the other clinical features of the patient with such results (6 marks)
(d) How would you confirm the definitive diagnosis (i.e. investigations and justify)? (11 marks)

7. Mr. Mabvuto Sakala is a 76-year-old male that arrives in AMEU at Levy Mwanawasa General Hospital in an ambulance. As an intern doctor on duty he is brought in your consultation room. He complains of shortness of breath for a week which seem to have gotten worse today. He complains of also a persistent dry cough especially at night.

He is known to be Diabetic and hypertensive on Losartan 50mg, Amlodipine 10mg and insulin therapy. He has no known drug allergies.
On assessment- Vitals BP: 218/110mmHg, RR-36b/min, Temp- 37.7, O_2 Sat 95% (Room oxygen), dusky nail beds, skin cool and moist with ankle edema. JVP is 10cm, Apex beat in the 6^{th} intercostal space anterior axillary line with a tachycardia and occasional ectopics. Rales noted right middle lobe and lower lobes bilaterally.

The following are investigations done on the patient:
Sodium 135
Potassium 3.9
Hb 12.5
Creatinine 220 μmol/L
CXR- bilateral pulmonary congestion with enlarged cardiac shadow
12 lead EKG: sinus tachycardia with occasional PVCS, Old anterior MI

(f) From the patient's chief complain and your initial assessment, what is the patient's primary problem? (4 marks)
(g) Describe the pathophysiology of CHF (congestive heart failure) (6 marks)
(h) What are the signs and symptoms of heart failure in this patient? (2 marks)
(i) What factors contribute to the patient's heart failure? (4 marks)
(j) What pharmacologic agents are used to improve performance in patients with CHF? (4 marks)

8. A 65-year-old man present with a 6-week history of cough, progressive shortness of breath and 10kg weight loss. He has 50-pack year smoking history and his family doctor orders a chest X-ray and blood work.

   The CXR shows a left lower lobe mass. His physical is normal. He is otherwise healthy and takes no regular medication
   (d) List 4 differentials for above patient (8 marks)
   (e) How would you further investigate this man in order to get a pathologist diagnosis- List 5 (5 marks)
   (f) If it is Bronchogenic carcinoma, what addition tests are required to properly stage this patient- List 7 (7 marks)

9. Mrs. Banda is a 27-year-old woman (unemployed) who was referred from VCT center after testing HIV positive 3 weeks ago. Her husband recently died from Cryptococcal meningoencephalitis during his hospitalization he tested positive for HIV causing her to pursue testing.

   Her medical history has been unremarkable except being diagnosed with extrapulmonary TB 4 months ago. She declined HIV test at the time of TB diagnosis.

   She is allergic to trimethoprim/Sulfamethoxazole which causes a diffuse erythematous rash. Her physical examination is notable for a thin, well developed

woman with no acute distress. Her ENT exam reveals Candida on the tongue and buccal mucosa. Heart, Lung and Abdomen examinations are normal.

Her Laboratory test
Hb- 11.7mg/dl
Platelets 167 000
HIV positive
CD4 4 410/μL

(e) For this patient, what evidence (history, physical examination, and/or laboratory data), support beginning antiretroviral therapy (ART) (4 marks)
(f) Do you identify any barriers to ARV adherence? List 3. What would you recommend to address these barriers? (6 marks)
(g) What antiretroviral medication would initiate? (4 marks)
(h) What toxicities could be associated with the anti-retroviral therapy you chose? 2 for each (6 marks)

10. Mr. Saili is a 74-year-old man who presents to your consultation room with his wife complaining of shortness of breath and fever. His wife did bring records from his last physician that he has Chronic Obstructive Pulmonary Disease (COPD). After evaluation you make a diagnosis of acute exacerbation in COPD.
(f) What is the mechanism of airflow limitation in COPD? (4 marks)
(g) What is the role of inflammatory mechanisms in COPD? (4 marks)
(h) What are the organisms commonly associated with exacerbation of COPD? (4 marks)
(i) What investigation would you order? (4 marks)
(j) How would you treat an acute exacerbation? (4 marks)

11. A 20-year-old young lady comes to the hospital complaining of fevers and oral ulcers for a week. She reports having had fevers in the recent past. She says she has no urinary symptoms. She feels tired and has no cardiac symptoms. She also has noticed her hair is thinning out. The registrar suspects she has a connective tissue disease.
(d) What else would you want to probe for in the history? (5 marks)

The patient is noted to have rash on her face that looks like a butterfly pattern and she also has joint tenderness in the hands. Your registrar further suggests that this could be Systemic Lupus Erythematosus (SLE).

(e) List the manifestations used in the criteria to make a diagnosis of SLE. (5 marks)
(f) What drugs can you use in a patient with SLE? (4 marks)

12. A 40-year-old HIV negative male patient presents to AMEU with four days of Jaundice, upper abdominal pain, nausea, vomiting and headache. He is a patient on sputum positive PTB on treatment for 6 weeks. He is currently on Rifampicin, Isoniazid, Ethambutol and Pyrazinamide. The patient has no other pertinent past medical history and uses no other medications.

    On physical examination, he is alert and oriented with the following vital signs: Blood pressure 113/62mmHg, heart rate 88b/min, respiratory rate 14 breaths/min, pulse oximetry 100% on room air, temperature 37.1 degree Celsius. His skin is jaundiced but without ecchymoses or petechiae. Eye examination reveals scleral icterus.

    Cardiovascular and pulmonary findings are unremarkable. His abdomen is soft, but diffusely tender to palpation without and organomegaly, rebound, guarding or rigidity.

    Initial pertinent laboratory results include: AST> 2600 IU/L, ALT>2600 IU/L, total bilirubin >20mg/dl, INR 3.7.

    (e) What is the primary problem with this patient? (2 marks)
    (f) How would you investigate this patient? List 4 important investigations (4 marks)
    (g) How does Isoniazid (INH) cause hepatotoxicity? (6 marks)
    (h) How would you manage this patient if it was purely due to INH? (8 marks)

13. Write short notes on:
    (e) Diagnosis of Myocardial infarction (5 marks)
    (f) Mechanism of diarrhea in Cholera (5 marks)

(g) Symptoms, signs and diagnosis of Organophosphate poisoning (5 marks)
(h) Treatment of organophosphate poisoning (5 marks)

14. The patient is a 41-year-old male who has a longstanding history of hypertension and diabetes and presents with a complaint of pruritus, lethargy, lower extremity edema, nausea and emesis. He denies any other medical illnesses.
On physical examination the patient is well-developed, well-nourished male in moderate distress. Blood pressure 180/110, pulse 80, respirations 24 and he was afebrile. Body weight 76.5kg. ENT exam was remarkable for fundoscopic findings of AV nicking and copper wire changes consistent with hypertensive injury. Cardiac exam had an S1, S2 and S4. The remainder of the exam was remarkable for 2+ lower extremity edema and superficial excoriations of his skin scratching.

Laboratory data

Chemistry		Normal Values	Urinalysis
Sodium	133	136-146 mmol/L	pH 6.0 Specific gravity 1.010 Protein 1+ Glucose negative Acetone negative Occult blood negative Bile negative Waxy casts
Potassium	6.2	3.5-5.3 mmol/L	
Chloride	100	98-108 mmol/L	
Total CO_2	15	23-27 mmol/L	
BUN	170	7-22 mg/dl	
Creatinine	16.0	0.7-1.5 mg/dl	
Glucose	108	70-110 mg/dl	
Calcium	7.2	8.9-10.3 mg/dl	
Phosphorus	10.5	2.6-6.4 mg/dl	
Alkaline Phosphatase	306	30-110 IU/L	
Parathyroid Hormone	895	10-65 pg/ml	
Hemoglobin	8.6	14-17 gm/dl	
Hematocrit	27.4	40-54 %	
Mean cell volume	88	85-95 FL	

24-hour urine protein and creatinine- volume 850ml, protein 600mg/dl and creatinine 180 mg/dl.

Renal ultrasound- Right Kidney 9 x 6.0 cm, Left Kidney 9.2 x 5.8cm

Both kidneys illustrate hyperechogenicity and no hydronephrosis

(g) "Presents with a complaint of pruritus, Lethargy, lower extremity edema, nausea and emesis." What do these symptoms suggest to you? (2 marks)
(h) What are the fundus changes in a hypertensive? (4 marks)
(i) What are the fundus changes of a diabetic? (4 marks)
(j) What does S4 signify? What cardiac findings will you expect to find in a hypertensive? (6 marks)
(k) What is the significance of the finding "superficial excoriations of his skin from scratching"? (2 marks)
(l) Why was a renal ultrasound ordered? (2 marks)

15. A 58-year-old woman comes to a physician's office complaining of feeling lightheaded for past week. She says she can feel her heart racing in her chest. She mentions she has been staying up late for the past few weeks because of her workload at work. The medical history reveals well controlled diabetes mellitus.

Physical examination reveals an anxious woman with pallor and mild diaphoresis. Cardiac examination reveals an irregularly irregular beat. Vital signs are as follows: Temperature: 36.1^{o}C, Respiratory rate 22b/min, Heart rate 142 bpm, BP 118/55mmHg and Glucose 7.7 mmol/L

(f) What is the most likely diagnosis?
(g) What clinical and ECG abnormalities are most commonly associated with this condition?
(h) What is the most appropriate treatment for this condition?
(i) How do Heparin and Warfarin work together to treat this condition?
(j) Why does paradoxical reaction sometimes occur after starting warfarin therapy?

16. A 38-year-old male present to AFC with profuse diarrhea, low grade fever, cough, shortness of breath for 3 days. On examination, BP: 85/40mmHg, HR: 110bpm, Temp 38.9^{o}C, RR: 32/min. CXR: bilateral infiltrates
    Part A

    Labs: sodium= 140 mmol/L, chloride=110 mmol/L, bicarbonate= 12, pH= 7.30, PCO_2= 20
    (e) What is the pH?
    (f) What is the primary disorder?
    (g) Is there any compensation>
    (h) What is the anionic gap and what is the complete diagnosis?

    Part B

    A 24-year-old female present with right flank pain and hematuria for 2 days' duration

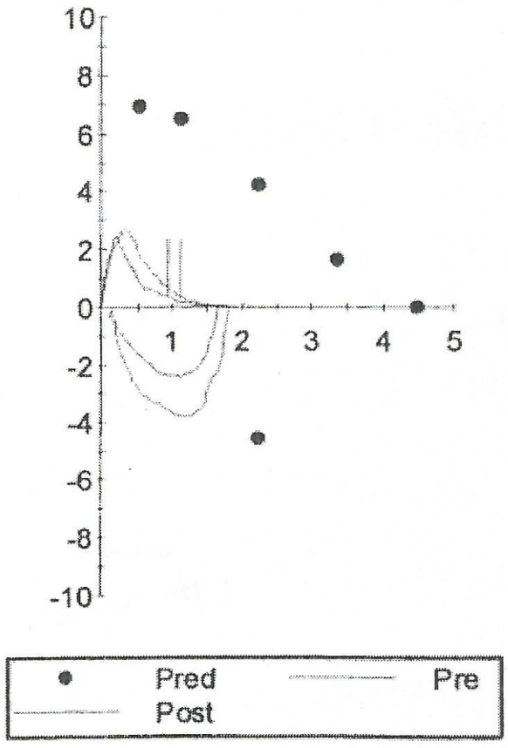
    Lab results: Sodium= 138, Chloride= 115, bicarbonate= 12, pH=7.35, Potassium=3.0

    (e) What is the pH?
    (f) What is the primary disorder?
    (g) Is there any compensation?
    (h) What is the anionic gap and what is the complete final diagnosis?

17. A 35 year-old previously health man presents with dyspnea, fevers, chills, and night sweats for the past 2 months. He is a non-smoker with no concerning habits or occupational exposures. His pulmonary function tests are as follows:

	Pre-Bronchodilator (BD)		
Test	**Actual**	**Predicted**	**% Predicted**
FVC (L)	1.66	4.48	37
FEV_1 (L)	0.94	3.67	26
FEV_1/FVC (%)	57	82	
RV (L)	1.39	1.66	84
TLC (L)	3.06	5.96	51
RV/TLC (%)	45	29	

His flow volume loops is as follows:



(e) Describe the pattern of the abnormality, if one is present
(f) Grade the severity of the abnormality
(g) Generate a differential diagnosis for the observed abnormality
(h) Outline management of Acute severe asthma

18. A 55-year old male presents with weakness in his legs and shortness of breath. Sodium 142mmol/L, Potassium 2.5 mmol/L, urea 8 mmol/L, Glucose 9.6mmol/L, bicarbonate 35mmol/L
    (e) What is the likely unifying diagnosis?
    (f) What cause is suggested by the data?
    (g) What 3 further investigations would you request?
    (h) Name 5 reasons why this person may have limb weakness

19. A 28-year-old man comes to your office complaining of a 5-day history of nausea, vomiting, diffuse abdominal pain, fever to 101°F (38.3° C) and muscle aches. He has lost his appetite, but he is able to tolerate liquids and has no diarrhea. He has not significant medical history of family history and he has not travelled outside the Lusaka. He admits to having 12 different lifetime sexual partners, denies illicit drug use, and he drinks alcohol occasionally but not since this illness began. He takes no medications routinely, but he has been taking acetaminophen, approximately 30 tablets per day for 2 days for fever and body aches since this illness began.

    On Examination his temperature 38.9°C, heart rate 98 bpm and blood pressure 120/74 mmHg. He appears jaundiced, his chest is clear to auscultation and his heart rhythm is regular without murmurs. His liver percusses 12cm and is smooth and slightly tender to palpation. He has no abdominal distention or peripheral edema.
    Laboratory values are significant for a normal full blood count, creatinine 92 µmol/L, Alanine aminotransferase (ALT) 3440 IU/L, aspartate aminotransferase (AST) 2705 IU/L, total bilirubin 24.5mg/dl, direct bilirubin 18.2mg/dl, alkaline phosphatase 349IU/L, serum albumin 3.0g/dl and prothrombin time 14 seconds.

    (a) What is the most likely diagnosis?
    Answer: Acute hepatic failure 2^0 acetaminophen induced toxicity (? Viral Hepatitis)

    (b) What is the most important immediate diagnostic test?
    Answer: Plasma paracetamol concentration estimate

20. A 28-year-old man comes to the emergency room complaining of 2 days of abdominal pain and diarrhea. He describes his stools as frequent, with 10 to 12 per day, small volume, sometimes with visible blood and mucus and preceded by a sudden urge to defecate. The abdominal pain is crampy, diffuse and moderately severe and it is not relieved with defecation.
In the past 6 to 8 months he has experienced similar episodes of abdominal pain and loose mucoid stools but the episodes were milder and resolved within 24 to 48 hours. He has no other medical history and takes no medication. He has neither traveled out of Zambia nor had contact with anyone with similar symptoms. He works as an accountant and dose not smoke or drink alcohol. No member of his family has gastrointestinal problems.

On Examination his temperature is 38^{o}C, heart rate 98bpm, and blood pressure 118/74mmHg. He appears uncomfortable, is diaphoretic and is lying still on the stretcher. His sclerae are anicteric and his oral mucosa is pink and clear without ulceration. His chest is clear and his heart rhythm is regular, without murmurs. His abdomen is soft and mildly distended, with hypoactive bowel sounds and minimal diffuse tenderness but go guarding or rebound tenderness.
Laboratory studies are significant for a white blood cell (WBC) of 15, 800/mm^3 with 82% polymorphonuclear leukocytes, hemoglobin 10.3g/dl, and platelet count 754, 000/mm^3. The HIV assay is negative. Renal function and liver function tests are normal. A plain film radiograph of the abdomen shows a mildly dilated air-filled colon with a 4.5cm diameter and no pneumoperitoneum or air/fluid levels.

(a) What is the most likely diagnosis?
Answer: Dysentery (most likely bacillary)

(b) What is your next step?
Answer:
- Stool for microscopy/culture and sensitivity.
- Give oral rehydration salts and analgesics
- Cover on Ciprofloxacillin 500mg BD for 3 days
- If bacillary dysentery continue Cipro
- If amoebic switch to metronidazole 800mg PO TDS followed by diloxanide furoate 500mg TDS for 10 days.

(c) How do you distinguish Amoebic dysentery from Shigella dysentery (please answer in table form)

Answer:

Feature	Bacillary dysentery (Shigella)	Amoebic dysentery
Causative organism	Usually Shigella but can also be caused by enterohemorrhagic *E.coli*, *Vibrio parahemolyticus*, *Campylobacter jejuni*	*Entamoeba histolytic*
Onset	Acute	Chronic
Fever	High grade	Low grade
Dehydration	Frequent	Moderate
Number of stools	Over 10 motions per day	6-8 motions per day
Amount	Small	Relatively copious
Odor	Odorless	Offensive
Color	Bright red	Dark red
Nature	Blood and mucus no feces	Blood and mucus mixed with feces
Nature of lesion	Suppurative due to diffusible toxins	Necrotic due to proteolytic ferment
Depth of ulcer	Shallow	Deep
Margin of ulcer	Uniform, clear-cut (sharp)	Ragged and undermined
Intervening mucosa	Inflamed	Normal
Type of necrosis (cellular level)	Karyolysis (Ghost cell and ring nucleus)	Pyknotic (Pyknotic body and mouse eaten cell)
Liver abscess	Rare	Common
Cellular response	Polymorphonuclear	Mononuclear

21. A 30-year-old male patient was admitted to the emergency Room with history of severe epigastric pain. His past medical history is unremarkable. He reports to have been fine, in fact he was from having a copious meal with some wine with his friends. You examined him and found a normal temperature but low blood pressure of 86/55mmHg. He is conscious but in severe pain.

(f) Discuss the differential diagnosis?
(g) What investigations would you do to confirm it?
(h) How would you classify this condition?
(i) Discuss the pathophysiology and common causes?
(j) Outline your management plan for this patient. Please fully manage him if all the facilities were available.

22. A 35-year-old female teacher presents with 2 weeks' complaint of general fatigue. She had previously been well, her past medical history is unremarkable and thought that it was work related fatigue. When it persisted, she came to see you in the OPD.

You examined her and note that she is stable, not pale nor jaundiced but has generalized lymphadenopathy and splenomegaly. The rest of examination is unremarkable.

You obtain the following lab results:
WBC 98 $x10^9$/L with 90% lymphocytes
Monocyte 1%
Eosinophils 2%
RBC 4.28 x 10^{12}/L
Hb 14.7
Platelet 240 x 10^9/L

(e) What is the possible diagnosis for this patient?
(f) What additional investigations are you going to order to confirm your diagnosis?
(g) List 3 differentials
(h) Outline your management plan

23. A 27-year-old female with SLE is in remission. Last year she had a life-threatening exacerbation of her disease. She is currently well controlled and her treatment consists of azathioprine 75mg/d and prednisolone 5mg/d. She comes for review and now strongly desires to become pregnant.
(e) Discuss the clinical manifestations of SLE

(f) Discuss the pathogenesis of SLE
(g) What investigations do you do in SLE and discuss relevance?
(h) What advice would you give her on her desire to conceive?

24. A 20-year old male presents with a 3-day history of lethargy and generalized malaise. He is confused and looks very unwell. His past medical history is unremarkable and he is HIV negative. On examination, you found a rapid feeble pulse with hypotension and cold extremities. He is tachypnoeic with clear lungs. Abdominal examination is normal.

The following blood tests are obtained:
Blood gasses:
PH: 7.0
Bicarbonate 11mmol/L (22-30)
PCO_2 20mmHg (35-45)

Electrolytes:
Potassium 2.7
Sodium 153
Chloride 124

Creatinine 70µmol/L
Urea: 5.2 mmol/L
Glucose 52mmol/L

(g) What further history would you like to get from the bedside?
(h) Describe the acid-base balance
(i) What is the diagnosis?
(j) What electrolyte abnormalities does the patient have?
(k) What further tests would you order in this patient?
(l) How are you going to manage this patient?

25. A 25-year-old patient was admitted to the Emergency Room with easy fatigability. His past medical history is remarkable for tooth extraction two weeks ago. He also reports history of fever on and off. On examination his temperature is 37.8^{o}C and BP 120/80mmHg. He is pale with tinge of jaundice. His chest is

clear and he has pansystolic murmur at the apex. Abdominal examination reveals splenomegaly. Urinalysis shows red blood cells in urine.

(e) What is your working diagnosis?
(f) What investigations would you do to confirm it?
(g) What criteria is used to diagnose this condition?
(h) Outline your management plan for this patient. Please fully manage him if all the facilities are available.

26. A 54-year-old man presents to his primary care provider with dyspnea and a cough. He is a non-smoker with no relevant occupational exposures.

Lung function test results are as follows:

	Pre-Bronchodilator (BD)			Post-BD Bronchodilator	
Test	Actual	Predicted	% Predicted	Actual	% change
FVC (L)	3.19	4.22	76	4.00	25
FEV1 (L)	2.18	3.39	64	2.83	30
FEV1/FVC (%)	68	80		71	4

(b) Describe the pattern of abnormality, if one is present
(c) Grade the severity of the abnormality
(d) What would be the management of this patient?

27. A 52-year-old woman with heart disease presents with shortness of breath, easy fatigability and swollen feet. She has longstanding hypertension and takes medicine when she feels unwell. She has been taking 2 bottles of wine on weekends for the past 6 years but denies history of smoking. She feels her condition is getting worse and can't now climb stairs at her place. On examination you noticed that her heart rate is 70 beats per minute irregular and her blood pressure is 100/60mmHg. Her JVP is raised, her chest is clear but she has tender hepatomegaly and pitting pedal edema. The doctor makes a diagnosis of heart failure.

(e) List the common causes of heart failure in our settings
(f) What is the pathophysiology of heart failure?
(g) What two investigations would you do to confirm this diagnosis?

(h) Which therapeutic modalities have been shown to improve survival in heart failure?

28. A 23-year-old male patient is brought to the emergency room with history of malaise and headache. Apart from history of palpitations and constipation, his past medical history was apparently unremarkable. His blood pressure on admission was 210/124mmHg. He had hyperpigmented lesions on the trunk. The mini-mental test score was 8/10. Both heart sounds were normal and chest was clear. He had tender liver and pitting edema of lower extremities. Fundal examination revealed grade III retinopathy. Urinalysis shows protein +++ and glucose trace. You obtain the following lab results: Hb 9g/dl, platelets 120 x 10^9/L, Urea 28 mmol/L, Sodium 138 mmol/L, potassium 7.4 mmol/L

(a) Discuss this patients' clinical presentation and lab results

Answer:

This is a patient that is having chest complaints (palpitations) with a very high blood pressure (210/124 mmHg- severe hypertension) suggesting a hypertension as an underlying condition. The fact that he is having headaches with a mini-metal test score of 8/10 is highly suggestive of hypertensive encephalopathy and the brain involvement as end-organ damage as a complication of the hypertension. Furthermore, the other target organ that seems to be involved are the kidneys as evidenced by the proteinuria 3+, lower extremity pitting edema, the rise in urea (28 mmol/L), and the rise in potassium (7.4mmol/L). Additionally, the factor that he is having malaise, headache, hyperpigmented lesions on the trunk, a tender liver and constipation could signify an infectious process with Typhoid fever being very likely though it would require further investigations to justify. The patient also has a low Hemoglobin and platelets

(b) What is the diagnosis?

Answer: Hypertensive emergency

(c) What further investigations would you order?

Answer:

- Blood:
  - RDT for malaria
  - Widal antigen test: to rule out typhoid fever

- Blood culture: to rule out any underlying infection, or sepsis
- Clotting panel to rule out any underlying coagulopathy
- Lipid profile: check for serum cholesterol, triglycerides, LDLs and HDLs
- Liver function test: to check for the integrity of the liver
- Cross match: because of low hemoglobin and platelets

➢ Imaging
- Abdominal X-ray: to rule out intestinal obstruction
- Abdominal ultrasound: to visualize and rule out any liver, kidney or abdominal pathology
- ECG and ECHO in view of the palpitations and extremely high blood pressure to check on the functionality of the heart. The ECG also to look out for arrhythmias due to hyperkalemia

(d) Outline your management plan

Answer:

➢ Admit patient
➢ Control blood pressure
- Hydralazine 10mg IV stat followed by 5mg IV every 30 minutes until diastolic pressure is less than 110mmHg (or Labetalol 50mg IV over at least a minute repeated after 5 minutes if necessary with a maximum dose of 200mg)
  - Note: sodium nitroprusside 0.5-8micrograms/kg/min continuous IV infusion till diastolic BP<110mmHg
- Add furosemide 40mg IV stat dose
- When diastolic blood pressure <110mmHg give Nifedipine 20mg PO BD
- Check blood pressure before each administration of hydralazine
- Daily blood pressure measurements and daily weighing

➢ For the hyperkalemia give
- 10mls of 10% calcium gluconate in 10 minutes to protect the heart. Repeat effect after 15 minutes
- 50mls of 50% dextrose over with insulin 10IU intravenously over 15minutes repeat after 2-4 hours if potassium is still raised
- Give furosemide 1mg/kg IV
- If present Kayexalate can be used
- Continuous ECG monitoring

- Continuous potassium monitoring
- If above measures failure refer for hemodialysis

- Cover on antibiotics: ceftriaxone 1g IV BD while awaiting blood culture and Widal antigen test results
- Repeat Urinalysis, Urea, electrolytes and creatinine after blood pressure controlled. Serial measurements if they are still deranged
- Before discharge counsel patient on diet (DASH diet), reduced salt intake, exercise and lifestyle modification
- Discharge on Nifedipine 20mg PO BD and review in a week to check blood pressure and look out for any other new developments.

29. Chanda a 24-year-old man is admitted complaining of headaches and confusion. His headache had developed over the past 3 weeks and has become progressively more severe. The headaches are now persistent and diffuse. He has lost 10Kg in weight over 6 months and has recently become increasingly more confused. His speech is slurred. While in AMEU he has a generalized tonic-clonic convulsion.

    Examination reveals that he is wasted and weighs 55kg. His temperature is 38.5ºC and has oral candidiasis but has no lymphadenopathy. Prior to the fit neurological exam showed him to be disoriented in time place and person with no focal neurological signs. Fundoscopy shows papilledema. The rest of the exam is normal. You order an HIV test and comes out positive for HIV-1.

Investigations:
Hb: 12.2g/dL
WCC: 12.1 X 10^9/L
Platelets: 365 X 10^9/L
K: 3.9 mmol/L
Sodium: 126 mmol/L
Creatinine: 73 umol/L
Urea: 6.2 mmol/L
Serum Glucose: 5.6 mmol/L
CD4: 22 cells/mL
Measured Osmolality: 255 osm/L

(a) What would be the cause of this man's headaches, confusion and fits? (name 3)

Answer:

- Cryptococcal meningitis
- CNS Toxoplasmosis
- Neurosyphilis
- Tuberculous meningitis

(b) What is his HIV WHO clinical stage?

Answer: WHO Stage 4

(c) Why is his sodium low and why is he having papilledema?

Answer:

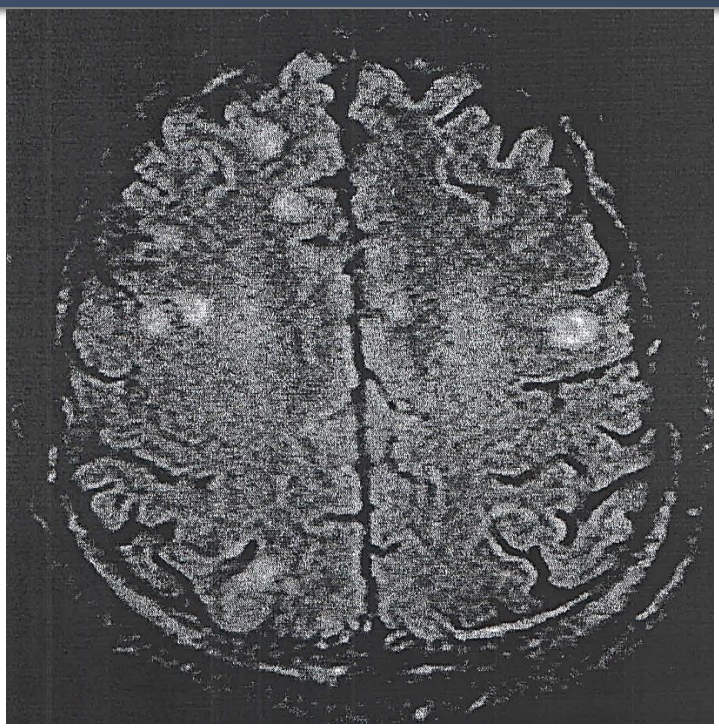
The low sodium may be attributed to the CNS opportunistic infection that causes release of ADH (syndrome of inappropriate ADH secretion) which retains water resulting in a Euvolemic type of hyponatremia and because of the CNS opportunistic infection and reabsorption of water there is increased intracranial pressure leading to papilledema.

(d) What further test should you order

Answer:

- Lumbar puncture for:
  - CSF microscopy, culture and sensitivity
  - CSF biochemistry
- Rapid diagnostic test for malaria
- Rapid plasma reagin (RPR) for syphilis
- Serum cortisol
- CT/MRI of the brain

A CT was done and the following Image was obtained



(e) What is the most likely diagnosis?

Answer: CNS Toxoplasmosis

(f) How would you treat this man and include the dosing?

Answer:

- Regimen one: Loading dose of pyrimethamine 200mg (loading dose 200mg, then 50mg daily) combined with sulfadiazine (2-4g/day) and folinic acid (10-20mg/day)
- Regimen two: Fansidar (Pyrimethamine 25mg + Sulfadoxine 500mg) + Folinic acid 10-20mg/day
    - Dose: 525mg (2 tabs) PO BD for 2 days and then 1-tab PO/day, if patient is very critical add Doxycycline 100 PO BD.
- Note: Clindamycin and pyrimethamine may be used in patients allergic to sulphonamide
    - Regimen 3: Pyrimethamine and Folinic acid plus Clindamycin 450mg 8 hourly
- Duration of treatment is 6 weeks or 3 weeks after complete resolution of lesions on CT.
- Continue suppressive therapy for life: Pyrimethamine 25mg/day + Sulfadiazine 2g/day + folinic acid 5-10mg/day.

HAART should be initiated as soon as the patient is clinically stable, approximately 2 weeks after acute treatment has begun to minimize the risk of IRIS.

Also administer: dexamethasone 8mg IV stat and then 4mg IV DIQ till the suppressive/maintenance therapy: Fansidar 1 tab per day should be continued. Suppressive therapy (Secondary prophylaxis) can be stopped when the CD4 count is more than 200 for 6 months.

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