2nd Edition

KSU 1427 COLLEGE OF MEDICINE

Team Presents

Clinical Medicine

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بعد الجهد المتواصل... وعمل الفريق الدؤوب ....وكفاح شق طريقه عبر صعاب هذه المادة العظيمة
نضع بين أيديكم خلاصة عطر استخلصته أيادي طلاب وطالبات فريق الميدسن

مذكرة 427 – الجزء الأول

وبإسهام كبير من أخينا عمر بن حسين .. من دفعة 426

خضعت هذه الملزمة للتنقيح والتعديل خلال فترة الإجازة الصيفية .. لكي نرتقي بالعمل إلى رفيع مستواكم ..
نتمنى ان نكون قد وفينا ما وعدناكم به .. و أن نكون قد نلنا استحسانكم في كل ما قدمنا
والتمسوا لنا العذر إن بدر منا أي تقصير
كل ما نريده ....دعوة في ظهر الغيب
بارك الله لنا العمل وتقبل منكم الدعاء..

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Diabetes Mellitus

Dr. Khalid Al-Rubeaan

Objectives :

- What is diabetes mellitus?
- The epidemiology of the diabetes.
- What is the types of the diabetes & pathology of the disease?

What is diabetes ?

- WHO define DM in 1985 as :
  is a disease associated with hyperglycemia as a result of either insulin deficiency or insulin sensitivity problem.
- Note : But is definition is not enough …. And we can't say the diabetes is a problem unless it associated with chronic complication ….
- So… the definition will be :
  Diabetes is metabolic disease associated with glucose metabolism abnormalities as a result of insulin deficiency or insulin resistance that is also related to chronic complication affecting nerves, vessels, kidney…

Epidemiology :

- The lowest percentages of the DM were recorded in rural area of Indonesia 0.2%.
- The highest percentages was recorded in Pima India was 50%.
- The prevalence of diabetes in KSA :
  - The prevalence in 1970 was 2.2 %.
  - The prevalence in 1980 was 5 %.
  - The prevalence in 1990 was 12.3 %.
  - The prevalence in 2004 was 24.7 %.

So .. the curve is going up.

- The in pt. admission is 34% diabetic pt., and they are in the hospital either due to diabetes directly or to it's complication.
- A survey was done among CCU pt. in Riyadh, the result was 50 % – 53 % of the pts were diabetic .And after one week 80% of pts who died were diabetic.

So we have very high mortality here in KSA

An other study .. we follow 10,000 pt. … after 10 years we calculate the mortality rate which was 11% … which mean 11% of the diabetic in KSA die every year. Which approximately equal to 200,000 deaths every year!!!

Diabetes classification (Types)

1) Type I DM (10%) :

- Very easy type occurs in children age.
- The youngest case was reported to a fetus before delivery.
- There is two peaks were the patient's usually present : 1st peak in age of 6-7 yr, & 2nd peak in age of 13-18 yr.
- The insulin level usually very low. And they usually develop DKA.
- This type of diabetes is genetic disease (V. Imp), However type II DM is a familial disease.
- **The genetic of DM I :** the gene located on the HLA of chromosome 6 (in the short limb) in DR 3 & 4. So, what happens in Type I DM ? What happens is that, for some environmental or unknown reasons the gene triggering occurs which will produce the ICA (islet cell antibody) this will attack the beta cell. This triggering of the gene occur either because of environmental factor OR spontaneously (!! الله أعلم ... مين شغله). In environmental factor like (coxsackie B & mumps virus) where they trigger the gene expression of the ICA, because the B lymphocyte produces antibody against this viruses by activation the gene which located adjacently to gene which produces the ICA, this means there is a chance that the ICA will also gets activated. Simply if you have that bad gene, does not mean that you will get the disease. You have first to activate that gene, for example… If you do a screening test to school children you will find a lot of them have DR 3 & 4 but NOT activated. But if you find an activated & patent ICA gene. Does that means that the child has the disease??? The ANSWER is NO, only 30% of the people who produce antibody get that disease… for unknown reason that ICA which has been produced in the rest (70%) doesn't attack the beta cell.

2) Type II DM (90%) :

- Occur in the old, the insulin level begin with high level then it switches to normal and finally to low. But usually the patients come at the last phase.
- The problem in this type is the peripheral tissue because the insulin resistant... that mean the beta cell have to put more insulin to fight that resistant that's why the patient first have normal glucose level then high insulin level. But after time the beta cell get fatigue & the insulin will fall to the normal level & the glucose rise result in mild hyperglycemia. If the patient not treated he will develop complete picture of DM that mean hyperglycemia & hypoinsulinima. There is no DKA in this type because of the insulinpenia (low insulin level) is enough to fight against DKA but not enough to lowering the glucose level. It is a familial disease.

The Risk to develop Type DM II ?

- If there is no DM in the family your chance to be diabetic is 5%.
- If either your mother or father have DM your chance to be DM will be 15%.
- If your mother & father have DM your chance to be DM will be 45%.
- If either your mother or father & one of the brother or sister have DM your chance to be DM will be 70%.

Can we reduce this percentage??

- Yes, you can reduce that by running 20 min. 3 times a week this will reduce 2/3 of the risk.
- If we maintain the normal body weight this will reduce the half of the risk.
- If you eat a healthy food this will reduce 1/3 of the risk.
- **Example :** Person have 45% risk to develop DM… we ask him to run every week 3 times for 20 min., this will reduce the risk to 15%. And we ask him to maintain his normal body weigh this will reduce the risk to the 7.5%, and finally we ask him to eat healthy food this will reduce the risk to 2.5%.

We reduce the risk from 45% to 2.5% … So we can prevent type II DM.

How familial disease differ from the genetic one ?

- The familial one caused by expression of multigenes together, that's why they call it a polygenic disease because there are many genes work togather like obesity gene, insulin resistant gene, beat gene function…
- However in Genetic disease we have just one gene.

3) IGT (impaired glucose tolerance) :

- This is the stage before the person gets type II diabetes.
- Note : if you catch the patient in that golden phase you can prevent type II diabetes up to 80%.
- What we do for them ? simply we give them synthesizer or we ask them to loss weight & to do exercise… we will notes that the insulin will come up again.
- It is a phase to type II diabetes.

4) Secondary DM :

- Rare, usually secondary (trauma to the pancreas which lead to remove it, recurrent pancreatitis, Cushing syndrome, glucagonoma, excess growth hormone secretion, acromigaly), or very rare genetics diseases.

5) Gestational DM (temporary DM) :

- This is due to placenta secrete human lactogens.
- This human lactogens like growth hormone induce insulin resistant.
- This is temporary DM that mean when the pregnancy terminate the DM will disappear. But there is a chance to continue after pregnancy.
- If this is the first time to be Diabetic with pregnancy the chance is 7-8%, if it's the second time the percentage will be 30%, and if it's the third time it will rise to 70%.
- The effect (danger) of gestational diabetes will be on the baby not on the mother because it can cause congenital malformation, intrauterine death… etc.

	Age	Weight	Insulin level	Ketone body production	Familial	Genetic
Type I (10%)	Children	thin	Very low	+ve **DKA** is common	-ve	+ve DR 3 & 4
Type II (90%)	Old	Obese	Normal Or high Or low	- ve	+ve	-ve
IGT (Less than 1%)						
Secondary DM Less than 1%						
Gestational DM (Temporary DM)						

- When a person has sedentary life, the insulin resistance will begin AND when the calories intake increase he/she will have obesity … when those two occur (insulin resistance + obesity) he/she will get type II DM.

Management & Complications of Diabetes Mellitus

Diagnosis of DM :

- This is very important because a lot of patient is wrongly diagnosed as diabetic, and a lot of diabetic patients are missed and they diagnosed to be normal which in fact they are diabetic. So we will know form each test the criteria for diagnosis.

❖ Fasting Blood Glucose :

- For this test we ask the patient to fast before he or she came to perform the test, and then we measure the blood glucose level.
- So if we found that the fasting blood glucose is high this mean for sure the patient is diabetic this mean this test is a specific test but if the patient has a normal fasting blood glucose in this situation we can't say you are not diabetic. This mean this test is not sensitive test.
- Note : you have to take minimum 3 reading to diagnose the patient as diabetic… so please don't jump and make diagnosis from single reading.

Random Blood Sugar :

- For this test we take blood sample from the patient in any time (this is why they call it random), then we measure the glucose level.
- So if we found that this patient has normal blood glucose level this mean he/she for sure is not diabetic but if the patient has high RBS we can't say you are diabetic.
- This means that this test is sensitive but is not specific.

Oral Glucose Tolerance Test : (the best)

- For this test you actually ask the patient to fast prior to the exam then you take one reading while the patient fasting then you give the patient constant load of glucose then you measure again the glucose level in the blood.
- In fact this is both specific and sensitive test because you are measuring the fasting glucose level and random one also.

Test to Follow the Patient :

- **Hemoglobin A1c :** how this hemoglobin formed ? actually when the protein in general start to be formed, in the middle glycation process (attachment of glucose to the protein) occur… the percentage of glycation in human normally is 5%. HGA1c can give us reading for the past 3 month (because the RBC has half life 3 month) so it can give us a reflection how good the diabetes at that time.

Complications of DM :

A. Acute Complication of Diabetes Mellitus :

- Hypoglycemia.
- DKA.
- Hyperosmolar non-ketotic coma.

1. Hypoglycemia

• General characteristics :

- ✓ **The primary organ at risk in hypoglycemia is the brain**: the brain uses glucose as its main energy source (except when using ketone bodies during fasting).
- ✓ Unlike other tissues, the brain cannot use free fatty acids as an energy source.
- ✓ Hypoglycemia is really due to an imbalance between glucagon and insulin.

• Physiologic Responses to Hypoglycemia :

- ✓ When glucose levels approach the low 80s, insulin levels decrease. This decrease is normally enough to prevent hypoglycemia.
- ✓ As glucose levels decrease further, glucagon levels increase (glucagon is the first line of defense against more severe hypoglycemia).
- ✓ Epinephrine is the next hormone to combat hypoglycemia. Cortisol and other catecholamines also play a role.
- ✓ As glucose levels decrease into the 50s and below, symptoms begin.

• Causes :

1. **Drug-induced :** Taking too much insulin is a common problem in diabetic patients attempting tight control of their disease.
2. Insulinoma.
3. **Ethanol ingestion**: due to poor nutrition that leads to decreased glycogen (loss of glycogenolysis).
4. Postoperative complications after gastric surgery (due to rapid gastric emptying).
5. Adrenal insufficiency.
6. Liver failure.

- **Clinical features :**
  - ✓ Symptoms occur at a blood glucose level of 40 to 50 mg/dL.
  - ✓ Sympathetic overactivity cause sweating, tremors, increased BP and pulse, anxiety, and palpitations.
  - ✓ **Neuroglycopenic symptoms** (decreased glucose for the brain - CNS dysfunction), resulting in irritability, behavioral changes, weakness, drowsiness, headache, confusion, convulsions, coma, and even death
- **Diagnosis :** Blood glucose level :
  - ✓ Symptoms generally begin when levels drop below 50. However, there is no cutoff value to define hypoglycemia.
- **Treatment :**
  - ✓ Acute treatment of hypoglycemia
    - ➢ If the patient can eat, give sugar-containing foods; if not, give intravenous dextrose (50ml of 50% dextrose into a large vein).
    - ➢ Intramuscular glucagon acts rapidly by mobilizing hepatic glycogen, and is useful in when intravenous access in difficult.
  - ✓ Appropriate management of underlying cause (e.g., diabetes, insulinoma)

2. Diabetic ketoacidosis (DKA)

- **General characteristics :**
  - ✓ DKA is an acute, life-threatening medical emergency that can occur in both type I and type II diabetic patients (more common in type I).
- **Pathogenesis**
  - This is secondary to insulin deficiency and glucagon excess, both of which contribute to accelerated severe hyperglycemia and accelerated ketogenesis.
  - Severe hyperglycemia leads to an osmotic diuresis, which causes dehydration and volume depletion.
  - Peripheral lipolysis leads to increase circulating fatty acids, which are converted in the liver to acidic ketones , leading to metabolic acidosis.
  - ✓ **Consequences of DKA include:** hyperglycemia, ketonemia, metabolic acidosis, and volume depletion.
- **Precipitating factors :**
  - ✓ Any type of stress or illness (e.g., infectious process, trauma, myocardial infarction, stroke, recent surgery, sepsis, GI bleeding)
  - ✓ Inadequate administration of insulin.

- **Clinical features :**
  - **Marked dehydration** , orthostatic hypotension, tachycardia secondary to water and electrolyte loss from the kidney.
  - **Kussmaul's respiration :** (rapid, deep breathing) as a sign of respiratory compensation to metabolic acidosis.
  - "**Fruity**" (acetone) breath odor.
  - Abdominal pain (more common in children) that may mimic surgical acute abdomen.
  - Altered consciousness, drowsiness, and frank coma may occur if not treated.
  - Nausea and vomiting.

- **Diagnosis :**
  - The diagnosis is based in demonstration of **hyperglycemia** in combination to **acidosis** and **ketosis.**

✓ **Hyperglycemia:** serum glucose > 250 mg/dL .

✓ **Metabolic acidosis**

- Blood pH <7.3 and serum.
- Increased anion gap: due to production of ketones.

✓ **Ketonemia** (serum positive for ketones) and ketonuria. .

- **Other laboratory value abnormalities :**
  - **Potassium:** Because of the acidosis, hyperkalemia may be present initially, although total body potassium is low (because the absence of action of insulin which allows potassium to shift out of the cell). As insulin is given, it causes a shift of potassium into cells, resulting in a hypokalemia, and this can happen very rapidly.
  - **Hyponatremia**—Serum sodium decreases because of the osmotic shift of fluid from the ICF to the ECF space. Total body sodium level is normal.
  - Phosphate and magnesium levels may also be low.
- **Treatment :**

The aim of treatment is to replace fluid and electrolyte loss, replace insulin, and restore acid-base balance over a period of about 24 hours.

✓ **Insulin**

- Give insulin immediately after the diagnosis is established.
- Continue the insulin until the anion gap closes and metabolic acidosis is corrected, then begin to decrease the insulin. Give SC insulin when the patient starts eating again.

✓ **Fluid replacement (normal saline)**

- Give fluids immediately after the diagnosis is established.
- Add 5% glucose once the blood glucose reaches 250 mg/dL to prevent hypoglycemia.

✓ **Replace potassium prophylactically with IV fluids.**

- Initiate within 1 to 2 hours of starting insulin.
- Ensure adequate renal function (urine output) before administering these.
- Monitor potassium, magnesium, and phosphate levels **very closely** and replace as necessary.

❖ **N.B.**

- Be certain that the patient is not hypokalemic before giving insulin.
- Cerebral edema (presenting with headache and reduced conscious level) could develop as complication of therapy if glucose levels and osmolality decrease too rapidly.
- In general , the Treatment of DKA is insulin, fluids, and potassium

3. Hyperosmolar hyperglycemic nonketotic syndrome (HHNS)

- **General characteristics :**

✓ A state of severe hyperglycemia, hyperosmolarity, and dehydration typically seen in elderly type II diabetic patients, without significant ketosis.

✓ Pathogenesis

- Low insulin levels lead to hyperglycemia. Severe hyperglycemia causes an osmotic diuresis, leading to dehydration.
- Ketogenesis is minimal because a small amount of insulin is released to blunt counterregulatory hormone release (glucagon).

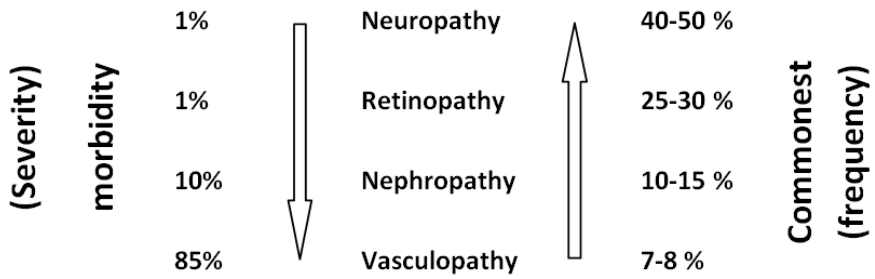
- Ketosis and acidosis are typically absent or minimal.
- Severe dehydration is due to continued hyperglycemic (osmotic) diuresis. The patient's inability to drink enough fluids (either due to lack of access in elderly/bedridden patients or to inadequate thirst drive) to keep up with urinary fluid losses exacerbates the condition.

✓ Precipitating events are similar to those of DKA.

- **Clinical features:**
  - Signs of extreme dehydration and volume depletion → hypotension, tachycardia.
  - Thirst, oliguria.
  - CNS findings and focal neurologic signs are common e.g. seizures (secondary to hyperosmolarity).
- **Diagnosis :**
  - ✓ **Hyperglycemia:** serum glucose > 600 mg/dL.
  - ✓ **Hyperosmolarity.**
  - ✓ Serum pH .7.3 (**no acidosis**)
- **Treatment**
  - Fluid replacement is most important (normal saline).
  - Insulin

	DKA	HHNS
Pathogenesis	Insulin deficiency → hyperglycemia, ketosis, acidosis, dehydration	Insulin deficiency →hyperglycemia, hyperosmolarity, profound dehydration
Lab. Findings	Hyperglycemia (<250) Metabolic acidosis (anion gap), serum pH ≤ 7.3 Ketosis	Hyperglycemia (<600) Hyperosmolarity Serum pH ≥ 7.3 (no acidosis)
Treatment	Insulin, IV fluids, Potassium	Aggressive IV fluids, Insulin

B. Chronic Complication :



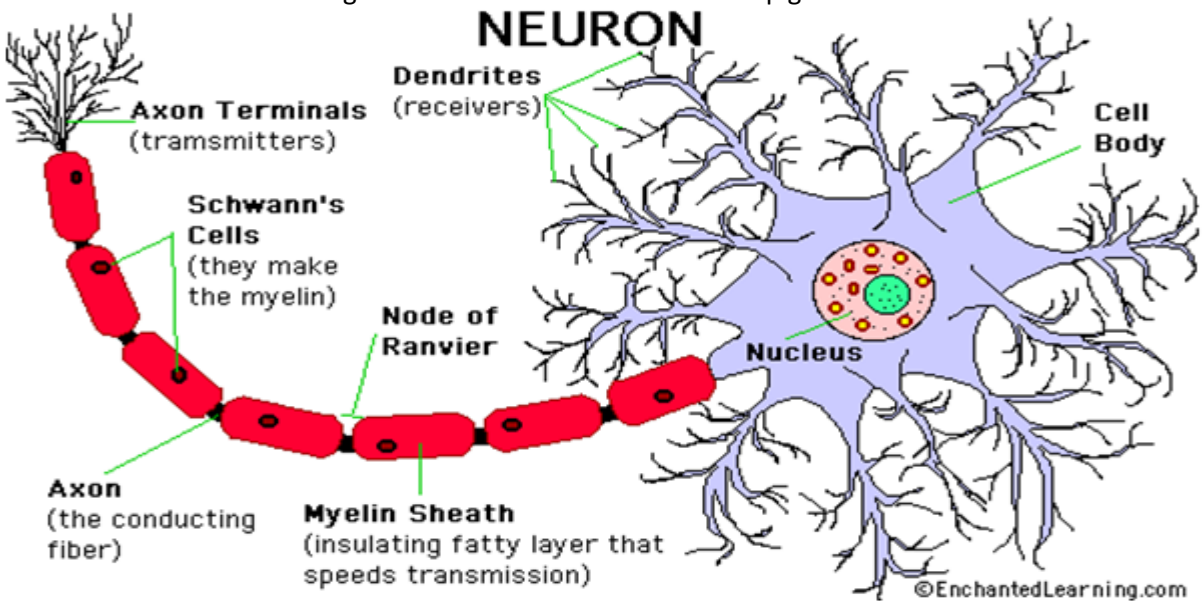
يعني اكثر واحد في Mortality & Morbidity هو Vasculopathy

و اكثر واحد في حدوثة هو Neuropathy

1. Neuropathy :

A. Note : the nerves are not dependant on insulin to take glucose like other cells… it will not affected by low insulin level.

B. But the nerves cells are encircled by shwann cell which work as facilitator to increase the velocity of conduction of the signals… which need insulin to take up glucose.



C. Some cells of the body can form energy from other source than glucose by breakdown the fat but other cells can't so(like shwann cell), these cells used other way (sorbitol pathway) → produce energy from protein & CHO → the problem in this way is the material produced by this way ((sorbinal)) → sorbinal accumulate in Shwann cells.

D. The sorbinal is very viscous material which will lead to increase the oncotic pressure and consequently the fluid will be absorbed, then shwann cell get swelling, and as the shwann cell encircles the axon of the nerve this will lead to pressure symptom on the nerve like **Tingling sensation**. (وخزات أو نغزات الدبوس)

E. After that if the patient neglect that sensation and the blood glucose still not control (the insulin level still low) the swilling get bigger and bigger that will cause more pressure on the axon of the nerve which will produce pain & hot sensation.

F. If the patient still neglect, and the insulin level still low then the more pressure will lead to complete cut to the nerve & subsequently complete loss of sensation.

Is it reversible process or not ?

- Yes it is reversible, unless complete cut to the nerve occur, in that time it is irreversible process.
- In phase of sorbitol pathway & pressure on schwann cell → by given the patient insulin → to switch off the sorbitol pathway, So :
  a. Sorbitol (sorbinal) decrease.
  b. Swelling of schwann cell decrease.
  c. But the patient fell worse by pain (because the sensation come back by release the pressure), but after time the pain decrease slowly.

■ Manifestation of the neuropathy :

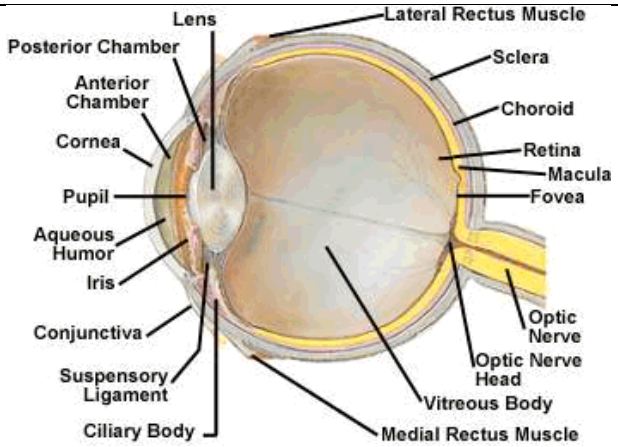
A. Either to be poly which is the commonest or mono neuropathy OR some thing called mononeuritis multiplex.

B. **Mononeuritis Multiplex :** is problem in the blood vessels wich supply ether the vessels or the nerves… so some time the patient came to you complain from dapple vision which was result from ischemia to the blood supply to the nerves which innervate the ocular muscles … and this is reversible just control the DM and he/she will be fine.

C. But the major problem is **Autonomic neuropathy** because there is problem with impotence, urinary retention & gastroparesis…etc but the autonomic neuropathy is not that common usually affect around 3%.

D. The treatment is <u>only</u> control diabetes; other is just symptomatic like analgesic for the pain… etc.

2. Retinopathy :



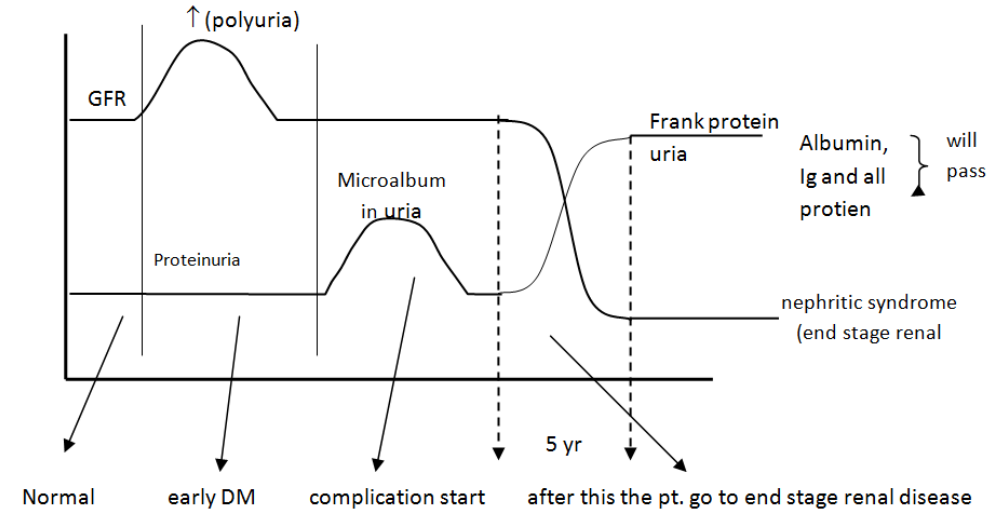
- Eye complication in the diabetic patient may be affect cornea, anterior chamber, lens, posterior chamber or retina. **It can produce :**
  - Cataract → affect lens (very frequent in DM).
  - Glaucoma → affect anterior chamber.
  - Retinopathy → affect retina.
- But we consider here the retina because it is related to blindness, and as we all know that the retinal artery is very delicate.
- What happen in the diabetic patient ? the rod and cons when the fell of inertia (because there is no insulin to push the glucose inside the rod & cons) they send signals to enhance the blood supply by make more and more branch of the retinal artery (prolefertive retinopathy)… but the problem in that the new branches is very delicate and it can get burse from minimal trauma or even just coughing. So when these vessels get burse the patient bleed in the posterior chamber (vitreous hemorrhage) after that there will be a clot and then organification of that clot so the patient will have retinal detachment, and this detachment responsible for the blindness which happen to the diabetic patient.
- So if the patient has prolefertive retinopathy can we regress the disease ?
  - Control the DM, will return the pt. to normal. So the control of DM can treat retinopathy.
- If the patient in risk of bleeding bcuz he has prolefertive retinopathy we can use LIZER cutely to obstruct that new vessels. So the LIZER <u>protect</u> the vision but it will <u>not improve</u> it. But <u>ones the retinal detachment occur there is NO treatment</u>.

3. Nephropathy :

- The hydrostatic & somatic pressure helps in filtration of blood through the glomeruli to remove the toxin in the urine.
- Normally there are Small pores to pass just small certain thing in the urine, But in DM the very high glucose will make alignment of the vessel getting shrink that will increase the pores size. So the first protein pass the small protein (micro albumin), the name of this phase in diabetic patient is **microalbuminuria**. After that the albumin will get deposit in that pores and causing fibrosis which will lead to further increase in the size of that pores and this is what called **glomerulosclerosis**, so the bigger protein will get leak now from that pores.

- So, to summarize : first the pt. begin with **microalbuminuria** then **proteinuria** then **overt proteinuria** and finally **complete sclerosis (end stage renal disease).**

GFR = Glomerular filtration rate



To explain that figure :

A. Normal : GFR is normal and protein is almost zero.

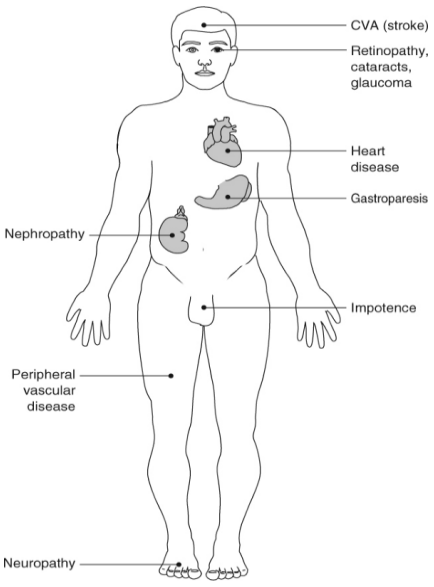
B. DM : actually in diabetic patient the GFR will increase bcuz of polyuria and polydipsia but protein will remain the same, after time when the microalbuminnuria phase start and after that proteinuria, the protein excretion will increase and the GFR will decrease. <u>It is very important phase</u> because the treatment start from this phase we use ACEI to decrease the hydrostatic pressure from the glomerulus. When you decrease the hydrostatic pressure the protein will not leak so you will decrease the sclerosis in the same time, so you can delay the proteinuria.

C. Fact : studies show that you can delay the renal failure <u>15 year</u>!

D. But when the patient with in the microalbuminuria phase and he progress to proteinutia and then <u>nephritic phase</u> (more than 3g of protein per 24hour) in this situation we will <u>wait 5 years</u> and the patient will start **end stage renal disease.**

4. Vasculopathy :

- **Vasculopathy (Macrovascular Complications)**
  - ✓ The main problem is **accelerated atherosclerosis**.
  - ✓ The manifestations of atherosclerosis include the following:
    - <u>Coronary artery disease (CAD) :</u>
      - Risk of CAD is two to four times greater in diabetic than in nondiabetic persons.
      - **Most common cause of death in diabetic patients.**
      - Silent myocardial infarctions are common.
    - <u>Peripheral vascular disease</u>—in up to 60% of diabetic patients.
    - <u>Cerebrovascular disease</u> (strokes).

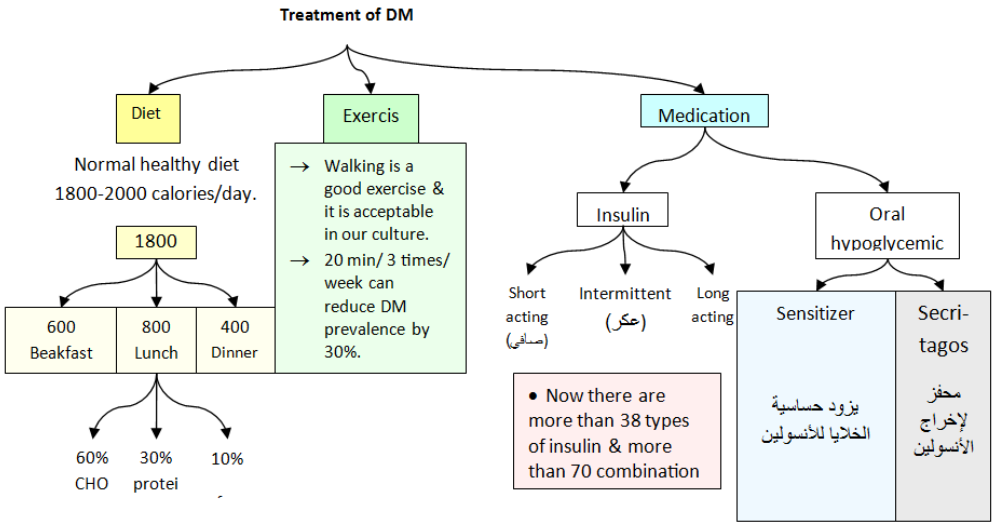


✓ **<u>N.B.</u>**

- The risk of coronary events is greatly reduced if the patient can eliminate or reduce other major cardiovascular risk factors (smoking, HTN, hyperlipidemia, obesity).
- All the other three chronic complications of diabetes are caused by **Microvascular diseases** (not Macrovascular).

Management of Diabetic Patients

- **All patients with diabetes require :**
  - ✓ Diet Therapy.
  - ✓ Regular exercise to reduce cardiovascular risk.
  - ✓ Oral hypoglycemic agents in Type II diabetes when conservative therapy (diet and exercise) fails.
  - ✓ Insulin : It is indicated :
    - In patients who present with ketoacidosis.
    - Usually in those under 40 years of age.
    - When hypoglycemic agents did not achieve satisfactory control of type II diabetes.



- **Diet Therapy :**

Recommendation of food for diabetic patients should :

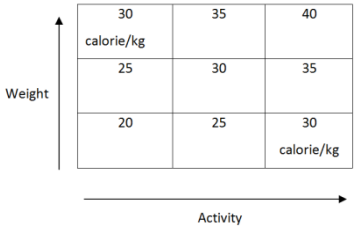
- Be low in sugar (though not sugar free).
- Be high in starchy carbohydrate (especially foods with high glycaemic index which is slowly absorbed and thus prevent rapid fluctuation in blood glucose). Carbohydrate should represent about 40-60% of total energy intake.
- Be high in fibers.
- Be low in fat (especially saturated fats) which should represent less than 35% of total energy intake.
- Include protein representing about 15% of total energy intake (1gm per kg ideal bodyweight).

The nutrient load should be spread throughout the day (three main meals with snacks in between and at bed time), which reduces swing in blood glucose.

<u>Normal healthy diet 1800-2000 calories/day.</u>

a. 600 → break fast.
b. 800 → lunch (60% CHO, 30% protein, 10% fat).
c. 400 → dinner.

- **Rule of 30-40 calories intake :**



- ## Exercise :
  - People with diabetes should accumulate a minimum of 150 minutes of moderate to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise.
- ## Oral Hypoglycemic Agents :
  - Use these in type II diabetic patients when conservative therapy (diet and exercise) fails.
  - Start with one agent (metformin or sulfonylurea are common choices). If monotherapy fails, use two agents from different classes in combination. Each agent has advantages and disadvantages, so clinical judgment is required in selecting the initial agent.

1. **Biguanides:** e.g. Metformin.
   - ✓ It reduces the rate of gluconeogenesis, and hence hepatic glucose output, and increases insulin sensitivity.
   - ✓ It does not affect insulin secretion, does not induce hypoglycemia and does not predispose to weight gain. It is thus particularly helpful as a monotherapy in overweight patients.
   - ✓ May be given in combination with sulfonylureas when a single agent has failed to control diabetes.
   - ✓ **Adverse effects include** anorexia and diarrhea. Lactic acidosis has occurred in patients with severe **hepatic or renal disease**, and metformin is **contraindicated** when these are present.

2. **Sulfonylureas :** e.g. Glibenclamide, Tolbutamide.
   - ✓ These act upon the beta-cell to promote insulin secretion.
   - ✓ They can cause hypoglycemia which could be fatal.
   - ✓ Sulfonylureas should be used with care in patients with liver disease. Patients with renal impairment should only be given those primarily excreted by the liver.
   - ✓ Tolbutamide is the safest drug in the very elderly because of its short duration of action.

3. **Meglitinides :** e.g. repaglinide, netaglinide.
   - ✓ They are short-acting agents that promote insulin secretion in response to meals.
   - ✓ They may lead to hypoglycemia.

4. **Thiazolidinediones" glitazones"** : e.g. rosiglitazones.
   - ✓ They enhance insulin sensitivity.
   - ✓ They reduce hepatic glucose production and also enhance peripheral glucose uptake.
   - ✓ **Adverse effects include :**
     - Weight gain.
     - Edema.
   - ✓ They are contraindicated in heart failure and hepatic impairment.

5. **Alfa-glucosidase inhibitors :** e.g. acarbose.
   - ✓ They delay carbohydrate absorption and thus reduce postprandial glucose peak.
   - ✓ **Adverse effects include** bloating, flatulence, and diarrhea.

- **Insulin :**

There are four main types of insulin :

1. Rapid-acting insulin : e.g. insulin aspart and insulin lispro.
   - ✓ The onset of action is within 15 minutes.
   - ✓ Short duration of action (2-4 hours).
   - ✓ Clear solution at natural pH.
   - ✓ They are the preferred insulin preparation for pre meal bolus.

2. Short-acting insulin : e.g. regular insulin.
   - ✓ The onset of action : 30-60 minutes.
   - ✓ They last for 4-6 hours.
   - ✓ Clear solution at natural pH.
   - ✓ They are the only insulin used in emergencies such as ketoacidosis or for surgical operations.

3. Intermediate acting insulin : Isophane (NPH).
   - ✓ The onset of action : 1-2 hours.
   - ✓ They last for 13-18 hours.
   - ✓ Given once or twice daily.

4. Long- acting insulin : e.g. insulin glargin
   - ✓ Onset of action : 2-4 hours.
   - ✓ They last for about a day.
   - ✓ They are slowly released from the site of injection and thus do not produce a peak after administration, so there is no risk of hypoglycemia.

Metabolic Bone Diseases

Prof. Riad Sulimani

◈ Biochemistry :

- Normal total calcium level in the blood is 2.1-2.5 mmol/l.
- Major source of Vitamin D is from the sun.
- The most potent form of Vitamin D is $1,25(OH)_2D_3$.
- The following are responsible for calcium metabolism:
  - ✓ PTH.
    - ↑ Ca Absorption from GI, ↑ Bone Resorption, ↑ Renal Reabsorption of calcium
  - ✓ Vitamin D.
  - ✓ Calcitonin.
- Calcium enters the body through the small intestine and eventually is excreted via the kidney. Bone can act as a storage depot. This entire system is controlled through a feedback loop; individual hormones respond as needed to increase or decrease the serum calcium concentration

◈ Metabolic Bone Diseases :

1. Hypercalcemia
2. Hypocalcemia
3. Osteoporosis
4. Osteomalacia
5. Other diseases

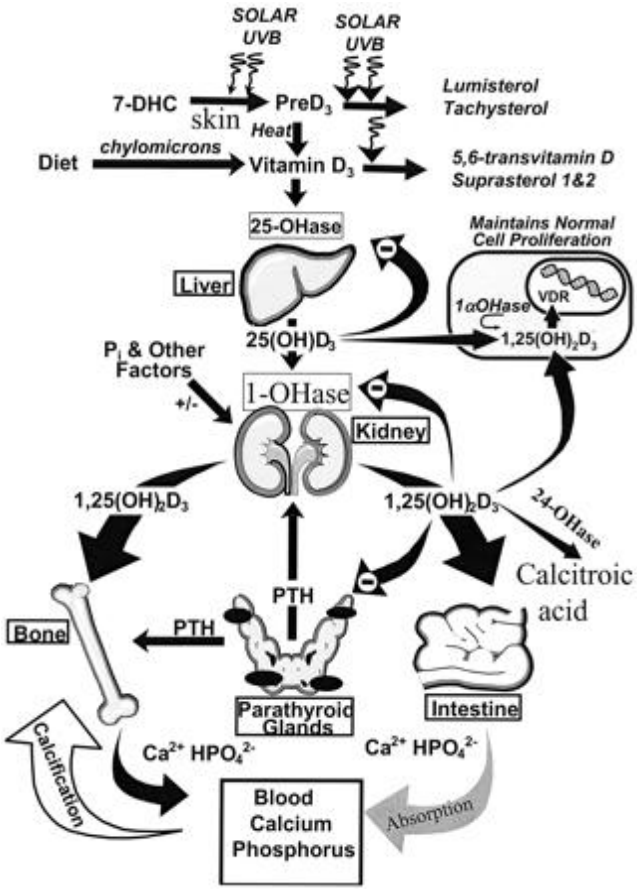
Hypercalcemic states

◈ Primary hyperparathyroidism

- Calcium is high.
- Phosphorus is low.
- **PTH is high.**
- Hyperparathyroidism is mostly from adenoma of one of the glands.
- Primary hyperparathyroidism is the most common cause of hypercalcemia.

◈ Other hypercalcemic states (associated with decreased PTH):

1. Sarcoidosis.
2. Thyrotoxicosis (hypercalcemia due to increased metabolism)
3. Adrenal insufficiency.
4. Drugs (e.g. Thiazides).
5. Hypervitaminosis D & A.
6. Immobilization.
7. MALIGNANCY. (e.g. multiple myeloma, lung cancer,…)



◈ Clinical Features:

- Symptoms of hypercalcemia depend on the underlying cause of the disease, the time over which it develops (rapid increases in calcium cause more severe symptoms), and the overall physical health of the patient.
- Mild elevations in calcium levels usually have few or no symptoms.

Increased calcium levels may cause the following "**Stones; Bones; Abdominal Moans; Psychic Groans":**

☒ **Renal "stones"**
- Nephrolithiasis
- Nephrogenic diabetes insipidus
- Dehydration
- Nephrocalcinosis

☒ **Skeleton "bones"**
- Bone pain
- Arthritis
- Osteoporosis
- Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)

☒ **Gastrointestinal "abdominal moans"**
- Nausea, vomiting
- Anorexia, weight loss
- Constipation
- Abdominal pain
- Pancreatitis
- Peptic ulcer disease

☒ **Neuromuscular "psychic groans"**
- Impaired concentration and memory
- Confusion, stupor, coma
- Lethargy and fatigue
- Muscle weakness
- Corneal calcification (band keratopathy)

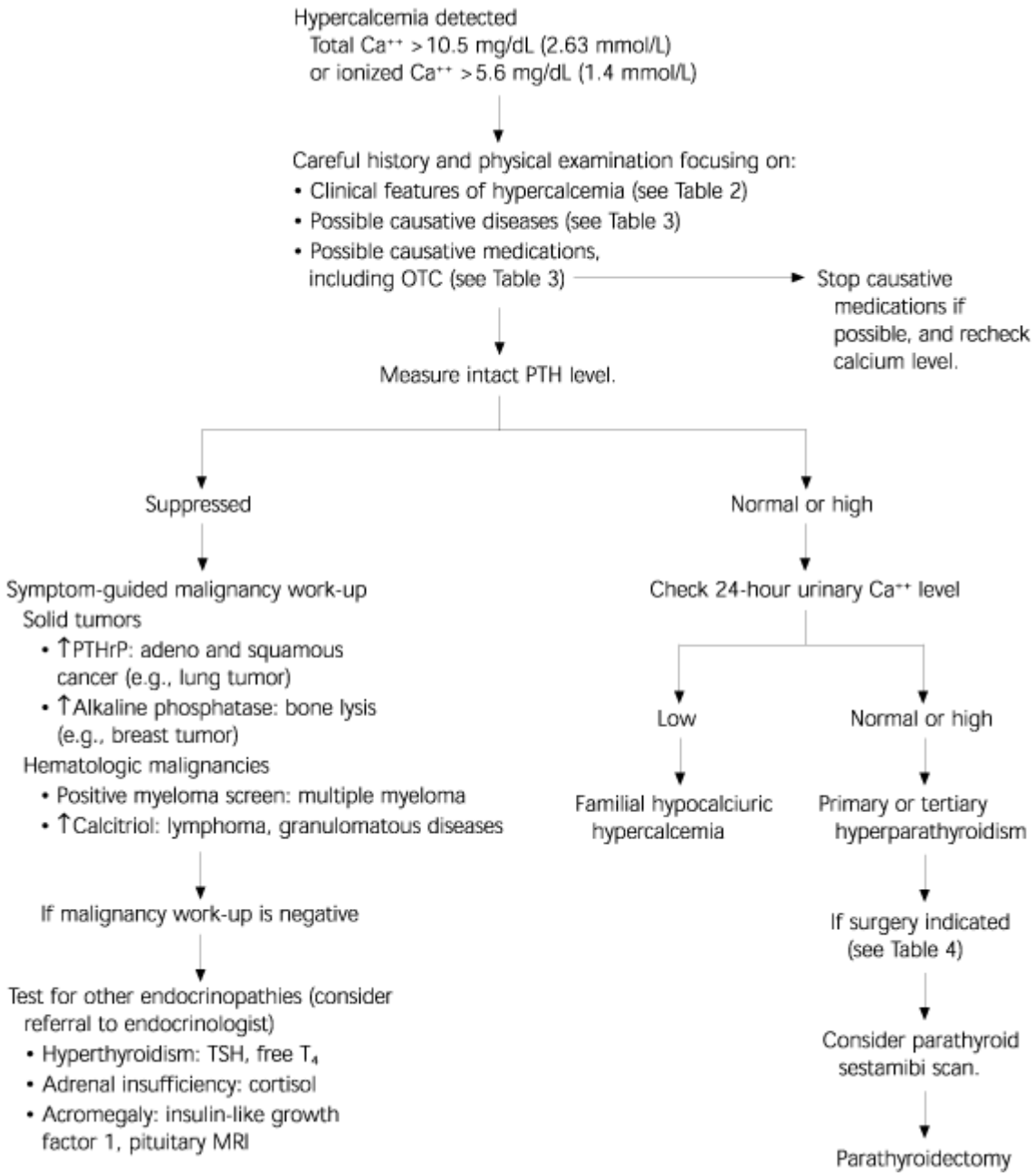
☒ **Cardiovascular**
- Hypertension
- Shortened QT interval on electrocardiogram
- Cardiac arrhythmias
- Vascular calcification

☒ **Other**
- Itching
- Keratitis, conjunctivitis

- Severe elevations in calcium levels may cause coma.
- Elderly patients are more likely to be symptomatic from moderate elevations of calcium levels.
- Hypercalcemia of malignancy may lack many of the features commonly associated with hypercalcemia caused by hyperparathyroidism. In addition, the symptoms of elevated calcium level may overlap with the symptoms of the patient's malignancy.

◈ Treatment of hypercalcemia :

- Remove cause.
- Hydration.
- Calcitonin/bisphosphnates (anti-osteoclastic agent ➔ decreased bone resorption ➔ less calcium goes to the blood from bone).
- Steroids (sarcoidosis, multiple myeloma, lymphoma, and vitamin D intoxification).
- In primary hyperparathyroidism : removal of the adenoma..


Hypercalcemia detected
Total Ca++ >10.5 mg/dL (2.63 mmol/L)
or ionized Ca++ >5.6 mg/dL (1.4 mmol/L)
Careful history and physical examination focusing on:
• Clinical features of hypercalcemia (see Table 2)
• Possible causative diseases (see Table 3)
• Possible causative medications, including OTC (see Table 3)
Stop causative medications if possible, and recheck calcium level.
Measure intact PTH level.
Suppressed
Normal or high
Symptom-guided malignancy work-up
Solid tumors
• ↑PTHrP: adeno and squamous cancer (e.g., lung tumor)
• ↑Alkaline phosphatase: bone lysis (e.g., breast tumor)
Hematologic malignancies
• Positive myeloma screen: multiple myeloma
• ↑Calcitriol: lymphoma, granulomatous diseases
If malignancy work-up is negative
Test for other endocrinopathies (consider referral to endocrinologist)
• Hyperthyroidism: TSH, free T4
• Adrenal insufficiency: cortisol
• Acromegaly: insulin-like growth factor 1, pituitary MRI
Check 24-hour urinary Ca++ level
Low
Normal or high
Familial hypocalciuric hypercalcemia
Primary or tertiary hyperparathyroidism
If surgery indicated (see Table 4)
Consider parathyroid sestamibi scan.
Parathyroidectomy

Hypocalcemia

- There is reduced **free** calcium levels in the blood.
- Causes : **hypoparathyroidism** (commonest), hypomagnesimia (magnesium is required for parathyroid gland function)
- Pseudohypoparathyroidism :
  - ✓ Type 1A : autosomal dominant. Resistance to PTH + somatic features.
  - ✓ Type 1B : isolated resistance.
- Clinical presentations : acute vs chronic. (Chronic moderate hypocalcemia may be completely asymptomatic).
- Clinical Points:
  - ✓ Eye: early cataract
  - ✓ CNS (EXTRAPYRAMIDAL): seizure and dementia

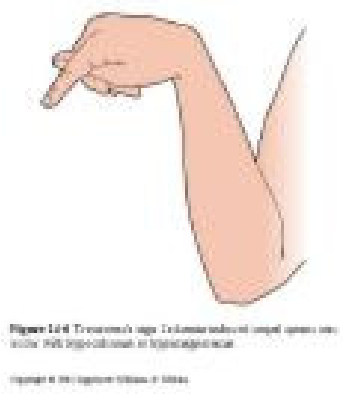
✓ CARDIAC: prolonged Q-T interval which predispose to ventricular tachycardia.

◈ Hypoparathyroidism :

- Low calcium.
- High phosphorus.
- Cause :
  - ✓ Surgical: Accidental removal during thyroid surgery is the most common cause.
  - ✓ Autoimmune hypoparathyroid is rare and it is usually in the young.
  - ✓ Severe vitamin D deficiency.

◈ Clinical presentation :

- Numbness.
- If severe hypocalcemia : tetany.
- **Trosseau sign:** seen when blood pressure in the cuff increases above the systolic blood pressure, the patients starts to feel pain in his hand and will have spasm in the muscles of forearm and hand. The wrist and Metacarpophalyngeal joints flex, the interphalengeal joints hyperextend, and the fingers adduct to each other.
- Chovstek sign (seen when zygomatic arch tapping will cause twitching to the tapped side).



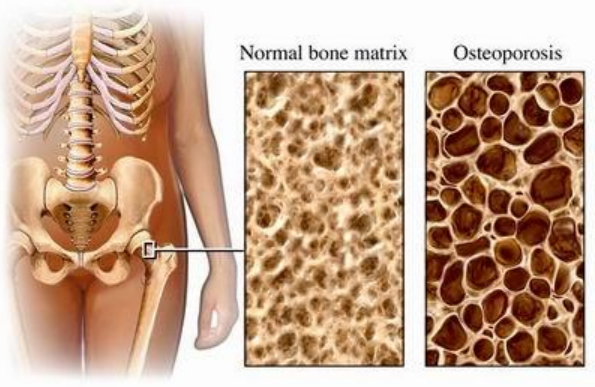
Trosseau sign

◈ Treatment of hypocalcemia :

- Start with Calcium preperations, if it's insufficient, vitamin D should be added.
- If severe with tetany : give 10 cc of 10% calcium gluconate slowly (careful in patients on digoxin).

Osteoporosis

- Definition.
- Differentiating Osteoporosis from Osteomalacia.
- Causes.
- Diagnosis.
- Prevention.
- Treatment.



◈ Definition of Osteoporosis :

- Low bone mass or density with micrarctictural disruption resulting in fracture from minimal trauma.

◈ Causes of Osteoporosis :

- Menopause.
- Old age (depletion of hormones).
- Calcium and vitamin D deficiency.
- Estrogen deficiency (important for bone mass).
- Use of steroids (decrease GI absorption of Ca, increase osteoclastic activity).

◈ Diagnosis of osteoporosis

- Plain x-ray : not very sensitive.
- Dual-energy x-ray absorptiometry **(DXA) (most sensitive)** measuring bone mineral density (BMD) and comparing it to BMD of a healthy woman.
- - 2.5 SD and less below average: osteoporosis.
- Between -1 and -2.5 SD below average: osteopenia.

◈ Treatment of Osteoporosis :

- Prevention: ask the patients to get adequate exposure to the sun to allow the synthesis of vitamin D
- Public awareness measures to reduce incdince of fracture
- Adequate calcium and vitamin D supplements.
- Bisphphosnates : reducing bone breakdown.
- When treating with cortisone, give lowest possible dose

◈ Steroid induced osteoporosis

- **Major impact on: axial** bone (important).

Osteomalacia

◈ Definition of Osteomalacia :

- Reduced mineralization of bone.
- Rickets occurs in growing bone. (Rickets = bowing, occurs in growing bones).

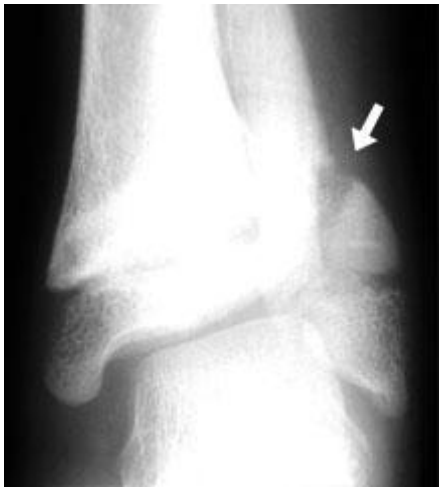
◈ Causes of Osteomalacia :

- **Vitamin D deficiency** (the most common).
- Ca deficiency.
- Phosphate deficiency.
- Vitamin D being affected by:
  - ✓ Liver disease.
  - ✓ Renal disease.
  - ✓ Malabsorption.

- Hereditary forms.
- (Intestinal and gastric surgery).
- Drugs.

◈ Clinical Presentation :

- Bony aches and pains (including dental pain) **Unlike osteoporosis**
- Muscle weakness.



◈ LAB :

- Low serum vitamin D.
- High PTH.
- High serum alkaline phosphatase (bone specific isoform)
- Low Ca level.
- Low PO_4 level.

◈ Radiology :

- X-ray :
  - ✓ Growing bones: rickets
  - ✓ Mature bones. Subperiosteal resorption , **Pathognomonic loosers zones** (psuedofracture)
- Bone scan.

◈ Treatment of Osteomalacia :

- Calcium and vitamin D supplements.
- Sun exposure.
- Results of treatment is usually very good.

◈ Treatment of Osteomalacia :

- Calcium and vitamin D supplements.
- Sun exposure.
- Results of treatment is usually very good.

Paget's disease of Bone

◈ Clinical presentation :

- Two thirds of patients are asymptomatic.
- Incidental radiological finding.
- Unexplained high alkaline phosphatase.
- Large skull, frontal bossing, bowing of legs, deafness, erythema, bony tenderness.
- Fracture tendency: vertebral crush fractures, tibia or femur. Healing is rapid.

◈ LAB :

- High alkaline phosphatase (Bone specific isoform).
- High urinary hydroxyproline.
- High osteocalcin.
- Bone profile : normal.
- Nuclear scanning.
- **X ray :** areas of osteosclerosis mixed with osteolutic lesions.

◈ Complications :

- Sensory deafness.
- Spinal stenosis.
- Osteoarthritis & gout.
- Osteosarcoma.
- Hypercalcemia (immobilization).
- Urolithiasis.

◈ Treatment of Paget's disease :

- Calcitonon.
- Bisphphosphonates.
- Plicamycin (rarely used).

Renal Osteodystrophy

◈ **Pathogenesis.**

◈ **Clinical presentations :**

- Osteitis fibrosa.
- Osteomalacia.
- Low serum calcium.
- High phosphorus.
- High alkaline phosph.
- High PTH 2ry → 3ry hyperparathyroidism (hypercalcemia).

◈ **How is vitamin D carried in blood ?**

◈ **What is VDR ?**

- Clinical applications ?
- Vitamin D-dependent rickets type 2 (lack of functioning VDR 1,25 OH 2 d 3 is very high.

◈ **Extrarenal Production of 1,25 (OH) 2 D3:**

- Macrophages : cause of hypercalcemia in sarcoidosis , lymphoma, and other granulomatous disease (regulated by cytokines & TNF).

◈ **Familial Hypocalciuric Hypercalcemia**

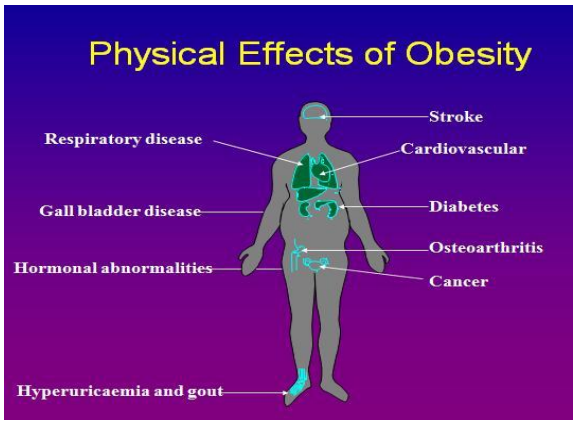
- Autosomal dominant.
- Hypercalcemia : mild ,with mild hypophosphatemia
- PTH : normal or slightly elevated.
- Hypocalciurea.
- Receptor problem.
- Avoid surgery.
- Mechanisms ?
- Management ?

Obesity

Dr. Assim Al-Fadda

Physical Effects of Obesity

- Hypertension
- Type 2 DM
- Coronary Heart Disease
- Gallbladder disease
- Certain Cancers ((Male → Colorectal cancer ,female → endometrial cancer, Brest cancer.



Obesity

- Abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired.
- Presence of an abnormal absolute amount or relative proportion of body fat.

Surrogate measures of adiposity

- Ideal body weight
- Weight
- Anthropometric measures
- Body mass index (BMI):
  - Recommended by WHO
  - Relatively reliable except in:
    - ✓ Extremes of age or height
    - ✓ Very fit individuals with muscular build

WHO recommended definition of obesity (2000)

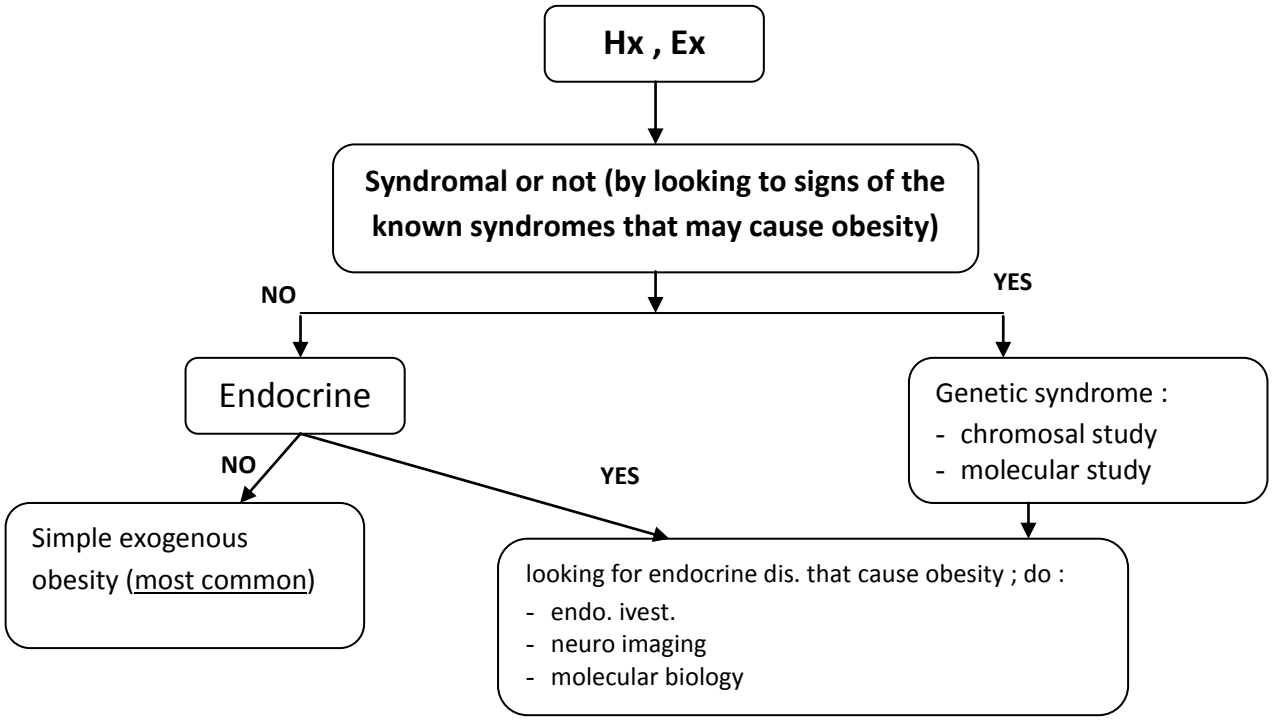
Classification	BMI(kg/m^2)	Risk of co-morbidities
Underweight	**<18.5**	**Low** (but risk of other clinical problems increased)
Normal range	**18.5-24.9**	**Average**
Overweight **Pre-obese**	**>25.0** **25-29.9**	**Mildly increase**
obese **Class I** **Class II** **Class III**	**>30** **30-34.9** **35-39.9** **>40.0**	 **Moderate** **Severe** **Very severe**

Central Obesity :

- Central or visceral obesity is associated with more metabolic disease:
  - ✓ DM_2
  - ✓ Hypertension
  - ✓ Dyslipidemia
- How to assess central or visceral obesity?
  - MRI (they are time consuming and expensive).
  - Dual X-ray absorptiometry (DEXA)
  - Single CT slice L4/L5
  - Waist: hip ratio
  - Waist circumference (based on population)

The Narrowest Circumference Midway Between The Lower Border of The Ribs and The Upper Border of The iliac Crest, Taken from The Side

How to assess cause of obesity clinically?



Obesity in children :

- Growth charts
- BMI-for-age reference charts

⊙ Etiology & Pathogenesis :

- Multifactorial
- Biochemical/Dietary/behavioral pathways.
- Imbalance between energy intake and energy expenditure
- **Body weight is ultimately determined by the interaction of**
  - ✓ Genetic
  - ✓ Environmental and
  - ✓ Psychosocial factors
  - ✓ Acting through several physiological mediators of food intake and energy expenditure

⊙ Etiological classification of obesity:

1- Neuroendocrine disease

- Ventromedial hypothalamus damage:
  - ✓ Tumors
  - ✓ Inflammatory lesions
  - ✓ Other hypothalamic disease
- Cushing disease
- GH deficiency
- Hypothyroidism

2- Drug-induced :

- Hyperinsulinism
  - ✓ Insulin
  - ✓ Sulfonylureas
- Antidepressants
- Antiepileptics
- Neuroleptics
- Steroid

3- Dietary

High carbohydrate diet

- Surplus carbohydrate energy is *not* converted to fat
- Instead, it will lead to accrual of body fat by sparing oxidation of dietary fat

High fat diet

(clinical studies on humans)

- The body fat mass was positively correlated with intakes of total fat, saturated and monounsaturated fatty acids
- Body fat did not correlate with total energy intake in this study
- It was concluded that fat intake, independent of energy intake, may be associated with body fatness
- Thus, at a given level of energy intake, specific sources of energy in the diet may differentially affect
- weight gain.
  (epidemiological studies)
- The relationship between dietary fat and body weight is suggestive but not definitive
- Cross-sectional studies: positive relationship between dietary fat and body weight
- longitudinal studies have shown inconsistent results
- The reasons for this inconsistency are not clear
- Several factors are involved:
  - ✓ Genetic.
  - ✓ Metabolic.
  - ✓ Physical activity.
  - ✓ Smoking habit.
  - ✓ Behavioral factors (dieting in response to weight gain).

4- Reduced energy expenditure

- Resting metabolism:
  - 800 to 900 kcal/m^2/24hr
  - Females < Males
  - Declines with age
- Physical exercise:
  - ~ 1/3 of daily energy expenditure
  - Most easily manipulated
- Dietary thermogenesis (thermic effect of food):
  - Energy expenditure which follow the ingestion of meal
  - May dissipate ~ 10% of the ingested calories
  - In the obese, the thermic effects of food are reduced (especially in patients with diabetes)
- Adaptive thermogenesis:
  - With acute over – or underfeeding
  - Shift in overall metabolism as large as 20%

5- Genetic factors

- Dysmorphic or syndromic obesity:
  - Bardet-Biel syndrome
  - Alström syndrome
  - Carpenter syndrome
  - Cohen syndrome
  - Prader-Willi syndrome
- Single-gene cause of obesity:
  - Leptin and leptin gene deficiency

    injection with leptin will decrease the appetite

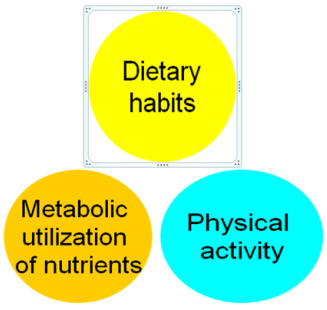
    some obese patients may have resistance to leptin and it's
  - **P**OMC deficiency (Pro-Opio Melano Cortin) hormone secreted by arcuate neucleus (part of center of appetite in hypothalamus) inhibiting appetite.
- Genetic defects with nonsyndromic obesity:
  - Melanocortin receptor system abnormalities: MC4R (Melanocortin-4 receptor) the receptor which POMC is acting on. *(This mutation is the commonest one between other mutations).*
- Genetic susceptibility to obesity:
  - If both parents are obese ~ 80% of the offspring will be obese
  - If only one parent ~ 10% of the offspring will be obese
  - Studies with identical twins:
  - Hereditary factors account ~ 70%
  - Environmental (diet, physical inactivity, or both) account ~ 30% of the variation in the body weight

- The notion that obesity is a genetic disorder is misleading:
  - The prevalence of obesity has increased markedly, world-wide, in recent years, yet genes have not changed.
  - Changes occur within population when migration occurs.

Phenotypic Expression of Genes for Obesity are Environment Specific Obesity is a Disorder of Gene-Environment Interaction

mGPD gene

- The mGPD can be considered a spendthrift enzyme that significantly contributes to obligatory thermogenesis
- The mGPD gene may play a role in the development of obesity if we consider the readiness with which some patients gain weight, and the difficulties the have to lose weight when undergoing a low calorie diets



Factors participating in body-weight maintenance

⊙ Management

1- Behavioral: Diet + Exercise.

- **Diet**
  - Careful Training in :
    - Selection of lower fat, lower carb foods
    - Modified food guide pyramid
    - Increase fruits & vegetables
    - Lower fat preparation techniques
    - Estimation of portion size
  - **Dangers of Atkins diet**
    - High saturated fat and cholesterol: CVD
    - High protein: decline in renal function, urinary calcium losses (osteoporosis)
    - Lack of fiber: increase colon cancer risk
    - Avoidance of carbs results in decreased intakes of essential vitamins (thiamin, folate,B6) and anti-oxidant phytochemicals
- **Exercise:**
  - Good to maintain muscle mass.
  - Helps not to gain weight.
  - **But has little effect on reducing weight.**
  - Also, encourage pt. to change life-style.
  - Also, ask family, friends to encourage and support pt.

N.B. when you loose weight →you loose fat + protein (muscles) but when you regain weight you gain fat only→ become bag of fat!!!

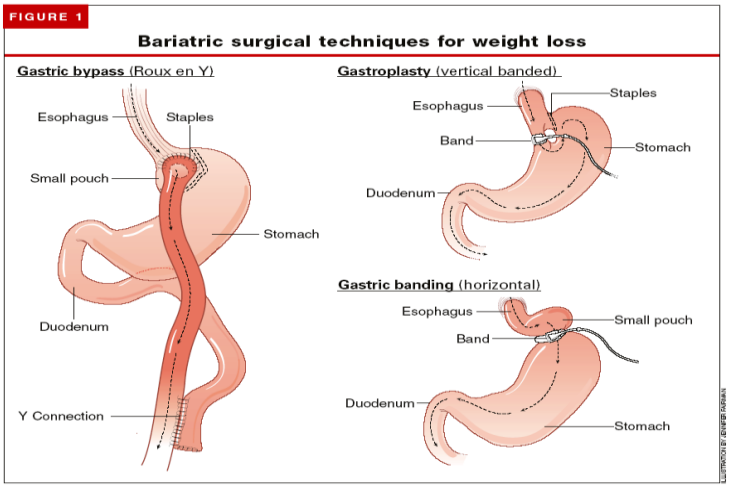
2- Drugs: (Orlistat)

- A lipase inhibitor, reduces the absorption of dietary fat
- Lowers Cholesterol (4-11%) & LDL (5-10%)
- It cause loss of 4 bonds in 4 weeks, if the loss is less than 4 it's mean the medication is not effective.
- Major C/I:
  - ✓ Chronic malabsorption syndrome
  - ✓ Cholestasis
  - ✓ Pregnancy and breast feeding
- Side effect:
  - ✓ Fecal incontinence
  - ✓ diarrhea "steatorrhea".
  - ✓ malabsorption of fat-soluble vitamins →"vit. supplement".
- Dose:
  - ✓ 120 mg/ immediately before, during, or up to 1 hour after each main meal (up to max. 360mg/day)
  - ✓ Max. period of treatment is 2 year

3- Surgery

- Considered for obesity of grade III or II with life-threatening complications.
- Pt. should be given a chance for dietary control, drugs.
- Needs multi-speciality team decision.
- Pt. should be followed-up, because it is associated with some complications.
- Two types:
  1. Restrictive "restrict Pt. to eat": e.g. banded gastroplasty:
     - Band placed over upper part of stomach.
     - More effective, less side effects: e.g. vomiting may be there.
  2. Malabsorptive "induce malabsorption of fat:
     e.g.Roux-en-Y gastric bypass "gastrojejunostomy":
     - Results in nutrient deficiency.**(late complication)**
     - Less effective**.**

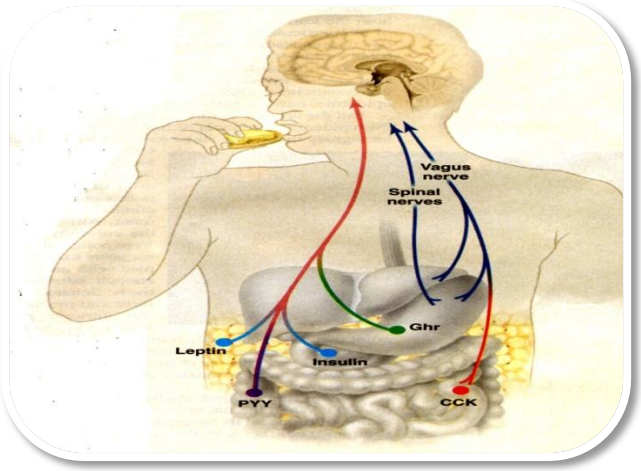
N.B: In bypass surgery there is more loss of weight than restriction surgery.



Gut to brain signaling:

Hypothalamic modulators of food intake:

Orexigenic	Anorexigenic
NPY	CART
AGRP	CCK
MCH	CRH
Galanin	a-MSH
Orexin	Insulin
Ghrelin	GLP-1
Noradrenaline	PYY 3-36
Endocannabinoids	Leptin
m, κ Opioids	Urocortin
Neurotransmitters	Bombesin



Most imp
Orexigenic: increase food intake (AGRP, Ghrelin and NPY)
Anorexigenic: decreas food intake (CCK, GLP-1, Insulin and Leptin)

Ghrelin :

Ghrelin is a recently discovered orexigenic hormone

Secreted primarily by the stomach and duodenum.

Has been implicated in both mealtime hunger and the long-term regulation of body weight

Health Benefits of wt loss:

- Decrease CVD
- Decrease glucose &insulin level
- Decrease BP
- Decrease LDL& Triglycerides ,increase HDL
- Decrease in severity of sleep apnea
- Decrease symptoms of joint

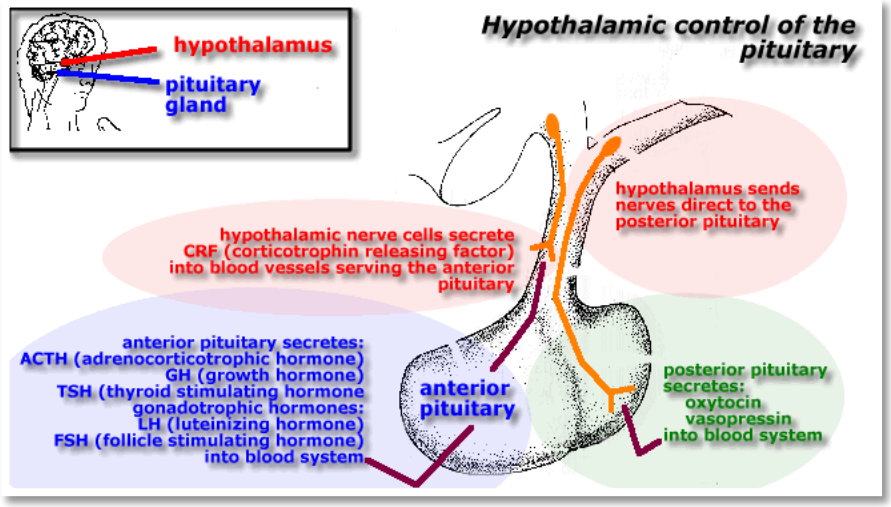
Pituitary Disorders

Prof. Riad Sulimani

Anterior Pituitary synthesizes and releases hormones under the influence of hypothalamic releasing hormones.
All releasing hormones of the hypothalamus are stimulatory, except:

- Dopamine → inhibits the prolactin release from anterior pituitary.
- Somatostatin → inhibits the Growth hormone (GH) release from the anterior pituitary.

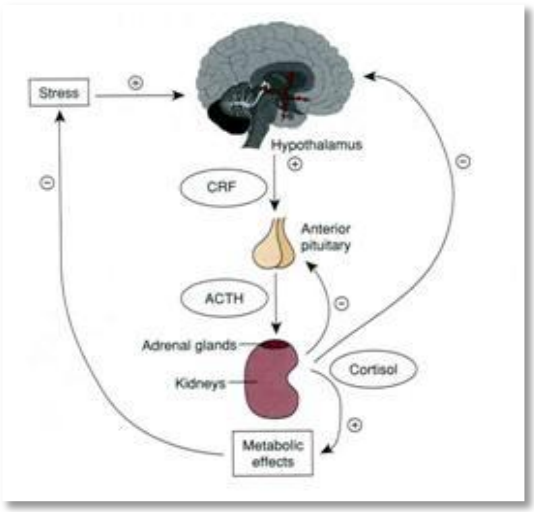
Hypothalamic pituitary axis



◈ Anterior Pituitary Hormones:

1. **GH** : increased by growth hormone releasing hormone (GHRH), sleep, stress, exercise, hypoglycemia, and clonidine.
2. **Prolactin** : increased by pregnancy, lactation, and when there is interference with Dopamine action or secretion.
3. **ACTH** : increased by Corticotropin-releasing hormone (CRH) and stress.
4. **TSH** : increased by Thyrotropin-releasing hormone (TRH) stimulation.
5. **FSH & LH** : increased by Gonadotropin-releasing hormone (GnRH) stimulation.
    a. FSH : stimulates testicular growth and spermatogenesis.
    b. In women : it stimulate production of estrogen and progesterone. It also stimulates ovulation.

⊙ Negative feedback mechanism (figure)→



◈ Amenorrhea and Galactorrhea :

- Caused by increased prolactin.
    - **Amenorrhea:** cessation of menstrual cycle in a woman of reproductive age.
        - **Primary** → Failure to start the spontaneous menstruation at the age of 16 years (no menarche).
        - Or **secondary** → pregnancy is a common physiological cause.
    - **Galactorrhea:** inappropriate secretion of milk in non-lactating woman.

■ Causes :

1. Primary hypothyroidism: because when thyroid hormones are low, TRH will increase → and high levels of TRH stimulate the synthesis of prolactin.
2. Drugs : which interfere with dopamine secretion or action :
   (Phenothiazines , Metoclopramide , Methyl-dopa). **(MCQ)**
3. Prolactinoma : prolactin secreting adenoma (associated with a very high levels of prolactin).
4. Renal failure : because of the retention of prolactin.

◈ Clinical Features :

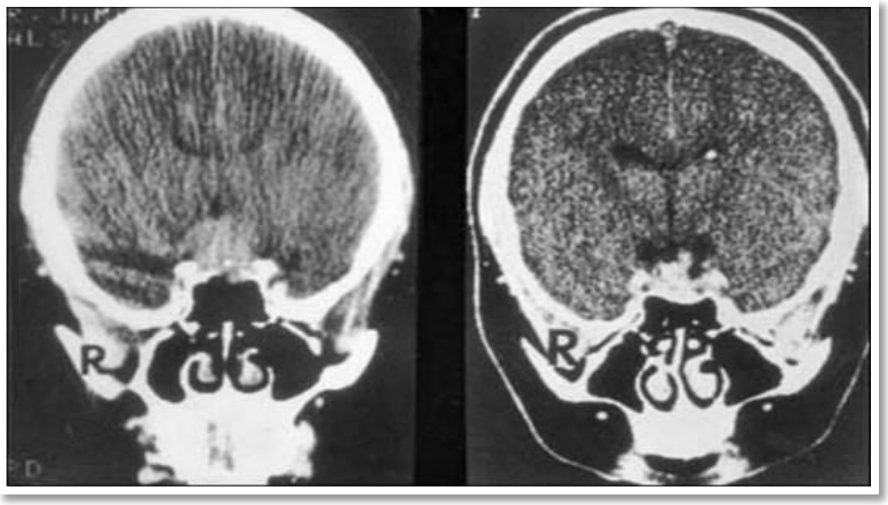
- **In women:** Galactorrhea, amenorrhea, and infertility.
- **In men:** decreased libido, impotence, and infertility.
  - These are because of prolactin interferes with the secretion of gonadotropin hormones.

◈ Diagnosis :

- **Hormonal :** Prolactin level (a very high level suggests prolactinoma)
- **Radiological :** in prolactinoma → CT or MRI of the pituitary :
  - < 1cm (**micro**adenoma).
  - > 1cm (**macro**adenoma).

◈ Treatment :

1. **Medical :** bromocriptine (dopamine agonist)
   - It is replaced now by Cabergoline, a long acting dopamine agonist with less nausea and vomiting.
2. **Surgical :** if tumor is causing pressure symptoms.



Response of prolactinoma to Dopamine Agonists (e.g. bromocriptine)

◈ Acromegaly :

Caused by GH producing adenoma, in childhood it is called Gigantism.

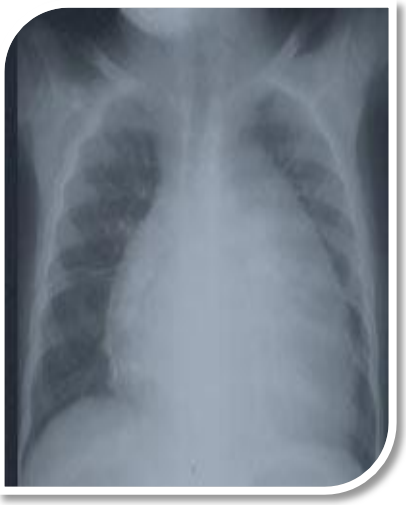
⊙ Clinical Features :

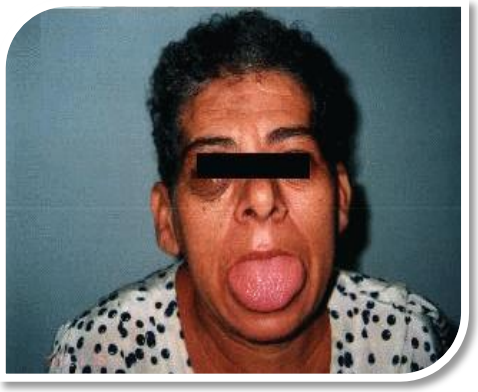
A. Due to the tumor (usually large **MACRO** adenoma more than 1 cm in size):
1. Headache, dizziness, bitemporal hemianopia.

B. Due to invasion and destruction of the pituitary of → decreases in secretion of other hormones.

C. Due to the increased GH production:
1. Acral (limbs) and soft tissues enlargement → large thick hands and feet.

2. Thick skin, oily, and sweaty (due to hypertrophy and hyperplasia of sweat and sebaceous glands).
3. Vesiromegaly.
4. Generalized symtomes → fatigue, lethargy, and increase sleepiness (obstructive sleep apnea).
5. Arthralgia and degenerative arthritis.
6. Carpal tunnel syndrome.
7. Impaired glucose tolerance and diabetes.
8. Cardiovascular effects : cardiomegaly and congestive heart failure.





⊙ Diagnosis :

1. **Clinical picture.**
2. **Hormonal diagnosis :** measure GH during OGTT (Oral Glucose Tolerance Test) , i.e. no suppression of GH.
3. **Measure IGF-1 :** high in all patients of acromegaly (Insulin Like Growth Factor is an indirect indicator of elevated GH which is produced from liver under the influence of GH).
4. **Radiological diagnosis :**
    a. Skull X-Ray : thick heel pad ≥ 22 mm.
    b. CT or MRI of the Sella Turcica.

⊙ Treatment :

1. **Surgical :** Trans-sphenoidal adenomectomy. (the treatment of choice).
2. **Radiotherapy.**
3. **Medical :** Somatostatin analogue.

Hypopituitarism

◈ Causes (7 i's)

1. Infarction → Sheehan's syndrome: pituitary necrosis after postpartum hemorrhage (due to blood loss & hypotension).
    ✓ Because at the period of pregnancy, the pituitary is increases in size and more blood supply is needed. So the pituitary is vulnerable to ischemia with a major blood loss and hypotension.
2. Iatrogenic : Radiation, surgery.
3. Invasive : Large pituitary tumors, e.g. **craniopharyngioma** (it arises from Rathke's pouch, and causes damage to hypothalamus-pituitary axis.
4. Infiltration : Sarcoidosis, hemochromatosis.
5. Injury : head trauma.
6. Infections : TB.
7. Idiopathic: e.g.
    a. Isolated GH syndrome (pituitary is normal).
    b. Kallmann syndrome: hypogonadotropin hypogonadisim with anosmia and colour blindness, usually in males.

◈ Clinical Picture of Hypopituitarism:

- **DEPENDS ON HORMONES LOST**
    1. **Lack of FSH & LH** → Hypogonadim: amenorrhea.
    2. **Lack of TSH** → Secondary hypothyroidism.
    3. **Lack of ACTH** → Adrenocortical insufficiency.
    4. **Prolactin deficiency** → Failure of postpartum lactation.
    5. **If all of the above** → Panhypopituitarism.
    6. **In children (decreased GH)** → Short stature.

◈ Testing Anterior Pituitary Function :

- **Clinical**: Hx and Px.
- **Biochemical studies:**
    - Baseline studies: TSH, ACTH, FSH, LH, prolactin GH.
    - Stimulation (**triple pituitary dynamic test**)
        A. TRH → stimulate the secretion of TSH and prolactin.
        B. Gn-RH → stimulates the secretion of FSH and LH.
        C. Insulin → hypoglycemia → stimulate the secretion of GH and ACTH.
- **Radiological** :
    a. Lateral skull X-Ray.
    b. CT.
    c. MRI : the method of choice.

◈ Treatment of Hypopituitarism:

1. Treat the cause.
2. Replacement therapy (depends on the hormone lost).
    a. Thyroxine in secondary hypothyroidism.
    b. Hydrocortisone for secondary hypoadrenalism.
        i. 20 mg at the morning.
        ii. 10 mg at the evening.
        iii. Increase the dose to double under stress (e.g. infection, surgery).
    c. Growth hormone : for children.
    d. Testosterone: monthly injections.
    e. Estrogen (1^{st} - 16^{th} of a month) + progesterone (16^{th} - 25^{th}).
    f. For induction of ovulation → FSH + LH.

Hypothalamic Posterior Pituitary Disorders

- The posterior pituitary stores and releases Antidiuretic Hormone (ADH) and Oxytocin which are produced by the hypothalamus.
- ADH could be high or low, resulting in deferent syndromes :
    a. Syndrome of polydypsia and polyurea (**Diabetes Insipidus**).
    b. Syndrome of inappropriate ADH (SIADH).

⊙ Causes of increased ADH secretion:

1. **Increased plasma osmolality :** more than 300 osmol/ml .
2. **Hypovolemia.**
3. **Neural stimuli :** stress, nausea, vomiting, pain.
4. **Drugs:** morphine, vincristine, cyclophosphamide, Chlorpropamide.

◈ Diabetes Insipidus:

Either no hormone (central) or no response (nephrogenic)

A. Central : ↓ ADH.
B. Nephrogenic : inability of kidney to respond to ADH.

A. Central Diabetes Insipidus :

- Neoplasm or infiltration.
- Surgery.
- Head trauma.
- Vascular.
- idiopathic

Clinically : polydipsia & polyurea

- ↑ Urine volume (3 – 20 L/day).
- ↓ Urine osmolality (diluted urine).
- ↓ Specific gravity.
- Serum Na+: usually high.

B. Nephrogenic Diabetes Insipidus :

- **Common Causes:**
    - Hypokalemia.
    - Hypercalcemia.
    - renal disease.
    - Drugs:
        1. lithium (MCQ)
        2. Demeclocycline.
        3. Diuretics

⊙ Deferential Diagnosis :

1. Diabetes Mellitus.
2. Primary polydypsia (psycogenic).

⊙ Diagnostic Tests:

- Rule out other causes.
- Water deprivation test

⊙ Water Deprivation Test :

- No fluid overnight.
- Collect urine sample every hour
- Then give ADH
- Measure the urine osmolality.

	Before giving ADH	After giving ADH
Central DI	Diluted urine	Urine concentrates (Osmolality ↑)
Nephrogenic DI	Diluted urine	No change
Psycogenic	Urine concentrates	No change

⊙ Treatment of Diabetes Insipidus :

1. Central DI→ Desmopressin (DDAP) : a synthetic replacement of ADH.
   a. If partial → Chlorpropamide
2. Neprhogenic:
   a. Correct underlying cause.
   b. Hydrochlorthiazide.
3. Primary Polydipsia: psychiatric management.

◈ Syndrome of inappropriate ADH (SIADH):

⊙ Clinical features:

- **Hyponatremia**. **(MCQ)**
  - **be careful that acute correction might cause central pontine myelinolysis.**
- Low serum osmolality
- ↑ urinary sodium
- ↑ inappropriate urine osmolality
- Euvolemia
- No oedema

⊙ Causes:

- CNS
  1. Meningitis.
  2. head trauma
- Tumors.
- Pulmonary:
  a) Pneumonia.
  b) TB
  c) Small cell carcinoma : paraneoplastic syndrome → ectopic ADH secretion (MCQ).
- Drugs:
  1. Chlorpropamide.
  2. Carbamazepine.
  3. Cyclophosphamide.
  4. Vincristine

⊙ Clinical Presentation :

- Confusion
- Nausea
- Irritability
- Fits
- Coma

⊙ Treatment :

- Treat the underlying cause.
- Restriction of fluid intake (0.5 – 1 L/day).
- Demeclocycline or lithium.
- **If severe :** I.V. hypertonic saline or normal infusion + Furosemide.

Thyroid Disorders

Dr. Assim Al-Fadda

◈ Patients with thyroid disease :

- Thyroid enlargement (goiter): diffuse or nodular
- Symptoms of hypothyroidism
- Symptoms of hyperthyroidism
- Complications of a specific form of hyperthyroidism-Graves' disease-which may present with:
  - Striking prominence of the eyes (exophthalmos)
  - Thickening of the skin over the lower leg (thyroid dermopathy)

◈ History :

- Exposure to ionizing radiation
- Iodide ingestion:
  - Kelp (extract of sea food which's contain a lot of iodide)
  - Iodide-containing cough preparation
  - IV Iodide-containing contrast media
- **Drugs that cause thyroid disease: Lithium carbonate, amiodarone and IV Iodide-containing contrast media(imp)**
- Residence in an area of low dietary iodide
- Family history
- Thyroid disease
- **Immunologic disorders:**
  1. Diabetes
  2. Rheumatoid disease
  3. Pernicious anemia
  4. Alopecia
  5. Vitiligo
  6. Myasthenia gravis
  7. MEN 2A➔ associated with medullary thyroid carcinoma

◈ Physical examination :

- Observe the neck, especially as the patient swallows
- Examine from the front, rotating the gland slightly with one thumb while palpating the other lobe with the other thumb
- Examine from behind, using three fingers and the same technique
- Determine the size of the thyroid lobes, consistency, presence of nodules

HYPOTHYROIDISM

The most common causes of hypothyroidism (in order):

1- Hashimoto 2- Surgery 3- Radioactive treatment

◈ Causes :

✪ Primary:

- Hashimoto's thyroiditis: (first cause of hypothyroidism)
  - With goiter
  - "Idiopathic" thyroid atrophy, presumably end-stage autoimmune thyroid disease, following either Hashimoto's thyroiditis or Graves' disease
  - Neonatal hypothyroidism due to placental transmission of TSH-R blocking antibodies
- Radioactive iodine therapy for Graves' disease
- Subtotal thyroidectomy for Graves' disease or nodular goiter
- Excessive iodine intake (kelp, radiocontrast dyes)
- Subacute thyroiditis
- Iodide deficiency
  - Other goitrogens such as lithium, amiodarone, antithyroid drug therapy
  - Inborn errors of thyroid hormone synthesis

✪ Secondary:

- Hypopituitarism due to:
  - Pituitary adenoma
  - pituitary ablative therapy
  - pituitary destruction

✪ Tertiary:

- Hypothalamic dysfunction (rare)

✪ Peripheral resistance of the action of thyroid hormone

(it's rare condition, thyroxin is normal or high with sign of hypothyroidism)

◈ Pathogenesis :

- Thyroid hormone deficiency affects every tissue in the body, so that the symptoms are multiple
- Accumulation of glycosaminoglycans-mostly hyaluronic acid- in interstitial tissues
- Increase capillary permeability to albumin
- Interstitial edema (skin, heart muscle, striated muscle)

◈ Clinical presentations and findings Adults :

- Common feature: easy fatigability, coldness, weight gain, constipation (low motility), menstrual irregularities, and muscle cramps.
- Physical findings: cool rough dry skin, puffy face and hands, hoarse husky voice, and slow reflexes, yellowish skin discoloration.
- <u>Cardiovascular:</u>
  - Bradycardia
  - Decreased cardiac output
  - Low voltage ECG
  - Cardiomegaly
  - Pericardial effusion
- <u>Pulmonary function</u>
  - Shallow and slow respiration
  - Respiratory failure
- <u>GI:</u>
  - Chronic constipation
  - Ileus
- <u>Renal function:</u>
  - Impaired GFR
  - Water intoxication & hyponatremia
- <u>Anemia:</u> (edema of intestine→ decrease the absorption of elements so we'll get different type of anemia (macro, micro and normo).
  - Impaired hemoglobin synthesis
  - Iron deficiency
  - Folate deficiency
  - Pernicious anemia, with B12 deficient megaloblastic anemia
- <u>Neuromuscular system:</u>
  - Severe muscle cramps
  - Paresthesias
  - Muscle weakness
  - Carpal tunnel syndrome
- <u>CNS:</u>
  - Chronic fatigue
  - Lethargy
  - Decreased concentration
  - Anovulatory cycles and infertility
  - Menorrhagia
  - Depression
  - Agitation

◈ Diagnosis :

- Low serum FT4(free thyroxin 4)
  - **(FT4 → decreased in primary and secondary)**
- Elevated serum TSH
  - (**TSH → increased in primary**
    → deceased in secondary)
- Thyroid antibodies
- TRH stimulation test

(imp):

- **Normal** FT4 with **increased** TSH (**subclinical hypothyroidism**)
  → do not treat it except in :
  - pregnancy
  - heart disease
  - hyperlipidemia
  - growing child
  - psycosis
  - positive thyroid antibody
  - goiter

◈ Complications :

1. **Myxedema coma (emergency)**
   - The end stage of untreated hypothyroidism
   - Progressive weakness, stupor, hypothermia, hypoventilation, hypoglycemia, hyponatremia, water intoxication, shock, and death.
   - **Associate illnesses and precipitating factors: (imp)** pneumonia, MI, cerebral thrombosis, GI bleeding, ileus, excessive fluid administration, and administration of sedatives and narcotics.
   - Three main issues: CO2 retention and hypoxia, fluid and electrolyte imbalance, and hypothermia.
2. **Myxedema and heart disease:**
   - (severe hypo + ischemic)→ difficult to treat because when we give them thyroxin it'll increase heart contractility→ increase the demand→which's precipitate the attack→ so treat it slowly.
3. **Hypothyroidism and neuropsychiatric disease**
   - because of the compliance (the pt may miss the dose or take overdose).

◈ Treatment :

- **Hypothyroidism :**
  - Levothyroxine (T4)
    - Thyroxin : it's given in the morning with empty stomach to increase the absorption
  - Follow serum Free T4 and TSH
  - Take dose in AM
  - Do blood test fasting before taking the daily dose
  - Adults: 1.7 ug/kg/d, but lower in elderly (1.6 ug/kg/d)
  - For TSH suppression (nodular goiters or cancer): 2.2 ug/kg/d
  - Increase dose of T4 in malabsorptive states or concurrent administration of aluminum preparations, cholestyramine, calcium, or iron compounds
    - (Space 4 hours between thyroxin and Ca or Aluminum)
  - Increase dose of T4 in pregnancy and lactation
  - The t1/2 of levothyroxine is 7 days:
    - One day missing of the tablet will not affect the plasma concentration of thyroxin.
- **Myxedema coma :**
  - Acute medical emergency
  - Monitor blood gases
  - Patient may need intubation and mechanical ventilation
  - Treat associated medical problems (precipitating factors)
  - Avoid excessive hydration→ water intoxication
  - Asses adrenal function and treat if needed
  - In pituitary myxedema, glucocorticoid replacement is essential
  - IV levothyroxine: loading 300-400 ug, daily maintenance 50 ug
  - Be cautious in patients with coronary artery disease
  - Active rewarming of the body is contraindicated→ slow rewarming to prevent vasodilation & hypotenstion because they have low BP)

- **Myxedema with heart disease :**
  - Start treatment slowly in long standing hypothyroidism and in elderly patients particularly those with known cardiovascular disease.
  - 25 ug/d x 2 weeks, increase by 25 ug every 2 weeks until a daily dose of 100-125 ug is reached

◈ Toxic effects of levothyroxine therapy :

- No allergy has been reported to pure levothyroxine
- If FT4 and TSH are followed and T4 dose is adjusted, no side effects are reported
- If FT4 is higher than normal: hyperthyroidism symptoms may occur:
  - ✓ Cardiac symptoms.
  - ✓ Osteopenia and osteoporosis.

HYPERTHYROIDISM & THYROTOXICOSIS

◈ Definitions :

- **Thyrotoxicosis:** is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone
- **Hyperthyroidism:** is the hyperactivity of the thyroid gland

◈ Conditions associated with thyrotoxicosis :

- Diffuse toxic goiter (Graves' disease)
- Toxic adenoma (Plummer's disease)
- Toxic multinodular goiter
- Subacute thyroiditis
- Hyperthyroid phase of Hashimoto's thyroiditis
- Thyrotoxicosis factitia(thyroxin from out side)
- Rare: ovarian struma, metastatic thyroid carcinoma (follicular), hydatiform mole, TSH secreting pituitary tumor, pituitary resistance to T3 and T4

◈ Diffuse Toxic Goiter (Graves' disease) :

- Most common form of thyrotoxicosis
- **Females > Males**
- Features:
  - Thyrotoxicosis
  - Goiter
  - Orbitopathy (exophthalmos)
  - Dermopathy (pretibial myxedema) – rare

N.B. chemosis → edema of conjunctiva

◈ Etiology :

- Autoimmune disease of unknown cause
- There is a strong familial predisposition
- Peak incidence in the 20- to 40- year age group

◈ Pathogenesis : not imp

Local viral infection → inflammatory reaction leading to the production of IFN-g and other cytokines by non-thyroid-specific infiltrating immune cells

↓

will induce the expression of HLA class II molecules on the surface of thyroid follicular cells.

↓

Subsequently, thyroid specific T-cells will recognize the antigen presented on the HLA class II molecules and will be activated

↓

The activated thyroid-specific T-cells stimulate B cells to produce

↓

TSH receptor-stimulating antibodies

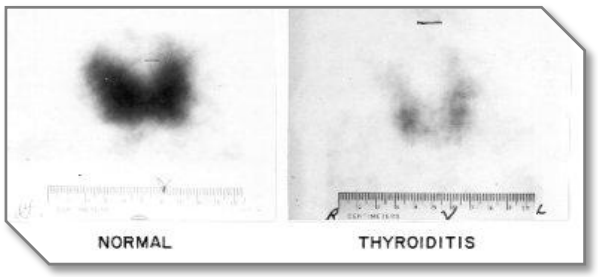
↓

Hyperthyroidism

◈ Diagnosis :

- Elevated Free T4
- Suppressed TSH
- Eye signs (Graves disease)
    - If (+) → No Further Test.
    - If (-) → Thyroid Scan → Thyrotoxicosis for investigation.
- Other Investigations:
    - TSH Receptor Ab stimulation
    - Free T3
    - Atypical presentations:
        - Thyrotoxic periodic paralysis.
        - Thyrocardiac disease.
        - Apathetic hyperthyroidism.
        - Familial dysalbuminemic hyperthyroxinemia.

◈ Radioiodine uptake scan :



- Elevated uptake:
    - **Graves' disease**
    - TMN(toxic multinodular goiter)
- Low uptake:
    - Spontaneous resolving hyperthyroidism
    - **Subacute thyroiditis**
    - Thyrotoxic phase of Hashimoto's thyroiditis
    - Iodine loaded patients
    - **Patients on LT4 therapy(external thyroxin)**
    - Struma ovarii

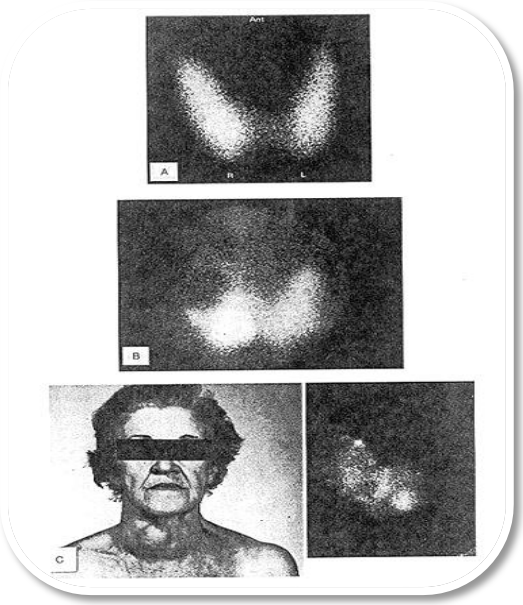


Figure 6-6. Thyroid Scans.

A. Normal thyroid imaged with 123I.

B. Cold nodule in the right lobe imaged by 99mTc.

C. Elderly woman with obvious multinodular goiter and the corresponding radioiodide scan on the right.

Complications :

- Thyrotoxic crisis (thyroid storm) **imp**
  - Predisposing conditions : graves' disease or long time with no treatment, have an infection or fever.
  - Clinical features:
    - ✓ Fever / Agitation
    - ✓ Altered mental status
    - ✓ Atrial fibrillation / Heart failure

◈ Treatment of Graves' disease :

- **Antithyroid drug therapy**
  - Propylthiouracil or methimazole
    - ✓ Propylthiouracil: used in pregnancy (less side effect)
    - ✓ methimazole : cheaper and available
  - Spontaneous remission 20-40%
  - Relapse 50-60%(80% of Saudi population relapse)
  - Duration of treatment 6 months – years
  - Reactions to antithyroid drugs
- **Surgical treatment:**
  - **indication of surgery :**
    - failed medication
    - large goiter
    - sever eye disease
  - Subtotal thyroidectomy
  - Preparation for surgery
  - **Complications:**
    - hypothyroidism/ hypoparathyroidism
    - Recurrent laryngeal nerve injury
- **Radioactive iodine therapy :**
  - **The most common treatment of graves' disease**
    - ^{131}I is **most** commonly used
    - **Dose =** $\frac{131\text{I(uci/g) x thyroid weight x } 100}{24\text{−hr RAI uptake}}$

- **Contraindication of radioactive therapy :**
  - Pregnancy→ absolute contraindication
  - Severe eye disease→ become worse

- **<u>beta blockers</u>**→to suppress the heart
- **<u>SSKI :</u> supersaturated potassium iodide**

◈ Treatment of Graves' disease complications :

- Thyrotoxic crisis
- Orbitopathy:
  - exophthalmos : Reversible in early stage
    Irreversible in late stage
- Thyrotoxicosis and pregnancy :

In this case, we try to lower the thyroxin level to upper limit of normal value which is physiologically seen in a pregnant lady.

◈ Treatment of other forms of thyrotoxicosis :

- **Toxic adenoma** : control + surgery
- **TMN** (toxic multinodular goiter): medication + surgery
- **Amiodarone** : not stop the amidarone but treat the thyroid condition.
- **Subacute thyroiditis**: steroid
- **Thyrotoxicosis factitia**
- **Struma ovarii**

◈ Other thyroid disorders :

- ✪ Nontoxic goiter
- ✪ Subacute thyroiditis (De Quervain's)
- ✪ Chronic thyroiditis
- ✪ Acute thyroiditis
- ✪ Thyroid nodules
- ✪ Thyroid cancer

Hyperlipidemia

Dr. Anwar A. Jammah

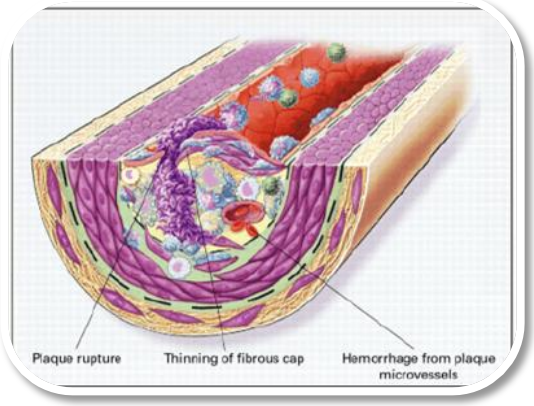
◈ Definition of hyperlipidemia:

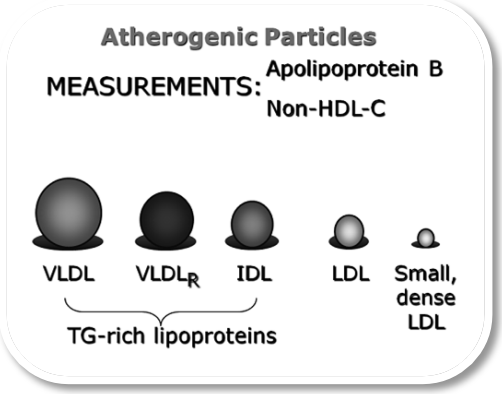
- Elevated levels of cholesterol and/or triglycerides.

◈ The story of lipids:

- Fat is transported in bloodstream as **lipoprotein** particles composed of: lipids (triglycerides + cholesterol + cholesterol esters), phospholipids, & proteins "apoproteins".
  1- **Chylomicrons** transport fats from the intestinal mucosa to the liver.
  2- In the liver, the chylomicrons release triglycerides and some cholesterol; and become LDL.
  3- **LDL** then carries fat and cholesterol to the body's cells.
  4- **HDL** carries fat and cholesterol back to the liver for excretion.

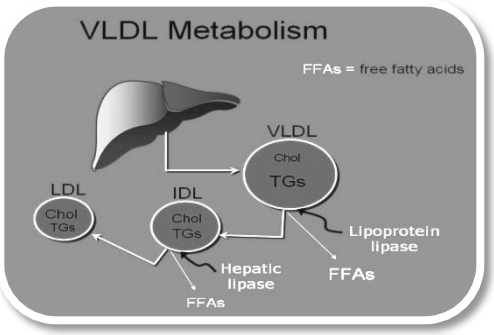
- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs; which causes atherosclerosis.
- HDL cholesterol is able to go and remove cholesterol from the atheroma.
- Thus, **atherogenic cholesterol → LDL**, **VLDL**, **IDL**.





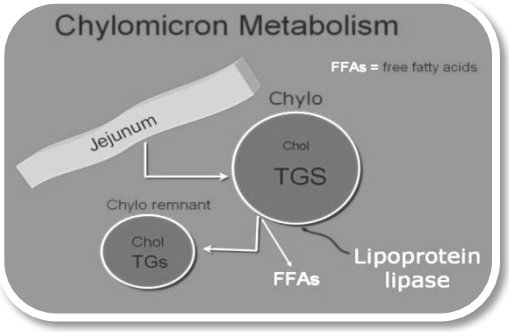
Abbreviations:	
LDL: low-density lipoproteins. HDL: High-density lipoproteins. VLDL: very low-density lipoproteins.	IDL: Intermediate-density lipoprotein. TC: total cholesterol. TG: triglycerides.

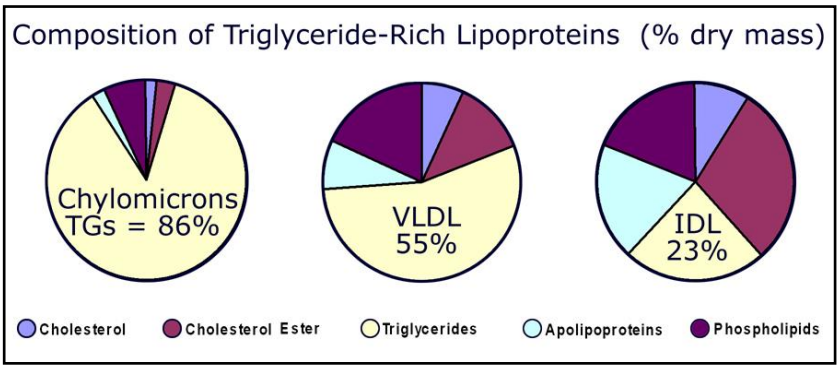
- **Lipid metabolism pathway:** ——————►



⊙ Lipoprotein types:

Type	Source	Major lipid	Apoproteins	ELFO	Athero-genicity
Chylomicrons	Gut	Dietary TGs	A-I, B-48, C-I, C-III, E	no mobility	- (pancreatitis)
VLDL	Liver	Endogenous TGs	B-100, E, C-II, C-III,	Pre-β	+
IDL	VLDL remnant	Ch esters, TGs	B-100, C-III, E	Slow pre- β	+
LDL	VLDL, IDL	Ch esters	B-100	β	+++
HDL	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	anti-atherogenic





Most IMP notes:

- Chylomicrons: rich in triglycerides with small amount of cholesterol esters; ↑↑ amount causes pancreatitis.
- VLDL: rich in triglycerides; atherogenic.
- LDL: rich in cholesterol & cholesterol esters; highly atherogenic (Bad cholesterol).
- HDL: smallest lipoprotein, rich in cholesterol esters, but it collect the cholesterol from the body to the liver; anti-atherogenic (Good Cholesterol).

◈ Classification of hyperlipidemia:

- **Hereditary (genetic) hyperlipidemia:**
  - Familial Hypercholesterolemia (FH): IMP
    - Co-dominant genetic disorder, occurs in heterozygous form.
    - Occurs in 1 in 500 individuals.
    - Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life.
    - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas and xanthelasmas of eyes.

FH (autosomal dominant) can be:

- Heterozygous (one abnormal copy) may have premature cardiovascular disease at the age of 30 to 40. Occur in 1:500 people.
- Homozygous (two abnormal copies) may cause severe cardiovascular disease in childhood (15-16 yrs). Occur in 1 in a million births.

  - Familial Combined Hyperlipidemia:
    - Autosomal dominant.
    - Increased secretions of VLDLs.
  - Dysbetalipoproteinemia:
    - Affects 1 in 10,000.
    - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL).
    - Increased risk for atherosclerosis, peripheral vascular disease.
    - Tuberous xanthomas, striae Palmaris.

◈ Fredrickson classification of hyperlipidemias:

◈ Primary Hyperlipidemia:

Phenotype	Name	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Athero-genicity	Rel. freq.	Treatment
I	Familial hyper-chylomicronemia	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	Familial hyper-cholesterolemia	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	Familial combined hyperlipidemia	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	Familial dysbeta-lipoproteinemia	IDL	↑↑	↑↑↑	+++	<1%	Fibrates
IV	Endogenous hyperlipemia	VLDL	Norm. to ↑	↑↑	+	45%	Niacin, fibrates
V	Familial hyper-triglyceridemia	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	+ pancreatitis	5%	Niacin, fibrates

◈ Secondary hyperlipidemia:

- Causes of hyperlipidemia:
  - Diet.
  - Hypothyroidism.
  - Nephrotic syndrome.
  - Anorexia nervosa.
  - Obstructive liver disease.
  - Obesity.
  - Diabetes mellitus.
  - Pregnancy.
  - Acute hepatitis.
  - Systemic lupus erythematosus.
  - AIDS (protease inhibitors).
  - Drugs and alcohol

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑↑↑	↑	↓	VLDL production ↑, LPL ↓, altered LDL
Hypothyroidism	↑	↑↑↑	↓	LDL-rec.↓, LPL ↓
Obesity	↑↑	↑	↓	VLDL production ↑
Anorexia	-	↑↑	-	bile secretion ↓, LDL catab. ↓
Nephrotic sy	↑↑	↑↑↑	↓	Apo B-100 ↑ LPL ↓ LDL-rec. ↓
Uremia, dialysis	↑↑↑	-	↓	LPL ↓, HTGL ↓ (inhibitors ↑)
Pregnancy	↑↑	↑↑	↑	estrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	-	-	↓	Lp-X ↑ ↑ no CAD; xanthomas
Alcohol	↑↑ chylomicr. ↑	-	↑	dep. on dose, diet, genetics
Many-many drugs	Please allways see for adverse effects before any drug presciption!!!			

- Dietary sources of Cholesterol:

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

⊙ **Checking lipids:**
- Non-fasting lipid panel: measures HDL and total cholesterol.
- Fasting lipid panel (10-14 hrs): Measures HDL, total cholesterol, & TGs.
  - LDL cholesterol is calculated: LDL cholesterol = TC – (HDL + TG/5)

⊙ **When to check lipid panel:**
- Two different Recommendations:
  1. Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP):
     - Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides.
     - Repeat testing every 5 years for acceptable values.
  2. United States Preventative Services Task Force:
     - Women aged 45 years and older, and men ages 35 years and older undergo screening with a total and HDL cholesterol every 5 years.
     - If total cholesterol > 200 or HDL <40, then a fasting panel should be obtained.
     - Cholesterol screening should begin at 20 years in patients with a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesterol levels or premature cardiovascular disease.

◈ Treatment Targets: (IMP)

1. LDL: To prevent coronary heart disease outcomes (myocardial infarction and coronary death).
2. Non-LDL (TC/HDL): To prevent coronary heart disease outcomes (myocardial infarction and coronary death).
3. Triglyceride: To prevent pancreatitis and may be coronary heart disease outcomes (myocardial infarction and coronary death).

✶ Our primary target in treatment is to reduce LDL & non-LDL, reducing risk of CHD; after that comes the TGs.
✶ TG comes as primary target in case of pancreatitis with level > 5.
✶ This is important because different treatment strategies are applied according to the primary target (e.g. statins are used for LDL & Fibrates are used for TG).

Treatment Guidelines to reduce LDL & Non-LDL (TC/HDL):

1. Framingham Heart Study to estimate 10-year risk for coronary heart disease outcomes [Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)]:
   - http://hp2010.nhlbihin.net/atpiii/CALCULATOR.asp?usertype=prof.
   - Consider :
     - Age
     - LDL-C
     - T-Chol
     - HDL-C
     - Blood Pressure
     - Diabetes
     - Smoking

i. Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia:

Risk Category	Begin Lifestyle Changes If:	Consider Drug Therapy If:	LDL Goal
High: CAD or CAD equivalents (10-yr risk > 20%)	LDL ≥ 2.58 mM	LDL ≥ 2.58 mM (drug optional if < 2.58 mM)	< 2.58 mM; < 1.8 mM optional
Moderate high: ≥ 2 risk factors with 10-yr risk 10 to 20%*	LDL ≥ 3.36 mM	LDL ≥ 3.36 mM	< 3.36 mM; < 2.58 mM optional
Moderate: ≥ 2 risk factors with 10-yr risk < 10%*	LDL ≥ 3.36 mM	LDL ≥ 4.13 mM	< 3.36 mM; < 2.58 mM optional
Lower: 0–1 risk factor	LDL ≥ 4.13 mM	LDL ≥ 4.91 mM (drug optional if 4.13–4.88 mM)	< 4.13 mM

ii. Canadian New Guideline: (IMP)

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets:* Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	*Treat when:* LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when:* LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.

◈ Treatment of Hyperlipidemia:

I. Lifestyle modification

- Low-cholesterol diet
- Exercise

II. Medications for Hyperlipidemia:

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Statins	↓LDL (18-55), ↑HDL (5-15) ↓Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	↓LDL (14-18), ↑HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid		↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓LDL ↑HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

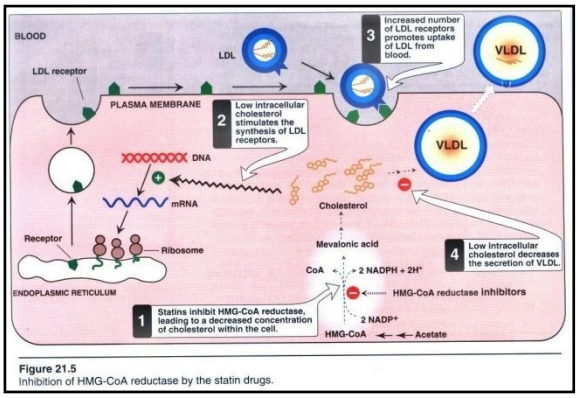


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

Acute Coronary Syndromes

Dr. Hussam Al-Faleh

Introduction:

- **There are 3 types of angina:** stable (typical), variant (prinzmetal`s) angina and unstable angina
- **In stable angina**, there is a fixed atherosclerotic plaque in the coronary artery that reduces the blood supply to myocardium only during exertion (angina of exertion). It is **asymptomatic at rest**.
- **In Variant angina**, there is coronary vasospasm on a fixed atherosclerotic lesion, but sometimes can occur in normal coronary arteries.
- Unstable angina is a serious condition (A.K.A **pre-infarction angina**). However, there is **no myocardial necrosis**.
- **Myocardial infarction is of 2 types:**
  - STEMI → ST elevation myocardial infarction (indicating **transmural infarction**)
  - NSTEMI → non ST elevation myocardial infarction (indicating **subendcardial infarction** "inner one third to one half of the wall")
- NSTEMI can be distinguished from unstable angina by measuring **cardiac enzymes** in the blood, which is present in case of NSTEMI coz there is myocardial cell death. It is very difficult to differentiate the two based on patient presentation.

◈ Acute coronary syndromes:

- The clinical manifestations of atherosclerotic plaque rupture and coronary occlusion.
- Term generally refers to unstable angina or acute MI (STEMI & NSTEMI).

Unstable Angina Pectoris

◈ General characteristics:

- **Pathophysiology**
  - With unstable angina (USA), oxygen demand is unchanged. Supply is decreased secondary to reduced resting coronary flow. This is in contrast to stable angina, which is due to increased demand.
  - USA is significant because it indicates stenosis that has enlarged via thrombosis, hemorrhage, or plaque rupture. It may lead to total occlusion of a coronary vessel.
  - The following patients may be said to have USA:
    - ✓ Patients with chronic angina with increasing frequency, duration, or intensity of chest pain.
    - ✓ Patients with new-onset angina that is severe and worsening.
    - ✓ Patients with angina at rest.

◈ Diagnosis:

- Perform a diagnostic workup to exclude MI in all patients.
- **Resting ECG:** look for ST segment or T wave abnormalities which could indicate unstable angina, especially if ST depression with negative cardiac enzymes.
- **Exercise stress test:** include stress ECG, stress echocardiography (more sensitive in detecting ischemia, valvular abnormalities and left ventricle size & function) and stress myocardial perfusion imaging (thallium 201 given IV during exercise).

- Patients with USA have a higher risk of adverse events during stress testing. These patients should be stabilized with medical management before stress testing or should undergo cardiac catheterization initially.
- Cardiac catheterization with coronary angiography – most accurate and definitive test for CAD.

◈ Treatment :

- Hospital admission on a floor with continuous cardiac monitoring. Establish IV access and give supplemental oxygen. Provide pain control with nitrates (below) and morphine.
- **Aggressive medical management is indicated :**
  - ✓ Aspirin.
  - ✓ β-Blockers – first-line therapy if there are no contraindications
  - ✓ Low-molecular-weight heparin (LMWH) (IV) or unfractionated heparin
    - Should be continued for at least 2 days
    - Keep PTT at 2 to 2.5 times normal if using unfractionated heparin; PTT not followed with LMWH
    - Enoxaparin is the drug of choice based on clinical trials
  - ✓ Nitrates are first-line therapy.
  - ✓ Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban) can be helpful adjuncts in USA, especially if patient is undergoing PTCA or stenting.

- **Cardiac catheterization/revascularization :**
  - ✓ More than 90% of patients improve with the above medical regimen within 1 to 2 days.
  - ✓ The choice of invasive management (early catheterization/revascularization within 48 hours) versus conservative management (catheterization/revascularization only if medical therapy fails) is controversial.
    - No study has shown a significant difference in outcomes between these two approaches.
    - Conservative management will be described here.
      - If patient responds to medical therapy, perform a stress ECG to assess need for catheterization/revascularization. Many patients with USA that is controlled with medical therapy eventually require revascularization.
      - If medical therapy fails to improve symptoms and/or ECG changes indicative of ischemia persist after 48 hours, then proceed directly to catheterization/revascularization.

- **After the acute treatment**
  - ✓ Continue aspirin (or other antiplatelet therapy), β-blockers, and nitrates
  - ✓ Reduce risk factors :
    - Smoking cessation, weight loss
    - Treat diabetes, HTN
    - Treat hyperlipidemia—patients with USA (or non–ST segment elevation MI) with elevated LDL cholesterol should be started on an HMG-CoA reductase inhibitor. Clinical trials of statins have shown the efficacy of such therapy for secondary prevention in CAD.
    - Consider folic acid—it is used for hyperhomocystinemia, but is also reported to have beneficial effects on endothelial function and as an antioxidant.

Myocardial Infarction (MI)

◈ A. General characteristics

- MI is due to necrosis of myocardium as a result of an interruption of blood supply (after a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis).
- Most cases are due to acute coronary thrombosis: Atheromatous plaque ruptures into the vessel lumen, and thrombus forms on top of this lesion, which causes occlusion of the vessel.
- MI is associated with a 30% mortality rate; half of deaths are pre-hospital.
- Most patients with MI have history of angina, risk factors for CAD, or history or arrhythmias.

◈ Clinical features :

- **Chest pain**
  - ✓ Intense substernal pressure sensation; often described as "crushing" and "an elephant standing on my chest"
  - ✓ Radiation to neck, jaw, arms, or back, commonly to the left side
  - ✓ Similar to angina pectoris in character and distribution but much more severe and lasts longer
  - ✓ Some patients may have epigastric discomfort.
  - ✓ Can be **asymptomatic** in up to one third of patients; painless infarcts or atypical presentations more likely in postoperative patients, the elderly, diabetic patients, and women.
- Dyspnea
- Diaphoresis
- Weakness, fatigue
- Nausea and vomiting
- Sense of impending doom
- Syncope
- **Sudden cardiac death** : usually due to ventricular fibrillation (VFib)

◈ Diagnosis

- **ECG**

  Markers for ischemia/infarction include:
  1. Peaked T waves: occur very early and may be missed
  2. S-T segment elevation indicates transmural injury and can be diagnostic of an acute infarct.
  3. Q waves: evidence for necrosis (specific) – Q waves are usually seen late; typically not seen acutely.
  4. T wave inversion is sensitive but not specific.
  5. S-T segment depression: subendocardial injury
- **Categories of infarcts:**
  - ✓ **ST segment elevation infarct:** transmural (involves entire thickness of wall); tend to be larger.
  - ✓ **Non–ST segment elevation infarct:** subendocardial (involves inner one third to one half of the wall); tend to be smaller, and presentation is similar to unstable angina—cardiac enzymes differentiate the two

- **Cardiac enzymes** : currently the diagnostic gold standard for myocardial injury
  1. **Creatine kinase-MB** (CK-MB) :
     - ✓ Increases within 4 to 8 hours and returns to normal in 48 to 72 hours; reaches a peak in 24 hours
     - ✓ When measured within 24 to 36 hours of onset of chest pain, has greater than 95% sensitivity and specificity
     - ✓ Levels of total CK and CK-MB should be measured on admission and every 8 hours thereafter for 24 hours.
  2. **Troponins (Troponin I and T)** : most important enzyme test to order
     - ✓ Increase within 3 to 5 hours and return to normal in 5 to 14 days; reach a peak in 24 to 48 hours
     - ✓ Greater sensitivity and specificity than CK-MB for myocardial injury
     - ✓ Obtain serum levels of either troponin T or troponin I on admission, and again every 8 hours for 24 hours.
     - ✓ Troponin I can be falsely elevated in patients with renal failure.

◈ Treatment

Aims of treatment :

- **Improve oxygen supply**
  1. Supplemental O2
  2. Antiplatelets drugs
  3. Antithrombotics
  4. Coronary vasodilators (Nitroglycerine)
  5. Reperfusion therapy
     a) Fibrinolytic therapy.
     b) Percutanous coronary intervention(PCI).
- **Reduce O2 demand**
  1. Beta blockers (Propranolol, Metoprolol)
  2. Analgesics (Morphine)
- **Other medications**
  - ✓ ACE inhibitors(Enalapril, Lisinopril)
  - ✓ Statin therapy

- **Antiplatelets :**
  1. **Aspirin (ASA)**
     - ✓ Antiplatelet agent reduces coronary reocclusion by inhibiting platelet aggregation on top of the thrombus.
     - ✓ Has been shown to reduce mortality and should be part of maintenance therapy long-term.
     - ✓ Should be administered as early as possible.
     - ✓ Chewable aspirin 160 to 325 mg at presentation then 75 to 325 mg daily.

2. **Clopidogril :**
   - ✓ More potent than ASA
   - ✓ Irreversible ADP receptor blockers
   - ✓ Adjunct to reperfusion therapy

- **β-Blockers**
  - ✓ Block stimulation of HR and contractility.
  - ✓ Reduce afterload.
  - ✓ Have been shown to reduce mortality and should be part of maintenance therapy.
- **ACE inhibitors**
  - ✓ Initiate within hours of hospitalization if there are no contraindications.
  - ✓ Have been shown to reduce mortality and should be part of maintenance therapy long-term.
- **Statins**
  - ✓ Reduce risk of further coronary events.
  - ✓ Stabilize plaques and lower cholesterol.
  - ✓ Should be part of maintenance therapy.
- **Oxygen**
  - ✓ May limit ischemic myocardial injury.
- **Nitrates**
  - ✓ Dilate coronary arteries (increase supply).
  - ✓ Venodilation (decrease preload and thus demand).
  - ✓ Reduce chest pain, although not as effective as narcotics.
- **Morphine sulfate**
  - ✓ Analgesia
  - ✓ Causes venodilation, which decreases preload and thus oxygen requirements
- **Heparin**
  - ✓ Initiate in all patients with MI (STEMI & NSTEMI) ; prevents progression of thrombus; however, has not been shown to decrease mortality
  - ✓ LMWH, specifically enoxaparin, is preferred over unfractionated heparin.

- **Reperfusion Therapy**
  - ✓ Benefit highest when **performed early**; time is more important than type of reperfusion chosen. Should be given during **a 12 hours window** , after 12 hours it is harmful.
  - ✓ Should be considered in all patients
  - ✓ Two forms of reperfusion exist: **thrombolysis (fibrinolytics)** and **PTCA**

- **Rehabilitation**
  - ✓ Cardiac rehabilitation is a physician-supervised regimen of exercise and risk factor reduction after MI.
  - ✓ Shown to reduce symptoms and prolong survival

Methods of Reperfusion

▪ Thrombolytic Therapy

- ✓ ONLY USED FOR STEMI (NOT NSTEMI).
- ✓ Reduces short and long term mortality.
- ✓ shown to be effective in numerous randomized trials involving over 100,000 patients.
- ✓ Should be given during a 12hr window, and given as soon as possible.
- ✓ 2 types of fibrinolytics:
  - Non Fibrin specific (Streptokinase)
  - Fibrin specific, e.g. tPA
    - Alteplase : 15 mg **bolus +** 90 min **effusion**.
    - Tenecteplase : 0.5 mg **single bolus**

• Contraindications to Thrombolytic Therapy

▫ Absolute Cotraindications :

1. Any prior intracranial hemorrhage.
2. Known structural cerebral vascular lesion.
3. Known intracranial neoplasm.
4. Suspected aortic dissection.
5. Ischemic stroke in the past 3 monthes.
6. Active bleeding.
7. Significant closed-head of facial trauma.

▫ Relative Contraindications :

1. Uncontrolled HTN (>180/110).
2. Recent (2-4 weeks) internal bleeding.
3. Pregnancy.
4. Active peptic ulcer.
5. Current use of anticoagulant.

▪ Percutaneous Transluminal Coronary Angioplasty (PTCA)

- ✓ An alternative to thrombolytic therapy. At most medical centers, PTCA is the first-line treatment for MI.
- ✓ Preferred in patients with contraindications for thrombolytic therapy; no risk of intracranial hemorrhage

◈ Complications of acute MI

A. Pump failure

1. Heart failure
   - ✓ Bad prognostic sign.
   - ✓ Most common cause of in-hospital mortality.
   - ✓ Reflects the size of the MI.
   - ✓ ACE inhibitors and diuretics is cornerstone therapy.
2. Cardiogenic Shock :
   - ✓ Happens with major MI's.
   - ✓ Carries high mortality (>50% in 30 days).
   - ✓ Should be rushed for cardiac cath. and either PTCA or Coronary bypass grafting.

B. Electrical complications:

1. **Tachyarrhythmias**
   a. Ventricular:
      - ✓ Ventricular Tachycardia.
      - ✓ Ventricular Fibrillation.
   b. Supraventricular:
      - ✓ Atrial Fibrillation.

2. **Bradyarrhthmias**
   - ✓ 1st, 2nd, and 3ed degree AV blocks
   - ✓ New Left Bundle Branch Block (LBBB), or Right Bundle Branch Block RBBB.

C. Mechanical complications:

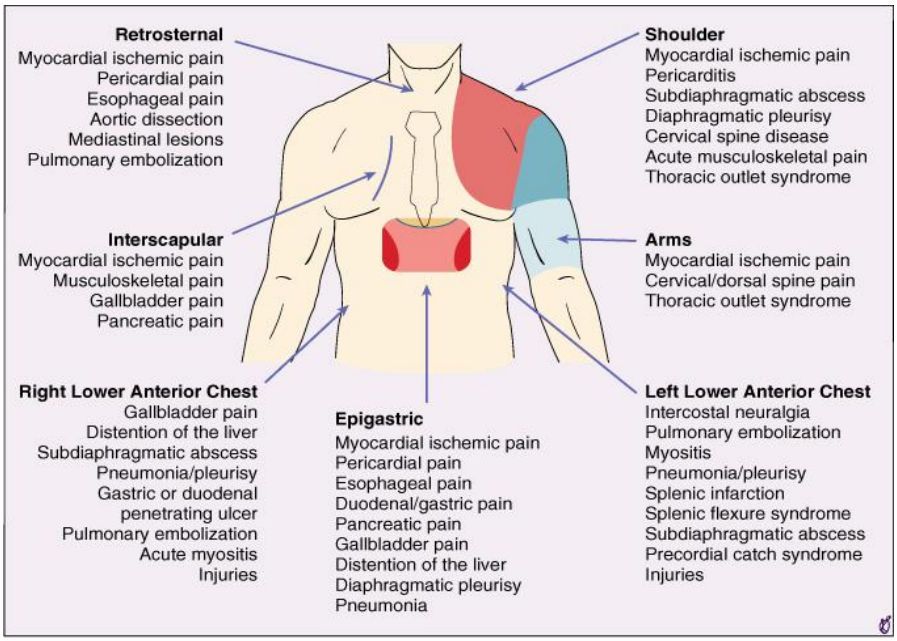
1. **Mitral regurgitation**
   - ✓ 2-7 days post MI.
   - ✓ Caused by papillary muscle rupture, due to decrease blood flow to them.

2. **Free LV wall rupture**
   - ✓ Rare.
   - ✓ 1st 24hr up to 2 weeks.

3. **Ventricular septal defect**
   - ✓ 1-3%
   - ✓ Occurs with inferior and anterior MI.

Approach to Chest Pain

Dr. Hanan Al-Backr



Objectives :

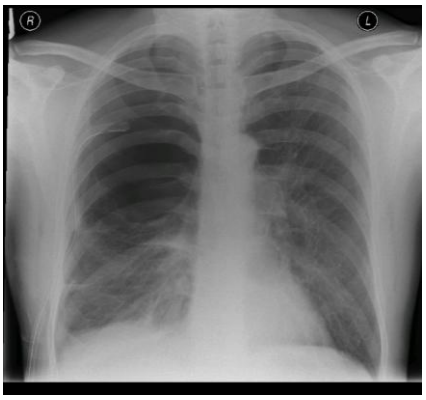
1. Establish a differential diagnosis for chest pain.
2. Know what clues to obtain on history to rule-in or out MI, PE, pneumothorax and pericarditis.
3. Identify risk factors for MI and PE.
4. Know how to do a focused physical exam, identifying features that would distinguish between MI, PE, pneumothorax, pericarditis, tamponade, pneumonia, and aortic dissection.
5. Identify investigations required in diagnosing MI, PE, pneumothorax and pneumonia and how to interpret results.
6. Outline management strategy in MI, PE, peumothorax and pneumonia.

Chest Pain :

- Common presentation to A&E (Accident and Emergency).
- Trivial to life-threatening causes.
- **Key** to diagnosis is history.
- Negative baseline investigations **DO NOT** rule out serious conditions.
- Life-threatening Causes of Chest Pain :
  - Myocardial infarct.
  - Unstable angina.
  - Thoracic aortic dissection.
  - Pulmonary embolus.
  - Tension pneumothorax.
  - Oesophageal rupture.
- Other Differentials :
  - Costochondritis.
  - Herpes Zoster.
  - Musculoskeletal.
  - Pancreatitis.
  - Anxiety.

CHEST PAIN ASSESSMENT :

- **History of the pain (vitally important) :**
  - Nature. Site. Severity.
  - Radiation. Onset. Exac/relieving factors.
  - Associated features. Duration. Previous similar pains.
- **RISK FACTORS :**
  - Family history. Smoking. Raised BP.
  - Raised cholesterol. Past Medical History (IHD, diabetes).
- **Initial Approach :**
  - Assume the worst! 100% Oxygen. IV access.
  - Monitoring. ECG quickly. Done in tandem with history taking.
- **Examination :**
  - **General Examination** : sweaty, clammy, pale, cyanosed, anaemic …etc pulse, BP
  - **Cardiovascular / Respiratory examination :** ? Failure (crackles, oedema, raised JVP)
  - **Heart Sounds :** rate, nature, quiet ? added heart sounds, murmurs ?



CHEST PAIN INVESTIGATIONS :

- 12 Lead ECG.
- Cardiac Enzymes (incl Troponins).
- CXR.
- ECG most important.
- 20% of patients having an MI will have a normal ECG initially.
- Negative cardiac enzymes in A&E are not helpful.
- CXR useful to rule out other causes.

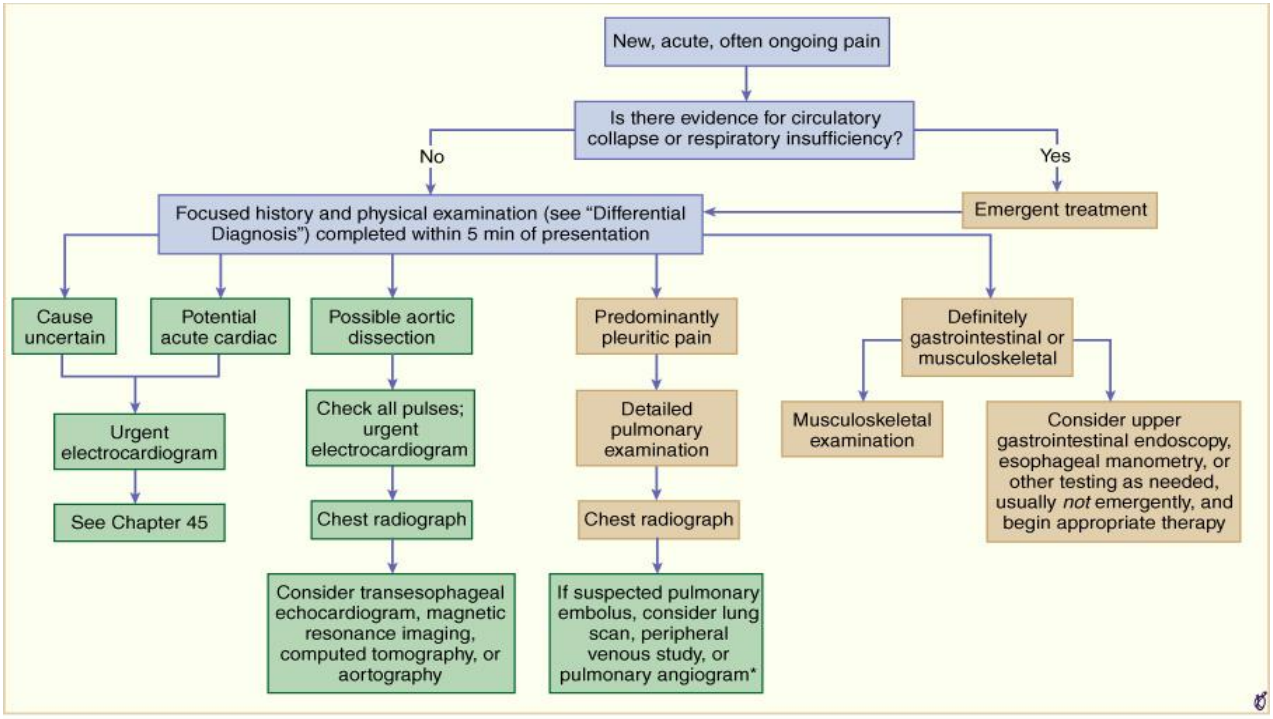


TABLE 7–3 Cardiovascular Causes of Chest Pain

Condition	Location	Quality	Duration	Aggravating or Relieving Factors	Associated Symptoms or Signs
Angina	Retrosternal region: radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms—left common	Pressure, burning, squeezing, heaviness, indigestion	<2-10 min	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal) angina may be unrelated to activity, often early morning	S_4, or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	Usually <20 min	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina, but can be pronounced. Transient cardiac failure can occur
Myocardial infarction	Substernal and can radiate like angina	Heaviness, pressure, burning, constriction	Sudden onset, 30 min or longer, but variable	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting
Pericarditis	Usually begins over sternum or toward cardiac apex and can radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia	Sharp, stabbing, knifelike	Lasts many hours to days; may wax and wane	Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward	Pericardial friction rub
Aortic dissection	Anterior chest; can radiate to back	Excruciating, tearing, knifelike	Sudden onset, unrelenting	Usually occurs in setting of hypertension or predisposition such as Marfan syndrome	Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurological deficit
Pulmonary embolism (chest pain often not present)	Substernal or over region of pulmonary infarction	Pleuritic (with pulmonary infarction) or angina-like	Sudden onset; minutes to <1 hr	Can be aggravated by breathing	Dyspnea, tachypnea, tachycardia; hypotension, signs of acute right-sided heart failure, and pulmonary hypertension with large emboli; rales, pleural rub, hemoptysis with pulmonary infarction
Pulmonary hypertension	Substernal	Pressure; oppressive		Aggravated by effort	Pain usually associated with dyspnea; signs of pulmonary hypertension

From Andreoli TE, Bennett JC, Carpenter CCJ, Plum F: Evaluation of the patient with cardiovascular disease. *In* Cecil Essentials of Medicine, 4th ed. Philadelphia, WB Saunders, 1997, p 11.

Case 1 :

A 65 year-old male presents with a 2-hour history of central chest pain. He describes it as "though an elephant is sitting on my chest". He gets similar symptoms when walking 2 blocks and is relieved with rest. Today's episode began after he walked to the bathroom and was not relieved by rest.

1) What is the most likely diagnosis? What other clues in his history would support the diagnosis?

2) What is the difference between stable angina and unstable angina?

- The patient's BP is 140/75 and his HR is 110 and regular. His JVP is at 3 cm ASA, he has no crackles, no murmurs and no peripheral edema. His EKG is EKG #1.

3) How would you manage this patient?

4) Would your management strategy change if he presented with EKG #2?

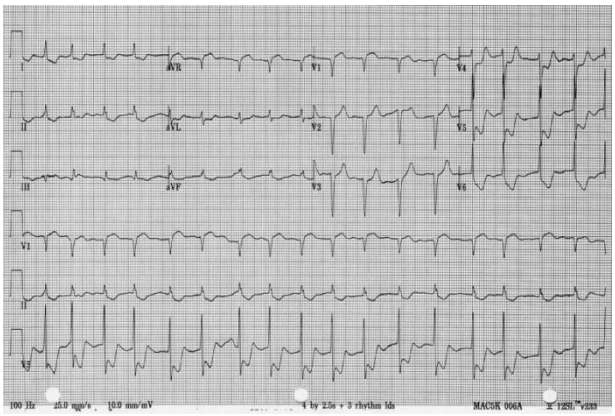
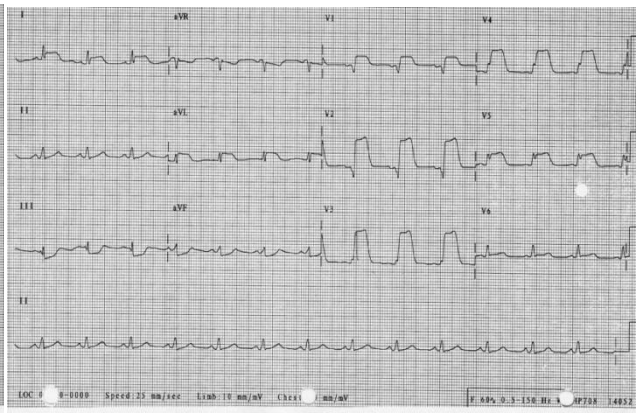
5) Outline the indications and contraindications to thrombolysis.

- **The patient stabilizes and is admitted to the CCU (Cardiac Care Unit). He develops chest pain again 2 days later but of a different quality. The pain is worse when he is supine and improves when he sits up.**

6) What is a possible diagnosis?

7) What clinical and diagnostic clues would help confirm the diagnosis?

8) What is the management? What should you look out for?

1) Myocardial ischemia or infarction :

- History :
  - Pressure-type of chest pain.
  - Generally involves central to left-sided pain with radiation to jaw or arms.
  - Exacerbated by activity, relieved with rest.
  - Relieved with nitro spray.
  - Associated with nausea, diaphoresis, syncope, shortness of breath.
  - Enquire about cardiac risk factors : age, sex, smoking history, diabetes, hypertension, hyperlipidemia, previous myocardial infarction and family history.
- Physical exam :
  - Does the patient look distressed?
  - ↓BP indicates cardiogenic shock.
  - ↓HR may indicate block or increased vagal tone, ↑HR may indicate an ischemia-related tachyarrhythmia.
  - ↑JVP, pulsatile liver and peripheral edema seen in right-sided heart failure.
  - Oxygen desaturation, crackles, S3 seen in left-sided heart failure.
  - New murmurs : mitral regurgitation murmur in papillary muscle dysfunction.
  - Look for other signs of vasculopathy (carotid, abdo, femoral bruits, peripheral pulses).
- Investigations :
  - EKG (should be knee-jerk reflex in chest pain scenario!) – see section on approach to EKG.
  - CXR to look for signs of congestive heart failure.
  - Cardiac enzymes : CK (will begin to rise 6 hours after infarct and remain elevated for 24-48 hours), troponin (will begin to rise 12 hours after infarct and remain elevated for 2 weeks).
    - Need to follow serially if first set negative.
  - Exercise-stress test, dobutamine stress echo, myocardial perfusion scan : useful to look for inducible ischemia if unsure.
  - Coronary angiography : gold-standard.
- Management :
  - **Morphine for pain.**
  - **Oxygen if hypoxic.**
  - **Nitro spray/drip for pain.**
  - **Aspirin.**
  - **Anticoagulation.**
  - **Lasix if in congestive heart failure.**
  - **Inotropes if in cardigenic shock.**
  - **Streptokinase (thrombolysis-TPA or TNK more commonly used).**
  - Also, think of beta-blockers (reduce heart rate and contractility but beware of worsening of CHF). Statins and Ace-inhibitors should be added as indicated.
  - Primary angioplasty may be indicated.

Case 2 :

A 78 year-old woman presents with sudden-onset, sharp right-sided chest pain. She has been coughing since the onset of her pain and has noted that she is dyspneic. Her pain significantly worsens with inspiration.

1) What diagnoses are you considering?
2) What clinical clues can help?

- **She reports some hemoptysis and has a documented fever. Her CXR shows some changes likely consistent with atelectasis in the right lower lung field.**

3) What is your next step?

- **On further questioning you get a history of calf tenderness just prior to the onset of chest pain.**

4) What test would you order?
5) What is your management strategy?

2) Pulmonary Embolus :

- History :
  - Sudden-onset sharp chest pain.
  - Exacerbated by inspiratory effort.
  - Can be associated with hemoptysis, sycope, dyspnea, calf swelling/pain from DVT.
  - Risk factors : immobilization, fracture of a limb, post-operative complications, hypercoagulable states (underlying carcinoma, high-dose exogenous estrogen administration, pregnancy, inherited deficiencies of antithrombin III, activated protein C, S, lupus anticoagulant, prior history of DVT/PE [Virchow's triad].
- Physical exam :
  - Anxious patient, sense of impending doom.
  - Tachycardia, tachypnea, hypoxia.
  - If severe, can get hypotension, syncope, and RV failure (↑JVP, RV heave and loud/palpable P2).
- Investigations :
  - ↓PaO^2 and ↓$PaCO^2$ from increase in overall minute ventilation.
  - Increased A-a gradient.
  - D-dimer is sensitive but has a low specificity. Do NOT order it to rule-in a PE!
  - CXR :
    - **a.** Frequently normal.
    - **b.** Often non-specific (atelectasis, pleural effusion).
    - **c.** May see Hampton's hump (area of infarction), Westermark's sign (area of oligemia/decreased vascular markings).
  - EKG : sinus tachycardia most common, S1Q3 inverted T3 with large embolus (classic, but rare!), look for right-axis deviation.
  - Echo : if large embolus, can see signs of right-sided compromise.
  - V/Q scan (Ventilation Perfusion Ratio) very sensitive but not specific.
  - Spiral CT with contrast show large, central emboli.
  - Pulmonary angiogram is gold standard but carries risk.
  - Consider Doppler U/S of legs.
- Management :
  - Anticoagulation to prevent further thrombus (heparin initially and then coumadin with therapeutic INR level of 2-3 for 6 months – length of therapy still controversial).
  - Thrombolysis if hemodynamically unstable.
  - Supportive treatment with oxygen, and fluids.

Case 3 :

A 23 year-old man with Marfanoid appearance presents to the ER with acute onset of sharp right-sided chest pain and SOB. His BP is 80/60 and he has decreased breath sounds on the right side.

1) What is the most likely diagnosis?
2) What is your next step?

- **The patient is appropriately managed but continues to be hypotensive. On further questioning he remarks that his chest pain radiates to his back between his shoulder blades.**

3) What additional diagnoses should be considered now?
4) What investigations would help confirm the diagnosis?
5) How would you manage this patient?

3) Pneumothorax :

- History :
  - Can be asymptomatic or present with acute pleuritic chest pain and dyspnea.
  - **Primary** pneumothorax predominantly in healthy young tall males.
  - **Secondary** :
    - **a.** Due to trauma (MVA accidents – associated with rib fractures, iatrogenic – during line placement, thoracentesis).
    - **b.** Increased alveolar pressure from asthma or barotraumas (BiPAP, ventilator-associated).
    - **c.** Rupture of bleb in COPD patients.
    - **d.** Necrosis of tissue in pneumonia, empyema, cancers.
- Physical exam :
  - Decreased expansion of chest, decreased breath sounds and decreased tactile/vocal fremitus on side of pneumothorax.
  - Hyperresonant percussion note.
  - In tension pneumothorax, where pleural injury produces a one-way valve, increased positive pressure can cause tracheal deviation away from the side of the pneumothorax, mediatinal shift with compression of contralateral lung, decreased venous return and CO and BP. This is an emergency.
- Investigations :
  - CXR : fine line of visceral pleural detached from parietal pleura seen on ipsilateral side.
  - In large pneumoathoraces, mediastinal shift and contralateral compression of lung can be seen.
- Management :
  - Watchful wait for small pneumothoraces – repeat CXR.
  - Chest tube insertion for large, hemodynamically unstable pneumothoraces.
  - In emergent situation, insert large bore needle in 2nd ICS, midclavicular line, followed then by chest tube insertion.

Heart Failure

Dr. Khalid Al Habib

◈ ***Definition :-***

- Inability to maintain a cardiac output adequate for the body's need.
- It is considered to be a clinical syndrome , because despite different causes , it is associated with cardiac dilation and impaired cardiac contractility .
- It is commonly termed congestive heart failure (CHF) since symptoms of increase venous pressure are often prominent

◈ ***Epidemiology :***

- It is Primarily a disease of old age , affecting 30% of people over 80 years.
- Improvements in the managements of acute MI & chronic heart disease has led to more heart failure rates , because more patients survive to develop it later in life .

◈ ***Prevalence***

- Prevalence 0.4-2% overall, 3-5 % in over 65s, 10% of over 80s
- Commonest medical reason for admission
- Annual mortality of 60% over 80s
- > 10% also have AF
- Progressive condition - median survival 5 years after diagnosis

◈ ***Aetiology:-***

- It is a common end point for many diseases of cardiovascular system
- It can be caused by :
  - Inappropriate work load (volume or pressure overload)
  - Restricted filling
  - Myocyte loss

Causes of Left heart failure:

1- Inadequate LV filling :

- Mitral stenosis.
- LV diastolic dysfunction (LVH)
- Pericardial diseases, Restrictive cardiomyopathy, tachyarrhythmia

2- Pressure overload :

- Aortic stenosis (outflow obstruction)
- Systemic Hypertension.

3- Volume overload :

- Aortic or mitral regurgitation.
- High output failure , e.g. anemia

4- LV muscle disease :

- Post Myocardial infarction .
- Cardiomyopathy.
- Myocarditis .
- **Chronic ischemia** (the commonest cause)
- Connective tissue diseases (Infection, Poisons)

Causes of Right heart failure :

1- Any Cause of LHF .

2- Pulmonary hypertension (lung disease) .

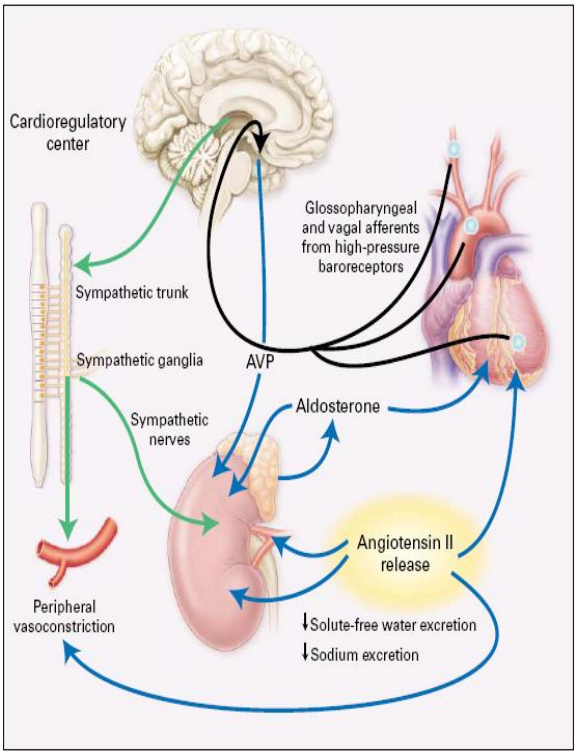
3- Atrial septal defect .

◈ ***Pathophysiology :-***

A. Hemodynamic changes

From hemodynamic stand point HF can be secondary to systolic dysfunction or diastolic dysfunction

B. Neurohormonal changes



⊙ ↑ **Sympathetic activity**

- Favorable effect:
  - HR ,↑ contractility, vasoconstriction. → ↑ V return, ↑ filling
- Unfavorable Effect:
  - Arteriolar constriction → Afterload→↑ workload →↑ O_2 consumption

⊙ ↑ **Renin-Angiotensin – Aldosterone,**

- Favorable effect: Salt & water retention→↑ VR
- Unfavorable Effect: Vasoconstriction → ↑ after load

⊙ ↑ **interleukins &TNF**α

- Favorable effect: May have roles in myocyte hypertrophy
- Unfavorable Effect: Apoptosis

⊙ ↑**Endothelin**

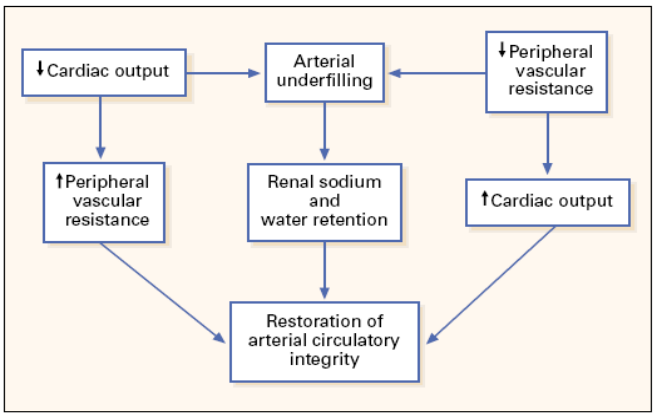
- Favorable effect: Vasoconstriction→↑ VR
- Unfavorable Effect: ↑ After load

C. Cellular changes:

- ✓ Changes in Ca^{+2} handling.
- ✓ Changes in adrenergic receptors:
  - Slight ↑ in α_1 receptors
  - β_1 receptors desensitization → followed by down regulation
- ✓ Changes in contractile proteins
- ✓ Program cell death (Apoptosis)
- ✓ Increase amount of fibrous tissue

❖ **Compensatory Mechanisms in CHF**

- Neurohormonal system
- Renin-angiotensin-aldosterone system
- Ventricular hypertrophy



Cardiac Damage → ↓Cardiac Output → Neuroendocrine Activation → Fluid Retention, And ↑Peripheral Resistance

❖ **Body-Fluid Volume**

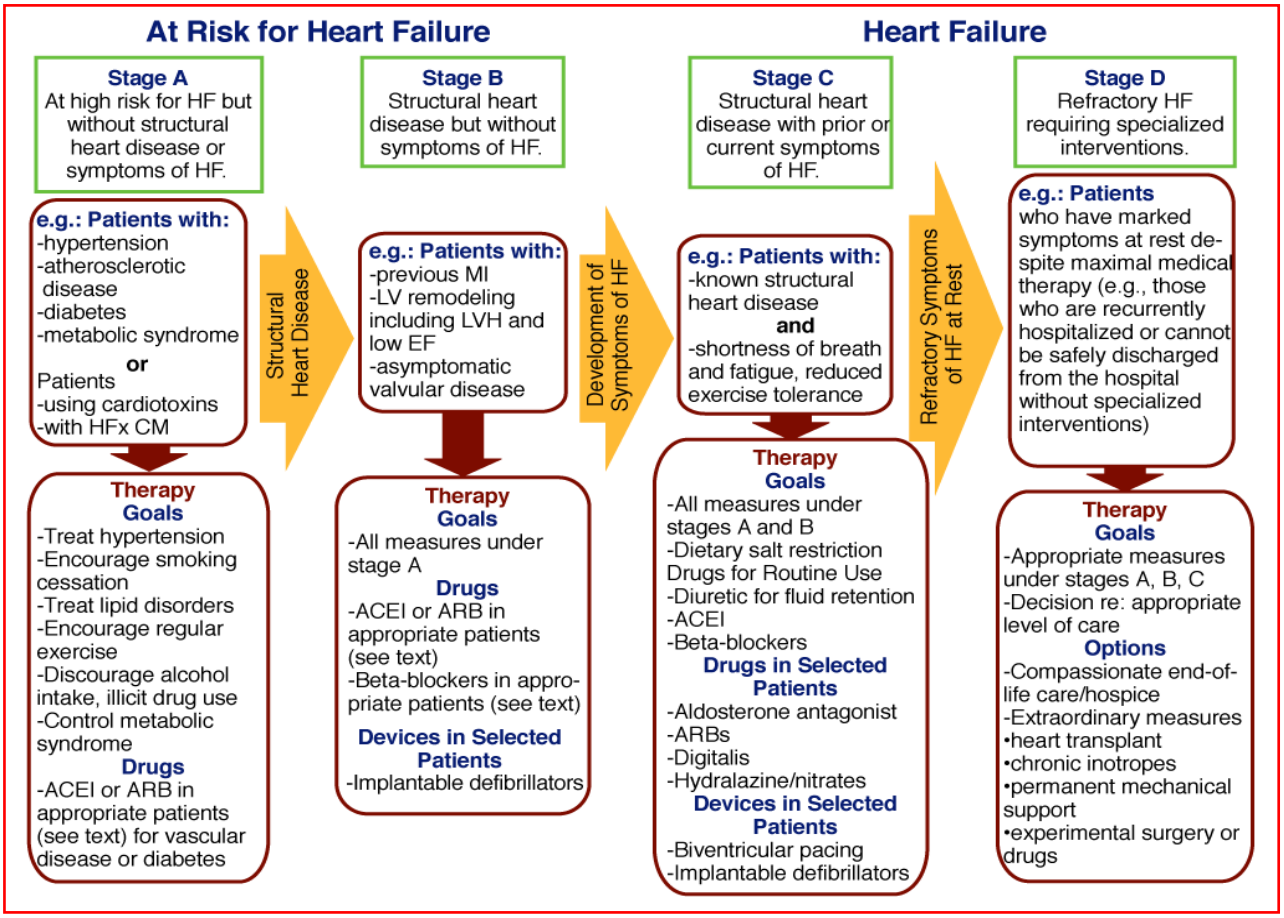
Renal Na and water excretion

- Dependent on arterial circulation
- Cardiac output and peripheral resistance
- Decrease in circulation leads to ***arterial underfilling***
- Decreased effective circulating volume

Neurohormonal reflexes are triggered

◈ *Stages of HF*

Stage	Description	Examples
A	**Patients at high risk for developing HF** because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium , myocardium , or cardiac valves and have never shown signs or symptoms of HF .	Systemic hypertension , coronary artery disease, diabetes mellitus, history of cardiotoxic drug therapy or alcohol abuse, personal history of rheumatic fever, family history of cardiomyopathy
B	**Patients who have developed structural heart disease** that is strongly associated with the development of HF **but who have never shown signs or symptoms of HF.**	Left ventricular hypertrophy or fibrosis, LV dilatation or hypocontractility, asymptomatic valvular heart disease, previous MI.
C	**Patients who have current or prior symptoms of HF** associated with underlying structural heart disease .	Dyspnea or fatigue due to LV systolic dysfunction, asymptomatic patients who are undergoing treatment for prior symptoms of HF.
D	**Patients with advanced structural heart disease and marked symptoms of HF at rest** despite maximal medical therapy and who require specialized intervention.	Patients who are frequently hospitalized for HF and cannot be safely discharged from the hospital, patients in the hospital waiting heart transplantation, patients at home receiving continuous IV support for symptom relieve or being supported with mechanical circulatory assist device.



◈ ***Typical Presentations Of Heart Failure***

- Syndrome of decrease exercise tolerance
- Syndrome of fluid retention
- No symptoms but incidental discovery of LV dysfunction

☙ HISTORY

- Underlying causes –CAD, valvular disease, hypertension, family history etc.
- Aggravating factors –arrhythmias (AF), anemia etc.
- Co-morbidities/differential diagnoses –COPD, obesity, chronic venous insufficiency, .. etc.

☙ Examination

- Raised JVP, peripheral edema, ascites
- Signs of poor tissue perfusion
- Pulse –tachycardia, irregular, thready, pulsus alternans
- Added heart sounds, murmurs, bibasilar inspiratory crackles

◈ ***Symptoms & Signs :***

- Symptoms
  - SOB, Orthopnea, paroxysmal nocturnal dyspnea
  - Low cardiac output symptoms
  - Abdominal symptoms:

    Anorexia, nausea, abdominal fullness, Right hypochondrial pain.
- Physical Signs:
  - High diastolic BP & occasional decrease in systolic BP (decapitated BP)
  - JVD (Jugular Venous Distension)
  - Rales *(Inspiratory)*
  - Displaced and sustained apical impulses
  - Third heart sound – *low pitched sound that is heard during rapid filling of ventricle*
    - Mechanism of S_3 sudden deceleration of blood as elastic limits of the ventricles are reached
    - Vibration of the ventricular wall by blood filling
    - Common in children
  - Fourth heart Sound (S_4)
    - Usually at the end of diastole
    - Exact mechanism is not known
    - Could be due to contraction of atrium against stiff ventricle
  - Pale, cold sweaty skin

- Left Heart Failure :	
■ **Symptoms :** Shortness of breath, Orthopnea, PND.	■ **Signs :** Tachypnoea, Tachycardia, 3rd heart sound on auscultation, Bibasilar pulmonary crepitations .

- Right Heart Failure :	
■ **Symptoms : Non specific such as :** Fatigue, Anorexia, Nausea .	■ **Signs :** JVP, Hepatomegaly, Pitting edema (ankles and pedal), Ascites, Functional tricuspid incompetence.

NYHA Class (Imp.)

•	**I**	No limitation of activities; They suffer no symptoms from ordinary activities
•	**II**	Slight, mild limitation of activity; They are comfortable with rest or with mild exertion
•	**III**	Marked limitation of activity; They are comfortable only at rest
•	**IV**	Confined to bed or chair; Any physical activity brings on discomfort and symptoms occur at rest

❖ Framingham Criteria for Diagnosis of Heart Failure

- **Major Criteria:**
  1. PND.
  2. JVD
  3. Rales.
  4. Cardiomegaly
  5. Acute Pulmonary Edema
  6. S_3 Gallop
  7. Positive hepatic Jugular reflex
  8. ↑ venous pressure > 16 cm H_2O
- **Minor Criteria**
  1. Lower Limb edema,
  2. Night cough,
  3. Dyspnea on exertion,
  4. Hepatomegaly,
  5. Pleural effusion,
  6. Tachycardia 120 bpm,
  7. Weight loss 4.5 kg over 5 days management

❖ Forms of Heart Failure

- **Systolic & Diastolic**
- **High Output Failure:** Pregnancy, anemia, thyrotoxicosis, A/V fistula, Beriberi, Paget's disease
- **Low Output Failure**
- **Acute**: large MI, aortic valve dysfunction---
- **Chronic**

◈ Right vs. Left sided heart failure:

◈ Right sided heart failure :

Most common cause is left sided failure **(Biventricular "congestive" Heat Failure is the most common)**
Other causes included : Pulmonary embolisms, Other causes of pulmonary HTN, RV infarction, MS.
Usually presents with: LL edema, ascites, hepatic congestion, cardiac cirrhosis (on the long run).

Differential diagnosis

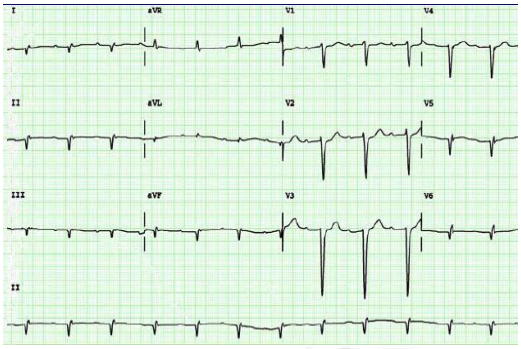
- Pericardial diseases
- Liver diseases
- Nephrotic syndrome
- Protein losing enteropathies

Laboratory Findings

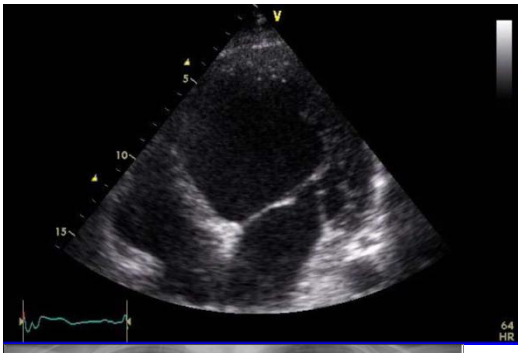
- Anemia
- Hyperthyroid
- Chronic renal insufficiency
- electrolytes abnormality
- Pre-renal azotemia
- Hemochromatosis

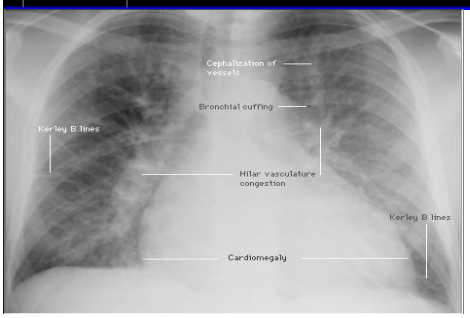
◈ ***Investigations :***

- ECG (Low sensitivity and specificity)
  - Old MI or recent MI
  - Arrhythmia
  - Some forms of Cardiomyopathy are tachycardia related
  - LBBB (Left Bundle Branch Block)→ *may help in management*
- Echocardiography
  - Function of both ventricles
  - Wall motion abnormality that may signify CAD
  - Valvular abnormality
  - Intra-cardiac shunts
- Chest x ray (Low sensitivity and specificity)
  - Size and shape of heart
  - Evidence of pulmonary venous congestion
    (dilated of upper lobe veins → perivascular edema)
  - Pleural effusion



- ***Cardiac Catheterization***
  - When CAD or valvular is suspected
  - If heart transplant is indicated
- Nuclear isotope scanning .
- 24 hr ECG to investigate arrhythmias .
- Blood tests (anemia)



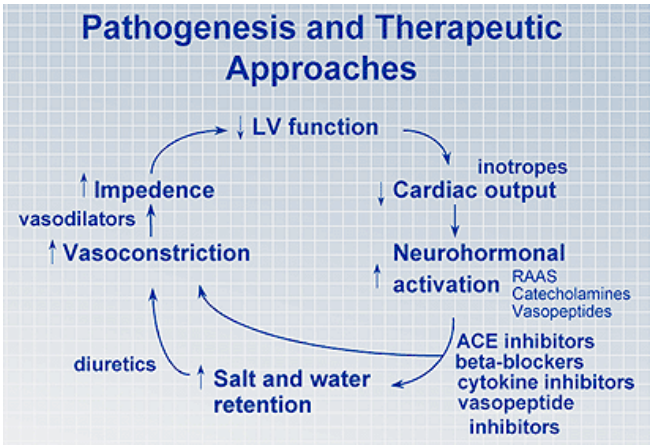


In conclusion, congestive heart failure is often assumed to be a disease when in fact it is a syndrome caused by multiple disorders.

◈ ***Treatment:***

General Measurement, Medical, Or Surgical

- Correction of reversible causes
  - Ischemia
  - Valvular heart disease
  - Thyrotoxicosis and other high output status
  - Shunts
  - Arrhythmia
    - atrial fibrillation, flutter, PJRT
  - Medications
    - Ca channel blockers, some antiarrhythmics



✓ General Measurements :

- **Treat the underlying cause.**
- **Treat HTN and CAD aggressively.**
- ***Diet and Activity***
  - Salt restriction
  - Fluid restriction
  - Daily weight (tailor therapy)
  - Gradual exertion programs

✓ Medical Treatment :

- Diuretics.
- ACE inhibitors .
- Angiotensin II receptor antagonist.
- B- blockers.
- Digoxin

❖ Diuretics are Classified into :

(A) Loop diuretics e.g. furosomide, bumetanide.

- MOA : Inhibit Na reabsorption in the ascending limb of the loop of Henle.
- They are potent .
- Side Effects : Marked renal k loss, Promote hyperuricemia, pre-renal azotemia, Hypokalemia, Skin rash, ototoxicity

Used for severe heart failure → loop diuretics

Lasix (20 – 320 mg QD), Furosomide , Or **Bumex** (Bumetanide 1-8mg), Or **Torsemide** (20-200mg) .

(B) Thiazides e.g. bendroflumethiazide.

-MOA : Inhibit Na reabsorption in the distal renal tubule.

-Mild diuretics **except metolazone** (which causes excess dieresis and used in severe & resistant heart Failure)

-S/E : -Hypokalemia, Hyperglycemia & hyperuricemia.

(C) K- sparing diuretics

spironolactone (Aldosterone inhibitor), **Triamterene & amiloride** (acts on distal tubules to ↓ K secretion)

recent evidence suggests that it may improve survival in CHF patients due to the effect on renin-angiotensin-aldosterone system with subsequent effect on myocardial remodeling and fibrosis

- MOA :Increase Na secretion on the distal nephron and inhibit K secretion.
- S/E :Gynaecomastia, nausea and abdominal pain.

❖ Inhibitors of renin – angiotensin - aldosterone system

- Renin - angiotensin - aldosterone system is activation early in the course of heart failure and plays an important role in the progression of the syndrome
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptors blockers
  - Spironolactone

❖ ACE Inhibitors :

- **E.g. captopril , enalapril , lisinopril .**
- *They block the R-A-A system by inhibiting the conversion of angiotensin I to angiotensin II → vasodilation*
  ↓ Na retention, and ↓ Water retention.
- *↓ Bradykinin degradation →* ↑ *its* level → ↑ *PG secretion & nitric oxide*
- Ace Inhibitors were found to improve survival in CHF patients
  - Delay onset & progression of HF in pts with asymptomatic LV dysfunction
  - ↓ cardiac remodeling
- MOA :
  - Inhibit angiotensin II.
  - Increase cardiac output by decreasing preload and afterload .
  - Decrease vascular resistance and PCWP (Pulmonary Capillary Wedge Pressure) .
- Common Side Effect :
  - **First dose hypotension** particularly in patients receiving diuretics**.**
  - So, the dose of diuretics, 24 hr before first dose of ACEI , should be started with low dose followed by gradual increase every 1-2 weeks.
  - Hyperkalemia.
  - Other S/E: angioedema, persistent cough(↑ *bradykinin)*, Renal insufficiency , and Rash
- **Contraindicated for patients with bilateral renal artery stenosis.**
- Studies Of LVD (SOLVD) .Enalapril.
  - Decrease all cause mortality 16% - Decrease mortality from HF 22%

❖ Angiotensin 2 receptor antagonist :

e.g. losartan ,valsartan.
They block binding of angiotensin 2 with type 1 receptors.
Do not produce cough, And Has comparable effect to ACE I
Can be used in certain conditions when ACE I are contraindicated (angioneurotic edema, cough)
Contraindicated for patients with bilateral renal artery stenosis.

❖ B – blockers : e.g. metoprolol, bisoprolol, carvedilol.

- Has been traditionally contraindicated in pts with CHF
- Now they are the main stay in treatment on CHF & may be the only medication that shows substantial improvement in LV function
- In addition to improved LV function multiple studies show improved survival
- The only contraindication is severe decompensated CHF

❖ **Digoxin :** ((No mortality benefit))

- The role of digitalis has declined somewhat because of safety concern
- Recent studies have shown that digitals does not affect mortality in CHF patients but causes significant
  - Reduction in hospitalization
  - Reduction in symptoms of HF
- Mechanism of Action
  - +ve inotropic effect by ↑ intracellular Ca & enhancing actin-myosin cross bride formation (binds to the Na-K ATPase → inhibits Na pump → ↑ intracellular Na → ↑ Na-Ca exchange
  - Vagotonic effect
  - Arrhythmogenic effect

- ***Digitalis Toxicity***
  - Narrow therapeutic to toxic ratio
  - Non cardiac manifestations (Anorexia, Nausea, vomiting, Headache, Xanthopsia sotoma, Disorientation)
  - **Cardiac manifestations**
    - Sinus bradycardia and arrest
    - A/V block (usually 2nd degree)
    - Atrial tachycardia with A/V Block
    - Development of junctional rhythm in patients with atrial fibrillation
    - PVC's (Premature Ventricular Complexes) , Ventricular Tachycardia/ Ventricular fibrillation (bi-directional VT).

  - Treatment of the toxicity:
    - Hold the medications
    - Observation
    - In case of A/V block or severe bradycardia → atropine followed by temporary PM if needed
    - In life threatening arrhythmia → digoxin-specific fab (Fragment-antigen-binding) antibodies
    - Lidocaine and phenytoin could be used – try to avoid D/C cardioversion in non life threatening arrhythmia

❖ ***Vasodilators***

- **Reduction of afterload** by arteriolar vasodilatation (hydralazin) → reduce LVEDP(Left ventricular end diastolic pressure), O_2 consumption, improve myocardial perfusion, ↑ stroke volume and COP
- **Reduction of preload** By venous dilation (Nitrate) → ↓ the venous return →↓ the load on both ventricles.
- Usually the maximum benefit is achieved by using agents with both action.

❖ ***Positive inotropic agents***

- These are the drugs that improve myocardial contractility (β adrenergic agonists, dopaminergic agents, phosphodiesterase inhibitors)
- dopamine, dobutamine, milrinone, amrinone
- Several studies showed ↑ mortality with oral inotropic agents
- So the only use for them now is in acute sittings as cardiogenic shock

❖ ***Anticoagulation (coumadine)***

- Atrial fibrillation
- History of embolic episodes
- Left ventricular apical thrombus

❖ ***Antiarrhythmics***

- Most common cause of Sudden Cardiac Death in these patients is ventricular tachyarrhythmia

- Patients with history of sustained ventricular tachycardia or SCD → ICD (Implantable Cardioverter Defibrillator) implant
- Patients with non sustained ventricular tachycardia
  - Correction of electrolytes and acid base imbalance
  - In patients with ischemic cardiomyopathy → ICD implant is the option after rule out acute ischemia as the cause
  - In patients with non ischemic cardiomyopathy management is ICD implantation

❖ ***New Methods***
- **Implantable ventricular assist devices**
- **Biventricular pacing** (only in patient with LBBB & CHF)
- **Artificial Heart**

✓ Surgery :

Cardiac transplantation .

- It has become more widely used since the advances in immunosuppressive treatment
- Has 90% 1-year survival after surgery .
- 75% alive after 5 years.
- Death usually due to :

  1- operative mortality.

  2- 2- organ rejection.

◈ ***Complications :***

- Thromboembolism
- AF
- Ventricular arrhythmia

◈ ***Prognosis***

- Annual mortality rate depends on patients symptoms and LV function
- 5% in patients with mild symptoms and mild ↓ in LV function
- 30% to 50% in patient with advances LV dysfunction and severe symptoms
- 40% – 50% of death is due to SCD

◈ ***Questions***

❖ What is New York HF classification ?

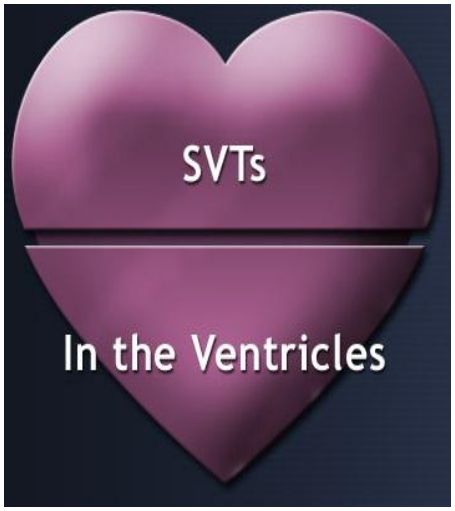
❖ What are the C/I of ACE inhibitors ?

Arrhythmia

Dr. Ahmad Hersi

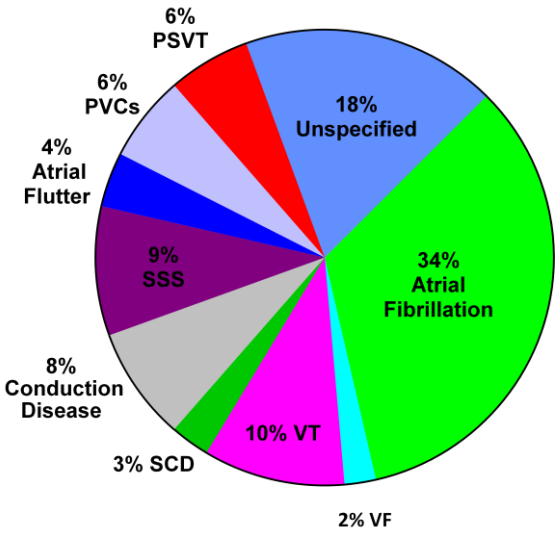
Arrhythmia is the absence of normal rhythm

- Sinus Tachcardia
- Atrial Tachycardia
- Atrial Flutter
- Atrial Fibrillation
- AVRT
- AVNRT
- Junctional Tachycardia



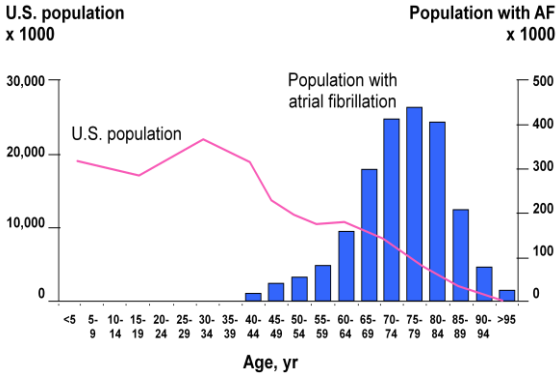
- Ventricular Tachycardia (VT)
- Ventricular Fibrillation (VF)
- Torsade de point
- Polymorphic VT

- **Atrial fibrillation accounts for 1/3 of all patient discharges with arrhythmia as principal diagnosis.**



Outline Atrial Fibrillation Description :

- In AF, the atrium beats rapidly and ineffectively as the ventricles respond at irregular intervals and the cardiac output will be affected .
- Normally, the AV node is responsible for slowing down the ventricular beats to protect it.
- AF is characterized by:
  - Chaotic and disorganized atrial activity.
  - Irregular heartbeat.
  - Can be paroxysmal, persistent or permanent (chronic).
  - Most common sustained arrhythmia.
  - Can be symptomatic or asymptomatic.
  - Incidence increases with age.
  - Atrial Fibrillation Demographics by Age.



Atrial Fibrillation :

- Common and age-dependent 2 - 4% over age 60.
- Significant risk of stroke 4% per year (Framingham Study) as a result of stagnation of the blood in the Left atrial appendage.
- High risk of embolism with cardioversion .
- **Incidence of AF :**
    - The Framingham Study 1982, *New England Journal of Medicine*.
    - Annual Incidence 0.1% Per Year.

Causes of Atrial Fibrillation :

- **Cardiac** :
    - Hypertensive heart disease.
    - Ischemic heart disease.
    - Valvular heart disease :
        - **Rheumatic :** mitral stenosis.
        - **Non-rheumatic :** aortic stenosis, mitral regurgitation.
    - Pericarditis.
    - Cardiac tumors : atrial myxoma.
    - Sick sinus syndrome.
    - Cardiomyopathy :
        - Hypertrophic.
        - Idiopathic dilated (? cause vs. effect).
    - Post-coronary bypass surgery.
- **Non-cardiac** :
    - **Pulmonary :**
        - COPD.
        - Pneumonia.
        - Pulmonary embolism.
    - **Metabolic** :
        - Thyroid disease : hyperthyroidism.
        - Electrolyte disorder like hypokalemia.
    - **Toxic :** alcohol ('holiday heart' syndrome).
- **"Lone" atrial fibrillation** :
    - Absence of identifiable cardiovascular, pulmonary, or associated systemic disease.
    - Approximately 0.8 - 2.0% of patients with atrial fibrillation (Framingham Study).
    - In one series of patients undergoing electrical cardioversion, 10% had lone AF.

Forms of AF :

- **Paroxysmal :** Paroxysmal lasting less than 48 hours, transient.
- **Persistent :** An episode of AF lasting greater than 48 hours, which can still be cardioverted to sinus rhythm by electrical cardioversion.
- **Permanent :** Inability of pharmacologic or non-pharmacologic methods to restore sinus rhythm.

Symptoms :

Palpitations, Presyncope, Fatigue, Chest pain, Dyspnea, Syncope.

Work-up :

EKG, ECHO, TFT, 24 h Holter, Others…

ECG Recognition :

- **Atrial Rate : > 300 bpm.**
- Rhythm : Irregularly irregular (the hallmark)
    - Ventricular Rate : Variable → Dependent upon :
        - AV node conduction properties.
        - Sympathetic and parasympathetic ton.
- **Recognition : Absence of P waves**

Atrial Fibrillation – Clinical Problems :

- Embolism and stroke (presumably due to LA clot).
- Acute hospitalization with onset of symptom.
- **Congestive heart failure :**
    - Loss of AV synchrony.
    - Loss of atrial "kick".
    - Rate-related cardiomyopathy due to rapid ventricular response.
- Rate-related atrial myopathy and dilatation.
- Chronic symptoms and reduced sense of well-being.

Management Strategies :

1. Prevention of Thromboembolis.
2. Rate control.
3. Restoration of sinus rhythm.

Therapeutic Approaches to Atrial Fibrillation :

- Anticoagulation.
- Antiarrhythmic suppression.
- Control of ventricular response :
    - Pharmacologic.
    - Catheter modification/ablation of AV node.
- Curative procedures :
    - Surgery (maze).
    - Catheter ablation.

1) Prevention of Thromboembolis

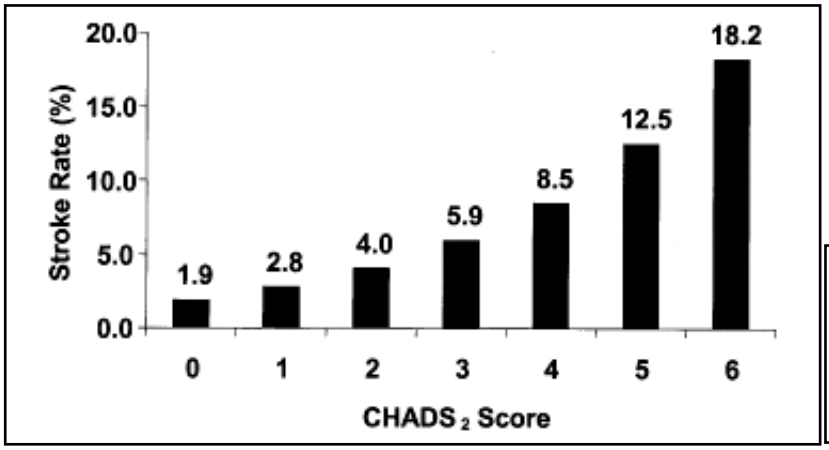
Atrial Fibrillation and Stroke :

- Risk : 5 - 8% per year in high-risk patients.
- Anticoagulant therapy is clearly indicated and beneficial in rheumatic atrial fibrillation.
- In non-rheumatic atrial fibrillation, major randomized trials have provided useful guidelines for identifying and treating patients at risk.

Anti coagulation therapy :
- We use aspirin with low risk group
- And use warfarin with high risk group
- We determinate these group by **CHADS score**

Predictors of Thromboembolic Risk in Atrial Fibrillation (CHADS2) :

- Congestive Heart Failure.
- Hypertension.
- Age ≥75 years.
- Diabetes.
- Stroke or TIA.



Risk Factors	Score
C Recent congestive heart failure	1
H Hypertension	1
A Age ≥75 yrs	1
D Diabetes mellitus	1
S_2 History of stroke or transient ischemic attack	2

$CHADS_2$ Score and Risk of Stroke

Notes

- CHADS is applied to NON valvular atrial fibrillation patients only.
- people with valvular disease they are at high risk to develop stroke so it's better to give them warfarin**.**
- the maximum number in CHADS score is 6
- Patient with score 2 and above is better to be treated with **warfarin**.
- patient with score blow 2 better to be treated with **aspirin.**
- the patient's INR (International Normalized Ratio for reporting prothrombin time) should be controlled when he start to take warfarin.
- Dabigatran (direct thrombin inhibitor) as good as warfarin but safer, so no need to do INR.

Examples :

- 70year old lady with diabetes and hypertension what is her CHADS score ?
  - **2 so we will give her warfarin.**
- 75 year old gentleman with no diabetes , no hypertension , no stroke and no heart failure what is his CHADS score ?
  - **1 so we will give him aspirin.**
  - If the patient live far away, we will give him aspirin even if his CHADS score 2 or above because of treatment complication (bleeding etc).

2) Restoration of sinus rhythm

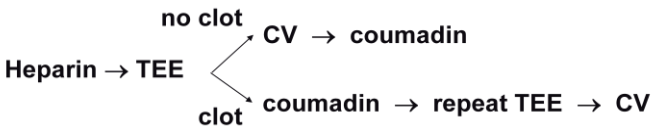
1. **Chemical: Antiarrhythmic Drugs to Suppress Atrial Fibrillation :**
   - **Class I agents** :
     - **IA : Quinidine, Procainamide, Disopyramide.**
     - **IC : Flecainide, Propafenone.**
   - **Class III agents** :
     - **Amiodarone, Sotalol.**

   Notes:

   - amiodarone : the most potent agent in restoring and maintaining sinus rhythm but has serious side effect ,so it used for elderly patients.
   - (flecanide , propafenone , sotalol) →are equally potent
   - Flecainide or peopafenone : the best in young patient.

2. **Electrical:**

   Timing of Cardioversion for Atrial Fibrillation :
   - **Chronic** : **1 month Coumadin → cardioversion (CV)**
   - **Uncertain duration : - Stable → 1 month Coumadin (trade name of warfarin)→ CV.**
     - Unstable → TEE → CV.
   - **Acute :**



3. **Surgical:** Open heart surgery(suturing the appendage)
4. **Catheter ablation** → 80 % successful

3) Rate control

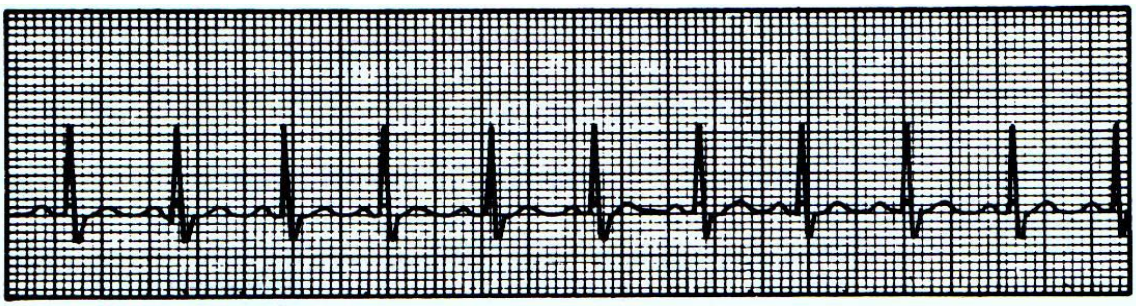
→it has to become less than 80 beat\min on rest & less than 110 on exertion

Control of Ventricular Rate in Atrial Fibrillation :

- **Digoxin.**
- **Calcium channel blockers : Verapamil, Diltiazem.**
- **Beta blockers**.

Notes:

- Ca blocker + b blocker → equally potent and superior than digoxin
- digoxin (weak – used only for elderly).
- Ca channel blockers used if the patient is asthmatic and beta blockers used if the patient is known to have IHD.



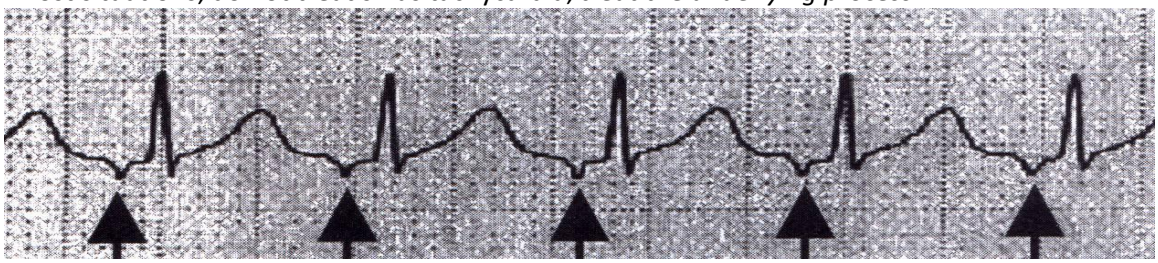
Sinus Tachycardia (ST)

Clinical Conditions Associated with Persistent Sinus Tachycardia :

- Fever.
- Volume depletion.
- Anemia.
- Sepsis (due to profound vasodilatation → reflex tachycardia).
- Pain / anxiety.
- Hypoxemia (PE / COPD).
- Cardiac conditions → decreased cardiac output (CHF / MI).
- Medications (B2 agonists).
- Drugs (crack / ephedrine).
- Hyperthyroidism.

Treatment of Sinus Tachycardia :

- Sinus tachycardia is almost always a *physiologic* response to a given stimulus or disease state.
- In most situations, do not treat sinus tachycardia, *treat the underlying process*.



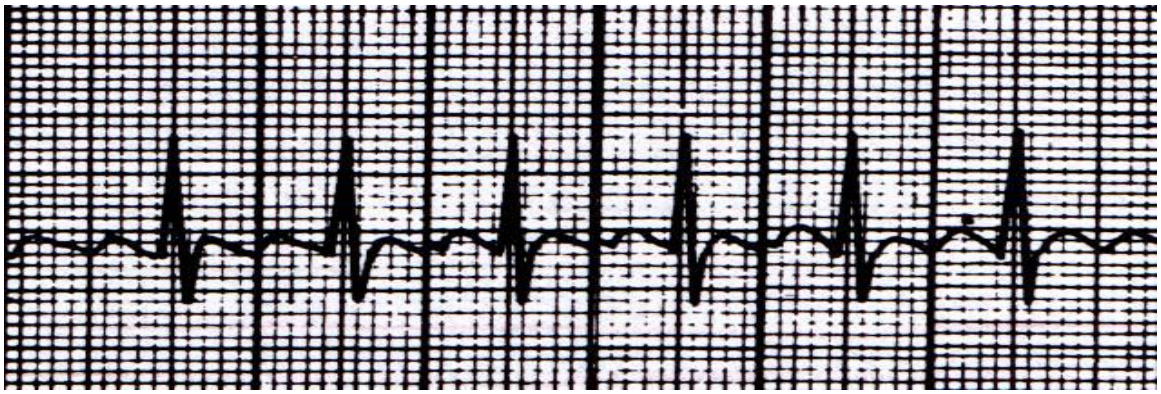
Focal Atrial Tachycardia

Causes of Atrial Tachycardia :

- Onset is often precipitated by increased sympathetic stimulation.
- **Specific examples :**
  - Digoxin toxicity (especially if AV block noted).
  - Theophylline (beta-agonist).
  - EtOH.
  - Myocardial ischemia.
  - Hypoxia.

Treatment of Atrial Tachycardia :

- **Rhythm often spontaneously resolves with normalization of sympathetic tone.**
- **If rhythm recurs repeatedly, consider Rx :**
  - *Step #1* – beta-blockers (BB).
  - *Step #2* – amiodarone (not if dig toxic).
  - Step #3 – radio-frequency ablation is **curative.**



Atrial Flutter with 2:1 AV block

Background - Atrial Flutter :

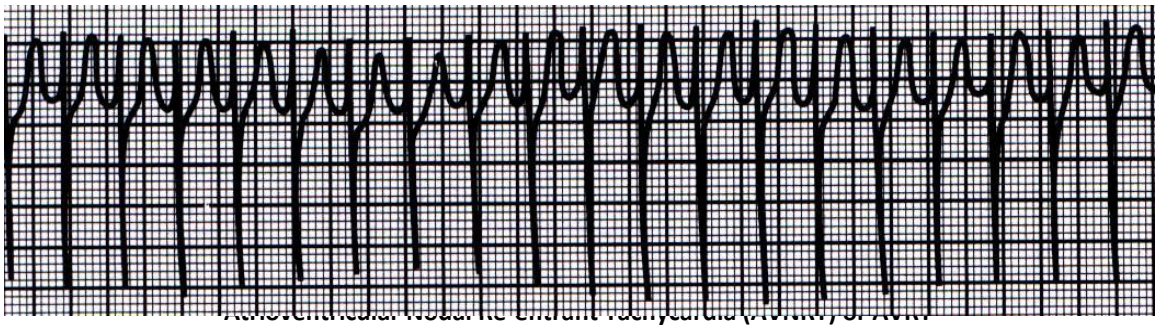
- **Underlying mechanism : large "macro re-entrant circuit" in the atrium, typically moves counter-clockwise**.
- Atrial rate range : 250-350 bpm**.**
- There is disturbance in diastole
- atrial flutter ECG shows saw-toothed like waves.
- If we see any disturbance in P interval → problem in atrium
- **Ventricular response depends on the degree of AV block :**
    - 2:1 block → ventricular rate = 150 bpm.
    - 3:1 block → 100 bpm.
    - 4:1 block → 75 bpm.

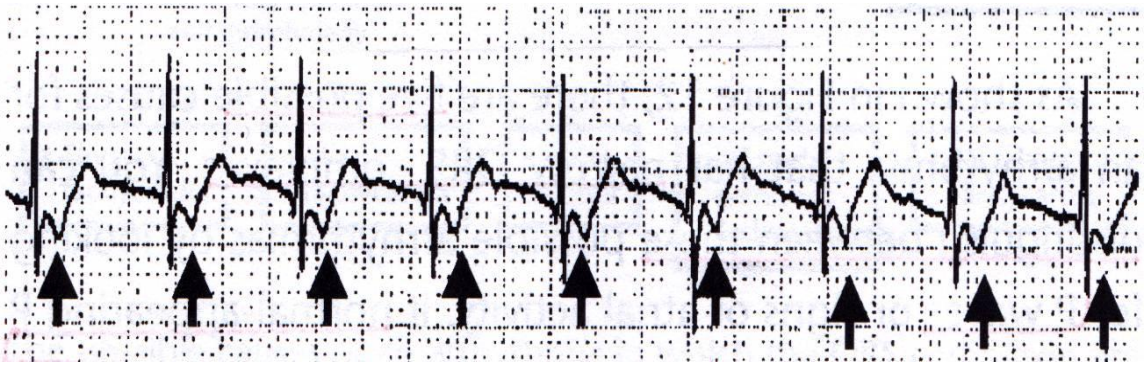
Causes of Atrial Flutter :

- **Most commonly occurs in male patients with dilated or distended atria with elevated left atrial pressure**.
- **Clinical scenarios :**
    - Systolic CHF with low EF.
    - Mitral regurgitation (MR).

Treatment of Atrial Flutter :

- ***Unstable*** patient (i.e. low BP / CP / AMS) :
    - Synchronized cardioversion as per ACLS.
    - 50J → 100J → 200J → 300J → 360J.
- ***Stable*** patient :
    - Rate control - just like atrial fibrillation (AFib).
    - Elective cardioversion - just like AFib.
    - Anti-coagulation – just like AFib.

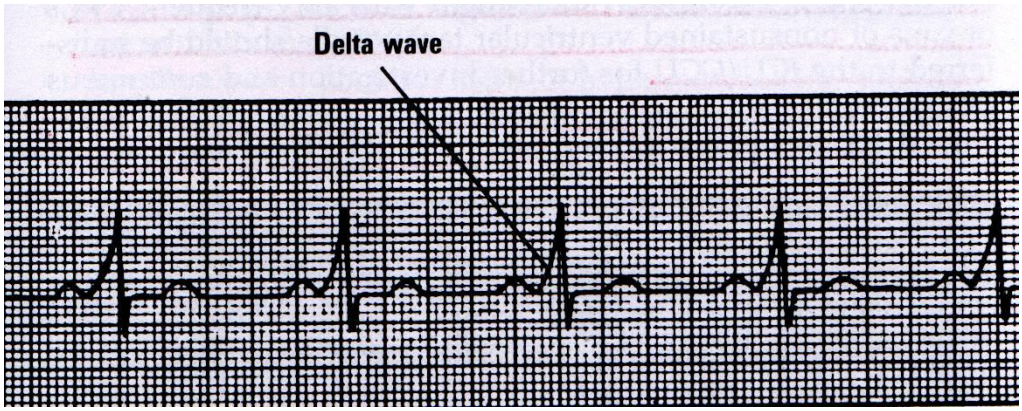




AVNRT or AVRT

Treatment of AVNRT / AVRT :

- ***Unstable*** **:**
  - Synchronized cardioversion start @ 50J (avoid if EF < 40%).
- ***Stable*** **:**
  - *Step #1* – attempt to terminate rhythm with vagal maneuvers (carotid massage / Valsalva).
  - *Step #2* – adenosine 6mg IVP → 12mg 2min later → 18mg 2min later.
  - *Step #3* – AV nodal blocking agents (BB / CCB > digoxin).
  - *Step #4* – amiodarone 150mg IV over 10min → 1mg/min x 6hrs → 0.5mg/min x 18hrs (max dose 2.2g/24hrs).
  - *Step #5* – in patients with bypass tracts not tolerating the medications, consider radio-frequency ablation.



Wolf-Parkinson-White (WPW) Syndrome

Take Home Messages – WPW :

- **Syndrome features :**
  - Short PR.

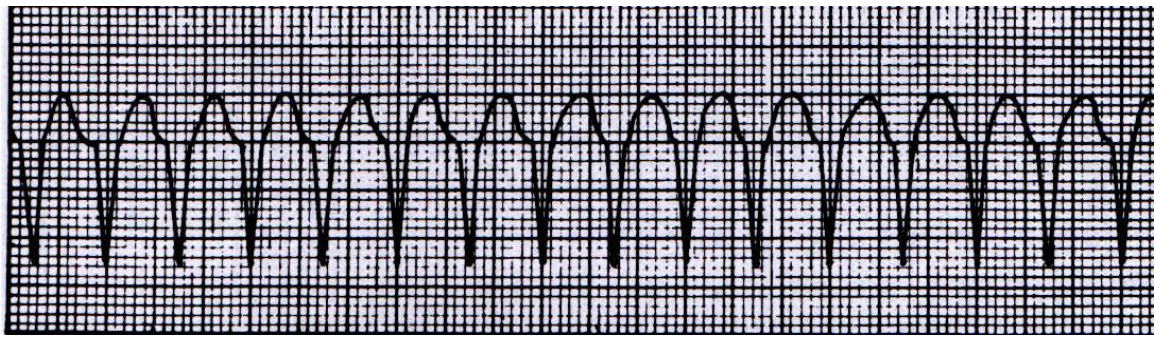
  - Broad irregular QRS complexes due to Delta waves.
  - Ventricular rates up to 300 bpm.
- **Conduction along the accessory pathway :**
  - Orthodromic – conduction to ventricles over normal AV node-His-Purkinje path.
  - Antidromic – conduction to ventricles via accessory path.
- **Medical Rx :**
  - ***1st choice*** **– procainamide** 20mg/min IV (max 17mg/kg).
  - ***Drugs to avoid*** **– AV nodal blocking agents!!!**
  - **Radio-frequency ablation curative > 95% cases.**

So What Is Actually Meant By Supraventricular Tachycardia (SVT) ?

- Arrhythmias of supraventricular origin using a re-entrant mechanism with abrupt onset & termination.
- AVNRT (60%).
- AVRT (30%).
- Atrial tachycardia (10%).

Notes:

- SVT is a benign condition.
- Treatment by : catheter ablation or medication (adenosine , ca channel blocker , β blocker)
- The ablation is the best
- AVNRT shows regular beats , no P-waves -
- Focal atrial tachycardia shows inverted p wave



Ventricular Tachycardia (VT)

- **Ventricular tachycardia is a fatal condition.**
- **Characterized by Wide and fast complex.**
- **Common in Ischemic heart disease (imp)**
- **Investigation : cath , ECG**

Brugada EKG Criteria for VT :

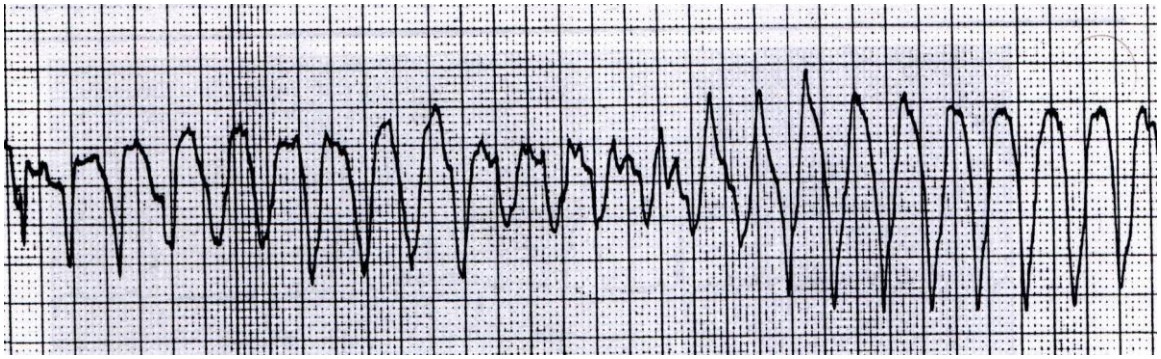
- AV dissociation.
- R-S interval > 100 ms.
- No RS morphology in pre-cordial leads.

Classification of VT :

- ***Duration*** **:**
  - Sustained VT **(> 30 seconds or hemodynamic compromise).**
  - non-Sustained VT **(< 30 seconds)**.
    - **Risk factor for sudden death among patients with heart diseases.**
- ***QRS morphology*** **:**
  - **Monomorphic (common in patients with CAD).**
  - **Polymorphic (usually associated with a prolonged QT).**

Treatment of VT :

- ***Hemodynamically Unstable :***
  - Unsynchronized cardioversion as per ACLS protocol for VF / pulseless VT
- ***Unstable (CP / AMS) :***
  - Synchronized cardioversion as per ACLS protocol
- ***Stable :***
  - **Rx ischemia.**
  - **Correct electrolytes (K / Mg / Ca).**
  - **Consider cardioversion (yes even in stable patients !!).**
  - ***EF > 40% :***
    - Procainamide / sotalol **(class IIa).**
    - amiodarone **(class IIb)**.
  - ***EF < 40% :***
    - amiodarone **(class IIa).**



Torsades de Pointes

Torsade de pointes (twisting around the point) = polymorphic VT

Causes of Torsades de Pointes :

- **Underlying Mechanism : prolongation of the QT interval coupled with R-on-T phenomenon.**
- **Medications** (Class Ia anti-arrhythmics / TCAs).
- **Electrolyte abnormalities** (Mg / K) .
- **Bradycardia** (usually s/p inferior MI).

Treatment of Torsades de Pointes :

- ***Unstable*** **:**
  - **Cardioversion** as per ACLS protocol for VT based on hemodynamics (*refer to prior slides*).
- ***Stable*** **:**

- **Correct electrolytes (K / Mg).**
- **Hold any culprit medications .**
- magnesium sulfate 2g IVP **+ repeat prn.**
- Transcutaneous overdrive pacing.

Summary – Wide :

- Ventricular tachycardia **(VT).**
- Torsades de Pointes **(sub-type of VT).**
- **Any** supraventricular tachycardia with aberrancy
  (e.g. sinus tachycardia with pre-existing bundle branch block).

ventricular fibrillation :

- treat it by : shock (no other choice)
- caused by : ischemia , cardiomyopathy , electrolytes abnormality , congenital prolonged QT syndrome, Brugada syndrome
- investigated by :ECG , cardio echo , cath , cardiac enzyme & electrolyte

Brugada syndrome is a genetic disease that is characterised by abnormal electrocardiogram (ECG) findings and an increased risk of sudden cardiac death.

Rheumatic and Infective Endocarditis

Dr. Abdullelah Al Mobeireek

Rheumatic fever is an inflammatory disease that occurs in children and young adult (the first attack usually occurs at between 5 & 15 years of age) as result of group A β-hemolytic streptococci(pharyngeal infection)

- It **affects** the : heart, skin, joints, and central nervous system .
- It represents a delayed immune response to infection with manifestation appearing after a period of 2-4 weeks .
- This is developed because of an autoimmune reaction trigged by molecular mimicry between the cell wall M proteins of the *strep. pyogenes* and cardiac myosin and laminin . The condition not due to direct infection of the heart or to the production of a toxin .

◈ Epidemiology:

- RF/RHD remain a major cause of morbidity and mortality in developing countries
- 15.6 millions have RHD worldwide
- 500,000 new cases of RF/yr worldwide nearly half develop carditits
- 230,000 death/yr due to RF/RHD worldwide
- Imposes a substantial burden on health care systems with limited budgets
- A disease of poverty and low socioeconomic status
- Rare in wealthy countries, due to improved living conditions, less overcrowding, and better hygiene.

Causal pathway	Preventive measure
↓	Primordial prevention: Housing Hygiene
Group A streptococcal infection	
↓	Primary prevention Sore throat treatment Vaccine (unavailable) Control of skin infections (unproved)
Acute rheumatic fever	
↓	Secondary prevention (because every recurrent attack makes it more damage) Secondary prophylaxis
Rheumatic heart disease	
↓	Tertiary prevention: Medication for heart failure, Valve surgery, anticoagulation.
Cardiac failure, stroke endocarditis, death	

❖ **Pathological lesion**: all the three layer of heart muscle maybe affected, the characteristic lesion is aschoff bodies(granulomatous lesion with central necrotic area) .

◈ Clinical features:

Onset : typically after 3-4 weeks after the bacterial infection

⊙ <u>Carditis:</u>

- A chronic condition, Occurs in 40-50% of cases.
- mainly affect the aortic &mitral valve .
- Pancarditis (all layers of heart).
- Only manifestation of ARF that leaves permanent damage.
- Murmurs of MR or AR may occur in acute stage while mitral stenosis occurs in late stage.
- Cardiomegaly and CHF may occur.
- Appearance of a pericardial effusion and ECG changes of pericarditis (*raised* ST segment)or myocarditis (*inverted or flattened* T wave).
- First degree or greater AV block or other Cardiac arrhythmias .

- Poly Arthritis
  - Most common feature (80%)
  - Earliest manifestation of ARF
  - Mainly affecting large joints , the knee , ankle , shoulder and elbow
  - Leave no permanent damage
  - Migrating fleeting polyarthritis
  - Duration : short < 1 week
  - Respond well to salicylates
  - Doesn't progress to chronic disease
- Sydenhham chorea
  - 5-10% is involvement of CNS
  - Abrupt purposeless involuntary movement of muscles of face, neck, trunk and limbs
  - May appear even 6 months after the attack
- Erythema marginatum:
  - Transient
  - Pink Rash with red borders center is pale
  - Rare: present in 5%.
  - Mostly on the trunk an limbs coalesce into crescent or ring shaped
  - Associated with carditis
- Subcutaneous nodules:
  - 10%, painless, pea sized, hard nodules beneath the skin .
  - May also occur, particularly over tendons, joints and bony prominences.
  - Usually 0.5-2 cm
  - Short lived : last for few days
  - Associated with sever carditis

Diagnosis:

2 major criteria

***OR** 1 major & 2 minor + evidence of group A β hemolytic streptococci.*

- **Major criteria** :
  1. Carditis
  2. Polyarthritis
  3. Chorea
  4. Erythema marginatum
  5. Subcutaneous nodules
- **Minor manifestations:**
  1. Fever
  2. Arthralgia
  3. Previous rheumatic fever or rheumatic heart disease
  4. Increased concentration of ESR/C-reactive protein (non-specific indicators of inflammation).
  5. Leucocytosis
  6. Prolonged PR interval on ECG
  7. Evidence of antecedent group A streptococcal infection:
     - Positive throat culture (antigen test positive for group A streptococcus).
     - Elevated antistreptolysin O titer or other streptococcal antibodies .
     - History of recent scarlet fever.

Investigations:

- Throat swab for culture
- CBC
- ESR
- C-reactive protein
- Serological changes (Anti Striptolysin O titer)
- ECG
- CXR
- Echo for valves.

Differential diagnosis:

- Juvenile rheumatoid arthritis
- infective endocarditis
- Sickle cell arthropathy
- Lupus
- Myocarditis
- Reactive arthritis
- Leukemia

Treatment of ARF:

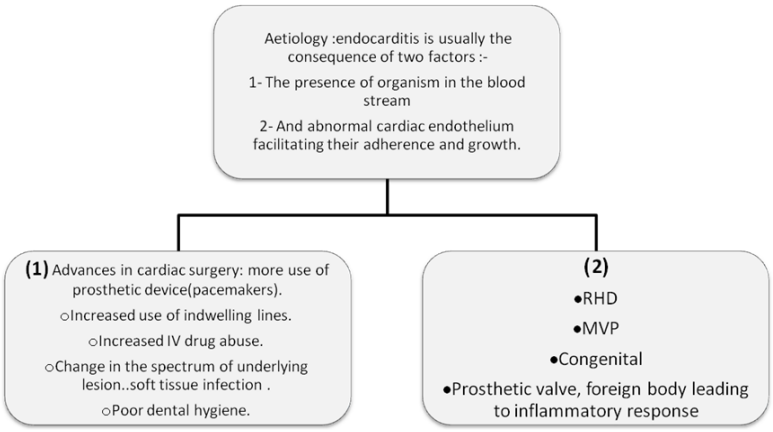
- Bed rest
- Salicylates: aspirin:
  - 75-100 mg/kg/day given as 4 divided doses for 6-8 weeks
  - Attain a blood level 20-30 mg/dl to prevent salicylate toxicity.
- Predinsolone:
  - 2 mg / kg /day taper over 6 weeks
  - Given when there is carditis to prevent inflammation.
- Treat heart failure if present
- Valve replacement later in life once symptoms develop or LV dysfunction occurs from severe valve regurgitation or valve stenosis
- Secondary prevention of rheumatic fever (prevention of recurrent attacks)
- Patients with a history of rheumatic fever should receive antibiotic prophylaxis with erythromycin or amoxicillin for dental/GI/genitourinary procedures .

- Duration of secondary rheumatic fever management:
  - Rheumatic fever with carditis and residual heart disease has to have long duration of treatment at least 10 years since last episode or until age of 40 years or life long.
  - Rheumatic fever without carditis 5 years of treatment until 21 years

Infective Endocarditis

- Infection of the endothelial lining of the heart
- May involve : valves , arteries ,ventricles , chordae tendonae, annulus
- Was uniformly fatal before the advent of antibiotics
- Today it remains fatal in up to 38 % of cases and cause considerable morbidity despite advances in medical care.>>Prevention is better than treatment.

Pathogenesis:



- Infected vegetations
  - Damaged vascular endothelium will promote platelet and fibrin deposition → these small thrombi that allow organisms to adhere and grow → as they grow, more fibrin and platelet are deposited, forming the characteristic infected vegetation .
- Jet lesion (platelet thrombi)
  - abnormal vascular endothelium can be the result of valvular lesions, which create areas of non-laminar blood flow ,or jet lesions resulting from ventricular septal defects or patent ductus arteriosus.

- Hemodynamic:
  - Infective endocarditis is less likely to develop where the hemodynamic disturbance is minimal (i.e. low pressure system)
  - Is more common in ventricular septal defects than atrial septal defects.
  - And rare in mitral prolapse without significant regurgitation .

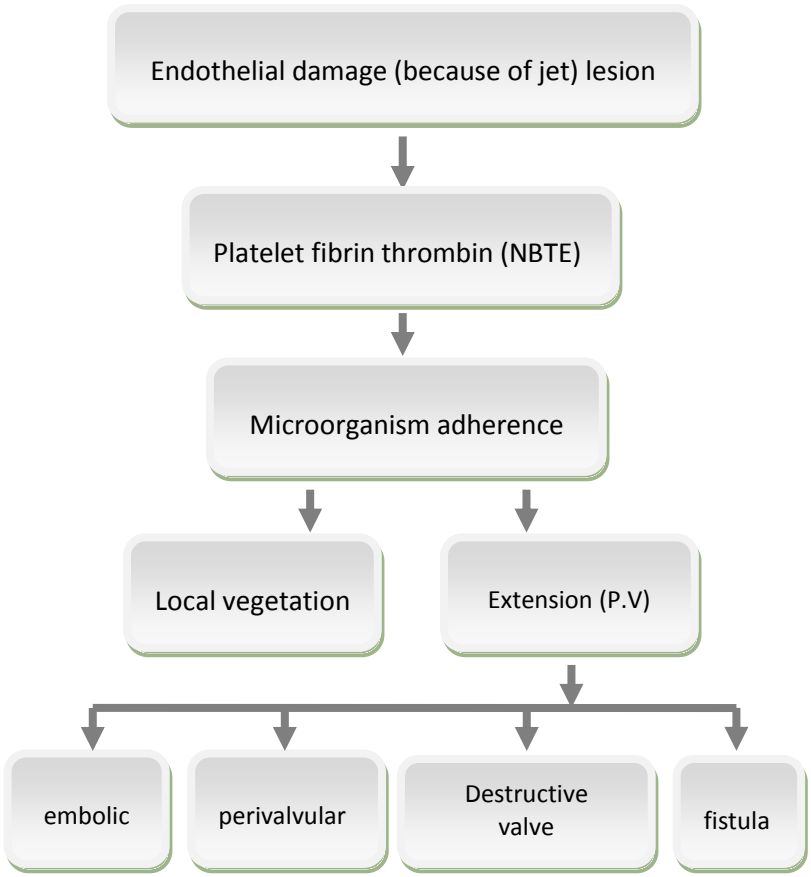
Hemodynamic factor :

- A high velocity jet: (Mitral regurgitation, ASD)
- Flow from High to low pressure chamber in MR → causing damage to the valves.
- A narrow orifice separating two chambers creating a pressure gradient

- Virulent pathogens such as *staphylococcus aureus* and *streptococcus pneumonia* may adhere and multiply on normal valve that has Sterile vegetation, NBTE (non bacterial thrombotic endocarditis), "marantic vegetations" which contain fibrin and platelets
- Transient bacteremia ——————▶

◈ Classification:

- Native (original) valve endocarditis → strept.viridance
- Prosthetic valve endocarditis
  - Early (less than 2 months)→ staph *epidermids* (coagulase negative)
  - Intermediate → *staph aureus*
  - Late (more than 1 year) →strept. *Viridans*
- IV drug abusers → *staph aureus* commonly affecting tricuspid valve (Rt.side endocarditis)
- Culture negative endocarditis :
  - Most common cause is recent use of antibiotics
  - variety of Fastidious organisms that fail to grow in normal blood cultures (e.g legionella)
  - Fungal → Immunocompromised patients may have fungal endocarditis → best modality is by serology because they are slowly growing organism
  - Intracellular agents: bartonella, chlamydia, viruses
  - Non infectious (marantic)
  - HACEK organisms are : (*Heamophilus species, Actinobacillus, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae)*
  - Large vegetation>> Bacteria +fibrin + platelets (may lead to thromboembolism)
  - Slow growing: hold culture for more than 3 weeks



◈ Clinical manifestation:

Clinical signs tend to arise from the fallowing pathological processes:

- Systemic features of infection
- Cardiac lesions
- Embolization → distal embolization may result in infraction of distal organ and/or spread of infection. The signs and symptoms depend on the organ involved.
- Immune complex deposition in blood vessels producing a vasculitis and petechial hemorrhages in the skin, under the nails (splinter hemorrhage), and in the retina (Roth's spots)

⊙ Symptoms:

Fever – Sweat – Chills – Anorexia – Malaise – Arthralgia - Weight loss.

⊙ Signs:

- Cardiac :New or changing heart murmurs, CHF.
- Splenomegaly
- Eye: (conjunctival and splinter hemorrhage - Roth's spots in the retina).
- Skin lesion (Osler's nodes (painful)-Janeway lesions (painless)- splinter hemorrhage – petechiae)
- Renal: Haematouria (glomerulonephritis)
- Neurologic : cerebral emboli – mycotic aneurysm

◈ Investigations:

- CBC : leukocytosis – normochromic normocytic anemia are common, thrombocytopenia or thrombocytosis may occur .
- Urea and electrolytes: renal dysfunction is complication of sepsis.
- High ESR, CRP, RF
- **Blood cultures (at least 3)**
- RFT (renal function test)
- Urine: Microscopic haematuria, proteinurea
- ECG: show evidence of MI or conduction defect
- CXR: show evidence of HF, pulmonary emboli and/or abscesses.
- **Echo** (can see vegetations).
- Hypergammaglubineamia ,but total complement are decreased.

- ***N.B→ blood culture and ECHO are the most important***

◈ Diagnosis:

Duke criteria: 2 major **OR** 1 major and 3 minor, 5 minor

- **Major:**
  1. Typical +ve blood culture (many blood cultures)
  2. Positive echocardiogram: vegetation, abscess, dehiscence of prosthetic valve (detach from its place), regurgitant blood stream flow, absence of an anatomical explanation.
- **Minor:**
  1. Predisposition (valvular disease or I.V drug users)
  2. Fever
  3. Vascular phenomena (arterial emboli, pulmonary infarct, intracranial hemorrhage, conjunctival hemorrhage, intracranial hemorrhage)
  4. Microbiological finding (single + cultures for coagulase – negative staphylococci & organism that don't cause endocarditis .
  5. Immunological phenomena (Roth spots, Osler's nodes, janeway lesions, glumerulonphritis, rheumatoid factor via laboratory analysis)

◈ Treatment:

Parenteral antibiotics based on culture results for extended periods (4 to 6 weeks)

- Streptococcus : penicillin prolong i.v + gentamicin
- MRSA: Vancomycin
- Staphylococcus : Vancomycin + gentamicin

◈ Indications of surgery:

1. Refractory CHF (commonest)
2. Local suppurative complications
3. More than one systemic embolic event
4. Uncontrolled infections(persistent infection despite therapy)
5. Large vegetations
6. Physiological significant valvular dysfunction (extensive damage to a valve)
7. Prosthetic valve endocaditis (valve replacement is usually required)
8. Ineffective antimicrobial therapy (fungal)
9. Mycotic aneurysm

◈ Prevention:

- No RCT (recommended continued treatment) for prevention
  - most incidence of IE to prior procedures
  - Wide variation of types
  - Large variety of procedures
- AHA (American heart association) guidelines: Antibiotic only for
  1. Prosthetic valve
  2. Previous IE
  3. CHD:
     - Unrepaired cyanotic CHD
     - Completely repaired CHD with prosthetic material or device during the first 6 months
     - Repaired CHD with residual defects
  4. Cardiac transplant with valvulopathy

N.B. No need for prophylaxis in patients with atrial septal defects

- Endocarditis prophylaxis for dental routine:
  - Only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis for dental procedures even if such prophylactic therapy were 100% effective
  - Infective endocarditis Prophylaxis for dental procedures should be recommended only for patient with underlying cardiac conditions associated with the highest risk of adverse outcomes
  - Prophylaxis is not recommended based solely on an increased lifetime risk of acquisition

◈ Conclusion:

- IE has considerable mortality & morbidity
- Recognize patient at risk
- Know what type of procedure require prophylaxis
- Educate patient on the importance of maintaining good oral hygiene.

Valvular Heart Diseases

Prof. Mohammed Arafah

✶ General characteristics of all valvular heart disease:

- ALL cardiac valves can be involved in pathological processes.
- **Etiology of valvular heart disease:**
  1- Congenital:
    - Bicuspid or unicuspid.
    - Subvalvular or supravalvular .

  2- Acquired:
    - Rheumatic.
    - Degeneration (myxomatous – calcification).
    - Ischemic.
    - Infective Endocarditis.
    - Valve ring dilatation.
- **Types of presentation of VHD:**
  - Chronic or Acute.
- **Hemodynamic consequences of VHD:**
  1- Pressure-overload:
    - Aortic stenosis → Left Ventricular hypertrophy.
    - Mitral stenosis → Left Atrial hypertrophy & dilatation.

  2- Volume-overload:
    - Chronic mitral regurgitation → Left ventricle & Left atria dilation.
    - Chronic aortic regurgitation → Left ventricle dilation.
    - Chronic tricuspid regurgitation → dilated right ventricle & right atria.
- **General symptoms of some VHD:**
  1- Exertional dyspnea/ PND (paroxysmal nocturnal dyspnea) / orthopnea.
  2- Palpitation.
  3- Chest pain.
  4- Fatigue
  5- Dizziness, prefainting , syncope .
  6- Symptoms of congestive heart failure (edema/ascites).
  7- Cough – Hemoptysis
  8- Symptoms of thromboembolic complication.
- **General signs of some VHD:**
  1. Abnormal look (mitral facies in mitral stenosis).
  2. Abnormal pulse (Atrial fibrillation).
  3. Apex beat abnormality.
  4. Sternal or parasternal heave.
  5. Thrill.
  6. Abnormal heart sounds.
  7. MURMURS (Systolic or Diastolic).
- **Investigations in ALL VHD:**
  a) ECG.
  b) Chest X-ray (CXR) .
  c) Echocardiology (test of choice for diagnosis).
    - M mode , 2D ,3D, 4D, TEE (Transesophageal echocardiography).
    - Doppler (to assess severity).

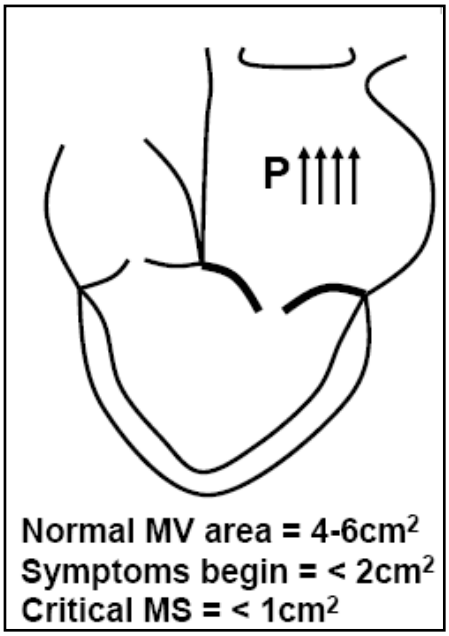
  d) 24 hours monitor for heart rhythm.
  e) MRI.
  f) Cardiac catheterization (helpful & confirmatory, needed if the patient is older suspecting IHD -look at the coronaries-).

✶ Types of valvular heart disease:

I) Mitral stenosis :

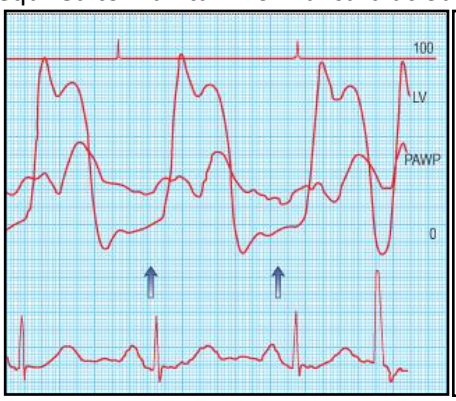
◈ Common etiology of MS:

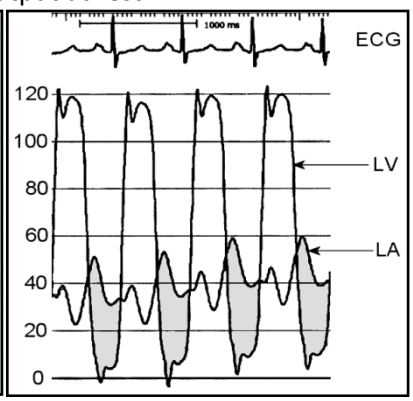
- Rheumatic Fever (most common):
  - Related to streptococcus infections, causing damage to the mitral valve and leading to mitral stenosis later in life.
  - Changes in the mitral valve consist of:
    1- Cusps thickening.
    2- Commissures fused together.
    3- Chordae tendinae thickening & shortening.
    4- Calcium deposition.
- Congenital.
- Degenerative (calcification & fibrosis) in elderly.
- SLE.
- Rheumatoid Arthritis.
- Atrial Myxoma.
- Malignant Carcinoid.
- Bacterial Endocarditis.



◈ Pathophysiology of MS:

- **Valvular orifice:**
  - Normal adults the mitral valve orifice is 4-6cm².
  - When the orifice is reduced to approximately 2cm² (mild mitral stenosis) → blood can flow from the left atrium to the left ventricle only if propelled by an abnormal pressure gradient (the hemodynamic hallmark of MS).
  - When the mitral valve opening is reduced to 1 cm² (critical mitral stenosis) → a left atrioventricular pressure gradient of approximately 20mmHg is required to maintain normal cardiac output at rest.





◈ Consequence of mitral stenosis:

⊙ ↑↑ Left atrial (LA) pressure →

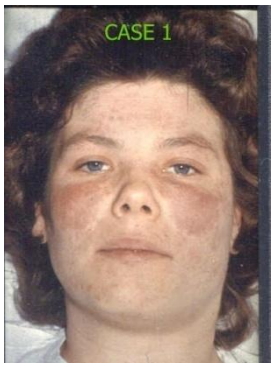
1- LA dilation & hypertrophy:
   - Atrial fibrillation → atrial thrombus formation & systemic embolus.
   - ↑ heart rate → ↓↓ left ventricle filling → ↓↓ cardiac output.

2- Back pressure to the pulmonary veins:
   - Pulmonary congestion.
   - Pulmonary venous vasoconstriction → pulmonary hypertension → Right heart failure (Rt Ventricular hypertrophy).

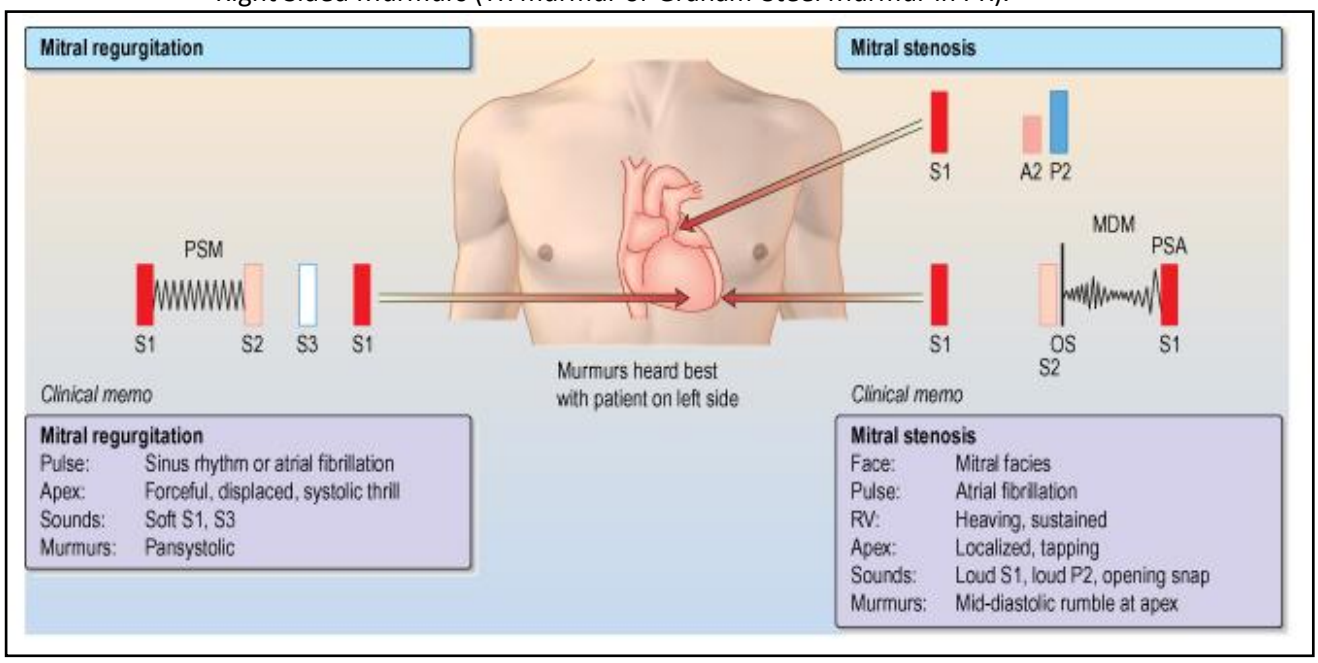
◈ Symptoms of MS:

1. DYSPNEA ON EXERTION (hallmark signs of the beginning of MS).
   - The first bouts of dyspnea in patients with mitral stenosis are usually precipitated by exercise, emotional stress, infection, or atrial fibrillation, all of which increase HR & the rate of blood flow across the mitral orifice → result in further elevation of Left atrial pressure & consequent pulmonary edema & congestion.
2. Paroxysmal nocturnal dyspnea (PND).
3. Orthopnea.
4. Fatigue.
5. Palpitations (due to AFib).
6. Cough & Hemoptysis (due to rupture of thin dilated bronchial veins).
7. Peripheral edema & symptoms of Rt heart failure.

◈ Signs of MS:



1) Mitral facies.
2) Apex beat: localized & tapping.
3) Left parasternal heave (due to Rt ventricular hypertrophy) & diastolic apical thrill (in Lt lateral position).
4) Heart sounds: Loud S1 (due to abrupt leaflet closure) & Loud P2 (due to ↑ pulmonary arterial pressure).
5) Added sounds: Opening snap (due to tension on valve leaflet).
   - Murmurs: Diastolic Apical Rumble (due to turbulent blood flow across the stenotic valve).
6) May be associated with:
   - MR or AS
   - Right Sided Murmurs (TR murmur or Graham-Steel Murmur in PR).



◈ Investigations (as discussed previously):

- ECG will show: AFib – Left atrial enlargement (LAE) – Right atrial enlargement (RAE) – Right ventricular hypertrophy (RVH).
- Echo will show: LA dilation & valvular stenosis.

◈ Complications of MS:

1- Atrial fibrillation.
2- Lung congestion.
3- Blood clots with systemic embolization.
4- Pulmonary hypertension.
5- Congestive heart failure.
6- Infective endocarditis.

◈ Treatment of symptomatic MS:

- ✓ **Medical Therapy (treats the symptoms not the cause):**
  1- Diuretics – for congestion.
  2- Digoxin, Beta and Ca Channel Blockers (anti-arrhythmics) – for Afib rate control.
  3- Anticoagulation – for AFib and LA clots.
  4- Subacute Bacterial Endocarditis Prophylaxis – prevent endocarditis.
- ✓ **Surgical Therapy (treats the cause):**
  a) Percutaneous Ballon Valvulaoplasty (=percutaneous transvenous mitral commissurotomy (PTMC)) → for a Non-calcified, pliable valve.
  b) Surgical commissurotomy.
  c) Mitral valve replacement.

II) Mitral regurgitation:

◈ Common etiology:

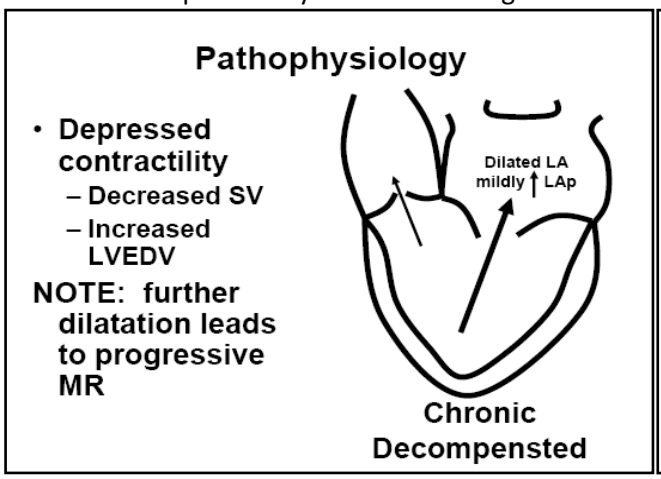
1- Alterations of the Leaflets, Commissures, Annulus of the valve:
- Rheumatic heart disease.
- Mitral valve prolapse (MVP).
- Infective endocarditis.

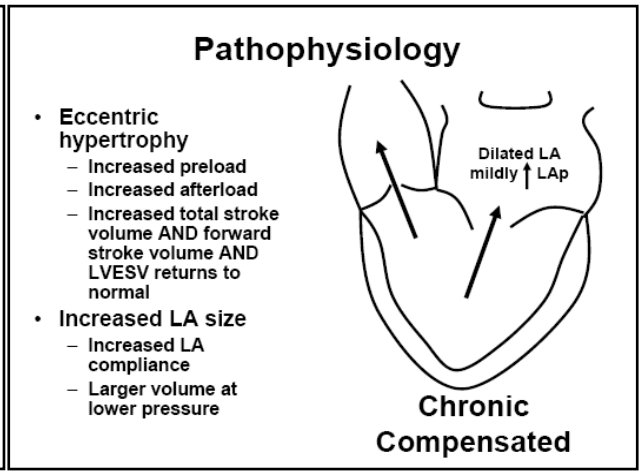
2- Alterations of LV or LA size and Function (functional MR):
- IHD.
- Myocarditis.
- Hypertensive heart disease.
- Cardiomyopathy (dilated , hypertrophic "HOCM").

3- Other:
- Connective tissue disorders (SLE).
- Collagen abnormalities (Marfan's syndrome).

◈ Pathophysiology of MR:

- Chronic MR (volume overload):
  1- Blood regurgitate to LA → LA dilation.
  2- ↓ CO.
  3- ↑ total stroke volume→ volume overload → LV dilation.
  4- Mild ↑ in LA pressure → may progress to ↑ pulmonary venous pressure → pulmonary edema & congestion.
- In acute MR, LA is not dilated, which result in high LA pressure, high pulmonary venous pressure, & severe pulmonary edema and congestion.





◈ Symptoms of MR:

- Same as MS except hemoptysis & systemic embolization are less common.
- Complication with infective endocarditis is more common.

◈ Signs of MR:

1) Apex beat: laterally displaced & diffuse forceful.
2) Systolic apical thrill (usually radiating to axilla).
3) Heart sounds: Soft S1 (due to incomplete leaflet closure), Split S2 (but is obscured by the murmur).
4) Added sounds: prominent S3 gallop (due to increased volume in dilated LV during diastole).
5) Murmurs: Holosystolic Apical Blowing (usually radiating to axilla).

◈ Investigations (as discussed previously):

- ECG will show: Lt atrial enlargement (LAE) – Lt ventricular dilatation.

◈ **Treatment:**

✓ Medical Therapy (treats the symptoms not the cause):

1- Diuretics – for congestion.
2- Vasodilators (ACE inhibitors) – to ↓ afterload.
3- Anticoagulation – for AFib and LA clots.
4- SBE Prophylaxis – prevent endocarditis.

✓ Surgical Therapy (treats the cause):

a) Mitral valve repair.
b) Mitral valve replacement.

III) Mitral valve prolapse (MVP):

- It is the prolapse of one or more of mitral valve leaflets back into the LA during systole.

◈ **Pathology of MVP:**

- Large mitral valve leaflets, an enlarged mitral annulus, abnormally long chordate, or disordered papillary muscle contraction.
- Demonstrate myxomatous degeneration of the mitral valve leaflets.
- Associated with Marfan's syndrome, thyrotoxicosis, rheumatic, or ischemic heart disease.

◈ **Symptoms of MVP:**

1) Atypical chest pain (the most common symptom).
2) Palpitations (because of the abnormal ventricular contraction or because of the atrial and ventricular arrhythmias).
3) Sudden cardiac death (due to fatal ventricular arrhythmias) – very rare but recognized complication.

◈ **Signs of MVP:**

1- Mid-systolic click (most common sign) – produced by the sudden prolapse of the valve and the tensing of the chordae tendineae that occurs during systole.
2- A late systolic murmur (owing to some regurgitation).

◈ **Complications of MVP:**

- Infective endocarditis.
- Progressive MR (acute – chronic).
- Thromboembolism.
- Atrial/ventricular arrhythmias.

◈ **Treatment of MVP:**

a) Beta-blocker → effective for the treatment of the atypical chest pain and palpitations.
b) Aspirin (Transient Ischemic Attacks without etiology).
c) SBE Prophylaxis (only if associated with MR).
d) In mitral valve prolapse associated with significant mitral regurgitation and atrial fibrillation, anticoagulation is advised to prevent thromboembolism.
e) In mitral valve prolapse associated with severe mitral regurgitation which has a risk of sudden cardiac death, surgery is advised.

IV) Aortic stenosis:

◈ **Common etiology of AS:**

1) Congenital (bicuspid) aortic valve.
2) Rheumatic heart disease (30-60 yrs).
3) Degenerative (>60 yrs){which is the most common cause}.

◈ **Pathophysiology of AS:**

1- Obstruction of LV flow → ↑↑ LV end-diastolic pressure. **2-** LV Concentric Hypertrophy.

◈ **Symptoms of AS:**

- Long asymptomatic phase.
- Symptoms in moderately severe AS:

Prognosis with Symptomatic Aortic Stenosis	
Clinical Symptoms	**Median Survival**
Angina	5 years
Syncope	3 years
CHF	2 years

Symptoms of Aortic Stenosis

- Angina
  - Imbalance between supply and demand
    - Elevated LVEDp decreases perfusion pressure
    - Myocardial hypertrophy increases demand
- Syncope with exertion
  - Inability to increase cardiac output and meet reduced SVR demands
- Congestive heart failure
  - Elevated LVEDp = elevated LAp = pulmonary venous congestion

◈ **Signs of AS:**

1) Pulse: Pulsus Parvus et Tardus (Carotid Impulse){ parvus= low volume,,, tardus= late}
2) Apex beat: Sustained bifid (from LVH).
3) Systolic thrill in aortic area (usually radiating to carotid).
4) Added sounds: S4 gallop (from LVH).
5) Murmurs: Harsh Systolic Ejection Murmur (radiating to carotid) – late peaking {its presence indicates severity}.

◈ **Investigations (as discussed previously):**

- ECG will show: Left atrial enlargement (LAE) – Left ventricular hypertrophy (LVH).

◈ **Treatment of AS:**

✓ Medical Therapy (treats the symptoms).
✓ Surgical Therapy → aortic valve replacement (Bioprosthetic vs Mechanical).

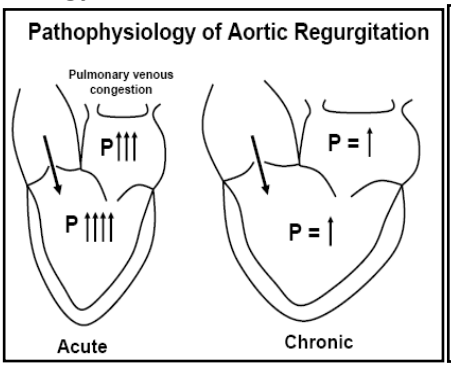
- In patients with aortic stenosis, symptoms are a good index of severity and all symptomatic patients should have aortic valve replacement.
- Asymptomatic patients should be under regular review for assessment of symptoms and echocardiography.

V) Aortic regurgitation:

◈ **Common etiology of AR:**

1) Abnormalities of the Leaflets: (Rheumatic, Bicuspid, Degenerative, Endocarditis).
2) Dilation of the Aortic Annulus "aortic root disease":
   - Aortic Aneurysm / Dissection.
   - Inflammatory Syphyllis, Giant Cell Arteritis, Coll Vasc Dis -Ankylosis Spondylitis, Reiters).
   - Inheritable (Marfans, Osteogensis Imperfecta).

◈ **Pathophysiology of AR:** Volume overload with LV dilation.



Pathophysiology of Aortic Regurgitation

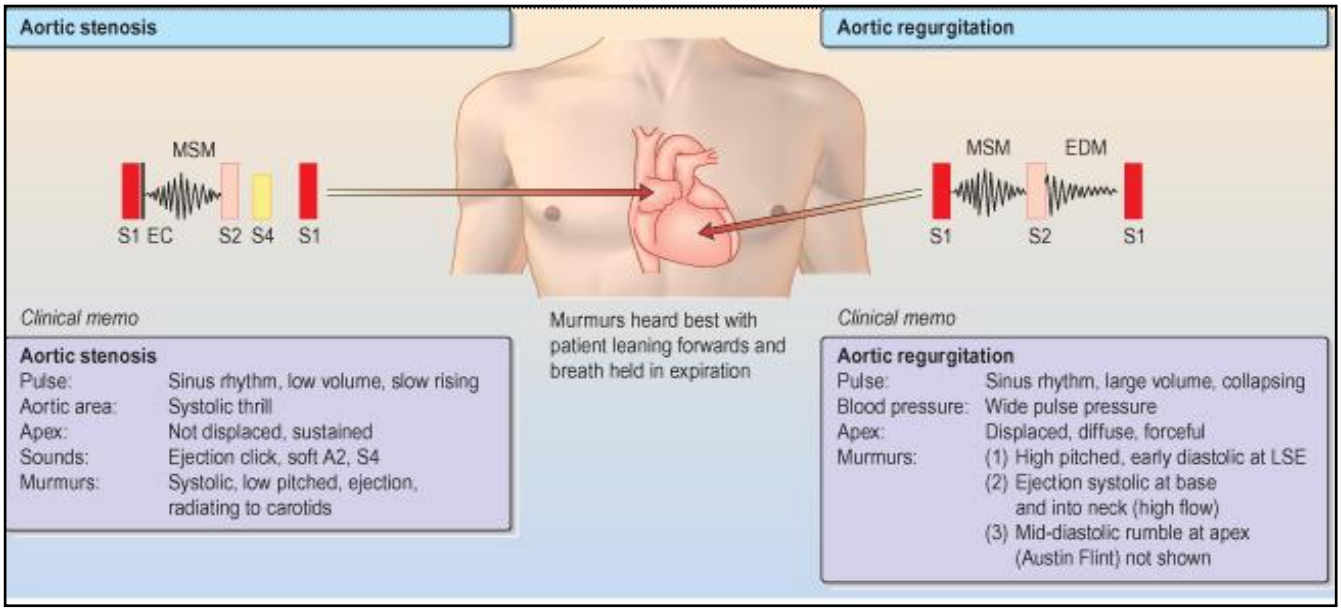
- Widened pulse pressure
  - Stroke volume increased (high SBP)
  - Regurgitant volume increased (low DBP)
- Imbalance between myocardial supply and demand
  - Decreased DBP = decreased perfusion pressure = decreased supply
  - Increased LV size (and thus wall stress) = increased demand

◈ Symptoms of AR:

- Pulmonary venous congestion :
  - ✓ Dyspnea on exertion.
- Inadequate cardiac output :
  - ✓ Fatigue.
  - ✓ Diminished exercise tolerance.

◈ Signs of AR:

1) Bounding (= collapsing) Pulses.
2) Wide pulse pressure.
3) Apex beat: Hyperdynamic {shifted apex}.
4) Added sounds: S4, S3 Gallop (in advanced AR).
5) Murmurs:
   - Early-Diastolic (Decrescendo) Blowing murmur at Lt sternal edge.
   - Mid-Diastolic Apical Rumble – "**Austin Flint Murmur**" (due to the vibration of the anterior leaflet of the mitral valve as it is buffetted simultaneously by the blood jets from the left atrium and the aorta).



◈ Investigations of AR (as discussed previously):

- ECG will show: Left atrial enlargement (LAE) – Left ventricular hypertrophy (LVH).

◈ Treatment of AR:

- ✓ **Medical Therapy (if there is NO significant symptoms):**
  1- Serial Checkups with Echos (evaluate EF, Severity AR).
  2- Diuretics – for congestion.
  3- Vasodilators (Nifedipine – ACE inhibitors) – to ↓ afterload.
  4- SBE Prophylaxis – prevent endocarditis.
- ✓ **Surgical Therapy (if symptomatic):** Aortic Valve Replacement.
  - Because symptoms do not develop until the myocardium fails and because the myocardium does not recover fully after surgery, operation is performed before significant symptoms occur.
  - The timing of the operation is best determined according to haemodynamic, echocardiographic or angiographic criteria.

VI) Pulmonary & Tricuspid valvular disease:

◈ Tricuspid Valve:

- Causes:
  1- Endocarditis (esp. in – IV drug abusers or input with IVs).
  2- Carcinoid Heart Disease (classically TS).
- Tricuspid Regurgitation
  - Common.
  - Benign.
  - May be secondary to Pulm HTN.

◈ Pulmonary Valve:

- Causes:
  1. In Pediatrics – Pulmonary Stenosis.
  2. Rheumatic HD – Pulmonary Regurgitation (Graham Steel Murmur).

◈ Right sided valvular lesions change in intensity with inspiration, while Left sided VHD change with expiration.

Approach to the Febrile Patients

Dr. Awadh Al-Anazi

- Fever : is an elevation of body temperature above the normal circadian range as the result of a change in the *thermoregulatory* center located in the anterior hypothalamus and pre-optic area.

Thermoregulation :

- Body heat is generated by : Basal metabolic activity, and
  Muscle movement
  and lost by : Conduction,
  Convection (which is increased by wind or fanning), and
  Evaporation which is increased by sweating.
- Body temperature is controlled in the hypothalamus, which is directly sensitive to changes in core temperature.
- The normal 'set-point' of core temperature is tightly regulated within 37 ± 0.5°C, as required to preserve normal function of many enzymes and other metabolic processes.
- In a hot environment, sweating is the main mechanism for increasing heat loss.
- This usually occurs when the ambient temperature rises above 32.5°C or during exercise.

FEBRILE RESPONSE :

- The initiation of fever begins when exogenous or endogenous stimuli are presented to specialized host cells, principally monocytes and macrophages, they will stimulates the synthesis and release of various *pyrogenic cytokines* including :
  1. Interleukin-1, interleukin-6
  2. TNF-α, and
  3. IFN-γ.

A) Exogenous pyrogens : stimuli from outside the host.
- Like : microorganism, their products, or toxins and it is called Endotoxin.
- **Endotoxin : lipopolysaccharide (LPS).**
  - LPS : is found in the outer membrane of all gram negative organism.
- **Action :**
  1. Through stimulation of monocytes and macrophages.
  2. Direct on endothelial cell of the brain to produce fever.

B) Endogenous pyrogens : polypeptides that are produced by the body (by monocytes and macrophages) in response to stimuli that is usually triggered by infection or inflammation stimuli.

Pyrogens :

- Substances that cause fever are called pyrogens.
- What are these pyrogens ?
  - Cytokines
    - Definition : Cytokines are regulatory polypeptides that are produced by :
      1. Monocytes / macrophages.
      2. Lymphocytes.
      3. Endothelial and epithelial cell and hepatocytes.
- The most important ones are :
  - Interleukin 1α and 1β → The most pyrogenic.
  - Tumor necrosis factor α.
  - Interferon.
  - Interleukin 6 → The least pyrogenic.
  - ↑ Cytokines → fever develop within 1hr of injection.

Mechanism of action :

- Cytokine-receptor interactions in the pre-optic region of the anterior hypothalamus activate phospholipase A.
- This enzyme liberates plasma membrane arachidonic acid as substrate for the cyclo-oxygenase pathway.
- The resulting mediator, *prostaglandin E2*, then modifies the responsiveness of thermosensitive neurons in the thermoregulatory centre.
- Diurnal variation
- 6 am : 37.2 …… 4 pm : 37.7
- Rectal temperature >0.6^{o} C oral temperature
- Fever : Morning : AM >37.2^{o} C
  Evening : PM >37.7^{o} C

PRESENTATION OF FEVER :

- ***Feeling hot*** : A feeling of heat does not necessarily imply fever.
- ***Rigors*** **:** profound chills with a accompanied by chattering of the teeth and severe shivering and implies a rapid rise in body temperature. Can be produced by :
  1. Brucellosis and malaria.
  2. Sepsis with abscess.
  3. Lymphoma.
- ***Excessive sweating*** : Night sweats are characteristic of tuberculosis, but sweating from any cause is usually worse at night.
- ***Headache*** : Fever from any cause may provoke headache.
  - Severe headache and photophobia, may suggests meningitis.
- ***Delirium*** **:** Mental confusion during fever is well described and relatively more common in young children and in old age.
- ***Muscle pain*** : Myalgia is characteristic of Viral infections such as influenza, malaria and brucellosis.
- **Hyperthermia :** is an elevation of core temperature without elevation of the hypothalamic set point.
  - Cause : inadequate heat loss.
  - Examples :
    1. Heat stroke.
    2. Drug induced such as tricyclic antidepressant.
    3. Malignant hyperthermia associated with psychiatric drugs.

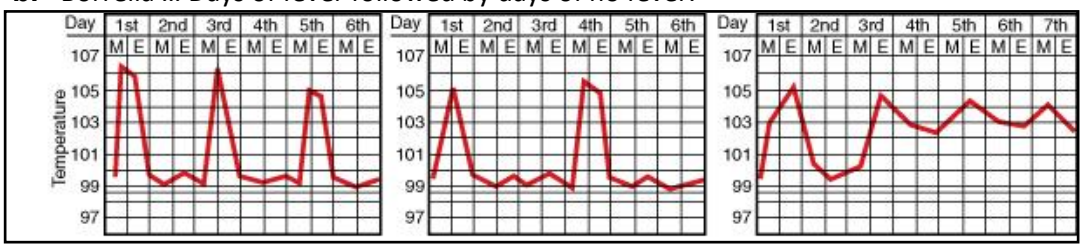
Why fever ?

- Elevation of body temperature increases chance for survival.
- Temperatures appear to increase :
  1. The phagocytic and Bactericidal activity of neurtrophils, and
  2. The cytotoxic effects of lymphocytes …so
     - The growth and virulence of several bacterial species are impaired at high temperature.

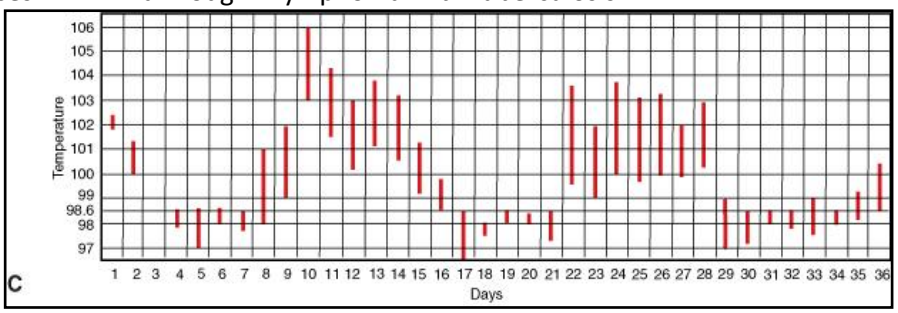
Fever Patterns :

- Intermittent fever, Remittent fever, Hectic fever, Sustained fever, and Relapsing.
- **Intermittent fever :** exaggeration of the normal circadian rhythm, and when the variation is large it is called hectic.
  - Cause : a. Deep seated infection.
    b. Malignancy.
    c. Drug fever.
- **Quotidian fever :** hectic fever that occur daily.
- **Remittent fever :** Temperature falls daily but not to normal.
  - Causes : a. Tuberculosis.
    b. Viral infection.
    c. Many bacterial infections.

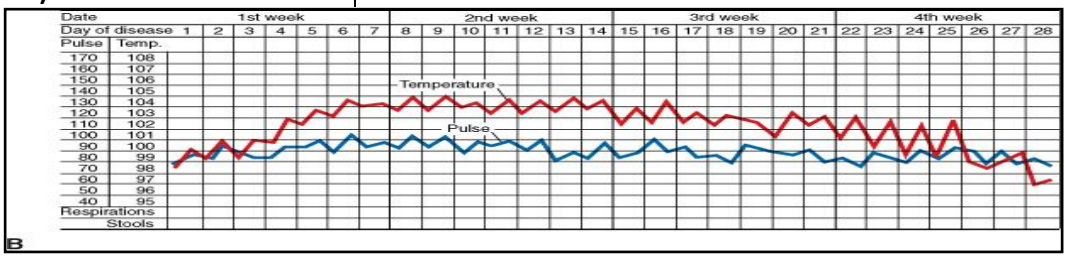
- **Relapsing fever :** febrile episodes are separated by intervals of normal temperature.
  - **a.** Malaria fever every 3days (tertian) Plasmodium Falciparam
    or every 4 days (quartan) Plasm. Vivax.
  - **b.** Borrelia … Days of fever followed by days of no fever.



- **Pel-Ebstein fever :** fever for 3 to 10 days followed by no fever for 3 to 10 days.
  - Causes : a. Hodgkin lymphoma. b. Tuberculosis.



- Fever pattern cannot be considered diagnostic for a particular infection or disease and the typical pattern is not usually seen because of use of :
  - **1)** Antipyretics.
  - **2)** Steroids.
  - **3)** Antibiotics.
- Temperature – pulse dissociation (Relative bradicardia) : is seen in
  - **a)** Typhoid fever.
  - **b)** Brucellosis.
  - **c)** Leptospirosis.
  - **d)** Factitious fever.
  - **e)** Acute rheumatic fever with cardiac conduction abnormality.
  - **f)** Viral myocarditis.
  - **g)** Endocarditis with valve ring abscess affecting conduction.



Fever Patterns – Degree :

- Fever with extreme fever : gram-negative bacteremia, Legionnaires' disease, and bacteremic pyelonephritis.
- Noninfectious cause of extreme pyrexia : heat stroke, intracerebral hemorrhage.

Physical examination :

- Fever may sometimes absent :
  - Seriously ill newborns,
  - Elderly patients,
  - Uremic patient,
  - Significantly malnourished individuals,
  - Receiving corticosteroids, or
  - Continuous treatment with anti-inflammatory or antipyretic agents.

Approach to the febrile patient :

- The most important step is Meticulous history.
- ***Rule out common infection***.
- Careful history :
  1) *Chronology of symptoms* : Detailed complain of the patient with the symptoms arranged chronologically.
  2) *Use of drugs* : Drug fever is uncommon and therefore easily missed.
  3) *Surgical or dental procedure* : Patient known to have rheumatic heart disease is at risk to develop infective endocarditis if not given prophylaxis
  4) *Nature of any prosthetic material or implanted devices* : prosthesis implant for the knee joint, prosthatic valve replacement.
  5) *Occupational history including* :
     a. Exposure to animals : brucellosis.
     b. Infected person at home : tuberculosis or influenza.
  6) Geographic area of living.. The south of Saudi Arabia : malaria.
  7) Travel history.
  8) Household pits.
  9) Ingestion of unpasteurized milk or cheeses.
  10) Sexual practice … HIV.
  11) IV drug abuse.
  12) Septicemia, HIV, Hepatitis B & C.
  13) Alcohol intake.
  14) Prior transfusion or immunization.
  15) Drug allergy.

1) HISTORY-TAKING IN FEBRILE PATIENTS :

- *Symptoms of common respiratory infections* :
  1. Sore throat, nasal discharge, sneezing … URTI (VIRAL).
  2. Sinus pain and headache … suggesting A sinusitis.
  3. Elicit symptoms of lower respiratory tract infection : cough, sputum, wheeze or breathlessness.
- *Genitourinary symptoms* : Ask specifically about :
  - Frequency of micturition, dysuria, loin pain, and vaginal or urethral discharge … suggesting :
    A. Urinary tract infection, | **B.** Pelvic inflammatory disease, and | **C.** Sexually transmitted infection (STI).
- *Abdominal symptoms* : Ask about diarrhea, with or without blood, weight loss and abdominal pain … suggesting :
  a. Gastroenteritis, | **c.** Inflammatory bowel disease,
  b. Intra-abdominal sepsis, | **d.** Malignancy.
- *Joint symptoms* : joint pain, swelling or limitation of movement. If present ask about :
  A) Distribution : mono, oligo or poly-arthritis.
  B) Appearance : fleeting or additive.
  - It suggest : 1) Infective arthritis … oligo.
    2) Collagen vascular disease … fleeting.
    3) Reactive arthritis.

- *Travel history* : Always ask about foreign travel.
  - Where have you been? …Endemic area or not ?
  - What have you done?
  - How long where you there?
  - Did you have insect bites or contact with animals?
  - Did you take precautions/prophylaxis against malaria.
  - If the patient has been in an endemic area, the most common final diagnoses :
    - Malaria,
    - Typhoid fever,
    - Viral hepatitis, and
    - Dengue fever.
  - *Malaria* must be excluded whatever the presenting symptoms.

- *Drug history* : Drug fever is uncommon and therefore easily missed.
  - The culprits include :
    - *penicillin and*
    - *cephalosporin*
    - *sulphonamide*
    - *anti tuberculous agents*
    - *anticonvulsants particularly <u>phenytoin</u>.*
- *Alcohol consumption* : Alcoholic hepatitis, hepatocellular carcinoma are all recognized causes of fever.
- *Family history of* :
  - Tuberculosis.
  - Arthritis.
  - Other infectious diseases.
  - Anyone with symptomatology of Polyserositis or bone pain.
- Ethnic origin of the patient is important e.g. Turks, Arabs, Armenians likely to have Familial Mediterranean fever.

2) Physical examination :

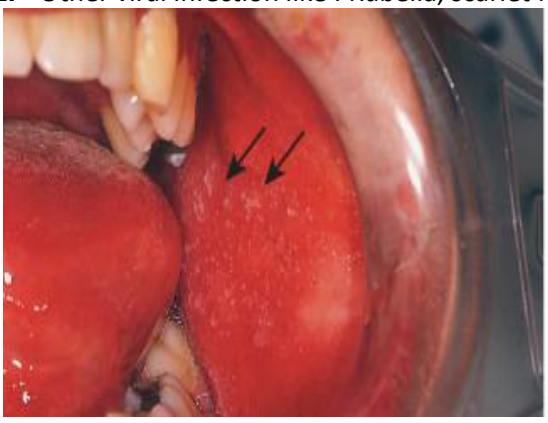
- Repeated meticulous examination on a regular basis until diagnosis is made.
- Temperature should be taken : Orally, or
  Rectally.
  - Axillary temperature is notoriously unreliable.
- Cautions while taking oral temperature :
  1. Recent consumption of hot or cold drinks.
  2. Smoking.
  3. Hyperventilation.

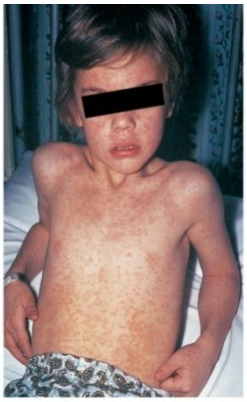
◈ EXAMINATION :

1) Document the presence of fever … and Do not miss **FACTITIOUS FEVER**.
- A careful examination is vital and must be repeated regularly.
- Particular attention should be paid to :
  - The skin … for skin rash.
  - Throat … for pharyngitis.
  - Eyes … for jaundice, scleritis.
  - Nail bed … for clubbing, splinter hemorrhage.
  - Lymph nodes … for enlargement.
  - Abdomen … for ascitis or sign of peritonitis.
  - Heart … for murmurs indicating endocarditis.

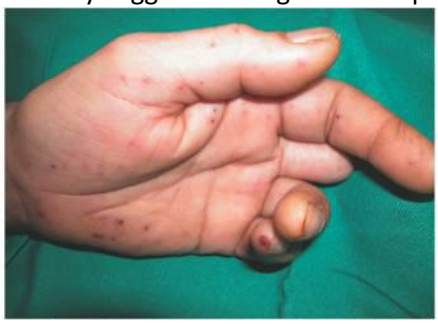
2) Look for RASH :

a. Erythmatous rash (rash that blanch on pressure).
- Causes :
  1. Meseals : often accompanied by upper respiratory tract symptoms and conjunctivitis.
  2. Other viral infection like : Rubella, scarlet fever.

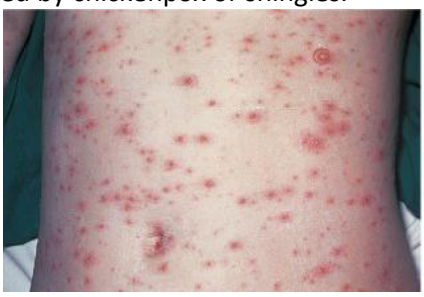




b. Purpuric or petechial rash : (do NOT blanch on pressure).
- May suggest meningococcal septicemia.

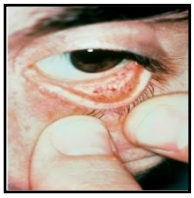


c. Vesicular rash : may be caused by chickenpox or shingles.



- Mouth and oropharynx :
  - Vesicular lesions ,tonsillar exudate … suggest Infectious etiology :
    1) Streptococcal pharyngitis.
    2) Coxsakie infection.
  - Hairy leukoplakia or oropharyngeal candidiasis suggest : HIV /AIDS.
  - Oropharyngeal candidiasis … suggest : Immunodeficiency syndrome.

- Eyes :
  - Conjunctival petechiae … may suggest : meningococcal meningitis.
  - Jaundice … may suggest : acute hepatitis A.



- Cervical lymph nodes enlargement : Tonsillar LN enlargement … suggest : Acute pharyngitis or tonsillitis.
- Posterior lymphadenopathy … suggest :
  1) Infectious mononucleosis. **2)** HIV infection.
- Axillary lymph node enlargement … may suggests :
  1) Sepsis. **2)** Leukemia. **3)** Lymphoma.
- Joints (any joint but commonly the knee and ankle) : Look for swelling, redness, heat and effusion … suggest : active arthritis ..? infective
- Neck : look for stiffness … may suggest : meningitis.
- Abdomen : look for tenderness especially in the RIF : acute appendicitis.
- Chest and heart :
  1. Sign of consolidation. **2.** Pleural effusion. **3.** Pericardial rub. **4.** Cardiac murmur … Endocarditis or acute rheumatic fever.

- Rectal examination : look for :
  1. Per anal abscess. **2.** Acute prostatitis.

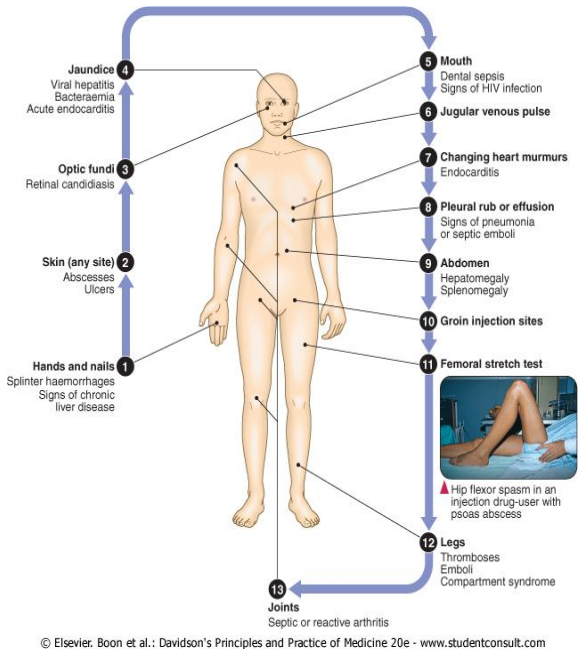
FACTITIOUS FEVER :

- This is defined as fever engineered by the patient by manipulating the thermometer and/or temperature chart apparently to obtain medical care.
- Uncommon, and typically presents in young women who work in paramedical professions.
- Examples include : the dipping of thermometers into hot drinks to fake a fever.
- The factitious disorder is usually medical but may relate to a psychiatric illness with reports of depressive illness.
- **Clues to the diagnosis of factitious fever :**
  - A patient who looks well.
  - Absence of temperature-related changes in pulse rate.
  - Temperature > 41°C.
  - Absence of sweating during defervescence.
  - Normal ESR and CRP despite high fever.
  - Useful methods for the detection of factitious fever include :
    1. Supervised (observed) temperature measurement.
    2. Measuring the temperature of freshly voided urine.

Drug-IV user :

- 20 years male who is heroin drug abuser for long time came to ER of left thigh pain and fever.
- Look at the picture and guess what is his problem ?

- The answer :
  Hip flexor spasm due to psoas abscess secondary to staphylococcus septicemia with seeding into the muscle and causing ***PSOAS ABSCESS***.

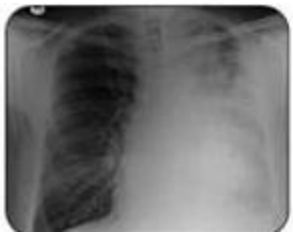


Laboratory tests :

- Laboratory investigation is indicated if The presentation suggest more than *Simple viral infection or acute phartngitis in children*, Lab test can be focused if the history is suggesting certain diagnosis.
- Clinical Pathology :
  1. CBC with differential :
     - Leukocytosis … infection.
     - Band forms and toxic granulation … suggest : bacterial infection.
     - Neutropenia : may be seen with :
       - Infection : Typhoid, brucellosis, viral infection.
       - Vasculitis : systemic lupus erythromatosis.
     - Lymphocytosis : may be seen in : Tuberculosis, brucellosis, Viral disease.
     - Monocytosis : is seen with :
       - Tuberculosis, typhoid and brucellosis.
       - Lymphoma.
     - Eosinophilia : is seen in :
       - Hypersensitivity drug syndrome.
       - Hodgkin disease.
     - *Blood films* to exclude Malaria.
     - *Urinanalysis*.
     - *Sample any fluid* (pleural, peritoneal or joint and examine for microbiology and biochemistry).
     - *Stool testing* : for pus cell, microscopy for ova and parasites and culture.

2. Chemistry : electrolytes, glucose, urea , and liver function.
3. Microbiology :
   - Samples from : sputum, urethra and other sites like joint, pleural fluid, ascetic fluid … and send for:
     a) Smears and culture.
     b) Sputum evaluation : 1) gram staining.
        2) culture.
   - Culture for : blood, abnormal fluid collection and urine.
   - CSF : if meningitis is suspected … gram stain and culture.

- SPECIAL BLOOD TEST : HIV screening for patient who has risk factor :
  1) Recent travel with sexual exposure.
  2) Injection drug user.
  3) Prostitutes (sex worker).
  4) Blood transfusion recipient.
- Radiology.
- Chest X-Ray is indicated for any patient with significant febrile illness.



Outcome of diagnostic efforts :

1) Patient recover spontaneously … suggesting : viral illness or some of the spontaneously recovering bacterial infection : mainly intracellular organism like *typhoid or brucellosis*.
2) Diagnosis is reached.
3) If fever persist for more than 2-3 weeks with no diagnosis is reached by :
   a. Repeated physical examination
   b. laboratory test … then → It is *pyrexia of unknown origin*.

Treatment of fever

- Is it fever or hyperthermia?
- Hyperthermia :
  1. Heat stroke (Classic heat stroke).
  2. Drug-induced hyperthermia.
  3. Malignant hyperthermia.
- Heat stroke : Thermoregulatory failure in association with a worm environment.
  1) **Exertional :** young person exercising at ambient temperature and or humidities that are higher than normal.
  2) **Non Exertional :** typically occur in elderly.
- Hyperpyrexia : more than 40 should be treated by : anti pyretics and physical cooling.
- While resting, the hypothalamic set point with antipyretic will speed the process.
- Antipyretics also help for : Headache, myalgia, chills.
- Low grade or moderate fever is not harmful,
  - So no antipyretics use except for :
    1. Pregnant lady.
    2. Child with history of febrile seizures.
    3. Diagnosis is established and the fever is too high.
    4. High grade fever with confusion.

Why no antipyretics for mild fever ?

- Obscure the natural history of the patient disease or syndrome.
- Gives false feeling of well being … may miss meningitis → Imminently life-threatening.

Antibiotics using :

- Pathogens.
- Infection focus.
- host factors (Immune factors).
- Common infection in ER :
  1. **UTI :**
     - Upper urinary tract infection.
     - Symptoms : fever, flank pain, dysuria.
     - Lab test : Pyuria, bacteria.
     - Treatment : cotrimoxasole, Cephalosporin or aminoglycoside.
  2. **Respiratory tract infection :**
     - Pneumonia : cough, fever, sputum or no clinical manifestations : consolidation.
     - CXR : opacity with air bronchogram, interstitial infiltrate.
     - Sputum : gram's stain.
     - Treatment : 3rd generation cephalosporin and macrolides.
     - Nosocomial fever : Fever acquired after 48hrs of admission to the hospital.
       1) Pneumonia.
       2) Catheter related infection.
       3) UTI.
     - Consider hospital pathogen while selecting antibiotics.
  3. **CNS infection :**
     - Bacterial meningitis :
       1. Aggressive antibiotics-due to prognosis and sequence.
       2. Cephalosporin.
          ± Vancomycin.
     - Viral meningitis : observation, s/s Tx.
     - TB meningitis :
       1. Anti-TB agents.
       2. Prognosis : variation.
     - Fungal meningitis : antifungal agents.
  4. **Cellulitis :**
     - Pathogens : common streptococcus, or staphylococcus.
     - Cellulitis →
     - Antibiotics : PCN G or oxacillin.

Pitfalls :

- Depend on laboratory data.
- Incomplete Hx and examination.
- Atypical presentation :
  1. Immunocompromised patient.
  2. Newborn.
  3. Early sign.
  4. Dehydration.

HIV & AIDS

Dr. Mogbil AlHedaithy

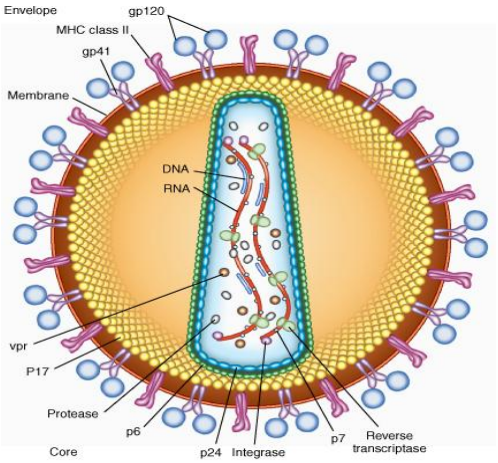
Objectives of this lecture :

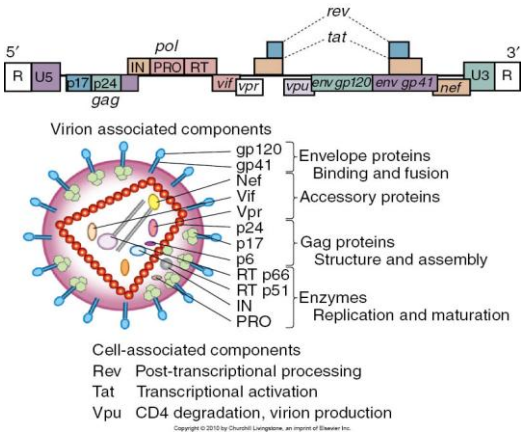
- To know HIV structure and modes of transmission
- To understand the pathogenesis of the disease
- To have an idea about the epidemiology and burden of the disease
- To have an idea about the classification of the HIV infection and the natural history
- To know when and who to diagnose HIV/AIDS
- To have an idea about the principles of treatment and control.

◈ HIV = Human Immunodeficiency Virus

- It is an **RNA virus** belong to the family *Retroviredae.*
- **Two** viruses HIV1 and HIV2.
- It causes **AIDS** in humans .
- AIDS = **A**cquired **I**mmune **D**eficiency **S**yndrome.

⊙ HIV structure



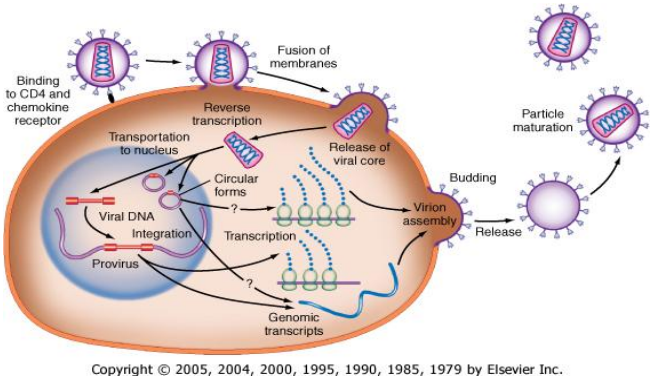


⊙ HIV Transmission

1. Sexual transmission (**the commonest**) heterosexual and male homosexual .
2. IVDU (intravenous drug use) .
3. Blood and blood products .
4. Perinatal transmission .
5. Transmission in health care setting .

- HIV is **not transmitted** by direct contact as shaking or close distance.
- It require a high viral load in order to be transmitted and cause a disease.

⊙ HIV life cycle

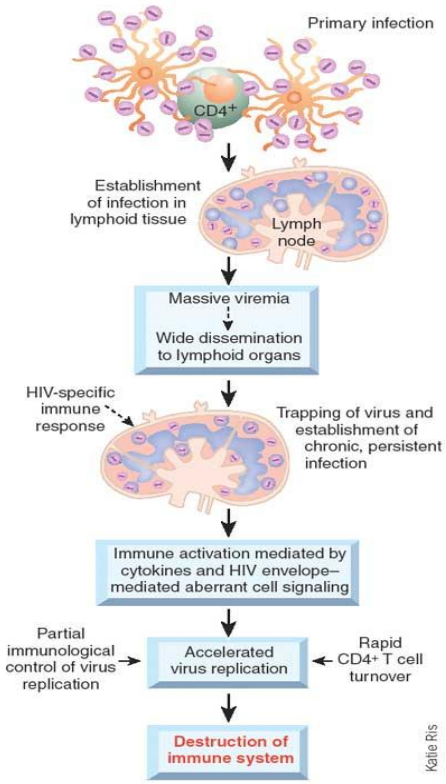


⊙ MODES OF TRANSMISSION and FACTORS INCREASING THE RISK OF ACQUISITION of HIV :

Common to all transmission categories	Sexual transmission
• High viral load • Lower CD4 cell count • AIDS • Seroconversion	• Sexually transmitted infections (STIs), especially genital ulcers • Cervical ectopy • Receptive vs insertive anal sex • Rectal or vaginal trauma • Menstruation • Male-male vs heterosexual sex • Non-circumcised • Increased number of partners
Vertical transmission	**Injection drug use transmission**
• Older gestational age • Prolonged rupture of membranes • Chorioamnionitis • Fetal trauma (e.g. scalp electrodes) • Lower birth weight • Vaginal vs elective caesarean delivery • No peripartum prophylaxis • First-born twin	• Sharing equipment • Frequency of use • Linked commercial sex • Lower income • Intravenous use • Cocaine use • Incarceration
Breastfeeding	**Occupational transmission**
• Longer duration feeding • Lower parity • Younger age • Mastitis	• Deep injury • Visible blood on device • Previous arterial or venous device siting

⊙ Pathogenesis of HIV infection

- Dendritic cells :
  - are **Macrophages** that are heavily found in sexual organs of males and females & in the skin.
  - These are large cells with large surface area which act as a bus →carry viruses from the site of infection (skin or mucous membranes) to the site of replication (T-lymphocyte) & introduce them to CD4 lymphocytes)
  - Then the viruses start to multiply in lymph nodes →go to blood → viremia { from hours to few days)
  - then they disseminate to any organ with lymphocyte (brain – spleen)
  - viruses after few days ↓↓ in the blood due to immunity .
  - destruction on immune system → ↑↑ virus load in blood .



⊙ Diagnosis

1. ***ELISA***: is the screening test ,very sensitive but .(Not Specific)
   test used to screen blood products and patients .
2. **Western blot**: confirmatory test
3. **PCR:** (polymerase chain reaction) used as confirmatory test and to asses the viral load

✓ Both Western blot and PCR : are not for screening

⊙ HIV Progression

— *Window Period is :*

- it is a period when we have a false negative test & a missed diagnosis .
- it occur within 2 week of infection
- becoming shorter with the newly methods for detection viruses in blood .

✓ 80-85 % of patients will die within 3yrs but now a days with treatments patients can live longer as they elongate the latent period .

✓ HIV infection is worst when we have ↑ load of virus & ↓ the immunity CD4

⊙ Staging (WHO):

- **Acute HIV infection**
- **Clinical stage1**: asymptomatic infection
- **Clinical stage2**:mild symptoms, lymphadenopathy.
- **Clinical stage3**:moderate symptoms
- **Clinical stage4**:severe symptoms, advanced immune deficiency

✶ Primary HIV infection

- Asymptomatic
- Acute retroviral syndrome

The Details of the stages were not discussed in the lecture !!

✶ Clinical stage 1

CDC A

- Asymptomatic
- Persistent generalized lymphadenopathy

✶ Clinical stage 2

CDC B

- Moderate and unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Recurrent oral ulcerations
- Popular pruritic eruptions
- Angular cheilitis
- Seborrhoeic dermatitis
- Fungal finger nail infections

✶ Clinical stage 3

CDC C

☒ ***Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations***

- Unexplained chronic diarrhea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Severe weight loss (>10% of presumed or measured body weight)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

☒ ***Conditions where confirmatory diagnostic testing is necessary***

- Unexplained anemia (< 80 g/l), and or neutropenia (<500/µl) and or thrombocytopenia (<50 000/ µl) for more than one month

✶ Clinical stage 4

CDC C

☒ ***Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations***

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary Tuberculosis
- Kaposi's sarcoma
- Central nervous system toxoplasmosis
- HIV encephalopathy

☒ ***Conditions where confirmatory diagnostic testing is necessary***

- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

Primary HIV infection	
▪ Symptomatic in 70-80% of cases. ▪ Usually occurs 2-6 weeks after exposure. ▪ Fever with rash. ▪ Pharyngitis with cervical lymphadenopathy	▪ Myalgia/arthralgia. ▪ Headache. ▪ Mucosal ulceration. ▪ Rarely, presentation may be neurological (aseptic meningitis, encephalitis, myelitis, polyneuritis)

Acute Retroviral Syndrome: Common Signs and Symptoms	
• Fever • Lymphadenopathy • Pharyngitis • Rash • Myalgia or arthralgia • Diarrhea	• Headache • Nausea and vomiting • Hepatosplenomegaly • Weight loss • Thrush • Neurological symptoms

HIV Mildly SYMPTOMATIC DISEASES

CDC Classification category B disease	
• Oral hairy leucoplakia • Recurrent oropharyngeal candidiasis • Recurrent vaginal candidiasis • Severe pelvic inflammatory disease • Bacillary angiomatosis • Cervical dysplasia	• Weight loss* • Chronic diarrhea* • Herpes zoster • Peripheral neuropathy • Low-grade fever/night sweats* • Idiopathic thrombocytopenic purpura

CDC Classification category C disease	
• Oesophageal candidiasis • Cryptococcal meningitis • Chronic cryptosporidial diarrhea • CMV retinitis or colitis • Chronic mucocutaneous herpes simplex • Disseminated *Mycobacterium avium intracellulare* • Pulmonary or extrapulmonary tuberculosis • *Pneumocystis carinii* (*jirovecii*) pneumonia	• Recurrent non-typhi *Salmonella* septicemia • Cerebral toxoplasmosis • Extrapulmonary coccidioidomycosis. • Invasive cervical cancer. • Extrapulmonary histoplasmosis. • Kaposi's sarcoma. • Non-Hodgkin lymphoma. • Primary cerebral lymphoma • HIV-associated wasting • HIV-associated dementia • Progressive multifocal leucoencephalopathy

⊙ Immunological staging (important)

✪ **CD4 positive T lymphocytes**

- level is the main method of assessing the immune status of the HIV positive patient.
  1. >500 cells/mm³ **normal** immunity.
  2. 350-500 cells/mm³ **mild deficiency**.
  3. 200-350 cells/mm³ **moderate immune deficiency**.
  4. <200 cells/mm³ **severe immune deficiency** (patient is known to have AIDS even if there is no symptoms .)

⊙ Common opportunistic infections in AIDS patients

1. TOXOPLASMOSIS
2. CMV retinitis , CMV commonest cause to cause blindness
3. Pneumocystis jiroveci (carinii) + PCP pneumonia
4. KOPOSI SARCOMA
5. CANDIDAISIS
6. ORAL HAIRY LEUKOPLAKIA

⊙ Eradication of HIV?

Not possible with currently available antiretroviral medications.

⊙ Goals of Treatment

- Improve quality of life
- Reduce HIV-related morbidity and mortality
- Restore and/or preserve immunologic function
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission

▪ Tools to Achieve Goals

- Selection of ARV regimen
- Preservation of future treatment options
- Rational sequencing of therapy
- Maximizing adherence
- Use of resistance testing in selected clinical settings , Pretreatment resistance testing

✓ Before Initiating ART

- Confirm HIV results
- Complete H&P
- CBC, chemistry profile
- CD4 cell count
- Plasma HIV RNA measurement
- Consider resistance testing
- Assess "readiness" for treatment and adherence

Additional Tests	
✓ RPR or VDRL ✓ PPD ✓ Chest X ray ✓ Hepatitis A,B,C serology ✓ Toxoplasma IgG	• Fasting glucose and lipids • Gynecologic exam with pap smear • Testing for chlamydia and gonorrhea • Ophthalmology exam (CD4+ T cell count <100 cells/µL)

⊙ Use of CD4 Cell Levels to Guide Therapy Decisions

✪ ***CD4 count***

- The major indicator of immune function
- Most recent CD4 count is best predictor of disease progression
- A key factor in decision to start ART or OI prophylaxis
- Important in determining response to ART
  - — Adequate response: CD4 increase 50-150 cells/µL per year

✪ ***CD4 monitoring***

- Check at baseline (x2) and at least every 3-6 months.

⊙ Use of HIV RNA Levels to Guide Therapy Decisions

✪ ***HIV RNA***

- May influence decision to start ART and help determine frequency of CD4 monitoring
- Critical in determining response to ART
  - — Goal of ART: HIV RNA below limit of detection (ie, <40-75 copies/mL, depending on assay)

✪ ***RNA monitoring***

- Check at baseline (x2)
- Immediately before initiating ART
- 2-8 weeks after start or change of ART
- Every 3-6 months with stable patients

◈ When to Start ART

■ Potent ART may improve and preserve immune function in most patients with virologic suppression, regardless of baseline CD4 count

- ART indicated for all with low CD4 count or symptoms
- Earlier ART may result in better immunologic responses and better clinical outcomes
  - Reduction in AIDS- and non-AIDS-associated morbidity and mortality
  - Reduction in HIV-associated inflammation and associated complications
  - Reduction in HIV transmission
- Recommended ARV combinations are considered to be durable and tolerable

■ Exact CD4 count at which to initiate therapy not known, but evidence points to starting at higher counts

■ Current recommendation: ART for all patients with CD4 <500 cells/μL

- For patients with CD4 >500 cells/μL, 50% of the panel recommend ART, 50% consider ART to be optional

- Randomized control trial (RTC) data support benefit of ART if CD4 ≤350
- No RTC data on benefit of ART at CD4 >350, but observational cohort data

■ Currently available ARVs are effective and well tolerated

Recommendations for Initiating ART	
Clinical Category or CD4 Count	**Recommendation**
▪ History of AIDS-defining illness ▪ CD4 count <350 cells/μL ▪ CD4 count 350-500 cells/μL ▪ Pregnant women ▪ HIV-associated nephropathy (HIVAN) ▪ Hepatitis B (HBV) coinfection, when HBV treatment is indicated*	Initiate ART

*** Treatment with fully suppressive drugs active against both HIV and HBV is recommended.**

Recommendations for Initiating ART	
Clinical Category or CD4 Count	**Recommendation**
CD4 count >500 cells/μL, asymptomatic, without conditions listed above	50% of the Panel favors starting ART; 50% views ART as optional

Current ARV Medications		
NRTI	**PI**	**Integrase Inhibitor (II)**
▪ Abacavir (ABC) ▪ Didanosine (ddI) ▪ Emtricitabine (FTC) ▪ Lamivudine (3TC) ▪ Stavudine (d4T) ▪ Tenofovir (TDF) ▪ Zidovudine (AZT, ZDV)	▪ Atazanavir (ATV) ▪ Darunavir (DRV) ▪ Fosamprenavir (FPV) ▪ Indinavir (IDV) ▪ Lopinavir (LPV) ▪ Nelfinavir (NFV) ▪ Ritonavir (RTV) ▪ Saquinavir (SQV) ▪ Tipranavir (TPV)	▪ Raltegravir (RAL)
NNRTI		**Fusion Inhibitor**
▪ Delavirdine (DLV) ▪ Efavirenz (EFV) ▪ Etravirine (ETR) ▪ Nevirapine (NVP)		▪ Enfuvirtide (ENF, T-20)
		CCR5 Antagonist
		▪ Maraviroc (MVC)

⊙ Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
  - 3 NRTIs
- Combination of NNRTI or PI + 2 NRTIs preferred for most patients
- Fusion inhibitor, CCR5 antagonist, integrase inhibitor not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

✶ Treatment for Pregnant Women

Any pregnant women should be treated to reduce risk of perinatal transmission:

- ART recommended for all pregnant women
- Suppress HIV viral load ideally to <50 copies/mL, and at least to <1,000 copies/mL

◈ Timing of Perinatal HIV Transmission

- Cases documented intrauterine, intrapartum, and postpartum by breastfeeding :
  - In utero 25%–40% of cases.
  - Intrapartum 60%–75% of cases.
  - Addition risk with breastfeeding.
    - 14% ↑ risk with established infection.
    - 29% ↑ risk with primary infection.
  - Current evidence suggests most transmission occurs during the intrapartum period.

⊙ Perinatal HIV Transmission

- Without antiretroviral (ARV) drugs during pregnancy, mother-to-child transmission (MTCT) has ranged from 16%–25% in North America and Europe
- 21% transmission rate in the U.S. in 1994 before the standard zidovudine (ZDV) recommendation during pregnancy
- With the change in practice, transmission was 11% in 1995
- Today, risk of perinatal transmission can be <2% with
  - effective antiretroviral therapy (ART)
  - elective cesarean section (C/S) as appropriate
  - formula feeding

Initial Treatment: Preferred	
NNRTI based	▪ EFV/TDF/FTC[1,2]
PI based	▪ ATV/r + TDF/FTC[2] ▪ DRV/r (QD) + TDF/FTC[2]
II based	▪ RAL + TDF/FTC[2]
Pregnant Women	▪ LPV/r (BID)[3] + ZDV/3TC
▪ 1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception. ▪ 2. 3TC can be used in place of FTC and vice versa.	

⊙ HIV and AIDS / Prevention

- Education of the high risk groups about the disease
- Voluntary screening and counseling.
- Screening of blood and blood products before transfusion
- Condom use
- Screening and treating pregnant women
- Male circumcision

Acute Viral Hepatitis

Prof. Faleh Al-Faleh

- Clinical Presentation.
- Diagnosis.
- Epidemiology of viral hepatitis infection A, B, C in KSA.
- Management.

Viral Hepatitis - Overview

	Type of Hepatitis				
	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Diagnosis of hepatitis :

- Patient history
- Physical examination
- Liver function tests
- Serologic tests

Symptoms and Signs :

- Pre-icteric phase :
  - Anorexia, Fatigue
  - Nausea, Vomiting
  - Arthralgia, Myalgia
  - Headache, Photophobia
  - Pharangitis
- Icteric phase :
  - Enlarged liver, Tender upper quadrant, Splenomegaly (10-20%)
  - Discomfort, General adenopathy
- Post-icteric phase.

Lab Findings :

- LFT increase >5-10 times of normal
- Markers of hepatitis B or C or A might be positive

Pathological findings :

- Pan lobular infiltration with mononuclear cells
- Hepatic cell necrosis
- Reticulum framework are intact

DDx :

- Infectious Mononucleosis
- Drug Induced Hepatitis
- Chronic Hepatitis.
- Alcohol Hepatitis
- Cholecystitis, Cholelithiasis

Complications :

1. Chronic hepatitis → cirrhosis- HCC.
2. Fulmnant hepatitis

FULMINANT HEPATITIS

- Definition: Hepatic Failure Within 8 Weeks Of Onset Of Illness.
- Manifestation: Encephalopathy and Prolonged PT
- Histopathology: Massive Hepatic Necrosis.

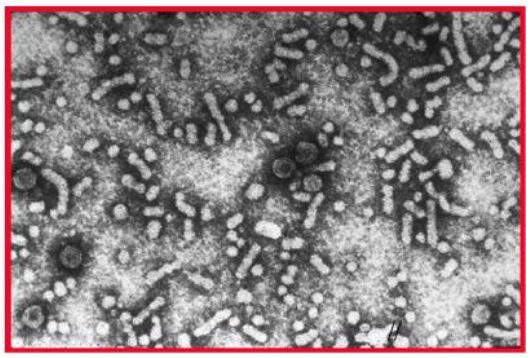
HBV infection

Hepatitis B : Clinical Features

- **Incubation period**: Average 60-90 days (Range 45-180 days)
- **Clinical illness (jaundice):** < 5 yrs, <10%
  ≥ 5 yrs, 30%-50%
- **Acute case-fatality rate:** 0.5%-1%
- **Chronic infection:** < 5 yrs, 30%-90%
  ≥ 5 yrs, 2%-10%
- **Premature mortality from chronic liver disease:** 15%-25%

Factors affecting transmission ability :

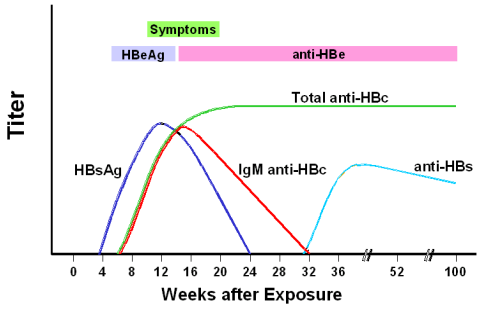
1. **Replicative status :**
   - HBeAg.
   - High HBVDNA.
2. **Route of infection :**
   - Percutanouse.
   - Transmucosal.
3. **Exposure frequency :** Single vs. Multiple.
4. **Inoculums size :** transfusion vs. needle stick.



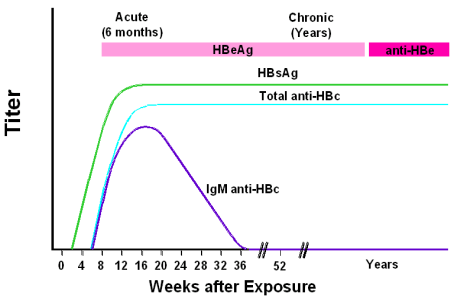
Hepatitis B serology :

- Anti-HBc → exposure (IgM = acute)
- HBsAg → infection (carrier)
- Anti-HBs → immunity
- HBeAg → viral replication
- Anti-HBe → seroconversion
- HBV-DNA → viral replication

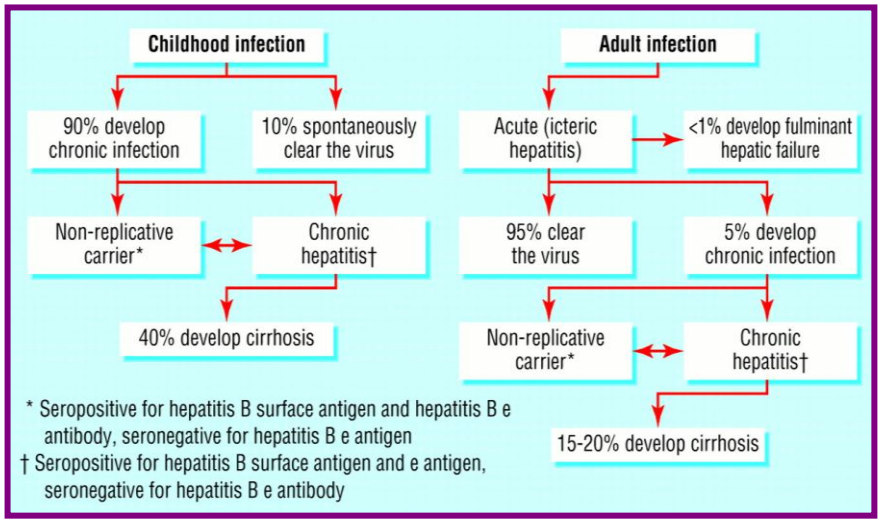
Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course

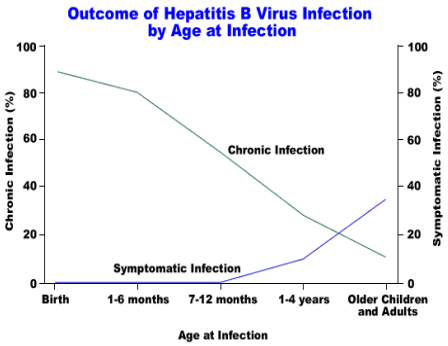


Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Natural History :





HBV: Modes of Transmission

- Sexual
- Parenteral
- Perinatal

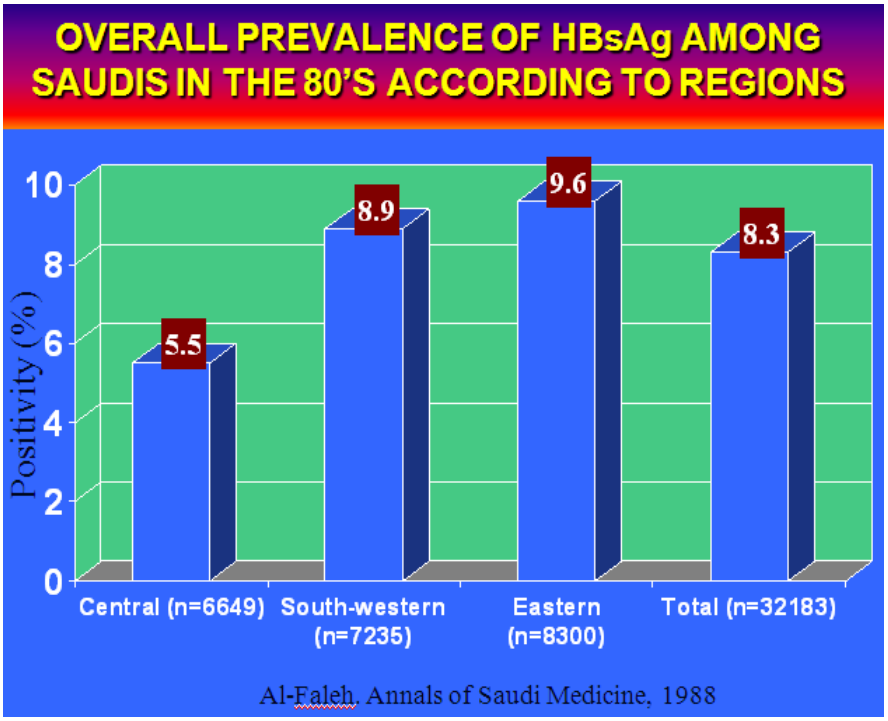
Concentration of Hepatitis B Virus in Various Body Fluids

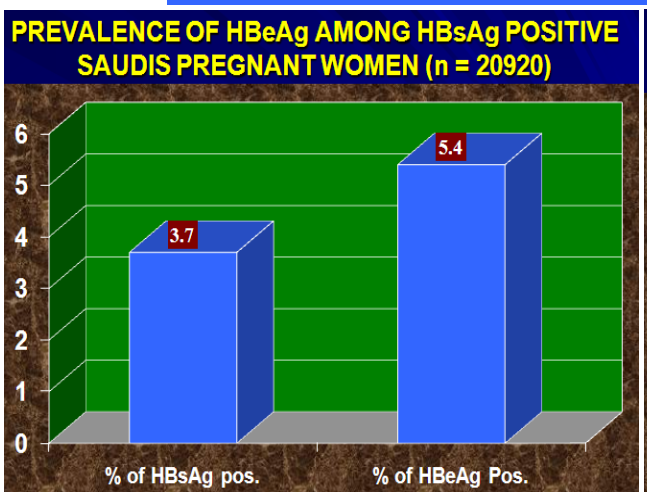
High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

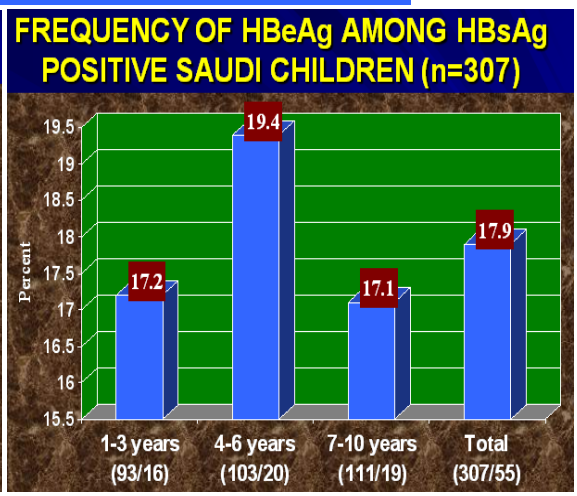
Possible transmission route of HBV in KSA :

- 1-Horisontal transmission (person to person) is the main transmission route
- 2-Perintal transmission (positive HBSAG mothers) especially if they are HBEAG positive
- 3- Heterosexual transmission
- 4-Illegal injection drug use
- 5- Contaminated equipment used for therapeutic injections and other health care related procedures
- 6- Folk medicine practice
- 7-Blood and blood products transfusion without prior screening

HBV INFECTION before and after vaccination program :





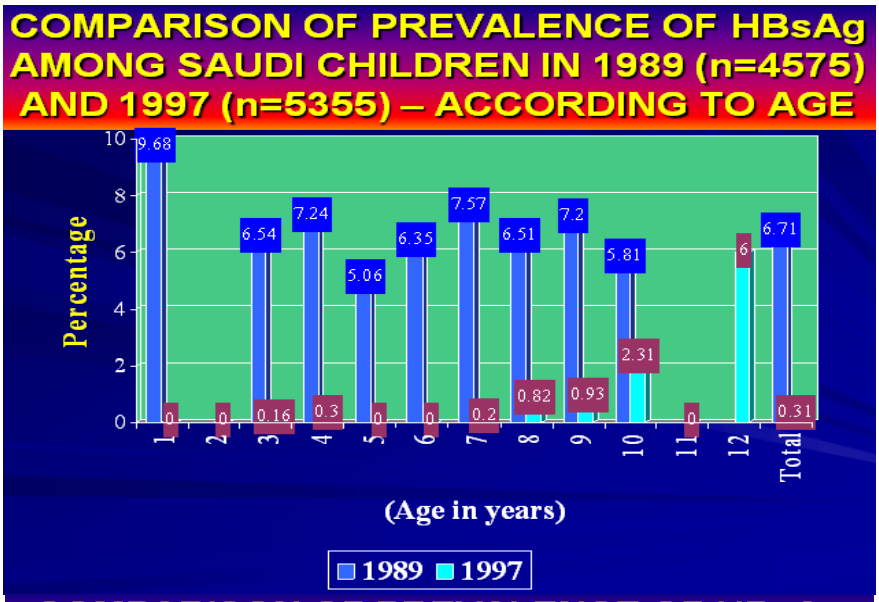


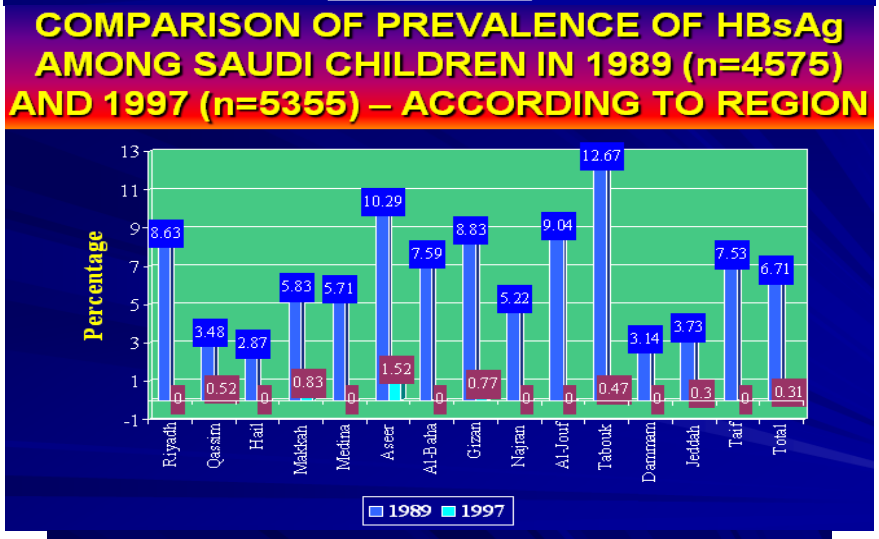
PREVENTION STRATEGIES OF MINISTRY OF HEALTH IN KSA :

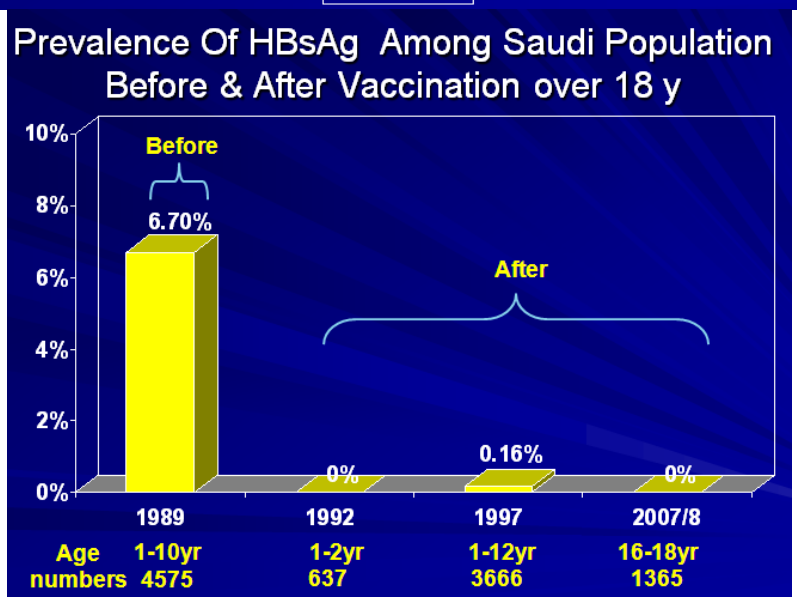
- Introducing HBV vaccine in EPI program; and
- Mandatory screening of blood donors and expatriates.
- Vaccination of risk groups.
- Health education especially among medical personnel.

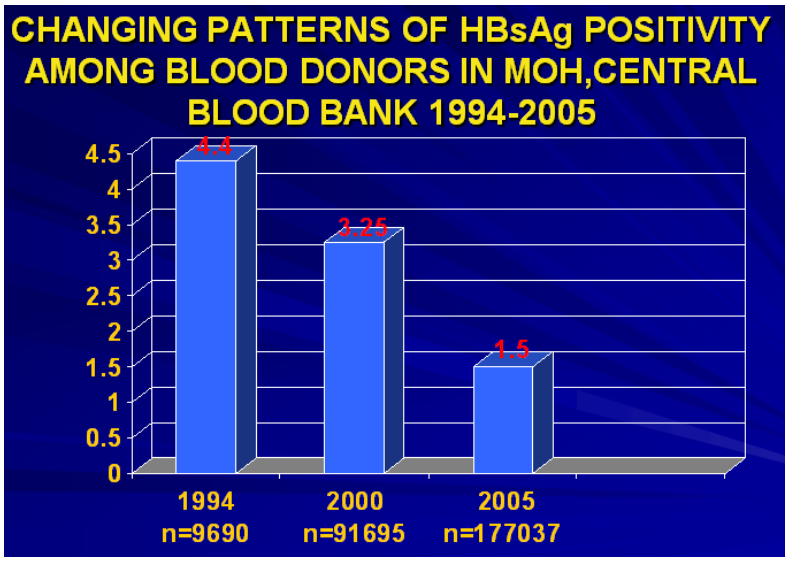
THE CURRENT EPI IN THE KINGDOM OF SAUDI ARABIA

1.	At birth	BCG +	HB1
2.	At 6 weeks	DPT1 + OPV1	Hb2
3.	At 3 months	DPT2 + OPV2	
4.	At 5 months	DPT3 + OPV3	
5.	At 5months	Measles	HB3
6.	At 12 months	MMR	
7.	At 18 months	(DPT + OPV)	Booster 1
8.	At 4-6 years	(DPT + OPV)	Booster 2


COMPARISON OF PREVALENCE OF HBsAg AMONG SAUDI CHILDREN IN 1989 (n=4575) AND 1997 (n=5355) – ACCORDING TO AGE
Percentage
(Age in years)
1989 1997


COMPARISON OF PREVALENCE OF HBsAg AMONG SAUDI CHILDREN IN 1989 (n=4575) AND 1997 (n=5355) – ACCORDING TO REGION
Percentage
Riyadh
Qassim
Hail
Makkah
Medina
Aseer
Al-Baha
Gizan
Najran
Al-Jouf
Tabouk
Dammam
Jeddah
Taif
Total
1989 1997

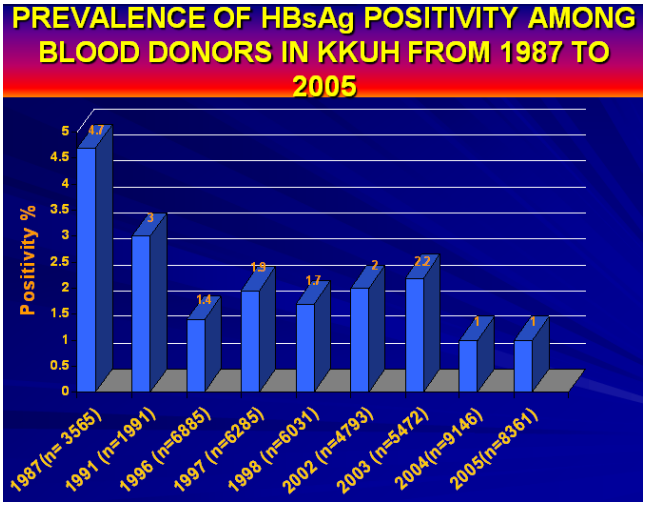

Prevalence Of HBsAg Among Saudi Population Before & After Vaccination over 18 y
Before
6.70%
After
0.16%
0%
0%
1989
1992
1997
2007/8
Age numbers
1-10yr 4575
1-2yr 637
1-12yr 3666
16-18yr 1365

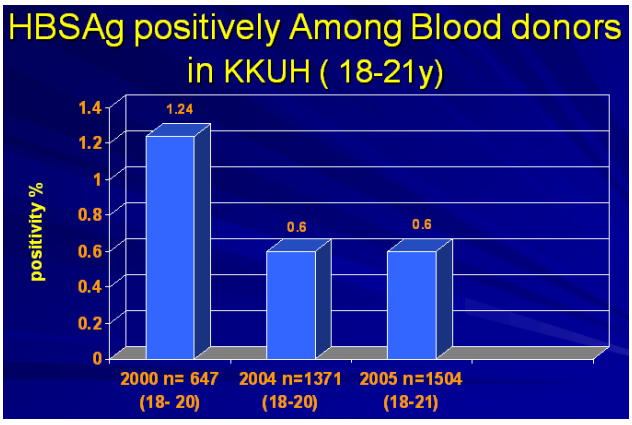


HCV INFECTION

Transmission of HCV :

- **Percutaneous :**
  - **Injecting drug use**
  - **Clotting factors before viral inactivation**
  - **Transfusion, transplant from infected donor**
  - **Therapeutic (contaminated equipment, unsafe injection practices)**
  - **Occupational (needlestick)**
- **Permucosal :**
  - **Perinatal**
  - **Sexual**
- EGYPT, mass campaigns of parenteral antischistosomal therapy (discontinued only in the 1980) may represent the WORLD, largest iatrogenic transmission of BLOOD BORNN PATHOGENS.





Features of Hepatitis C Virus Infection :

- Symptomatic patients may clear HCV
- Spontaneous clearance usually occurs by 6 weeks, almost always by 12 weeks.
- Start treatment for asymptomatic infections at 8weeks .
- Start treatment for symptomatic infections if still positive at 8weeks.
- Standard dose of PEG-IFN weekly x 24 weeks will achieve SVR (Systemic Vascular Resistance)in 85%-100%.
- Incubation period : Average 6-7 weeks (Range 2-26 weeks)
- Acute illness (jaundice) : Mild (≤20%)
- Case fatality rate : Low
- Chronic infection : 75%-85%
- Chronic hepatitis : 70% (most asx)
- Cirrhosis : 10%-20%
- Mortality from CLD : 1%-5%

Household Transmission of HCV :

- Rare but not absent
- Could occur through percutaneous/mucosal exposures to blood
  - Theoretically through sharing of contaminated personal articles (razors, toothbrushes)
  - Contaminated equipment used for home therapies
    - Injections
    - Folk remedies

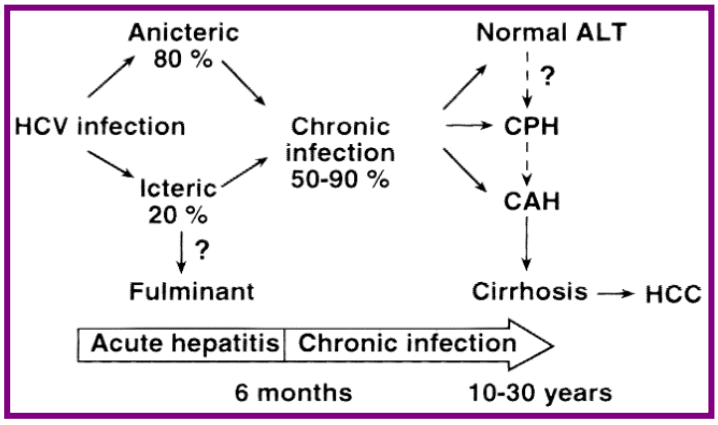
Sexual Transmission of HCV :

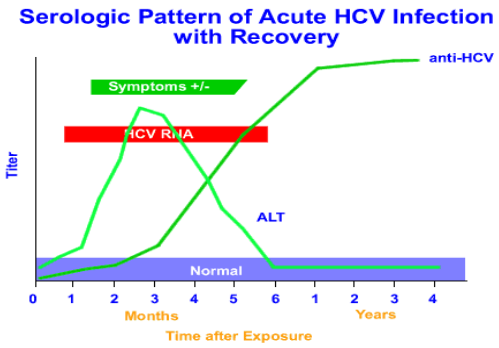
- Occurs, but efficiency is low
  - Rare between long-term steady partners
  - Factors that facilitate transmission between partners unknown (e.g., viral titer)
- Accounts for 15-20% of acute and chronic infections in the United States
  - Sex is a common behavior
  - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners

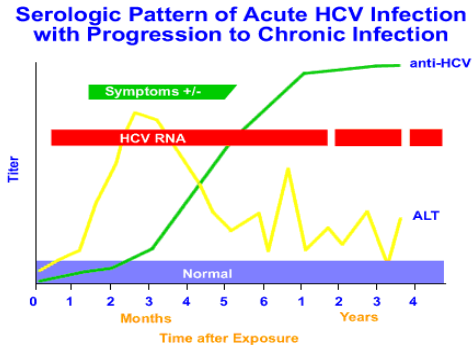
Nosocomial Transmission of HCV :

- Recognized primarily in context of outbreaks
- Contaminated equipment
  - hemodialysis
  - endoscopy
- Unsafe injection practices
  - plasmapheresis, phlebotomy
  - multiple dose medication vials
  - therapeutic injections

Natural history :

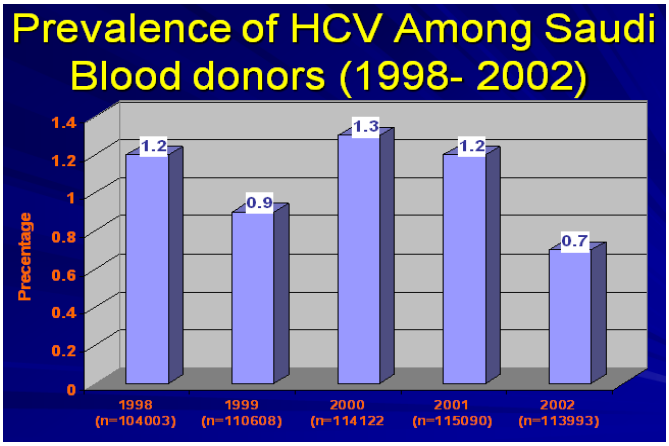


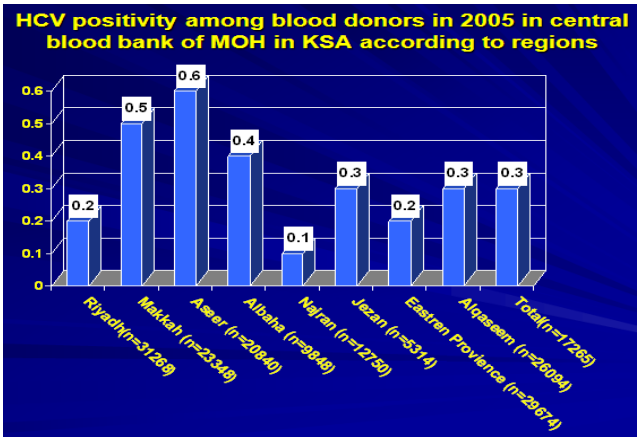


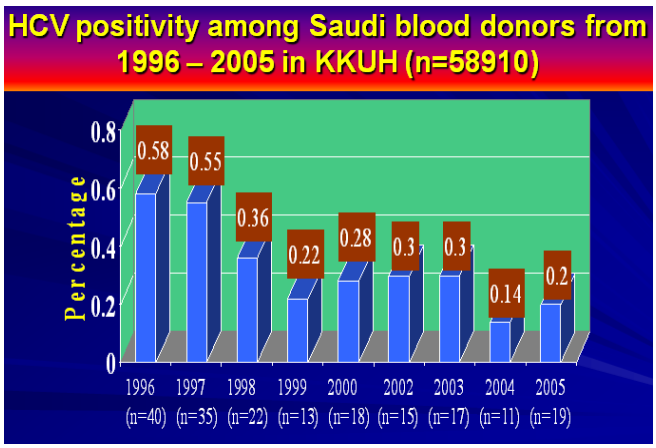


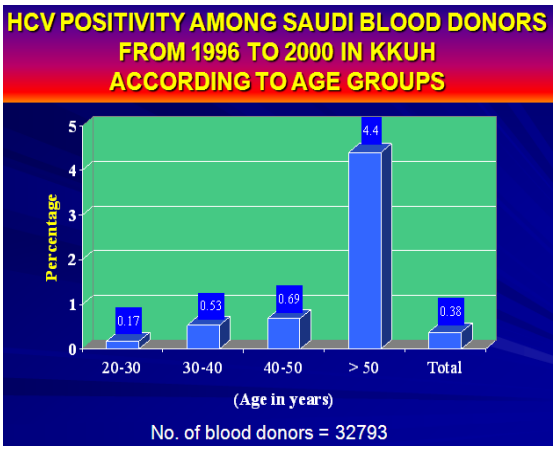
COMPARISON OF PREVALENCE OF ANTI-HCV IN SAUDI CHILDREN IN 1989 AND 1997 STUDIES			
1989		**1997**	
No. of children	Positive (%)	No. of children	Positive (%)
4496	39 (0.87%)	5350	2 (0.04%)
Diagnostic test only by 1st-generation EIA kit.		Diagnostic test by 3rd-generation EIA kit and confirmatory test by RIBA kit.	

Overall prevalence rate of HCV infection in KSA among children and adolescent during the last 18 yrs					
1989		**1997**		**2008**	
No. of children	Positive (%)	No. of children	Positive (%)	No. of students	Positive (%)
4496	39* (0.87%)	5350	2** (0.04%)	1357	(5)3 0.22%
Diagnostic test only by 1st-generation EIA kit.		Diagnostic test by 3rd-generation EIA kit and confirmatory test by RIBA kit.		Diagnostic test by PCR for anti- HCV Positive cases.	







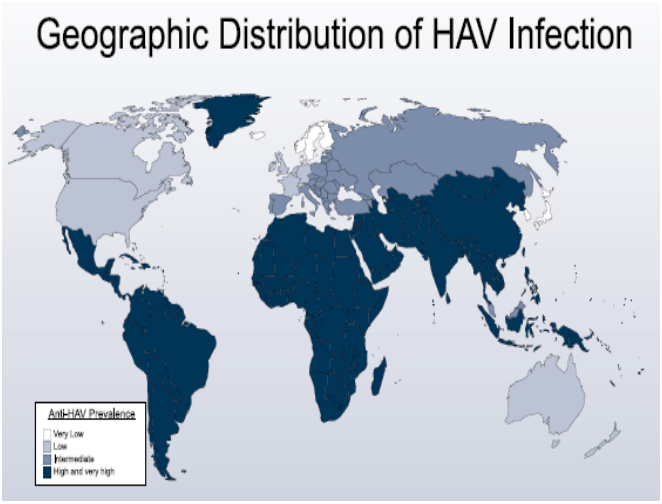


Prevalence of HCV Positivity Among Different Saudi population		
Type of patient	**number**	**Prevalence(%)**
Children from 1-18y	3854	0.1
Pregnant women	3127	0.7
Hemodialysis patients	29054	55.8
Drug addicts	9137	14

Prevention Of HCV Transmission :

- Avoiding shared use of Razors or brushes and any item that pierces the skin.
- Strict adherence of the universal precautions in health facilities.
- Educating and training of HCW's to the proper use of standard precautions
- Folk medicine?!

HAV INFECTION



Modes of HAV transmission

- Faeco-oral route (95%)

==> person-to-person contact
==> contaminated food or water
==> salads and fruits washed in contaminated water
==> contaminated shellfish

- Infected plasma (<5%)
- Sexual route (<5%)

HEPATITIS A VIRUS TRANSMISSION

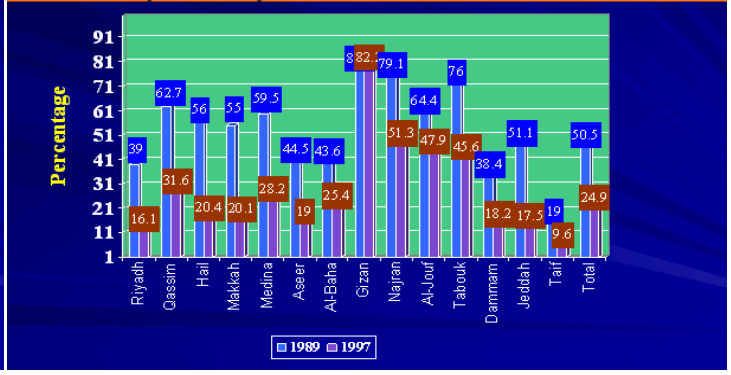
- Close personal contact (e.g., household contact, sex contact, child day-care centers)
- Contaminated food, water (e.g., infected food handlers)
- Blood exposure (rare) (e.g., injection drug use, rarely by transfusion)

HEPATITIS A - CLINICAL FEATURES

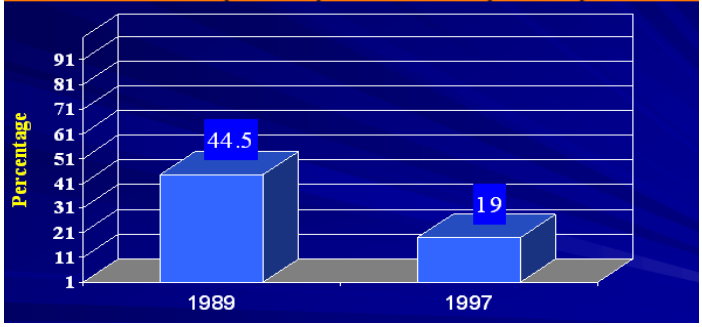
•Jaundice by age group:	<6 yrs	<10%
	6-14 yrs	40%-50%
	>14 yrs	70%-80%
•Rare complications:	Fulminant hepatitis Cholestatic hepatitis Relapsing hepatitis	
•Incubation period:	Average 30 days Range 15-50 days	

COMPARISON OF PREVALENCE OF ANTI-HAV AMONG SAUDI CHILDREN IN 1989 (n=4375) AND 1997 (n=5255) – ACCORDING TO AGE

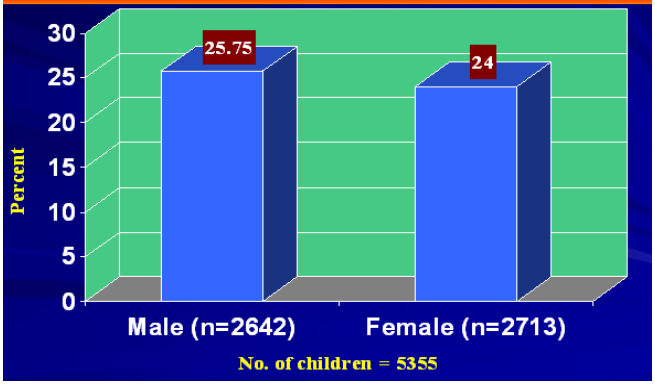
COMPARISON OF PREVALENCE OF ANTI-HAV AMONG SAUDI CHILDREN IN 1989 (n=4375) AND 1997 (n=5255) – ACCORDING TO REGION

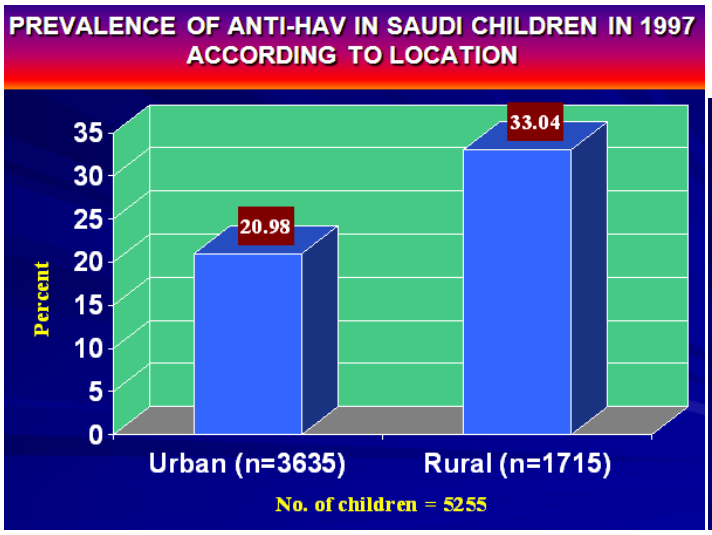


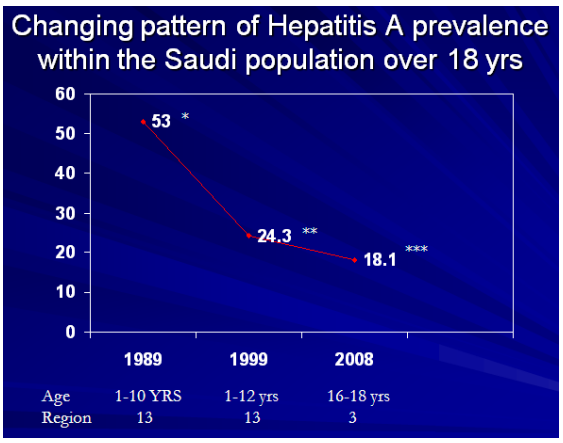
COMPARISON OF PREVALENCE OF ANTI-HAV IN ASEER REGION AMONG SAUDI CHILDREN IN 1989 (n=476) AND 1997 (n=411)



PREVALENCE OF ANTI-HAV IN SAUDI CHILDREN IN 1997 ACCORDING TO SEX







Age Specific Prevalence of Anti-HAV in Saudis From Riyadh, Central Region					
Age (Years)	1986		1994		P
	No. Positive/ No. Tested	%	No. Positive/ No. Tested	%	
1 – 9	103/194	53.0	81/210	38.6	3.4 x 10.3
10 – 19	164/193	85.0	110/180	61.1	1 x 10.4
20 – 30	182/200	91.0	188/240	78.3	3 x 10.4
Total	449/587	76.5	379/630	60.2	1 x 10.4

PREVENTING HEPATITIS A

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)

HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A Vaccines

Schedule Vaccine	Age (yrs)	Dose	Volume (mL)	2-Dose (mos)
HAVRIX ®#	1-18	720 (EL.U.*)	0.5	0, 6-12
	>18	1,440	1.0	0, 6-12
VAQTA ®##	1-18	25 (U**)	0.5	0, 6-18
	>18	50	1.0	0, 6-18

Means to control hepatitis A

- provision of clean water
- proper disposal of faeces
- passive immunization
- active immunization

Infections in the Immunocompromized Host

Prof. Mogbil Al-Hedaithy

Objectives :

- To review the components of the host defense mechanisms.
- To recognize the importance of immunodeficiency and infections.
- To know the common infectious complications in major immunodeficiency categories (other than HIV & AIDS).

◈ Definitions :

- Immunodeficient: No cell-mediated or humoral immunity
- Immunocompromised: Any form of defect, e.g. burned skin , or patient treated with immunosuppressives.

◈ Components of Host Defenses :

- **Mechanical barriers :**
  - Skin
  - mucous membranes
  - epiglottis
  - cilia. (for expelling bacteria)
- **Granulocytes:** 2nd line , after the entery of organisms and invasion of mechanical barriers.
- **Cell mediated Immunity :** Macrophages, T-lymphocytes, NKC, cytokines.
- **Humoral Immunity :** B-lymphocytes, immunoglobulins, complements.
- **Spleen :** acts as a filter, helps in antibodies recognition of bacteria.

The importance of infections in IC host :

- Increasing numbers of Immunocompromised patients : more people with transplanted organs, advanced intensive care units and improved treatments for cancer all ↓ed the NO. of death and ↑ed the NO. of IC patients.
- Seriousness of infections in those patients.
- Infections with unusual, nonpathogenic microorganisms : Pathogens that doesn't cause inf. In healthy people e.g. pneumocystic carnii and CMV.
- Atypical presentation of infections by common pathogens: usual pathogen but unusual presentation, it won't be recognized, so it won't be diagnosed or might be diagnosed late, thus the mortality will increase.

◈ Causes of immune deficiency :

- **Primary (congenital) :**
  - Rare, more common in children.
  - E.g. chronic granulomatus disease, combined immunedifiency syndrome, specific Ig deficiency, others.
- **Secondary (acquired) :**
  - The commonest, there are many causes.
  - E.g. extremes of age, pregnancy, infections, malignancy, chemotherapy, steroids, burns, trauma, procedures, connective tissue diseases, chronic diseases like DM,CRF… etc.

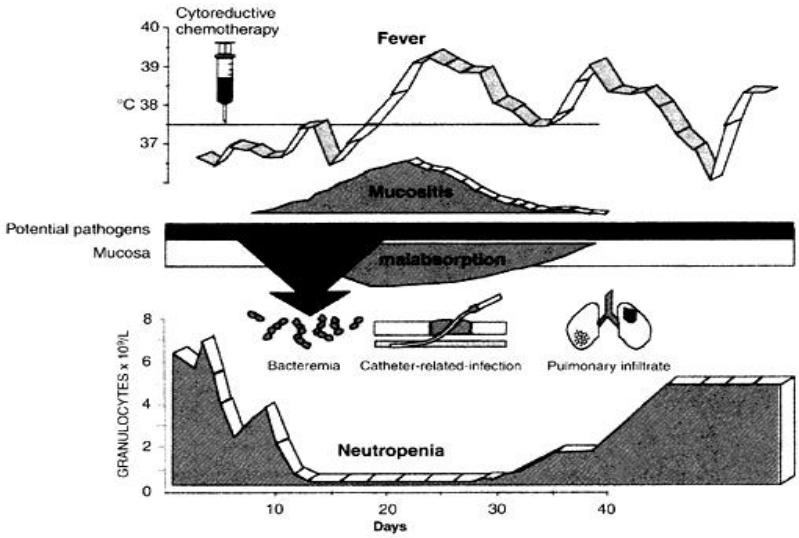
Host Defects and Associated Prevalent Pathogens :

Defect	Pathogen
Granulocytopenia Chemotherapy is the main cause	Staph. Aureus,CNSS, V strep, Enterococci, E. coli, Pseudomonas aeruginosa, K.pneumoniae, other gram –ve bacilli, Aspergillus spp
Damaged skin and mucous membrane	CNSS (Coagulase negative staph species.), Staph. Aureus, pseudomonas aeruginosa and other gram-ve bacilli, candida spp, V. strep, enterococci, HSV.
Impaired CMI	HSV, VZ, EBV, CMV, RSV, M. tuberculosis, Aspergillus spp and other fungi, Toxoplasma gondi.
Impaired humoral immunity	Streptococcus pneumoniae, Haemophilus influenzae
Spleen dysfunction*	Streptococcus pneumoniae, Haemophilus influenzae Neisseria meningitides.
Complement deficiency → congenital (Usually) or connective tissue disease e.g. SLE	Neisseria meningitides, Neisseria gonorrhea

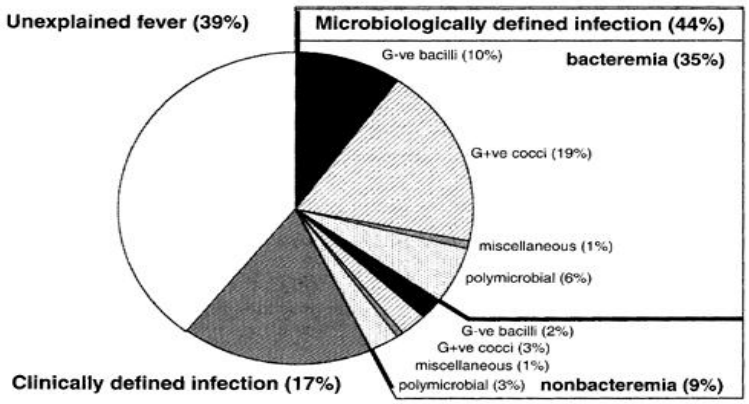
*Spleen dysfunction → either because the spleen is not functioning as in sickle cell anemia or that it's immature due to a congenital disease, or in some cases it might be surgically removed which is relatively frequent due to rupture of the spleen. This will lead to loss of spleen's function and the patient will be prone to infections.

◈ Fever In Neutropenic Patient :

- **Definition :**
  - **Fever :** Oral temperature of 38c for more than two hours or single temperature of 38.3c or more.
    - **Neutropenia :** A Neutrophil count of <500 cells/mm³ or a count of <1000 cells/mm³ with a predicted decline to 500/mm. (normal neutrophils > 1000 cells/mm³)
- **Approach to patient :**
  - Careful history and examination, investigations (like blood cultures, urine culture, CXR, others), then start antibiotic therapy to cover the most likely organisms.



^ Sequential Infective Events



^ Causes of fever in neutropenic patients

◈ Causes of fever:

- Most common cause of fever is **INFECTIONS**.
- Bacteremia (35%) is the COMMONEST cause of INFECTIONS followed by fungi e.g. candida.
- Gm +ve mostly staph. & strept.
- Gm –ve mostly pseudomonas
- Mucositis leads to ulcerations in mouth,will cause bacteremia , this is the cause of the associated fever.

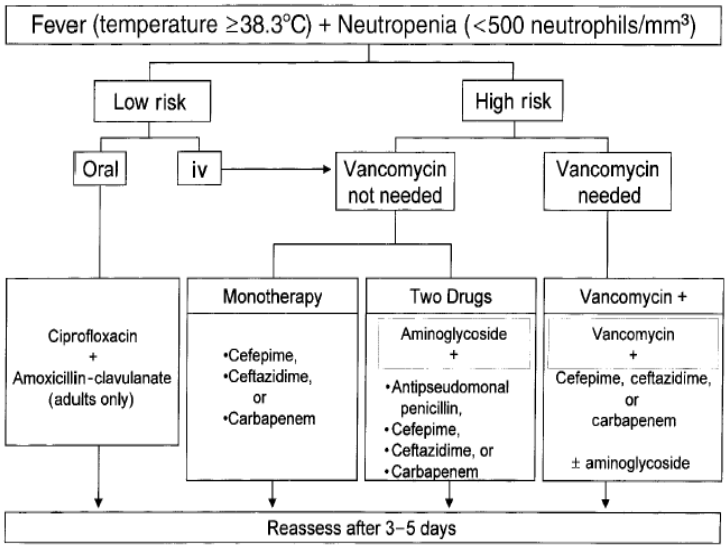


Figure 1. Algorithm for initial management of febrile neutropenic patients. See tables 3 and 4 for rating system for patients at low risk. Carbap

Table 3. Factors that favor a low risk for severe infection among patients with neutropenia.

Absolute neutrophil count of ⩾100 cells/mm³
Absolute monocyte count of ⩾100 cells/mm³
Normal findings on a chest radiograph
Nearly normal results of hepatic and renal function tests
Duration of neutropenia of <7 days
Resolution of neutropenia expected in <10 days
No intravenous catheter–site infection
Early evidence of bone marrow recovery
Malignancy in remission
Peak temperature of <39.0°C
No neurological or mental changes
No appearance of illness
No abdominal pain
No comorbidity complications[a]

NOTE. Data are adapted from [4, 42–49, 51–53].

[a] Concomitant condition of significance (e.g., shock, hypoxia, pneumonia or other deep-organ infection, vomiting, or diarrhea).

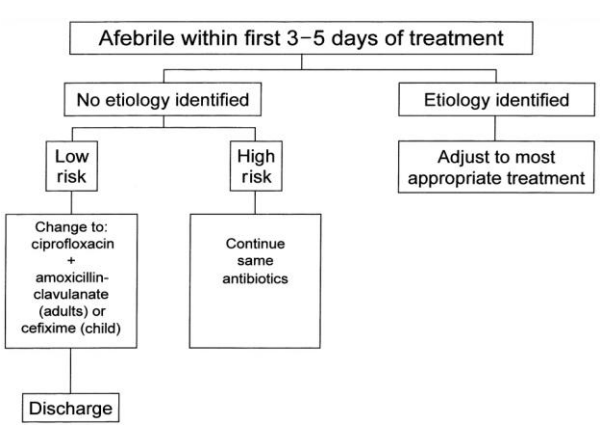
Table 4. Scoring index for identification of low-risk febrile neutropenic patients at time of presentation with fever.

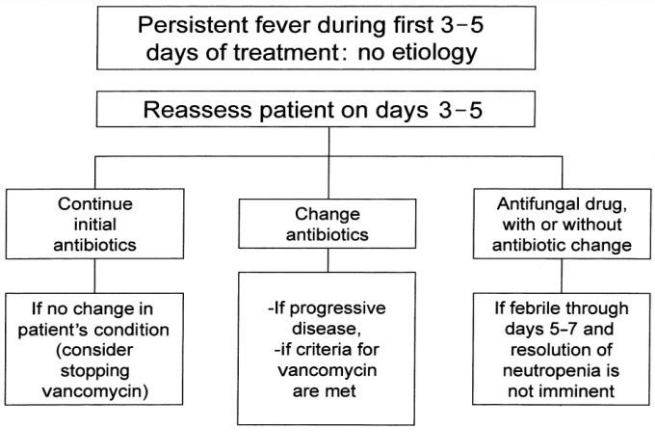
Characteristic	Score
Extent of illness[a]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age <60 years[b]	2

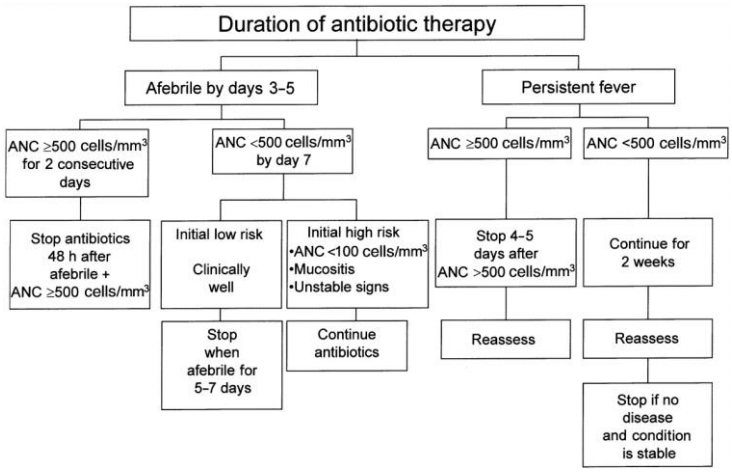
NOTE. Highest theoretical score is 26. A risk index score of ⩾21 indicates that the patient is likely to be at low risk for complications and morbidity. The scoring system is derived from [50].

[a] Choose 1 item only.

[b] Does not apply to patients ⩽16 years of age. Initial monocyte count of ⩾100 cells/mm³, no comorbidity, and normal chest radiograph findings indicate children at low risk for significant bacterial infections [46].







◈ Treatment :

- **Antibacterial like :** pipracilline+ aminoglycoside or ceftazidime + aminoglycoside or Imipenem, vancomycine.
- **Antifungal like :** Amphotericine B, Fluconazole.
- **Antiviral like :** Acyclovir. (antiviral not usually used)
- **Granulocyte stimulating factors.** → not antibiotics. They stimulate bone marrow to produce neutrophils to shorten the duration of neutropenia.
- Duration of treatment is variable.
  If there is abscess, drain it, send aspiration to lab , then start antibiotic.

We use a combination of antibiotics to cover all possible organisms. (Empiric Rx)
High risk groups are the ones with hematological malignancies.
Low risk groups are usually patients with solid organ tumors because the duration of neutropenia is low and their immunity is considered to be good. Oral antibiotics can be used with this group, but in general we prefer IV AB.

Infections in Solid-Organ Transplant Recipients :

- **Factors affecting the incidence of infections :**
  - The type of organ transplanted.
  - The degree of immunosuppression (immunosuppressants used for transplant are directed to suppress cell mediated immunity)
    Why *are we concerned about suppressing the cell mediated immunity?* Because rejection of transplanted organ is by cell-mediated immunity
  - The need for additional antirejection therapy.
  - The occurrence of surgical complications.
  - Presence of latent infection in the donor or recipient.
- **Common infection in Specific Organ transplant :**
  - Bone marrow transplant → Bloodstream infections, pneumonia, viral infections.
  - Kidney transplant → Urinary tract infections.
  - Liver transplant → Intra abdominal infections.
  - Heart and Heart-Lung transplant → Chest, Mediastinitis.

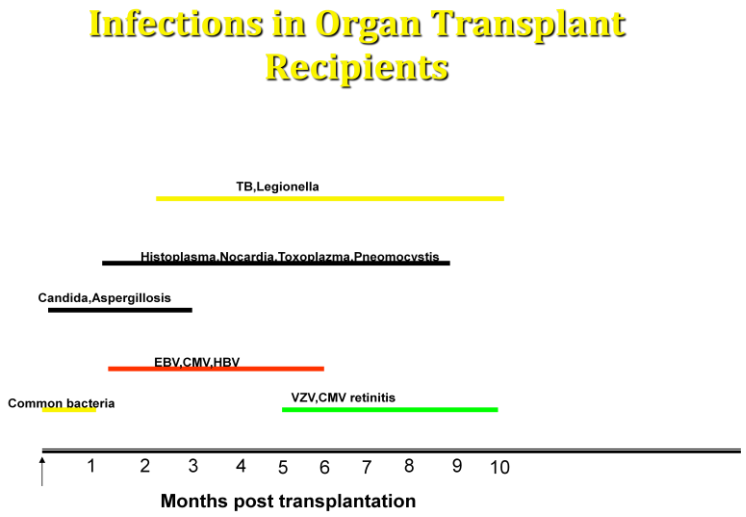
The duration of immunosuppression varies according to the transplanted organ:

- Bone marrow→ very high, very intensive immunosuppression
- kidneys→ significant amount of immunosuppression
- liver → less amounts of immunosuppression
- cornea → may not require any

TABLE 1. Evolving risk of infection in the bone marrow recipient

Time	Infectious agent
Early (neutropenic period)	Bacteria
	Common gram-positive and gram-negative pathogens
	Fungi
	Candida spp.
	Aspergillus spp.
	Fusarium spp.
	Viruses
	HSV
	RSV
	Protozoa
	T. gondii
Middle (following marrow recovery)[a]	Viruses
	CMV
	VZV
	HHV-6
	Adenovirus
	RSV
	Fungi
	Aspergillus spp.
	P. carinii
	Protozoa
	T. gondii
Late (>100 days post-transplantation)	Bacteria
	S. pneumoniae
	S. aureus
	Viruses
	VZV
	CMV
	RSV
	Fungi
	P. carinii
	Protozoa
	T. gondii

[a] More common in patients experiencing GVHD or infection with immunomodulating viruses.



Tuberculosis

Dr. Awadh Al-Anazi

Clinically Relevant Major Species of Mycobacterium :

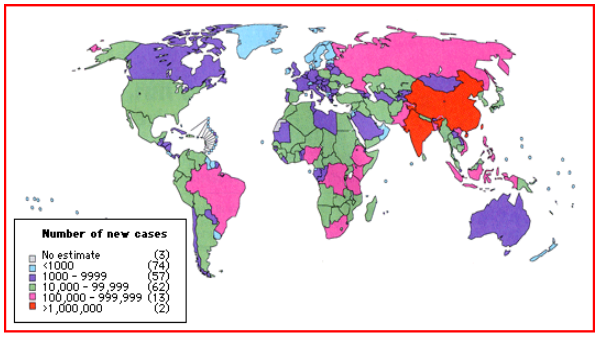
Group	Strict Human Pathogens	Occassional/Potential Human Pathogens	Usually Environmental Rarely Human Pathogens
M. tuberculosis complex	M. Tuberculosis M. Leprae M. Africanum M. Ulcerans	M. Bovis	
Photochromogens		M. Kansasi M. Marinum M. Simiae M. Asiasticum	
Scotochormogens		M. Scrofulaceum M. Szulgai M. Xenopi	M. Gordonae M. Flavescens
Nonchromogens	M. Genavense	M. Avium M. Intracellulare M. Hemophilum M. malmoense	
Rapid growers		M. Fortuitum M. Chelonei	M. Smegmatis

Microbiology :

- MTB : fastidious, slowly growing, acid alcohol fast, aerobic bacterium (AAFB – Acid Alcohol Fast Bacilli).
- Cell wall composed of complex peptidoglycans and long chain lipids.
- These lipids make MTB hydrophobic thus resistant to many stains routinely used in Laboratory, e.g. Gram & Giemsa stains as well as AA fastness (Once stained, cannot be decolorized by alcohol, acid solutions).

Epidemiology :

- MTB : Common deadly disease worldwide.
- 33% world population has been infected with MTB.
- 30 million active cases of tuberculosis at any time.
- Mid 1980s, rising case rate at 3% while it was declining by 5% ----?



Estimated number of new tuberculosis cases by country, 2001
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Medical conditions predisposing to active tuberculosis :

- Once person infected with organism :
  - **a)** HIV infection.
  - **b)** Prior MTB (fibrotic changes on Chest X-ray).
  - **c)** Diabetes.
  - **d)** Steroid or other immuno suppressive meds.
  - **e)** Silicosis (remember job Hx).
  - **f)** Hematologic diseases, e.g. lymphoma.
  - **g)** ESRD (End Stage Renal Disease) / Dialysis patients.
  - **h)** Post gastrectomy and malabsorption states.
  - **i)** Others, malignant wt. Loss …. Etc.

Transmission :

- Respiratory route : Inhalation of airborne droplets following :
  - **Coughing.**
  - **Sneezing.**
  - **Speaking** where organism remain airborne and infectious for a period of time.

Group of People at high risk for MTB :

1. HIV infected persons.
2. Close contact (eg, family members) of patients infected with MTB.
3. Underlying medical condition that increase risk of acquiring MTB.
4. Alcoholic IVDU.
5. H.C.W.
6. Long term care facilities, nursing homes, etc.

N.B. Several months of exposure needed to get infection with MTB, however, close contacts of infected persons puts others at risks of acquiring infections.

Degree of contagiousness of a patient depends on :

- Number of organism in sputum (open TB).
- Cavitary lung disease.
- Amount of coughing.
- Length of time on anti TB Rx.
- Others.

Clinical Syndromes :

- ✶ Primary infection.
- ✶ Latent infection.
- ✶ Reactivation TB.
- ✶ P. TB and E.P. TB.

Primary Tubercolosis :

- First exposure to MTB often a symptomatic.
- Typically pul. Infiltrates : mid or lower lung fields with or without hilar adenopathy, these infiltrates non-specific in appearance and not cavitory.
- In most cases pneumonitis clears without specific therapy and latent infections established.
- In some cases, primary infection may progress, resembling reactivation disease.

Latent Infection :

- Following primary infection many persons remain asymp.
- Organisms remain latent within macrophages indefinitely.
- Tuberculosis skin test (T-PPD) → very important to discover these persons.
- If no preventive therapy given, 1:10 persons with MTB infection will develop clinical disease at some time in their lives.

Reactivation Tuberculosis :

- Consitutional sx and generalised wasting.
- Weight loss.
- Fever at night, sweating.
- Diagnosis maybe difficult as pul sx mild or lacking.

Pulmonary Tuberculosis :

- Majority of cases of active pul TB result from reactivating of latent organism.
- Reactivation occurs more likely in upper lobes and superior segment of lower. Lobes (why?)
- However any area of the lungs may be involved, especially elderly diabetics, AIDS patients, etc.
- Absence of apical infiltrates would DDX not exclude TB.
- Practically : TB should be included in DDX Any undiagnosed pneumonia.
- P. TB extent quite variable : Ranging from subtle CXR infiltrate with minimal cough to classic cavitary TB with Hemopthysis.
- If Untreated : pul. lesions develop caseation or central necrosis with liquefaction.

EXTRA PULMONARY TUBERCULOSIS :

- TB outside lungs may be even more difficult to diagnose.
- E. P. TB may manifest clinically during phase of primary infection especially in children.
- More commonly, E.P TB represents Reactivation of Latent Infection.
- Pulmonary lesions may be absent in more than 50% cases of E.P. TB.
- It is more uncommon to see CXR with active pulmonary infiltrate or cavities in cases of E.P. TB.
- E.P. TB Includes :
  - Pleural disease with effusion : commonest and forms of E.P TB.
  - TB meningitis : usually Ch. Meningitis but may be as :
    - Fulminant as pyogenic together with cranial nn. Deficits : TB meningitis must be considered (because there is often basilar meningitis).
    - CSF : High protein, Low glucose, lymphocytic pleocytosis.
    - This CSF pattern seen in other disease, thus if TB meningitis highly suspected, Anti – TB Rx should be initiated.
  - Pericarditis and peritonitis.
  - TB adenitis or scrofula (ch – TB infection of cervical L. nodes).
  - Osteomyelitis including **pott's disease** (TB of spine).
  - G.U. TB + GI TB.
  - Ocular infection including chorioretinitis.
  - Cutaneous TB (Lupus vulgaris).
  - Miliary Tuberculosis : disseminated form of TB into lymphohematogenous system during primary TB infection or more commonly during reactivation.
    - This type can also be difficult to diagnose, CXR can be normal in the early stages of the disease.

DIAGNOSIS :

- High index of suspicion is essential.
- MTB manifestations are protean, thus lab. Confirmation is also essential.
- Close communication between the clinician and microbiology lab. Is mandatory to identify microorganism causing disease and determine their susceptibility to antimicrobial agent that assist in their eradication.
- Tuberculosis skin (PPD, mantoux) test important first step in identifying infected patients.
- Lab. Techniques for MTB identification :
  - A.F.B. smear and cultures of resp. secretion (e.g. sputum).
  - A.F.B. smear and cultures of potentially infected body fluids or tissues.
  - CSF, gastric fluid, urine, LN BX bone marrow BX, joint fluids, etc.
  - Rapid methods: PCR (polymerase chain reactions) and nucleic acid probes.

DIAGNOSTIC TESTS / PROCEDURES :

- **Acid fast stain :**
  - AFB Smear.
  - A typical mycobacterium smear.
  - Kinyoun stain.
  - Mycobacterial smear.
  - TB smear.
  - Ziehl – Neelson stain (ZN stain).
  - Auramine – Rhodamine stain.
- **Acid Fast Bacilli :**
  - Because surrounded by waxy lipid containing envelope that resistant to destaining by acid alcohol.
  - Stain can penetrate cell wall by :
    - a) heat (classic ZN) method, or
    - b) detergent (tergitol Kinyoun) method.
  - Once stained: acid fast bacteria resist de colorization (AAFB), Whereas other bacteria (Destained) with acid alcohol.

TREATMENT :

- TB treatment based on certain principles :
  - MTB resistance to drugs occurs at random, sponteneous, genetic mutation, eg. INH natural resist. Occurs at 1: 10^6 and Rif at 1 bacterium in 10^8.
  - Regimen containing multiple drugs to which organism susceptible should be used and sensitivity testing should be done on all isolates.
  - Both Isoniazid – resistant MTB and MDR – MTB are increasing problems.
  - In case of poor compliance, D.O.T. given 3x weekly in outpatient setting should be considered strongly.
  - Failure of therapy often due to noncompliance.
  - Non-compliance may lead to emergence of MDR organisms.
  - Patient immune status must be taken into account.

DRUG THERAPHY :

- **First Line drugs :**
  - Isoniazid (INH).
  - Rifampicin.
  - Pyrazinamide.
  - Streptomycin, Ethambutol.
- **Second Line drugs :**
  - Capreomycin, Ciprofloxacin.
  - Cycloserine, Ethionamide.
  - Kanamycin, Ofloxacin.
  - Para-Amino Salicylic acid (PAS).
    - *These drugs :*
      - *less effective*.
      - *more expensive*.
      - *more toxic*.

Commonly Used Regimends to treat TB :

- Initial phase (first two months) 3-4 drugs : INH, RIF, PZA, Streptomycin or Ethambutol.
- Continuation phase (4-10 months) : INH, RIF.

Duration of Drugs Therapy for TB :

- **Depends on the site of disease :**
  - Pulmonary TB → 6 months.
  - Cervical lymphacloropathy → 6-9 months.
  - Hilar adenopathy → 9 months.
  - **E.P. TB.**
    - **TB Meningitis**
    - **Bone / Joint**
    - **Disseminated Disease.**

    } **2 months with 4 drugs + 10 months with INH + RIF.**

Common Indemic Infections in KSA

Prof. Abdulkarim Al-Aska

1) BRUCELLOSIS

MICROBIOLOGY :

- 6 SPECIES, 4 CAN BE TRANSMITTED TO MAN.
  - Brucella miltensis → through goat & sheep (the commonest in KSA)
  - B. abortis → cows
  - B. canis → dogs
  - B. swis → pigs

- **Brucella Miltensis, Brucella Abortis and brucella Swis (in pigs)** and brucella canis are communicable to human while brucella ovale is limited to animals.
- GRAM NEGATIVE, NON-MOTILE, NON-SPORE FORMING.
- THE ORGANISM IS FACULATIVE.
- CULTURE CAN TAKE LONG TIME.
- SURVIVAL CAN BE VERY LONG.
- OPTIMUM TEMPERATRE IS 37 °C (20-40 °C).

BRUCELLOSIS & OTHER RISK FACTORS

Risk factor	Odds ratio	P value
Caring for delivering animal	20.4	0.00001
Placental membrane	12.9	0.00001
Consumption of raw milk products	4.2	0.001

- **others risk factors including:**
  - Undercooked meat
  - Inhalation (rare)
  - Human-human sexually (rare)

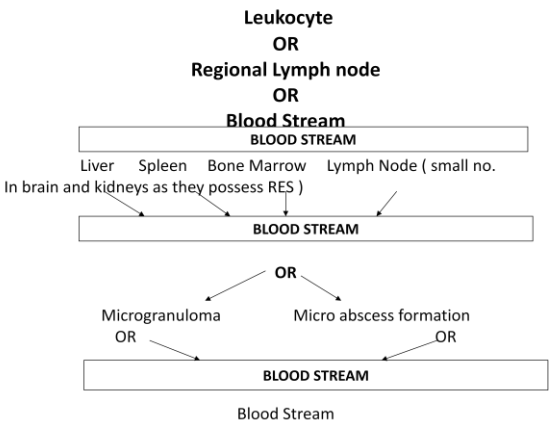
REGIONAL DISTRIBUTION OF SEROPOSITIVITY ACCORDING TO THE MICROPLATE AGGLUTINATION TEST

REGION	TOTAL SAMPLE	POSITIVE	PERCENTAGE
EASTERN	**2939**	**1193**	**40.6**
WESTERN	**7131**	**3839**	**53.8**
NORTHERN	**3152**	**1320**	**41.9**
SOUTHERN	**4794**	**2421**	**50.5**
CENTRAL	**5597**	**2718**	**48.5**
TOTAL	**23613**	**11491**	**48.9**

Prevalence of Brucellosis in Al-Qaseem Area

Tube Agg. B. abortus	No.	%
40	40	2.6
80	123	1.5
160	66	0.8
320	25320	0.3
640	16	0.2
1280	6	0.1
2560	6	0.1
>5120	2	0.01
Negative	7664	94.4%
Total	8120	
Active Dis.		1.51%

AFTER ENTERING THE BODY



◈ Pathogenesis :

Organisms are engulfed by monocytes → reticuloendothelial system → lymph node. Then, they are eradicated or multiply & escape →to blood stream → circulate & cause fever (**Mediterranean fever** or **undulant fever)**

It also mediates psoas abscess & micro abscess surrounded by chronic inflammatory cells

FREQUENCY OF COMMON SYMPTOMS IN STUDIES FROM SAUDI ARABIA

STUDY	RMH	AL-KUHER TEACHING HOSPITAL	KFNGH
SYPMTOM	FREQUENCE OF SYMPTOM		
FEVER	100&	90%	56%
BODY ACHES	100%	N/D	32%
LETHARGY	100%	N/D	24%
BACK PAIN	64%	34%	35%
JOINT PAIN	64%	34%	21%
SWEATING	56%	33%	27%
ANOREXIA	33%	17%	28%
IRRITABILITY	10%	N/D	7%
HEADACHE	25%	30%	20%
WEIGHT LOSS	26%	N/D	15%

CLINICAL FINDINGS

SPLENOMEGALLY	29 %
JOINT TENDERNESS	28 %
HEPATOMEGALLY	20 %
SPINAL TENDERNESS	13 %
SACRO ILEITIS	13 %
LYMPHADENOPATHY	10 %
IMPAIRED STRAIGHT LEG RAISING	6 %

POSITIVE BLOOD CULTURES FOR BRUCELLA only 50% r +ve
(when brucella is suspected, the culture is kept in the lab for weeks)

TIME IN WEEKS	NUMBER OF POSITIVE CULTURES
1	2
2	5
3	4
4	1
9	1
10	1
TOTAL	14

SEROLOGICAL TESTS :

- STANDARD TUBE AGGLUTINATION TEST(is the most commonly used)
- MICROPLATE AGGLUTINATION TEST.
- 2-MERCAPTOETHANOL AGGLUTINATION TEST(This test is good, but not widely used due to its bad smell)
- COOMBS TEST.
- COMPLEMENT FIXATION TEST.
- ROSE BENGAL TEST.
- ENZYME-LINKED IMMUNOSORBENT ASSAY.
- GEL PRECIPITAITON TEST.

- As in malaria, the fever is relapsing and recurrent because the bact. Does not always remain in the blood stream but comes and goes.

Note: in brucella, cellular immunity is more important in eradicating brucella

ACTIVE DISEASE :

- Clinical evidence (symptoms & signs) of brucellosis plus :
  - Positivity at > 1:160 by STAT.
  - Positivity at > 1:140 by 2-ME test.
  - Positivity by ELISA (high IgG & low IgM).
- Chronic disease so diagnosed by +ve IgG not IgM.
  - **Treatment** :

(Streptomycin +doxycycline) is mostly used.

TREATMENT FOR HUMAN BRUCELLOSIS
Remember Doxy (no BBB) preciptates in bone and STM (BBB) has to be taken by injection so not suitable for children under 8 year.

Category	Treatment	Dose	Duration
Adult & children (>8 years)	Doxy + STM	100 mg bid 1.0 g bid	6 w 2 – 3 w
Children < 8 years	Rif + TMP-SMZ	15 g (kg-d) 30-60 mg (T*)/kg-d	2 or 8 3 or 8
Preg. Women 1st Trim. 2nd & 3rd Trim.	Doxy + Rif + TMP-SMZ	100 mg bid 900 mg bid	6 w 3 w

TREATMENT FOR HUMAN BRUCELLOSIS

Category	Treatment	Dose	Duration
Bone & Joint	STM + Rif. Doxy	1.0 g bid 900 mg/d 100 mg bid	3 12 12
Meningio-Enceph.	Rif. + TMP-SMZ ? Doxy	900 mg/d 300 mg(T)/kg-d	12 2 12
Endocarditis	STM + Rif. + TMP-SMZ + Doxy	1.0 g bid 900 mg/d 30 mg(T) kg-d 100 mg bid	13 13 3 12

COMPARATIVE STUDY OF 3 DRUGS REGIMENS

Regimen	Drug(s)	Dose	Duration (Days)	Cure Rate
A	Oral Rif. + Doxycycline	900 mg/d 200 mg/d	45 45	95% "
B	Streptomycin Doxycycline	1.0 g/d 200 mg/d	14 45	96% "
C	Streptomycin	1.0 g/d	14	59%
(WHO)	Tetracycline	2.0 g/d	21	59%

Vaccines Attenuated Strains :

- Effective for short durations, that's why it is avoided.
- B. abortus strain 19.
- B. melitensis strain Rev I.
- B. suis strain 2s.
- B. abortus strain 45/20.
- B. melitensis strain H38.

PREVENTION :

- "ELIMINATION OF THE DISEASE IN ANIMALS".
- PERSONAL HYGIENE (WASHING EXPOSED CLOTHES).
- ENVIRONMENTAL SANITATION (DISPOSAL OF CONTAMINATED SUBSTANCES).
- PASTURIZATION OF DIARY PRODUCTS.
- HEALTH EDUCATION.
- IMMUNIZATION.

2) SCHISTOSOMIASIS

- **There are three main strains :**
  - **S. Japanicum**.
  - **S. Mansoni (for GI only)** → the most common in KSA
  - **S. Haematobium (can cause urinary and GI diseases)**.

Prevalence (%)

Station	No. of Persons Examined	S. Haema-tobium	S.Man-soni	Overall Preva lence+
Bisha	16.766	0.4	8.5	8.9
Najran	8.820	1.6	9.9	11.5
Mahael	5.783	7.6	---	7.6
Hayil	4.335	---	14.2	12.2
Riyadh	15.129	---	5.6	5.6
Makkah	25.894	2.5	3.0	5.5
Al-Jouf	12.577	1.3	1.6	2.9

• PREVALENCE OF SCHISTOSOMIASIS AS REPORTED BY THE STATION

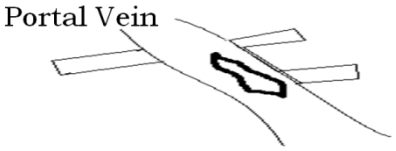
Prevalence (%)

Station	No. of Persons Examined	S. Haema-tobium	S.Man-soni	Overall Preva-lence+
Al Baha	20.142	--	13.0	13.0
Jizan	30.883	7.0	1.2	8.2
Taif	39.559	0.2	7.7	7.9
Abha	23.013	1.7	4.9	6.6
Madinah	17.591	1.9	3.6	5.5

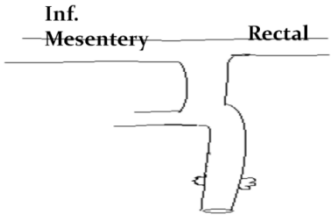
Shistosoma Simplified Life Cycle :

- Ovum -- miracidium -- goes to snail -- then circaria -- penetrate human skin -- excreted in water as ovum – miracidium.
- Not found in eastren countries.

- The shistosoma enters the body through the skin, causing pruritis and swimmers iching in papules. The circaria goes through the skin to the portal vein and pulmonary circulation which when arrives cause generalized sym. Like fever, arthralgia and dry cough. The fever is called Katayama fever.



- When the circaria becomes an adult, it migrates to the mesentric vessels and reproduce forming larvae that can stay in the GI tracts, get excreted in stools or migrate to the hepatic ciculation which if a lot they can obstruct the portal vein and cause granuloma and periportal fibrosis but still the normal function is still retained.



KATAYAMA FEVER : (KATAYAMA River, Japan)

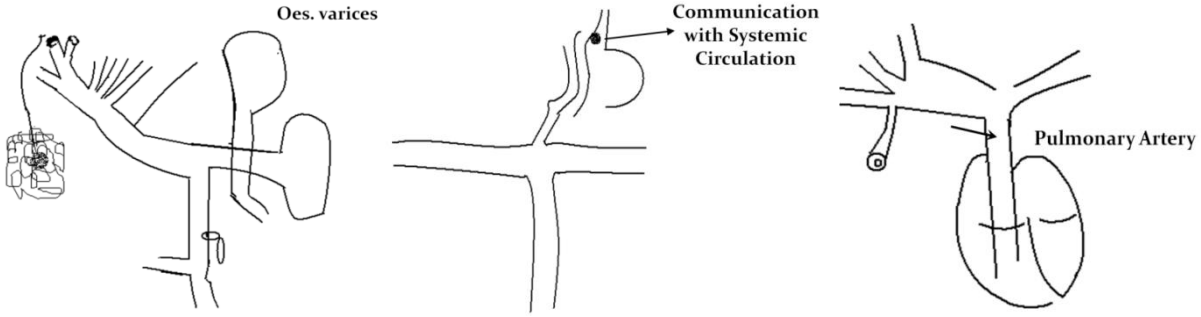
- SEVERAL DAYS – 2-3 WEEKS.
- **FEVER**, CHILLS, **HEADACHE**, MALAISE, EDEMA, CONFUSION.
- **HEPATOSPLENOMEGALLY**.
- **LYMPHADENOPATHY**.
- EOSINOPHILIA – parasitic infection.
- CEREBRAL EDEMA (CT) (rare with S. mansoni but may occur with S. japanicum).

S. MANSONI (SYMPTOMS)

SYMPTOM	CASES
Abdominal Pain	258
Fatigue	221
Blood in Stool	205
Mucous in Stool	191
Tenesmus	121
Depression	108
Diarrhea	54
Constipation	1

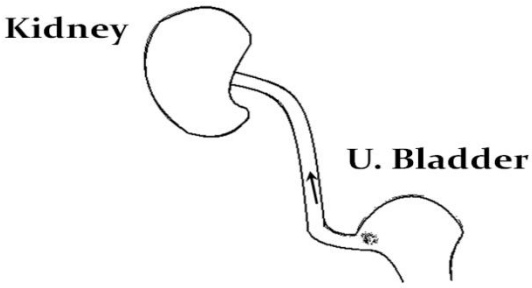
What is the most serious common complication of Schistosomiasis infection ?

Answer : portal hypertension and its common complications (varices and portosystemic anastomosis).



- Note: Schistosomia causes **fibrosis** but not cirrhosis

- **SCHISTOSOMIASIS (also called bilhaziasis) may cause hydronephrosis.**



S. HAEMATOBIUM

SYMPTOMS	
Haematuria	89
Dysuria	77
Abdominal Pain	43
Frequency	40
Tiredness	33
Blood in Stool	23
Mucous in Stool	22
Depression	8

- **Treatment**: mostly with praziquantel

SIDE EFFECTS OF ANTISCHISTOSOMAL DRUGS (%)

METRIFONATE	OXAMNIQUINE	**PRAZIQUANTEL**	SYMPTOMS
40	30	56	NONE
10	36	20	DIZZINESS
12	25	12	ABDOMINAL PAIN
10	12	10	JOINT PAIN
6	10	8	NAUSIA
2	4	6	**RASH**

3) SALMONELLA / TYPHOID FEVER

CLASSIFICATION OF SALMONELLA :

- According to their ecologic niches.
- Serotyping [kanfmann white] :
  - O antigen A-I.
  - H antigen (subtypes).
- Over 2000 serotypes.

- Spectrum of clinical manifestations of salmonella.

- Gastroenteritis.
- Enteric fever.
- Bacteremia
  - With metastatic disease.
  - Without metastatic disease.
- Asymptomatic carrier state.

PATHOGENESIS :

- ID 10^6 – 10^9.
- Penetration of the distal ileum mucosa.
- Multiplication in the payer patches.
- Diarrhea is caused by :
  - Prostlaglandin Induced ^ (c-AMP).
  - Local Inflamatory rasponce.
  - S. enterotoxin.

TYPHOID FEVER :

- **Enteric (abdominal pain) Fever (fever) + 2S (splenomegaly and spots) + 2D (diarrhea and delirium).**
- **Definition :** A disease characterized by prolonged fever, abdominal pain, diarrhea, delirium, rash (rose spots) & splenomegally.
- Patient could come with diarrhea or constipation

- **Etiology :** Salmonella Typhi & paratyphi A & B-A motile gram-negative bacilli, which possess :
  - H-Antigen (associated with flagella).
  - O-Antigen (a LPS associated with cell wall).
  - VI-Antigen (a PS associated with cell capsule).
    Inside – H – O – VI

- **Diagnosis by**: Ag-Ab reaction
- O antigen is diagnostic → O-Ab titre
- Treatment: 3rd generation of cephalosporin

EPIDEMIOLOGY :

- It affects all age groups.
- No sex difference.
- **Common in developing countries.**
- Infecting dose 7x10(6) in Africa, Asia & Latin America.
- Transmission is through Oral-fecal route. (remem. Enteric)
- Affected individuals may become asymptomatic carriers particularly females & older males (Underlying cholecystitis).
- S-Typhi is resistant to drying & cooling.

SYMPTOMS & SIGNS

	Symptoms	Signs	Pathology
1st wk.	Fever, Chills headache	Abdominal tenderness	Bacteremia
2nd wk.	Rash, abdominal pain,	Rose spots	Mononuclear vasculitis of skin, hyperplasia of peyer's batches typhoid nodules
3rd wk	Intestinal bleeding, perforation & shock	Melena Ulcerations, perforation rigid abdomen with peritonitis. ileus, coma	
4th week & later	Resolution relapse weight loss	Recurrence of acute disease, cachexia.	Cholecystitis, chronic fecal carriage of bacteria

ANTIBIOTIC USED FOR SALMONELLA TYPHI :

- Chloramphenicol.
- Ampicillin, Amoxil.
- Co-trimoxazole.
- 3rd generation cephalosporins.
- Quinolones.

PROGNOSIS :

- Case fatality dropped from 12% to 4%.
- **It is still +\- 10% in developing countries.**
- Perforation +\- 5%.
- Chronic fecal carriers 1-3%.

VACCINATION FOR S.TYPHI :

- **Inativated S.typhi :**
  - 2 SC injections.
  - 55-88% protection for 3-5yr.
- **Attenuated S.typhi :**
  - Liquid 3 doses.
  - Enteric coated capsules.
  - Protection 60-70%.

4) LEISHMANIASIS

- It is the result of the infection with one of or other species of protozoa (leishmania).
- Conveyed by : Sandflies (Phlebotomus).
- Visceral Leishmaniasis : L. donovani.
- Mucocutaneous : L. Braziliensis.

Cutaneous : L. tropica major } Old
L. tropica minor } world

New World : L. Braziliensis
L. Mexicana

PATHOLOGY :

- L. donovani parasitizes the reticu. endoth. cells.
- Great proliferation of macrophage.
- Cells result : Liver – spleen enlarg.
- The red bone marrow extend.

CLINICAL PICTURE :

- **Incubation** : 2 weeks – 18 months
- Early stages is not easy for diagnose.
- There is no constant physical signs
- BP ↓ , Pulse ↓ , - Fever.
- Changes in the blood picture particularly *Leucopenia*.
- Outstanding physical sign is the enlargement of the spleen 3 cm a month.
- **Liver : enlarged spleen + liver are neither tender nor painful.**
- **Sometimes : Jaundice = prognost. significance.**
- **Enlarged : Lymph node, could be but its not a feature of the disease.**
- **Wasting : Emaciated pat with a protuberant.**
- **Abdomen (liver + spleen enlarged).**
- **Fever : Without subjective symptoms of fever – no delirium.**
- **Sometimes : there is no fever.**
- **Skin : dry, rough. The natural pigmentation of the skin over the bone and around the mouth is deepened. (Kala azar??)**
- **Hair : fallout.**
- **Lungs : Bronchopneumonia.**
- **GIT : Diarrhea, dysentery.**

DIAGNOSIS :

1) **Needle aspiration :**
   - Bone – sternum – liver, spleen.
   - Histology – culture.
   - L. donovani body.
2) **Leucopenia** : Neutropenia – relative mononucleosis.
   Progressive fall with the red cell count.
3) **Formalin gel (aldehyde**) :
   - 2 drops formalin + 2 ml serum.
   - After 20 min, white ring.
4) **Complement fixation and fluorescent :** False positive trypanosomal infection.
5) **The complement fixation** : early positive – negative after cure. Sometimes +/– lung. Other diseases.
6) **Fluorescent antibody.**
7) **IV + V :** In trypanosomal infection.
8) **Skin test (Montenegro)**
   - Delayed hypersensitivity reaction.
   - 0.2 ml. suspension.

PROPHYLAXIS :

- **Immunity :** Kala Azar permanent immunity to all L. Donovani.
- L. tropica major crass immunity to L. tropica minor. Not the opposite.
- L. brazillienses to L. mexican + but not vice versa.
- **Vaccine :** L. tropica major – living leptomonads.
  L. donovani : Intradermally or s.c.
  Local leishmanial infection.
  (Leichmanioma) Developing immunity.
  No visceral L.

TREATMENT :

1) **Antimonial :**
   - **a)** Urea, stibamine, pentavalen + antmonyia :
     - I.V. daily or every 2 days.
     - 6 – 10 dose.
     - First 100 mg then 200 then 250.
     - Total dose 2 – 5 g. adult.
     - **Side Effect :** Nausea, vomiting, joint pain, abdominal pain, diarrhea.
     - **Contraindication :** Liver and kidney failure.
   - **b)** Sodium stibogluconate (Pentostam) :
     - I.M. – 600 mg total daily for 6-10 days.
     - Repeated after 14 days; if needed.
     - **Side effect :** Anaphylactic shock.
2) **Diamidiem :**
   - Pentamidine isothionate.
   - Dose 3 -4 mg / kg / BW total 300 mg.
   - **Side effect : Hypoglycemia.**

Common Viaral Infections

Dr. Mogbil AlHedaithy

- They are very important because they are common and to some extend, they are treatable. Herpes viruses are common in adults as well as in children.

1) **Herpes Simplex Virus type1 (HSV-1)**
2) **Herpes Simplex Virus type2 (HSV-2)**

1,2 are very important. They were the earliest to be discovered.

3) **Varicella Zoster Virus (VZV)**

3 causes chicken pox. is very imp. and common

4) **Cytomegalovirus (CMV)**
5) **Epstein-Barr Virus (EBV)**

4,5 are common worldwide especially in immunocompromised patients.

6) **Human Herpes Virus 6 (HHS-6)**
7) **Human Herpes Virus 7 (HHS-7)**
8) **Human Herpes Virus 8 (HHS-8)**

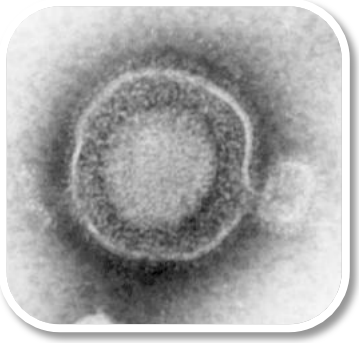
aren't clinically as significant as the rest .

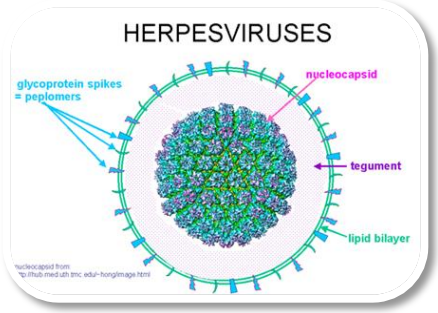
Characteristics:

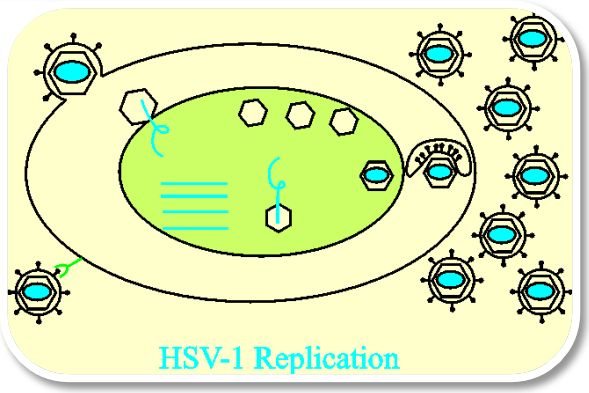
- They are all **DNA viruses**
- All are **encapsulated**
- All have **latency** after the initial infection which means the virus stays dormant inside the body. The viruses then reactivate when the patient 's immunity is suppressed.
- Mostly require close contact for transmission except for VZV can be transmitted by droplets and airborne transmission.
- **Human** is the ONLY reservoir

Structure

All Herpes viruses look the same under the microscope







Virus	Infection
HSV Type 1	▫ Herpes labialis ('cold sores') ▫ Keratoconjunctivitis ▫ Finger infections ('whitlows') ▫ Encephalitis ▫ Primary stomatitis ▫ Genital infections
HSV Type 2	▫ Genital infections ▫ Neonatal infection (acquired during vaginal delivery)
Varicella zoster virus (VZV)	▫ Chickenpox ▫ Shingles (herpes zoster)
Cytomegalovirus (CMV)	▫ Congenital infection ▫ Disease in immunocompromised patients ▫ Pneumonitis ▫ Retinitis ▫ Enteritis ▫ Generalised infection
Epstein-Barr virus (EBV)	▫ Infectious mononucleosis ▫ Burkitt's lymphoma ▫ Nasopharyngeal carcinoma ▫ Oral hairy leucoplakia (AIDS patients)
Human herpes virus 6 (HHV-6) and 7 (HHV-7)	▫ Exanthem subitum ▫ ? Disease in immunocompromised patients
Human herpes virus 8 (HHV-8)	▫ Associated with Kaposi's sarcoma

HSV-1 vs HSV-2

- Non-genital vs Genital Herpes infection
- Primary vs Recurrent infections
- Neonatal infection

- They are very similar ***except*** for the mode of transmission and the site of infection.

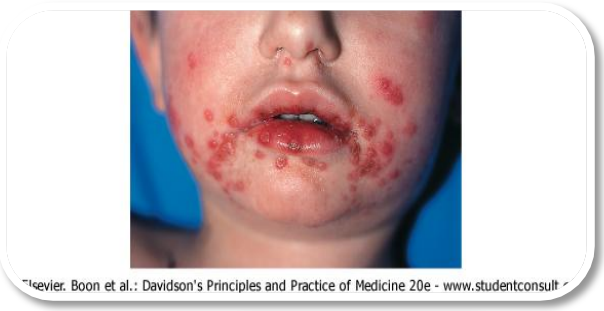
HSV-1	HSV-2
Oral, gingivostomatitis and skin infections	Genital infections, neonatal infections
Common in children and young adults	Sexually active adults
1ary infections which are usually very severe and extensive	1ary infections which are usually very severe and extensive
Recurrent infections which are milder	Recurrent infections
Transmission is through oral secretions when kissing or hugging or through contact with contaminated utensils such as the pt's towel.	Through genital secretions, in the semen and vaginal secretions

- **Transmission** : by close contact with body secretions
- Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus and initiation of its replication in cells of the epidermis and dermis → as it *may goes to blood & cause fever*
- After initial infection the virus infect the sensory and autonomic nerves and become dormant in the ganglion (trigeminal nerve for HSV1 and sacral rout for HSV2)
- **Neonatal infections** are from the vaginal canal due to vaginal delivery of a mother with an active HSV-2 (not only skin lesions. They can be very severe. Can lead to systemic infections such as pneumonia ,meningitis, encephalitis, and can lead to high mortality)

HSV Gingivostomatitis

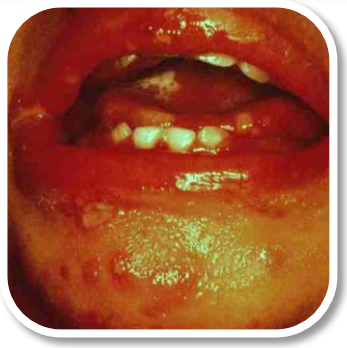
- Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first-episode **HSV-1** infection
- Pts are not always symptomatic and they shed the virus through saliva. This is why HSV-1 keeps circulating in children.

  - Most commonly in **children of age 3-5 yrs**



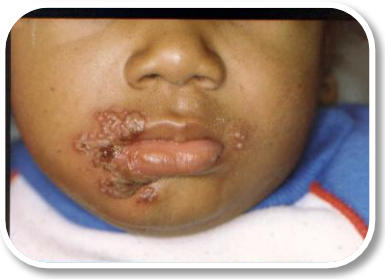
Clinical manifestations

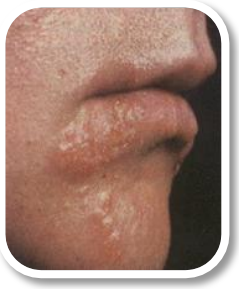
- include fever, the child not feeling well and pain.
- Then vesicles develop and they rupture. Ulcers form in the face and inside the mouth.
- It usually spreads through auto-inoculation (child spread the virus by touching his skin by his contaminated hands) or saliva dribbling.
- If the child was not treated, he can be malnourished and dehydrated.
- They usually maintain for 2 wks if not treated and for lesser than one week with treatments.



Herpes Labialis

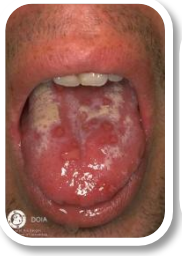
- Recurrent herpes labialis is the most frequent clinical manifestation of **reactivation HSV infection**
- Reccurance of HSV infection.
- painful and burning lesions on the angle of the mouth.





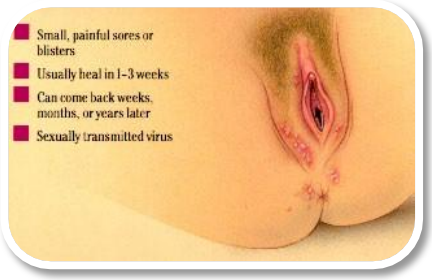
NON-GENITAL HSV

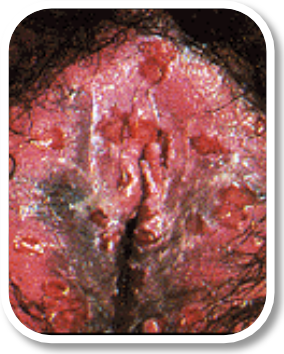
- Usually in immunocompromised pts.
- Painful lesions that effect the mucus membranes and may reach the esophegus

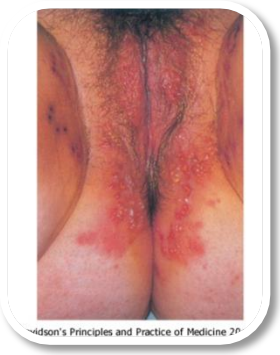


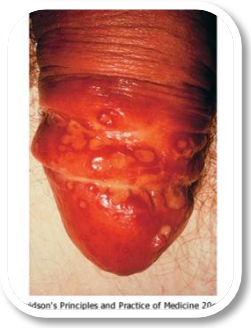
◈ GENITAL HSV

- Fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy
  - primary infection is very severe.
  - Main risk factor is illegal sexual contact





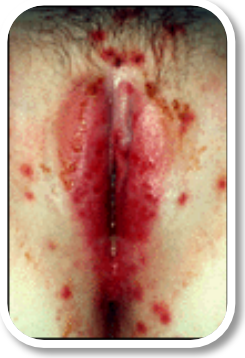


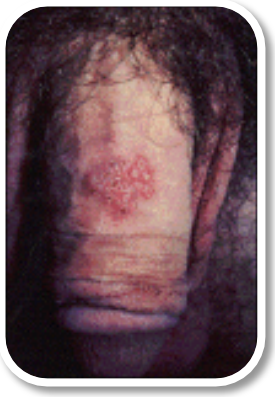


- ✪ In females: cervicitis, vulvulitis and sometimes around the anus.
- ✪ In males: usually milder

✶ As in HSV-2, the virus is continually secreted particularly in vaginal secretions.

- **Clinical picture** : very obvious, u can pick it up easily.
- **Viral culture** : The virus can be cultured easily too. It takes 3-5 days.
- **Cytology** : an old method that isn't used any more
- **PCR** : is the method used nowadays when we are in doubt.





◈ HSV TREATMENT

- acyclovir 200 mg five times daily. is the only drug given IV
- famciclovir 250 mg 8-hourly.
- valaciclovir 500 mg 12-hourly.
- The treatment is usually for 5 days

-Both HSV-1 and HSV-2 are treatable.
-We should know all drugs but not their doses.

VARICILLA ZOSTER VIRUS

➔ **Primary infection**

Chickenpox

➔ **Recurrent infection**

Herpes zoster

- Can be transmitted through direct contact to secretions or lesions.
- It is highly infective, can reach 90%

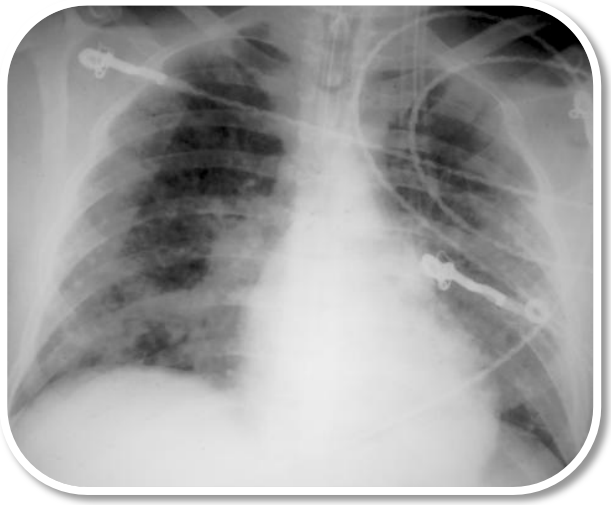
- ▫ The virus is spread by the **respiratory route** and replicates in the nasopharynx or upper respiratory tract.

- After the virus gains access to the respiratory route. It will multiply in the mucus membranes of the URT e.g. nasopharynx. Then it will enter the blood leading to fever and pt feeling unwell. Then it will spread to all tissues including the skin and rash appears.
- Followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and, ultimately, viremia.
- The virus establishes latency within the dorsal root ganglia.

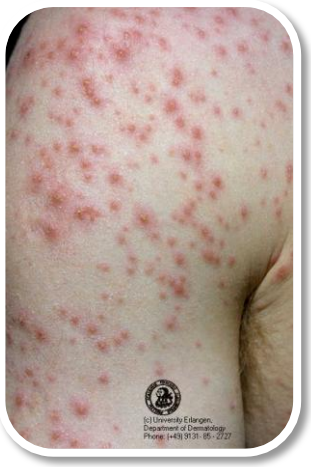
- When reactivation of VZV occurs →painful lesions occur(varicilla zoster) which follows specific sensory dermatomes.
- It starts as pain → redness on skin → rash → vesciles
- Multiple rash may fuse together → one large pustule.

CHICKENPOX

Overall, chickenpox is a disease of childhood, because 90% of cases occur in children younger than 13 years of age.



- Chicken pox is a disease of children but can happen in adults.
- The incubation period is around 1-3 weeks with an average of two weeks. Then the child will have fever for 1-2 days afterwards the rash will appear.
- The person is infectious 1or 2 days before the rash appears and until it totally disappears or at least most of the lesions are crusted.
- Lesions usually affect the face and trunk and, to a lesser extend ,the limbs.
- The skin rash has different stages:
  1- appear as a macule (small red spot).
  2- Within few hours become palpable & raised →papule.
  3- After few days → vesicle (contain clear fluid)
  4- then it will turn to a pustule (yellow in color due to pus and necrotic tissue).
  5- Finally it will be crusted.
- What is a characteristic of chickenpox, is that ***all stages can be seen at the same time on the same patient.***
- Chickenpox complications include pneumonia especially in pregnant ladies and immunocomprimised adults, meningitis and encephalitis. However, it is a benign disease in childhood.

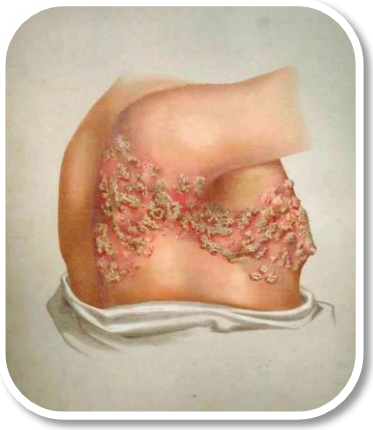
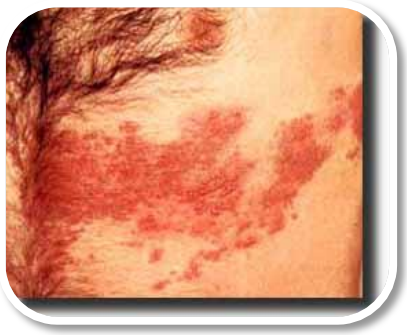
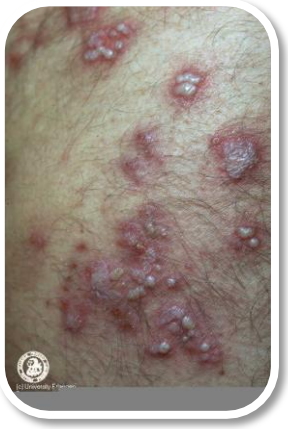
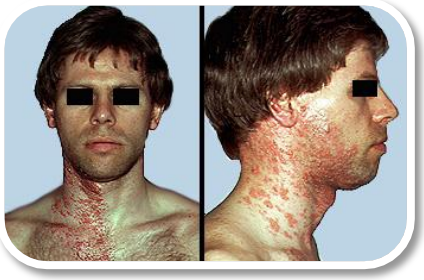
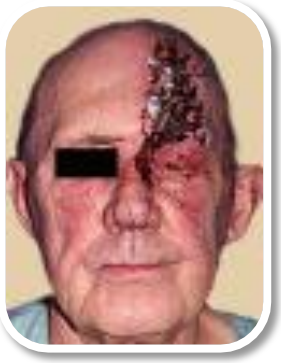
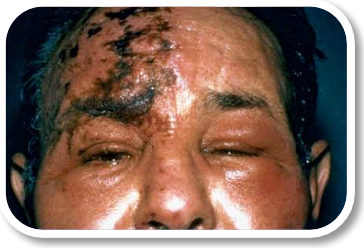


Chickenpox	Smallpox
Mainly present on the face and trunk	Mainly on the periphery
All stages can be seen at the same time	One stage at a time
Heels leaving no scars	Heels leaving scars
Reoccur as herpes zoster	Permanent immunity

*Smallpox had been eradicated

Reactivation of VZV leads to VZ

VARICILLA ZOSTER

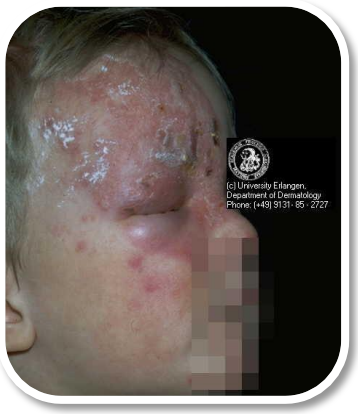
- Vercilla zoster is **very painful**. It can effect the ophthalmic division of the trigeminal nerve that may effect the eye and cause its blindness.
- Lesions heel within 10 days to 2 weeks. But the most serious complication is the post herpetic neuralgia, which is very severe pain.

⊙ VZV Diagnosis

- VZ is very clear, usually we **do not need** any investigations and depend on the clinical diagnosis but PCR can be made if you are in doubt.

⊙ VZV treatment

- Acyclovir
- Valacyclovir
- Famciclovir



- Treatment is the same as HSV but probably of **higher** doses.
- We treat the patient to shorten the duration of the disease, so if u saw a pt after a week, there is no need to treat him/her because it wont be effective unless there were complications.

⊙ VZV Prevention

- VZV vaccination
- VZV immunoglobulin (VZIG)

- VZV immunoglobulin (VZIG) it is **only given** as passive immunization to decrease the risk of baby getting infected and in immunocompromised patients.

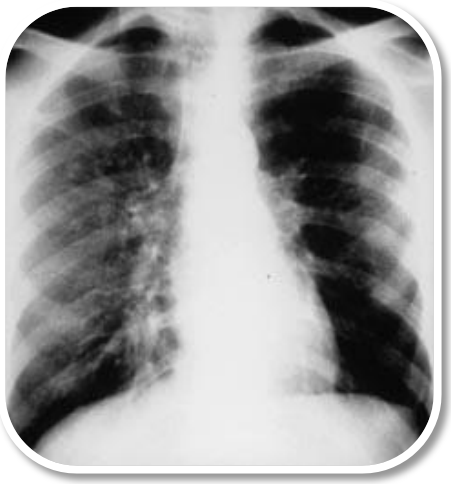
Cytomegalovirus (CMV)

- The largest virus that infect human being
- World wide distribution
- Latency after primary infection
- Infection ranges from asymptomatic to sever multisystem disease
- More in undeveloped countries.
- Not clear in which cells it becomes dormant, but most likely the
- reticuloendothelial cells such as lymphatic tissues.
- It's importance comes when it effects immunocompromised patients

Seroepidemiology

Primary infection

- Asymptomatic most likely
- Infectious mononucleosis

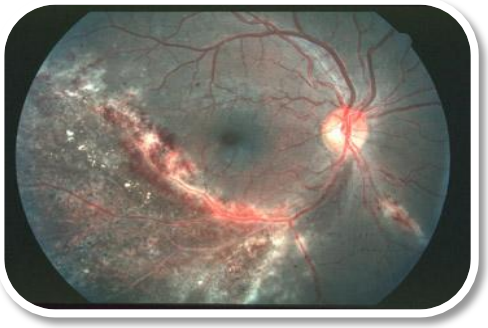


Secondary infection

- Pneomonitis
- Retinitis
- GI
- Multisystem

CMV Retinitis

- Retinitis is relatively common in AIDS pts.



CMV Diagnosis

- Diagnosis almost always depends on laboratory confirmation and cannot be made on clinical grounds alone.
  - Viral cultures from blood ,urine ,tissue.
  - Serologic tests (antigen detection)
  - PCR
- Difficult to diagnose, not as simple as VZ or HSV. It needs specific serology and its presentation isn't that easy either because the pt usually comes with unspecific fever and lymphadenopathy.
- Viral culture is not easy and not done in all labs.

CMV TREATMENT

- ganciclovir
- foscarnet
- cidofovir

  - Treatment is difficult which doesn't cure the disease but controls the infection.

Epstein-Barr Virus (EBV)

- Ubiquitous human herpes virus.
- By adulthood 90 to 95% of most populations are positive.
- Spread occurs by intimate contact between susceptible individuals and asymptomatic shedders of EBV.
- Mostly causes asymptomatic infections.
- but can cause the typical infectious mononucleosis especially in children and young adults.

- Strong association with African Burkitt's lymphoma and Nasopharyngeal carcinoma.
- Associated with malignancies

Infectious mononucleosis

- **Clinical**
  - **Fever, Sore throat ,Lymphadenopathy**
  - If it appeared as infectious mononucleosis, it has a similar presentation to tonsillitis.
  - Tonsils may enlarge and obstruct the airways.
  - Patient can have low platelets count and may suffer from spleenomegaly, and at great risk of spleen rupture.
- **Hematologic**
  - **>50% mononuclear cells (**Large percentage), which differentiates it from tonsillitis)
  - **>10% atypical lymphocytes** (**<u>20 %)</u>**
- **Serologic**
  - Transient appearance of heterophile antibodies
  - Permanent emergence of antibodies to EBV

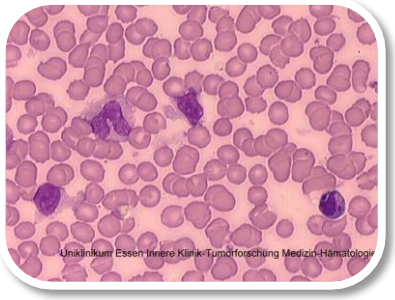
Confirmed by serology in an easy and cheap way

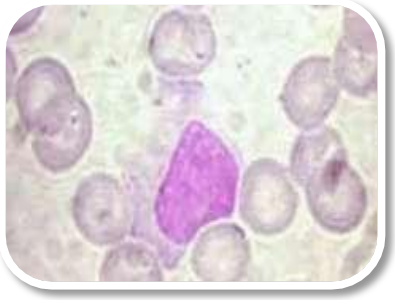
EBV Diagnosis:

- Heterophile Antibodies is present in about 90%
- Hematologic Findings

  Lymphocytosis, neutropenia , throbocytopenia
- EBV specific antibodies
- Not easily cultured

EBV Infection , Atypical Lymphocytes





EBV Treatment:

- is largely supportive because more than 95% of the patients recover uneventfully without specific therapy
- Corticosteroids
- There is no specific treatment for the EBV, but we use:
  - Paracitamol→ for fever
  - Steroids→ to prevent airway obstruction
- Unfortunately, <u>if antibiotics were prescribed for the patient , he/she will develop a generalized rash</u>.

Health Care Associated Infections

Prof. Abdulkarim Al-Aska

Definition :

- Hospital acquired– Nosocomial
- Occurring after admission
- Neither presenting or incubating at the time of admission
- Occasionally the illness may develop weeks or months after discharge.

History :

- Earliest Europeans hospitals were established in middle ages
- No resemblance to modern hospitals in either structure or function
- There were lack of space and shifts were ordered for patients and occasionally more than one patients in beds.
- Consequences:
  - Increased physical contact promoting infection spread
  - The squalid situations led to the hospitals called ''pest houses''
  - 19th century reports
  - Surgery almost always followed by infection
  - 60% of limb amputations resulted in fatal infection

Observation :

- In 1846 there was differential mortality of childbed fever between 2 obstetrics wards 1 & 2 at University of Geneva.
- 11.4% vs 2.7%.
- Investigation was then launched by Ignaz Phillip Semmelweis who was the director of Obstetrics services
- Then Pathologist doing post mortem died of similar illness having nicked his hand with scalpel.
- Conclusion from infectious materials.
- Hospital staff and students were subsequently ordered to wash their hands with calcium hypochlorite after examining each patients.
- Mortality rate dropped from 11.4% to 1.3% in ward 1— **decline of 89%.**
- Hand washing also ordered for ward 2, rate **declined by 52%.**
- This clearly demonstrated the spread and prevention of hospital infection
- Ignaz Phillip Semmelweis was later regarded as the Father of Hospital Epidemiology.
- The discovery of penicillins in the 30s and 40s led to lower infection rate.
- Subsequently MRSA became problem.
- The 1990s saw the emergence of Vancomycin resistant Enterococci
- Advancement in medicine also posed new challenges like catheter related blood stream infection and ventilator associated pneumonia.
- Last two decades, increase number of susceptible patients as a result of survival to immune modifying disease or effect of therapy.
- Resulting in patients expose to life threatening diseases due to change in natural or acquired immunities.

Importance of Hosp. Infection :

- Estimates in the 70s, 6-8 per 100 patients admitted.
- Additional suffering and mortality for patients
- Nosocomial infection also increased length of hospital stay and extra costs to authorities.

Prolongation of Hospital Stay due to Nosocomial Infections in the USA :

Infection Site	Excess Days
Surgical Wound	6.0
Urinary tract	1.2
Pneumonia	4.0
Bacteremia	7.0
Other sites	4.2

Annual Costs and Benefits of Infection Control Program in a Hypothetical 250-bed Hospital

Each $1000 invested in infection control will return $3000 in net direct cost savings

Estimated reduction of direct costs from infections prevented	$246,700
Estimated infection control program expenses	$60,000
Hospital savings	$186,700

Hospital-acquired Infection – why worry ?

- 10-15% of patients will get infected during a stay in hospital
- Costs > £1 billion per year in UK
- A single large outbreak can cost 10-100K
- Effects of nosocomial infection :
  - Increased mortality & morbidity
  - Prolonged hospital stay
  - Increased drugs bill
  - Increased staffing costs
  - Demoralising for staff & patients
  - Decreased public confidence in hospitals & doctors

Why is hosp-acquired infection different from community-acquired infection ?

- Many vulnerable patients in close proximity to each other for prolonged periods of time
- Many patients have impaired immunity :
  - After anti-cancer chemotherapy
  - After transplants
  - Extremes of age
- Many patients have impaired normal physiological defences :
  - Breaches in skin
  - Implanted foreign bodies (biofilms)
  - Impaired physiology (Peristalsis, mucociliary escalator)

Antibiotic-Resistant Infections :

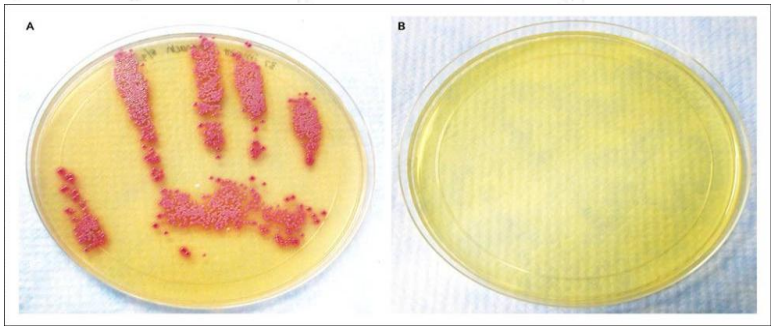
- Associated with extended illness
- Longer hospital stay
- Higher risk for death
- Increased costs to health system
- Microbes with mutation for resistance has a selective advantage to:
- **Survive, proliferate and spread.**
- Controlling antibiotic prescriptions within hospitals had helped in reduction of resistant organism emergence.
- Contact precautions with gowns and gloves had prevented the spread of MRSA and VRE.
- Transmission facilitated by hospital staff who rarely :
  - Wash their hands
  - Disinfect or dispose their clothing
  - Disinfect their equipment

Hand washing :

- **Method** :
  - Wet hands with clean (not hot) water
  - Apply soap
  - Rub hands together for about 20 seconds
  - Rinse with clean water
  - Dry with disposable towel or air dry
  - Use towel to turn off faucet

Alcohol-based Hand Rubs :

- Effective if hands not visibly soiled
- More costly than soap & water
- **Method** :
  - Apply appropriate (3ml) amount to palms
  - Rub hands together, covering all surfaces until dry



UTI :

- Thirty per cent of all nosocomial infections
- Rate of 1% with single in-out catheterisation
- Risk of 3 to 6% per catheter-day for prolonged usage.
- Higher for females than males
- Post 10-14 days, half of pateints have bacteriuria.

NNIS Data (CDC) :

- E. coli
- Enterococcus spp.
- P. aeruginosa
- Candida spp.
- Coagulase -ve Staph
- Other fungi
- Citrobacter spp.
- S. aureus
- K. pneumoniae
- Enterobacter spp.
- Proteus mirabilis

- Preventive measures have confirmed the advantage of closed drainage system.
- Also the use of silver alloy urinary catheter

Pneumonia :

- Mainly from aspirated gastric contents.
- Also from microbes-laden secretions of upper respiratory tract.
- Septic emboli from infected CVP or A-V fistula
- Rarely, inhalation of pathogens from the air for example M tuberculosis and Aspergillus fumigatus

S. aureus
P. aeruginosa
Enterobacter spp.
K. pneumoniae
E. coli

- Most patients are ventilated in ICU.
- Rates from 6 to 30%.
- Risk of 1 to 3% per day.
- Higher inocula with patients on either H_2 blocker or antacid therapy.
- Less with sucralfate.
- Preventive measures :
  - Keeping patients at an angle of 45 degrees.
  - Use of device for subglottic suction to reduce the pooling of secretions.
  - Led to less clinical aspirations and lower pneumonia rates.

Surgical Site Infections (SSI) :

S aureus
Coagulase –ve Staph
Enterococci
E coli
Enterobacter
Klebsiella
Candida

- Still occur despite aseptic techniques
- Clearly the obese and diabetic patients require adequate preparations.
- Use of dry shaving a day before surgery is better than clippers hours before.
- Emergent surgery on inherently contaminated organs like the colon.

Blood Stream Infections :

- Primary 80%: mainly from infected vascular catheter.
- Secondary 20%: local infection in another organ.
- Catheter-related BI begins with colonization of the catheter with microbes.
- Femoral more prone than IJ and SC
- Cultured tips of catheter in cardiac surgery are infected within 1-2 hours of insertion.
- Earlier on tackled by the body's immune system.
- Subsequently microbes moved through the catheter tract to enter the blood stream.
- By 10 days there is an increasing frequency of intra-luminal contamination.
- Multiple randomised trials had shown that antiseptic preparation with chlorhexidine is far superior in risk reduction of colonisation as compared with alcohol or povidone-iodine preparations.
- Chlorhexidine-silver sulphadiazine treated catheter has been shown to reduce colonization and blood stream infection by about half.
- Cotton gauze covered by tape were associated with lower risk of colonization versus transparent dressings.
- Antibiotic-coated catheter reduced colonization by 55% as compared with standard catheters.
- Comparative study had shown that the capacity of minocycline/rifampicin coated catheter were superior in resisting infection versus chlorhexidine-silver sulfadiazine catheter.

Organization for Infection Control :

- Surveillance
- Outbreak investigations
- Education
- Hospital employee health
- Antimicrobial utilization
- Policy development
- Quality assessment

Infection Control Programs :

- Size and intensity of program predicts infection rates.
- Most effective associated with 32% reduction compared with hospital without program.
- One hospital with effective program in 1985 reported saving costs of $2million for the year.

Infection Control in hospital :

- Interrupt transmission
  - Human-to-human
    - Hand washing
    - Ward routine (e.g. wet mopping)
    - Aseptic technique
    - Sterilisation & disinfection
    - Isolation procedures
  - Environment
    - Food hygiene, pest control, theatre design

Precautions :

- Standard
- Specific : ■ Airborne ■ Droplets ■ Contact

Standard Precautions :

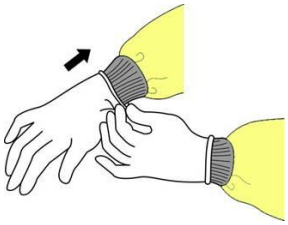

- Perform hand hygiene
- Wear gloves
- Wear gowns
- Wear a mask and goggles and glasses
- Hand hygiene
- Respiratory hygiene and cough etiquette
- Personal protective equipment (PPE)
  Based on risk assessment to avoid contact with blood, body fluids, excretions, secretions
- Safe injection practices
- Environmental control
- Patient placement
- Specific Isolation Categories

Airborne precautions :

- Use a negative-pressure room
- Keep doors closed
- Wear grade N95 or better mask
- If patient transport is necessary, then patient to wear surgical mask
- TB, Measles, Chickenpox

Droplet precautions :

- Keep doors closed
- Wear a surgical mask if entering the room
- Discard mask after leaving the room
- If patient transport is necessary, patient to wear surgical mask
- Meningitis, Mumps, Pertussis, Rubella



Contact precautions :

- Wear a gown and gloves to enter the room
- Use a dedicated stethoscope and thermometer
- Remove gown and gloves before leaving the room
- Acute infectious diarrhea, Abscess/draining wound

Occupational Exposures – Risk for Hepatitis :

- Hepatitis B is much more frequent occupational infection and a cause of deaths among HCWs.
- Standard precautions and vaccination had reduced infection.
- Ten per cent of HCWs do not respond to vaccination.
- No vaccine yet for Hepatitis C
- General steps in management
  - Wash and clean wounds
  - Flush mucous membranes immediately
- **Unvaccinated Exposed HCW**
  - Injury from HBsAg +ve source, give HBIG 0.06mL per Kg and initiate HB vaccine
  - Injury from HBsAg -ve source, initiate HB vaccine
  - Injury from unknown status of HBsAg initiate HB vaccine and determine HBsAg of source.

- **Vaccinated HCW/unknown Ab status**
  - Injury from HBsAg +ve source, do anti- HBS on exposed person :
    - If titer > 10milli-IU/ml no treatment.
    - If titer < 10milli-IU/ml, give HBIG 0.06mL per Kg + 1 dose of HB vaccine
  - Injury from HBsAg -ve source, no treatment is necessary.
  - Injury from unknown status of HBsAg do anti-HBS on exposed person :
    - If titer > 10milli-IU/ml no treatment.
    - If titer < 10milli-IU/ml, give 1 dose of HB vaccine plus HBIG if source high risk
- **Hepatitis C exposure :**
  - Determine anti-HCV from both exposed person and source.
  - If source known +ve and exposed –ve follow up HCV testing advised.
  - Baseline and serial LFTs
  - HCV RNA after 2 weeks of exposure.
  - No recommended prophylaxis; immune globulin not effective.
  - Monitor for early infection as therapy may reduce risk of progression to chronic hepatitis.
  - Risk factors from case control study.
  - Needle from artery and veins.
  - Deep injury.
  - Male HCW.
  - Source ≥ 6 million copies/mL.

Occupational Risk for HIV Infection :

- Approximately 1 in 300-400 needle sticks injuries will transmit HIV.
- Chances increased with large-bore hollow needle
- Wash wounds and flush mucous membranes.
- Baseline HIV test, CBC, renal and hepatic tests
- Viral load of source.
- HIV testing should be repeated as follows : 3-4 weeks and 3 & 6 months
- PEP should be started within hours
- **Regimens :**
  - Treat for 4 weeks
  - Monitor drug side-effects fortnightly
  - **Basic regime** : Zidovudine + Lamivudine or Stavudine + Lamivudine
  - **Expanded regime** : Above + Lopinavir + Ritonavir

Occupational Risk for TB :

- Infection occurs in setting lacking isolation techniques
- These are :
  - Absence of negative-pressure ventilation rooms
  - Lack of administrative control measures
- Further recommendations
  - Annual and semi-annual PPD testing
  - Training and retraining of staff
- An extract from the work book of Dr Fester, aged 24, newly qualified house officer...
- 50 lines as punishment for poor hand hygiene.

- I promise to wash my hands between patients
- I promise to wash my hands between patients
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- .....

Approach to Abdominal Pain

Prof. Ibrahim Al-Mofleh

◈ Abdominal pain :

- One of the most common causes for OP & ER visits.
- Multiple abd and non-abd pathologies can cause abd pain, therefore an organized approach is essential.
- Some pathologies require immediate attention.

Types :

- Visceral pain.
- Somatoparietal pain.
- Referred pain.

Categories :

- Bright pain.
- Dull pain.
- Undifferentiated pain.

Definitions :

- **Acute** abdominal pain with recent onset within hours-days.
- **Chronic** abdominal pain is intermittent or continuous abdominal pain or discomfort for longer than 3 to 6 months.

History :

- PMH :
  - Similar episodes in past.
  - Other relevant medical problems.
  - Systemic illnesses such as scleroderma, lupus, nephrotic syndrome, porphyrias, and sickle cell disease often have abdominal pain as a manifestation of their illness.
- PSH : Adhesions, hernias, tumors, trauma.
- Drugs : ASA, NSAIDS, antisecretory, antibiotics …etc.

NSAIDs are the 2nd common cause of peptic ulcer , and H. pylori is the first .

- GYN : LMP (last menstrual period) , bleeding, discharge.
- Social : Nicotin, etanol, drugs, stress.
- Family : IBD, cancer …ect.
- **Associated symptoms** :
  - Anorexia.
  - Weight loss.
  - Nausea/vomiting.
  - Bloating.
  - Constipation.
  - Diarrhea.
  - Hemorrhage
  - Jaundice.
  - Dysurea.
  - Menstruation.

Anorexia and weight loss are constutional symptom for TB and lymphomas

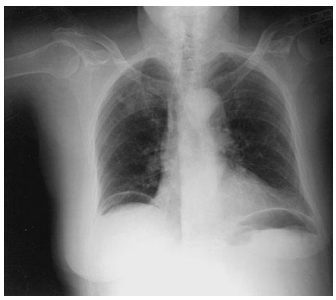
- **Aggravating and alleviating factors :**
  - Eating & drinking. E.g. eating relieve the pain in case of duodenal ulcer , aggravate pain in gastric ulcer .
  - Drugs.
  - Body position.
  - Defecation.

Physical Exam :

- General appearance : Ambulant, Healthy or sick, In pain or discomfort, Stigmata of CLD (chronic Liver Disease).
- Vital signs.
- **Abdomen** :
  1. Inspection : Distention, scars, bruises, hernia.
  2. Auscultation : Abd sounds (present, hyper, or absent).
  3. Palpation : Often the most helpful part of exam (Tenderness, Guarding, Rebound, Masses).
  4. Signs : Murphy's sign is positive in Cholecystitis , Iliopsoas, Rovsing's
  5. PR.
- **Extra-abdominal :**
  1. General appearance.
  2. Vital signs.
  3. Pelvic/scrotal exams.
  4. Lungs, heart.
  5. Remember it's a patient, not a part.

Laboratory Testing :

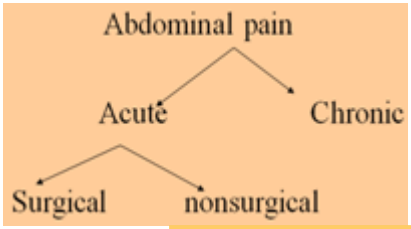
- **CBC:** e.g. elevated WBC in infection, anemia caused by ulcers or tumors.
- **Liver profile:** e.g. increased alkaline phosphatase which might indicate obstructive jaundice.
- **Amylase** → In pancreatitis, amylase is increased 3-4 times .
- **Glucose:** e.g. Diabetic ketoacidosis which can cause abdominal pain.
- **Urine dipstick:** e.g. hematuria due to stones or tumors.
- **Pregnancy test:** abdominal pain can be due to ectopic pregnancy.

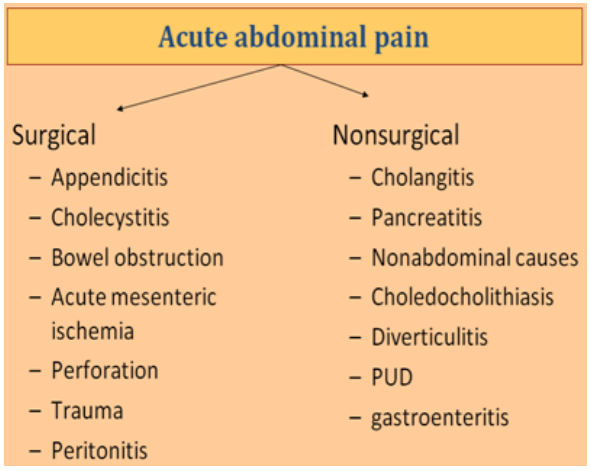


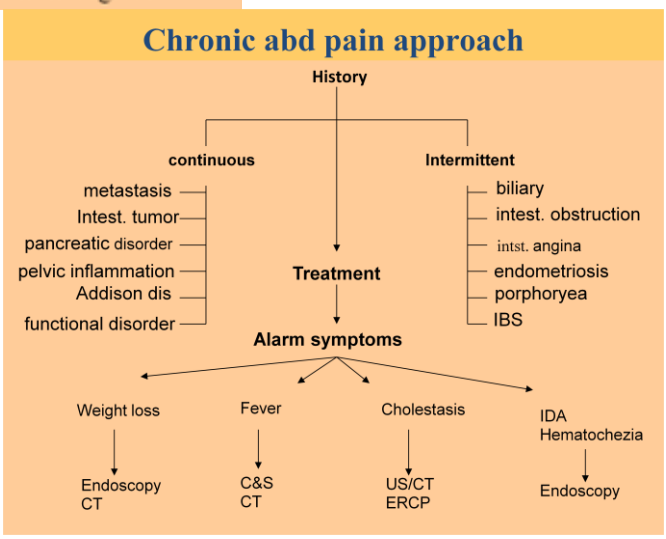
Imaging :

- Plain films.
- Ultrasonography.
- Computed Tomography.
- **Endoscopy :**
  - EGD (Esophagogastroduodenoscopy).
  - Colonoscopy.
  - ERCP (Endoscopic retrograde cholangiopancreatography) / EUS (Endoscopic ultrasound)

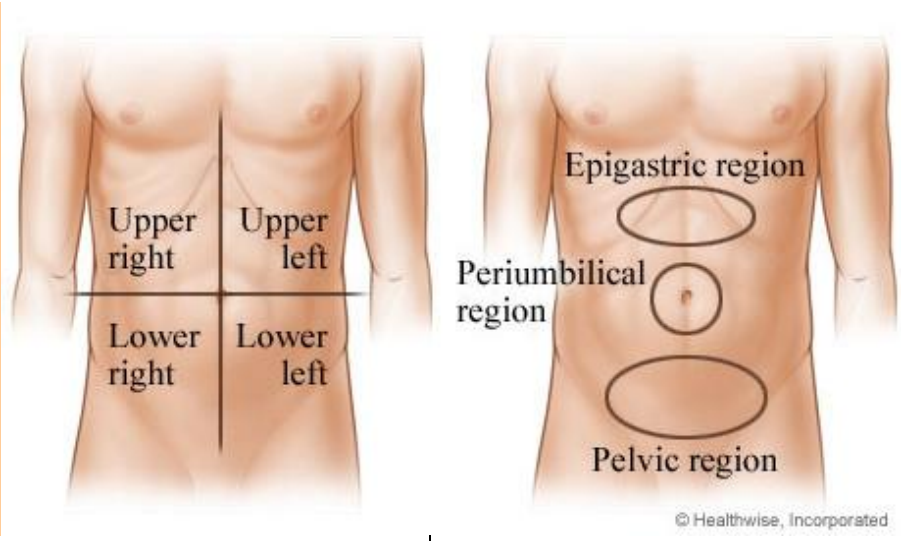
◈ Approach :







◈ PAIN LOCATION :



- **RUQ-PAIN** :
  1. Cholecystitis.
  2. Cholangitis.
  3. Hepatitis.
  4. RLL pneumonia.
  5. Subdiaphragmatic abscess.
- **LUQ- PAIN** :
  1. Splenic infarct.
  2. Splenic abscess.
  3. Gastritis/PUD (peptic ulcer disease).
- **RLQ-PAIN :**
  1. Appendicitis.
  2. Inguinal hernia.
  3. Nephrolithiasis.
  4. IBD.
  5. Salpingitis.
  6. Ectopic pregnancy.
  7. Ovarian pathology.
- **LLQ-PAIN** :
  1. **Diverticulitis.**
  2. Inguinal hernia.
  3. Nephrolithiasis.
  4. IBD.
  5. Salpingitis.
  6. Ectopic pregnancy.
  7. Ovarian pathology.
- **Epigastric-Pain :**
  1. PUD.
  2. Gastritis.
  3. GERD.
  4. Pancreatitis.
  5. Cardiac (MI, pericarditis, etc).
- **Periumbelical-Pain** :
  1. Obstruction.
  2. Pancreatitis (pain increase with lying down) .
  3. Early appendicitis.
  4. Small bowel pathology.
  5. Gastroenteritis.

Umbilical hernia may cause periumbelical-pain .

- **Pelvic-Pain** :
  1. UTI.
  2. Prostatitis.
  3. Bladder outlet obstruction.
  4. PID (pelvic inflammatory disease).
  5. Uterine pathology.
- **Diffuse Pain :**
  1. Gastroenteritis.
  2. Ischemia.
  3. Obstruction.
  4. DKA.
  5. IBS.
  6. Others : FMF (Familial Mediterranean fever), AIP (Acute intermittent porphyria) , Vitamin D deficiency, Adrenal insufficiency.

- Abdominal pain can be caused by non-abdominal pathologies e.g. Myocardial infarction or pneumonia of the basal surface of lung
- Sometimes <u>back pain</u> can be referred to the abdomen

Irritable Bowel Syndrome (IBS) :

- IBS is characterized by abdominal discomfort associated with altered bowel habits in the absence of structural or biochemical abnormalities.

Irritable bowel syndrome is a psychosomatic disorder.

- **Assoc. Extraintestinal Disorders** :
  1. Fibromyalgia.
  2. Psychic disorders.
  3. Urinary symptoms.
  4. Sexual dysfunction.
- **Epidemiology** :
  1. Worldwide point prevalence 10-20%.
  2. Prevalence higher below 50 years.
  3. More in women.
  4. May occur in pediatrics usually > 6 yrs.
  5. 3x absence from work compared to non IBS patients.
  6. HRQL (health-related quality of life) is significantly lower than healty individuals and RA, DM, BA and GERD.
  7. Economic impact 8-30 billion dollars (in USA).
- **Pathophysiology** : **Three interrelated factors :**
  1. Altered gut reactivity (Motility, Secretion) : Meals, Bacteria, Environmental.
  2. Hypersensitive gut with enhanced pain perception.
  3. Altered gut brain axis with greater reaction to stress and modified pain perception.

IBS – Diagnostic Criteria :

- **Manning Criteria :**
  - Pain relieve with defecation.
  - More frequent stools at the onset of pain.
  - Looser stools at the onset of pain.
  - Sensation of incomplete evacuation.
  - Passage of mucus.
  - Visible abdominal distention.
- **Rom Criteria : Contin. or recurrent abd. pain or discomfort for>12 wks, onset >6 months prior to diagnosis and includes at least 2 of :**
  - Improvement with defecation.
  - Onset assoc. with change in frequency of stool.
  - Onset assoc. with change in form of stool.
- **Symptoms cumulatively supporting the diagnosis :**
  - Abnormal stool frequency (>3/d or <3/wk).
  - Abnormal stool form (lumpy/hard or loose/watery).
  - Abnormal stool passage (straining, urgency or sense of incomplete ev).
  - Passage of mucus.
  - Bloating or feeling of abd. distension.
- **Rom III Criteria:**
  - 3 months or more.
  - Abd. discomfort or pain at least 3d/month.
    - Relieved by defecation.
    - Assoc. with change in stool form.
    - Assoc. with change in stool frequency.

Surgical abdomen :

- Is a clinical diagnosis.
- Early identification is essential.
- Early initiation of treatment.
- Early surgical consultation.
- Fevers, tachycardia, hypotension, tender, rigid abdomen.
- These findings may diminish with : Advanced age, Immunosuppression.

1. **Peritonitis :**
   - Perforation, large abscess, severe bleeding.
   - Patient usually appears ill.
   - Rebound, rigidity, tender to percussion or light palpation, pain with shaking bed.
2. **Obstruction :**
   - Acute or acute on chronic.
   - Abdominal distention.
     - **Distal** – distention, Tympany bowel sounds absent or high-pitched.
     - **Proximal** – similar, but distention and Tympany may be absent.
   - Pain.
   - Persistent vomiting.
   - Absent bowel sounds suggest paralytic ileus or peritonitis , but hyper bowel sounds are heard with bowel obstruction .
3. **Mesenteric ischemia :**
   - Usually seen in patients with CAD.
   - Pain out of proportion to exam.
   - Later present with peritonitis.

Indications for referral To whom ?

1. **Gastroenterologist :**
   - Endoscopy. o Indefinitive diagnosis. o IBS not responding to therapy.
   - Suspected : IBD, Deverticulitis, Chronic bowel ischemia, Pancreatitis, Pancreatic cancer.
2. **Surgeon :**
   - Acute abdomen. o Hemodynamic instability. o Free intraperitoneal gas.
   - Suspected : Appedicitis, Acute cholecystitis, Acute ischemic bowel, Intestinal obstruction.
3. **Urologist :**
   - Large stone.
   - Failure to pass the stone within 6 weeks.
   - Uretral obstruction.
   - Fever.
4. **Gynecologist :**
   - Lower abd pain and pos. pregnancy test.
   - Suspected : Pelvic inflammation, Adnexal torsion, Endometriosis.

Take Home Points :

- Good history and physical exam is important (History is the most important step of the diagnostic approach).
- Lab studies limitations.
- Imaging studies selection (appropriate for presentation and location).
- Alarm symptoms oriented investigations.
- Early referral of sick patients.
- Treatment initiation.

Inflammatory Bowel Disease

Dr. Abdurrahman Al-Jebreen

Introduction :

- IBD characterized by a tendency for chronic or relapsing immune activation and inflammation within the GIT.
- Crohn's disease (CD) and ulcerative colitis (UC) are the 2 major forms of idiopathic IBD.
- **Less common entities are :**
- Microscopic colitis (collagenous and lynphocytic).
- **Others :**
    - Diversion colitis.
    - Radiation colitis.
    - Drug induced colitis.
    - Infectious colitis.
    - Ischemic colitis.
- CD is a condition of chronic inflammation potentially involving any location of the GIT from mouth to anus.
- UC is an inflammatory disorder that affects the rectum and extends proximally to affect variable extent of the colon.

Epidemiology :

- CD : 1st peak 15-30 years of age, 2nd peak around 60 y.
- UC :
    - High incidence areas: US, UK, northern Europe.
    - Young adults, commoner in females.

Genetics :

- Studies suggested that 1st degree relatives of an affected patient have a risk of IBD that is 4-20 times higher than that of general population.
- The best replicated linkage region, IBD1, on chromosome 16q contains the CD susceptibility gene, NOD2/CARD15.
- Having one copy of the risk alleles confers a 2–4-fold risk for developing CD, whereas double-dose carriage increases the risk 20–40-fold.

Etiology :

- Mutations within the NOD2/ CARD15 gene contribute to CD susceptibility.
- Functional studies suggest that inappropriate responses to bacterial components may alter signaling pathways of the innate immune system, leading to **the development and persistence of intestinal inflammation.**
- **Initiating pathogen?**
    - Infectious?
    - ? Possibly non-pathogenic commensal enteric flora.

Pathogenesis :

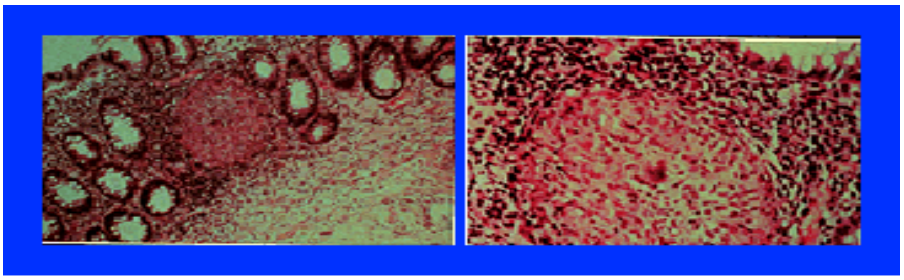
- The mucosa of CD patients is dominated by Th1 (T helper), which produce interferon-γ and IL-2.
- Activation of Th1 cells produce the down-regulatory cytokines IL-10 and TGF-.
- In contrast, UC dominated by Th2 phenotype, which produce transforming growth factor (TGF-) and IL-5.

Environmental Precipitants :

- **Factors :**
    - NSAIDs use (?altered intestinal barrier), and
    - Early appendectomy (increase UC incidence).
    - Smoking (protects against UC but increases the risk of CD).

CD – PATHOLOGY :

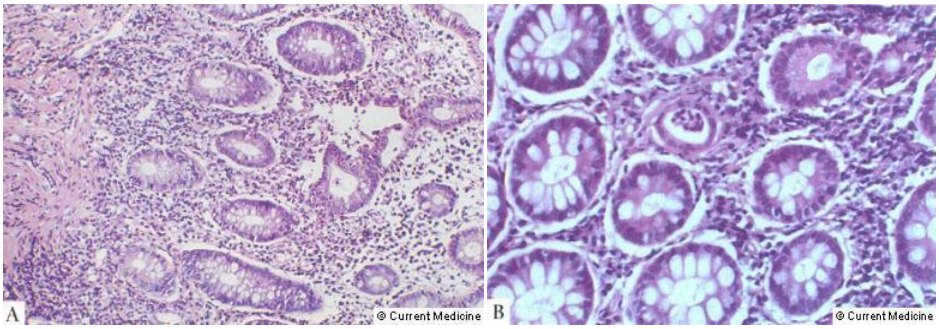
- **Early Findings :**
    - Aphthous ulcer.
    - The presence of granulomas.
- **Late findings :**
    - Linear ulcers.
    - The classic cobble stoned appearance may arise.
    - Transmural inflammation.
    - Sinus tracts, and strictures.
    - Fibrosis.



Typical granuloma of Crohn's disease Light micrographs showing granulomatous lesion that is diagnostic of Crohn's disease. Low and high power views show a central giant cell surrounded by epitheliod cells and rimmed by lymphocytes. Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.

UC – PATHOLOGY :

- The inflammation is predominantly confined to the mucosa.
- **Non-specific (can be seen with any acute inflammation) :**
  - The lamina propria becomes edematous.
  - Inflammatory infiltrate of neutrophils.
  - Neutrophils invade crypts, causing cryptitis & ultimately crypt abscesses.
- **Specific (suggest chronicity) :**
  - Distorted crypt architecture, crypt atrophy and a chronic inflammatory infiltrate.

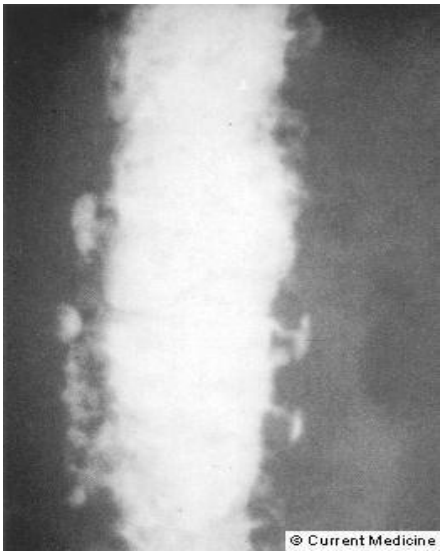


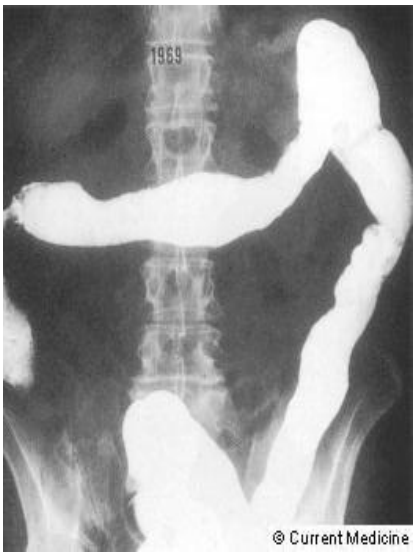
Diagnosis :

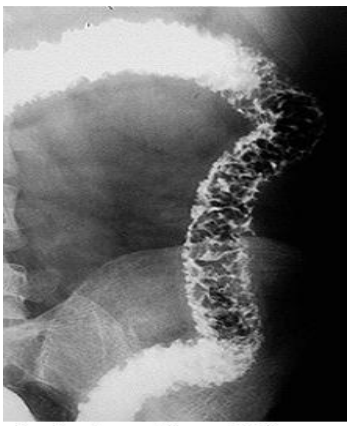
- Exclude other possibilities , need:
  - Good history
  - Physical exam
  - Labs (CBC, ESR, CRP, U& E, LFT, serology)
  - Imaging (CT abdomen, SBFT, MRI enterocolysis & MRI pelvis)
  - Endoscopy with biopsy (histopathology).
- There are many distinguishing features of CD and UC.
- In about 5% it is classified as indeterminate because of overlapping features.

FEATURE	CD	UC
Distinguishing characteristics		
Location	SB or colon	Only colon (rarely "backwash ileitis"
Anatomic distribution	Skip lesions	Continuous, begins distally
Rectal involvement	Rectal spare	Involved in >90%
Gross bleeding	Only 25%	Universal
Peri-anal disease	75%	Rare
Fistulization	Yes	No
Granulomas	50-75%	No
Endoscopic features		
Mucosal involvement	Discontinuous	Continuous
Aphthous ulcers	Common	Rare
Surrounding mucosa	Relatively normal	Abnormal
Longitudinal ulcer	Common	Rare
Cobble stoning	In severe cases	No
Mucosal friability	Uncommon	Common
Vascular pattern	Normal	distorted
Pathologic features		
Transmural inflammation	Yes	Uncommon
Granulomas	50-75%	No
Fissures	Common	Rare
Fibrosis	Common	No
Submucosal inflammation	Common	Uncommon
Radiologic features		
Feature	Nodularity, Granularity Cobble stoning, String sign of SB	Collar button ulcers

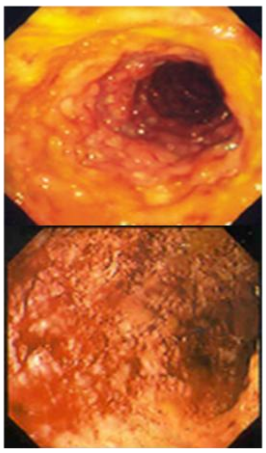
UC

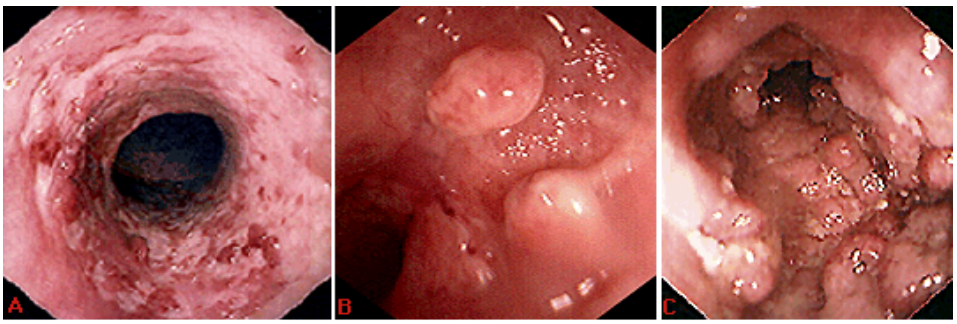






Acute ulcerative colitis Double contrast barium enema demonstrates extensive mucosal ulceration and inflammation throughout the colon. Courtesy of Jonathan Kruskal, MD



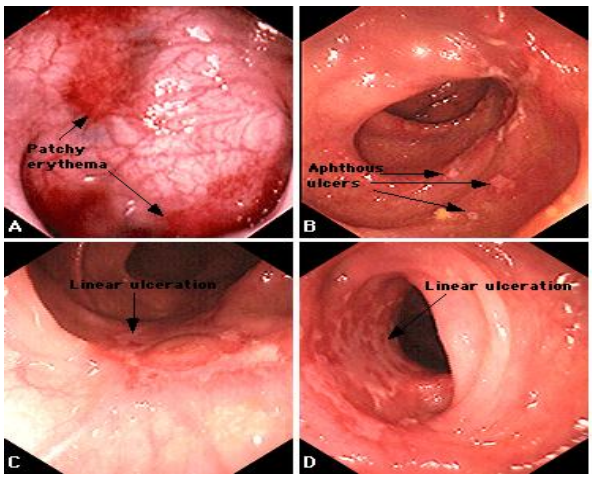


Ulcerative colitis Endoscopic appearance of ulcerative colitis. Extensive ulceration of the mucosa is the most common endoscopic finding (panel A). The surface is irregular, friable, and erythematous, with loss of the normal vascular markings. Pseudopolyps may form as a reaction to inflammation (panel B); these can become quite extensive (panel C). Courtesy of James B McGee, MD.

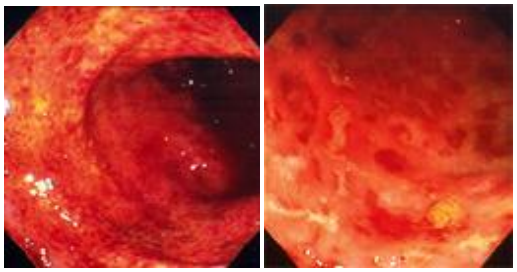
UC – Clinical Presentation :

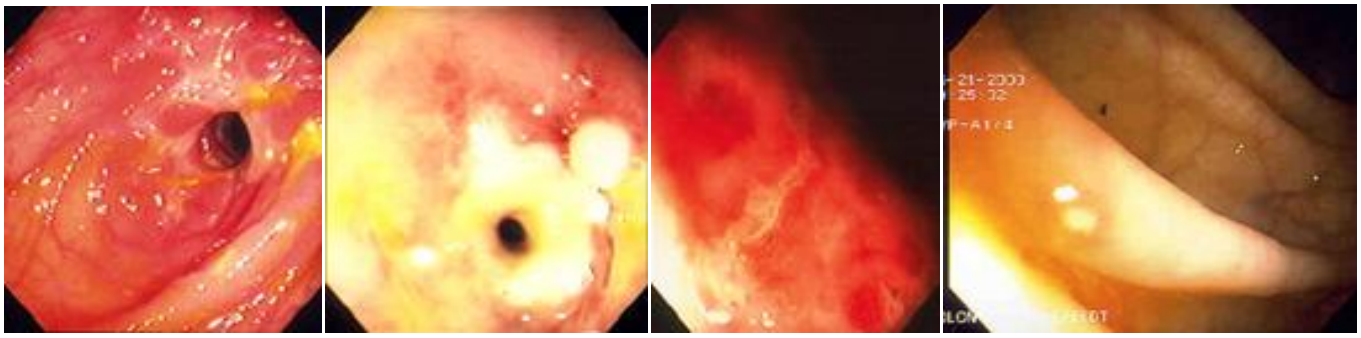
- Must exclude infectious cause before making Dx.
- **Rectal Bleeding.**
- **Diarrhea :** Frequent passage of loose or liquid stool, often associated with passing large quantities of mucus.
- **Abdominal Pain :** It is not a prominent symptom.
- Anorexia, nausea, fever…
- **DDX of UC** :
  - Infectious.
  - Drug induced.
  - Microscopic colitis.
- Mild attack : Most common form, mainly left sided colitis, <4 BM/day with no blood.
- Moderate attack : 25% of all patients, 4-6 BM/day with blood.
- Severe or fulminant colitis : ~ 15% of cases, >6BM/day, bloody, fever, weight loss, diffuse abd tenderness, elevated WBC, most refractory to medical therapy.

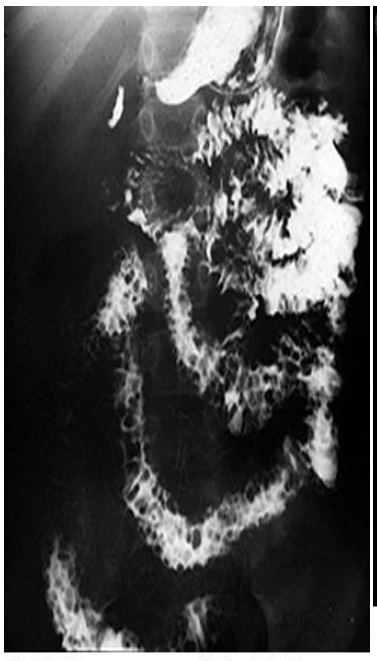
CD



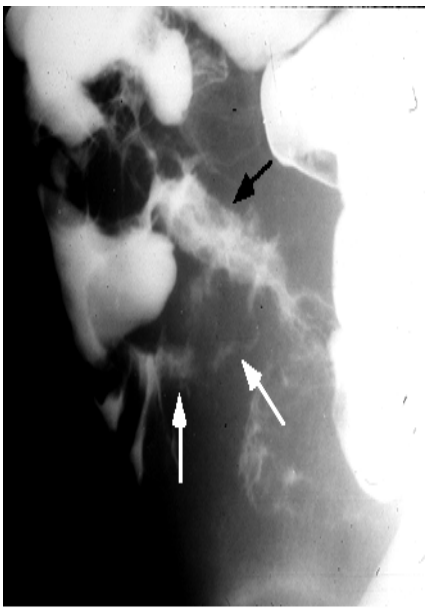
Endoscopic progression of Crohn's disease Ulcers are the dominant endoscopic feature in Crohn's disease. These tend to be linear and discontinuous, or "skip lesions". Early changes may be only patchy erythema (panel A) or aphthoid ulcers (panel B). Linear ulcers (panel C) are seen with more advanced disease, culminating in very deep and long serpiginous ulcers (panel D). Courtesy of James B McGee, MD.



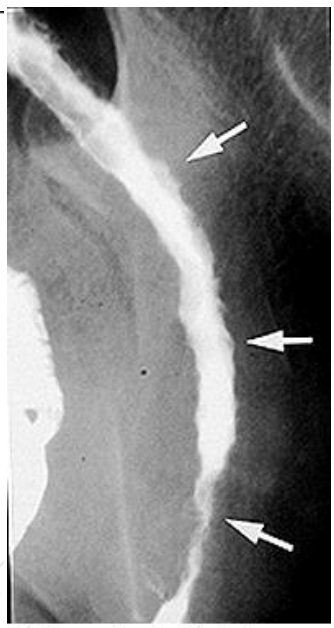




Cobblestone appearance in Crohn's disease Small bowel follow through study demonstrates diffuse thickening of the small bowel mucosa in a patient with Crohn's disease. The cobblestone appearance is produced by barium being dispersed between the edematous inflamed mucosa. Courtesy of Norman Joffe, MD.



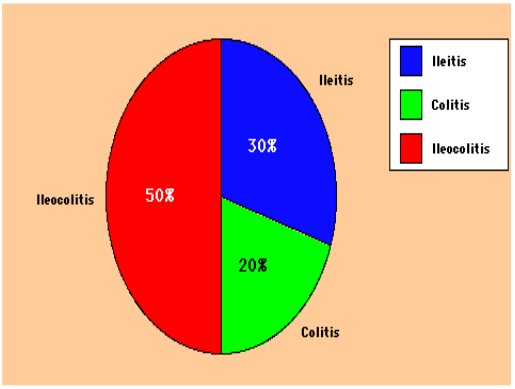
Ileocecal fistulae in Crohn's disease Small bowel follow through examination demonstrates nodular thickening of the terminal ileal mucosal folds in a patient with Crohn's disease (black arrow). Several fistulae extend from the terminal ileum to the adjacent cecum (white arrows). Courtesy of Jonathan Kruskal, MD, PhD.



String sign in Crohn's disease Small bowel follow through study shows marked narrowing, irregularity and ulceration in the distal ileum (arrows) in a patient with Crohn's disease. Courtesy of Jonathan Kruskal, MD, PhD.

CD :

- Anatomic distribution.
- CD activity index.
- DDx (lymphoma, Yersinea Enterocolitis, TB).



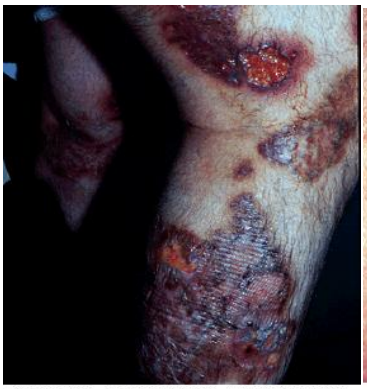
Distribution of Crohn's disease Approximate frequency of ileal and colonic involvement in Crohn's disease. Crohn's disease can involve the enti gastrointestinal tract from mouth to perianal area. (Courtesy of the Americ Gastroenterological Association©. This slide cannot be downloaded but may purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.)

CD – Clinical Presentations :

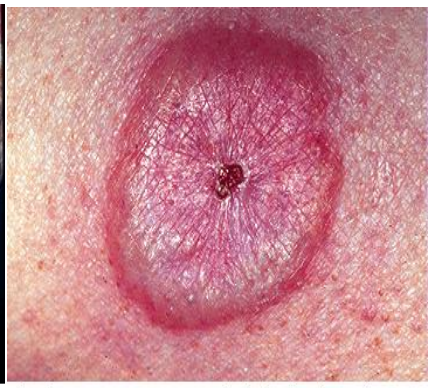
- ***Disease of the ileum :***
  - May present initially with a small bowel obstruction.
  - Patients with an active disease often present with anorexia, loose stools, and weight loss.
- ***Perianal disease*** **:**
  - In 24% of patients with CD.
  - Skin lesions include superficial ulcers, and abscesses.
  - Anal canal lesions include fissures, ulcers, and stenosis.
- **CD ilitis – DDx :**
  - Lymphoma,
  - Yersinea Enterocolitis, and
  - TB.
- ***Colonic disease*** **:** The typical presenting symptom is diarrhea, occasionally with passage of obvious blood.
- ***Proctitis*** **:** May be the initial presentation in some cases of CD.

Extra-intestinal manifestations of IBD :

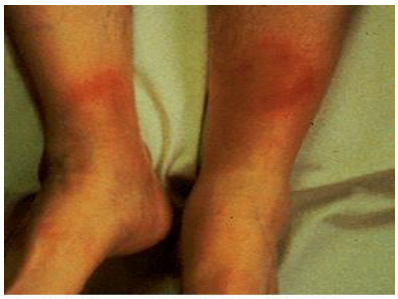
- **Arthritis :**
  - Peripheral arthritis, usu paralels the disease activity.
  - Ankylosing Spondylitis, 1-6%, sacroiliitis.
- **Ocular lesions :**
  - Iritis (uvietis) (0.5-3%), episcleritis, keratitis.
- **Skin and oral cavity :**
  - Erythema nodosum 1-3%.
  - Pyoderma Gangrenosum 0.6%.
  - Aphthus stomatitis, metastatic CD.



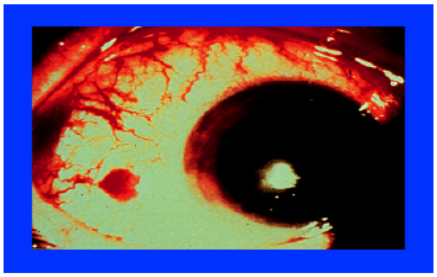
Pyoderma gangrenosum Multiple active and healing lesions of pyoderma gangrenosum with cribriform scarring in patient with inflammatory bowel disease. Courtesy of Samuel Moschella, MD.



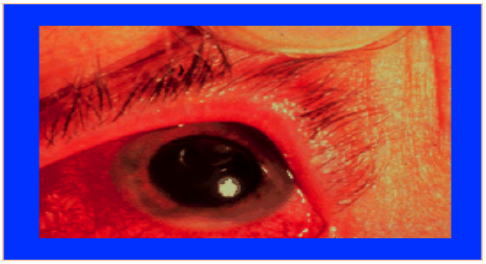
Pyoderma gangrenosum Early lesion in pyoderma gangrenosum presenting as a pustular and violaceous plaque with incipient breakdown. Courtesy of Cynthia Magro, MD.



Erythema nodosum Patient with inflammatory bowel disease with red nodular areas on the shins which are characteristic of erythema nodosum. (Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.)

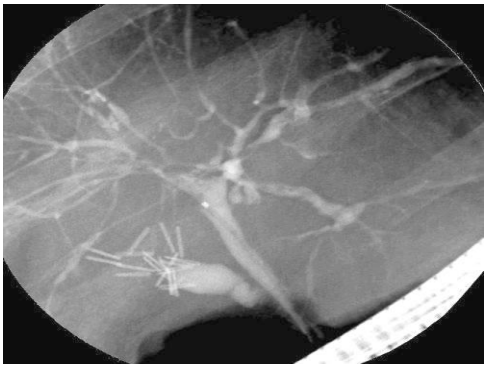


Episcleritis Patient with episcleritis associated with inflammatory bowel disease showing the characteristic injection of the ciliary vessels. (Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.)



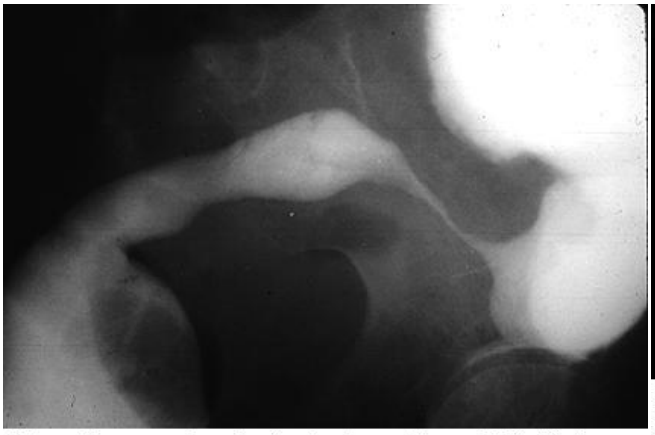
Anterior uveitis Anterior uveitis in a patient with inflammatory bowel disease is characterized by injection of the conjunctiva and opacity in the anterior chamber. Courtesy of the American Gastroenterological Association©. This slide cannot be downloaded but may be purchased as part of a set from the AGA through Milner-Fenwick, Inc at 1-800-432-8433.

- **Liver and Biliary tract disease :**
  - Pericholangitis, fatty infiltration, PSC (1-4%, more with UC), cholangiocarcinoma, gallstones.
- Thromboembolic disease, vasculitis, Renal disease (urolithiasis, GN), clubbing, amyloidosis.

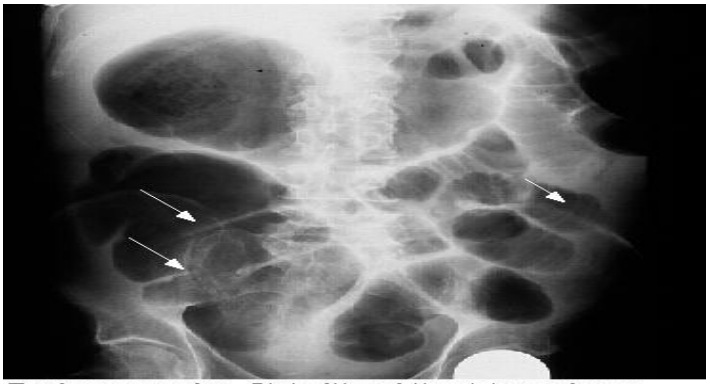


Complications of IBD :

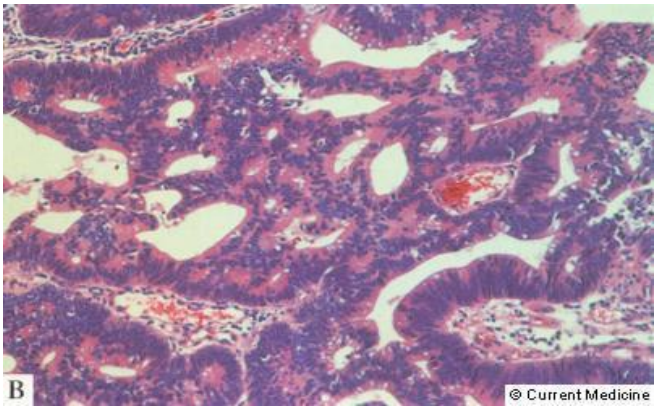
- Bleeding.
- Stricture.
- Fistula.
- Toxic megacolon.
- Cancer.
- Multiple abdominal abscess

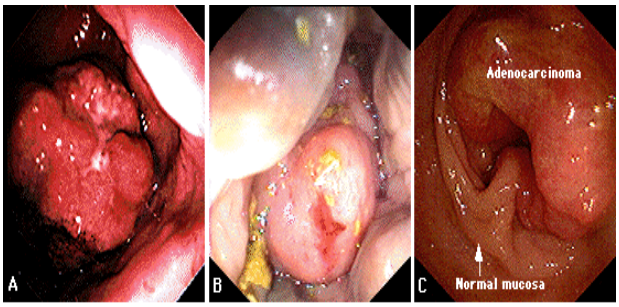


Sigmoid cancer developing in ulcerative colitis Barium enema study demonstrates a focal stricture in the sigmoid colon caused by an infiltrating cancer. The adjacent bowel is featureless and folds are absent, findings characteristic of chronic ulcerative colitis. Courtesy of Norman Joffe, MD.



Toxic megacolon Plain film of the abdomen from a patient with toxic megacolon associated with C. difficile infection. The large and small intestines are grossly dilated. Dilatation of the small bowel, which has the thin transverse folds of the valvulae conniventes (short arrow), is seen best in the left lower quadrant. Large bowel dilation occupies most of the right lower quadrant and has characteristic thick haustral markings that do not extend across the entire lumen (long arrows). Courtesy of J Thomas LaMont, MD.





Adenocarcinoma of the colon Adenocarcinoma of the colon may have a variety of appearances on endoscopy. Panel A: a typical exophytic mass; Panel B: a friable polypoid mass; Panel C: circumferential adenocarcinoma. Courtesy of James B McGee, MD.

Treatment :

- **Goals of therapy :**
  - Induce and maintain remission.
  - Ameliorate symptoms.
  - Improve pts quality of life.
  - Adequate nutrition.
  - Prevent complication of both the disease and medications.
- **5-Aminosalicylic Acids :**
  - The mainstay treatment of mild to moderately active UC and CD (induction).
  - 5-ASA may act by :
    - blocking the production of prostaglandins and leukotrienes,
    - inhibiting bacterial peptide–induced neutrophil chemotaxis and adenosine-induced secretion,
    - scavenging reactive oxygen metabolites.
  - For patients with distal colonic disease, a suppository or enema form will be most appropriate.
  - Maintenance treatment with a 5-aminosalicylic acid can be effective for sustaining remission in ulcerative colitis but is of questionable value in Crohn's disease.

Side Effects of Sulfasalazine and Aminosalicylates

	Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Sulfasalazine	Nausea/headache Fever/rash Male infertility	Pancreatitis	Hepatitis Pneumonitis Neutropenia Hemolysis Agranulocytosis Otalgia
Aminosalicylates	Watery diarrhea (olsalazine) Fever/rash	Pancreatitis Colitis exacerbation	Pneumonitis Pericarditis Nephritis Thrombocytopenia

- **Corticosteroids** :
  - Topical corticosteroids can be used as an alternative to 5-ASA in ulcerative proctitis or distal UC.
  - Oral prednisone or prednisolone is used for moderately severe UC or CD, in doses ranging up to 60mg/day.
  - IV is warranted for patients who are sufficiently ill to require hospitalization; the majority will have a response within 7 to 10 days.
  - No proven maintenance benefit in the treatment of either UC or CD.
  - Many and serious side effects.
  - **Budesonide :**
    - less side effects,
    - its use is limited to patients with distal ileal and right-sided colonic disease**.**

Major Side Effects Associated with Corticosteroid Therapy

Dermatologic and soft tissue
- Skin thinning and purpura
- Cushingoid appearance
- Alopecia
- Acne
- Hirsutism
- Striae
- Hypertrichosis

Eye
- Posterior subcapsular cataract
- Elevated intraocular pressure/glaucoma
- Exophthalmos

Cardiovascular
- Hypertension
- Perturbations of serum lipoproteins
- Premature atherosclerotic disease
- Arrhythmias with pulse infusions

Gastrointestinal
- Gastritis
- Peptic ulcer disease
- Pancreatitis
- Steatohepatitis
- Visceral perforation

Renal
- Hypokalemia
- Fluid volume shifts

Genitourinary and reproductive
- Amenorrhea/Infertility
- Intrauterine growth retardation

Bone
- Osteoporosis
- Avascular necrosis

Muscle
- Myopathy

Neuropsychiatric
- Euphoria
- Dysphoria/depression
- Insomnia/akathisia
- Psychosis
- Pseudo tumor cerebri

Endocrine
- Diabetes mellitus
- Hypothalamic-pituitary-adrenal insufficiency

Infectious disease
- Heightened risk of typical infections
- Opportunistic infections
- Herpes zoster

- **Immunosuppressive Agents :**
  - These agents are generally appropriate for patients in whom the dose of corticosteroids cannot be tapered or discontinued.
  - **Azathioprine** & **6-MP** :
    - The most extensively used immunosuppressive agents.
    - The mechanisms of action unknown but may include **suppressing the generation of a specific subgroup of T cells.**
    - The onset of benefit takes several weeks up to six months.
    - Dose-related BM suppression is uniformly observed.
  - **Methotrexate** :
    - Effective in steroid-dependent active CD and in maintaining remission.
  - **Cyclosporine** :
    - Severe UC not responding to IV steroid &need urgent proctocolectomy.
    - 50% of the responders will need surgery within a year.

- **Anti-TNF Therapy – Infliximab :**
  - It is a chimeric monoclonal antibody, binds soluble TNF.
  - Prompt onset, effects takes 6weeks to max of 6m.
  - Indicated in fisulizing crohns, refractory CD and refractory UC.
  - Complications (it is safe and usu tolerable) :
    - Acute infusion reactions, which may include chest tightness, dyspnea, rash, and hypotension.
    - Delayed hypersensitivity reactions, consisting of severe polyarthralgia, myalgia, facial edema, urticaria, or rash, are an unusual complication occurring from 3 to 12 days after an infusion.
  - **Infliximab – side effects :**
    - Increase risk of upper respiratory infections.
    - Any patient suspected of having a pyogenic complication of CD or any serious infection should undergo adequate drainage and treatment with antibiotics before starting infliximab.
    - Reactivation of tuberculosis has been observed and has resulted in disseminated disease and death.

INDICATIONS FOR SURGERY :

- **In patients with UC :**
  - Severe attacks that fail to respond to medical therapy.
  - Complications of a severe attack (e.g., perforation, acute dilatation).
  - Chronic continuous disease with an impaired quality of life.
  - Dysplasia or carcinoma.
- **In patients with CD :**
  - Obstruction, severe perianal disease unresponsive to medical therapy, difficult fistulas, major bleeding, severe disability.
  - 30 % relapse rate.

IBD Sequelae :

- **UC :**
  - Risk of cancer begins after 8 years, risk of pancolitis 7% at 20 years and 17% at 30 years.
  - Increased risk: early age of onset, pancolitis.
  - Need for colonoscopic screening after 8 years.
- **CD :**
  - True incidence of cancer is uncertain, but could be as high as UC.
  - Need the same screening policy.

Conclusion :

- It is a chronic disorders.
- Need to exclude other possibilities.
- Need to differentiate between the two.
- Need long term management with primary goal to induce then maintain remission and prevent complications of both the disease and drugs.

Gastrointestinal Bleeding

Dr. Khaled Al-Sawat

Objectives :

- Recognize that GI bleeding is a medical emergency. Understand common terminology and causes of GI bleeding (hernaternesls, melena, hematochesia, variceal and nonvariceal bleeding).
- Understand the risk factors for the main types of GI bleeding.
- To know how to recognize the severity and prognosis of patients presented with GI bleeding.
- Understand a systematic clinical approach in managing patient with GI bleeding.

Categories :

- Upper GI bleeding :
  - Variceal bleeding
  - Non-variceal bleeding.
- Suspensory muscle of the duodenum (Ligament of Teritz).
- Lower GI bleeding.
- Bleeding can occur from any site in the GI tract.

Mild <==> severe +/- shock
Medical emergency
Reflection of bleeding: • **Site.** • **Etiology.** • **Rate.**

Clinical Presentation :

- Hematemesis.
- Melena.
- Hematochezia.
- Occult bleeding.

◈ Hematemesis :

- Bloody vomitus (bright red or coffee-grounds).
- Always means an upper source
- Coffee ground because the exposure of blood to gastric acid and oxidation of Fe

◈ Melena :

- Black, larry, foul-smelling stool.
- Usually means upper GI bleeding (sometime from slow proximal colonic bleeding or lesion in the small intestine).
- Blood hours in the gut.
- Degradation into haematin and other hemochromes by colonic bacteria.
- Note : History of Fe therapy and bismuth may be confused with melena.

◈ Hematochezia :

- Passage of bright blood through the rectum.
- Means :
  - lower GI source
  - brisk upper GI source (10 % of the cases)
- NG tube may help (with a 16% false negative rate) in cases where the bleeding may be duodenal.
- Other possible clues are hyperactive bowel sounds and an elevated BUN (Blood Urea Nitrogen) from digested hemoglobin.

◈ Fecal occult blood :

- Positive fecal occult blood test with or without iron deficiency anemia in absence of visible bleeding to patient and the physician.
- Result from small amount of bleeding at any site in the gut.

◈ Epidemiology :

- Annual incidence of hospitalization: 1 00i1 00,000 persons The incidence is double in males than females.
- The incidence increases with age.
- Upper GI Bleeding 5 times more common than Lower GIB.

- Overall mortality is about 10% but mortality in low risk groups like under 60 with no co morbidities may be as low as 0.6%.
- Continued or recurrent bleeding - mortality 30-40%.

Causes of Upper Gastrointestinal Bleeding :

- Peptic ulcer disease :
  - Duodenal ulcer.
  - Gastric ulcer.
- Mallory-Weiss tear.
- Portal hypertension :
  - Esophagogastric varices.
  - Gastropathy.
- Esophagitis.
- Neoplasm :
  - Gastric cancer.
  - Gastric lymphoma.
  - Kaposi's sarcoma.
- Dieulafoy's lesion.
- Vascular anomalies.
- Hemobilia.
- Hemorrhagic gastropathy.
- Aortoenteric fistula.

Diagnosis	% of total
Peptic ulcer	**55**
Varices	14
Angioma	6
Mallory-Weiss tear	5
Erosions	4
Tumor	4

Causes of lower GI bleeding :

- Diverticulosis.
- Colitis :
  - IBD (UC » CD).
  - Ischemia.
  - Infection.
- Vascular anomalies (Telangectasia).
- Neoplasia.
- Anorectal :
  - Hemorrhoids.
  - Fissure.
- Dieulafoy's lesion.
- Varices :
  - Small bowel.
  - Rectal.
- Aortoenteric fistula.
- Kaposi's sarcoma.
- UPPER GI CAUSE.

Approach to pt with GI bleeding

Resuscitation & stabilization Assess hemodynamic status

- ✶ Obtain important laboratory tests, including cross match blood
- ✶ Restoration of intravascular volume
- ✶ Correct coagulopathy
- ✶ Protect airway

◈ Assess hemodynamic status

- The best tool for assessment of severity ➔hemodynamic status (Heart rate and blood pressure)
- If baseline blood pressure (BP) and pulse within normal limits ➔ check for **orthostatic hemodynamic changes** postural tachycardia (rise in pulse rate >>15 beats/minute. Postural hypotension (drop in systolic BP >10 mm Hg) on sitting or standing from supine position
- Orthostatic changes; loss of 10-20% of circulatory volume.
- The hemoglobin may not fall immediately, even with massive bleeding

Important investigations

- Complete blood count (CBC)
- Coagulation profile; PT, INF, PTT
- Kidney and liver function tests
- Blood group and cross match blood. Packed PBCs 4-6 units (depends on the severity of bleeding and result of hemoglobin)

◈ Restoration of intravascular volume

- IV access: 2 large-bore intravenous-access catheters (e.g.; 16-18 gauges) or central venous line (urgent)
- Fluids: fluid resuscitation with saline or ringer lactate solution (depends on the hemodynamic status) be careful in elderly and patients with congestive heart failure)
- Blood transfusion: in patient with severe bleeding or low hematocrit

◈ Blood transfusion

- Target hematocrit varies
- In elderly or patient with IHD : ~30%
- Young can tolerate 20-25% (if no ongoing bleeding)
- Better not to exceed 27% in cases of portal hypertension
- **Correction of coagulopathy (fresh frozen plasma and platelets transfusion)**
- Patient with abnormal coagulation or
- Those who require transfusion of more than 10 units of packed RBCs.

◈ Target of resuscitation

- ✶ Fall in pulse rate (improvement in tachycardia)
- ✶ Rising BP or CVP (5-10 cm H20)
- ✶ Adequate urine output (30 ml/h)

◈ Constant monitoring or frequent assessment of vital signs is essential

- Adequate resuscitation is essential prior to endoscopy.
- The vigor of resuscitation is proportional to the severity of bleeding
- Monitor v/s, ECG, O2, urine output
- O2 & intubation (in some pt,)
- ICU
- Transfusion
- Protection of the airway by elective intubation:
  - ✓ Severe uncontrolled Variceal bleeding
  - ✓ Change in level of consciousness severe encephalopathy
  - ✓ Inability to maintain oxygen saturation above 90%
  - ✓ Aspiration pneumonia

◈ After resuscitation

1) Detailed history
2) Physical Examination
3) Check results of laboratory tests
4) Consult gastroenterologist
5) Start specific medication according to the case
6) Endoscopy

⊙ History

- Age
- Nature of bleeding
- Associated symp. (abd.pain, change in bowel habit. Wt loss. Fatigue, dizziness)
- Past GI history (GI bleeding, GI and liver diseases, abdominal surgery)
- Medications (e.g. aspirin, NSAIDS)
- Other co-morbidities

⊙ Examination

- Pallor
- V/S: orthostatic hypotension and tachycardia
- Ext: cold clammy, thready pulse (if severe)
- Stigmata of CLD
- Pigmented lesions
- Vascular skin lesions
- Lymphadenopatyhy
- Full abdominal examination (tenderness, organomegaly)
- Rectal exam and color of stool

⊙ Laboratory evaluation

- Hematocrit
- Several hours to fall
- Normal or slightly depressed should not underestimate the severity of bleeding
- MCV normal in acute, low indicate iron deficiency and possibly chronic bleeding
- Coagulation profile
- BUN: may increase in upper GI bleeding (breakdown of blood protein by intestinal bacteria and mild reduction in GFR)

❖ Poor prognostic variables

- Old age
- morbid conditions (liver, cardiac, renal)
- Shock or hypotension on presentation
- Red blood in the emesis or stool
- Requiring multiple units of blood transfusion
- Active bleeding at the time of endoscopy
- Variceal (versus no variceal)
- Bleeding from a visible or spurting vessels
- Bleeding from a large ulcer (>2cm)

❖ Diagnosis of GI bleeding

1. Endoscopy (upper GI endoscopy, colonoscopy, etc)
2. Angiography
3. RBC scan
4. Capsule endoscopy
5. Barium studies
6. Surgery

⊙ Treatment of GI bleeding

- NB: remember **after adequate resuscitation and stabilization:**
- Goal to stop bleeding and prevent rebleeding:
- Pharmacologic
- Endoscopic (most important next step)
- Angiographic
- Surgical

■ Pharmacologic

- IV acid suppression therapy: proton pump inhibitors (e.g. omeprazole, pentazole, etc)
- H2 blockers are less potent
- For suspected varices (e.g. known patient with cirrhosis) start octerotide or terlipressin
- For lower GI bleeding: no specific pharmacologic therapy unless upper GI cause is suspected

■ Endoscopic therapy

- **Thermal:**
  - ✓ Bipolar probe
  - ✓ Monopolar probe
  - ✓ Argon plasma coagulator
  - ✓ Heart probe
- **Mechanical**
  - ✓ Hemoclips
  - ✓ Band ligation
- **Injection**
  - ✓ Epinephrine
  - ✓ Alcohol
  - ✓ Ethanolamine
  - ✓ polidocal

- **Timing of endoscopy**

  Endoscopy for GI bleeding:
  - A semi elective procedure (minor bleeding)
  - Urgently (major bleeding)

- Angiographic therapy
  - Rarely required
  - Those with severe persistent bleeding when endoscopic therapy is unsuccessful or unavailable and surgery is too risky

✪ Surgery

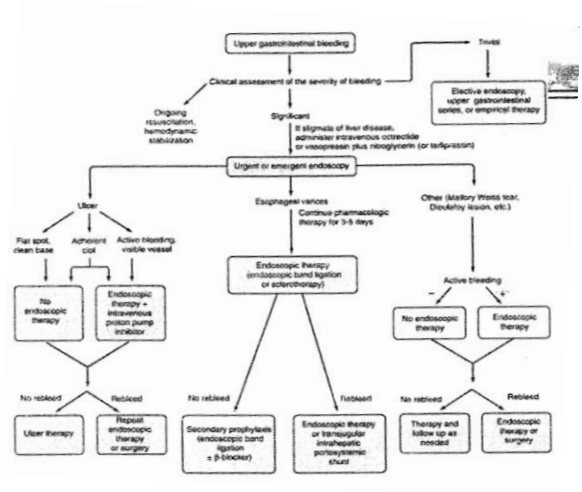
- ✓ Need for surgery is steadily declining. Probably as a result of the widespread use of acid-decreasing agents
- ✓ For patient with bleeding difficult to control by endoscopy or recurrent bleeding

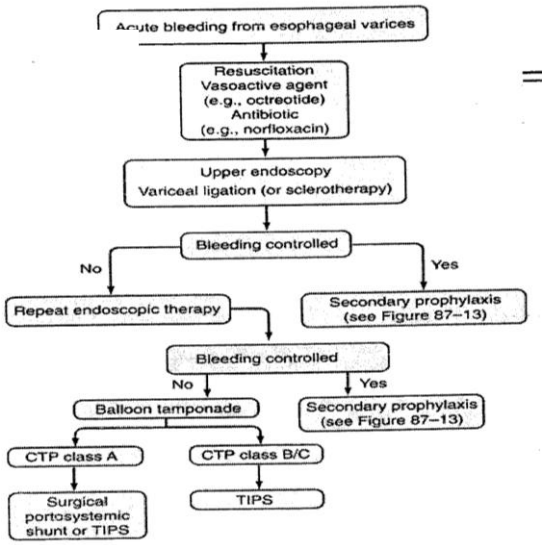
◈ Long term management of GI bleeding

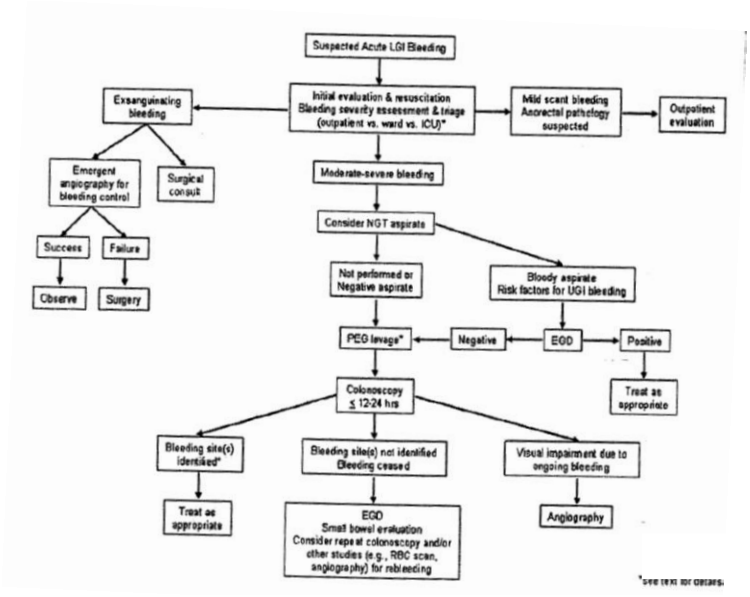
- Treat the underlying cause
- Avoid risk factors (e.g. NSAIDs) or use with prophylaxis (proton pump inhibitor)
- Treat H. pylori
- For varices: repeat endoscopy for eradication, use B blockers, TIPS and transplant in some patients
- For lower GI bleeding: treat the underlying cause

◈ Important to remember

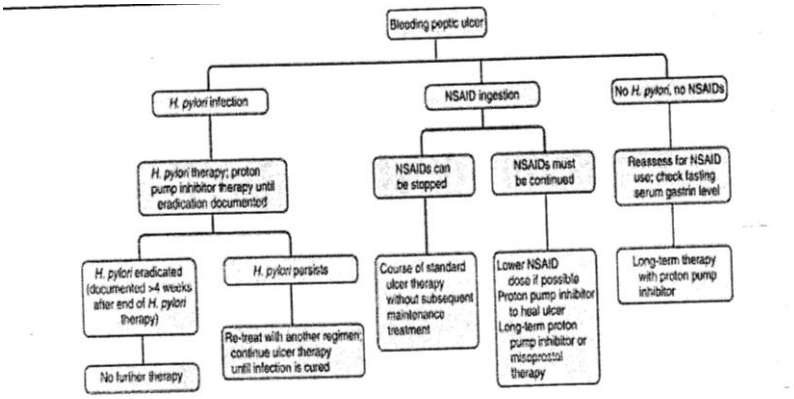
- Definitions
- Causes
- Approach: stabilization & resuscitation
- History
- Examination
- Important lab
- Treatment (pharmacologic, endoscopic, angiographic, surgical)







Long-term management of GI bleeding due to PUD



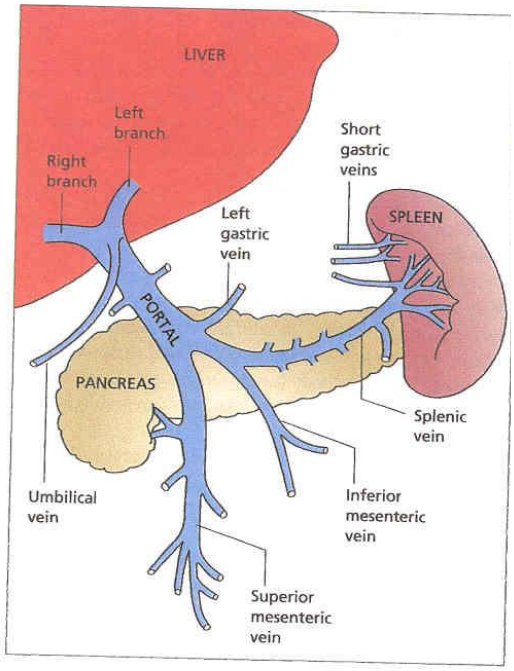
Complications of Liver Cirrhosis

Dr. Ayman Abdo

Objectives :

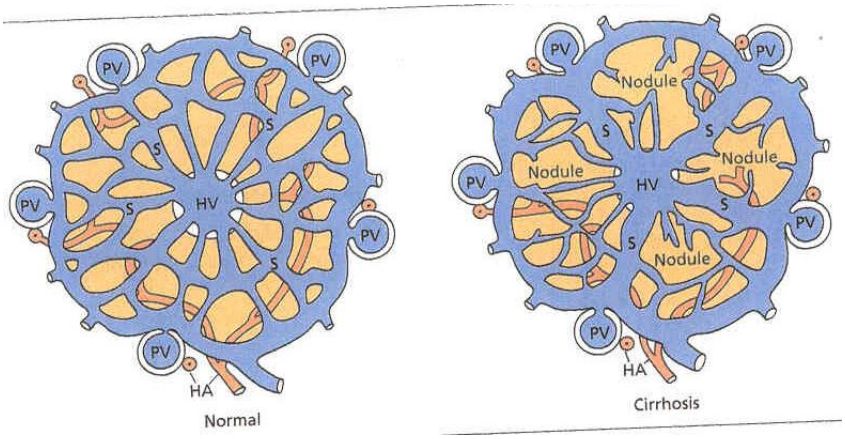
1. Understand the basic mechanisms of portal hypertension.
2. Recognized the classic presentations of portal hypertension complications.
3. Get an idea on the management of these complications.

- **What is Liver Cirrhosis ?**
  - Diffuse fibrosis of the liver with nodule formation.
  - Abnormal response of the liver to any chronic injury.
- **Causes of Cirrhosis :**
  1. Chronic viral hepatitis.
  2. Metabolic: hemochromatosis, Wilson dis, alfa-1-antitrypsin, NASH.
  3. Prolonged cholestasis (primary biliary cirrhosis, primary sclerosing cholangitis).
  4. Autoimmune diseases (autoimmune hepatitis).
  5. Drugs and toxins.
  6. Alcohol.



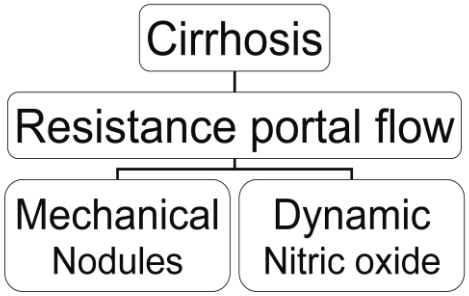
Anatomy of the portal venous system

◈ The Effect of the Liver Nodule in Cirrhosis:



- *Portal HTN is the end result of cirrhosis.*

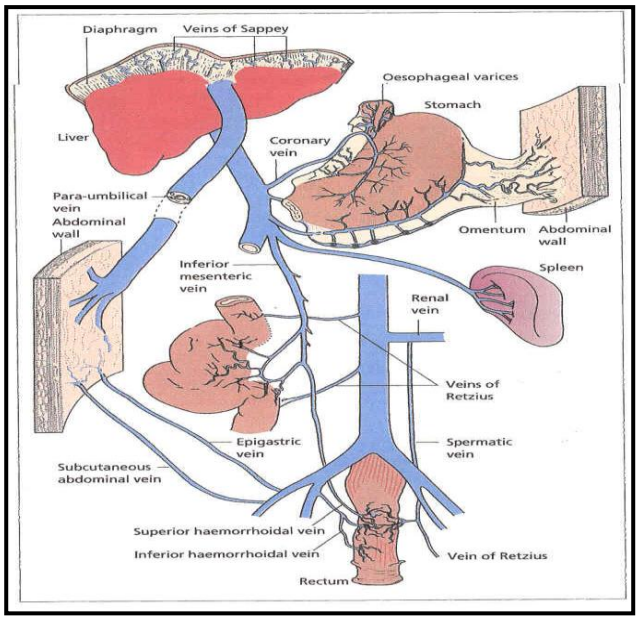
◈ Mechanism of Portal HTN :



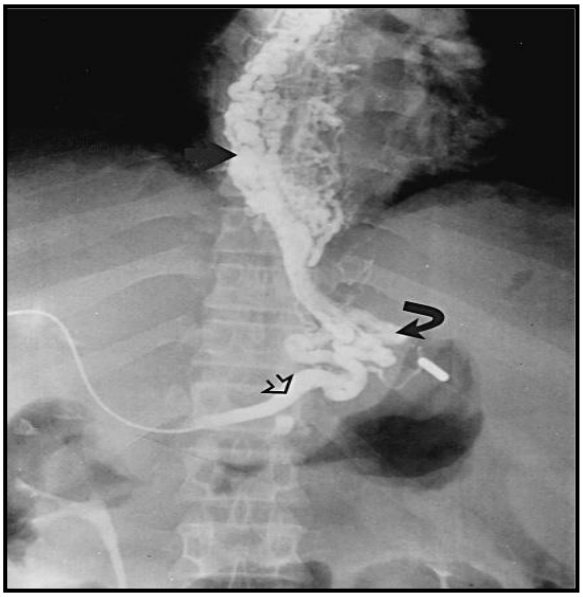
- *Any management of the liver cirrhosis complications starts with treating the underlying cause & ends with liver transplantation.*

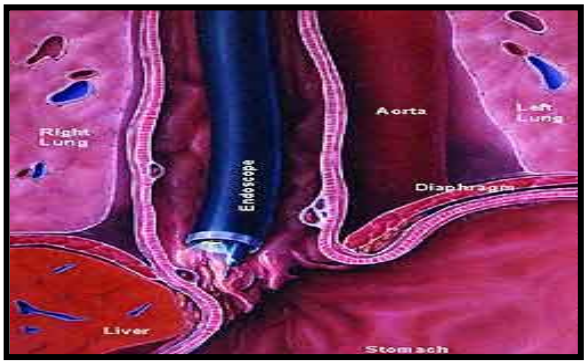
Complications of Portal Hypertension

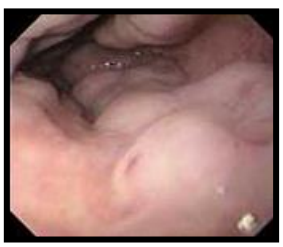
1) Varices :

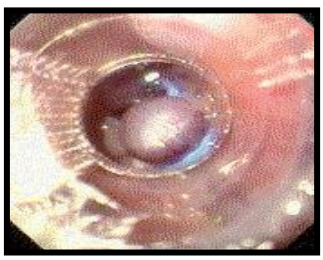


- **Collaterals:**
  - Esophagus.
  - Gastric.
  - Colo-rectal.
  - Portal hypertensive gastropathy.
- **Diagnosis :**
  - *(Usually asymptomatic unless it ruptures).*
  - History : Hematemases, melena.
  - Physical examination.
  - Ultrasound abdomen.
  - Endoscopy.
- **Management-General (*MCQ*) :**
  - ABC.
  - 2 IV Lines.
  - Type and cross match.
  - **Resuscitation:**
    - IVF (*IV fluid is the quickest management in the resuscitation of varices*).
    - Blood.
  - Platelet transfusion (platelet <75,000).
  - Fresh frozen plasma (Correct Pt).
- **Management-Specific (*MCQ*) :**
  - IV vasoconstrictors (Octreotide).
  - **Endoscopic therapy :**
    - Banding.
    - Sclerotherapy .
  - **Shunting :**
    - Surgical.
    - TIPS.
- **Prevention :**
  - Treat underlying disease.
  - Endoscopic banding protocol.
  - B-blockers.
  - Liver transplantation.









Variceal Banding

◈ Types of Shunts:

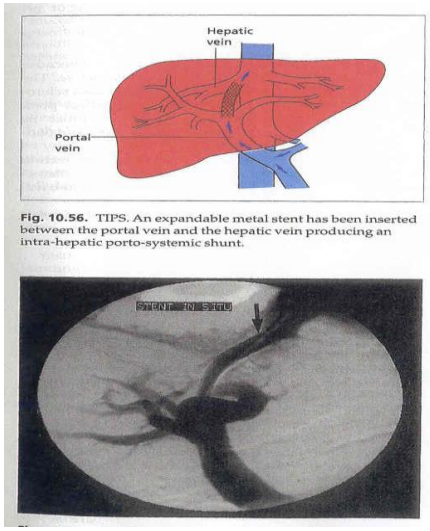
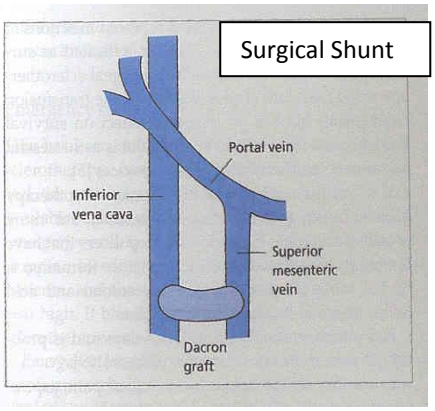


Fig. 10.56. TIPS. An expandable metal stent has been inserted between the portal vein and the hepatic vein producing an intra-hepatic porto-systemic shunt.

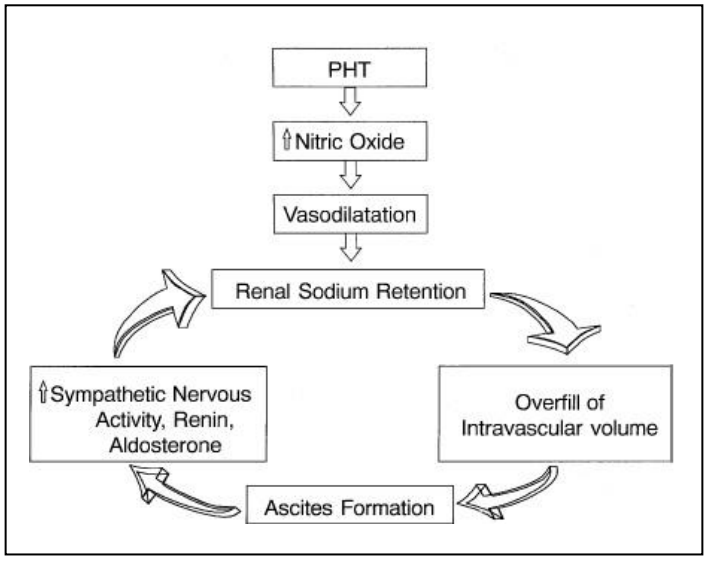


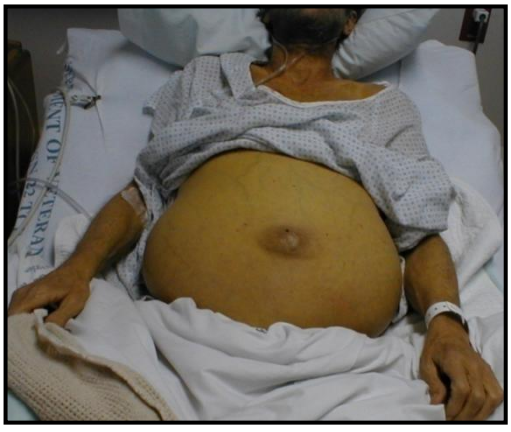
TIPS (Transjugular intrahepatic portosystemic shunt)

TIPS is done between a branch of portal vein & a branch of systemic veins

2) Ascites :

- **Definition:** fluid in the peritonial cavity.
- **Mechanism of Ascites :**





- **Causes of Ascites :**
  1. Liver disease: cirrhosis.
  2. Right sided heart failure.
  3. Kidney disease (nephrotic syndrome).
  4. Low albumin (malnutrition, bowel loss).
  5. Peritonial infection (TB…)
  6. Peritonial cancer.
- **Presentation :**
  - **History :**
    1. Increased abdominal girth.
    2. Increased wt.
  - **Physical exam :**
    1. Bulging flanks. 2.Shifting dullness. 3. Fluid wave.

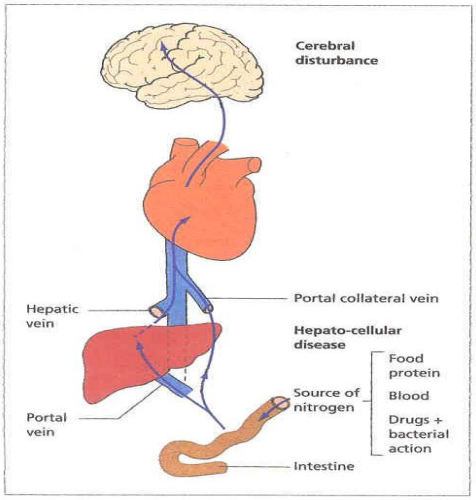
- **Diagnosis (*MCQ*) :**
  - Physical examination.
  - Ultrasound.
  - **Ascitic tap**
    - WBC (>250 PMN: SBP). (PMN = Polymorphonuclear Cells)
    - RBC.
    - **SAAG (serum albumin to ascitic fluid albumin gradient) [*MCQ*]**
      - **>11 mg/dl : portal hypertension.**
      - <11 mg/dl : Other.
- **Treatment-General :**
  - Treat the underlying disease.
  - Salt restriction (<2gm/d).
  - **Diuretics**
    - Loop diuretic (Lasix).
    - Aldosterone inhibitor (Spironolactone).
- **Treatment-Resistant :**
  - Recurrent tapping.
  - Peritoneal-venous shunt.
  - TIPS.
  - Liver transplantation.
- **Spontaneous Bacterial Peritonitis *(MCQ)*:**
  - Infection of ascitic fluid.
  - Usually gram negative (E.Coli).
  - Presentation variable.
  - Mortality is high.
  - **Dx : ascitic tap = PMN>250 *(MCQ)*.**
  - **Treatment :** third generation cephalosporin IV.

Classification of Ascites by the Serum Albumin-Ascites Gradient

High albumin gradient (SAAG ≥1.1 g/dL)	Low albumin gradient (SAAG <1.1 g/dL)
Cirrhosis	Peritoneal carcinomatosis
Alcoholic hepatitis	Peritoneal tuberculosis
Congestive heart failure	Pancreatitis
Massive hepatic metastases	Serositis
	Nephrotic syndrome
Portal hypertension or heart failure	**Peritonial disease or kidney disease**

3) Hepatic Encephalopathy :

- Reversible decrease in neurological function secondary to liver disease.
  - **Acute :** seen with acute liver failure.
  - **Acute on chronic :** established cirrhosis.
- **Mechanism :**



- *Mechanism of hepatic encephalopathy:* *portal collateral vein contains nitrogenous waste products (toxic materials) which bypass the liver, reaching the brain & causing cerebral disturbance.*

- **Clinical features :**
  - Reversal of sleep pattern.
  - Disturbed consciousness.
  - Personality changes.
  - Intellectual deterioration.
  - Fetor hepaticus.
  - Astrexis.
  - Fluctuating.
  - Flapping Tremor.
  - Drawing Tests.

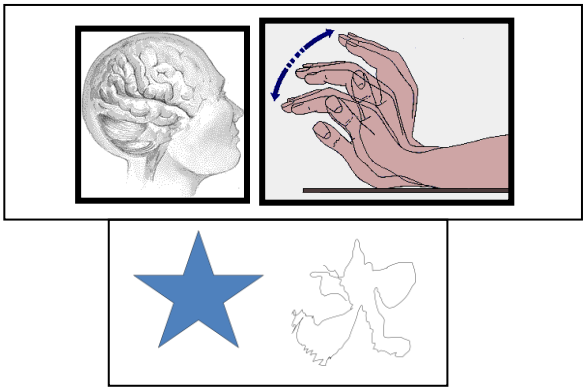
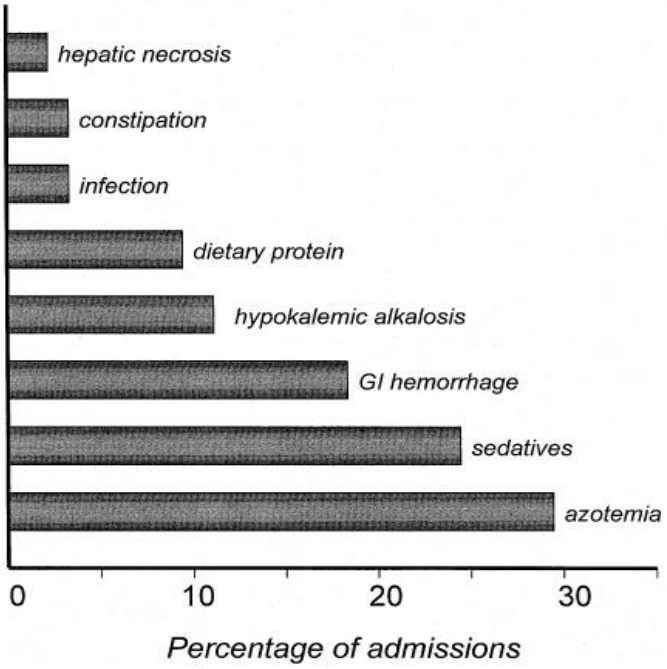


Table 79–1 | **Clinical Stages of Hepatic Encephalopathy**

CLINICAL STAGE	INTELLECTUAL FUNCTION	NEUROMUSCULAR FUNCTION
Subclinical	Normal examination, but work or driving may be impaired	Subtle changes on psychometric or number connection tests
Stage 1	Impaired attention, irritability, depression, or personality change	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory and computation, sleep disorders	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion and disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, and muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing; oculocephalic reflex; absence of response to stimuli in advanced stages

- **Exacerbating factors *(MCQ)* :**



- **Treatment :**
  - Identify and treat precipitation factor.
  - Treat underlying liver disease.
  - Normal protein diet (*not low)*.
  - Antibiotics (Neomycin, metronidazole).
  - Lactolose.
  - Transplantation.

4) Hepatocellular Carcinoma :

- One of the most common cancers in Saudi Men.
- It develops in patients with cirrhosis usually.
- Detected by ultrasound and diagnosed by CT pr MRI.
- Poor prognosis.
- Multiple treatment modalities.

SUMMARY :

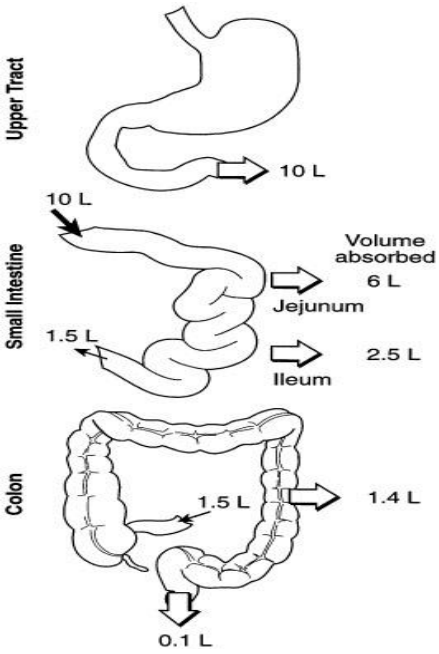
1. Mechanical compression of blood flow plus hemodynamic changes leads to portal hypertension
2. Common complications of portal hypertension are :
   - **Collateral formation (Varices).**
   - **Ascites.**
   - **Hepatic encephalopathy.**
3. The most important step in variceal bleed management is **resuscitation**.
4. The most important step in management of hepatic encephalopathy is the identification of the precipitating factor.

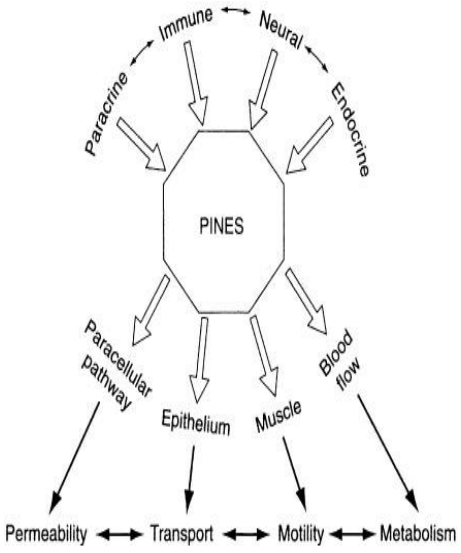
Chronic Diarrhea

Prof. Saleh Al-Amri

- **Chronic diarrhea**, defined as the production of loose stools with or without increased stool frequency for more than 4 weeks.

Mechanism of Diarrhea :





- Normal ,small and large intestine absorb 90% of both oral intake and endogenous secretions.
- 2 mechanism of diarrhea :
  - **A.** Osmotic diarrhea.
  - **B.** Secretory diarrhea.

Osmotic diarrhea :

- Due to ingestion of poorly absorbed substance e.g. sugar.
- High osmotic gap >125.
- Improve with fasting.
- Lactose deficiency, magnisum ingestion.

Secretory diarrhea :

- Due to increase in exogenous or endogenous secretagogues or loss of surface area of the intestine which lead to inhibition of absorption and stimulate the secretion.
- Fecal osmotic gap <125.
- Not improved with fasting.

Table 9–1 | **Mechanisms of Diarrhea**

MECHANISM	CAUSES	EXAMPLES
Secretory diarrhea	Exogenous secretagogues	Enterotoxins (e.g., cholera)
	Endogenous secretagogues	Neuroendocrine tumors (e.g., carcinoid syndrome)
	Absence of ion transporter	Congenital chloridorrhea
	Loss of surface area	Intestinal resection, diffuse mucosal disease
	Ischemia	Mesenteric atherosclerosis
	Rapid transit	Intestinal hurry due to vagotomy
Osmotic diarrhea	Ingestion of poorly absorbed agent	Magnesium ingestion
	Loss of nutrient transporter	Lactase deficiency

- Other mechanism of diarrhea is mixed of both.

- Dysmotility like in ,IBS,DM scleroderma.

Clue for diagnosis :

- Acute versus chronic.
- Small bowel versus large bowel.
- Osmotic versus secretary.
- Inflammatory versus fatty versus secretory.

Table 9–3 | **Differential Diagnosis of Diarrhea by Duration and Stool Characteristics**

Acute Diarrhea
Infection
- Bacteria
- Virus
- Protozoa
- Multicellular parasites

Food poisoning
Food allergies
Medication
Initial presentation of chronic diarrhea

Chronic Diarrhea
Watery diarrhea
- Osmotic diarrhea
  - Osmotic laxatives (e.g., Mg^{+2}, PO_4^{-3}, SO_4^{-2})
  - Carbohydrate malabsorption
- Secretory diarrhea
  - Congenital syndromes (e.g., congenital chloridorrhea)
  - Bacterial toxins
  - Ileal bile acid malabsorption
  - Inflammatory bowel disease
    - Ulcerative colitis
    - Crohn's disease
    - Microscopic colitis
      - Lymphocytic colitis
      - Collagenous colitis
    - Diverticulitis
  - Vasculitis
  - Drugs and poisons
  - Laxative abuse (stimulant laxatives)
  - Disordered motility/regulation
    - Postvagotomy diarrhea
    - Postsympathectomy diarrhea
    - Diabetic autonomic neuropathy
    - Irritable bowel syndrome
  - Endocrine diarrhea
    - Hyperthyroidism
    - Addison's disease
    - Gastrinoma
    - VIPoma
    - Somatostatinoma
    - Carcinoid syndrome
    - Medullary carcinoma of the thyroid
    - Mastocytosis
    - Pheochromocytoma
  - Other tumors
    - Colon carcinoma
    - Lymphoma
    - Villous adenoma
  - Idiopathic secretory diarrhea
    - Epidemic secretory (Brainerd) diarrhea
    - Sporadic idiopathic secretory diarrhea

Inflammatory diarrhea
- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease
  - Diverticulitis
  - Ulcerative jejunoileitis
- Infectious diseases
  - Pseudomembranous colitis
  - Invasive bacterial infections (e.g., tuberculosis, yersinosis)
  - Ulcerating viral infections (e.g., cytomegalovirus, *Herpes simplex*)
  - Invasive parasitic infections (e.g., amebiasis, strongyloides)
- Ischemic colitis
- Radiation colitis
- Neoplasia
  - Colon cancer
  - Lymphoma

Fatty diarrhea
- Malabsorption syndromes
  - Mucosal diseases (e.g., celiac sprue, Whipple's disease)
  - Short bowel syndrome
  - Small bowel bacterial overgrowth
  - Mesenteric ischemia
- Maldigestion
  - Pancreatic exocrine insufficiency
  - Inadequate luminal bile acid concentration

- A careful history can provide clues to the cause of chronic diarrhea. The following 14 points should be assessed as part of a comprehensive history in a patient with chronic diarrhea :
  1. The characteristics of the onset of diarrhea congenital, abrupt, or gradual in onset.
  2. The pattern of diarrhea should be recorded: Are loose stools continuous or intermittent.
  3. The duration of symptoms should be identified clearly.
  4. Epidemiological factors, such as travel before the onset of illness.
     - Likely cause of diarrhea in certain epidemiologic classifications :
       - Travelers : bacterial, protozoal, tropical sprue.
       - Diabetics patients.
       - AIDS patients infections, drugs.
       - Hospitalized patients : drugs, infections, ischemia , C.D toxin.
  5. Stool characteristics stools are watery, bloody, or fatty.
  6. The presence or absence of fecal incontinence should be determined.
  7. The presence or absence of abdominal pain . Pain often is present in patients with inflammatory bowel disease, irritable bowel syndrome, and mesenteric ischemia.
  8. The presence of weight loss. weight loss is more likely to be caused by nutrient malabsorption, neoplasm, or ischemia.
  9. Aggravating factors, such as diet and stress, should be recorded.
  10. Mitigating factors, such as alteration of diet and use of both prescription and over-the-counter drugs.

Table 9–5 | **Drugs and Poisons Associated with Diarrhea**

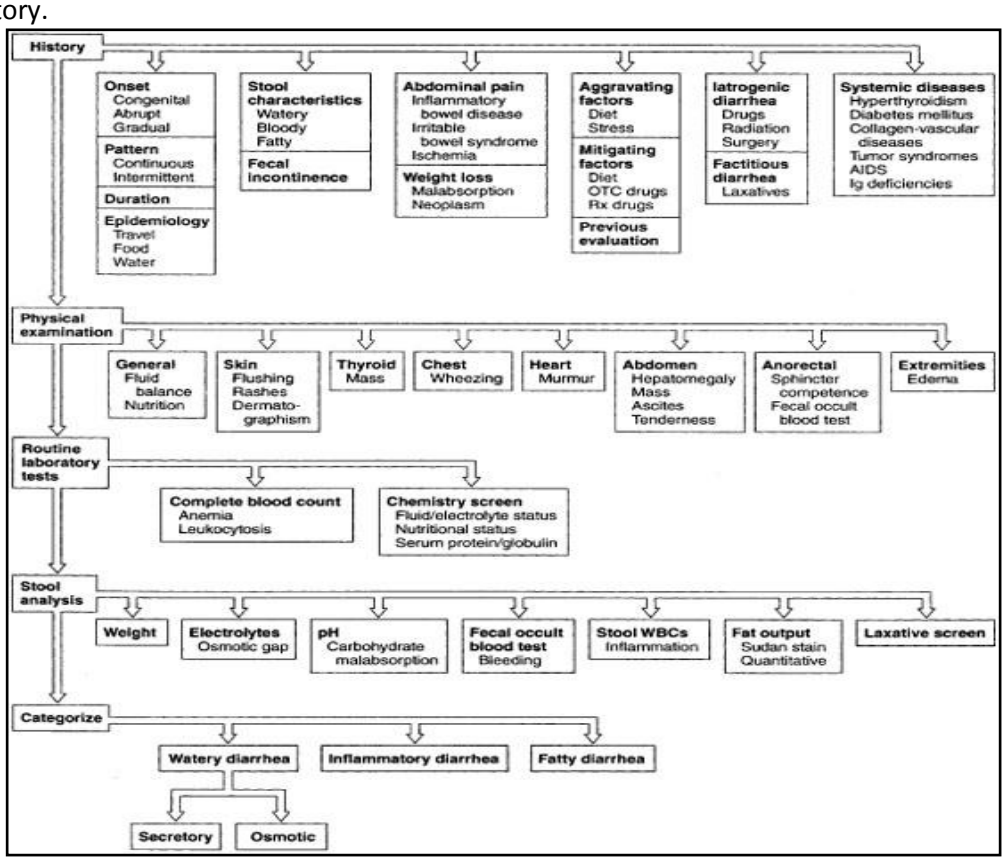
Antibiotics (most)
Antineoplastic agents (many)
Anti-inflammatory agents (e.g., NSAIDs, gold, 5-aminosalicylates)
Antiarrhythmics (e.g., quinidine)
Antihypertensives (e.g., β-adrenergic receptor blocking drugs)
Antacids (e.g., those containing magnesium)
Acid-reducing agents (e.g., H_2-receptor antagonists, proton-pump inhibitors)
Colchicine
Prostaglandin (e.g., misoprostol)
Theophylline
Vitamin and mineral supplements
Herbal products
Heavy metals

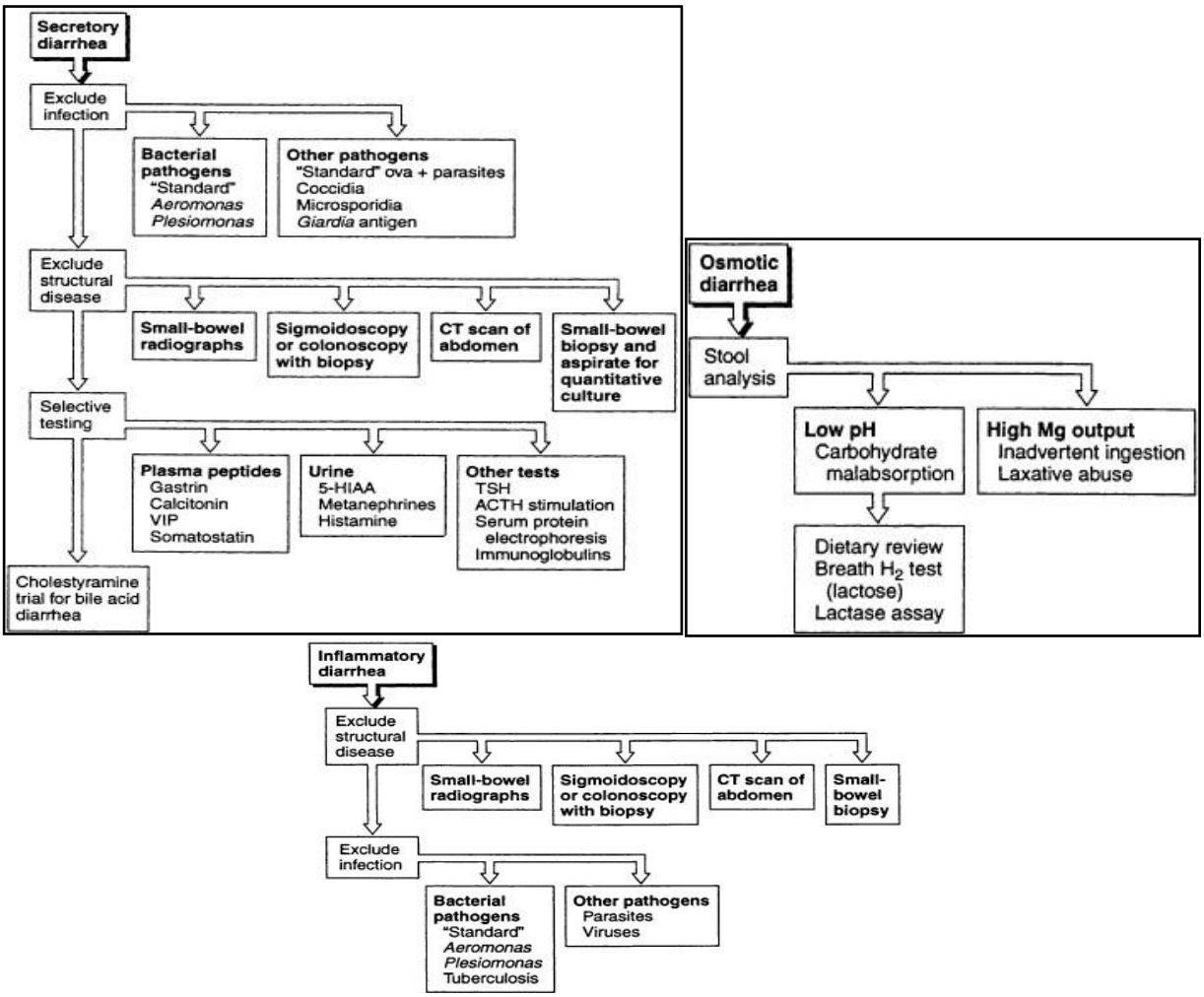
NSAIDs, nonsteroidal anti-inflammatory drugs.

11. Previous evaluations should be reviewed whenever possible.
12. Iatrogenic causes of diarrhea , detailed medication history and a history of radiation therapy or surgery.
13. Factitious diarrhea caused by surreptitious laxative ingestion
    - Markers of factitious diarrhea, such as a history of eating disorders,
    - or a history of malingering, should be sought.
14. A careful review of systems should be conducted to look for systemic diseases, such as:
    - Hyperthyroidism, diabetes mellitus, collagen-vascular diseases and other inflammatory conditions.
    - Tumor syndromes, acquired immunodeficiency syndrome, and other immune problems.

Evaluation of patient with diarrhea :

- History.
- Physical examination.
- Laboratory.
- Radiological.
- Endoscopy.





Malabsorption

Pathophysiology :

- In general, the digestion and absorption of food materials can be divided into **3 major phases :**
  - The **luminal phase** where dietary fats, proteins, and carbohydrates are hydrolyzed and solubilized by secreted digestive enzymes and bile.
  - The **mucosal phase** relies on the integrity of the brush-border membrane of intestinal epithelial cells to transport digested products from the lumen into the cells.
  - In the **postabsorptive phase**, nutrients are transported via lymphatics and portal circulation from epithelial cells to other parts of the body.

Causes :

- The best way to classify the numerous causes of malabsorption is to consider the 3 phases of digestion and absorption.
- **Luminal phase :**
  - Impaired nutrient hydrolysis :
    - The most common cause is pancreatic insufficiency due to chronic pancreatitis, pancreatic resection, pancreatic cancer, or cystic fibrosis.
  - Inactivation of pancreatic enzymes by gastric hypersecretion, as seen in Zollinger-Ellison syndrome.
  - **Impaired micelle formation :**
    - Impaired micelle formation causes lead to fat malabsorption.
    - This impairment is due to different reasons, including :
      1) Decreased bile salt synthesis from severe parenchymal liver disease (e.g. cirrhosis).

2) Impaired bile secretion from biliary obstruction or cholestatic jaundice (e.g. primary biliary cirrhosis, primary sclerosing cholangitis).
3) Impaired enterohepatic bile circulation, as seen in small bowel resection or regional enteritis
4) Bile salt deconjugation due to small bowel bacterial overgrowth.

- **Luminal availability and processing :**
  - Luminal bacterial overgrowth can cause a decrease in the availability of substrates, including carbohydrates, proteins, and vitamins.

- **Mucosal phase :**
  - Impaired brush-border hydrolase activity :
    - Disaccharidase deficiency.
    - Lactase deficiency.
    - Immunoglobulin A (IgA) deficiency.
  - **Impaired nutrient absorption :**
    - Acquired disorders are far more common and are caused by
      1) Decreased absorptive surface area, as seen in intestinal resection.
      2) Damaged absorbing surface, as seen in **celiac sprue, tropical sprue, giardiasis, Crohn disease, AIDS enteropathy, chemotherapy, or radiation therapy**.
      3) Infiltrating disease of the intestinal wall, such as lymphoma and amyloidosis.
- **Postabsorptive phase :**
  - Obstruction of the lymphatic system, both congenital (e.g. intestinal lymphangiectasia).
  - Acquired (e.g. Whipple diseases , lymphoma, tuberculosis).

Clinical presentation – History :

- Diarrhea, wt. loss, steatorrhea , flatulence and abdominal distention, edema, anemia, metabolic defects of bones.

Clinical presentation – Physical :

- **General :**
  - Patients may have orthostatic hypotension.
  - Signs of weight loss, muscle wasting, or both may be present.
  - Patients may have signs of loss of subcutaneous fat.
  - Cheilosis, glossitis, or aphthous ulcers of the mouth.
- **Abdominal examination :**
  - The abdomen may be distended, and bowel sounds may be hyperactive.
  - Ascites may be present in severe hypoproteinemia.
- **Dermatological manifestations :**
  - Pale skin.
  - Ecchymoses due to vitamin K deficiency.
  - Dermatitis herpetiformis, erythema nodosum, and pyoderma gangrenosum may be present.
  - Pellagra, alopecia, or seborrheic dermatitis.
- **Neurological examination :**
  - Motor weakness, peripheral neuropathy, or ataxia may be present.
  - The Chvostek sign or the Trousseau sign may be evident due to hypocalcemia.

Lab Studies :

- **Hematological tests :**
  - A CBC. o Serum iron, vitamin B-12, and folate. o Prothrombin time.
- **Electrolytes and chemistries :**
  - Hypokalemia, hypocalcemia, hypomagnesemia, and metabolic acidosis.

- Protein malabsorption may cause hypoproteinemia and hypoalbuminemia.
- Fat malabsorption can lead to low serum levels of triglycerides, cholesterol.
- ESR which is elevated in Crohn disease and Whipple disease.

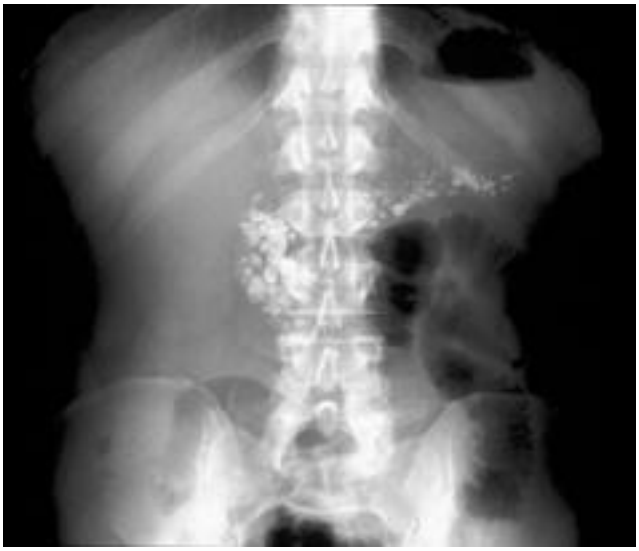
- **Stool analysis :**
  - Stool pH may be assessed. Values of <5.6 are consistent with carbohydrate malabsorption.
  - Stool C/S.
  - Pus cell in the stool e.g. IBD.
- **Tests of fat malabsorption :**
  - For a quantitative measurement of fat absorption, a 72-hour fecal fat collection.
  - Qualitative test Sudan III stain of stool,less reliable.
- **D-xylose test :**
  - If the 72-hour fecal fat collection results demonstrate fat malabsorption**,** then DO → the D-xylose test is used to document the integrity of the intestinal mucosa.
  - Proximal intestine mucosa primarily absorbs D-xylose.
  - Approximately half of the absorbed D-xylose is excreted in urine, unmetabolized.
  - If the absorption of D-xylose is impaired due to either a luminal factor (e.g. bacterial overgrowth) or a reduced or damaged mucosal surface area.
- **Schilling test :**
  - Malabsorption of vitamin B-12 may occur as a consequence of deficiency of intrinsic factor (e.g. pernicious anemia, gastric resection), pancreatic insufficiency, bacterial overgrowth, ileal resection, or disease.
  - 3 step Schilling test :
    1. Oral Vit. B12.
    2. Vit. B12 orally + intrinsic factor.
    3. Vit. B12 orally + intrinsic factor + oral antibiotics.

Bacterial overgrowth :

- Bacterial overgrowth cause an early rise in breath hydrogen.
- **JEUJENAL CULTURE.**
- 14C–xylose breath test ,high sensitivity and specificity.

Serology :

- No serologic tests are specific for malabsorption.
- Serum antigliadin and antiendomysial antibodies can be used to help diagnose celiac sprue.
- Serum IgA to rule out IgA deficiency.
- Determination of fecal elastase and chymotrypsin (2 proteases produced by the pancreas) can be used to try to distinguish between pancreatic causes and intestinal causes of malabsorption.



Imaging Studies :

- **Plain abdominal x-ray film :** Pancreatic calcifications are indicative of chronic pancreatitis.
- **Small bowel barium studies :**
  - Flocculation.
  - Small bowel dilation.
  - Diverticulosis.
  - Stricture, ulceration, and fistula formation.
- **CT scan of the abdomen :**
  - Chronic pancreatitis.
  - Enlarged lymph nodes are seen in Whipple disease and lymphoma.
  - Luminal disease.
- **Endoscopic retrograde cholangiopancreatogram (ERCP) :** pancreatitis.

- Upper endoscopy with small bowel mucosal biopsy… Examples :
    - Celiac sprue,
    - Giardiasis,
    - Crohn disease,
    - Whipple disease,
    - Amyloidosis,
    - Abetalipoproteinemia, and lymphoma.

Healthy normal villi of the small intestine (as seen under the microscope).

Damaged villi of the small intestine. Villi of a person with undiagnosed coeliac disease.

Treatment of causative diseases :

- A gluten-free diet helps treat celiac disease.
- Similarly, a lactose-free diet.
- Protease and lipase supplements are the therapy for pancreatic insufficiency.
- Antibiotics are the therapy for bacterial overgrowth.
- Corticosteroids, anti-inflammatory agents, such as mesalamine, and other therapies are used to treat CD.

Nutritional support :

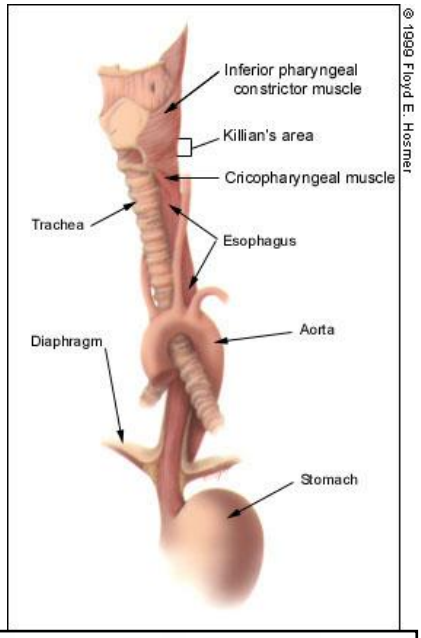
- Supplementing various minerals calcium, magnesium, iron, and vitamins.
- Caloric and protein replacement also is essential.
- Medium-chain triglycerides can be used for lymphatic obstruction.
- In severe intestinal disease, such as massive resection and extensive regional enteritis, **parenteral nutrition** may become necessary.

Approach to Dysphagia

Prof. Saleh Al-Amri

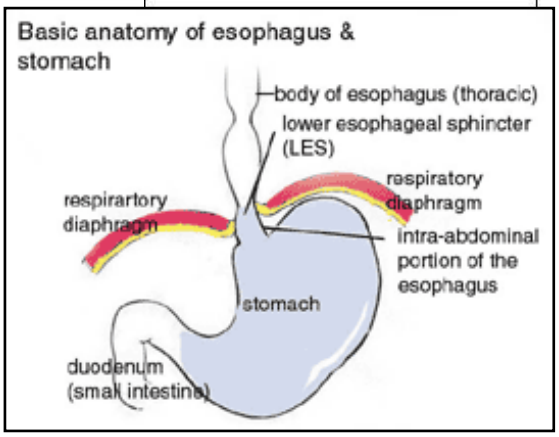
Esophageal Diseases :

- **Two function of esophageal :**
  - Transport of food by peristalsis.
  - Prevention of gastric regurgitation by LES/UES.
- **Dysphagia :**
  - Sensation of obstruction of food passage.
  - Difficulty in swallowing
  - **Dysphagia is considered an alarming symptom, requiring immediate evaluation : Classified as :**
    - Oropharyngeal.
    - Esophageal.
  - **Oropharyngeal dysphagia also called transfer dysphagia : Arises from disease of :**
    - Upper esophagus.
    - Pharynx.
    - Upper esophageal sphincter.
  - **Esophageal dysphagia arises from :**
    - **Esophageal body.**
    - **Lower esophageal sphincter.**
    - **Cardia.**



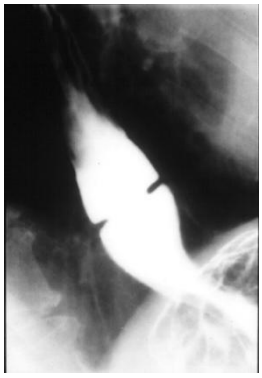
Questions to ask patients with dysphagia :

1. Do you have problems initiating a swallow or do you feel food getting stuck a few seconds after swallowing?
2. Do you cough or is food coming back through your nose after swallowing?
3. Do you have problem swallowing solids, liquids, or both?
4. How long have you had problems swallowing and have your symptoms progressed, remained stable, or are they intermittent?
5. Could you point to where you feel food is getting stuck?
6. Do you have other symptoms such as loss of appetite, weight loss, nausea, vomiting, regurgitation of food particles, heartburn, vomiting fresh or old blood, pain during swallowing, or chest pain?
7. Do you have medical problems such as diabetes mellitus, scleroderma, Sjorgen syndrome, overlap syndrome, AIDS, neuromuscular disorders (stroke, Parkinson's, myasthenia gravis, muscular dystrophy, multiple sclerosis), cancer, Chagas' disease or others?
8. Have you had surgery on your larynx, esophagus, stomach, or spine?
9. Have you received radiation therapy in the past?
10. What medications are you using now (ask specifically about potassium chloride, alendronate, ferrous sulfate, quinidine, ascorbic acid, tetracycline, aspirin and NSAIDs)? (Pill esophagitis can cause dysphagia.)



- Some patients – no cause can be.
- Identified → functional dysphagia.

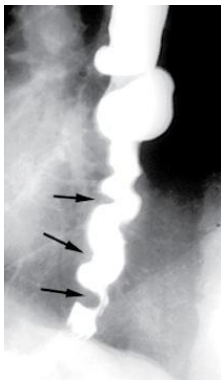
Esophageal dysphagia classify to :



A. Mechanical dysphagia : may be due to :

1. **Large food bolous.**
2. **Instrinsic narrowing :**
   - e.g. i) Esophagitis (viral/ fungal).
     ii) Stricture (benign).
     iii) Tumor.
     iv) Web/ rings.
3. **Extrinsic compression :**
   - e.g. i) Enlarge thyroid.
     ii) Diverticulum.
     iii) Left atrial enlargement.

B. Motor dysphagia : Diseases of striated or smooth. Muscles of esophagus.



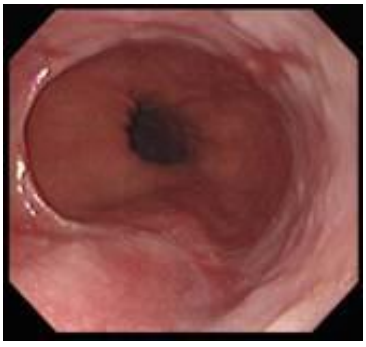
- **Striated muscle disease :**
  - Motor neron dis.
  - CVA.
  - Myasthenia gravis.
  - Polymyositis.
- **Smooth muscles disorder :**
  - Scleroderma.
  - Achalasia.
  - Esophageal spasm.

Physical examination :

- Sign of bulbar paralysis.
- Dysarthria.
- Ptosis.
- CVA.
- Goitre.
- Changes in skin – CTD.

GERD (Gastro-oesophageal reflux disease) :

- **Reflux esophagitis :** Damaged esophageal mucosa by reflux of gastric content.
- **Pathophysiology :**
  - **Antireflux mechanism includes :**
    - LES.
    - Esophageal peristalsis.
    - Resistant of esophageal mucosa.
    - Saliva.
    - Gastric peristalsis.

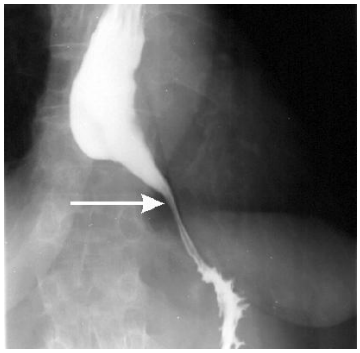


- **Major factor involved in GERD :**
  - **Loss of LES pressure :**
    - TLESR.
    - Sustained.
    - Increased Intragastric pressure.
    - Scleroderma.
    - Surgical resection.
  - **Hiatus hernia.**
  - **Aperistalsis.**
  - **Reduce saliva.**
  - **Delayed gastric emptying :** Mech. / Motor – obstruction

- **Damage depends on :**
  - Refluxed material.
  - Duration of reflux / frequency.
- **Manifestation :**
  - HB.
  - Dysphagia – complication.
  - Chest pain.
  - Regurgitation.
- **Diagnosis :**
  - Endoscopy.
  - 24 Hours pH – motility.
  - Barium swallow.
- **Complication :**
  - Bleeding.
  - Barrett's esophagus.
  - Stricture formation.
- **Treatment :**
  - Antireflux measure.
  - Acid supressing agent.
  - Surgery.

Achalasia :

- A motor disorder of esophageal smooth muscle.
- **Character by :**
  - High LES pressure, that does not relax properly.
  - Absent distal peristalsis.
- **Pathophysiology :** Loss of intramural neurons of esophageal body & LES.
- **Clinically :**
  - Dysphagia – both liquid and solid.
  - Regurgitation and pulmonary aspiration.
  - Chest pain.
- **Diagnosis :**
  - **Chest X-ray :**
    - Absent of gastric bubble.
    - Wide mediastinum.
    - Fluid level.
  - **Ba. Swallow:**
    - Esophageal dilatation.
    - Terminal part of the esophagus is beak like.



  - **Manometry :**
    - Elevated LES P with no or partial relaxation amplitude contraction, no propagating (simultaneous).
    - Terminal part of the esophagus is beak like.
- **Treatment :**
  - **A) Medical :**
    - **Nitroglucerin.**
    - **Ca – channel blocker.**
  - **B) Pneumatic dilatation.**
  - **C) Surgical.**

Infectious Esophagitis :

A) Viral esophagitis :

- Herpes simplex.
- Varicella Zoster.
- CMV.

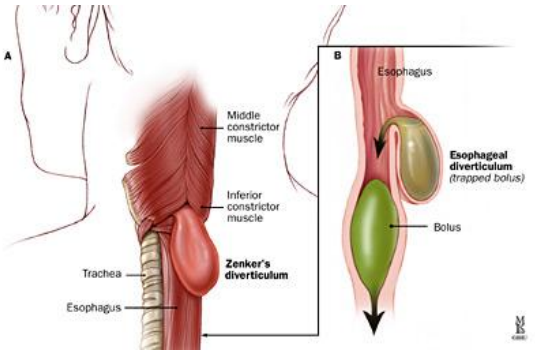
B) Bacterial.

C) Fungal.

- C/O – Dysphagia. Odynophagia. Bleeding.
- **Diagnosis :**
  - Ba. Swallow.
  - End.
  - Bx.

Diverticula :

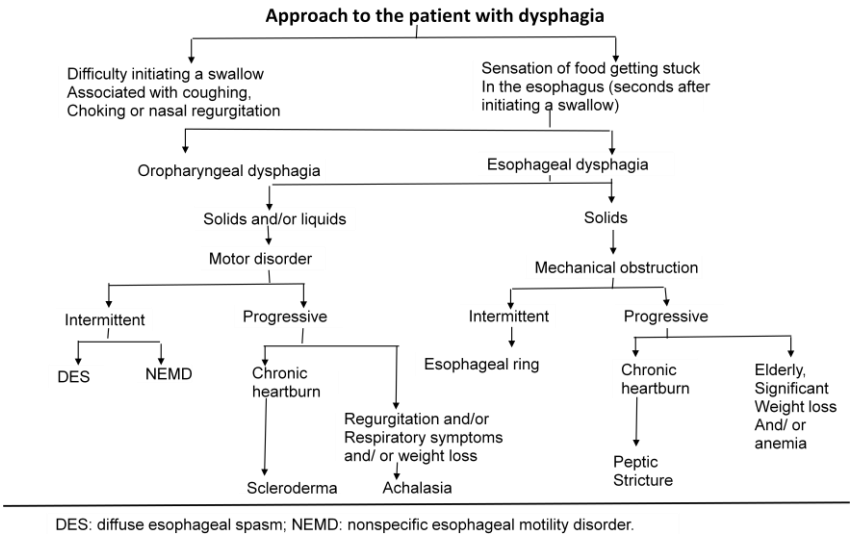
- Outpouchings of the wall of the esophagus.
  - Zenker – upper.
  - Epiphrenic – lower part.
- C/O – Asymptomatic
  Typical :
  - Regurgitation of food consumed several days ago.
  - Dysphagia.

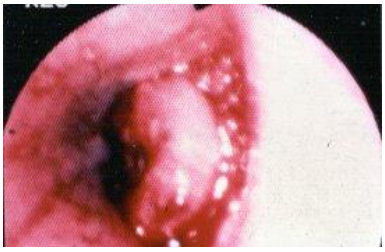


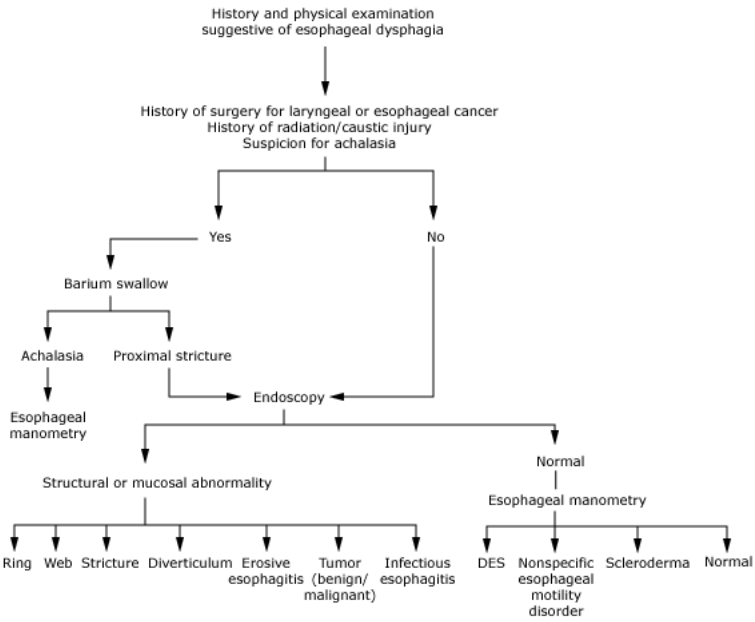
Esophageal Cancer :

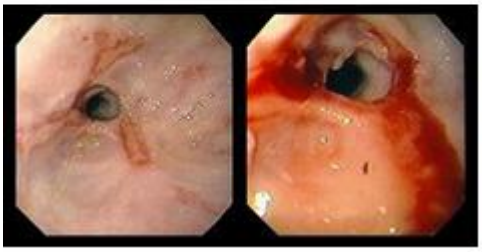
- Disease more in Males > 50 Y.
- **Causation factors :**
  - Excess alcohol.
  - Cigarette smoking.
  - Fungal toxin.
- **Mucosal damage :**
  - Hot tea.
  - Radiation induced stricture.
  - Barrett's esophagus.
  - Esophageal web.
- **Clinically :**
  - 15% in upper 1/3.
  - 45% in middle 1/3.
  - 40% in lower 1/3.
- **Pathology :**
  - Squamous cell carcinoma > 75%.
  - Adenocarcinoma.
    - Progressive dysphagia.
    - Weight loss.
    - Odynophagia.
    - Regurgitation.
    - T-E Fistula.
- **Once symptom appear incurable.**
- **Patient may have Hypercalcaemia.**
- **Diagnosis :**
  - Ba. Swallow.
  - Endoscopy & Bx.
- **Treatment :**
  - Surgical, if localized.
  - Paliative.
- Prognosis in poor, 5 Y survival ≅ 5%.

Diagnosis of dysphagia :









Rheumatoid Arthritis and Osteoarthritis

Dr. Husain Al-Arfaj

Rheumatoid arthritis is an **inflammatory disease**,
whereas **Osteoarthritis** is a **degenerative disease**.

◈ Causes of arthritis :

- SLE
- Rheumatoid arthritis
- Osteoarthritis
- Infections
  - Septic arthritis
  - Infective endocarditis

Rheumatoid Arthritis

- Systemic chronic inflammatory disease.(Thickening and hypertrophy of the synovium)
- Mainly affects synovial joints.
- Variable expression.
- Prevalence about 3%.
- Worldwide distribution.
- Female : male ratio 3 : 1.
- Peak age of onset: 25-50 years.
- Unknown etiology :
  - Genetics.
  - Environmental.
  - Possible infectious component.
- Autoimmune disorder.

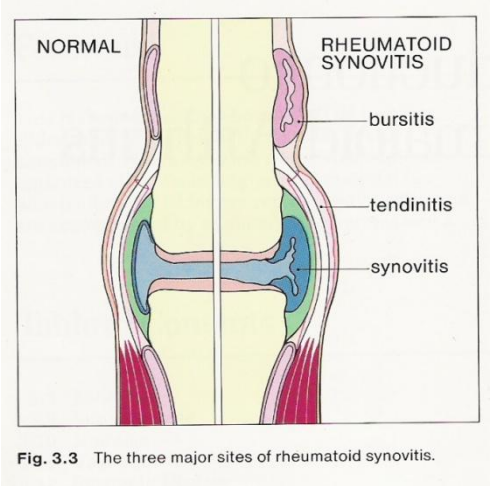


Fig. 3.3 The three major sites of rheumatoid synovitis.

◈ THE PATHOLOGY OF RA :

- Serositis :
  - Synovitis.
  - Joints.
  - Tendon sheaths.
  - Bursae.
- Nodules.
- Vasculitis.

Pannus formation:
Infiltration of the synovium to the cartilage and /or bone (invasion)

Signs and Symptoms :

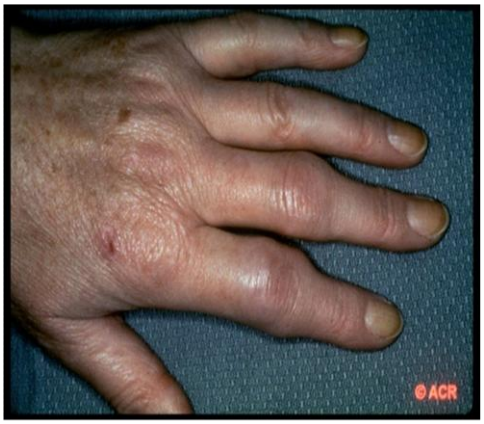
- Joint inflammation :
  - Tender, warm swollen joints.
  - Symmetrical pattern.
- Pain and stiffness.
- Symptoms in other parts of the body :
  - Nodules.
  - Anemia.
- Fatigue, occasional fever, malaise.

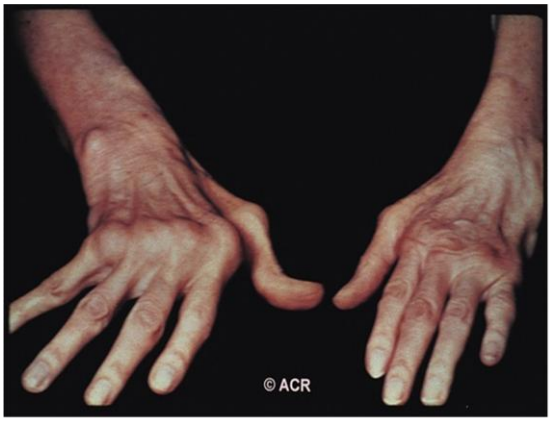
JOINT INVOLVEMENT ON PRESENTATION OF RA :			
Polyarticular 75%		**Monoarticular 25%**	
Small joints of hands and feet	60%	Knee	50%
Large joints	30%	Shoulder Wrist Hip Ankle Elbow	50%
Large and Small joints	10%		

Articular features seen in the Rheumatoid Hand :

In rheumatoid arthritis, inflammation and swelling are in proximal interphalangeal joints, whereas in seronegative spondyloarthritis, usually there is swelling of the whole finger causing “sausage” like fingers.

- **Wrist :**
  1. Synovitis.
  2. Prominent ulnar styloid.
  3. Subluxation and collapse of carpus.
  4. Radial deviation.
  5. In some cases, ankylosis of the wrist may form
- **PIPs :**
  1. Synovitis.
  2. Fixed flexion or extension deformities.
  3. (Swan neck: MCP flexed, PIP hyper extended, DIP flexed
  4. or boutonniere deformity: PIP flexed, DIP hyper extended).
  5. Spindling joints: only in the proximal
- **MCPs :**
  1. Synovitis.
  2. Ulnar deviation.
  3. Subluxation.
  4. ULNAR deviation
- **Thumbs :**
  1. Synovitis.
  2. ‘Z’ deformity.





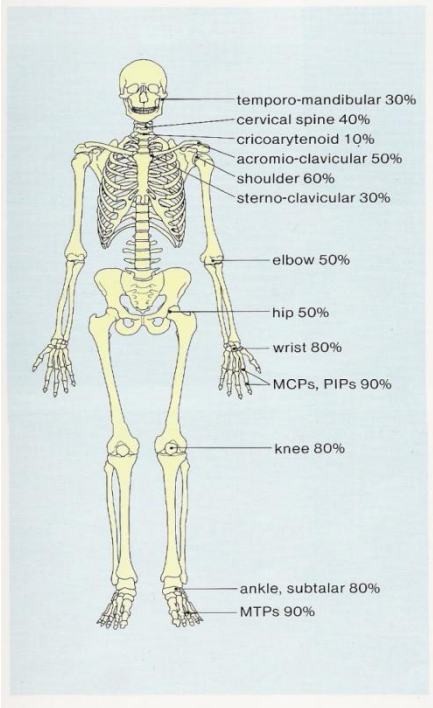
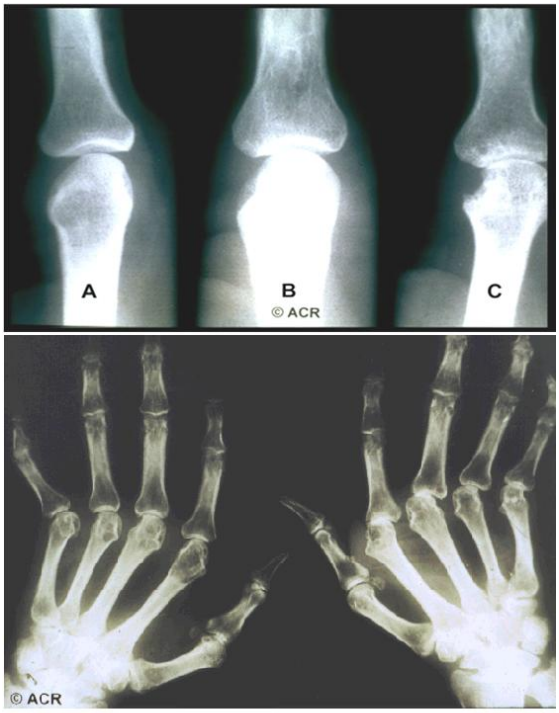


Fig. 3.6 Frequency of involvement of different joint sites in established RA.

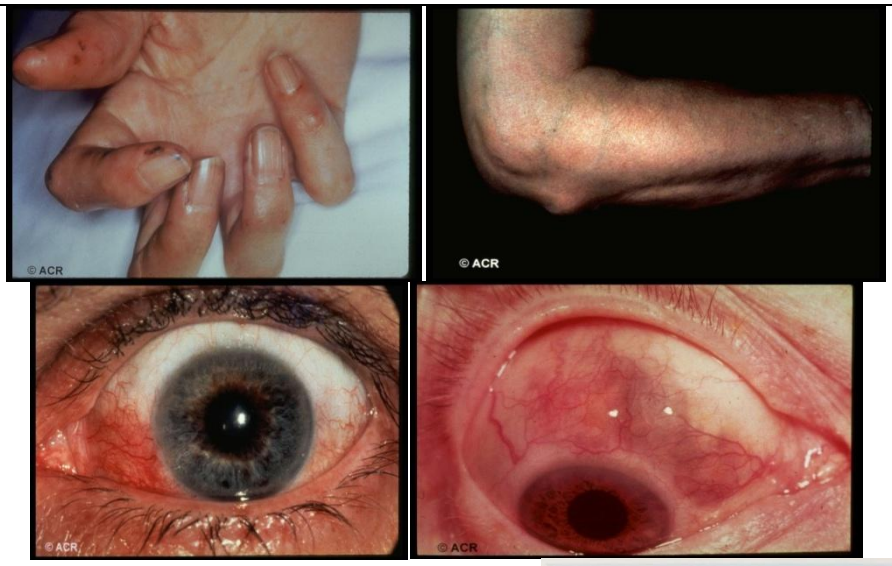


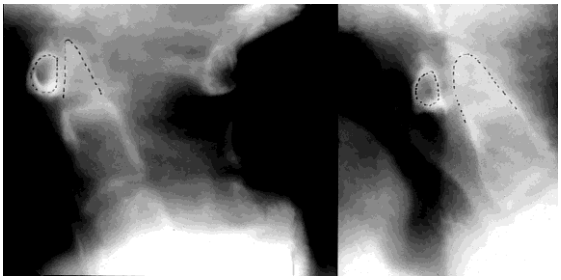
Joint Destruction

Extra-articular manifestations :

- General : fever, lymphadenopathy, weight loss, fatigue.
- Dermatologic : palmar erythema, nodules, vasculitis.
- Ocular : episcleritis/scleritis, scleromalacia perforans, choroid and retinal nodules.
- Cardiac : pericarditis, myocarditis, coronary vasculitis, nodules on valves. If the pt is on steroids, this will magnify the effect.
- Neuromuscular : entrapment neuropathy (carpal tunnel syndrome) , peripheral neuropathy, mononeuritis multiplex(Because in rheumatoid arthritis there is vasculitis, which affects vasa nervosa vessels of nerve trunks) .
- Hematologic : Felty's syndrome (RA, neutropenia and splenomegaly), large granular lymphocyte syndrome, lymphomas.
- **Cutaneous:** Subcutaneous rheumatoid nodules.
- Pulmonary : pleuritis, nodules, interstitial lung disease, bronchiolitis obliterans, arteritis, effusions.
- Others : Sjogren's syndrome, amyloidosis →may cause nephrotic syndrome. (can cause proteinuria. a point of difference between proteinuria in RA and proteinuria in SLE should be emphasized. In RA, proteinuria is due to amyloid accumulation and deposition in kidneys. In SLE, proteinuria is due to antibody complexes which damage the glomeruli)

RA doesn't directly cause nephrotic syndrome. This may happen secondary to amyloidosis.





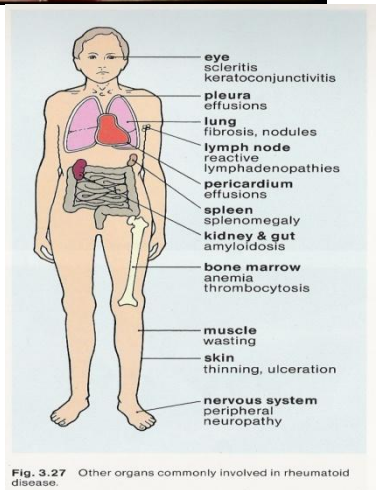


Fig. 3.27 Other organs commonly involved in rheumatoid disease.

Investigations :

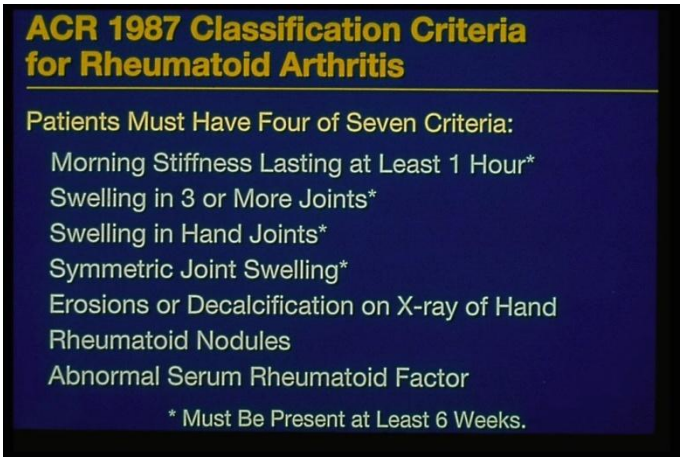
- Hematology : CBC→- Normocytic Normochromic anemia (anemia of chronic illness)
  -iron deficiency anemia may occur due to the usage of some drugs.
  -neutropenia, thrombocytosis
  ESR.
- Biochemistry : LFT→ Liver Function Test: mildly increased
  Renal profile.
- Serology : RF→ Rheumatoid Factor: immunoglobulin IgM against the patient's IgG.
  - Not specific, Not diagnostic
  - Present in 80% of patients with RA.
  - If it's - ve ➔ Not exclude RA.

If +ve, doesn`t diagnose RA. If it's –ve, doesn`t exclude RA. It only help in the diagnosis

Anti-CCP→ Anti-Citrullinated Cyclic Peptide: very specific but not very sensitive.

If its +ve it means that this is RA. It may also predict RA in people who don`t have RA

- Radiography : Joints , Spines ,Chest(to check for erosions, periarticular osteopenia).

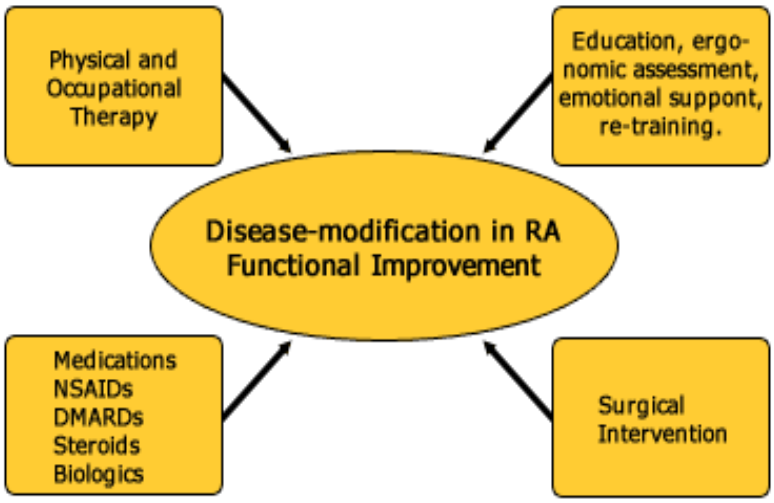


Treatment Goals :

- Relieve pain.
- Reduce inflammation.
- Prevent/slow joint damage.
- Improve functioning and quality of life.

Treatment Approaches :

- Lifestyle modifications.
- Rest with gradual physiotherapy (to prevent atrophy or stiffness).
- Physical and occupational therapy.
- Medications.
- Surgery.



Rationale for the Early Treatment of RA :

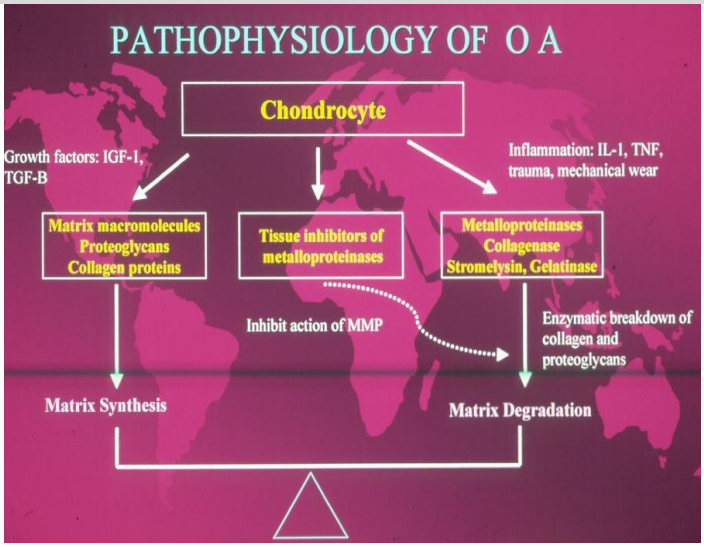
The more active the disease, the most likely to develop changes.

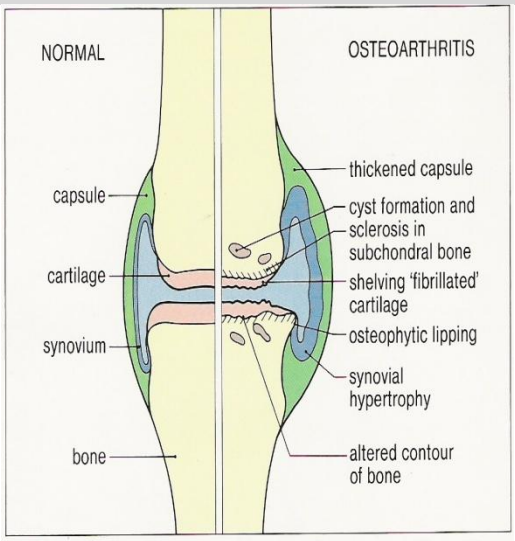
- Erosions develop early in the disease course.
- Destruction is irreversible.
- Disease activity is strongly associated with joint destruction later in the disease course.
- Early treatment can slow down radiographic progress.
- Disease activity must be suppressed maximally in its early stages to prevent destruction and preserve function.

Drug Treatments :

1) **Nonsteroidal anti-inflammatory drugs (NSAIDs).**
   - **Traditional NSAIDs :** Aspirin, Ibuprofen, Ketoprofen, Naproxen.
   - **COX-2 Inhibitors :** Celecoxib, Rofecoxib.
   - To relieve pain and inflammation.
   - Use in combination with a DMARD.
   - Gastrointestinal side effects.
2) **Disease-modifying antirheumatic drugs (DMARDs). 2nd line drugs**
   - Hydroxychloroquine, Sulfasalazine, Methotrexate, Leflunomide, Gold, Azathioprine.
   - Control symptoms.
   - No immediate analgesic effects.
   - Can delay progression of the disease (prevent/slow joint and cartilage damage and destruction).
   - Effects generally not seen until a few weeks to months.
   - **Hydroxychloroquine :**
     1. Mild non-erosive disease.
     2. Combinations.
     3. 200 mg bid.
     4. Eye exams because irritation of the retina or cornea may occur.
   - **Sulfasalazine :**
     1. 1 gm bid - tid.
     2. CBC, LFTs.
     3. Onset 1-2 months.
   - **Methotrexate :**
     1. Most commonly used drug.
     2. Fast acting (4-6 weeks).
     3. po, SQ – weekly.
     4. CBC, LFTs.
   - **IM Gold : not commonly used. Has lots of side effects.**
     1. Slow onset (3-6 months).
     2. Weekly then monthly injections.
     3. CBC, UA before each injection.
   - **Oral Gold :**
     1. Less effective.
     2. Slow acting (4-6 months).
     3. Daily.
     4. CBC, UA.
3) **Biologic response modifiers :** Etanercept, Infliximab, Anakinra.
   - Etanercept and infliximab target tumor necrosis factor alpha (TNF-α)
     Anti(TNF-α) will block the inflammatory process.
   - Anakinra targets interleukin-1 receptor.
4) **Corticosteroids.** Not recommended in high doses or for long term therapy because of their side effects

Osteoarthritis





OSTEOARITHRITIS:

- Degeneration of the cartilage.
- Anything that affects cartilage will decrease its ability to absorb trauma which will lead to microfractures of the bone.
- The repairing system in bone is thus activated, and osteolytic and osteoblastic activity is increased, resulting in osteophyte (bone spurs) formation, which limit joint movement and causes pain.

MULTIFACTORAL ETIOLOGY OF OA :

- Joint instability.
- Age.
- Hormonal factors→ more in females.
- Trauma→ Macrotrauma(fractures, ligament injury).
  Repeated microtrauma (due to the pt's occupation or athletic activity) .
- Altered biochemistry e.g. gout.
- Inflammation.
- Genetic predisposition (runs in families).
- ? Others.

SYMPTOMS AND SIGNS OF OA :

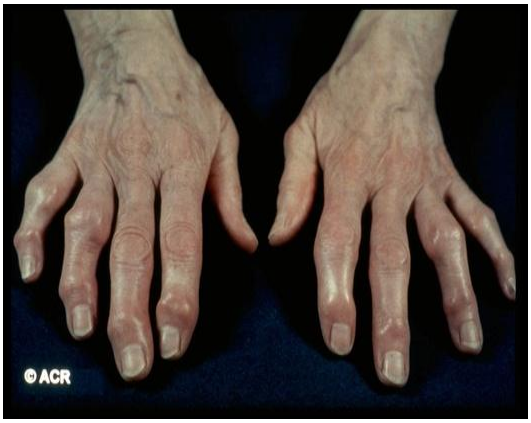
- Pain – worse on use of joint→This is caused by the movement of one joint surface against another(bone on bone) because of cartilage loss. There are no pain fibers in cartilage, so its insidious destruction over time goes unnoticed. Once it is completely worn out, the bones (which do have pain fibers) start rubbing against each other, producing the pain of osteoarthritis .
- Stiffness – mild after immobility (less than RA).
- Loss of movement.
- Pain on movement/restricted range.
- Tenderness (articular or periarticular).
- Bony swelling.
- Soft tissue swelling.
- Joint crepitus.

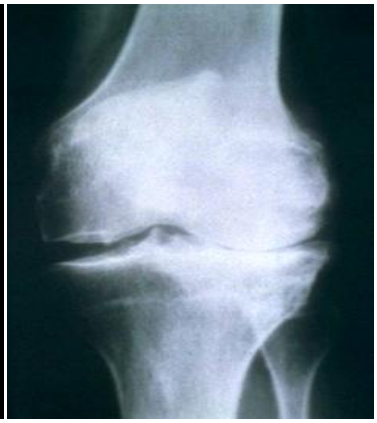
RADIOLOGICAL FEATURES OF OA :

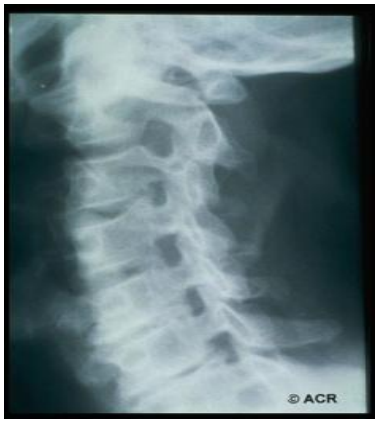
Two common signs of OA:

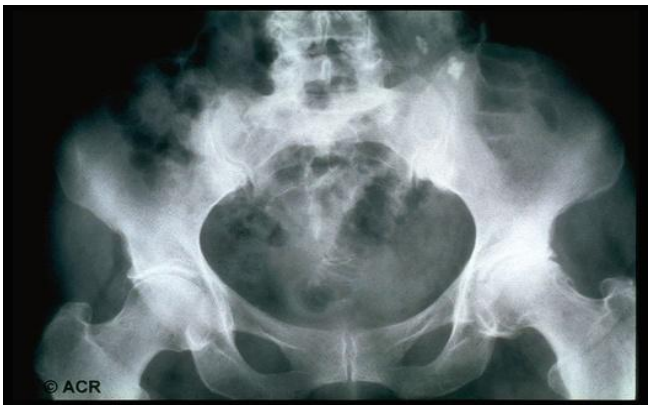
- **Bouchard's nodes:** bony overgrowth ad significant osteoarthritic changes (i.e. osteophytes) at the **PIP** joints.
- **Heberden's nodes:** bony overgrowth ad significant osteoarthritic changes (i.e. osteophytes) at the **DIP** joints.

- Narrowing of joint space.
- Osteophytosis.
- Altered bone contour.
- Bone sclerosis and cysts.
- Periarticular calcification.
- Soft-tissue swelling.









MANAGEMENT OF OSTEOARTHTITIS :

- **Confirm diagnosis.**
- **Initial Therapy :**
  - Pysiotherapy.
  - Wt. loss.
  - Local therapy.
  - Paracetamol.

Joint immobility reduces the pain, but physiotherapy is important to prevent muscle atrophy.

- **Second-line approach :**
  - NSAIDS.
  - Intra-articular therapy :
    - steroids → we try to avoid them in OA
    - hyalurinate.
  - Opioids →: tramadole, only if the patient is in severe pain.

We usually avoid prescribing addictive drugs.

  - Glucosamine → not of proven effect.
  - Arthroscopy.
  - Surgery.

OA	RA
Degenerative disease	**Systemic**, chronic, **inflammatory** disease
Affects cartilage	Affects synovial joints
Hypertrophy of bone at the articular margins & degeneration of cartilage	Thickening & hypertrophy of the synovium
There is a great increase in risk of developing OA by the age 65 or older	Peak age: 25-50 But it can affect any age
Often monoarticular joint involvement	Mainly (75%) polyarticular joint
No systemic involvement, no erythema or warmth	A systemic disease!
Any joint can be affected, but weight baring joints are most commonly involved (hips, knees, cervical & lumbar spine)	Most commonly involved joints are wrists, PIPs, MCPs & thumbs
Radiological features - Joint space narrowing (due to loss of cartilage) - Osteophytes - Sclerosis of subchondral bony end plates adjacent to diseased cartilage (most severe at points of maximum pressure) - Subchondral cysts occur as a result of increased transmission of intra-articular pressure to the subchondral bone.	**Radiological features** - Loss of juxtaarticular bone mass (periarticular osteoporosis) near the finger joints. -Narrowing of the joint space (due to thinning of the articular cartilage) is usually seen late in the disease. - Bony erosions at the margins of the joint.

Chronic Arthritis and Chronic Back Pain

Dr. Sultan Al-Mogairin

Chronic arthritis :

1- **Monoarthritis** → involves single joint.
2- **Oligoarthritis**→ 4 joints or less (4, 3, or 2) , which is called (pauciarthritis) . usually affect large joints but might affect small ones.
3- **Polyarthritis** → more than 4 joints → usually affect small & large joints.

Signs of arthritis

1- Redness .
2- Evidence of effusion.
3- Localized tenderness along the joint line.
4- Significant limitation in active and passive movements.

Mono-arthritis	Oligo-arthritis	Poly-arthritis
One joint	equal or less than 4 **(4, 3, or 2)**	More than 4
Deferential diagnosis of monoarthritis: 1. Infective : ✓ TB. ✓ Brucella 2. Osteoarthritis. 3. Chronic malignancy .	axial involvement is common.	Axial involvement is rare expet cervical in RA
	Asymmetrical peripheral	Symmetrical.
	Predominant involvement of lower limb joints.	Affect both lower and upper limbs.
	Any system can be involved but mainly eye ,skin, GI or GU system involvement. <u>cutanous manifestation</u> : psoriatic rash, keratoderma blenorrhagica, Circinate balanitis, Onycholysis (elevation in the nail and hyperkertosis) Erythema nodosum <u>Eye:</u> conjuctivitis or uveitis	any system can be involved . commonly: <u>skin rash</u> : malar rash , discoid rash, Heliotrope rash (in upper eyelid & forehead which is sign of dermatomyositis.) *polyarthritis is associated with macular & popular lesions(<u>vasculitis)</u> **Some features of Vasculitis :** Vasculitic rash Splinter hemorrhage Gangrene Oral ulceration
e.g: OA, pigmented villonodular synovitis .	e.g: ankylosing spondylitis, reactive arthritis, psoriatic arthritis.	e.g.: RA , SLE , primary OA .

Arthritis is classified into two main categories:

1- <u>Inflammatory arthritis</u>

- usually causes stiffness with rest, especially morning stiffness(lasting for more than 30 min and classically more than 1 hour).
- It is usually symmetrical (affects joints on both sides of the body), and occasionally asymmetrical such as ***Reactive Arthritis***.
- Example: ***rheumatoid arthritis*** .

2- <u>Non-inflammatory arthritis</u>

- usually causes pain that is aggravated by <u>movement</u> and weight bearing and is relieved by rest (mechanical arthritis).
- Asymmetrical joint Involvement.
- Example**:** ***osteoarthritis***.

- **How to differentiate between inflammatory and non-inflammatory type of arthritis ?**

The following features are present in inflammatory arthritis:

- ✓ Morning stiffness.
- ✓ Pain relieved with exercise (& worsen after rest).
- ✓ Systemic manifestation (fever, rash).
- ✓ Extra-articular manifestation.

Septic arthritis:

- Usually involves one joint with fever. It could be oligo if the patient is immunocompromised.
- The infection get to the joint either by hematological spread or direct implantation of the organism.
- The most common bacteria that cause chronic arthritis are brucella and tuberclus bacilli (note the low grade fever, night sweat and loss of appetite).
- The most commonly affected joints are the weight bearing joints like hip, knee and ankle.

The seronegative spondyloarthritis :

Group of diseases share certain clinical features:

- A predilection for axial inflammation .
- Asymmetrical peripheral arthritis .
- Absence of rheumatoid factor (that's why it is called seronegative) .
- Inflammation of the enthesis (junction of the ligament or tendon and bone).
- A strong association with HLA-B27 , (testing for HLA-B27 is not routine , diagnostic , confirming or used for screening because many people have HLA-B27 and very few get one of the diseases.
- E.g. **Ankylosing Spondylitis**, **Psoriatic Arthritis,** and **Reactive Arthritis**.

(1) Ankylosing Spondylitis:

- ✓ Inflammatory disorder of the back.
- ✓ Mainly affect young adults. (Late teens , early 20s)
- ✓ Affects male more than female (so they are more likely to present with symptoms of the disease)

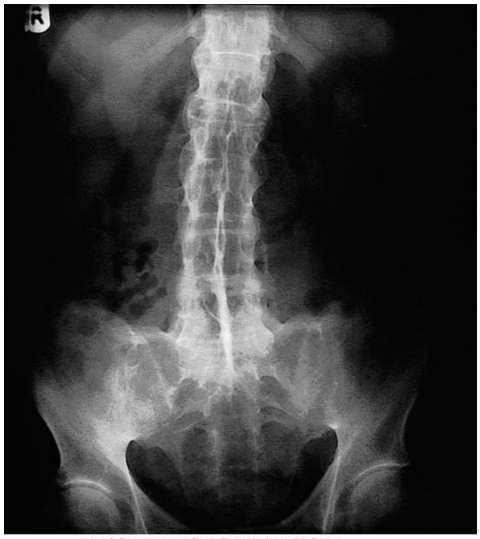
- **Clinical Features:** Patient presents with:
  - ✓ Increasing lower back pain.
  - ✓ Morning stiffness also in the lower back (usually lasting for more than 30 minutes – 1 hour)
  - ✓ Both pain and stiffness **improves** with exercise but not with rest.
  - ✓ There is a progressive loss of spinal movement.

- **By inspection of the spine, two abnormalities are found:**
  1. Loss of lumber lordosis and increased kyphosis.
  2. Limitation of lumbar spine motility in both saggital and frontal planes.

     i.e. **Positive Schober's test** :
     - ✶ The examiner makes a mark approximately at the level of L5 then places one finger 5 cm below this mark, and another finger 10 cm above it. The patient is asked to touch his/her toes. By doing so, the distance between the two fingers of the examiner increases. However, a restriction in the lumbar flexion of the patient reduces this increase; if the distance increases less than 5 cm, then there is an indication that the flexion of the lower back is limited "may suggest ankylosing spondylitis".

- **Other Features include :**
  - ✓ Achilles tendinitis.
  - ✓ Plantar Fasciitis (enthesitis).
  - ✓ Tenderness around the pelvis and chest wall.
  - ✓ Reduction in chest expansion (< 2.5 cm on deep inspiration measured at the 4th intercostal space).

- **Non-articular features:**
  - ✶ Iritis (25%).
  - ✶ Aortic incompetence (rare).
  - ✶ Cardiac conduction defects (rare).
  - ✶ Apical Lung Fibrosis (rare).
- **Investigations**:
  - ✓ **ESR & CRP** : Often Raised.
  - ✓ **X-ray**: normal or show erosions and sclerosis at the margins of sacroiliac joints (will lead to ankylosing – which is immobility and fusion of the joint-)
  - ✓ In the spinal column, vertebrae will be square because of erosions of its corners.
  - ✓ **Bamboo spine:** because of the progressive calcification of the interspinous ligaments.
  - ✓ **MRI** : shows early changes, increased signal from bone and bone marrow suggests osteitis and edema.



X-ray of bamboo spine in ankylosing spondylitis. In advanced disease there is calcification of the interspinous ligaments and fusion of the facet joints as well as syndesmophytes at all levels. The sacroiliac joints fuse.

- **Prognosis**:
  - ✓ Most patients live a normal active life and remain at work.
  - ✓ In severe cases
    1. Spine becomes completely fused and brittle.
    2. Risk of fracture even with minimal trauma.
    3. Cord compression.
    4. Fixed kyphosis of the cervical and thoracic spine may impair ventilation.

(2) Psoratic Arthritis:

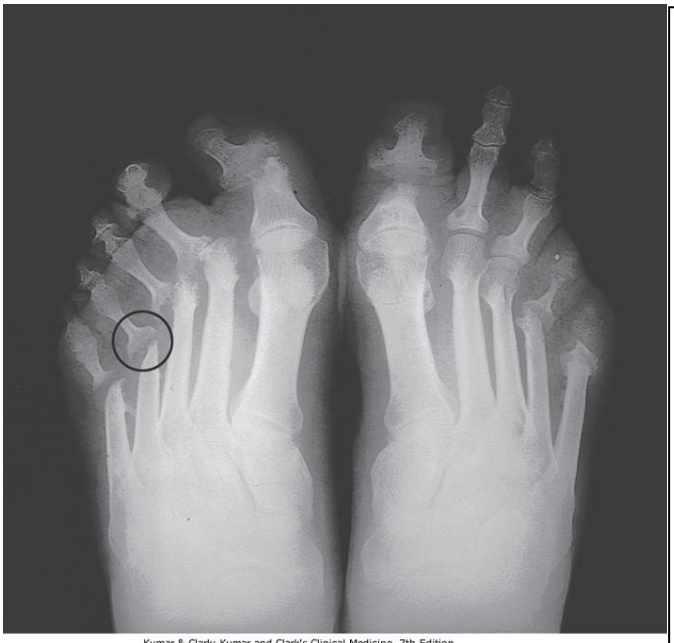
- Arthritis occurs in 5-8 % of patients with psoriasis, particularly in patients with nail disease.
- May precede the skin disease, but definitive diagnosis cannot be made without evidence of skin or nail changes.
- **Psoriasis:** a common inherited condition characterized by the eruption of reddish, silvery-scaled maculopapules, predominantly on the elbows, knees, scalp, and trunk.

- **Clinical feature of Psoratic arthritis:**

There are several types:

1. *Asymmetrical* involvement of the small joints of the hand including the distal interphalangeal joints.
2. *Symmetrical* seronegative polyarthritis resembling Rheumatoid arthritis.
3. *Arthritis mutilans*, severe form with destruction of small bones in the hands and feet.
4. *Ankylosing spondylitis* occurs with increased frequency in patient with psoriasis.

- **Investigations:**
  - ESR : often normal ,, thus routine blood tests are not helpful in the Dx.
  - X-ray: may show erosions and periarticular osteoporosis in the terminal interphalangeal joints.



X-ray of psoriatic arthritis. There is osteolysis of the metatarsal heads and central erosion of the proximal phalanges to produce the 'pencil in cup' appearance (circle). All the lesser toes are subluxed.

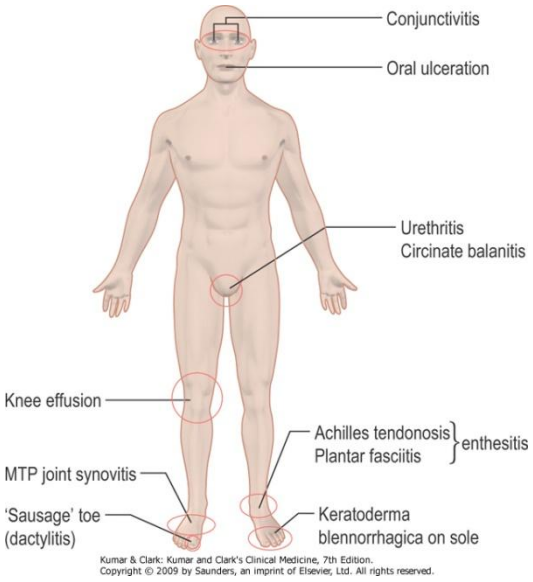
(3) Reactive arthritis

- It is a sterile synovitis , which occurs following an infection, either:
  1) **GI infection** : with Shigella, Salmonella, Yersinia or Campylobacter .
  2) **Sexually acquired infection** : non- specific urethritis in the male or cervicitis in the female due to infection with Chlamydia Trachomatis or Ureaplasma Urealyticum .
- Persistent bacterial antigen in the inflamed synovium of affected joints is thought to drive the inflammatory process .

• Clinical features

- ✓ It most commonly strikes individuals **aged 20-40**, is more common in men than in women.
- ✓ The typical case is a young man who presents with an acute arthritis shortly (within 4 weeks) after an enteric or venereal infection (infection transmitted by sexual intercourse) ,which may have been mild or asymptomatic . The joints of the lower limbs are particularly affected in an asymmetrical pattern; the knee, ankles and feet are the most common sites .
- ✓ The **skin lesions** resemble psoriasis. Circinate balanitis cause superficial ulcer around the penile meatus which harden to a crust in the circumcised male. Red plaques and pustules that resemble pustular psoriasis (keratoderma blenorrhagica) are found on the palms and soles of the feet. Nail dystrophy may also occur.
- ✓ Additional features are acute **anterior uveitis** (eye inflammation) , **enthesitis** (plantar fasciitis, Achilles tendonitis) and the classical triad of **Reiter's syndrome** (**urethritis**, **reactive arthritis** and **conjunctivitis**).

- **Investigations**
  The diagnosis is clinical . The erythrocyte sedimentation rate (ESR) is raised in the acute stage. Aspirated synovial fluid is sterile, with a high neutrophil count.
- **Prognosis**
  The acute arthritis resolves within a few months. However, 50% of patients develop recurrent arthritis, iritis or ankylosing spondylitis .



Clinical features of reactive arthritis.

Back pain

- **The danger signs of back pain :**
  1- Neural involvement due to spinal compression or prolapsed disc which may lead to paraplegia.
  2- Low grade fever & night sweating→ infection (e.g POTTs spine in TB)
  3- Loss of appetite & weight → malignancy or chronic infection.
  4- Persistent & progressive →high possibility of CA, metastasis
- **lumbar back pain**
  - ✓ Is an extremely common symptom experienced by most people at some time in their lives. Only a few patients have a serious underlying disorder.
  - ✓ Mechanical back pain is a common cause in young people . It starts **suddenly**, is **often unilateral** , and may be helped by rest. It may arise from the fecet joints, spinal ligaments or muscle. The history, physical examination and simple investigations will also often identify the minority of patients with other causes of back pain.
  - ✓ The age of the patients helps in deciding the aetiology of back pain because certain causes are more common in particular age groups.

Causes of lumbar back pain		
History and Examination		
Mechanical	1. Prolapsed disc. 2. Fractures (the former two conditions are usually with acute back pain, but might present with chronic back pain as well) 3. Osteoarthritis. 4. Spondylolisthesis. 5. Spinal stenosis.	✓ Often sudden onset. ✓ Pain worse in the evening. ✓ Morning stiffness is absent. ✓ Exercise aggravates pain.
Inflam matory	Ankylosing spondylitis infection.	▪ Gradual onset. ▪ Pain worse in the morning. ▪ Morning stiffness is present. ▪ Exercise relives pain.
Serious causes	1.metastatic carcinoma. 2.myeloma 3.tuberculosis osetomyelitis 4.cord or cauda equine compression	These are the Red Flags in patient with back pain: ▪ Neurological deficit. ▪ Persistent , progressive pain , waking the patient from sleep. ▪ Back pain in individuals with a history of cancer (especially cancers known to spread to the spine like breast, lung and prostate cancer). ▪ Bladder, bowel or sexual function deficits. ▪ Weight loss , loss of appetite. ▪ fever , night sweating.
Others	Osteomalacia , paget's disease, referred pain from pelvic/abdominal disease	

- **Notes:**
  - ✓ **Spondylolisthesis :** describes the anterior displacement of a vertebra or the vertebral column in relation to the vertebrae below.
  - ✓ **Spinal stenosis :** is a medical condition in which the spinal canal narrows and compresses the spinal cord and nerves.
  - ✓ **Spondylosis** :(degeneration of the vertebrae) is one of the commonest cause of back pain.
  - ✓ **Hyperlordosis :** when the lumbar region experiences stress or extra weight and is more common in obese patients.

- **Investigations:**
  - **A detailed history and physical examination** will lead to the diagnosis in many cases. The key points are age, speed of onset, the presence of motor or sensory symptoms, involvement of the bladder or bowel , and the presence of stiffness and the effect of exercise . Young adults with a history suggestive of acute non severe mechanical back pain and with no physical signs don't need further investigation.
  - **Blood count** is usually normal . The ESR may be raised with inflammatory back pain and tumors .
  - **Serum biochemistry** . A raised Ca and alkaline phosphatase suggest metastases. Typically with myeloma the Calcium is raised , with a normal alkaline phosphatase . A raised alkaline phosphatase with a normal ca occurs with metabolic bone disease. Prostate-specific antigen should be measured if secondary prostatic disease is suspected.
  - **Radiology x-ray** may be useful for excluding serious disease , although they may be misleading , e.g. Degenerative disease is virtually always present in older people.
  - **Technetium Bone Scan** will show increased uptake with infection or malignancy.
  - **MRI** is useful when neurological symptoms and signs are present. Its useful for the detection of disc, cord lesion and paraspinal mass.

Your Targets in Clinical Approach to Patient with Rheumatological Problem Using Both History and Clinical Examination

1- Type of Pain

- *Where is it? Is it diffuse skeletal pain (joints, muscles and bones) or **limited to joints**?*
- *Is it arising from joints, the spine, muscles or bone?*
- *You should be able to know and differentiate between the following terms:*
  - ✓ **Arthritis :** pain &inflammation
  - ✓ **Arthralgia** :presence of joint pain but in examination there is no signs of arthritis (no erythema, hotness, or effusion).
  - ✓ **Myalgia** : pain in the soft tissue & limitation of movement usually in one direction.
  - ✓ **Bony pain** : pain in the bone itself.
  - ✓ **Neuralgia** (due to nerve compression or inflammation) : if there is numbness or tingling along the coarse of the nerve
- *Could it be referred from another site?*
- *Is it constant, intermittent or episodic*? *How severe is it*
- *Are there aggravating or precipitating factors?* (activity, rest)
- *Are there any associated neurological features?* Numbness, pins and needles and/or loss of power suggest 'nerve' pain.

2- Stiffness :

1. *Duration.*
2. *Is it worse in the morning and relieved by activity?*

3- Swelling :

1. *Is it constant or episodic?*
2. *Is there associated inflammation (redness, warmth or effusion)?*

4- Which joints are involved?

1. axial or peripheral?
2. large or small joints?
3. Joints distal to wrist & ankle→ small
4. Joints proximal to wrist & ankle→ large

5- Symmetrical or not?

6- How many joints are affected ?

- ✓ "or" is it mono, oligo, or polyarthritis?

7- the presence of extra-articular manifestation

- ✓ Most commonly cutaneous (skin, nails, mucous membranes, hair) e.g. "**rash, changes in nail, ulcers in mm**" or other systemic manifestation.

- ***How to differentiate between intra & extra inflammation ?***
  - ✓ If there is **no significant limitation** in passive movement of joint → extraaritcular problem(in tendons , bursa , muscle)
    If there is limitation in both active and passive movement→**intraarticular** (**arthritis**)
  - ✓ 3 Test for patellar effusion, **one of the three** should be positive to indicate arthritis:
    1- **Milking sign** : for mild effusion.
    2- **Fluctuation test** : for moderate and large effusion.
    3- **Patellar tap :** for moderate and large effusion.

Systemic Lupus Erythematosus & Scleroderma

Prof. Abdurrahman Al-Arfaj

Definition :

- Chronic, multisystem inflammatory disease characterized by autoantibodies directed against self-antigens, immune complex formation, and immune dysregulation resulting in damage to essentially any organ.
- It is a syndrome of silent symptoms & lab abnormality.
- Self AGs mean every Ag in our body such as skin, hair follicles, joints, blood ….etc

Background :

- First written description in 13th century (Rogerius) named it lupus (Latin for wolf) as cutaneous similar to a wolf bite.
- Osler recognized systemic features without skin .
- Diagnosis with (LE) cells in 1948.
- In 1959, anti-DNA.
- There are 11 criteria's for SEL :
- You need 4 of these to diagnose it .
- These design for studies not for picking up the patients
- You suspect SEL by signs & symptoms even there is only 3 of them
- Viral infections may mimic SLE because they can give you the hematological & skin changes that resemble SLE changes.

Epidemiology :

- Locally : 2 cases of SLE among 10,372 studied (prevalence of 19.28 per 100,000).
- Internationally : variable prevalence :
    - Denmark (21.7/10,000).
    - Britain, 12 cases per 100,000.
    - India prevalence (3.2/100,000).
    - 39 cases per 100,000 population in Sweden.

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR b) Pericarditis--documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or grater than 3+ if quantitation not performed OR b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) **Hemolytic anemia**--with reticulocytosis OR b) **Leukopenia**--less than 4,000/mm<>3<> total on 2 or more occasions OR c) **Lyphopenia**--less than 1,500/mm<>3<> on 2 or more occasions OR d) **Thrombocytopenia**--less than 100,000/mm<>3<> in the absence of offending drugs
10. Immunologic disorder	a) "Positive finding of **antiphospholipid** antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed byTreponema pallidum immobilization or fluorescent treponemal antibody absorption test."Standard methods should be used in testing for the presence of b) **Anti-DNA:** antibody to native DNA in abnormal titer OR c) **Anti-Sm:** presence of antibody to Sm nuclear antigen OR d) **False positive serologic test** for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Aetiology :

- **Specific cause(s) of SLE is unknown.**
- **Multiple factors are associated include :**
  - Genetic
  - Hormonal
  - Racial
  - Environmental factors
- **Genetic predisposition :**
  - Multitude of genetic associations suggests a complex genetic predisposition.
  - Concordance rate in monozygotic twins is 25-70%.
  - If a mother has SLE, her daughter's risk of developing the disease is 1:40, and her son's risk is 1:250.
  - Relatives have a high prevalence of other autoimmune diseases.
  - HLA-DR2 and HLA-DR3 and other HLA genes occur more often in SLE than in the general population.
  - null complement alleles and congenital deficiencies of complement (C4, C2, and other early components) are associated with an increased risk of SLE.
- **Hormonal factors:**
  - F : M ratio of prevalence in different age groups :
    - In children, F : M ratio is 3 : 1
    - In adults, F : M ratio is 10-15 : 1
    - In older, the ratio is approximately 8 : 1
  - **Age at onset :**
    - 65% have onset between 16 and 55.
    - 20% before age 16, and
    - 15%t after age 55.
  - Higher prevalence in men with Klinefelter disease. [male with more X chromosome]
  - Exogenous estrogen and exacerbations of SLE.
  - Men at all ages have the same risk of disease as women who are prepubertal or postmenopausal
  - Males do not have an age-related peak in incidence.
- **Racial and geography :**
  - Higher prevalence (2.5- to 6-fold) in USA African American women than in white women.
    - But, cf occurs infrequently in Blacks in Africa.
  - Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, and Asian Indians.
  - More common in urban than rural areas .
  - Also In New Zealand, 50 per 100,000 Polynesians, but only 14.6 cases per 100,000 in the whites.
  - In France, more common among immigrants from Spain, Portugal, North Africa, and Italy.
- **Environmental :**
  - Worldwide variability of prevalence the disease(black in africa and US).
  - Influence of environmental factors on the course of the disease, e.g. :
    - Ultraviolet light.
    - Viruses.
    - Drugs cause or exacerbate.
    - Silica dust.
    - Cigarette smoking.
    - Alfa alfa sprouts. Produce ANA positive.
      - NB : alfa alfa sprouts is a kind of vegetable in western used in salads.

Pathophysiology :

- Disturbances in the immune system :
  - High ratio of CD4+ to CD8+ T cells.
  - Defects in immune cell tolerance leading to :
    - Production of autoantibodies targeting antigens located in nuclei, cytoplasm, on cell surfaces, and in plasma proteins.
  - Autoantibodies leads to mostly immune complex formation (e.g. kidney) and direct antibody-mediated cytotoxicity (hemolytic anemia, thrombocytopenia).
  - Cell-mediated autoimmunity also play part.
  - Tissue damage follows.

Organ Involvment in SLE :

- Joints 90%
- Skin :
  - Rashes 70%
  - Discoid lesions 30%
  - Alopecia 40%
- Pleuropericardium 60%
- Kidney 50%
- Raynaud's 20%
- Mucous membranes 15%
- CNS (psychosis/convulsions) 15%

- Patient May pressent with arthralgia.
- Arthritis May be similar to RA affect smal & larg joints, usually symmetrical, deformable but not erosive.

Primary Central Nervous System Lupus : Neurologic Signs or Symptoms

Cerebrum
- Dementia
- Strokes
- Subarachnoid hemorrhage
- Migraine
- Other headaches
- Seizures
- Chorea
- Rigidity
- Tremor
- SIADH

Meninges
- Headache

Meningismus
- Cerebellum
- Ataxia

Spine
- Multiple sclerosis-like disorder
- Paraparesis

Cranial and peripheral nerves
- Cranial and peripheral sensory,motor
- Mononeuritis multiplex
- Myasthenia gravis
- Guillain-Barre syndrome
- Neuropathies

Special considerations

Drug-induced lupus : (consider before diagnosing native lupus)

- Sex ratios are nearly equal.
- Nephritis and CNS not common.
- No anti- native DNA or hypocomplementemia.
- resolution on discontinuation of drug.

Definite association

- **Chlorpromazine**
- **Methyldopa**
- **Hydralazine**
- **Procainamide**
- **Isoniazid**
- **Quinidine**

Unlikely Association

- Allopurinol,
- Penicillin, Chlorthalidone, Phenylbutazone, Gold salts, Reserpine,Griseofulvin,Streptomycin,Methysergide,Tetracyclines,Oral contraceptives

Possible Association

- Betablockers
- Methimazole
- Captopril
- Nitrofurantoin
- Carbamazepine
- Penicillamine
- Cimetidine
- Phenytoin
- Ethosuximide
- Propylthiouracil
- Hydrazines
- Sulfasalazine
- Levodopa
- Sulfonamides
- Lithium
- Trimethadione

TREATMENT : (General Considerations)

- **Prevention :**
  - Avoid UV light and sun (sunsceening).
  - Antimalarial to prevent relapses.
  - Treat hypertension and dyslipidemias .
- **Treat depending on the organ system(s) involved :**
  - Skin, musculoskeletal, and serositis
    - NSAIDs, HCC, local cs.
  - More serious organ involvement (CNS, renal)
    - Immunosuppression with high-dose steroids, AZA and/or cyclophosphamide, mycophenolate, rituximab.
  - **Other treatments :**
    - Plasma exchange for TTP or diffuse alveolar hemorrhage, and

    Intravenous immunoglobulin for severe steroid-nonresponsive thrombocytopenia.

Prognosis :

- Poor prognostic factors for survival in SLE include :
  - Renal disease (especially diffuse proliferative glomerulonephritis).
  - **Hypertension.**
  - **Renal and central nervous system (CNS) disease.**
  - Less education (?poor compliance)
  - Poor socioeconomic status (? inadequate access to medical care).
  - Black race (? low socioeconomic status).
  - Presence of antiphospholipid antibodies.
  - High overall disease activity.
- Male sex :
  - Men similar freq of renal,skin,arthritis,and CNS as women,
  - But less photosensitivity,
  - More serositis,
  - An older age at diagnosis, and
  - A higher one year mortality.
- Young age :
  - SLE in children more severe, higher malar rashes, nephritis, pericarditis, hepatosplenomegaly, and hematologic abnormalities.

Remission :

- After appropriate therapy :
  - Many patients go into a clinical remission requiring no treatment.
  - A long-term follow-up of 667 patients noted :
    - ≈25 % had at least one treatment-free clinical remission lasting for at least one year.
    - The mean duration of remission was 4.6 years (?underestimate since one-half of the patients were still in remission at the end of follow-up).
    - A long history of SLE or the presence of renal or neuropsychiatric disease did not preclude remission.

Progressive Systemic Sclerosis :

- Preliminary Diagnostic Criteria : Patient must has major criterion or 2 minor criteria :
  - **Major criterion : Proximal scleroderma.**
  - **Minor criteria :**
    - Sclerodactyly.
    - Digital pitting or scars or loss of substance from finger pads.
    - Bibasilar pulmonary fibrosis.

Classifications of Scleroderma :

1. Localized :
   - Morphea : plaque like, guttate, generalized linear.
   - Scleroderma.
   - Scleroderma 'en coup de sabre' (± facial hemiatrophy).
2. Generalized :
   - With diffuse visceral involvement.
   -
   -
   -
   -
   -

- CREST syndrome.
- Overlap with other connective tissue disease.

3. Chemical-induced scleroderma-like conditions.
   - e.g. vinyl chloride disease.
4. Diseases with skin changes mimicking scleroderma.
   - e.g. scleredema.

Eosinophilic fasciitis.

Systemic Manifestations of Sclero-Derma :

Pulmonary	**Gastrointestinal**	**Renal**
Dyspnea	Dysphagia	Proteinuria
Cough	Dyspepsia	Azotemia
Hemoptysis	Constipation	Hypertension
Pleuritic pain	Diarrhea	Renal failure
Clubbing of nails	Malabsorption	
	Distension of esophagus	
Musculoskeletal	**Cardiovascular**	
Polyarthralgia	Arrhythmias	
Swelling of joints	Myocardial failure	
Contractures		

Criteria for the Diagnosis of MCTD :

Positive Criterion	**Algorithm of**	
	Alarcon-Segovia and Villareal	Kahn and Appelboom
Serological test	Anti-(U1-RNP) titer ≥ 1:1600	Anti-(U1-RNP) titer ≥ 1:1200 in a patient with an ANA titer ≥ 1:2560 and a speckled ANA pattern
Clinical features	≥3; one of which must be synovitis or myositis, with others	≥3; one of which must be Raynaud's phenomenon, with others
	To include: • Swollen hands • Raynaud's phenomenon • Acrosclerosis	To include: • Swollen fingers • Synovitis • Myositis

Clinical and Laboratory Features of MCTD :

- Polyarthritis.
- Raynaud's phenomenon.
- Swollen hands or sclerodactyly.
- Abnormal esophageal motility.
- Myositis.
- Low incidence of lupus nephritis.
- Hyperglobulinemia.
- Positive ANA (often speckled pattern).
- Antibody to nRNP.

Antibodies Associated with Rheumatic Diseases : Percentages of Patients Affected

Antibodies to…..	Percentages of patients
Native DNA	SLE : 50% - 60%
Sm antigen	SLE : 30%
Histones	Drug-induced SLE : 95% SLE : ≤ 60% Rheumatoid arthritis : 20%
SS-A	Sjogren's syndrome : 70% SLE : 30% - 40% Scleroderma and mixed connective Tissue disease : frequency and titers low
SS-B	Sjogren's syndrome : 60% SLE : 15%
RNP	Mixed connective tissue disease : 95% - 100% SLE : 30% at low titers Scleroderma : 10% - 20%
Scl-70	Scleroderma : 10% - 20%
Nucleolar antigens	Scleroderma : 40% - 50%
Centromere antigens	CREST : 80% - 90%
PM-1	Polymyositis : 50% Dermatomyositis : 10%

Summaries

Page

ACUTE VIRAL HEPATITIS

Clinical Features:

features	Hep. A	Hep. B	Hep. C
Incubation period Average: Range:	30 days 15-50 days	60-90 days 45-180 days	6-7 wks 2-26 wks
juandice	<6 yrs <10% 6-14 yrs 40%- 50% >14 yrs 70%- 80%	< 5yrs <10% ≥ 5yrs 30%- 50%	Mild (≤ 20%)
Case fatality rate	---	0.5%- 1%	low
Chronic infection	rare	< 5yrs 30%- 90% ≥ 5yrs 2%- 10%	75%-85%
Mortality from chronic liver disease	---	15%- 25%	1%- 5%

Viral Hepatitis - Overview

	Type of Hepatitis				
	A	**B**	**C**	**D**	**E**
Source of Virus	Feces	Blood/Blood-Derived Body Fluids	Blood/Blood-Derived Body Fluids	Blood/Blood-Derived Body Fluids	Feces
Route of transmission	Fecal-Oral	Percutaneous Permucosal	Percutaneous Permucosal	Percutaneous Permucosal	Fecal-Oral
Chronic Infection	No	Yes	Yes	Yes	No
Prevention	Pre/post-Exposure immuniztion	Pre/post-Exposure immuniztion	Blood Donor Screening; risk behavior modification	Pre/post-Exposure immunization; risk behavior modification	Ensure safe drinking water

Approach to Abdominal Pain

<table>
<tr><th colspan="3">Abdominal pain</th></tr>
<tr><th>Types of pain</th><th colspan="2">Pain location</th></tr>
<tr><td rowspan="5">1. Somatic parital.
2. Visceral.
3. Reffered pain</td><td>Rt upper quadrent</td><td>Lt upper</td></tr>
<tr><td>▪ Cholecystitis
▪ Cholangitis
▪ Hepatitis
▪ RLL pneumonia
▪ Subdiaphragmatic abscess</td><td>▪ Splenic infarct
▪ Splenic abscess
▪ Gastritis/PUD</td></tr>
<tr><td>Rt lower</td><td>Lt lower</td></tr>
<tr><td>▪ Appendicitis</td><td>▪ Diverticulitis</td></tr>
<tr><td colspan="2">▪ Inguinal hernia
▪ Nephrolithiasis
▪ IBD
▪ Salpingitis
▪ Ectopic pregnancy
▪ Ovarian pathology</td></tr>
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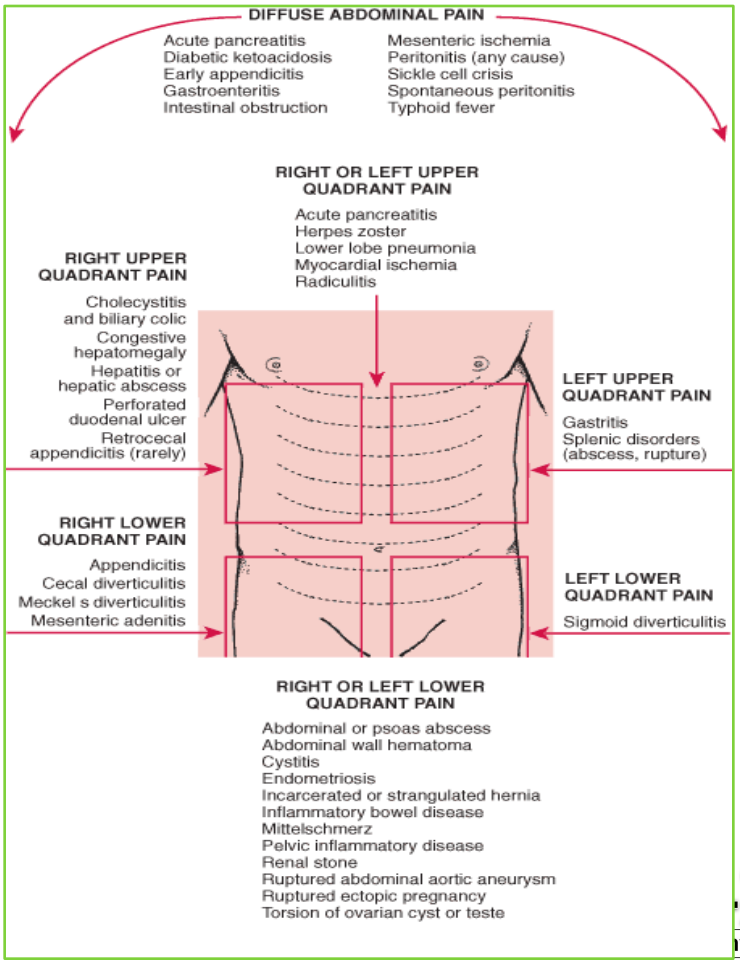


GI Bleeding

Clinical presentation:

Hematemesis	Melena	Hematochezia	Fecal occult bld
Bloody **vomitus** -bright red -coffee grounds→ because of bld exposure to gastric acids & oxidation of Fe	Black, lary foul-smelling **stool**→ because bld is in the gut for hrs and degraded into haematin & other hemochromes by colonic bacteria	Passage of bright bld through the **rectum.**	**Positive** fecal bld test **in absence** of visible bleeding to pt and physician→ because of small amnt of bleeding
Always means an upper source.	**Usually** means upper GI bleeding but **sometimes** from slow proximal colonic bleeding or lesions in the small int.	Means lower GI source or brisk upper GI source.	Bleeding at **any site** of the gut.
	History of Fe therapy or bismuth may be confused w/ melena	NG tube may help when the bleeding may be duodenal	
		Hyperactive bowel sounds & ↑BUN may be other possible clues	

Some causes of Upper GI bleeding:

Diagnosis	% of total
Peptic ulcer	55
Varice1s	14
Angioma	6
Mallory-Weiss tear	5
Erosions	4
Tumor	4

Some causes of Lower GI bleeding:

Diverticulosis	Varices
Aortoenteric fistula	Colitis
Vascular anomilies	
Neoplasia	
Anorectal: (Hemorrhoids – Fissure)	

Epidemiology:

- Incidence in Males double than in females
- Incidence ↑ with age
- Upper GI bleeding more common than lower GI bleeding.

Approach to any pt with GI bleeding should follow these principles:

1. Resuscitation & stabilization

Target of resuscitation:

-Fall in pulse rate (improvement in tachycardia)
-Rising BP or CVP (5-10 cm H2O)
-Adequate urine output (30 ml/hr)

2. Determine source of bleeding by detailed history, physical examination & lab investigations (hematocrit, MCV, coagulation profile & BUN).
3. Stop active bleeding.
4. Treat underlying abnormalities.
5. Prevent recurrent bleeding.

Liver Cirrhosis and Complications

Cirrhosis

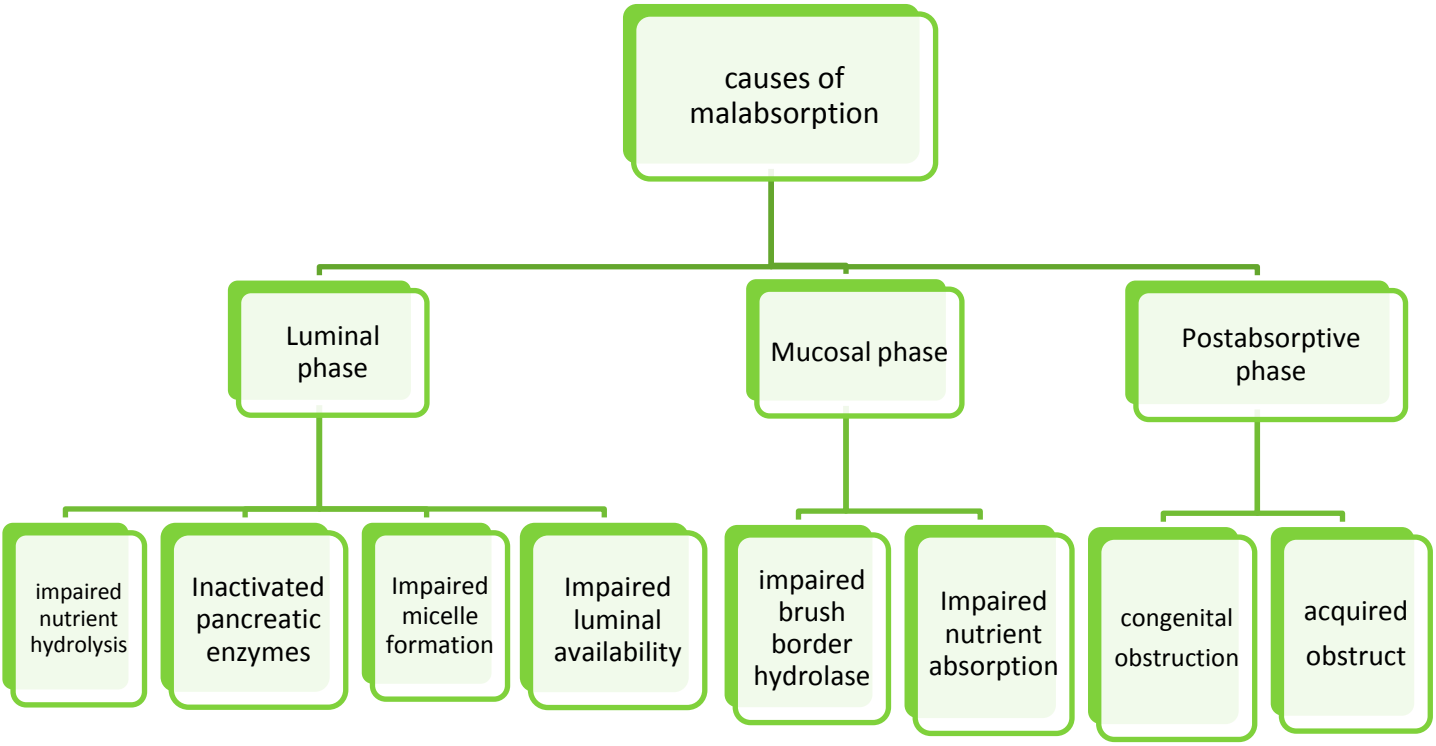
↓

Portal hypertension (PHT)

↓

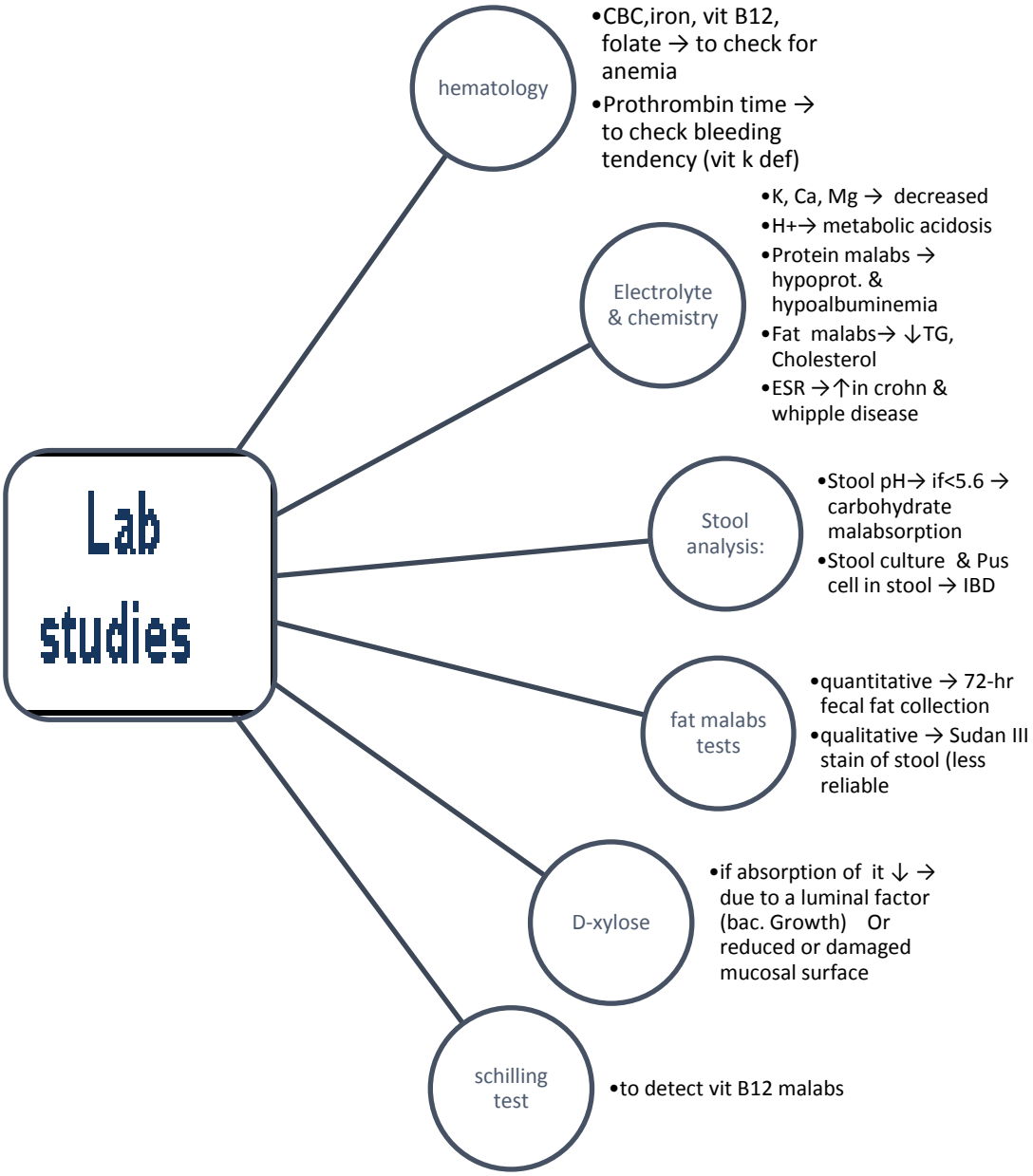
	1. Variceal hemorrhage	2. Ascites	3. Hepatic encephalopathy	4. Hepatocellular carcinoma
Pathogenesis	↑ PHT → diversion of blood into collaterals → varices (esophageal – gastric) → rupture → hemorrhage (melena – hematemesis).	↑ PHT → ↑ NO → vasodilation → ↑ sympathetic & renin-angiotensin-aldosterone → renal water & salt retention → overfill of intravenous volume → ascites formation.	PHT → blood (from the gut) bypass liver through collaterals → no detoxification in liver → toxic substances (ammonia) reaches brain → cerebral disturbance.	
		Investigations: Ascitic tap (paracentesis): •WBC count (> 250 neutrophil in SBP). •**SAAG**: ▪High (**> 11 g/L**) = transudate → **PHT – heart** failure. ▪Low (**< 11 g/L**) = exudates → **peritoneal– kidney** disease.	Exacerbating factors: • **Azotemia.** • **Sedative drugs** • **GI hemorrhage.** • **Hypokalemic alkalosis.** • **High dietary protein.** • **Infection.** • **Constipation.** • **Hepatic necrosis.**	
Management	1-ABC – **resuscitation** (2 IV lines – fluid & blood). 2-IV constrictors – endoscopic therapy – shunts (surgical – TIPS).	1-↓ Salt intake / diuretics. 2-Recurrent tapping. 3-TIPS.	Identify & **treat exacerbating factor**: 1-Lactulose (laxative). 2-Antibiotics. 3-Normal protein diet.	
		Complications: Spontaneous bacterial peritonitis (**SBP**) → common gram negative (E.coli) – diagnosed with WBC count (**>250 neutrophil**).	Features: ▪Fluctuating. ▪Reversal of sleep patterns. ▪Asterixis – constructional apraxia. ▪Disorientation – personality changes.	

Approach to Chronic Diarrhea



Clinical presentation

general	Abdominal	Dermatological	Neurological
•orth hypotension (electrolyte imbalance) •wt loss, ms wasting, edema, ascites (↓prot. abs) •Cheilosis(angular stomatitis),glossitis, aphthous ulcer	•Distention • diarrhea •↑bowel sounds •↓ fat absorp →steatorrhea , loss of subcutaneous fat	•pale skin (anemia due to def. of vit B12, iron or folate) •↓vit K → ecchymoses •Dermatitis herpetiformis, erythema nodosum, pyoderma gangrenosum • ↓ vit B 3 (niacin) → pellagra •alopecia, seborrheic dermatitis	•Motor weakness •↓ vit B 12 → peripheral neuropathy • ataxia •↓Ca → Chvostek or Trousseau sign, metabolic defects of bones



Serology:

- EMA & antigliadin antibodies → celiac sprue
- IgA →in IgA deficiency
- Fecal elastase & chymotrypsin(pancr. Enz) to diff between pancreatic & intestinal causes

Diabetes Mellitus

	Type 1 10%	Type 2 90%
Definition	Is a metabolic disease associated with glucose metabolism abnormalities as a result of insulin deficiency or insulin resistance. Leading to chronic complications in : nerves – vessels – kidney. Responsible for { ESRD , Blindness & limb amputation }	
Factor	Genetic	Familial
	One gene { gene located in HLA of ch6 in DR 3&4 }	Polygenic
Location	Production of islet cell antibody (ICA) → destruction of β cells in the pancreas.	Peripheral (insulin resistant)
Age	Children	Adult
Onset	Suddenly	Gradually
Weight	Thin	Obese
DKA	YES	NO
Insulin level	LOW	1st HIGH → Normal → LOW

♣ Other types include: (IGT, 2ry DM & Gestational DM)

Diagnosis of DM:

	FBS	***RBS***	***OGTT***	***Hb A_1C***
Sensitive	**-**	**+**	**+**	Can give us the reading for the past 3 months ↓ Used to *follow up* DM control
Specific	**+**	**-**	**+**	
	Good for diagnosis	Good for screening	The best Both sensitive & specific	

The Risk to Develop DM Type II

No DM in the family → (x 3) → Mother or Father → (x 3) → Both parents

5 % → 15 % → 45 %

♣ If one parent has DM & one of the siblings the chance will be 70 %.

Can we Reduce DM Percentage!!

If the person have 45 % chance → (Running 20 min, ÷ 3) → 15 % → (Ideal Kg, ÷ 2) → 7.5 % → (Healthy food, ÷ 3) → 2.5 %

• so we can reduce and prevent type II DM

Complications of DM

Acute			Chronic			
Hypoglycemia	DKA	Hyperosmolar non-ketotic coma	Neuropathy	Retinopathy	Nephropathy	Vasculopathy
	Hyperglycemia WITH ketonuria.	Severe hyperglycemia withOUT ketonuria.	Commonest			Most severe
			Due to sorbitol accumulation in schwan cells	*Due to* proliferative changes in the retinal vessels (neovascularization)	*Due to* glomerulosclerosis & disruption of the glomerular membrane	*Result in:* • IHD. • Cerebral ischemia (stroke – TIA). • Peripheral vascular disease.
			Result in: Sensory Polyneuropathy. Mononeuropathy. Mononeuritis multiplex. Autonomic neuropathy.	*Result in:* Vitreous hemorrhage → retinal detachment & blindness.	*Result in:* microalbumiuria (early sign) → proteinuria → nephrotic syndrome → end stage renal disease ESRD.	

Metabolic Bone Diseases

Hypocalcaemia	Vit. D deficiency	Phosphorus deficiency
Causes : – The commonest cause is hyperparathyroidism. – Hypomagnesaemia because magnesium is required for parathyroid gland function. Symptoms : • Eye involvement of hypocalcaemia is early cataract. • CNS involvement may include seizure and dementia. • Extra pyramidal symptoms could be seen (Due to low calcium and high magnesium deposits formed and might affect the basal ganglia). • Cardiac effects include prolonged Q-T interval which predispose to ventricular tachycardia. • Tetany & paraesthesia. • Trousseau sign (is seen when blood pressure in the cuff increases above the systolic blood pressure, the hand will be painful and will have spasm in the muscles of forearm and hand. The wrist and MetacarpoPhalyngeal joints flex, the InterPhalengeal joints hyperextend, and the fingers adduct to each other). • Chovstek sign is seen when zygomatic arch tapping will cause twitching to the tapped side. Treatment : **Treatment of hypocalcaemia:** – Vitamin D • Ask the patient to get exposed to the sun • In renal or liver failure give 1,25 vitamin D • In malabsorption of Vitamin D, you can give the patient injection. – Calcium gluconate 10% slowly and carefully and **under ECG monitoring** (in case of tetany).	Causes: 1. Inadequate synthesis in the skin (Inadequate sunlight exposure without dietary supplementation.) 2.Low dietary intake 3.Malabsorpation : ✓ *Chronic steatorrhea (pancreatic)* ✓ *Malabsorption (gluten-sensitive enteropathy), coeliac disease, Crohn's disease.* ✓ *Surgical resection.* ✓ *Formation of biliary fistulas.* ✓ *chronic cholestasis (e.g. primary biliary cirrhosis)* 4. Impaired synthesis of 1, 25(OH) 2D3 by the kidney. ⦿ *Nephron loss, as occurs in chronic kidney disease* ⦿ *Functional impairment of 1, 25(OH) 2D3 hydroxylase (eg. In hypoparathyroidism)* ⦿ *Congenital absence of 1, 25(OH) 2D3 hydroxylase* ***(vit. D-dependency rickets type I).*** ⦿ *Suppression of 1, 25(OH) 2D3 production by endogenously produced substance (cancer).* 5. Target cell resistance to 1, 25(OH) 2D3 e.g. absent, or diminished number of 1, 25(OH) 2D3 receptors, as in **(vit.D-dependency rickets type II).** 6. Anticonvulsant therapy (esp. phenytoin and phenobarbital " they are enzyme inducer ") affects vit. D metabolism and predisposes to vit. D deficiency.	Dietary ➢ Low intake of phosphate. ➢ Excessive ingestion of aluminum hydroxide. Impaired renal tubular reabsorption of phosphate ➢ X-linked hypophosphataemia. ➢ Adult-onset hypophosphataemia. ➢ Other acquired & hereditary renal tubular disorders associated with renal phosphate loss (Fanconi's sydnrome, Wilson's disease). ➢ Tumor-associated hypophosphataemia PTH: plasma level rise in response to a full in serum ionized Ca , the effects are several all serving to increase plasma Ca and decrease plasma phosphate : • ↑osteoclastic resorption of bone . • ↑ Intestinal absorption of Ca . • ↑synthesis of 1,25-$(OH)_2D_3$. • ↑renal tubular reabsorption of Ca.

Disease	Osteomalacia	osteoporosis	Paget's disease
Definition	Inadequate mineralization of the osteoid framework, leading to soft bones produce rickets in children & osteomlasia in adult . {The mineralization is abnormal }	Is a term that denotes increased porosity of the skeleton resulting from reduction in the bone mass. It may be localized →disuse osteoporosis of a limb. Or may involve the entire skeleton, as a metabolic bone disease. • Primary (post menopausal-Senile) • Secondary (Endocrine Disorders) {The mineralization is normal but the bone mass is abnormal}	Also called osteitis deformans ⦿ "Collage of matrix madness", with furious osteoclastic bone resorption (osteolytic phase), hectic bone formation (mixed osteoclastic/osteoblastic phase), burnt-out osteosclerotic stage (gain in bone mass, but bone is disordered) ⦿ Mainly affect middle-age
Pathophysiology	⦿ Decrease in the product of concentrations of calcium and phosphate in the extra-cellular fluid so that the supply of minerals to bone forming surfaces is inadequate. ⦿ Abnormal or defective collagen production and a decrease in the PH at sites of mineralization (any condition that cause acidosis(e.g. drugs – renal failure)→ well cause hypocalcaemia → osteomalacia . ⦿ Deficiency of vit D (the causes vit. D Deficiency well cause osteomlacia ☺) ⦿ Liver failure , Anticonvulsant.	Menopause: ⦿↓ serum estrogen ⦿↑ IL-1,IL-6 levels ⦿↑ osteoclast activity AGING: ⦿↓ replicative activity of the osteoprogenitorcells ⦿↓ Synthetic activity of the osteoblasts. ⦿↓ Activity of the matrix bound growth factors. Genetic factors Nutritional effects	viral etiology (doge virus)
Clinical presentation	non-specific skeletal pain and muscular weakness, fractures ,characteristic waddling gait (duck gait) ,hypotonia ,expurgated reflexes	<u>DXA is the gold standard in the osteoporosis diagnosis</u> Asymptomatic disease until fractures occur, well established osteoporosis dorsal Kyphosis and loss of height occurs. Type I: Colle's fracture-Crush & Wedge fractures. Type II: Femure neck fracture	The chief symptom is bone pain over lesions (not diffused) , joint pains. Deafness can occur and is related to bony abnormalities of the internal and external auditory apparatus. **mainly affects the axial skeleton

Treatment	⦿ Oral vit. D (elgocalciferol) (dietary - lack of exposure to sunlight) ⦿ I.V./I.M. ergocalciferol (malabsorption) ⦿ Ca	Prevention is patter than treatment of established disease ⦿All pt. should be given calcium and vit. D supplements and Lifestyle advice such as (stopping smoking , reducing alcohol intake , regular wt – bearing exercise and reassessed after 2 y. ⦿Drug (bisophosphonates- SERM-HRT) ⦿Prevention of osteoporosis in pt. receiving corticosteroid: ➢ Reeducation of the dose to a minimal ➢ Alternative route of administration (e.g. rectal rote in distal UC) ➢ Alternative immunosuppressive agents	All suppresses the number and activity of the abnormal bone cells by acting through different mechanisms ⦿ Calcitonin (decreases bone resorption by decreasing the number of active osteoclasts). ⦿ Diphosphonates(inhibit both bone resorbtion and formation). ⦿ and mithramycin(a cytotoxic drug that inhibits bone resorbtion).

Vit. D and PTH are the major factors that control plasma Ca concentration and bone turnover .Bone metabolism also controlled by calcitonin ,thyroid hormone , glucocorticoides ,sex hormone and growth hormone .

Bone cells : Osteoblasts(bone forming cells) ,Osteocytes(permits translocation of mineral in and out of regions of bone removed from surfaces) ,Osteoclasts(bone resorption cells).Types of Bone: Cortical Bone & Trabecular Bone

Heart Failure

(Complex of syndromes → cardiac output (CO) ≠ body demand – Which result from structural or functional cardiac disorders).

Pathophysiology

1-HF initial event.

2-Compensatory mechanisms:

- Sympathetic stimulation → ↑ HR & contractility - ↑ vasoconstriction → ↑ VR (preload) & afterload - ↓ coronary perfusion.
- RAAS stimulation (due to ↓ed renal perfusion) → arterial vasoconstriction & salt/water retention → ↑ afterload.
- Remodeling: ventricular dilation & hypertrophy.

3-Failure of compensation (overwhelmed) → HF.

Types

Acute vs. chronic

Systolic vs. diastolic

High output vs. low output

Rt. Vs. Lt

Congestive (biventricular)

Lt	Rt
Common cause: ▪ IHD. ▪ HTN. ▪ Cardiomyopathy. ▪ MS/AS.	Common cause: ▪ Secondary to Lt HF.
Symptoms: ▪ Lung congestion → exertional dyspnea – PND – orthopnea – pulmonary edema. ▪ ↓ CO → fatigue – cold extremities – cyanosis. ▪ Nocturia. ▪ Chronic non-productive cough.	Symptoms: ▪ Tissue congestion → peripheral edema – oligouria & nocturia.
Examination: ▪ Gallop rhythm. ▪ Creptation – ronchi. ▪ Pulmonary HTN (loud P2). ▪ Cardiac cachexia.	Examination: ▪ Tachycardia. ▪ Raised JVP (+ve hepatojugular reflex). ▪ Petting peripheral edema. ▪ Hepatomegaly. ▪ Ascites/pleural effusion. ▪ Cardiac cachexia.

Investigation & diagnosis

A. Chest X-ray.

B. ECG

C. Natriuretic peptide (BPN) level → ↑ in HF (sensitive – if normal, exclude HF).

D. Blood test & other:

1. CBC → for anemia.
2. Liver enzyme → for hepatic congestion.
3. Glucose → for DM.
4. Urea & electrolytes → before starting drugs.
5. Thyroid function test → for thyrotoxicosis.
6. Cardiac enzymes → for MI.
7. Myocardial biopsy.
8. Cardiac catheterization.

E. Echocardiography.

<u>Patient approach:</u>

1) History & examination.
2) Investigations:
   a. CXR – ECG – plasma BNP → if normal, NO HF.
   b. Echocardiography → if normal, NO HF.

Management of congestive HF:

I) ⇊ CO	II) ⇊ salt/water retention	III) Stimulate contractility (inotropic agents)	IV) Other :
▪ Rest & Weight loss. ▪ Small meals. ▪ Drugs → vasodilators (ACE inhibitors – nitrate – hydralazine).	▪ Restriction. ▪ Drugs: diuretics.	▪ Drugs (digitalis – β blockers).	▪ ICD implant. ▪ Biventricular pacing. ▪ Heart transplant.

Drug	Effect	Side effect	Note
ACE inhibitor	<u>Initial therapy</u> to prevent progression & improve survival.	▪ Angiodema. ▪ Hypotension. ▪ Renal insufficiency. ▪ Dry cough/rash.	When contraindicated → use angiotensin II antagonist.
Diuretics	<u>MOST effective</u> in <u>relieving</u> symptoms of moderate to severe HF.	▪ Hyponatremia. ▪ Hypokalemia (except Spironolactone). ▪ Pre-renal Azotemia. ▪ Hyperuremia/Hyperglycemia	Thiazide → mild HF. Loop diuretics → severe HF. Spironolactone → severe HF (also ↓ remodeling).
Digitalis	<u>Significant symptom improvement</u> in patients with AF or not responsive to diuretic therapy.	Highly toxic ▪ Sinus arrest. ▪ Heart block. ▪ Ventricular tachycardia/fibrillation.	<u>Toxicity management:</u> ▪ Stop agent. ▪ Atropine for bradycardia. ▪ Lidocaine & phenytoin for vent. tachy/fib. ▪ Anti-digoxin antibodies (Fab-fragment) in overdose.

HF classes & stages

NYHA class	HF stages
Class I → no limitation of activities. Class II → mild limitation (HF symptoms with ordinary activities). Class III → marked limitation (HF with less than ordinary). Class IV → symptoms with rest.	Stage A → high risk (NO symptoms/disease). Stage B → disease (NO symptom). Stage C → disease with symptoms. Stage D → advanced with severe symptoms.

Tuberculosis

<table>
<tr><th>Cause</th><th>Transmission</th><th>Predisposing factors (which ↓ immunity)</th><th>Pathophysiology</th><th colspan="2">Types</th></tr>
<tr><td rowspan="2">Mycobacteria (acid-fast bacilli)</td><td rowspan="2">DROPLETS (coughing/sneezing)</td><td rowspan="2">Environmental:
• Malnutrition/poverty.
• Over-crowding.
• Alcohol.
• Heavy smoking.
Pathological:
• DM.
• Steroids/cytotoxic drugs.
• Chronic lung disease.
• Lymphoma.
• HIV & immunocompromised.</td><td rowspan="2">Mycobacteria → stimulate T-cell mediated immunity (forming caseous granulomatous lesions)</td><td>Pulmonary
▪ Initial exposure (usually asymptomatic).
▪ Latent TB (with +ve tuberculin test).
▪ Secondary pulmonary TB.
▪ Miliary TB

Clinical features:
▪ Fever/night sweats.
▪ Weight loss/Fatigue.
▪ Cough.
▪ Sputum (purulent/mucoid).
▪ Hemoptysis.
▪ Pneumonia & pleural effusion.</td><td>Extra-pulmonary
▪ Pleural TB (common).
▪ Bone & joints.
▪ Pericardial TB.
▪ Meningitis.
▪ GI & GU.
▪ Peritoneal.</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="3"></td></tr>
<tr><th colspan="3">Investigations</th><th colspan="3">Treatment</th></tr>
<tr><td colspan="3">1- Sputum for AFB smear → ZN stain or auramine phenol.
2- Culture (sputum – aspiration – biopsy) → slow growing in L/J medium.
3- Chest X ray.
4- Tuberculin test (PPD) → it maybe false negative in AIDS patients.</td><td colspan="3">▪ Combination therapy (to prevent resistance).
▪ 2 line drugs, the 2nd (more toxic – expensive – long duration – less effective)</td></tr>
</table>

Common Endemic Infections in KSA

1) Brucellosis

Microbiology:

- 6 species ,4 can be transmitted to man
- Burcella Miltensis (also gout and sheep) → commenst in KSA Brucella Abortis (cow) and brucella Swis (in pigs) and brucella canis (dogs) are communicable to human while brucella ovale is limited to animals .
- G-ve , non motile ,non spore forming, facultative
- Culture can take long time, survival can be very long
- Optimum temperature is 37 C (20-40 C)

Risk factors :

- Caring for delivering animal
- Placental membrane - consumption of raw milk products
- Undercooked meat - Inhalation (rare)
- Human-human sexually (rare)

Pathogenesis :

Organism is engulfed by monocytes → reticuloendothelial system → lymph node where they are either eradicated or multiplies & escape → blood stream → circulate & cause fever (**Mediterranean fever** or **undulant fever)**

It also mediates psoas abscess & micro abscess surrounded by chronic inflammatory cells

Common symptoms :

- Fever (relapsing and recurrent) - Body aches - Lethargy - back
- pain- joint pain - Sweating - anorexia - irritability – head ache
- weight loss

Clinical finding :

- Spleenomegally - joint tenderness
- Hepatomegally - spinal tenderness

2) Schistosomiasis

There are 3 main strains :

- S.Japuanicum
- S.Mansoni (for GI only) → most common in KSA
- S.Haematobium (can cause urinary & GI disease)

Shistosoma simplified life cycle :

- Ovum – micracidum – goes to snail – then circaria –penetrate human skin—execrated in water as ovum – mircacidium .
- Not found eastern countries .
- The shistosoma enters the body through skin → purities & swimmers itching in papules . the circaria goes through the skin to the portal vain & pulmonary circulation which when arrives cause generalized symp. Like fever ,arthralgia & dry cough .the fever is called Katayama fever.
- When the circaria becomes an adult, it migrate to the mesenteric vessels & reproduce forming larvae that can stay in the GI tracts, get excreted in stools or migrate to the hepatic circulation which if a lot they can obstruct the portal vain & cause granuloma & periportal fibrosis but still the normal function is still retained.

Katayama Fever :

- Several days , 2-3 weeks
- Fever, chills ,headache, malaise, edema, confusion.
- Hepatosplenomegally
- Lymphadenopathy
- Eosinophilia – parasites infection
- Cerebral edema (CT) rare with S.mansoni but may accur with S.japanicum

Symp of S.mansoni :

- Sacro ileitis - eymphdenopathy
- Impaired straight leg raising

Serological tests

- Standard tube agglutination test → is the most commonly used
- Microplate agglut. Test
- 2-mecraptoethanol agglut. Test
- Coombs test
- Complement fixation test
- Rose Bengal test
- Enzyme-linked immunosorbent assay
- Gel precipitation test

Note: in brucella, cellular immunity is more important in eradicating brucella.

Active disease :

Clinical evidence (symp. & signs)

- +ve at > 1:160 by STAT
- +ve at > 1:140 by 2-ME test
- + ve > by ELISA (high IgG & low IgM)

Chronic disease so dignosed by +ve IgG NOT IgM .

Treatment :

- Regimen A → oral Rif. + Doxycycline → cure rate 95 %
- regimen B → streptomycin , Doxycycline → both have cure rate 96% (mostly used)
- regimen C → streptomycine → cure rate 59%
- WHO regimen → tetracycline→ cure rate 59%

Vaccines attenuated strains:

- Effective for short duration ,thatz why it is avoids
- B.abortus atrain 19
- B.mellitensis strain Rev I.
- B.suis strain 2s
- B.abortus strain 45/20

- Abd. Pain - fatigue - blood in stool - mucous in stool –
- tenesmus - depression -diarrhea - constipation

the most common complication of schistosomasis infection → portal hypertension and its common complication (varices & port systemic anastomosis)

- schistosomasis (also called bilharziasis) my cause hydronephrosis.

NOT E: schistosoma cause fibrosis but not cirrhosis

Symp of S.Hepatomium :

- haematuria - dysuria - abd.pain - frequency – tiredness –
- blood in stool - mucous in stool - depression

treatment :

- metrifonate
- oxamniquine
- paraziquantel (mostly)

- B.melitensis strain H38

Prevention :

- Elimination of the disease in animals
- Personal hygiene (washing exposed clothes)
- Environmental sanitation (disposal of contaminated substances)
- Pasteurization of dairy products
- Health education
- Immunization

3) salmonella / typhoid fever

Classification of salmonella :

- according to their ecologic niches
- serotyping (kanfmann white) :
  O antigen A-I , H antigen(subtypes)
- over 2000 serotype
- spectrum of clinical manifestation of salmonella
- gastroenteritis
- enteric fever
- bacteremia : with metastatic , without metastatic disease
- asymptomatic carrier state

Pathogenesis :

- Infective dose 10^6 - 10^9
- Penetration of distal ileum mucosa
- Multiplication in the payer patches
- Diarrhea is caused by : - prostaglandin induced (c-AMP)
  Local inflammatory response - S.enterotoxin

Typhoid Fever :

- Enteric (abd. Pain) fever + 2S (splenomegally & spots) + 2D (diarrhea & delirium) .
- Pt could be come with diarrhea or constipation

Definition : A disease characterized by prolonged fever ,abd pain

4) leishmaniasis

- Infection with one r other species of protozoa (leishmania)
- Conveyed by : sand flies (phlebtomus)
- Visceral leishmaniasis : L. donovoni
- Mucocutanous : L. Braziliensis
- Cutanous → old world : L. tropica major ,, L. tropica minor
- New world → L.Brazilensis ,, L. Mexicana

Pathology :

- L donovani parastize the recticulo.endoth.cells
- Great proliferation of microphage
- Cells result : liver –spleen enlarge
- The red bone marrow extended

Clinical pic:

- Incubation :2 weeks – 18 months
- Early stage not easy for diagnose
- There is constant physical signs
- BP ↓ , pulse ↓ , fever
- Change in blood picture particularly ***Leucopenia***
- Outstanding physical sign is enlarge. Of spleen 3 cm a month
- Liver : enlarge.spleen + liver neither tender nor painful

,diarrhea ,delirium, rash (rose spots) & splenomeagally

Etiology : salmonella typhi & para typhi A &B – motile G-ve bacilli .

- H antigen → associated with flagella
- O- antigen → a lypopolysacchrides associated with cell wall
- VI -antigen →a polysacchraides associated with cell capsule

Epidemiology :

- Affects all group
- Common in developing countries
- Transmission through oral-fecal route (remem.entric)
- Affecting individuals may become asymptomatic carriers particularly females &older males (underlying cholecystitis)
- S.Typhi is resistant to drying & cooling

	symp	signs	pathology
1st wk	Fever,chills,headache	Abd.pain, tenderness	Bacteremia
2nd wk	Rash , abd.pain	Rose spots	Mononuclear , vasculitis of skin , hyperplasia of peyer's batches ,typhoid nodules
3rd wk	Intestinal melena , bleeding , perforating & chock	Ulceration ,perforation,rgid abd. With peritonitis , ileus, coma	-
4th wk resolution & later	Recurruance relapse of acute dis , wt loss,	cachexia	Cholecystists , chronic fecal carriage of bacteria

Antibiotic used for salmonella typhi :

- Chloramphenicol
- Ampcillin ,amoxil

- Sometimes : jundice = prognost . significance
- Enlarged : lymph node , could be but it's a feature of the disease.
- Wasting : emaciated pat with a protuberant .
- Abdomen (liver + spleen enlarged)
- Fever : without subjective symptoms of fever – no delirium
- Sometimes : there is no fever .
- Skin : dry , rough , the natural pigmentation of skin over the bone and around the mouth is deepened . (kala azar)
- Hair : fallout .
- Lungs : bronchopneumonia
- GIT : diarrhea , dysentery

Diagnosis :

1- Needle aspiration
2- Leucopenia
3- Formalin gel (adhyde)
4- Complement fixation and fluorescent
5- Complement fixation
6- IV +V : in trypansomal infection
7- Skin test (Montenegro)

Prophylaxis:

- Immunity : kala azar permanent immunity to all L.Donovani
- L.tropica major cross immunity to L. tropica minor ,not the opposite
- L.brazillienses to L.mexican but not vice versa

Vaccine :

- L.tropica major – living leptomondas
- L.donovani : intradermally or sc
- Local leishmanial infection . leishmanioma developing immunity
- No visceral L.

Treatment :

1- Antimonial :

- Co-trimoxazole - 3rd gen. cephalosporine - Quinolones **Vaccination :** - Inactivated S.typhyi : 2SC injection ,, 55-88% protection for 3-5 yrs. - Attenuated S.typhi : Liquid 3 doses,, enteric coated capsule ,,protection 60-70%	a- urea ,stibamine , pentavalen + antamonia (IV) **SE:** nausea ,vomting,joint pain,abd. Pain,diarrhea **Contraindication :** liver and kidney failure b- Sodium stiboguconate (pentostam) (IM) **SE:** anaphylactic shock *2- Diamidiem* Pentamide isothionate **SE:** hypoglycemia

Rheumatoid Arthritis and Osteoarthritis

OA	RA
Degenerative disease	Systemic, chronic, inflammatory disease.
Affects cartilage	Affects synovial joints.
Hypertrophy of bone at the articular margins & degeneration of cartilage.	Thickening & hypertrophy of the synovium.
There is a great increase in risk of developing OA by the age 65 or older.	Peak age: 25-50 But it can affect any age.
Often monoarticular joint involvement	Mainly (75%) polyarticular joint involvement.
No systemic involvement, no erythema or warmth	A systemic disease!
Any joint can be affected, but weight baring joints are most commonly involved(hips, knees, cervical & lumbar spine)	Most commonly involved joints are wrists,PIPs, MCPs & thumbs.
Radiological features: -joint space narrowing(due to loss of cartilage) -osteophytes -sclerosis of subchondral bony end plates adjacent to diseased cartilage(most severe at points of maximum pressure) -subchondral cysts occur as a result of increased transmission of intra-articular pressure to the subchondral bone.	-loss of juxtaarticular bone mass (periarticular osteoporosis)near the finger joints. -narowing of the joint space (due to thinning of the articular cartilage) is usually seen late in the disease. -Bony erosions at the margins of the joint.

SLE and Scleroderma

SLE

(multisystem CT disease → with Autoantibodies – circulating immune complexes – immunological tissue destruction)

Characteristic	Predisposing factors:	Pathogenesis
• Peak age: 20-40 yrs. • Female to male ratio (9:1).	– Genetics (HLA – DR2 & - DR3). – Gender (♀). – Environmental: ▪ Drugs. ▪ UV light. ▪ Viral infection.	Multifactorial ▪ ↑ CD4:CD8 ratio. ▪ Uncontrolled production of: – Autoantibodies → against cells. – Immune complex → deposition in tissue.

Clinical features:		
1. Systemic manifestations	– Fatigue	– Fever – ↓ weight & anorexia
2. Musculoskeletal (>90%)	• Arthralgia • Myalgia	• Intermittent arthritis (same as RA: symmetrical small joint, but NOT erosive).
3. Skin (80%)	▪ Butterfly rash (cheeks & face). ▪ Photosensitivity/ Alopecia	▪ Discoid lesions (erythromatous with scaliness & later scaring).
		▪ Oral ulcers. ▪ Raynaud's phenomenon.
4. Kidney (50%)	– Range from proteinuria to nephrotic syndrome & renal failure.	– Hypertension.
5. CNS (60%)	• Headache, depression, & psychosis.	• Seizures – cerebellar dysfunction – meningitis
6. Hematological	• Hemolytic anemia.	• Lymphopenia. • Thrombocytopenia.
7. CVS & respiratory	• Pericarditis – myocarditis.	• Non-infective endocarditis. • MI.
	• Pleurisy & pleural effusion.	• Lupus pneumonitis.
8. Eye	• Retinal vasculitis.	• Blindness

<table>
<tr><th colspan="2">Investigations:</th><th>Diagnosis criteria (≥ 4 out of 11)</th></tr>
<tr><td>Blood</td><td>Immunological findings</td><td rowspan="2">1. Malar rash.
2. Discoid rash.
3. Photosensitivity.
4. Oral ulcers.
5. Arthritis.
6. Serositis (pleurisy or pericarditis).
7. Renal disorder.
8. CNS (seizures or psychosis).
9. Hematological disorder.
10. Immunological disorder.
11. ANA antibodies.</td></tr>
<tr><td>▪ Anemia.
▪ Leukopenia.
▪ Lymphopenia.
▪ Thrombocytopenia.</td><td>• ANA (not specific).
• Anti-DNA.
• Anti-Sm (specific).
• Anti-phospholipid antibodies (3 types):
1- Lupus anticoagulants.
2- Anticardiolipin antibody.
3- False positive serologic test for syphilis.
• Low complement level.</td></tr>
<tr><td colspan="3"></td></tr>
<tr><th colspan="2">Prognosis (10 yr survival)</th><th>Treatment</th></tr>
<tr><td colspan="2">Poor with:
• Renal & CNS involvement.
• Hypertension.
• Presence of anti-phospholipid.
• Poor socioeconomic status.</td><td>NO cure, only management:
– Mild symptoms (arthralgia) → NSAIDs.
– Cutaneous symptoms → chloroquine & Hydroxychloroquine.
– Severe symptoms (CNS & renal) → corticosteroids – immunosuppression.</td></tr>
<tr><td colspan="3"></td></tr>
<tr><th colspan="3">Note:</th></tr>
<tr><td colspan="2">Drug-induced SLE</td><td>– Hydralazine & Procainamide are the most common.
– Usually NO CNS & kidney involvement.
– Positive ANA, but NO anti-DNA & NO hypocomplementemia.</td></tr>
</table>

Systemic sclerosis "scleroderma"

(chronic multisystem disease → fibrosis & degeneration of skin – vessels – visceral organs)

<table>
<tr><th colspan="5">Types</th><th>Clinical manifestations:</th></tr>
<tr><td colspan="2">Systemic</td><td colspan="2">Localized (skin ONLY)</td><td>Other</td><td rowspan="3">− Raynaud's phenomenon.
− Skin changes
− Pulmonary (dyspnea – cough – lower lobe fibrosis).
− GI (dysphagia – heartburn – malabsorption).
− Kidney (failure – hypertension).</td></tr>
<tr><td>Diffuse cutaneous scleroderma (40%)</td><td>Limited cutaneous scleroderma (60%) "CREST syndrome"</td><td>Morphea</td><td>Linear scleroderma</td><td rowspan="2">♦ Overlap with other CT disease.
♦ Chemical-induced.</td></tr>
<tr><td>− Skin changes then Raynaud's phenomenon.
− Skin changes are widespread.
− Early involvement of other organs.</td><td>− Raynaud's phenomenon then skin changes.
− Skin changes are limited to head & distal extremities.
− Less involvement of other organs.</td><td>Plaques of skin induration & sclerosis.</td><td></td></tr>
<tr><td colspan="6"></td></tr>
<tr><td colspan="6">Investigations:
− ANA with nucleolar pattern.
− Anticentrome antibodies (ACA) in CREST syndrome.
− Anti-Scl70 in diffuse scleroderma.</td></tr>
</table>