INTRODUCTION TO ENDOCRINOLOGY

Classes of hormones

1. Aminoacid derivatives:
   - Thyroid hormones - T3, T4
   - Catecholamines - Adrenaline, Noradrenaline, Dopamine
     - These are the derivatives of aminoacid Tyrosine
     (Derivatives of tryptophan are not hormones, they are neurotransmitters i.e, Serotonin & melatonin)

2. Vitamin derivatives:
   - Vit A
   - Vit D

3. Small peptides (<50 Aminoacids):
   - Most of the Hypothalamic pituitary hormones.
   - Most Neuropeptides like Neotensin, Neuropeptide Y, Enkephalins, Endorphin etc.
   - Except FSH, LH, TSH ➔ These are glycoproteins They contain >200 Aminoacids
   - Have common α subunit

4. Large peptides:
   - Insulin
   - PTH
   - Renin

5. Steroid hormones:
   - Hormones from the Adrenal cortex
     - Mineralocorticoid - Aldosterone
     - Glucocorticoid - Cortisol
     - Adrenal androgens/Sex steroids
     - Dihydroepiandrosterone sulfate ➔ Androstenedione
       ➔ Gonadal hormones - Testosterone
       - Estrogen
       - Progesterone
Endocrine System

Hormones

GROUP I

Intracellular receptors

cell membrane receptors

cyttoplasmic nuclear

GROUP II

G-Protein coupled
Tyrosine kinase
Jakstat
Serine threonine kinase

Group I hormones

- Steroid hormones
- Gonadal hormones
- Vit A & Vit D
- Thyroid hormones

Group I Hormones

Type-1 Receptors (Receptors in cytoplasm)
Steroid Hormones

Type-2 Receptors (Receptor in Nucleus)
Vit A & Vit D Thyroid Hormones

Steroids receptor is bound to Heat shock protein (HSP) in the resting state.

Dissociation of HSP conformational change in receptor when Ligand binds to receptor.

Receptor with Ligand moves into the nucleus & binds to GRE (Glucocorticoid Responsive elements) → Protein translation.

- Thyroid receptors are located inside the nucleus.

Binds to TRE (Thyroid Responsive Elements)

Protein translation.

- Steroid receptors - Homodimer receptors - co activator binding
- Thyroid receptors - heterodimer receptors - co repressor inhibition followed by co activator binding
Orphan receptors

- Orphan receptors are “Constitutively activated”
  - Eg: SF-1 Required for Gonadotrope cell growth, they are actually transcription factors.
  - HNF-4 α - also transcription factors
    - mutation produces MODY- Type 1 (maturity onset DM in young)

Group- II hormones

- They have got receptors in the cell membrane

1. GPCR : [G- Protein Coupled Receptors]
   - They have Seven membrane Spanning domains - α, β, γ, complex bound to GDP.
   
     \[
     \text{GDP} \rightarrow \text{GTP}
     \]

   (in resting state)
   when hormone comes and binds, there will be change in the configuration.

   \[
   \text{GTP} \rightarrow \text{GDP}
   \]

   α- GTP dissociates and bind to effectors.
   effector = and messenger
   (cAMP, IP3/ DAG, cGMP)
   cAMP- Gs or Gi
   IP3/ DAG - Gq
   cGMP - Gt (transducin)
Hormones acting via cGMP:
- Vasodilators act via cGMP.
  
  \( \text{E.g.: NO, ANF (Atrial Natriuretic Factor)} \)

Hormones acting via cAMP:
- \( \text{cAMP } \rightarrow \text{inactive Protein Kinase A} \)
- \( \downarrow \)
- \( \text{Active Protein Kinase A} \)
- \( \downarrow \)
- \( \text{Protein Phosphorylation} \)
- So, the system is called \( \text{cAMP / PKA System} \).

Hormone acting via IP3/DAG system:
- \( \text{Phosphoinositol pyrophosphate (PIP}_2 \) \text{Phospholipase C} \)
- \( \text{Diacyl Glycerol (DAG)} \)
- \( \downarrow \)
- \( \text{Activate Protein Kinase 'C'} \)
- \( \downarrow \)
- \( \text{IP3} \)
- Activates "Ca-Calmodulin pathway"
- Most vasoconstrictors act via IP3 DAG pathway.

Hormones acting via cAMP & IP3/DAG pathway

- Hypothalamus
  - CRH
- Pituitary (Anterior)
  - ACTH, FSH, LH
  - \( \text{TH + V}_2 / V_3 \)
- Vasoconstrictors
  - AT-II, Substance P
- Pancreas
  - Glucagon, Somatostatin (\( \text{G}_i \))
- GI T
  - Secretin
  - \( \text{cCK, Gastrin} \)
- ANS
  - Alpha \( \text{A}(\text{Gi}) \), Beta
  - Alpha \( \text{I} \), Muscarinic Ach
- Miscellaneous
  - PTH, Calcitonin

Most potent vasoconstrictor in the human body - urotensin
- \( \alpha_1, \beta_1, \beta_2, \beta_3 \) - act via cAMP
- \( \text{ACH} \) - acts via IP3/DAG.
- All the hormones mentioned above under cAMP are Gαs (Gα-stimulatory) hormones, that means they increase cAMP.
- Example of Gβ hormone - somatostatin & α₂ receptors - they decrease cAMP.

\[ \text{b tyrosine kinase} \]
\[ \text{c Janus kinase (JAK)} \]

\[ \text{Both exists as monomers} \]

Once the hormones come and binds, there will be intracellular dimerisation.

Then, the protein gets phosphorylated either Tyr. Kinase/Janus Kinase

Translocated to nucleus.

---

**Hormones acting via Thyrosine kinase, JAK-STAT & Serine kinase**

<table>
<thead>
<tr>
<th>Tyrosine Kinase</th>
<th>JAK-STAT</th>
<th>serine Kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>GH</td>
<td>TGF (Transformation GF)</td>
</tr>
<tr>
<td>EGF (Epidermal)</td>
<td>prolactin</td>
<td>Activin</td>
</tr>
<tr>
<td>IGF (Insulin)</td>
<td>EPO</td>
<td>inhibin</td>
</tr>
<tr>
<td>NGF (Nerve)</td>
<td>erythropoietin</td>
<td>BMP</td>
</tr>
<tr>
<td>PDGF (Platelet derived)</td>
<td></td>
<td>(Bone Morphogenic Protein)</td>
</tr>
<tr>
<td>FGF (Fibroblast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Growth Factors (GF)</td>
<td>act via Tyr. kinase except TGF αβ</td>
<td></td>
</tr>
</tbody>
</table>

- Most potent fibrogenic cytokine in the human body “TGF β”
- GH & prolactin are together called as twin hormones.
ANTERIOR PITUITARY

Introduction

- Anterior pituitary is the master gland of endocrine
- CD₄ + T cells are the important components of immune system

Hormones produced by the anterior pituitary:

- 6 hormones are produced by the anterior pituitary
  - a. Prolactin - Produced by lactotrophs
  - b. Growth hormone - Produced by somatotrophs
  - c. LH/FSH - Produced by gonadotrophs
  - d. TSH - Produced by thyrotrophs
  - e. POMC - Produced by corticotrophs

- First cells to develop in the anterior pituitary at 6 weeks of gestation are the corticotrophs, they produce POMC (Pro Opio melanocorticotrophic hormone) - has 4 derivatives

\[
\begin{align*}
POMC & \\
\rightarrow & \\
ACTH & \text{MSH} & \beta - \text{enkephalin} & \beta - \text{endorphin} & \\
\uparrow & \uparrow & & \\
\text{in ACTH} & \text{in MSH} & & \text{hyperpigmentation}
\end{align*}
\]

- All the anterior pituitary hormones are regulated by hypothalamus

- Hypothalamus produces trophic hormone factors - TRH, CRH, GnRH, GNRH → trophic factors are secreted into hypothalamohypophyseal portal system via the pituitary stalk → reach anterior pituitary

- Prolactin inhibitory factor produced by hypothalamus regulates prolactin

- Prolactin is the only hormone that is under inhibitory control of the hypothalamus
- The pathway through which dopamine inhibits prolactin → tubuloinfundibular pathway
- Relationship between hypothalamus and anterior pituitary → hypophysiotrophic relationship

\[ \text{Hypothalamus} \]
\[ \downarrow \]
\[ \text{Supraoptic nucleus (major)} \quad \rightarrow \quad \text{Vasopressin (ADH or AVP)} \]
\[ \downarrow \]
\[ \text{Para ventricular nucleus} \quad \rightarrow \quad \text{Arginine vasopressin} \]
\[ \quad \uparrow \]
\[ \text{Neurohypophysis}^* \]
\[ \quad \uparrow \]
\[ \text{Co-peptin}^* \]

- ADH produced in the hypothalamus goes to the posterior pituitary → stored there via nerve fibers in the stalk
- The relationship between the posterior pituitary and hypothalamus → neurohypophysial relationship

**Development of anterior pituitary**

- Development of anterior pituitary is from Rathke's pouch → neuroectodermal derivative, actually a diverticulum or upgrowth
- Posterior pituitary develops as a down growth from the floor of the 3rd ventricle
- Most common cause of congenital hypopituitarism → pituitary dysplasia
- In pituitary dysplasia, the hormones of posterior pituitary are intact
- Cells from the Rathke's pouch need to migrate across the midline to reach the anterior pituitary → in pituitary dysplasia, midline craniofacial defects are present

**Anatomy:**
- The anterior pituitary is situated in a bony cage called Sella turcica.
Posterior relationship:
- Posterior relationship of anterior pituitary is sphenoid sinus
- Surgery → preferred approach is trans sphenoidal approach

Lateral relationship:
- Pituitary tumour can expand to cavernous sinus/ lateral wall of cavernous sinus/ temporal lobe
- Inside cavernous sinus - 6th nerve, internal carotid artery
- On lateral wall of cavernous sinus - 3,4,5 (ophthalmic, maxillary branch)
Anterior/ventral relationship:
- Ventrally covered by a layer of dura called as Diaphragma sellae.
- The line of least resistance for the tumor is ventral.
- On T₁ sagittal image, the white spot or bright spot helps in the identification of posterior pituitary.
- When a tumor enlarges, it first compresses the pituitary stalk before it compresses the optic chiasma to cause heteronymous or bitemporal hemianopia.

Effects of tumor:
1. Hormonal effect: Producing acromegaly, prolactinoma, etc.
2. Stalk effect: Compression on the stalk, affects control of hypothalamus on the anterior pituitary hormones. So, hormones reduce. Prolactin increases, this phenomenon of hypopituitarism + hyperprolactinemia is called stalk effect.
Blood supply of pituitary:

- Metastasis to pituitary are carried by inferior hypophyseal artery
- MC malignancy to metastasise to pituitary: carcinoma breast
- MC manifestation of pituitary metastasis absence of ADH [central diabetes insipidus]
- The first cells to develop at 6 weeks are corticotrophs
- Transcription factors are required for the release of anterior pituitary hormones
- TSH, ACTH, GH, PROLACTIN - Pit -1 & PROP-1 are the transcription factors
- For FSH, LH - SF -1 & DAX 1
- % of total secretory cells in the anterior pituitary - 50% are growth hormone secreting cells

* GH cells > FSH, LH > ACTH > TSH, LH
  1st - GH cells
  2nd - Prolactin producing cells

- In hypopituitarism, the first hormone to decrease is growth hormone

Table - Hormone secreting cells of the human anterior pituitary gland

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Hormones secreted</th>
<th>% of total secretory cells</th>
<th>Stain affinity</th>
<th>Diameter of secretory granules (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactotrope</td>
<td>prolactin</td>
<td>10-30</td>
<td>Acidophilic</td>
<td>200</td>
</tr>
<tr>
<td>Corticotrope</td>
<td>ACTH</td>
<td>10</td>
<td>Basophilic</td>
<td>400-550</td>
</tr>
<tr>
<td>Thyrotrope</td>
<td>TSH</td>
<td>5</td>
<td>Basophilic</td>
<td>120-200</td>
</tr>
<tr>
<td>Gonadotrope</td>
<td>FSH, LH</td>
<td>20</td>
<td>Basophilic</td>
<td>250-400</td>
</tr>
<tr>
<td></td>
<td>growth hormone</td>
<td>50</td>
<td>Acidophilic</td>
<td>300-400</td>
</tr>
</tbody>
</table>

- Next hormones to decrease are FSH & LH & ACTH
- Even in the absence of TSH, Thyroid can produce T3 & T4; hypothyroidism not a component of hypopituitarism
- GH & Prolactin producing cells - Acidophilic - twin hormones
- ACTH, TSH, FSH & LH producing cells - Basophilic
- Largest diameter of secretory granules - corticotrophs

Prolactin

- Produced by lactotrophs and acts via JAK STAT receptor
  (peptide hormone)
Function:
- It induces and maintains lactation in a breast already primed by estrogen
- Prolactin is also produced from placenta, uterus and other parts of CNS

Physiological inhibitor:
- Physiological inhibitor of prolactin is dopamine → pathway called tubuloinfundibular pathway

Physiological stimulators
- Estrogen
- TRH
- VIP
- Oxytocin

Hyperprolactinemia:
- Fasting prolactin levels - normal - <25 μg/L
- Physiological hyperprolactinemia - 25-40 μg/L
  Causes:
  a) Pregnancy & lactation
  b) REM sleep
  c) Stress
  d) Chest wall stimulation
- Prolactin levels - 40 - 100 μg/L - a) Drugs  b) Systemic disorders
- Prolactin levels - >100 μg/L - Probably due to tumors
- Prolactin levels - >250 μg/L - Tumor
  Tumor size corresponds to prolactin levels

Causes of prolactin levels between 40-100 μg/L:

Drugs: a) D₂ blockers
1. Typical antipsychotics - blocks mesocortical, tubuloinfundibular
   & nigrostriatal pathways
   mesocortical block - worsening of negative symptoms
   Tubuloinfundibular block - ↑ prolactin
   Nigrostriatal block - extrapyramidal S/E
2. Atypical antipsychotics - Only Risperidone produces hyper prolactinemia.
b) Antiemetics - metoclopramide -

cross BBB - hyperprolactinemia

Domperidone - doesn’t cross BBB -

No hyperprolactinemia

- Hyperprolactinemia due to drugs - value normalises within 72 hours
  c. TCA/ SSRIs - Can cause hyperprolactinemia, mild effect on D2
  d. Opiates
  e. Verapamil
  f. H2 blockers
  g. α – methyldopa.

- Systemic disorders with 40 – 100 µg/l of prolactin:
  1. CKD
  2. Chronic liver disease
  3. PCOS
  4. Hypothyroidism ** - TRH levels ↑

TRH can physiologically increase the prolactin levels
PROLACTINOMA

Prolactinoma

- mc tumor of pituitary is prolactinoma.
- α - Subunit of FSH secreting tumors are more common than Prolactinomas, but they're clinically insignificant.
- There are 3 types of Prolactinomas:
  - a. 90% of the Prolactinomas have < 1 cm size - microadenomas - 20 : 1 (F : m)
  - b. 9% of the Prolactinomas have 1-4 cm size - microadenomas - 1 : 1 (F : m)
  - c. 1% of the Prolactinomas have > 4 cm size - giant prolactinomas - 1 : 1 (F : m)

- Prolactinomas generally occur at the age of 25–45 yrs, mostly in females.
- A Prolactinoma which is occurring at an age <20 yrs is due to a Genetic Syndrome unless proven otherwise.
- The 3 Genetic syndromes associated with Prolactinomas are
  1. MEN-1 syndrome
  2. McCune Albright syndrome
  3. Carney's complex

- A tumor occurring in a female (25-45 years) generally presents with hormonal effects rather than mass effect or stalk effect because 90% of them are microadenomas. In males, they are diagnosed late.

- Clinical presentation in 25-45 year old females:
  1) GALACTORREA AMENORRHEA COMPLEX (mc)
     a) INFERTILITY FOR EVALUATION (luteal phase dysfunction)
- In males, the mc presentation - loss of libido, erectile dysfunction.
- Prolactinomas can produce osteoporosis of spine.
- Prolactinomas can also cause insulin resistance.
Diagnosis of prolactinoma

Screening test of choice:

Fasting prolactin levels
- If >100 μg/L - it can probably due to a tumor
- If >250 μg/L - its definitely a tumor

Hook effect:
The patient has got a tumor, but prolactin levels are normal
The patient will have symptoms
Repeat the test in serial dilutions

Macroprolactin:
very high prolactin levels in the absence of tumor. Patient is asymptomatic. This is functionally insignificant macroprolactin.
Measure the levels of macroprolactin (macro) specifically

Confirmatory test:
- Gadolinium enhanced MRI
- Prolactinomas do not take up contrast uniformly

![MRI images showing prolactinoma](image)

Indications of treatment:
- All macroadenomas and symptomatic microadenomas must be treated
- Asymptomatic microadenomas are not treated.
Repeat MRI after 6-8 weeks → increase in tumor size → treated
Treatment:
- Goal of the treatment is
  a. Prolactin levels should be normalized
  b. Tumor should shrink in size
  c. Hypogonadism must be corrected.
- The first line of treatment of prolactinoma is always medical irrespective of the size of tumor

DOC:
- Oral Dopaminergic agonists - Cabergoline > Bromocriptine
- Cabergoline has long t1/2 so, given twice weekly - 0.25 mg
- S/E of cabergoline are less - vomiting & postural hypotension are less compared to Bromocriptine.
- Bromocriptine is preferred in pregnancy

Follow up:
- Medical treatment for 1 month → repeat prolactin levels, (usually gets normalized.)
- Tumor shrinkage takes 3 months - 6 months
- Symptomatically patient gets better by 1 month
- If symptoms are not reduced or prolactin levels are still high, the patient is considered as dopamine agonist resistant tumor after 1 month of treatment with drugs.
- Dopamine agonist resistance is seen in < 20% patients
- Generally dopamine agonist resistant patients are also dopamine agonist intolerant.
  - In dopamine agonist resistance → surgery
dsurgery
dopamine agonist intolerant
- If patient is improving on drugs, to be given for “2 years”

- Risk of malignancy in prolactinoma - < 0.01%
- Marker of malignancy - Ki67
- Bromocriptine in pregnancy → stopped 7 days prior to lactation
Indications of surgery:

a. Dopamine agonist resistance
b. Dopamine agonist intolerant
c. Mass effects not improved after 1 month
d. Pregnancy, no response in 1 month
e. Bleeding into pituitary - pituitary apoplexy - white on T, image

Surgery - Transsphenoidal resection

Radiotherapy:

- Only if patient is medically unfit for surgery

- T, W image showing invasive giant prolactinoma in 28yr old lady (left)
- T, W image of same patient after 9m of medical treatment showing complete disappearance of tumor (right)
MANAGEMENT OF PROLACTINOMA

ELEVATED PROLACTIN LEVELS

Exclude secondary causes of hyperprolactinemia
MRI evidence for pituitary mass

Symptomatic Prolactinoma

Microadenoma

Macro adenoma

Test visual fields

Test pituitary reserve function

Tritrate dopamine agonist

Drug intolerance

Tritrate dopamine agonist

Serum PRL

Change dopamine agonist

Repeat MRI within 4 months

<20

20-50

>50 (µg/L)

No tumor shrinkage
Or tumor growth
Or persistent hyperprolactinemia

Monitor PRL
And repeat MRI annually

Consider surgery

Reassess diagnosis
Increase dose

Maintenance Rx
ACROMEGALY

Pituitary adenoma.

Prolactinoma > GH secreting > ACTH
most common adenomas secreting adenoma
(microadenoma) (macroadenoma) (macroadenoma)

FSH
LH
TSH

Secreting adenoma rare

Growth Hormone (GH) 00:02:15

* Produced by somatotrophs
* Constitutes >50% cells in anterior pituitary (Acidophilic)
* GH & Prolactin acts by JAK - STAT pathway

Twin hormones

* t½ : 5 - 20 min
* Pulsatile release

<table>
<thead>
<tr>
<th>GH</th>
<th>VS</th>
<th>Prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase during stage 2</td>
<td></td>
<td>Increase during REM sleep</td>
</tr>
<tr>
<td>&amp; 4 NREM sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological stimuli</td>
<td></td>
<td>Physiological stimuli</td>
</tr>
<tr>
<td>1) GHHRH from hypothalamus</td>
<td></td>
<td>1) Estrogen</td>
</tr>
<tr>
<td>2) Ghrelin from stomach</td>
<td></td>
<td>2) TRH</td>
</tr>
<tr>
<td>Physiological inhibitor</td>
<td></td>
<td>3) VIP</td>
</tr>
</tbody>
</table>

Somatostatin
Stimulating factor GH for release

- Hypoglycemia
- Exercise
- Fasting

Inhibiting factor for GH release

- Aging
- Obesity
- Hypocaloric state / malnutrition

Causes GH resistance

Paradoxical GH release:
TRH given to a normal person → GH production will not increase
TRH given to a GH secreting → GH production doubles

Adenoma pt

Paradoxical GH release

Peripheral actions of GH

- Executed by IGF-1
- Produced from the liver in response to GH binding to its receptors in liver
- IGF-1 also known as somatomedins C
- Structurally similar to insulin
- GH & IGF-1 has no effect on intrauterine height
- Intrauterine height depends on IGF-2 which is produced by diverse tissues
Acromegaly / GH secreting adenoma

- Growth hormone secreting tumor / adenoma
- Occurs after 40 yrs - after epiphyseal closure
- Only peripheral (acral) parts enlarge
- Results in acromegaly
- All the organs, soft tissue, cartilage enlarged
- If GH secreting adenoma occurs < 20 years age
  \[ \text{Before epiphyseal closure} \]
  \[ \text{Gigantism} \]

Acromegaly

- Common in M > F
- Macroadenomas
- > 40 years
- If occurs in young pt < 20 years (genetic syndromes)
  1) MEN - 1
     a) Carney’s complex
     3) McCune-Albright syndrome
- 98% of acromegaly are due to GH secreting adenoma
- Densely or sparsely granulated
- Of this, 80% are somatomammotrophic adenoma
  (Prolactin + GH secreting)
- Remaining 2% causes
  1) Paraneoplastic GH secretion
     Due to pancreatic islet cell tumor
  2) GHRH secreting tumor of hypothalamus
     Due to Hypothalamic Hamartoma
  3) Paraneoplastic GHRH Release
     Due to Bronchial carcinoid > small cell carcinoma lung
- Patient presents with
  1) Hormonal effect → GH excess
  2) Stalk effect
  3) Mass effect
Features of acromegaly

Coarse facial features
1) Prominent supra orbital ridges
2) Thick lips
3) Macroglossia
4) Frontal bossing
5) Prognathism
6) Jaw malocclusion
7) Deep husky voice
8) Large hands and feet

Systemic changes:
1) Nerve, muscle
   - Entrapment neuropathies
   - Myopathy - Due to atrophy of type II muscle fibres
2) Joints
   - Arthritis involving large joints especially
   - Due to synovial hypertrophy

3) Eyes
   - Angle closure glaucoma

Cardiovascular system
- Hypertension
- Asymmetrical LVH → Leads to Diastolic heart failure

Respiratory system
- Soft tissue proliferation
  ↓
  Obstructive sleep apnea
  ↓ leads to
  Pulmonary hypertension

Thyromegaly
- IGF - 1 acts on thyroid → Goitre

Colonic polyposis:
- Increased risk of malignancy compared to general population
Increased metabolic rate:
- Results in hyperhidrosis
- Seborrhoea

Increased salt & H₂O retention
- Due to ↑ Aldosterone levels
- One of the reasons for hypertension

Reproductive system
- Large tumor → Injury to stalk
  ↓
  Stalk effect
  ↓
  ↓ FSH, LH release
  ↓
  Hypogonadism
- Females with GH excess can have hirsutism

Metabolic issues
1) Hyperglycaemia → Insulin resistance
2) Hypertriglyceridaemia / Hyperlipidemia
3) ↑ production of 1, 25 (OH)₂ cholecalciferol
  ↓
  Excess Ca²⁺ & phosphorous absorption
  ↓
  Leads to hypercalcemia, hyperphosphatemia
  ↓
  Leads to hypercalcuria
  ↓
  Ca²⁺ oxalate stones
- Ectopic GH - Pancreas
- Pseudoacromegaly - conditions with acromegalic facies
  - Obesity
  - Hypothyroidism
  - Phenytoin therapy
  - IgA₂ tumors
  - Insulinoma
- GH excess - Insulin resistance - Acanthosis nigricans
Increased metabolic rate:
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  - Obesity
  - Hypothyroidism
  - Phenytoin therapy
  - IGIA tumors
  - Insulinoma
- GH excess - Insulin resistance - Acanthosis nigricans
MRI

T1, sagittal image post contrast
- Patchy uptake

T1, coronal post contrast MRI
- Patchy uptake
- Hence it is macroadenoma, patchy uptake of contrast
  ▼ GH secreting tumor

Acromegaly
- Young female facial asymmetry
  ▼ McCune Albright syndrome
  due to presence of polyostotic fibrous dysplasia.

Diagnosis

1) Screening test:
- IGF -1 levels are measured
  IGF -1 ▼ Long t½, non pulsatile release

2) Confirmatory test
- Oral glucose suppression test
  75 gm oral glucose ▼ Hyperglycemia
    ▼ After 1 hr Suppress GH release
    ▼ GH levels < 1 ng/ml In normal person
If GH levels are > 1 ng/ml → Acromegaly
GH levels normally decreased due to
  1) ↑ glucose
  2) Somatostatin

If GH level > 40 ng/ml (very bad prognosis)

Investigation of choice:
  Gadolinium enhanced MRI

Treatment

1) Always surgery – 1st line
   Transphenoidal surgical resection
   Only 50% macroadenoma are cured
   - Microadenoma → 80% cure
   - Relapse is common
   - Immediate post-op GH estimation

   GH detectable
   - Risk of relapse is high
     Drugs – 2nd line

   GH not detectable
   - Risk of relapse is low

2) Somatostatin analogues
   - Lanreotide (drug of choice)

3) GH receptor antagonist
   ‘Pegvisomant’

4) D₂ agonists
   - Cabergolin
   - Bromocriptine

Relapse cases:
  - Go for 2nd surgery
• Patient medically unfit for surgery go for gamma knife stereotactic radiotherapy

Pituitary function tests:
• Done in all patients with acromegaly
• Because these are macroadenoma
  ↓
  Stalk effect
  ↓
  All the hormones are decreased except prolactin
NON-FUNCTIONAL PITUITARY MASSES

- Non endocrine tumors of pituitary
- These tumors causes stalk effect and mass effect

Stalk effect:
- Hypopituitarism → Because they are under positive control of hypothalamus
- Hyperprolactinoma → Because it's negatively regulated by Dopamine

Mass effect:
- Due to compression
- Due to increased intracranial tension

Bleeding into tumor → known as pituitary apoplexy

Clinical presentation:
- Headache
- Apoplexy
- Visual symptoms
- Cavernous sinus thrombosis
- Hypopituitarism / Hyperprolactinemia

Non functional pituitary masses:
1) Craniopharyngioma
2) Rathke's cyst

Craniopharyngioma

- Most common non-functional pituitary tumor
- Bimodal age distribution: 5-15 yrs and 50-74 yrs
- 90% occurs in childhood
Craniopharyngioma

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% suprasellar + sellar</td>
<td>10% suprasellar</td>
</tr>
<tr>
<td>m &gt; F</td>
<td>m = F</td>
</tr>
<tr>
<td>adamantinomatous</td>
<td>Papillary</td>
</tr>
<tr>
<td>Cystic with machinery oil</td>
<td>Solid</td>
</tr>
<tr>
<td>appearance &gt;&gt;&gt;&gt; solid</td>
<td></td>
</tr>
<tr>
<td>wet keratin nodules</td>
<td></td>
</tr>
<tr>
<td>calcification ++</td>
<td>---</td>
</tr>
<tr>
<td>Hyperintense on T, with</td>
<td>Hypointense</td>
</tr>
<tr>
<td>vivid enhancement</td>
<td></td>
</tr>
</tbody>
</table>

**MRI findings:**

- T₁, sagittal precontrast
  - macroadenoma can be functional, non-functional

- Functional Tumors → Hypointense on T₁
- Non-Functional Tumors → Hypo & hyperintense on T₁
- T₁, sagittal Post-contrast MRI
- vivid uptake of contrast → craniopharyngioma

**Clinical features:**

- Child of 5-15 yrs
- Presents with stalk effect followed by mass effect
- GH deficiency
- FSH/LH deficiency
- ACTH deficiency
- ADH deficiency
- Increased prolactin

Investigation of choice:
- Gadolinium enhanced MRI

Treatment:
- No medical treatment
- Transphenoidal surgery

- T₁, sagittal precontrast image of normal pituitary
  - Anterior pituitary
    - Slightly hypointense
  - Bright spot

A-T, MRI image
- Slightly hypo to hyperintense lesion

B-T₁ MRI image
- Completely hypotense

Suggestive of craniopharyngioma
Rathke's cyst

- Headache and visual disturbance
- Presents as stalk effect.

Rathke's cyst    v/s    craniopharyngioma
1) 4th to 5th decade    mostly in children
2) Site: Rathke's cleft    Infundibulum
3) Unilocular    Multilocular
4) Well circumscribed    May or may not be circumscribed
5) Sellar mass    Suprasellar + sellar mass
6) No calcification    Calcification present
7) Lined by simple    Adamantinomatous and
columnar epithelium    Papillary

MRI of Rathke's cyst:
1) T1 sagittal pre contrast image
   - Hypointense lesion

Scanned with CamScanner
a) T1 sagittal Post contrast image

- Only margins are taken up the contrast
- Characteristic of Rathke’s cyst
- This sign is called ‘Claw sign’
- Nodule inside the cyst
  ↓
  Dot sign
- Posterior ledge sign

Case presentation:

1. Large lobulated suprasellar mass within 3rd ventricle causing obstructive hydrocephalus- Germinoma
2. Calcification / bony hyperostosis / Pneumosinus dilatans- Meningioma
3. Notochordal remnant with clivus destruction- Chordoma
4. Ring enhancing lesion- Pituitary abscess (mcc)
5. Claw sign / posterior ledge sign / dot sign- Rathkes cyst
CONGENITAL HYPOPITUITARISM

Hypopituitarism

Congenital  Acquired

Causes:

1) Pituitary dysplasia which is always associated with midline cranio-facial Anomaly

midline defects in patients with hypopituitarism,

(a) bifid uvula,

(b) single central incisor

2) Transcription factor defect

Prop 1 > Pit - 1

• most often posterior pituitary will be intact

• Because anterior pituitary development is different from posterior pituitary
3) Syndromes associated with congenital hypopituitarism
   • Kallmann syndrome
   • Laurence moon Biedl Bardet syndrome
   • Septo-optic dysplasia
   • Prader – willi syndrome
   • Angelman syndrome

4) Other Genetic cause
   • Leptin Receptor mutation

Deficiency of anterior pituitary hormones

Growth Hormone \[\rightarrow\] FSH, LH \[\downarrow\] ALTH \[\downarrow\] TSH \[\downarrow\] Prolactin

Doesn't manifest in a child
Thyroid still can produce \(T_3, T_4\)
Not required for child

... manifest as
- short stature
- Hypogonadism

So, child presents with
• Growth Hormone deficiency
• Hypogonadism (Hypogonadotropic hypogonadism)

\[\downarrow\]
FSH, LH - Low

Sex Hormones - Low

Growth hormone deficiency

• Normal I.Q at every point in time
• Normal height at birth (in utero → it depends on IGF-a)
• Child present with hypoglycemia ± seizures
• Prolonged physiological jaundice
• microphallus
- As the child grows → Centripetal obesity
  - Short stature
  - Delayed sexual development
  - Delayed dentition
  - High pitched voice even after puberty

- Short neck
- Proportionate short stature
- Growth velocity low since birth

- Round face with
  - Frontal bossing
  - Depressed nasal bridge
  - Midline defects - cleft lip/palate / single central incisor / bifid epiglottis

microphalera,
delayed puberty
short stature
Short stature

- Height for Age is low by >2 standard deviation
- Or Height for Age <93%
  
  Height for Age
  
  >95% - Normal
  90 - 95 % - Grade I stunting
  85 - 90% - Grade II stunting
  80 - 85% - Grade III stunting
  < 80% - Dwarf

- Eg: 10 yr old child, height = 124 cm
  
  Expected height of 10yr old child = 6 x Age + 77
  = 6 x 10 + 77
  = 137 cm

- So, he is <93% ⇒ He is a short stature

Proportionate short stature

Constitutional short stature:

- Normal height at birth, height at 1 yr age also normal
- Normal height in Parents
- At 1-3 yr Age → Stops growing
- After 3 yr → Grows normally
- Delayed puberty by 2 yrs
- Eventually height becomes normal

  Height Age (HA) = Bone Age (BA) < Chronological Age (CA)
Familial short stature
- Low height at birth
- Parents also have short stature
  \[ \text{HA} < \text{BA} = \text{CA} \]

GH deficiency:
\[ \text{HA} < \text{BA} < \text{CA} \]

Treatment:
- Replacing GH - recombinant GH
- Dose: 0.18-0.35 mg/kg/week, S.C route
- &gt;12 cm/yr ➔ expected gain in height
- Side effects of GH:
  - Hypertension
  - Gynecomastia
  - ↑ risk of leukemia

Laron dwarfism

- GH Receptor mutation in liver
- Basal GH levels are high
- IGF - 1 levels very low
- IGF - 1 Binding proteins are very low
- Severe short stature
- Treatment - recombinant IGF
  \[ \downarrow \]
  Iplex (recombinant IGF + IGF Binding Protein)

Hypogonadism

In a child it manifests as
- Decreased body hair
- Eunuchoid Body Proportions (Armspan > height)
- Small prostate
- Scrotum smooth without rugosity
- Testicular volume < 6 cm³
- Penile length < 5 cm
- Testicular length < 2.5 cm
Post pubertal onset hypogonadism does not affect:
1) prostate size
2) penile length
3) scrotum
4) skeletal proportions

**Syndromes associated with congenital hypopituitarism**

**Septo-optic dysplasia.**
- *HESX1* mutation
- Degeneration of septum pellucidum
- Hypopituitarism + optic atrophy

**Kallman syndrome**
- X-linked recessive
- **KAL gene** on X-chromosome
- Agenesis of olfactory bulb → Anosmia
- Degeneration of GnRH producing neurons in Hypothalamus
  \[ \text{Hypogonadotrophic hypogonadism} \]
  - It's associated with 3C's - optic atrophy (very rare)
    - Cleft palate
    - Cerebellar ataxia
    - Color blindness

**Laurence moon biedl bardet syndrome**
- Autosomal Recessive condition
- Hexadactyly or Polydactyly
- Obesity
- Hypogonadotropic Hypogonadism
- Severe mental Retardation
- Horse-shoe kidney
- Retinitis Pigmentosa
Prader willie syndrome vs Angelman syndrome

- Genomic imprinting
- Maternal genes are imprinted (inactivated/silenced)
- Paternal gene deletion
- Or uniparental maternal disomy

- Genomic imprinting
- Paternal genes are imprinted (inactivated/silenced)
- Maternal gene deletion
- Or uniparental paternal disomy

Features common in both Prader willie and Angelman

- Severe mental retardation
- Severe short stature
- Severe obesity
- Early onset diabetes
- Hypogonadism
- Acromelia (small hands)

Specific to Angelman syndrome

- Severe muscle hypotonia.
- Emotional issues → Inappropriate Laughter

Happy puppet syndrome
ADULT HYPOPITUITARISM

Acquired hypopituitarism

Causes:

1. Stalk effect [ mc cause of Acquired hypopituitarism ]
   1. Pituitary macroadenomas [ Functional or Nonfunctional ]
   2. Infiltrative
      1. Sarcoidosis
      2. Hemochromatosis
      3. Langerhan cell histiocytosis
      4. Autoimmune
         - Lymphocytic hypophysitis
   3. Infections
      1. TB
      2. Pneumocystis carinii pneumoniae
      3. Histoplasmosis
      4. Toxoplasmosis
   4. Traumatic resection of stalk

II. Pituitary infarction or necrosis
   1. Postpartum pituitary necrosis → Sheehan syndrome
   2. Russel viper venom bite.

III. Secondary Empty Sella Syndrome [ Tumor or bleed ]

---

Hormones involved

<table>
<thead>
<tr>
<th>GH</th>
<th>FSH/LH</th>
<th>ACTH</th>
<th>ADH</th>
<th>TSH</th>
<th>Prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not involved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Due to "stalk effect"

It shows involvement of
Anterior and posterior pituitary
- Due to "pituitary dysplasia"
- Development of anterior and posterior pituitary is different.
- So, posterior pituitary is not affected

<table>
<thead>
<tr>
<th>Congenital hypopituitarism</th>
</tr>
</thead>
</table>

Order of Hormones:
GH > FSH/LH > ACTH
Isolated hormone deficiencies may be seen in any order
In emergencies (bleeding or apoplexy) ⇒ "ACTH"

Adult GH deficiency

1. Impaired quality of life → energy or self esteem concentration
2. Body composition (decrease in lean body mass - centripetal obesity)
3. Reduced exercise capacity
4. Cardiac issues
   1. Atherosclerosis
   2. Hyperlipidemia

Adult FSH/LH deficiency

- Hypogonadism
  - Male → Decreased libido
    - Defective ejaculation / erection
    - Sexual drive ↓ ↓
    - Decreased body hair
      - "Osteoporosis" ++

In-post pubertal onset → Serotonin [normal]
- Penile length [normal]
- Skeletal proportions [normal]
- Prostate [normal]

Female
- Amenorrhea / Oligomenorrhea
- Infertility
- Hot flushes
In Clinical presentation Wise : Female > male
hypergondism > hypergondism

ACTH Deficiency 00:11:24

↓ Cortisol
Fatigue / asthenia / tiredness
Loss of appetite
Loss of weight

unexplained Hypoglycemia
unexplained Hypotension → Due to primary cause.

Central Diabetes Insipidus
Polyuria

Pituitary Function Test 00:12:53

TSH, FSH, LH, Prolactin, GH, ACTH
Can be estimated directly
Two hormones cannot be estimated directly
• GH
• ACTH

GH :
GH provocative Tests [ < 3ng/dl ]
In this Test, we administer 1. GHRH
2. Arginine
After giving these, GH level is expected to increase above
3ng/dL; if not, it is considered as GH deficiency
[ L - dopa, clonidine, glucagon are used but not approved ]

ACTH :
1. Insulin tolerance Test
2. metyrapone Test
3. ACTH stimulation Test ( cortisol deficiency )
   It is not a pituitary function test, used to access adrenal reserve

Insulin Tolerance Test [ Not done ; risky Test ]
0.1 unit / kg of Regular insulin
I.V eg : 50kg → 5 units.
After 0, 30, 60, 90 min etc. look for cortisol level
Done after recording fasting cortisol [ should be Normal ]
when insulin is administered to a Normal person → Hypoglycemia →
Increase in cortisol level [ > 20 ng/dl ]

If it is > 20 ug/dl → low ACTH reserve

Interpretation of the Test:
1. ACTH low or Cortisol low → Test +ve
2. metyrapone Test [ Steroid Synthesis Inhibitor ]
on giving Metyrapone → Deoxycortisol is not converted to Cortisol → So, in normal person
ACTH level will be increased .

If ACTH levels fail to increase then it is considered as positive Test .
This implies ACTH is poor .

metyrapone test is better than insulin tolerance test ; because Insulin
tolerance test is positive in both adrenal and pituitary

Sheehans Syndrome

- postpartum pituitary necrosis
- > 75% necrosis required for its manifestation .
- Anterior pituitary doubles in size during pregnancy
- In post partum Hemorrhage
  In 1/10,000 deliveries,
  Low pressure portal System is unable to ↑↑ se
  blood supply → Abrupt onset of hypotension →
  hypoperfusion → Infarction or Necrosis .

Progression of hormone loss :
GH > FSH ; LH > ACTH > TSH

LH > FSH
[ posterior lobe is spared ]

Clinical Features :
- Fatigue
- Failure to resume periods
- Failure of lactation
  +
  Hypothyroidism
Goon, Lh, Pclh, PRL, TSH
ADH ➔ mostly Normal

Sheehan syndrome complications:
1. Adrenal crisis ➔ Hypotension
2. Severe hyponatremia
3. Severe osteoporosis
4. Weight loss

Important differential diagnosis Lymphocytic Hypophysitis

**Lymphocytic hypophysitis**

Autoimmune inflammation of Pituitary only seen in "post partum period" present as inflammatory mass in the pituitary

mass is made up IgG containing lymphocytes and plasma cells.

mostly seen in females having Autoimmune Illness.

Naturally have stalk effect + mass effect

Any post partum female presenting with a pituitary mass has to be given a trial of steroids.
<table>
<thead>
<tr>
<th>Sheehan</th>
<th>Lymphocytic hypophysitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pituitary necrosis</td>
<td>mass ++</td>
</tr>
<tr>
<td>No mass</td>
<td>stalk effect</td>
</tr>
<tr>
<td>Hormonal profile:</td>
<td>hormonal profile:</td>
</tr>
<tr>
<td>GH, FSH, LH, TSH, ACTH</td>
<td>GH, FSH, LH, TSH, ACTH</td>
</tr>
<tr>
<td>prolactin all are low</td>
<td>TSH all are low</td>
</tr>
<tr>
<td>ADH → Normal</td>
<td>prolactin → ↑ ↑</td>
</tr>
<tr>
<td></td>
<td>ADH → low</td>
</tr>
<tr>
<td></td>
<td>mass takes up contrast</td>
</tr>
<tr>
<td></td>
<td>in imaging study</td>
</tr>
</tbody>
</table>

macroadenoma in acromegaly will take patchy uptakes of contrast.

**Features of lymphocytic hypophysitis**
1. pituitary enlargement.
2. headache, visual disturbances
3. hypopituitarism
4. hyperprolactinemia
5. associated autoimmune disease.

**Empty sella syndrome**

Empty Sella Syndrome → Sella is Empty

Primary empty Sella: Does not produce hypopituitarism

Secondary empty Sella: Produce hypopituitarism
cause - Tumors
- Post bleeding
Primary empty sella syndrome

↑ ICT → CSF sweeping down into pituitary
Because rim of pituitary is intact patient generally does not develop hypopituitarism
↑ ICT → Benign intracranial hypertension
or
pseudo tumor cerebri.

Pituitary apoplexy

Acute intra pituitary hemorrhage.
In patients with post partum necrosis
or
or
Spontaneously [ Hypertension or DM or sickle cell Anaemia ]
present with History of 1-2 days Headache / vomiting ± meningeal irritation

Clinical presentation - Acute Hypoglycemia / Hypotension / worsening headache
In bleeding → Hormone most affected is ACTH
In pituitary apoplexy → Bleeding ++ So, All hormone are " low."

Treatment:
IV Steroids + urgent surgical decompression

Treatment of hypopituitarism

Steroids
Due to sort duration of action - Oral Hydrocortisone
If vomiting or hypotension - I.V hydrocortisone
If there is stress / infection - Double the dose
Based on circadian Rhythm:

\[
\begin{array}{ccc}
10mg & 5mg & 5mg \\
[8-9 am] & [1-2 pm] & [4-5 pm]
\end{array}
\]
Conversion dose:

1 mg Dexe = 4 mg Methyl Prednisolone = 5 mg prednisolone
= 20 mg Hydrocortisone = 25 mg cortisone

L-Thyroxine 50mg/day → 200mg/day
L-thyroxine can worsen Hypocortisolemia.
so L-Thyroxine given after steroids.

FSH/LH replacement

In males:
Testosterone gel or patch or I.m Testosterone enanthate
200mg once in every 2 weeks
Desiring fertility → GnRH

In females: [who completed their family]
Estrogen 1mg Day 1 → 25
Progestrone 5mg Day 16→25
For Fertility → Gonadotrophins or Ovulation induction agents.

GH therapy in adults

GH → 1 mg s/c once daily (or)
oral GH - 0.3 mg/day

ADH
ADH → Intranasal desmopressin 5-10 mg BD
or
Oral desmopressin 0.3-0.4 mg once daily

Genetic syndrome involving pituitary

Patient with prolactinoma or Acromegaly [in young patient]
Consider three syndromes in young patients with prolactinoma or acromegaly

LMEN -1 syndrome
Prolactinoma > GH secreting tumor

2. McCune Albright Syndrome
Gsα mutation
features
a) cafe au lait spots
b) precocious puberty
c) Polyostotic fibrous dysplasia with facial asymmetry
d) pituitary adenoma [GH > Prolactin]

3. Carney's Complex / Syndrome
   PPKAR - 1a gene
   a) Lentigenes [Spotty skin lesions]
   b) Adrenal cushing [Lean cushings]
   c) Atrial myxoma
   d) Pituitary [GH > Prolactin]

Carney's triad → GIST + Pulmonary Chondroma + Paraganglioma

Nelson syndrome

ACTH secreting macroadenoma.
Rapid progression due to loss of negative feedback.
Extreme hyperpigmentation.
Symptoms due to expanding intrasellar mass lesion.
Transsphenoidal surgery.

Sheehan and its complications:

Wringkling → due to GH deficiency.
Dry face / expressionless → due to hypothyroidism.
First Hormone to be lost → GH
Second Hormone → TSH

Complications:
- Adrenal Crisis → Hypotension
- Severe Hyponatremia.
- Severe osteoporosis.
- Weight loss.
- Pituitary apoplexy.
POSTERIOR PITUITARY

Posterior pituitary [neurohypophyseal relation] 00:00:30

Hormones → Hypothalamus
    ↓
      Via stalk
Stored in the
Posterior pituitary
Released when required

Posterior pituitary → [down growth from the floor of 3rd ventricle]

ADH / Vasopressin or Arginine Vasopressin (AVP) 00:01:40

Produced from Supraoptic nucleus or paraventricular nucleus of Hypothalamus

Preproarginine vasopressin

↓

Neurohypophysin a  Copeptin  ADH

Receptors:

$V_1(V_{1,a})$

$V_2$

$V_3(V_{1,b})$

$V_1(V_{1,a})$:

Blood vessels → vasoconstriction
Platelets → Aggregation
Liver → Glycogenolysis
Uterus → Contraction
Myocardium → Hypertrophy

$V_3(V_{1,b})$:

Anterior pituitary → ↑ACTH release
$V_a$:

Vascular endothelium $\rightarrow$ Release VWF $\rightarrow$ Platelet adhesion $\rightarrow$ Kidney

Function of ADH:

ADH doesn't undergo glomerular filtration $\downarrow$

From efferent arteriole it enters into Peritubular capillary plexus $\downarrow$

Binds at $V_a$ receptor seen at cells of Cortical collecting duct (cells) principal cells $\downarrow$

$\uparrow$ cAMP $\downarrow$

$\uparrow$ Aquaporins expression from Apical Membrane [Aquaporins stored in vesicle] $\downarrow$

AQP

"Reabsorb free water" (Solute free)

**Two types of water reabsorption**

<table>
<thead>
<tr>
<th>Obligatory water reabsorption</th>
<th>Facultative $H_2O$ Reabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Independent of ADH</td>
<td>- Dependent on ADH</td>
</tr>
<tr>
<td>- Acts at proximal convoluted tubule</td>
<td>- Acts at collecting duct</td>
</tr>
<tr>
<td>- Aquaporins involved:</td>
<td>- Aquaporins involved:</td>
</tr>
<tr>
<td>AQP&lt;sub&gt;1&lt;/sub&gt;</td>
<td>AQP&lt;sub&gt;a&lt;/sub&gt;</td>
</tr>
<tr>
<td>AQP&lt;sub&gt;7&lt;/sub&gt;</td>
<td></td>
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</table>
Aquaporins

<table>
<thead>
<tr>
<th></th>
<th>AQP_1; AQP_7</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>AQP_4</td>
<td>Apical membrane</td>
</tr>
<tr>
<td>3</td>
<td>AQP_3; AQP_4</td>
<td>[B/L] Basolateral membrane of collecting duct</td>
</tr>
<tr>
<td>4</td>
<td>AQP_6</td>
<td>Inside vessels of collecting duct</td>
</tr>
<tr>
<td>5</td>
<td>AQP_5</td>
<td>No Role in kidney</td>
</tr>
</tbody>
</table>

Glomerular Filtrate

Normal: Serum osmolality 285-290 mosm/kg of H_2O

Osmolarity of the filtrate remains same after reabsorption in PCT [sr. osm -285-290] This phenomenon is called "Iso osmotic reabsorption"

At tip of loop of Henle (Sr.osm-1300mosm) H_2O is reabsorbed in the thin descending limb to reach maximum filtrate osm -1300 mosm

This process is called "Counter current multiplication"

Lowest filtrate Osmolality [50 mosm] At DCT

[.:.Through Thick Ascending limb → Solute are reabsorbed]

From 50 mosm to 800-900 mosm/kg

Concentration gradient ↑ by using ADH

Factors required for ADH to function:

1. Medullary Interstitial Osmolality
2. Urea
3. Vasarecta

Counter current exchange
Defence mechanism to prevent hyponatremia

Both hypo and hypernatremia are the disorders of water metabolism.

\[
\text{Serum osmolality} = 2\times \text{Na} + \frac{\text{Blood glucose}}{18} + \frac{\text{BUN}}{2.8}
\]

\[
= 285 - 290 \text{ mosm/kg of H}_2\text{O}
\]

Low osmolality = Low Na.
Low osmolality = Hyponatremia = "True Hyponatremia."
If Na⁺ low but Osmolality Normal or High
\[
= \text{Pseudo – Hyponatremia}
\]

High Na⁺ is never equal to High osmolality:
Osmolality is Normal < 285-290 mosm/kg
\[\therefore \text{ADH levels are kept below 1 ng/l}\]

\[
> 280 - 285 \text{ mosm/kg}
\]
\[\downarrow\]
\[\text{ADH} \uparrow \uparrow\]
\[\downarrow\]
\[\text{Free H}_2\text{O reabsorption}\]
\[\downarrow\]
\[\text{Osmolality Normal}\]

High Na⁺ = High Osmolality:
In Neurosurgery cases: Patient with head injury or on ventilator;
Pituitary apoplexy → ADH not released → hypernatremia, otherwise hypernatremia is rare.

Adipsic hypernatremia

Disease of Hypothalamus → Damage to osmoregulatory centres of supraoptic nucleus.
Low Osm = Low Na⁺
High Osm ≠ High Na⁺

Normally ADH is < 1 ng/l, when osmolality ↑↑ = ADH release ↑↑ = Brings Osmolality to Normal

If, ADH is released with a low osmolality:
SIADH (Syndrome of Inappropriate ADH)
Low Na⁺ = Hyponatremia

SIADH

1. Head Injury
2. Paraneoplastic
   - SCC lung
   - Ca duodenum
   - Ca pancreas
   - Thymoma
3. Drugs
   - Chlorpropamide
   - Clofibrate
   - Cyclophosphamide
   - Carbamazepine
   - Chlorpromazine
   - TCA / SSRI
   - Vincristine
   - Oxytocin, Nicotine
4. Acute necrotizing pneumonias
5. Acute meningoencephalitis
6. Acute intermittent porphyria

Criteria

1. Low serum Osmolality
2. Urine Osmolality > Serum Osmolality
3. Clinically euvoletic
4. Urinary Na⁺ > 20 mg/L
5. Absence of pituitary, adrenal, thyroid, renal and liver disease
If free $H_2O$ reabsorption more $\rightarrow$ Tendency for $\uparrow$ intravascular volume $\rightarrow$ RAS(-) inhibited $\rightarrow$ Aldosterone $\downarrow$ urinary $Na^+$ $\uparrow\uparrow$
$\rightarrow$ Atrial Natriuretic factor $\uparrow\uparrow\rightarrow$ So, urinary $Na^+$ $> 20$ meq/L

**Diabetes Insipidus [DI]**

No ADH $\rightarrow$ Central DI

Resistance to ADH $\rightarrow$ Peripheral or Nephrogenic DI to ADH

Polyuria: [$>50$ml/kg/24hrs or 3.5L/24hrs]

\[ \downarrow \]

Solute diuresis

1. Tubular injury
2. Mannitol
3. Urine dipstick $+$ve for glucose

\[ \downarrow \]

Water diuresis

1. $>7L$
2. Urine dipstick $-$ve
3. Urine osm $< 500$ mosm
4. Urine specific gravity $< 1.010$

**Causes for water diuresis**

1. Central DI
2. Nephrogenic DI
3. Psychogenic polydipsia

To differentiate water deprivation test

**Water deprivation test**

Urine Osmolality

- Central DI $< 250$ mosm
- Nephrogenic DI $250-450$ mosm
- Psychogenic DI $450-600$ mosm
at 4.00AM

Baseline urine osmolality noted

water deprivation

12 noon

Loss of > 3% of body weight

Repeat urine osmolality

Stop the test

Urine osmolality has increased to more than 650-700mosm

Urine osmolality still low

[Psychogenic polydypsia]

D.I

* If urine osmolality still low after 12 noon give intranasal desmopresison on S/C aqueous vasopressin and check at 2pm and 4pm for urine osmolality

At 4 pm

If urine osm ↑ by > 50% → Central D.I

[in 4hrs] [12-4pm]

If urine osm ↑ by < 10% → Nephrogenic D.I

[in 4hrs]

If urine osm ↑ by 10 - 50% → Partial central D.I

[in 4hrs]

Central D.I

00:50:44

Acquired

Acquired

Genetic [AR]

Pituitary adenoma [MCC]

DIDMOAD syndrome [WOLFRAM]

- Functional/Non-functional

- Infiltrative

[Autoimmune; Histiocytosis]

- Infection [TB; PCP; Toxoplasmosis, Histoplasmosis]

- Traumatic

Acquired

- Diabetes insipidus

- DM

- Optic atrophy

- Deafness

Acquired

- Sarcoidosis; LCH
II Pituitary infarction [eg: Sheehan; ADH deficiency rare]
III Pregnancy [vasopressinase]

Major symptoms:
Polyuria
The patient able to drink water
↓
No hypernatremia

Nephrogenic DI [peripheral]

I Drugs
Lithium
Demeclocycline
Cisplatin
Aminoglycoside
Foscarnet
Amphotericin B

II Chronic tubulo interstitial disease [ADH resistance]
Causes:
• 2 Autoimmune disease [Sjogren; Sarcoidosis]
• 4 metabolic
  ↑ Ca
  ↓ K
  ↑ Uric Acid
  Huper oxaluria.
• Childhood Fanney disease
  Reflux Nephropathy

III Pregnancy
IV Sickle cell Anaemia.

Genetic causes
• \( v_2 \) Receptor Mutation [XLR] more common
• AQP2 mutation [AR]
Treatment

Central DI:
Intranasal desmopressin 10-20g bd

Partial DI:
Aqueous S/C vasopressin
Or
Clobibrate
Or
Carbamazepine

Peripheral DI:
Lithium Induced DI \rightarrow Amiloride or Triamterene

Other drug used for peripheral DI \rightarrow Thiazide diuretics
Action: Volume contraction
↑ responsiveness of other parts of tubule
SIADH v/s CSWS

2. Causes for Hyponatremia post - head injury
   1. SIADH
      a. Cerebral salt wasting syndrome [CSWS]

(CSWS) Cerebral Salt Wasting Syndrome

↓

Dysautonomia

↓

C - type Brain Natriuretic Peptide [endothelium]

↓

Natriuresis and diuresis

↓

Je cells affected

↓

No RAS activity

↓

Salt and H₂O wasting

Present as Dehydration

Hypovolemia

Hypovolemic Hyponatremia

Occurs in 1-2 weeks after Head injury resolves in 3 - 4 weeks

Normal uric acid levels

<table>
<thead>
<tr>
<th>CSWS</th>
<th>SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Polyuria</td>
<td>No polyuria</td>
</tr>
<tr>
<td>2. Hypovolemic hyponatremia</td>
<td>Euvolemic hyponatremia</td>
</tr>
<tr>
<td>3. Dehydration</td>
<td>No dehydration</td>
</tr>
<tr>
<td>4. Present after 1-2 weeks of head injury</td>
<td>Presents immediately after head injury</td>
</tr>
<tr>
<td>5. Treatment: Fluids [Hydration]</td>
<td>&gt; 48 hrs water restriction</td>
</tr>
<tr>
<td>6. normal uric acid levels</td>
<td>Decreased uric acid levels</td>
</tr>
</tbody>
</table>
WATER METABOLISM

Hyponatremia and Hypernatremia

Hyponatremia [Disorders of H₂O metabolism]
According to European care of intensive care unit
Serum Na⁺ < 130-135 meq/L are associated with symptoms
::: [There is no strict normal value for Na⁺ differs from person to person]

115-120/125 meq/L → GI symptoms
Anorexia
Nausea / vomiting
Cramps

<110/115 meq/L → mild neurological
Agitation
Confusion
Dizziness
Ataxia
↓ concentration

<100-105 meq/L → Serious neurological symptoms Cerebral edema.
↑ ICT
[Cerebral edema → in hyponatremia- blood osmolality is low - water diffuses from high to low concentration (from capillaries into interstitium)

STEP 1: True vs Pseudo Hyponatremia
Low osmolality High osmolality or Normal osmolality
eg- serum Na⁺ - 92, BUN- 28, blood glucose- 90

\[
\text{Serum Osmolality} = a \times \text{Na}⁺ + \frac{\text{Blood glucose}}{18} + \frac{\text{BUN}}{2.8}
\]

\[
= a \times 92 + \frac{90}{18} + \frac{28}{2.8}
\]

\[
= 184 + 5 + 10
\]

\[
= 199 \text{ mosm/kg/H₂O}
\]

= True Hyponatremia
**Pseudo hyponatremia**

Low Na⁺; Osmolarity ↓ or ↑ sed

**a) Translocational Pseudo Hyponatremia**

Certain solutes that easily cross from blood to cell membrane "ineffective solute"

Eg: Alcohol

Certain solutes that cannot easily cross from blood to cell membrane remain in blood compartment; So, this ↑se osmolality of blood compartment; water from cell diffuses to blood; So, more water in blood results — Hyponatremia. These solutes are "effective solutes”

1. Glucose
2. Mannitol
3. Glycine
4. Maltose

Eg: Polyuria [in DM]

**b) Methodology**

Flame spectro photometry to measure Na⁺ [old]

\[ \text{↑ se proteins} \quad \text{↑ se lipids} \quad \rightarrow \quad \downarrow \text{Na}^+ \]

This is also considered as "pseudo hyponatremia."

Ion sensitive electrodes [New]

This is not seen here
Causes for pseudohyponatremia:
1. Glucose
2. Mannitol
3. Glycine
4. Maltose

5. ↑ proteins
6. ↑ lipids

Step 2: Evaluation of hyponatremia

Steps:
To assess whether

Hypervolemic  Euvoletic  Hypovolemic

Hypovolemic Hyponatremia
- CKD
- Cirrhosis
- Congestive Heart Failure
- Nephrotic syndrome

Pathogenesis -
Aldosterone ← RAS ← Depleted intravascular volume
  ↓ absorb Na⁺ and H₂O [Na⁺ < H₂O]
  ↓

Hyponatremia
Treatment: "Loop Diuretics"
Drug induced hyponatremia – thiazide or furosemide

Thiazide >> furosemide Thiazide: ↑ responsiveness of other parts of tubules

↓

More H₂O and solute will be reabsorbed

↓

Contribute to medullary interstitial osmolality

↓

Medullary interstitial osmolality will be normal

↓

By ADH action free water reabsorbed

↓

Hyponatremia

Furosemide:

Potent diuretic

Excrete salt and water

It excretes more water than sodium

Hypovolemic hyponatremia

Non renal loss

1. Vomiting
2. Diarrhea
3. 3rd space loss
   → Burns
   → Pancreatitis
   → Rhabdomyolysis

Renal

1. Overuse of diuretics
2. Acute tubular injury
3. Renal tubular acidosis
4. Aldosterone insufficiency

Cerebral salt wasting syndrome → Also cause Hypovolemic Hyponatremia

Euvolemic hyponatremia

1. Cortisol insufficiency
2. Hypothyroidism
3. SIADH
Criteria – SIADH

Five criteria:
1. ↓ serum osmolality
2. Urine osmolality > serum osmolality
3. Clinical euvolemia
4. ↑ urine Na⁺
5. Absence of pituitary, Adrenal, Renal
6. Thyroid, Liver disease

Common cause SIADH → Head injury
manifest with → Hyponatremia.

Treatment

Hypovolemic Hyponatremia:
Fluids are the mainstay

1L of a fluid = \frac{\text{Infusate Na} - \text{SrNa}}{\text{T.BW} + 1} \ (\text{Total body water})

1L of NS 154 meq of Na = \frac{154 - 100}{60\% \times 80 + 1} \ (\text{Body weight 60 kg})
= \frac{154 - 100}{36 + 1} = \frac{54}{37} \ (60\% \ of \ 80)

1 L normal saline will increases sodium by 1-2 meq/L [max: 1.5 meq/L]

Target correction ⇒ max = 8 meq/L / day
5 litres of normal saline per day required.
Treatment of acute SIADH

Acute symptomatic Hyponatremia.

[within 48 hrs] It is considered as emergency to use Na+Fluid of choice: Hypertonic saline or 3% saline

\[1 \text{ L} = 513 \text{ meq of Na}^+\]
\[100 \text{ ml} = 5.13 \text{ meq of Na}^+\]

Treatment option - 1

100 ml if 3% saline over 10 min repeated thrice

\[\text{Infuse Na}^+ - \text{Sr. Na (95)} \quad \frac{\text{TBW + 1}}{37} = \frac{513 - 95}{37} = \frac{418}{37} = 12 \text{ meq/L [11-12 meq/L]}\]

1 L [3% NS] = 11 meq/L
500 ml = 5.5 meq/L
250 ml = 2.75 meq/L

[3-4 meq/L]

Treatment option - 2: "Round the clock"

If we want to correct 8 meq/L

\[\text{Ex:} \quad \frac{513 - 95}{37} = [11-12 \text{ meq/L}]\]

1 L [3% NS] = 11 meq/L

\[\frac{1}{11} \times 8 = \frac{8}{11} = 700 \text{ ml}\]

So, 700 ml [3% NS] (100 ml) → 24 Hrs

7 Bottles over 24 Hrs

1 Bottle every 3.25 hrs

Treatment option 1 >> Treatment option 2
Central pontine myelinosis

If ↑ ICT symptoms present
  ↓
  Same management

After 48 hrs → Brain compensates

1. Solutes to CSF

Blood

Brain cell

2. Osmolality ↓↓

3. $\text{H}_2\text{O}$ will move from brain cell to blood
  ↓
  4. Brain will shrink in size to assume optimum position

5. After 48 hrs 3% saline if given - blood osmolality further ↑, more $\text{H}_2\text{O}$ diffuses from brain cell to blood and it causes further shrinkage in brain

If Na⁺ corrected > 135 meq/L in 24 hrs or using 3% NS
  ↓
  after 48 hrs without symptoms,
  causes
  ↓
  osmotic demyelination → Central pontine myelinosis

Central pontine myelinolysis manifest like a pseudobulbar palsy - $\mathcal{O}$/L
  Hypertonia; $\mathcal{O}$/L Hyper reflexia; Rigidity ↑ Tone
Chronic asymptomatic or mildly symptomatic hyponatremia

Sr. Na⁺ Correct upto [120 meq/L]

↓

Water restriction → Treatment of choice
Salts
Urea

DOC: Vaptans [V₂ Antagonists]
Demeclocycline [(-) cAMP]

Vaptans

1. Non-selective [V₁⁺V₂]
2. Selective [V₂]

Non-Selective: Conivaptan IV or oral
Vaptans → No Role in Acute condition
In chronic Asymptomatic or Mild Symptomatic

↓

Use, selective vaptans [V₂]: Tolvaptan (5 mg) [oral]
Tolvaptan → Major side effect → Hepatotoxicity

Is contraindicated in Hypovolemia
Can be used in Hypervolemia.

<table>
<thead>
<tr>
<th>Class of receptor block</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselective (mixed V₁⁺V₂)</td>
<td>Conivaptan</td>
</tr>
<tr>
<td>V₁ Selective (V₁RA)</td>
<td>Relcovaptan</td>
</tr>
<tr>
<td>V₂ Selective (V₂RA)</td>
<td>Nelivaptan</td>
</tr>
<tr>
<td>V₂ Selective (V₂RA)</td>
<td>Lixivaptan</td>
</tr>
<tr>
<td></td>
<td>Mozavaptan</td>
</tr>
<tr>
<td></td>
<td>Satalvaptan</td>
</tr>
<tr>
<td></td>
<td>Tolvaptan</td>
</tr>
</tbody>
</table>
**Hyponatremia**

"State of water deprivation" or water deficit

Preferred fluids: ½ NS;
5% dextrose;
Free H₂O

Max. correction of Sr. Na → 8 meq/L

\[
\text{Water deficit} = 0.6 \times BW \times \left[ \frac{\text{Na} - 140}{140} \right]
\]

eg: Sr. Na - 140, BW - 60

\[
= 0.6 \times 60 \times \left[ \frac{140 - 140}{140} \right]
\]

\[
= \frac{36 \times 20}{140}
\]

\[
= \frac{360}{140} = 5 \text{ L}
\]

Half normal saline infusion Na⁺ = 77 meq/L

1 L of Half normal saline = \[
\frac{77 - 140}{37}
\]

\[
= \frac{83}{37} = 2 \text{ meq/L}
\]

1 L of ½ NS → ↑Na⁺ by 2 meq/L
4 L of ½ NS → ↑Na⁺ by 8 meq/L

Here, water deficit = 5 L

With ½ NS correct up to 4 L

Remaining will be corrected in other way (free water by IL) Ryle’s Tube

5% Dextrose → No Infusate Na⁺

1 L of 5% dextrose = 4 meq/L = \[
\frac{0 - 140}{37}
\]

2 L of 5% dextrose = 8 meq/L

4 L of ½ NS >> 2 L of 5% dextrose
ADRENAL MEDULLA – BASICS, PHEOCHROMOCYTOMA

- Adrenal medulla → 20% of adrenal gland
- Neural crest cell (neuroectodermal) derivative
- Medulla develops before cortex - 45 days of gestation
- Synthesize 3 major hormones (peptide hormones) from tyrosine

<table>
<thead>
<tr>
<th>Adrenaline</th>
<th>Nor adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>(epinephrine)</td>
<td>(nor epinephrine)</td>
</tr>
<tr>
<td>(80%)</td>
<td>(15-18%)</td>
</tr>
</tbody>
</table>

- Large dense granules → Noradrenaline
- Small dense granules → Adrenaline
- Opioids & chromogranin A are produced from the granules
- Adrenomedullin is produced from vascular endothelium
  - Not adrenal medulla in response to free radical injury
  - Functions:
    1) Vasodilation
    2) Free radical scavenger
- Nor-adrenaline
  - Phenylethanolamine - N - methyl transferase
    - (last step) (stimulated/induced by cortisol)
  - Adrenaline

Pheochromocytoma

- Catecholamine secreting neural crest cells tumor arising from
  1. Adrenal gland - Adrenal pheochromocytoma
  2. Sympathetic / Parasympathetic ganglia - Extraadrenal pheochromocytoma / paraganglioma

- ‘Rule of 10’ is outdated and no longer applicable
- Adrenal pheochromocytoma (75%) (adrenaline > Noradrenaline)
  rarely dopamine
- Extra adrenal pheochromocytoma (25%) (exclusively Noradrenaline)
  - Sympathetic ganglia (20%)
  - Parasympathetic ganglia (5%)
- Sympathetic ganglia → Paraganglioma develops in abdomen or mediastinum
  (mc site - organ of zuckerkandl)
- Parasympathetic ganglia → Carotid body > jugular bulb

Sporadic vs familial
- 60% sporadic; 40% familial (mostly bilateral)
- Familial are associated with
  1) MEN -a
  2) VHL
  3) NF-1
- Sporadic presents in 40-50 yrs of age (m = f)
- Familial presents in 20-25 yrs of age (m = f)

Clinical presentation

- mc presentation → Panic attacks (75%)
  (but <1% with panic attack have pheochromocytoma)
- 25% presents as incidentaloma (25%)
- Classical triad →
  1) Episodic headache
     (mc symptom - 90 to 95%)
  2) Profuse sweating
  3) Tinnitus
- Can present as episodic HTN (60%) > sustained HTN (20%)
- Can also presents with orthostatic hypotension
  ↑ Catecholamines → Deplete intravascular volume
- "6FW" of pheochromocytoma
  1) Pain
  2) Pallor
  3) panic attack
  4) Palpitation
  5) Hypertension
  6) Weight loss
- Weight loss, volume depletion and hyperglycemia in pheochromocytoma is due to increased sympahtetic drive

- Normally, in pheochromocytoma, there is ↑ erythropoietin - polycythemia. (if there is pallor, suggestive of malignancy)

- Abdominal pain in pheochromocytoma is due to hypercalcemia

- Hypercalcemic can also leads to,
  1) Polyuria (nephrogenic D1)
  2) Stones

- Surest sign of malignancy → metastasis

- malignancy → Extraadrenal > adrenal

- Succinate dehydrogenase B (SDH B) mutation is associated with malignancy

**When to suspect?**

- According to endocrine society of india (ESID)
  1) Hyperadrenergic spells
  2) Resistant young hypotension
  3) MEN -a / VHL / NF-1
  4) Incidental adrenal mass
  5) Family h/o pheochromocytoma.

- mc sign → episodic hypertension

**Pathology**

- Neural crest cell markers
  1) Chromogranin
  2) Synaptophysin
  3) S 100

- Zeilballein pattern appearance

- Organ maximally affected → Heart (pheocardiomyopathy)

  Due to pheocrisis / HTN crisis

- In heart →
  1) ↑ HR
  2) ↑ excitability
  3) ↑ O₂ consumption
  4) ↑ force of contract

- ↓ plasma volume; Hypercalcemia
- Carbohydrate metabolism \( \rightarrow \) Diabetic state
- 75% of patients would have experienced postural hypotension at some point of time
- Sympathetic paraganglioma is more functional than parasympathetic
- Familial syndromes are bilateral except neurofibromatosis
- Catecholamines are released in a pulsatile manner, there is no point in measuring blood or urine catecholamines levels
  \[
  \text{metabolites of catecholamines (fractional metanephrines) is measured}
  \]

**Screening test**

- Patient presents with panic attacks
  
  24 hours urine fractionated metanephrine (98% sensitivity, 98% specificity) \( \rightarrow \) Negative
  
  Still having features suggestive of genetic syndrome or family history

  (100% sensitivity) Plasma fractionated metanephrines

- 24 hours urine fractionated metanephrine
  
  Positive \( \rightarrow \) IOC (Gallium 68 - Dotatate scan) (octreotide scan)

- MRI abdomen is done first then only Gallium 68 - Dotatate scan
- For extraadrenal pheo, directly do Gallium 68 - Dotatate scan
- MIBG scan is not used anymore

**Treatment**

1. Sporadic pheo \( \rightarrow \) Laparoscopic retroperitoneal Adrenalectomy (u/L)
2. Genetic pheo \( \rightarrow \) B/L partial adrenalectomy
Preparation for surgery:
1) Admit 7-10 days prior to surgery
   a) Volume repletion
2) 7 days prior to surgery → **Non-selective, irreversible, long acting**
   α-blocker (phenoxybenzamine) →
   10 mg OD
   b) Phenotolamine
   a) Prazosin also used

3) 3 days prior to surgery → **β-blockers** (Propranolol 50 mg Q6H then once daily)

4) 3 days prior to surgery →

5) Nefcardipine, metyrosine – can also be tried

- Patient develops hypertensive crisis → DCC (sodium nitroprusside)
  Next line →
  d) Nicardipine
  a) Phenotolamine

- Clonidine suppression test (0.3 mg clonidine is given)

- Clonidine – presynaptic α 2 agonist – normally blocks catecholamines
  - In pheochromocytoma, release is not blocked

- Drugs interfering with metanephrine assay:
  a) TCA
  a) L-dopa

- Drugs precipitating HTN crisis
  a) β-blockers alone
  a) Glucagon

- Post op follow up with 24 hr urine fractionated metanephrines
ADRENAL MEDULLA: MEN, MEON, PGA SYNDROME

Multiple endocrine neoplasia (MEN)

MEN-1 (Wermer syndrome): 
- Due to mutation in MEN1 gene (Chromosome 11q)
- MEN1 gene is tumor suppressor gene (TSG)
- mc mutation → Inframe deletion (frame shift mutation)

Major manifestations

1. Parathyroid
   - Every single patient by 40 yrs in MEN-1 have parathyroid involvement
   - Usually seen by 20-35 yrs
   - mc & earliest manifestation of MEN-1
   - B/L parathyroid gland hyperplasia
     \[\text{Primary hyperparathyroidism (100\%)}\]

Sporadic 1°  MEN-1 RELATED 1°

1. > 60 yrs  < 40 yrs
2. F >> m  F = m

\[\text{Hypercalcemia} \]

11. Adenoma >> Hyperplasia  Hyperplasia >> Adenoma
12. Asymptomatic hypercalcemia  Aggressive hypercalcemia
   i) Recurrent abdominal pain due to stones/UTI
   2) Acute abdomen
   3) Neuropsychiatric symptoms

\[\text{Sestamibi scan is used to visualize PTH gland}\]

\[\text{Treatment} \rightarrow \text{Near total parathyroidectomy}\]
II. Pancreas:
- Pancreas involvement in 30 to 50% of patients with MEN-1
- mc → Neuroendocrine tumor of pancreas
  1) Non-functional Poma (pancreatic polypeptide secreting tumor)
    a) Gastrinoma
    b) Insulinoma
    c) Glucagonoma
    d) VIPoma

<table>
<thead>
<tr>
<th>Sporadic gastrinoma</th>
<th>MEN-1 gastrinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40 yrs</td>
<td>20-40 yrs</td>
</tr>
<tr>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Unifocal</td>
<td>Multifocal</td>
</tr>
<tr>
<td>Passaro's triangle</td>
<td>Duodenal wall</td>
</tr>
<tr>
<td>50-70% malignant</td>
<td>Less malignant (&lt;10%)</td>
</tr>
<tr>
<td>Treatment - high dose PPI + surgery</td>
<td></td>
</tr>
</tbody>
</table>

- In MEN-1 associated gastrinoma lymph node enlargement is present
- Gastrinoma are highly responsive to large dose PPI (60-80mg)
- Surgery is not required for gastrinoma except in pancreatic tumor with size > 2cm (MEN-1 related gastrinoma)
- For sporadic gastrinoma → Surgery done
- Insulinoma.
  1. Sporadic → >40 yrs (Head > body > tail) (90% benign)
  2. MEN-1 → <40 yrs (Head = body = tail) (50% benign)

III. Pituitary
- 15 to 20% of patient with MEN-1
- Prolactinoma > GH secreting adenoma > ACTH secreting adenoma
- In prolactinoma < 20 yrs in MEN-1, 20-45 yrs in sporadic

Minor manifestations

1) Adrenal adenoma / inciendtaloma / cortical tumor
   - mostly benign
a) Primitive Neuro endocrine tumor
   - Thymic carcinoid
   - Foregut carcinoid
   - Bronchial carcinoid

3) Cutaneous
   - Angiofibroma, > collagenoma, > lipoma

4) CNS tumors
   - meningioma

5) Pheochromocytoma (<0.05%)

MEN II syndrome

- RET proto oncogene mutation (chromosome 10)
- Autosomal dominant (M=m)
- Point mutation (cysteine → Arginine)

MEN = AA

1. Classical MEN AA
2. MEN AA with cutaneous lichen amyloidosis
3. MEN AA with Hirschprung disease (megacolon)
4. Familial medullary thyroid Ca

- Classical MEN AA
  1) Medullary thyroid Ca (100%)
     - marker → Calcitonin
     - FNAC for diagnosis
     - Near total thyroidectomy

2) Pheochromocytoma (50%)
   - Bilateral
   - MC : Benign

3) 1st hyperparathyroidism
   - Hyperplasia > Adenoma
men 28 (men 3):

1) medullary thyroid cancer
   2) Pheochromocytoma
   3) marfanoid habitus
   4) mucosal ¶ intestinal ganglioneuromatosis
   5) myelinated corneal nerve fibre

- megacolon (very rare)

men - 4

- Due to cyclin dependent kinase 1B mutation
  1) Parathyroid
  2) Pituitary
  3) Testicular / Ovarian tumor
  4) Adrenal / renal tumor

MEON

- Multiple endocrine ¶ organ neoplasia

I. Carney’s complex
   - PPARG 1A mutation
   - Atrial myxoma.
   - Pituitary (GH) (or) Adrenal tumor
   - Adrenal tumor is more common

II. VHL disease:
   - VHL gene
   - RCC
   - Cerebellar hemangioblastoma
   - Pheochromocytoma. (malignant †)

III. McCune Albright syndrome
   - GS α mutation
- Polyostotic fibrous dysplasia
- Pituitary tumor (GH > Prolactin)

IV. NF - 1
- Neurofibromin mutation
- Optic nerve glioma
- Pheochromocytoma

V. Cowden syndrome
- PTEN (TSG)
- Hamartoma
- Adenocarcinoma breast
- Endocrine involvement - thyroid

VI. Hyperparathyroidism jaw tumor syndrome
- Parafibromin mutation
- Jaw tumor
- ↑ PTH
ADRENAL CORTEX

- Adrenal cortex forms 80% of adrenal gland
- Adrenal medulla develops at 45 days of intrauterine life
- Adrenal cortex starts to develop towards the end of 2nd month (6-8 weeks) from coelomic epithelium (mesothelium) which invades the primordial medulla (neural crest)
- Hormone synthesis (cortical) starts by 8-9 weeks
- Fetal cortex development is complete by 12 weeks
- In fetus, adrenal is bigger than kidney
  Post birth, fetal cortex involutes and is replaced by adult cortex

Relations of adrenal gland

- **Right adrenal gland**
  - Anterior
    - IVC
    - Right lobe of liver
  - Posterior
    - Right crus of diaphragm

- **Left adrenal gland**
  - Anterior
    - Stomach
    - Pancreas
    - Spleen
  - Posterior
    - Left crus of diaphragm

- Removal of adrenal is by laparoscopic retroperitoneal adrenalectomy
- Blood supply
  1. Superior suprarenal → branch of inferior phrenic artery
  2. Middle suprarenal artery → Direct branch of abdominal aorta
  3. Inferior suprarenal artery → Branch of renal artery

Page 1/1
**Physiology**

I. Zona glomerulosa (15-20%)
   - Mineralocorticoid (aldosterone)

II. Zona fasciculata (60-70%) [Large lipid laden cells] +
   - Cortisol

III. Zona reticularis (<10%)
   - Only after birth
   - Adrenal androgens
     1. Dihydroepiandrosterone (DHEA)
     2. Androstenedione

   - Principal fetal adrenal hormone → DHEA

   - Aldosterone is not under any pituitary regulation, so even after hypophysectomy, levels are normal

   - Aldosterone is under the control of RAAS

   - Renin is produced by juxtaglomerular cells by 3 stimuli:
     1. Defective renal perfusion
     2. \( \beta \) receptors
     3. PGE_2, PGI_2

   Cortical collecting ducts
     1. Principle cell (P cell)
     2. Intercalated cell (I cell)

   - Aldosterone is not filtered but reaches basolateral membrane via peritubular capillary plexus

   Binds to its receptor & activates protein inside cell

   - Protein inside P cell activates ENaC channel
     
     1. ENaC retains \( Na^+ \), \( H_2O \)
     2. Aldosterone excretes \( K^+ \), \( H^+ \)

   - Hyperkalemia is due to renal failure unless proved otherwise

   - Hyperkalemia with renal function near normal or slightly deranged → Suspect aldosterone deficiency (adrenal insufficiency)
- Pseudohypoaldosteronism:
  → Normal aldosterone levels but can't bind due to fibrosis of tubules of kidney
  ↓
  Renal tubular acidosis (type 4)

Zona fasciculata

- Cortisol → Cortisone

  11-β-OH steroid
  Dehydrogenase

- Cortisol: both glucocorticoid & mineralocorticoid action
- Cortisone: Only glucocorticoid

- Cushing syndrome → Acquired deficiency of 11-β OH dehydrogenase deficiency

Zona reticularis:
- Secretes
  1. DHEA
  2. Androstenedione

- Functions →
  1. Axillary & pubic hair
  2. Libido

Congenital Adrenal Hyperplasia (CAH)

Cholesterol (Outer mitochondria)

↓

STAR protein (Rate limiting step)

Cholesterol (Inner mitochondria)

↓

11-α hydroxylase

Pregnenolone → progesterone → Deoxycorticosterone → Aldosterone

11-α Hydroxylase

↓

17-β OH Pregnenolone → 17-β OH Dehydrogenase → 22-α Hydroxylase → 11-β Hydroxylase

11-Deoxy cortisol → Cortisol

17-α Hydroxylase

↓

DHEA → Androstenedione → Testosterone → DHT
- mc deficiency $\rightarrow$ 11 $\alpha$ hydroxylase
- 2$^{nd}$ mc $\rightarrow$ 11 $\beta$ hydroxylase
- 3$^{rd}$ mc $\rightarrow$ 17 $\alpha$ hydroxylase
- 4$^{th}$ mc $\rightarrow$ 3-$\beta$-OH dehydrogenase
ADDISON’S DISEASE

- Adrenal insufficiency
  - 80% → Due to problem in adrenal gland
    → Primary adrenal insufficiency
  - 20% → Due to problem in the pituitary
    → Secondary adrenal insufficiency

- Primary adrenal insufficiency:
  - Zona glomerulosa → Aldosterone ↓↓
  - Zona fasciculata → Cortisol ↓↓
  - Zona reticularis → DHEA, Androstenedione ↓↓
  - ACTH ↑↑

- Secondary adrenal insufficiency:
  - Low ACTH
  - Zona fasciculata → Cortisol low
  - Zona reticularis → DHEA ↓↓
  - Aldosterone normal

Etiology

- Primary adrenal insufficiency:
  - m/c/c (India): TB
  - m/c/c (Worldwide): Polyglandular autoimmune syndrome
    (type 1, type 2) (autoimmune)
    ↓
    21 hydroxylase autoantibodies
  - m/c infection (worldwide): Histoplasmosis

- Secondary adrenal insufficiency:
  - m/c/c: Acquired hypopituitarism (most often cause: Tumors)
Primary adrenal insufficiency

- **Cortisol ↓↓**: Fatigue, asthenia, tiredness, loss of appetite, loss of weight, repeated episodes of hypoglycaemia and hypotension, euvoletic hyponatraemia.

- **Aldosterone ↓↓**: Loss of salt and H₂O → Orthostatic hypotension
  - Giddiness
  - Dizziness
  - Salt craving
  - Hyperkalemia, hypovolemic hyponatraemia.

- **↓↓ DHEAS and androstenedione**: Loss of libido
  - Dry skin
  - Decreased body hair

- **↑ ACTH**: Widespread hyperpigmentation seen on skin and mucus membranes (spares tongue)

Metabolic issues:
1. Hyponatraemia
2. Hyperkalemia
3. Hypercalcaemia
4. Hyperglycaemia
5. ↑ mg²⁺

Secondary adrenal insufficiency

- All features of cortisol ↓↓
  - Sex steroid ↓↓
- Aldosterone normal and ACTH ↓
- Other pituitary hormones ↓↓
<table>
<thead>
<tr>
<th>Disease</th>
<th>Primary Adrenal</th>
<th>Secondary Adrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>TB, Autoimmune</td>
<td>Pituitary</td>
</tr>
<tr>
<td>GC deficiency</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>MC deficiency</td>
<td>+++</td>
<td>----</td>
</tr>
<tr>
<td>Androgen deficiency</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Salt craving, postural hypotension</td>
<td>++++</td>
<td>----</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>++++</td>
<td>----</td>
</tr>
<tr>
<td>Loss of axillary hair</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>++++</td>
<td>----</td>
</tr>
<tr>
<td>ACTH</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>S. Potassium</td>
<td>High</td>
<td>N</td>
</tr>
<tr>
<td>S. Sodium</td>
<td>Low</td>
<td>N</td>
</tr>
</tbody>
</table>

- Primary adrenal insufficiency > a° adrenal insufficiency
- Autoimmune > TB
- GC deficiency produces - Fatigue, weight loss, anorexia, hypoglycaemia.
- MC deficiency - Hyponatremia, hyperkalemia, acidosis, hyperpigmentation
- Insidious in onset
- Fatigue / Weakness / Tiredness / Constipation / Abdominal Pain / Postural hypotension
- Hyperpigmentation (90%)
- Loss of axillary and pubic hair with dry itchy skin

**Work up for Addison's**

Screening test: 8 AM plasma cortisol

\[\text{\( \text{Low} \): } >30 \text{ µg/dl} \]
\[\text{<3 µg/dl: Adrenal insufficiency}\]
• Confirmatory test: ACTH stimulation test / Cosyntropin stimulation test / Synacthen stimulation test
  ↓
  We give 250 μg ACTH IV (or) IM
  ↓
  Cortisol level after 1 hr
  ↓
  Cortisol: >20 μg/dl : ☑
  < 20 μg/dl : Addison's

• In CT: B/L asymmetrical adrenal enlargement (↑ ACTH)
  ↓
  Finally may lead to atrophy

Electrolyte abnormalities

• Hyponatremia.
• Hyperkalemia.
• Hypercalcemia.
• Hypoglycemia.
• Hypotension

Management

• Chronic adrenal insufficiency: Steroids
  (short acting hydrocortisone)
  10 mg - 5 mg - 5 mg
  (8-9 Am) (1-2 Pm) (4-5 Pm)
  +
  Fludrocortisone (50-100 μg)

Acute addisonian / adrenal crisis

• Causes:
  • Rapid tapering / non compliance to steroid
  • Any form of stress in a patient with adrenal insufficiency
• Presentation: Acute abdominal pain
  +
  Vomiting
  +
  Circulatory failure
  Hypotension
  Hypoglycaemia.

• Management: 3L of NS / Dextrose in NS
  ↓
  Start IV hydrocortisone
  100 mg IV Q6H × day 1
  100 mg IV Q8H × day 2
  50 mg IV Q8H on day 3
  Convert to oral steroids

Children with adrenal insufficiency

• Causes:
  1) Congenital adrenal hyperplasia (CAH)
  2) X-linked adrenoleukodystrophy (very long chain fatty acids)
CONN'S SYNDROME

Primary HyperAldosteronism (PHA)

- a causes:
  - 60%: B/L adrenal hyperplasia
  - 40%: U/L adenoma → conn's syndrome

- Can occur in any age group
- m = F (>30 yrs)

- Aldosterone excess:
  - Salt and water retention → HTN (diastolic)
  - Loss of H+ (Hypokalemia)
  - Loss of H+ (Alkalosis)
  - No edema due to ↑ ANF (excrete Na+)

Presentation: HTN (OR) hypokalemia

↓

Young HTN
  (OR)

Screen for a* causes for HTN

Resistant HTN (3 or more drugs with one diuretic)
  (OR)

HTN related target (LVH OR Retinopathy)
  (OR)

Organ damage (disproportionate)
  (OR)

Predominant diastolic HTN

¬ a causes for HTN → Renal

Endocrine:
  1) Conn's (PHA)
  2) Liddle's
  3) Pheochromocytoma
  4) Cushing's
- Hypokalemia with
  
  Renal K⁺ loss → spot urine K⁺ >15 meq/L

  ↓

  Acidosis

  ↓

  Alkalosis

  ↓

  Hypertension (HTN)

  ↓

  i) Conn's
  ii) Liddle's
  iii) Cushing's
  iv) AHE (Apparent MC excess)
  v) ERA (GC remediable aldosteronism)

**Work up for Conn's syndrome**

- Screening test:
  1) Plasma Aldosterone concentration (↑↑) >10 mg/dl
     +
  2) Plasma renin activity (↓↓) <1 mg/ml/hr

- Stop spironolactone 6 weeks before test

- If > values while patient on ACE/ARB/B-blocker/Diuretic, stop the drugs for 4 weeks and repeat the test

- Confirmatory test:
  1) Done in patients with PAC > 10 mg/dl and PRA < 1 mg/ml/hr
  2) Saline infusion test
     
     Infuse 2L of NS over 4 hrs

     Infusion aldosterone → Still high (confirmatory)

- IOC: CT-abdomen visualizing adrenal gland

  ↓

  i) ≤1 adenoma (<40 yrs) → u/L adrenalectomy
  ii) ≥1 hyperplasia → medical management

Aldosterone antagonist: Spironolactone

  OR

Eprenone (free of gynecomastia)
• U/L adrenoma (> 40 yrs)
  ↓
  Adrenal venous sampling
  ↓
  Aldo levels in both the adrenal veins
  ↓
  If there is considerable difference: Lateralization
  ↓
  Indication for adrenalectomy on the side with ↑ aldo levels

→ No lateralization: medical management
  ↓
  Salt restriction with spironolactone

**Mendelian forms of genetic low renin HTN**

1) Liddle
   - Hypokalemia
2) AME
   - Alkalosis
3) GRA
   - HTN

**Liddle**
- Autosomal dominant
- Gain of function mutation of **ENAC**
  ↓
  Na⁺ & H₂O retention → HTN

- **K⁺** and **H⁺** excretion: Alkalosis & Hypokalemia
- ⊗ RAS
  ↓
  Low renin
  Low aldosterone

**Rx:** ENAC,
   - Amiloride
   - Triamterene
Apparent mineralocorticoid excess

- Autosomal Recessive
- Deficiency of 11β-OH steroid dehydrogenase

\[
\text{Cortisol} \quad \rightarrow \quad \times \quad \text{Cortisone}
\]

- so. Cortisol accumulate
- MC + GC action
- Hypokalemia
- Alkalosis
- HTN

- \( \ominus \) RAS \( \rightarrow \) Low renin
  \( \rightarrow \) Low aldosterone

- Rx: Inhibit cortisol: Dexamethasone (inhibit ACTH)

GRA glucocorticoid-remediable aldosteronism

- AD
- m/c/c for mendelian low renin HTN

\[
\text{ACTH} \quad \rightarrow \quad \text{Renin}
\]

\[
\text{Cortisol} \quad \rightarrow \quad \text{Aldo} \quad \rightarrow \quad \text{Hypokalemia, Alkalosis, HTN}
\]

Steroid
CUSHING’S SYNDROME

- Cortisol $\xrightarrow{11\beta\text{ OH steroid dehydrogenase}}$ Cortisone
- Acquired deficiency of 11 $\beta$ OH steroid dehydrogenase
- Cortisol $\uparrow$ (Hypercortisolism)
  \[\text{mineralocorticoid + glucocorticoid action}\]

**Classification**

- m/c/c: Iatrogenic
- Endogenous cushing syndrome:
  - ACTH dependent (90%):
    - ACTH secreting adenoma of Pituitary (Cushing's disease)
    - Paraneoplastic (Bronchial or Pancreatic carcinoids) - 15%:
      - Medullary thyroid cancer
      - Small cell lung cancer
  - ACTH independent (10%):
    - Adrenal adenoma - 5-10%
    - Adrenal carcinoma - very rarely

**Presentation**

- Cortisol:
  - Glucocorticoid action:
    - Carbohydrate metabolism
    - Fat metabolism
    - Protein metabolism
  \[\rightarrow\text{Carbohydrate: } \uparrow \text{gluconeogenesis}\]
  \[\text{(adrenal diabetes)}\]
  \[\rightarrow\text{Fat: } \text{Redistribution of body fat } \rightarrow \text{Centripetal obesity}\]
  \[\text{Some lipolysis } \rightarrow \text{Buffalo hump}\]
Protein: catabolic action and anabolic action

↓

1) Muscle proteins broken down

→ Proximal myopathy

2) Bone → Severe osteoporosis / Short stature

3) Collagen → Purple striae

4) Defective platelet adhesion → Bruising, ecchymosis

5) Facial plethora

→ Sex steroid action:

Acne
Hirsuitism
Amenorrhea

- Mineralocorticoid Action:

Hypokalemia
Alkalosis
HTN

* Can cross BBB → Psychosis or depression

Screening to be done in patients

1) Central obesity with protein catabolism

→ Proximal myopathy

→ Facial plethora, bruise and rarely purpura

→ violaceous stria due to loss of collagen

→ Bruising & ecchymosis

2) Osteoporosis at a young age

3) Short stature with obesity and delayed BA

4) Metabolic syndrome + Hirsuitism due to ACTH

5) Incidental adrenal mass

1) Cardiac issues:

HTN → Atherosclerosis

Dyslipidemia

Diabetes

2) M/c menstrual abnormality → Amenorrhea

3) Blood abnormalities: ↑ WBC count, but still more prone to infection

Eosinopenia

4) Hypercoagulable state
- Incidentaloma:
  - 90% of them are benign
  - Out of this, 90%, 65-70% are endocrine inactive
  - Of the endocrine active incidentalomas, m/c is cushings
    2nd is pheochromocytoma.
  - Features of malignancy on an incidentaloma:
    a) Size > 4 cm
    b) CT density > 20 HU
    c) CT contrast wash out < 40%

Work up for cushings

- Highly Sensitive Test: To rule out early → midnight serum cortisol
cushing syndrome or (or)
mild cushing syndrome
  midnight salivary cortisol
  
- Highly specific test: To rule in PCOS/metabolic syndrome:
  Overnight DST (dexamethasone suppression test)
  (or)
  Low dose DST

- Overnight DST: 1mg oral dexamethasone around 11 pm
  Cortisol level at 8 Am
  ( ): < 1.8 mg/dl
  Cushings: > 1.8 mg/dl

- Low dose DST: 0.5 mg oral Dexamethasone Q6H for 2 days
  (more specific)
  3rd day morning 8 Am cortisol
  ( ): 1.8 mg/dl
  Cushing: > 1.8 mg/dl

- Florid cushing syndrome: Any test can be done
- In pseudo cushing syndrome: Obese, alcoholic, depression
  hypercortisolism ++
  Low dose DST
  CRH stimulation (3rd day morning: 1mg/kg CRH i.v.)
  True cushing: Cortisol will not be suppressed
  If sr. cortisol < 1.8 mg/dl → Pseudo Cushion

Scanned with CamScanner
- Part II of the work up: ACTH levels

**Acth dependent**

(>20 pg/ml)

↓

MRI brain with Gadolinium contrast

↓

mass +

→ Trans sphenoidal Resection

↓

Paraneoplastic

(or)

<6 mm mass

↓

High dose DST

↓

2 mg oral Dexta Q6H x 2 days

3rd day serum cortisol

If suppressed → Pituitary

Not suppressed → Paraneoplastic

↓

• High dose DST (+ve or -ve)

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mass on MRI</td>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Inferior petrosal Sinus sampling</td>
<td>PET Scan</td>
</tr>
</tbody>
</table>

\[
\text{Pituitary sinus ACTH} = \frac{\text{Pituitary sinus ACTH}}{\text{Blood ACTH}} \]

úa = Pituitary cause for Cushing syndrome

↓

Trans sphenoidal hypophysectomy

**Acth independent**

(<=500/ml)

↓

Cause is in the adrenal

∴ adrenal CT done

↓

mostly w/l adenoma

↓

w/l adrenalectomy

• Rarely b/l Hyperplasia

↓

b/l adrenalectomy
Treatment

- Transsphenoidal surgery in cushings disease
- 75% remission rate
- Following which medical management done
  - DOC: Ketoconazole
  - Other drugs: Pasireotide
    - metyrapone
    - etomidate
    - Cabergoline
- MITOTANE in adrenal cancer
- Fractional external beam radiotherapy in patients medically unfit for surgery
- B/L adrenalectomy only for B/L adrenal hyperplasia

Childhood cushings

- M >>> F
- Adrenal causes predominates
- Less protein catabolism
- Obesity with hypoglycemia
- Precocious puberty
- Radiotherapy equally effective as surgery in children (for pituitary cause)
- Loss of diurnal variation in cortisol secretion is the first change in cushings
Diabetes mellitus

- m. Endocrinopathy
- Group of common metabolic disorders that share the phenotype of hyperglycemia

Ominous octet of DeFronzo
- Pancreas:
  1. ↓ Insulin secretion
  2. ↑ β-cell activity; ↑ Glucagon

(Causes - m. endocrinopathy - in type 2DM there is resistance to insulin in alpha, cell- alpha cell proliferates - increased glucagon-hyperglycemia)
- Liver:
  3. ↑ Gluconeogenesis
- Intestine:
  4. ↑ Glucose absorption
- Adipose Tissue:
  5. ↑ Lipolysis
- Kidney:
  6. ↑ Glucose reabsorption (SGLT2)
- Muscle:
  7. ↓ Glucose uptake
- Brain:
  8. Neurotransmitter dysfunction

Criteria For The Diagnosis of DM (American Diabetes Association)

- FBS ≥ 126 mg/dl
- PPBS ≥ 200 mg/dl
- HBA,C ≥ 6.5%
- RBS ≥ 200 mg/dl + symptoms
### Glycosylated Hemoglobin

- 4 to 8 weeks control

- Best sensitivity and specificity for impaired glucose tolerance test (IGT)

- Value of HbA1C in:
  - Anaemia: Falsely low
  - CKD-uremia: Falsely low
  - Thalassemia: Falsely low
  - Hereditary persistence of fetal Hb: Falsely low or high

### Types of DM

**Type 1.5 DM**

It is of 2 types

a) Ketosis Prone Diabetes (KPD)

b) Latent Autoimmune Diabetes in Adults (LADA)

**Ketosis Prone Diabetes (KPD)**

- Patient with type -2 DM presents as type -1 DM with ketosis

**Latent Autoimmune Diabetes in Adults (LADA)**

- Patient with type -1 DM presents as type -2 DM
### Difference between type-1 DM & KPD, type 2 DM & LADA

<table>
<thead>
<tr>
<th>Type - 1 DM with ketosis</th>
<th>Ketosis Prone Diabetes (KPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Autoantibodies present</td>
<td>* No autoantibodies</td>
</tr>
<tr>
<td>* No stigmata of insulin resistance</td>
<td>* Insulin resistance present</td>
</tr>
<tr>
<td>* Lean, tall, fair, boys</td>
<td>* Acanthosis nigricans, obesity, hirsutism, balanoposthitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type - a DM</th>
<th>LADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>* No autoantibodies</td>
<td>* Autoantibodies present</td>
</tr>
<tr>
<td>* Insulin resistance +</td>
<td>* No feature of Insulin resistance</td>
</tr>
<tr>
<td>* No feature of autoimmune illness</td>
<td>* Feature of autoimmune illness - lean, tall, fair</td>
</tr>
</tbody>
</table>

### LADA & KPD - Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>LADA</th>
<th>KPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Age</td>
<td>Young adults (20-35)</td>
<td>Young adults (15-25)</td>
</tr>
<tr>
<td>* Gender</td>
<td>Male = Female</td>
<td>Male &gt; Female</td>
</tr>
<tr>
<td>* Presentation</td>
<td>Insidious</td>
<td>Explosive</td>
</tr>
<tr>
<td>* Body weight</td>
<td>Lean</td>
<td>Obese</td>
</tr>
<tr>
<td>* Ketosis</td>
<td>Uncommon</td>
<td>At onset</td>
</tr>
<tr>
<td>* Antibodies</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>* Initial management</td>
<td>Oral hypoglycemic agents (OHA)</td>
<td>Insulin</td>
</tr>
<tr>
<td>* Long term management</td>
<td>Insulin</td>
<td>OHA</td>
</tr>
</tbody>
</table>

In KPD  
⇒ Stigmata of insulin resistance (Acanthosis nigricans, balanoposthitis)  
⇒ Dark, hirsute, obese male  
⇒ Hyperinsulinemia → marker  
⇒ LADA → lean, fair patients with stigmata of autoimmune illness

Current concepts in I.S Diabetes  
- Careful quantitative measurements of GAD,ICA, IAA are required in all type -2
- Check for Fasting serum c-peptide and c-peptide response after 1 mg glucagon administration.

- Low fasting c-peptide level indicates type 1 DM < 1.8 mg/dl after 1 mg glucagon administration.

- c-peptide level is a measure of endogenous Insulin level.

Endocrinopathies associated with diabetes

1. Pituitary : Acromegaly
2. Adrenal cortex : Cushing syndrome, Conn’s syndrome
3. Adrenal medulla : Pheochromocytoma
4. Thyroid : Hyperthyroidism
5. Parathyroid : Hyperparathyroidism
6. Pancreas : Glucagonoma, Somatostatinoma
PHYSIOLOGY OF INSULIN

Insulin

- Pancreas
  - Exocrine: 98%
  - Endocrine: 0.2% → Islet of Langerhans
- α cells: Glucagon
- β cells: Insulin (Maximum Number of cells)
- γ cells: Somatostatin
- F - cells: Pancreatic polypeptide

Insulin:
- Large protein (51 Amino acids)
- Polypeptide made up of 2 chains (A1 AA and 30 AA) connected by disulfide bond
- Acts on tyrosine kinase receptor

Metabolic effects

1. Carbohydrate metabolism
   - Insulin dependent glucose uptake (GLUT - 4) in adipose tissue and muscle
   - ↑ Glycogen synthesis and ↓ glycogenolysis
   - ↓ gluconeogenesis in liver

   ➞ In insulin deficiency or insulin resistance
     - Hyperglycemia
     - Glycosuria
     - Osmotic diuresis (Polyuria, Polydipsia, polyphagia)

   ➞ For every 100 mg/dl increase in blood glucose, serum Na⁺ falls by 1.6 meq/L

2. Lipid metabolism:
   - Insulin keeps lipolysis under control
   - Lipolysis occur with the help of enzyme hormone sensitive lipase
   - Insulin inhibits hormone sensitive lipase
- In insulin deficiency or insulin resistance:
  - ↑ lipolysis → ↑ Free fatty acids (FFA)
  - FFA enters liver and leads to ↑ gluconeogenesis, ↑ TG, ↑ VLDL and promote ketosis.

III. Protein Metabolism:
- Insulin - anabolic hormone
- Insulin increases the uptake of amino acid
- Increases protein synthesis
- In insulin deficiency or resistance → Negative nitrogen balance
  It leads to weakness, muscle wasting, susceptibility to infection

IV. Potassium Transport:
Insulin activates Na⁺- K⁺ ATPase
K⁺ enters into cell : Hypokalemia

<table>
<thead>
<tr>
<th>Metabolic defect</th>
<th>Chemical abnormality</th>
<th>Clinical abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓↓ Glucose uptake by tissues (muscle, adipose tissue, liver)</td>
<td>Hyperglycemia ↓</td>
<td>Polyuria, Polydipsia, Polyphagia</td>
</tr>
<tr>
<td>↑↑↑↑ Glucose production secondary to Glycogenolysis and gluconeogenesis in liver</td>
<td>Glycosuria ↓</td>
<td>Blurred vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminished mental alertness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dehydrated (→ death)</td>
</tr>
<tr>
<td>Protein metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ uptake of amino acids</td>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td>↓ Protein synthesis</td>
<td>↑ Levels of branch chain amino acid</td>
<td>Poor resistance to infections</td>
</tr>
<tr>
<td>↑ Proteolysis</td>
<td>↑ Blood urea nitrogen level</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Lipolysis</td>
<td>↑ Plasma FFAs</td>
<td>Loss of adipose tissue → weight loss</td>
</tr>
<tr>
<td>↑ Lipogenesis</td>
<td>↑ Plasma glycerol</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>↑ Triglycerides,</td>
<td>↑ Hypertriglyceridemia</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>FFA Production</td>
<td>↑ Plasma and urine Ketone</td>
<td>Hyperventilation →</td>
</tr>
<tr>
<td>↑ Ketone production</td>
<td>↑ Plasma LDL and VLDL</td>
<td>Hyperventilation → deaths</td>
</tr>
<tr>
<td>↑ Ketone excretion</td>
<td></td>
<td>Atherosclerotic vascular disease</td>
</tr>
<tr>
<td>↑ Production of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL and VLDL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of insulin release

Glucose enters pancreatic islet cell via GLUT-2

Glycolysis

ATP released

ATP inhibits ATP-sensitive K⁺ channel

↑ K⁺ level inside the cell (depolarisation)

↑ Entry of Ca²⁺ into the cell by voltage gated calcium channel

↑ cAMP and release insulin from secretory granules
Insulin is produced from rough endoplasmic reticulum and stored inside secretory vesicle of Golgi apparatus.

Insulin is released along with C-peptide and islet associated pancreatic polypeptide (Amylin / IAPP).

Drugs that inhibit ATP-sensitive K⁺ channel:
- Sulfonylureas
- Meglitinide analogues: Rapaglinide, Nateglinide

**Glucose transporters**

**GLUT-4** ⇒ Insulin dependent glucose uptake: Predominantly adipose tissue, muscle & heart

**GLUT-2** ⇒ Liver, β-cells of pancreas

**GLUT-1** and **GLUT-3** ⇒ Brain, Placenta ⇒ Insulin independent

**GLUT-5** ⇒ Small intestine— for absorption of glucose (Facilitated diffusion)
⇒ Fructose is also transported by GLUT-5

**Secondary Active Transport**
- **SGLT₁**: Present in small intestine
  - For glucose and galactose absorption
- **SGLT₂**: Present in proximal convoluted tubule in kidney
  - For sodium and glucose

**SGLT₂ inhibitors** ⇒ Canagliflozin
- Dapagliflozin
- Empagliflozin

**Mechanism of action**

- Tyrosine Kinase receptor
- Intracellular dimerization occurs
- Growth related properties of insulin mediated via PI3 kinase
Case scenario
1. Undetectable C-Peptide and high glucose  ⇒ Type 1 DM
2. High levels of C-Peptide and blood glucose  ⇒ Type 2 DM with insulin resistance
3. High level of C-Peptide and low glucose  ⇒ Insulinoma
4. Low levels of C-Peptide and low glucose  ⇒ Exogenous Insulin
Diabetes - pathogenesis

Thrifty Phenotype Hypothesis
- Fetal maternal, uteroplacental insufficiency contributed by
  - Maternal HTN hypertension (HTN)
  - Maternal DM diabetes mellitus (DM)
  - Fetal malnutrition

Type - 1 diabetes mellitus
- Immune dysregulation (autoimmune attack on β-cells [T-cell + β-cell])
- Pathology: Insulitis
- Genetic susceptibility (influenced by low birth weight)
  It is triggered by infections (rubella, mumps, coxsackie)
- Disease can develop at any age
- 70-80% beta cells are destroyed before the patient presents with clinical manifestations
- Honeymoon phase
  Period from 70% loss to 100% loss of cells during which patient may remain asymptomatic
- **HLA association**
  - MHC class 2 association
  - DQ ⇔ Causative - DQAI, OSOF, DQBI, O102
  - DR ⇔ Protective - DRBI, 1501

- Family history not significant
- Either parent having DM, chance of DM is 5%
- If both parents have DM, chance of getting DM is 15%
- Upto 50-70% concordance in identical twins

![Diagram](image)

- **Autoantibodies**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>Exists in two isomeric forms GAD65 and GAD67, based on molecular weight. Most persistent autoantibody and is also useful in the diagnosis of LADA. Catalyzes the conversion of glutamic acid to the inhibitory neurotransmitter GABA (γ-aminobutyric acid).</td>
</tr>
<tr>
<td>IA-2A</td>
<td>Member of the protein tyrosine phosphatase family and is a transmembrane protein. Less common at T1DM onset. Autoreactivity to the predominant C-terminal epitope of IA-2A is known as ICA90 autoantibodies.</td>
</tr>
<tr>
<td>ICA</td>
<td>Detected in T1DM individuals with T1DM. First antibody to appear in T1DM. Declines in few years after diagnosis and about less than 5% of individuals remain positive for longer periods. Most difficult antibody to measure because ICA assays are subject to variations in pancreatic tissue, conjugate incubation time, etc. Reacts against insulin and RIA conjugate, an insulinoma-associated autoantigen.</td>
</tr>
<tr>
<td>IAA</td>
<td>Is the only specific β-cell autoantibody. Most common in the new onset young T1DM than adults. IAA determinations in serum are no longer valid once insulin treatment is initiated in patients with T1DM. Most difficult to accurately measure and reproduce.</td>
</tr>
<tr>
<td>ZNT8A</td>
<td>Is a 36kDa, 6-transmembrane ZnT8 protein that concentrates Zn in insulin secretory granules. The Znt8 protein is encoded by SLC30A8 gene. Alleles of SLC30A8 have been shown to be also associated with T1DM.</td>
</tr>
</tbody>
</table>
Types 2 diabetes mellitus

- Polygenic and multifactorial
- 70-90% concordance in identical twins
- Either parent having type II DM, chance of getting DM is 25%
- Both parent having type II DM, chance of getting DM is 40%
- HLA is less significant
- Insulin resistance followed by decreased secretion

Metabolic syndrome

Adult Treatment panel III operational definition:
Any 3 of the following:
1. Waist circumference: Male > 102 cm
   Female > 88 cm
2. T4 level > 150 mg/dl
3. HDL cholesterol: Male < 40 mg/dl
   Female < 50 mg/dl
4. Fasting blood sugar: > 100 mg/dl
5. BP > 130/85 mmHg
**Central Features**
- Abdominal obesity
- Dyslipidemia
- Hypertension
- Glucose intolerance/Diabetes

**International diabetes federation definition**
Central obesity (based on waist circumference) + any of the two below or specific Rx for the condition
- Fasting serum TGL >500 mg/dL
- TBP >150/85 mm Hg
- Serum HDL cholesterol
  - Male <40 mg/dL
  - Female <50 mg/dL
- Impaired fasting glucose >100 mg/dL
- Previously diagnosed T2DM
- "European population"
- Male ≥94 cm
  - Female ≥80 cm

\[ \text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in m})^2} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO</th>
<th>INDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18.5 -24.9</td>
<td>18 -22.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 - 29.9</td>
<td>23 -24.9</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt;30</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>

**Diabetes/adiposopathy**
00:22:02

- Diabetes + obesity
- There is ↑ CRP
  ↓ Adiponectin
- In central obesity, α receptors are changed to β,
  ↓ Lipolysis
  Free fatty acid (FFA) enters portal circulation and then into liver
### Fatty acid cannot go into mitochondria

As carnitine palmitoyl transferase is not expressed on the surface of inner mitochondria.

### Promote Resistance

- Hypertension
- Prothrombotic state
- Asian Indian phenotype

### Type 1 DM vs Type 2 DM

<table>
<thead>
<tr>
<th></th>
<th><strong>TYPE 1 DM</strong></th>
<th><strong>TYPE 2 DM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>-</td>
<td>- Older</td>
</tr>
<tr>
<td>Thinner</td>
<td>-</td>
<td>- Obese</td>
</tr>
<tr>
<td>Family History rare</td>
<td>- Family History rare</td>
<td>- Family History Common</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-</td>
<td>- Obese</td>
</tr>
<tr>
<td>Osmotic symptoms - common</td>
<td>-</td>
<td>- Osmotic symptom-variable</td>
</tr>
<tr>
<td>Low C peptide</td>
<td>-</td>
<td>- Higher C peptide</td>
</tr>
<tr>
<td>No acanthosis nigricans</td>
<td>-</td>
<td>- Acanthosis nigricans +</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>-</td>
<td>- Dyslipidemia + + +</td>
</tr>
<tr>
<td>Hyperuricemia absent</td>
<td>-</td>
<td>- Hyperuricemia + + +</td>
</tr>
<tr>
<td>PCOS rare</td>
<td>-</td>
<td>- PCOS +++++</td>
</tr>
<tr>
<td>Antibodies ++</td>
<td>-</td>
<td>- Antibodies absent</td>
</tr>
<tr>
<td>DKA- common</td>
<td>-</td>
<td>- DKA- rare</td>
</tr>
</tbody>
</table>

**Note:**

- In PCOS ⇒ HAIR - AN Syndrome is seen
  
  ⇒ Hyperandrogenism (HA), Insulin Resistance (IR) and Acanthosis Nigricans (AN)
- Genetic factors are more important in type - 2
- Insulin is increased in early Type -2 DM and normal later
- HLA DR3 and HLA DR4 in type -1 DM
- Early insulitis is a feature of type - 1

**Genetic syndromes with insulin resistance**

1) **Type A Syndrome**
   - Seen in young females (< 20 years)
   - Defect in insulin receptor (post receptor signalling)
   - Characterized by obesity, Hyperandrogenism and acanthosis nigricans

2) **Type B Syndrome**
   - 30-40 years females
   - Antibodies against insulin
   - Associated with other autoimmune illness

3) **Rabson Mendenhall Syndrome**
   - Seen in children
   - Characterized by Acanthosis nigricans + nail changes + face and neck changes

4) **Lipoatrophic DM**

**Genetic syndromes with diabetes**

- Obesity related syndromes
  - Prader willi syndrome
  - Laurence-Moon syndrome
  - Alstrom syndrome
- Myotonic dystrophy
- Werner syndrome (progeria)
- Down syndrome
- Klinefelter syndrome
- Wolfram syndrome (diabetes insipidus + DM + Optic atrophy + deafness)

**Maturity Onset Diabetes of the Young (MODY)**

- Autosomal dominant
- Adolescent or early adulthood (<25 years)
- Male = Female
Types
Type 1 - HNF-4α mutation
Type 2 - Glucokinase
Type 3 - HNF-1α
Type 4 - Insulin promoter factor
Type 5 - HNF-1β
Type 6 - NeuroD1
Type 7 - KLF

⇒ All are transcription defect except type - 2 (enzyme defect)
⇒ MC type most common (MC) type in India & worldwide = Type 3
⇒ Type 2 MODY is seen in children (Type -2 does not require any drugs)
⇒ High risk for complication - Type 5
- No Stigmata of Insulin resistance
- No risk for micro / macro complications
- No risk for DM
- Well controlled with Sulfonylurea's
- Insulin release is inappropriate for the degree of hyperglycemia
- Prognosis: Excellent
- Decreased S & L, Receptors - Glycosuria + strong family history
(3 generation involved)

Type - 3 diabetes

1. Type 3a DM
   - Also Known as Hybrid diabetes
     Double diabetes
     Brain diabetes
   - Alzheimers dementia

2. Type 3b diabetes
   i. Psychiatric drugs: SSRIs, Olanzapine
   ii. Renal: Thiazide diuretic, Tacrolimus
   iii. Endocrine drugs: Steroids, OCP, Growth hormone
   iv. Anti - HIV drug: Protease inhibitors
   v. Oncology drug: L. Asparaginase

00:45:15

Active space
vi. β-agonist
vii. Diazoxide
viii. CNS drug: Phenytoin

⇒ Drugs that cause diabetes independent of insulin
  - Nicotinic Acid
  - Statin
  - Aspirin

iii. Type 3c: Pancreatic diabetes
  - Seen in
    i) Fibrocalculous chronic pancreatitis
    ii) Cystic fibrosis
    iii) Hemochromatosis

- 15-25 years
- 70% male
- Present in catastrophic fashion
- Acute severe abdominal pain
  + Steatorrhea.
  + DM with
    Extensive pancreatic calcification
- Risk of nephropathy
- Macro complications are rare
- Lean young
- Ketosis negative diabetes
- Gold standard for diagnosis - ERCP

<table>
<thead>
<tr>
<th></th>
<th>Tropical chronic Pancreatitis</th>
<th>Alcoholic chronic pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>2nd &amp; 3rd decade: 70% male</td>
<td>4th and 5th decade mostly male</td>
</tr>
<tr>
<td>Alcohol Intake</td>
<td>Usually non-alcoholic</td>
<td>Usually chronic heavy alcoholic</td>
</tr>
<tr>
<td>Nature &amp; Incidence of diabetes</td>
<td>more aggressive, occurs in 90%</td>
<td>Slower, 50-60%</td>
</tr>
<tr>
<td>Pancreatic calculi</td>
<td>Large, discrete margins</td>
<td>Small, ill defined margin</td>
</tr>
<tr>
<td>Nature and location</td>
<td>Large ducts and marked dilation</td>
<td>Small duct and mild dilation</td>
</tr>
<tr>
<td>Fibrosis of gland</td>
<td>Marked</td>
<td>Less severe</td>
</tr>
<tr>
<td>Risk of pancreatic cancer</td>
<td>Very High</td>
<td>Higher than in the general population</td>
</tr>
</tbody>
</table>

**Type-4 diabetes**

- Patient > 60 years developed hyperglycemia for the first time
- FBS < 100-250 mg/dl
- No features of insulin resistance
- No micro or macro complications
- Good prognosis
- Easily managed on oral hypoglycemic agents (OHAs)
- ↑ T-regulatory cells (CD4, CD8, CD25, Fox P3 - marker)

**New proposed classification of diabetes**

<table>
<thead>
<tr>
<th>Types of Diabetes</th>
<th>Autoantibody Status</th>
<th>BMI</th>
<th>Metabolic Control</th>
<th>Insulin deficiency or Resistance (HOMA-β &amp; HOMA-IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAID</td>
<td>Positive</td>
<td>Low</td>
<td>Poor</td>
<td>Insulin deficiency</td>
</tr>
<tr>
<td>SIDD</td>
<td>Negative</td>
<td>Low</td>
<td>Poor</td>
<td>Insulin deficiency</td>
</tr>
<tr>
<td>SIRD</td>
<td>Negative</td>
<td>High</td>
<td>Poor</td>
<td>Severe IR</td>
</tr>
<tr>
<td>MORD</td>
<td>Negative</td>
<td>High</td>
<td>Modest derangements</td>
<td>Mild or no IR</td>
</tr>
</tbody>
</table>
Type - 1  ↔  SAID - Severe Autoimmune diabetes  
      SIDD - Severe insulin deficiency diabetes  

Type - 2  ↔  mild - mORD - mild obesity related diabetes  
      Severe - SIRD - Severe insulin resistance diabetes  

Type - 4  →  mARD - mild age related diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Throughout childhood</td>
<td>Pubertal / Postpubertal</td>
<td>Pubertal / Post-pubertal</td>
</tr>
<tr>
<td>Gender</td>
<td>Female = Male</td>
<td>Female = Male</td>
<td>Female = Male</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>All (low incidence in</td>
<td>Native American</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Asians)</td>
<td>African - American</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hispanic</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Acute Severe</td>
<td>Insidious</td>
<td>Gradual</td>
</tr>
<tr>
<td></td>
<td>DNA common</td>
<td>Ketosis less common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Obesity</td>
<td>As in the population</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Reanthonis</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>nigricans</td>
<td>Very low/absent</td>
<td>Variable</td>
<td>Variably decreased</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Permanent</td>
<td>Episodic</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Insulin dependency</td>
<td>ICA (GADA) positive</td>
<td>ICA negative</td>
<td>ICA negative</td>
</tr>
<tr>
<td>Antibodies</td>
<td>40-100 GADA positive</td>
<td>GADA positivity ±</td>
<td>GADA negative</td>
</tr>
<tr>
<td>Family history</td>
<td>5-15%</td>
<td>75-90%</td>
<td>100%</td>
</tr>
<tr>
<td>mode of inheritance</td>
<td>Non - Mendelian, sporadic</td>
<td>Non - Mendelian, familial</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>
## ACUTE COMPLICATIONS OF DIABETES

### Intensive treatment (IT) / Lowering of glucose

<table>
<thead>
<tr>
<th>Intensive glucose control trials</th>
<th>microvascular complications</th>
<th>macrovascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC type I diabetes</td>
<td>IT reduced overall</td>
<td>Trend towards lower risk of CVD events with IT</td>
</tr>
<tr>
<td></td>
<td>microvascular complications</td>
<td>Relationship between glucose control and microvascular complications extended into range of normal Ac with no glycaemic threshold</td>
</tr>
<tr>
<td>унидс (used FPG goals) type 2 diabetes</td>
<td></td>
<td>1.5% reduction in CV complications with IT</td>
</tr>
<tr>
<td>Rabion</td>
<td>IT significantly reduced overall microvascular complications</td>
<td>No significant reduction in microvascular complications with IT</td>
</tr>
<tr>
<td>VADT</td>
<td>No significant reduction in microvascular complications with IT</td>
<td></td>
</tr>
<tr>
<td>Record</td>
<td>Terminated glycemic control study because of increased mortality in patients receiving IT with Ac &gt;6.5%</td>
<td></td>
</tr>
</tbody>
</table>

- IT with target Hba1c 6.5% has found to significantly reduce microvascular complications and no significant ↓ in macrovascular complications

### Infections unique to diabetes

1. Rhinocerebral mucormycosis:
   - Mucor / Rhizopus
   - Angioinvasion with ‘black necrotic turbinate’ in diabetics
   - Crosses cribriform plate of ethmoid
   - Neurological complications 🌟
   - IOC: MRI brain
   - Doc: Liposomal amphotericin B
   - Only oral azole used: Posaconazole

![MRI images of brain](image-url)
II) Malignant otitis externa:
- Pseudomonas, nocturnal ear ache
- Skull base paralysis, LMN cranial nerve palsy
- IOC/MRI
- DOC: Ceftazidime / Cefepime

III) Emphysematous pyelonephritis

- E. coli → Ferments glucose to produce gas
- Bad prognosis → High mortality
- IV antibiotics (medical management) superior
- Complicated UTI-like presentation

IV) Emphysematous cholecystitis:
- E. coli → Gas in gall bladder
- Clostridium
- Acute → Surgical emergency → Can produce gall bladder perforation, necrosis and gangrene
- Surgery carries 20% mortality risk
- Least mortality of aforementioned 4 conditions / Complications

➡️ melioidosis:
- Burkholderia pseudomallei
- In diabetics → Weight loss, fever
- CT: multiloculated abscesses in liver and spleen

**Acute complications – DKA and HHS**

- DKA (Diabetic Ketoacidosis): Insulin deficiency + Glucagon / Counter regulatory hormone excess
→ Carbohydrate metabolism:
  - ↓ Fructose 2,6 bisphosphate → Instead of glycolysis, gluconeogenesis happens
  - Insulin-dependent glucose uptake due to GLUT 4 (adipose, muscle, heart) ↓

→ Protein metabolism:
  - Proteolysis → Amino acid, lactate → Substrates for gluconeogenesis

→ Fat metabolism: ↑ HSL (Hormone Sensitive Lipase) → ↑ lipolysis
  → ↑ free fatty acid
    → Substrate for gluconeogenesis
    → ↑ VLDL
    → Drawn into mitochondria [↑ Glucagon] → CPT
      [Carnitine Palmitoyl Transferase] expressed → β oxidation
      → ↑↑↑ acetyl CoA → ketone body pathway via
        HMG CoA → β hydroxyl butyrate → Acetone
        → Acetoacetate

• MCC of death in DKA (children): Cerebral edema

• DKA always has precipitation events:
  → Infection
  → Inadequate insulin
  → Infarction
  → Pregnancy
  → Cocaine

• Presentation
  → Uncontrolled nausea, vomiting
  → Acute abdominal pain
  → Acidotic breathing → disproportionate dyspnoea → Kussmaw's breathing
  → Lethargy, obtundation
  → ↑ HR, ↑ RR, ↓ BP/Postural hypotension
Management of DKA

- **Investigations:**
  - Patient catheterized → urine tested for ketone bodies
    - **Rothera's test:** Cannot detect β - hydroxybutyrate
  - A peripheral blood lines placed → blood sent for CBC, electrolytes, S.Ca^2+, S.PO_4^3-
  - ABG analysis

- **Treatment**
  - **One peripheral line:** Fluid replacement
    - Average fluid required 9 l
    - 2 l of NS over 1st 8 hrs
    - 3 l of NS over next 6 hrs
    - 3 l of ½ NS / 5% D (If glucose <200) over next 12 hrs
    - Bicarbonate replacement: When pH <7.1
  - **Other peripheral line:**
    - 0.1 u/kg of regular insulin, IV stat ⇒ 0.1 u for 60-70 kg patient
    - 0.15 u/kg/hr infusion
    - For 50 kg patient
    - **500 ml NS**
      - 25 u insulin added
      - infused for 5 hrs
      - 5 u/hr → For first 5 hrs
  - **500 ml NS**
    - 15 u insulin
    - Shrs
    - 3 u/hr → For next hrs
  - **500 ml NS**
    - 5 u insulin
    - 5 hrs
    - 1 u/hr → For next 5 hrs ⇒ Try overlapping here with s.c.insulin, which is continued later

- **Complication of treatment:** Hypokalemia, hypophosphatemia
  ⇒ To prevent for every 2 pint / 1 l NS ⇒ add √1 amp KCL = 10 ml
  - 1 ml = 2 meq K^+ ⇒ 10 ml = 20 meq of K^+
HONK / HHS

- HHS [Hyperosmolar hyperglycemic state] / HONK [Hyperglycemic hyperosmolar non-ketotic coma]
  - more in elderly
  - Definite intercurrent illness (+), e.g. URTI/LRTI
  - Presents in comatose state

<table>
<thead>
<tr>
<th>Table - laboratory values in diabetic Ketoacidosis (DKA) and hyperglycemia hyperosmolar state (HHS) (representative ranges at presentation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/L (mg/dL)</td>
</tr>
<tr>
<td>Sodium, meq/L</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Chloride</td>
</tr>
<tr>
<td>Phosphate</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Osmolality (mosm/mL)</td>
</tr>
<tr>
<td>Plasma Ketones</td>
</tr>
<tr>
<td>Serum bicarbonate, meq/L</td>
</tr>
<tr>
<td>Arterial pH</td>
</tr>
<tr>
<td>Arterial pCO2, mmHg</td>
</tr>
<tr>
<td>Anion gap (Na-Cl+HCO3)</td>
</tr>
</tbody>
</table>

- Severe hyperglycemia develops (>500 mg/dL generally)
- No counter-regulatory hormone excess → No ketosis
- Severe volume depletion → Acute volume correction → Can cause cerebral edema → ↓: Slow correction / ½ NS preferable
CHRONIC COMPLICATIONS OF DIABETES

Microvascular complications

→ Diabetic retinopathy
→ Diabetic neuropathy
→ Diabetic nephropathy

Diabetic nephropathy:

- Risk in T2DM = T2DM
  30-40% 50-60% in India
  \[ \text{Develop diabetic nephropathy} \]

- Control to be achieved in first 5 yrs
- ‘Nephrone underdosing’ at birth → mothers with HTN, DM
- Pathogenesis:
  - Uncontrolled hyperglycemia → alternate pathways of metabolism
    [Protein Kinase C; Sorbitol; Aldose reductase] → Growth factors,
    Cytokines → Afferent arteriolar vasodilatation → ↑ RBF, ↑ GFR
    → Hyperfiltration [Stage 1] → ↑ intraglomerular pressure →
      Normally dissipates; but, in
      Diabetes → Loss of renal autoregulation → intraglomerular HTN
      [1st major pathological change]

Podocyte loss proteins leak into urine (albumin)
↓ Potent tubulotoxic
Parietal epithelium begins to fuse with Gbm → Interstitial inflammation
↓ Bowman space obliterated TGF β → Fibrosis
→ synechia formation IFTA [Interstitial Fibrosis]
→ sclerosis Tubular Atrophy
↓ Glomerulosclerosis
- **Stage I:**
  - "Hyperfiltration", ↓ in podocytes → endothelial dysfunction

- **Stage II:**
  - "Exercise induced microalbuminuria"
  - SHTN → Ambulatory PP widening
    → Absence of nocturnal dipping

- **Stage III:**
  - "Incipient diabetic nephropathy" → microalbuminuria
    → Towards stage 3 end → Proteinuria
    → HTN starts
  - 3 pathological findings;
    → Earliest / universal finding → GBM thickening
    → mesangial expansion
    → Afferent and efferent arteriolar hyalinosis

- **Stage 1+2+3 → ACEIs started → Can reduce proteinuria.**

- **Stage IV:**
  - "Overt diabetic nephropathy" → ↑ S.Creatinine
  - Diffuse glomerulosclerosis: ~ 90% → due to diffuse mesangial expansion, non specific → degree of expansion ‘always’ correlate with renal failure
  - Nodular glomerulosclerosis: ~ 50% → KW – Kimmelstiel-Wilson
    → pathognomonic → due to presence of large asymmetrical nodules → number of nodules never correlate with renal failure

- **Stage V:**
  - "ESRD – End stage renal disease" → AV/a, AVfTA – GS
  - Non specific lesions:
    - Arteriolar - Ebstein lesions (due to tubular injury)
    - Capsular drops
    - Hyaline caps

- Target HbA1C = 6.5 – 7%
→ T2DM patient, S. Creatinine = 1.5 mg/dl with diabetic nephropathy

\[
GFR = \frac{(40 - \text{age}) \times 80}{72 \times \text{S. Creat}} = \frac{(40 - 60) \times 72}{72 \times 1.5} = \frac{80}{1.5} = 53 \text{ ml/min}
\]

- Rate of fall of GFR in diabetic nephropathy = 8-10 ml/min/yr
  ⇒ ESRD [<15 ml/min GFR] in 4 yrs and becomes dialysis dependent
  • Anemia can independently ↑ rate of fall of GFR

- Indications of biopsy:
  i) Absence of retinopathy in diabetics
     [Retinopathy → 100% in T1DM, 65-70% in T2DM]
  ii) Presence of edema → SGLT2 receptor activation → Intra and extravascular edema, if edema + → Biopsy
  iii) Proteinuria → If absent → Biopsy
  iv) Systemic HTN → Absent → Biopsy
  v) Presence of microscopic hematuria / Nephrotic syndrome → Biopsy

- Treatment:
  - Metformin [contraindicated if GFR < 40 ml/min]
  - Sulfonylureas → Gliclazide; Glipizide
  - Linagliptin → Safe in renal failure
  - SGLT2 inhibitors [contraindicated if GFR < 30 ml/min]
  - GLP, agonist → Liraglutide safe in renal failure → cardiac benefits

### Diabetic retinopathy

- **Screening:**
  → T1DM: Once every 5 years
  → T2DM: At diagnosis

- **Types:**
  → Non-proliferative [NPDR]: microaneurysm [earliest], hemorrhage, exudates, macular edema
    [MCC for visual loss]
  → Proliferative [PDR]: “neovascularization”, vitreous hemorrhage, retinal detachment
Non-proliferative stage

• Soft exudates/cotton wool spots: Pseudoexudates → Due to stasis of axoplasmic flow in outer nerve fibre layer

Skin manifestations in DM

• Necrobiosis lipoidica diabeticorum

• Scleroderma

• Acanthosis nigricans

• Diabetic dermopathy

▌ [shin spots]

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Indication for Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 50 years</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>&gt; 1 mg/dL (&gt; 0.25 mmol/L) above upper limit of normal</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td></td>
</tr>
<tr>
<td>a) T score of ≤ 2.5 (osteoporosis)</td>
<td></td>
</tr>
<tr>
<td>b) Vertebral fracture on imaging study</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
</tr>
<tr>
<td>a) Reduced to &lt; 60 mL/min</td>
<td></td>
</tr>
<tr>
<td>b) 24-hour urine for calcium &gt; 400 mg/day and increased stone risk by biochemical stone risk analysis</td>
<td></td>
</tr>
<tr>
<td>c) Nephrolithiasis or nephrocalcinosis on imaging study</td>
<td></td>
</tr>
</tbody>
</table>

• Granuloma annulare: Symmetrical papular, annular lesions distributed on arms → Have erythematous border and flat centre
Diabetic neuropathy

- $T_{2,DM} > T_{1,DM}$
- Symmetrical polyneuropathies:
  - Distal to proximal, symmetrical sensory $\rightarrow$ motor small fibre neuropathy
  - Rarely $\rightarrow$ Large fibre neuropathy
  - Spinothalamic tract involved
- Focal and multifocal neuropathy:
  - Carpal tunnel syndrome
  - Mononeuritis
  - Pupil sparing 3rd nerve palsy (+)
- Asymmetric lower limb motor neuropathy:
  - Diabetic amyotrophy
  - Mostly involves quadriceps
- Autonomic neuropathy:
  - Postural hypotension
  - Erectile dysfunction
  - GI motility disorder
  - Gustatory sweating
  - Nocturnal diarrhea

$\rightarrow$ Small fibre neuropathy: C type; Pain, temperature; Hyperalgesia, constant burning; Gloves and stocking sensory loss;
Deformities absent; Motor deficit +; Tendon reflexes lost

$\rightarrow$ Large fibre neuropathy: A delta type; Fine touch, vibration +;
Sensory ataxia/ulcers; small muscle wasting +; Motor deficit +++; Tendon reflexes lost ++++

- Drugs used: TCA, Gabapentin, Carbamazepine, Duloxetine, SSRI
MANAGEMENT OF DIABETES

Treatment goals for diabetes

- HbA1c: <7% [Ideal: 4.5-7%]
- FBS: 80-130 mg/dl
- PPBS: <180 mg/dl
- BP: <130/80 mm Hg
- LDL: <100 mg/dl
- HDL: Females: > 50 mg/dl
  Males: > 40 mg/dl
- TG: <150 mg/dl

Diet and exercise

- Aerobic exercise: 5 times/week; Duration: 30-45 mins
- Carbohydrate: \[\uparrow\] complex carbohydrate consumption: Roti, Oats, fruits, whole wheat, vegetables; Fructose preferred over sucrose
- Protein:
  - 1g/kg protein
  - Class I protein: Low fat milk, egg white, fish, soybean, skinless chicken
- Fat:
  - No transfat; MUFA recommended; visible fat added while cooking;
  - 3 tsp - 5 tsp [refined oil or cheese]

Lipid level in diabetes:
- Total cholesterol \[\uparrow\]
- VLDL \[\uparrow\], Apo B 100 \[\uparrow\]
- TG \[\uparrow\]
- HDL: Low
- LDL: Normal
- Small dense LDL: \[\uparrow\] atherogenic
DIABETIC DYSLIPIDEMIA

- **Management:**
  - Age < 40 yrs
    - Non-atherosclerotic → Saroglitazar
    - Atherosclerotic vascular disease → Saroglitazar + statin
  - Age > 40 yrs
    - non atherosclerotic vascular disease → Saroglitazar + Statin

- Doc for diabetic dyslipidemia → Saroglitazar [dual peroxisome proliferator - activated receptor - (PPAR) α and γ agonist]
- If no ASVD, target LDL to be achieved is <100 mg/dl and if there is ASVD, target LDL = <70 mg/dl
- To achieve target, statin + Ezetimibe small PCSK9 inhibitors can be used
- Statins used: Atorvastatin: 40-80 mg | Rosuvastatin: 20-40 mg
Drug therapy

$\overset{\rightarrow}{\text{HbA}}_c > 9\%$
$\overset{\rightarrow}{\text{Presentation with diabetes complication}}$
$\overset{\rightarrow}{T_1DM}$
$\rightarrow \text{Start insulin}$

- Apart from above conditions; OHAs (Oral hypoglycemic agents) started

- **Biguanides:**
  - **Metformin** (biguanide of choice): 500 mg BD [1 g maximum dose]
  - 1 g maximum dose as single drug
  - **MFA:**
    - ↑ activity of AMP kinase and thus decreasing hepatic glucose production
    - ↑ GLUT_4 mediated glucose uptake in skeletal muscle, heart and adipose tissue
  - **Advantages:**
    - Combats insulin resistance
    - Potency: HbA1c reduction potential = 1.5–2%
    - Weight loss
    - No hypoglycemic risk
  - **Disadvantages:**
    - Renal excretion unchanged [C/v in GFR <40 ml/min]
    - If used in RF → Cause lactic acidosis
    - Vit B12 deficiency

$\rightarrow \text{HbA}_c < 7\%$ if not achieved with metformin;
- Any ASVD risk → Risk + → GLP, agonists
  - SGLT_2 inhibitors
- No risk → SGLT_2
  - GLP, (⊕)
  - DPP4 (⊕) → Less potency
  - Thiazolidinedione → more side effects

- **SGLT_2 (⊕):**
  - Na^+ dependent GLUT_2
  - Dapagliflozin (5 mg or 10 mg), empagliflozin, canagliflozin
- Advantages:
  - Weight loss; SBP ↓; No hypoglycemia risk
  - Potency: 1-1.8%
  - Cardioprotective → mostly for empagliflozin

- S/E's:
  - Genitourinary infections → especially *Candida*
  - ↑ risk for osteoporosis; ↑ LOXL
  - ↑ risk of ketosis

**Other OHAs**

- **Sulfonylureas:**
  - ATP sensitive K⁺ channels ⊕
  - Long acting sulfonylureas (glibenclamide) disadvantages:
    → Hypoglycemic risk
    → Weight gain
    → Cardiac safety

- Advantages: Potency 1-2%; Cheap

- **Gliclazide** (only sulfonylurea approved):
  - ⊕ Platelet aggregation
  - Anti-oxidant action ⊕
  - Prevents endothelial injury
  - Cardioprotective
  - Prevents weight gain
  - 80 mg → 330mg dose
  - Safe in renal failure or glipizide 5 – 10 mg

- **Meglitinide analogues:**
  - HbA₁c reduction potential 0.5%
  - Nateglinide, repaglinide
  - Used for post prandial hyperglycemia.

- **Thiazolidinediones:**
  - Pioglitazone; PPAR γ agonist
  - Combats insulin resistance
- Enhance glucose uptake via GLUT4.
- Potency: 0.5 - 1.4T
- S/E: Weight gain, edema, bone #, ↑ risk of CA bladder

- α - glucosidase Θ:
  - Acarbose, voglibose, miglitol
  - Anti-hyperglycemic
  - S/E: Abdominal discomfort and belching

**Incretin effect**

*Incretin hormones*

* IV glucose v/s oral glucose: Amplification of insulin release due to hormones produced from GIT
* Due to 2 hormones;
  - GLP-1 [Glucagon like peptide - 1]
  - GIP [Glucose dependent insulinotropic polypeptide a/k/a gastric inhibitory polypeptide]

* GLP-1 and GIP act on pancreas → ↑ β cell responsiveness → Augment insulin release
* They have extremely short T½ → GLP - 1 → 1-2 mins
  → GIP → 5-7 mins
* Rapidly degraded by DPP-4 [Dihydro peptidyl peptidase - 4]

Source : GLP-1 L cells of ileum & colon

GIP - K cells of jejunum

GLP-1 is more potent than GIP
• GLP-1 is superior to GIP
  → Suppresses glucagon release
  → Delays gastric emptying
  → Activates satiety centre → associated with weight loss
  → But, it stimulates β cell expansion pancreatic disorders

• Recombinant GLP-1
  → Not degraded by DPP-4
  → Given s.c.

• DPP-4 inhibitors:
  → Given orally
  → ↑ Physiological $T_{1/2}$ of GLP-1 and GIP

<table>
<thead>
<tr>
<th>Source</th>
<th>GLP-1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose dependent insulin release</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Enhances beta cell glucose responsiveness</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Suppresses glucagon release</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Stimulates beta cell expansion</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Enhances satiety</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Reduces body weight</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Half life</td>
<td>1-2min</td>
<td>5-7min</td>
</tr>
</tbody>
</table>

• Recombinant GLP-1 analogues: Eg: Exenatide, liraglutide, semaglutide

• Liraglutide is preferred → Long acting, given OD, dose 0.6mg

• Advantages:
  - Potency: 1-1.2%
  - Promotes weight loss (act on satiety centre)
  - Suppresses glucagon
  - Inhibits gastric emptying
  - No risk for hypoglycemia
  - Cardiovascular benefit
- **s/e's:**
  - Nausea, vomiting
  - Acute pancreatitis
  - Medullary thyroid cancer

**Gliptins**

- It is DPP4 *Gi*; prolongs physiological T½ of GLP-1 and GIP
- **Advantages:**
  - Weight neutral drug [no weight loss/gain]
  - No hypoglycemia
  - Cardio-neutral drug [no cardiac toxicity / benefit]
- **Disadvantages:**
  - Cost
  - Potency 0.5-0.75% ; pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Vildagliptin</th>
<th>Saxagliptin</th>
<th>Alogliptin</th>
<th>Linagliptin</th>
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<tbody>
<tr>
<td>Dose</td>
<td>100</td>
<td>50 mg bd</td>
<td>5</td>
<td>25</td>
<td>5 mg</td>
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<tr>
<td>Half life</td>
<td>Long</td>
<td>Short</td>
<td>Short</td>
<td>Long</td>
<td>Very Long</td>
</tr>
<tr>
<td>Frequency</td>
<td>Once</td>
<td>Twice</td>
<td>Once</td>
<td>Once</td>
<td>Once</td>
</tr>
<tr>
<td>Active met</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Yes</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>HIGH</td>
</tr>
<tr>
<td>Renal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Drug interactions</td>
<td>NO</td>
<td>NO</td>
<td>Yes</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>GLP-1</td>
<td>DPP-4</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>----------------------</td>
<td>-------</td>
<td>-------</td>
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<td></td>
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</tr>
<tr>
<td>Mode of administration</td>
<td>s/c</td>
<td>oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism</td>
<td>GLP-1</td>
<td>GLP-1 and GIP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmenting insulin release</td>
<td>++++</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppressing glucagon</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>delayed</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular benefits</td>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Amylin agonist**

- **Pramlintide**:
  - Given S.C.
  - Approved for both Type I DM and Type 2 DM
  - Hypoglycemia risk +
  - Dose: 15 mg prior to meals
  - Advantages: ↓ glucagon, slows gastric emptying, improves satiety

**Newer drugs**

- **Colesevelam**: Bile acid sequestrant
- **Lorcaserin**: SHT2c antagonist
- **Imeiglimin**: Oxidative phosphorylation blocker
- **Telmisartan**: Only ARB acting on PPARγ
- **Ruboxistaurin**: Protein Kinase C inhibitors
- **Epahrestat**: Aldose reductase inhibitors
  - Bromocriptine, HCQ yet to be approved
Mechanism of action of OHA – summary

Liver
- Insulin secretagogues
  - Sulfonylureas and meglitinides
  - DPP IV
- Biguanides
- Thiazolidinediones
- Alpha glucosidase inhibitors
- Carbohydrates
- Fat cells
- Fat absorption
- Carbohydrates
- Fat
- Incretin
- Small intestines
- Muscle cell
- Intestinal lipase inhibitors
- Peripheral glucose uptake

Blood glucose
- Insulin secretion and release
- Insulin release and action
- Pancreas
- Vagal mediated insulin secretion and release
- D3 Agonists (Bromocriptine)

Glucagon release

mechanism of action of oral antidiabetic agents (OAs)
(SGLT2: Sodium glucose co-transporter 2; DPP-IV: Dipeptidyl-peptidase 4 inhibitors)
INSULIN THERAPY IN DIABETES

Components of continuous glucose monitoring system (CGMS)

Continuous blood glucose monitoring system

Flash glucose monitor

Continuous glucose monitoring system

Samarai effect

- Morning blood sugar check is "elevated"
- Bedtime blood sugar check is "in-range"
- Undetected hypoglycemia

Blood glucose level (mg/dL)

<table>
<thead>
<tr>
<th>Time</th>
<th>9 pm</th>
<th>10 pm</th>
<th>11 pm</th>
<th>12 am</th>
<th>1 am</th>
<th>2 am</th>
<th>3 am</th>
<th>4 am</th>
<th>5 am</th>
<th>6 am</th>
<th>7 am</th>
<th>8 am</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>200</td>
<td>220</td>
<td>230</td>
<td>240</td>
<td>250</td>
<td>260</td>
<td>270</td>
<td>280</td>
<td>290</td>
<td>300</td>
<td>310</td>
<td>320</td>
</tr>
</tbody>
</table>
Somogyi effect causes: excess night dose of insulin

\[ \text{Nocturnal hypoglycemia.} \]

\[ \text{counter regulatory hormone excess} \]

\[ \text{early morning hyperglycemia.} \]

Dawn phenomenon

* cause: due to inadequate night dose of insulin

\[ \text{Early morning hyperglycemia.} \]

* Night dose of insulin to be \(\uparrow\uparrow \text{increased}\) in dawn

\[ \text{↓↓ decreased in somogyi pen insulin} \]
### Insulin preparation

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Onset of action</th>
<th>Peaks</th>
<th>Effective duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra short acting</td>
<td>Lispro aspart</td>
<td>&lt;15 mins</td>
<td>1-1.5 hrs</td>
<td>4 hrs</td>
</tr>
<tr>
<td></td>
<td>glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular</td>
<td>30 mins</td>
<td>1-3 hrs</td>
<td>3-6 hrs</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NPH</td>
<td>2-4 hrs</td>
<td>4-10 hrs</td>
<td>10-14 hrs</td>
</tr>
<tr>
<td>Long</td>
<td>Glargine</td>
<td>1 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(acidic-can’t be</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mixed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
<td>2-3 hrs</td>
<td>peakless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depludec</td>
<td>2-3 hrs</td>
<td>peakless</td>
<td>&gt;40 hrs</td>
</tr>
</tbody>
</table>

- Limitations of glargine - mitogenic risk
  - Ca. thyroid
  - Weight gain
  - Inter-individual variation
Insulin

- Triple drugs
  - HbA1C > 7%
  - Continue triple drugs
    +
    - Long acting/
    - Ultra long acting insulin
    - Glargine 12 units (daily)/
    - Degludec 12 units (alternate day)

- Complications
  - HbA1C > 9%
  - (40 units of insulin)
    - 2/3rd regular
      - (4 units)
    - 1/3 long acting
      - (6 units) →
  - Glargine at night
  - Degludec (alternate day)

- Step up by 4 units
  - or
- Step down by 2 units
HYPOGLYCEMIA

- RBS < 70 mg/dl
- Confusion or altered level of sensorium or seizure rule out Hypoglycemia.

- Whipple’s Triad
  Clinically relevant hypoglycemia is characterized by:
  1) Characteristic neuroglycopenic symptoms
  2) Low blood glucose concentration (≤ 70 mg/dl)
  3) Resolution of symptoms with return of blood glucose concentration to ≥

Symptoms:

Autonomic
- Sweating
- Trembling
- Pounding heart
- Hunger
- Anxiety

Neurologic
- Confusion
- Drowsiness
- Speech difficulty
- Inability to concentrate
- Incoordination

Non Specific
- Nausea
- Tiredness
- Headache

Physiologic responses to decreasing plasma glucose concentration

<table>
<thead>
<tr>
<th>Glucose Level (mg/dl)</th>
<th>Response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-85</td>
<td>Insulin Falls</td>
<td>First defense</td>
</tr>
<tr>
<td>65-70</td>
<td>Glucagon ↑</td>
<td>Second defense</td>
</tr>
<tr>
<td>65-70</td>
<td>Epinephrine ↑</td>
<td>Third defense (critical when glucagon is deficient)</td>
</tr>
<tr>
<td>65-70</td>
<td>Cortisol and Growth hormone ↑</td>
<td>Incase of prolonged hypoglycemia</td>
</tr>
<tr>
<td>50-55</td>
<td>Symptoms</td>
<td>Prompt behavioral defense (Food ingestion)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Cognition ↓</td>
<td>Comprises behavioral defense</td>
</tr>
</tbody>
</table>
• Hepatic glycogen stores are enough to maintain glucose levels for 8hrs only
• Brain requires glucose but, cannot Synthesize / utilize fatty acids
• In prolonged hypoglycemia, there is activation of cortisol and GH
• Dynamic thresholds — Higher than normal to be maintained in diabetic population
• CNS Glucose deprivation + sympathoadrenal discharge + Ach release (sweating)
• Increase platelet aggregation and inhibit fibrinolysis

**Hypoglycemia in diabetics**

• Drug induced — Insulin
  Sulfonlurea
• CKD — Prolonged t½ of insulin
  ↓ Renal Gluconeogenesis

Hypoglycemia associated autonomic failure (HAAF)
• Reversible entity

**Early T2DM**:

( Relative β cell failure)
↓
Marked absolute
Therapeutic — Hyperinsulinemia
↓
Falling glucose level
↓
Isolated episodes of Hypoglycemia
Advanced T2DM & T1DM:

(Absolute β-cell failure)

↓

Relative/mild - moderate absolute
Therapeutic Hyperinsulinemia
Falling glucose levels

↓

β-cell failure

↓

No ↓ Insulin & No ↑ Glucagon

↓

Episodes of hypoglycemia.

↓

Exercise

 ↓

Sleep

↓

Attenuated sympathetic adrenal response to hypoglycemia.

↓

Adrenomedullary epinephrine response

↓

Defective Glucose Counterregulation

↓

Hypoglycemia, unawareness

↓

Recurrent Hypoglycemia

↓

Hypoglycemia without DM

- Drugs - Ethanol
  Beta Blockers
- Critical illness / Sepsis
- Addisons / GH deficiency
- Non - islet cell tumor dependent hypoglycemia in mesenchymal tumors - increased IGFa
- β-cell hypertrophy - Nesidioblastosis
Endogenous hyperinsulinemia

- Insulinoma
- Antibodies to insulin receptor
- \( \beta \)-cell secretagogues (sulfonylurea, meglitinide)

\[ \text{plasma insulin} \geq 3 \text{micro IU/ml} \]
\[ \text{plasma C-peptide} > 0.6 \text{nmol/ml} \]
\[ \text{RBS} < 55 \text{mg/dl} \]
\[ \text{plasma pro insulin} > 5 \text{pmol/l} \]

- check for \( \beta \) - hydroxybutyrate

**Insulinoma**

*Symptoms of Hypoglycemia*

- *Autonomic*
  - Tremulousness
  - Palpitations
  - Sweating
  - Anxiety
  - Warmth
  - Feelings of "Impending Doom"

- *Neuroglycopenia*
  - Impaired concentration
  - Fatigue
  - Headache, dizziness
  - Slurred speech
  - Confusion
  - Disorientation
  - Coma
  - Seizures

**Symptoms produced by an insulinoma are generally those of Neuroglycopenia.**

---

Hirata’s disease (IAS)

- Insulin Autoimmune syndrome
- Antibodies against insulin
- \( > 40 \) Post prandial hypoglycemia
- Autoimmune association
- precipitated by methimazole
- Insulin molecule dissociates quickly causing marked hypoglycemia
- Spontaneous recovery in \( 80\% \)

**Hirata's disease v/s insulinoma**

1. Insulin / C-peptide ratio \(< 1 \rightarrow \square\)
If Insulin / C-peptide ratio > 1

Either C-peptide low or Insulin ↑↑↑
Insulin ↑↑
[Exogenous insulin] C-peptide ↑
[Hiratas disease]

Treatment of Hypoglycemia

- Rule of 15 → 15g oral glucose & Check after 15mins
- Symptomatic cases → 100ml of 25% dextrose – repeat
- If no IV access give IM or S/C Glucagon 1mg
BONE AND MINERAL METABOLISM

- **Cortical bone (80%)** — bony cylinders arranged around central Haversian canal — diaphysis
- **20% trabecular bone** — more BMD / turnover
- **Bone cells (1%)** organic matrix (25%) mineral phase (75%)
- **95% of organic matrix is type 1 collagen**
- **Skeleton is highly vascular** — 10% of total CO is to bones

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cortical</th>
<th>Trabecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonyms</td>
<td>Compact bone</td>
<td>Cancellous, spongy</td>
</tr>
<tr>
<td>Contribution to total bone mass</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Predominant sites</td>
<td>Shaft of long bones</td>
<td>End of long bones, vertebra.</td>
</tr>
<tr>
<td>Porosity</td>
<td>5–15%</td>
<td>30–90%</td>
</tr>
<tr>
<td>Haversian system</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Metabolic activity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Remodelling rate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Predominant hormonal control</td>
<td>PTH, thyroxine</td>
<td>Gonadal steroids, glucocorticoids</td>
</tr>
</tbody>
</table>
Constituents of bone

Cells (3%)  →  matrix (98%)
- Osteoblasts
- Osteoclasts
- Osteocytes (95%)
- Bone lining cells

Inorganic (60-70%)
- Calcium
- Phosphate
- Magnesium

Organic (30-40%)
- Type I collagen (90%)
- Non-collagenous proteins (5%)
  - Osteocalcin
  - Osteopontin

Common (non-collagenous constituents)
- Osteopontin
- Osteocalcin
- Thrombospondin
- Matrix Gla protein
- Fibronectin
- Proteoglycans

Collagen

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SEEN IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Bone</td>
</tr>
<tr>
<td>Type II</td>
<td>Cartilage, vitreous humor</td>
</tr>
<tr>
<td>Type III</td>
<td>Extensible connective tissue</td>
</tr>
<tr>
<td></td>
<td>(skin + vascular)</td>
</tr>
<tr>
<td>Type IV</td>
<td>Basement membrane</td>
</tr>
<tr>
<td>Type V</td>
<td>Type I</td>
</tr>
<tr>
<td>Type VI</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Type VII</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Type VIII</td>
<td>Endothelium</td>
</tr>
<tr>
<td>Gene or enzyme</td>
<td>Disease</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td>COL 1A1, COL1A2</td>
<td>Osteogenesis imperfecta, type 1 (MIM 1566300) osteoporosis&lt;sup&gt;*&lt;/sup&gt; (MIM 166710) Ehlers-Danlos syndrome type VII autosomal dominant (130060)</td>
</tr>
<tr>
<td>COL2A1</td>
<td>Severe chondrodysplasias osteoarthritis&lt;sup&gt;*&lt;/sup&gt; (MIM 120140)</td>
</tr>
<tr>
<td>COL3A1</td>
<td>Ehlers-Danlos syndrome type IV (MIM 130050)</td>
</tr>
<tr>
<td>COL4A3 – COL4A6</td>
<td>Alport syndrome (including both autosomal and X-linked forms) (MIM 104200)</td>
</tr>
<tr>
<td>COL7A1</td>
<td>Epidermolysis bullosa, dystrophic (MIM 137560)</td>
</tr>
<tr>
<td>COL10A1</td>
<td>Schmid metaphyseal chondrodysplasia (MIM 156500)</td>
</tr>
<tr>
<td>Lysyl hydroxylase</td>
<td>Ehlers-Danlos syndrome type VI (MIM 225400)</td>
</tr>
<tr>
<td>Procollagen N-proteinase</td>
<td>Ehlers-Danlos syndrome type VII autosomal recessive (MIM 225410)</td>
</tr>
<tr>
<td>Lysyl hydroxylase</td>
<td>Menkes disease (MIM 309400)</td>
</tr>
</tbody>
</table>

mineralization

Amorphous CaPO₄₃

↓

Calcium hydroxyapatite
(on the matrix vesicles on the metaphyseal end)

Enzymes inside vesicle
- ALP
- Annexins
- 5' nucleotidase

- Functional unit of a cortical / compact bone is called osteon
- Functional unit of spongy / cancellous bone: trabeculae
- Cancellous bone has increased surface area to mass ratio and hence responsible for 80% of total bone turnover
- Cancellous bone shows increased BMD while being treated for
Osteoblasts

- mesenchymal origin
- Secretes organic matrix which is further mineralized and then cell becomes an osteocyte (mature)
- Osteocytes secrete FGFR-23, mechanoreceptor function
- Transcription factor – Runx2

Collagen (I)
Alkaline phosphatase
Osteocalcin, osteopontin
Bone saltprotein
- Osteocytes are the master regulators of bone formation and resorption.
- FGF-23 (Phosphaturic) inhibits 1α-hydroxylase (in kidneys).
- Alkaline phosphatase is a marker for bone formation.
  - Ligand independent activation → Jansen's disease
  - of receptor (PTH/PTH-rp) → metaphyseal chondro dysplasia
  - FGFR-3 → Achondroplasia
- Carbonic anhydrase → Osteopetrosis
- RANK ligand is produced by osteoblasts which recruits osteoclasts. Sclerostin is produced by osteoblasts which prevents osteoclastogenesis.

**Osteoclasts**

- Derived from macrophage.
- RANK ligand is produced by osteoblasts and binds to RANK receptor on the surface of osteoclast progenitor.
- PTH + Vit.D increase RANK ligand production from osteoblasts thus increasing bone resorption.
- Calcitonin binds to receptor on basal surface of osteoclasts and thus inhibits action.
- Calcitonin causes hypocalcemia by stimulation of renal calcium clearance.
- Estradiol decreases osteoclast number inhibiting bone resorption.
- Irregular cavity formed by osteoclast resorption: Howships lacunae.

**Activation of osteoclast/Resorption/Formation/Reversal/Mineralization Stages**

- Stages → 1  2  3  4  5
- Osteocytes regulate osteoblast by producing potent inhibitor of WNT pathway called sclerostin.
Vitamin – D

Vit D₃ – Cholecalciferol (animal) ➔ 25 (OH)₂ D₃ (liver)
Vit D₂ – Ergocalciferol (plant) ➔ >30 ng/ml ➔ 1,25 (OH)₂ D₃ (in kidney) calcitriol.

- Potent stimulant – PTH
- Potent inhibitor – FGF 23

PTH ➔ Stimulates
1, 25 (OH)₂ D₃ (in kidney)

Induce calbindin on the jejunal cell
(vit D antiproliferative action)

osteocalcin and osteopontin ➔ induced by vit D

<table>
<thead>
<tr>
<th>PTH</th>
<th>Vitamin D</th>
</tr>
</thead>
</table>
| Intestine
  - ↑ Ca⁺⁺ and ↑ PO₄⁻⁻ absorption (by increased 1,25(OH)₂ D₃ production)
| Increased calcium and PO₄ absorption by 1,25 (OH)₂ D₃ |
| Kidney
  - ↓ Ca⁺⁺ excretion
  - ↑ PO₄⁻⁻ excretion
| Ca⁺⁺ and PO₄⁻⁻ excretion may be decreased by 25 (OH)₂ D₃ and 1,25 (OH)₂ D₃ |
| Bone
  - Ca⁺⁺ and PO₄⁻⁻ resorption increased by high dose, low doses may increase bone formation
| ↑ Ca⁺⁺ and PO₄⁻⁻ resorption by 1, 25(OH)₂ D₃; bone formation may be increased by 24, 25 (OH)₂ D₃ |
| No effect on serum
  - Serum calcium increase, serum phosphate decreased
| Serum calcium and phosphate both increased |

Amino acid residues | Amino acid residues
---|---
1 30 84 | 1 30 84 139
PTH:
- Intermittent PTH in low dose increases bone formation
- Continuous PTH increases bone resorption
- Estrogen kills osteoclasts / 15-20% of bone mass is lost following menopause
- Senile osteoporosis - shift of mesenchymal stromal cells from osteoblast to adipocyte
- RANK ligand - RANK interaction is required for osteoclast differentiation
- Increase flow of calcium from bone to blood (PTH)
- Reduces renal clearance of calcium, increase Ca\(^{42}\) reabsorption in DCT
- Induces 1 - \(\alpha\) hydroxylase in PCT
- Inhibits phosphorus reabsorption at PCT
- Serum calcium is the most important regulator of PTH and \(\text{Parathyroid Hormone} \) impairs PTH release
- Loss of function mutation of \(\text{CaSR} \) produces familial hypocalciuric hypercalcemia
- Double antibody immunometric assays (estimation of intact PTH)

Markers of bone formation & resorption

- Osteopontin / Fibronectin / Thrombospondin
- Osteonectin
- Osteocalcin
- ALP
- Procollagen peptide
- Markers of bone formation
- TRAP (Tartarate Resistant Acid Phosphatase)
- Free deoxy pyridinoline in serum and urine
- Type I collagen N and C - Telopeptide breakdown products in serum and urine
Difference between PTH and PTHrP

- Enchondral ossification
- ↑ trabecular bone formation
- Distinct receptor or nuclear action
- Slow blood vessel invasion
- Ligand independent activation
  - Jansen’s disease

Decrease in alkaline phosphatase
- Malnutrition
- Zn/Mg deficiency
- Milk alkali syndrome
- Celiac disease
- Hypothyroidism
CALCIUM METABOLISM – I

- Body stores of calcium → 1 g - 1.3 g
  - 99.3% in bone
  - 0.4% in soft tissue
  - 0.1% in ECF
- Daily diet has 1 g of calcium of which 20% is absorbed (200 mg)
- 24 hours urinary Ca<sup>2+</sup> → 4 mg/kg
- 1<sup>st</sup> response to ↑ in Ca<sup>2+</sup> → (calcium sensing receptor) in parathyroid
- Sustained ↑ Ca<sup>2+</sup> sensed by → CaSR in kidney
  (Normal response → ↑ Ca<sup>2+</sup> in blood → ↑ Ca<sup>2+</sup> in urine)
- Familial Hypocalciuric Hypercalcemia (FHH):
  - CaSR in kidney is non functional so, ↑ Ca<sup>2+</sup> in blood is not sensed → ↓ Ca<sup>2+</sup> in urine
- Blood levels → 8.6 to 10.3 mg/dl
  - (Free ionized form → 48%)
  - (Protein bound form → 40%)

Adjusted total Ca<sup>2+</sup> → Total Ca<sup>2+</sup> + 0.8 (4-S. Albumin)

Calcium absorption in intestine

- Absorption by active transcellular pathway (95%)
  - Passive pathway (5%)
- Active absorption by TRPV<sub>5</sub> & TRPV<sub>6</sub> in jejunum which is tightly regulated by 1,25 (OH)<sub>2</sub> D<sub>3</sub> via calbindin
- Passive absorption is not tightly regulated, so if Ca intake >4g/d, Ca<sup>2+</sup> will enter system → milk alkali syndrome
- Milk alkali syndrome → Hypercalcemia + hypercalciuria

Calcium in kidney:

- 60% passive reabsorption at proximal tubule
- 20-35% via paracellular pathway at thick ascending limb of Henle
  (through paracellulin or claudin)
- 10% in DCT via active transport (through TRPV<sub>5</sub> & TRPV<sub>6</sub>)
Hypercalcemia:

- Patient no. I → 60 yrs old male, generalized tiredness, malaise, fatigue, weight loss, muscle weakness, bone pain (S. Ca\textsuperscript{2+} → 13 mg/dl)

- Patient no. II → 50 yrs old female, Recurrent episodes of UTI, with stones

- Patient no. III → 25 yrs old male with acute abdomen (pancreatitis), constipation, vomiting

- Patient no. IV → Referred from psychiatry department with psychiatric symptoms

Hypercalcemia (adjusted total S. Ca\textsuperscript{2+} > 10.4 mg/dl)

↓

Confirm Hypercalciiuria (>4 mg / kg) (↑↑)
(Only exception → FHH)

↓

Check PTH levels iPTH (intact PTH)
PTH levels
(0 - 50 - 100pg/ml)

- PTH (↑↑)
  - Hyperparathyroidism (s. phosphorous ↓)
    - Present as patient number 1 (or) 2
      - PTH-rp (↑↑)
        - Squamous cell Ca of lung
        - Head & neck (paraneoplastic syndrome)
          - i. as (OH) D₃, 1, 25 (OH)₂ D₃ both (↑↑)
            - Vitamin D intoxication
          - ii. as (OH) D₃, 1, 25 (OH)₂ D₃ (↑↑)
            - Tumor producing 1,25 (OH)₂ D₃
          - iii. as (OH) D₃, 1, 25 (OH)₂ D₃ (↓)
            - miscellaneous causes

- PTH (↓↓)
  - Evaluate PTH-rp levels
    - PTH-rp (↑↑)
      - Check as (OH) D₃, 1, 25 (OH)₂ D₃

- Patient no. 1 & 2 have PTH (↑↑)
  - Evaluated by visualizing parathyroid gland with sestamibi scan (TC)
    - Adenoma, hyperplasia, carcinoma.


**X-ray findings in 1° hyperparathyroidism:**

1. **Bone resorption**
   - Diffuse
   - Mostly seen on
     - Radial side of index
     - Middle finger
     - (proximal & middle phalanx)

2. **Acral osteolysis**
   - (Tufting of phalanx)

3. **Osteitis fibrosa cystica**
   - (Amorphous Ca⁺³ Phosphate)

4. **Brown tumour**
   - Radiolytic areas where pseudotumor made of macrophages, blood & connective tissue

5. **Rugger jersey spine**
6) Intracortical bone resorption (diffuse)
7) Endosteal bone resorption
8) Subperiosteal bone resorption
9) Skull
   - Trabecular bone resorption
   - Salt and pepper skull
   - Pepper pot skull

Management

1. Symptomatic → Surgery (removal of adenoma)
   (if B/L Hyperplasia → near total parathyroidectomy)

2. Indications for surgery in asymptomatic individual;
   1. S. Ca²⁺ > 1mg/dl from baseline
   2. GFR < 60 ml/min
   3. ↓ Bone density
   4. Age < 50 yrs

- 24 hour urinary Ca²⁺ is not an indication for surgery
- No drugs are used for 1° Hyperparathyroidism

- Humoral hypercalcemia of malignancy
  (due to ↑ PTH-rP) (low 1,25 (OH)₂ D₃)
SCC of lung / head / neck / cervix

- Treatment → management of primary cause
- Osteolysis in multiple myeloma can also cause hypercalcemia for which steroids may benefit

\[
\begin{align*}
\text{PTH} & \downarrow \\
\text{PTH-rp} & \downarrow \\
25-\text{OH} \text{ D}_3 & \downarrow \\
1,25 \text{ (OH)}_2 \text{ D}_3 & \uparrow \\
\text{Catastrophic presentation (patient no. 3)} & \\
\text{Tumor / Granuloma (Sarcoïd / Lymphoma)} & \\
\end{align*}
\]

- Steroids are also useful in vitamin D related hypercalcemia

**Miscellaneous causes:**

1. Pheochromocytoma
2. Addison's disease
3. Acromegaly
4. Hyperthyroidism
5. Drugs → Thiazides
   - Lithium
   - Bones, Stones, Abdominal groans, Psychiatric moans

- Other symptoms:
  1. Nephrogenic DI symptoms
  2. Bradycardia (short QT interval)
  3. Muscle weakness (Hyperreflexia)
  4. Band keratopathy

\[
\begin{align*}
\text{PTH stimulates 1, 25 hydroxylase} & \\
\text{PTH-rp inhibits 1, 25 hydroxylase} & \\
\end{align*}
\]
FHH:
- ↑ Ca\(^{2+}\) in blood; ↓ Ca\(^{2+}\) in urine
- Autosomal dominant
- Under 10 years
- Loss of CaSR in ThAC, DCT, Parathyroid gland
- Loss of CaSR only in kidney → mild hypercalcemia
- Very resistant to treatment

**Hypercalcemic crisis:**

- Characterised by severe dehydration, ↑↑ S. Ca\(^{2+}\)
- Severe dehydration is due to Nephrogenic DI
- Management →
  1. IV fluids (500 ml/hr) then depending on output
     (no role for Lasix)
  2. Calcitonin 4 units/kg stat if response given bd
- Calcitonin is associated with Tachyphylaxis
  3. IV Bisphosphonate
     - Zoledronate 4 mg IV over 15min. (or)
     - Pamidronate 60 mg-90 mg IV over 2 hours
       (starts to act in 1-2 days)
- Osteolysis in multiple myeloma or vit.D related crisis--> glucocorticoids
- No role for mithramycin
- If nothing works → hemodialysis
- Denosumab (monoclonal antibody against RANK can be tried)
Hypocalcemia:
- S. Ca\(^{2+}\) ≤ 8.6 to 10.3 mg/dl
- S. Ca\(^{2+}\) ≤ 8.4 - hypocalcemia (8.5 considered as borderline)
- S. Ca\(^{2+}\) ≤ 7.4 mg/dl - severe hypocalcemia.

True adjusted Ca\(^{2+}\) = S.Ca\(^{2+}\) + 0.8 (4-S. Alb)
- 50% of this is ionised Ca\(^{2+}\)

- H\(^{+}\) and Ca\(^{2+}\) is competing to bind with albumin
  - In acidosis - \(\uparrow\) H\(^{+}\) Free ionised Ca\(^{2+}\)
  - In alkalosis - \(\downarrow\) H\(^{+}\) Free ionized Ca\(^{2+}\)

- Symptoms of hypo / hypercalcemia is due to increase / decrease in "ionised Ca\(^{2+}\)"

  Acidosis = Hypercalcemia
  Alkalosis = Hypocalcemia

↓ in S.Ca\(^{2+}\)
↓
Immediate response from Parathyroid Gland
↓
↑ in PTH

↓ stimulates 1α - Hydroxylase
↓Ca\(^{2+}\) reabsorption from distal tubules
↓Ca\(^{2+}\) reabsorption from bones
\(\uparrow\) Phosphate excretion

Hypophosphatemia.

- Hypophosphatemia is due to inhibition of phosphate absorption → gets excreted more
Approach to hypocalcemia

**Basic workup:**
- Check for the levels of S. Alb, ↑ in H⁺ or ↓ in H⁺
- S. mg levels - normal - 1.5-1.9 meq/L

\[
\text{S. mg level} \\
\downarrow \\
< 0.8 \text{ meq/L} \quad \downarrow \\
\text{PTH resistance} \\
\downarrow \\
\text{HYPOCALCENIA}
\]

\[
\downarrow \\
> 5 \text{ meq/L} \quad \downarrow \\
\text{Supress PTH secretion}
\]

- Usage of drugs like cisplatin → Severe hypomagnesemia.
- Infusion of large amounts of citrate, (chelator) → ,
  Hypocalcemia.
- Plasmapheresis, massive blood transfusion can also lead to
  Hypocalcemia.
- Antiviral drugs like Foscarnet → Produce more amount of
  citrate Hypocalcemia.

**Proper workup:**
- Check the levels of S.phosphate

\[
\text{Hypocalcemia.} \\
\downarrow \\
\text{S.Ca↓, S.Po}_4\uparrow \\
\downarrow \\
\text{Check the levels of PTH} \\
\downarrow \\
\text{PTH - Low} \\
\downarrow \\
\text{True Hypoparathyroidism}
\]

\[
\text{S, Ca↓, S. PO}_4\downarrow \\
\downarrow \\
\text{Vit D deficiency} \\
\downarrow \\
\text{PTH - High} \\
\downarrow \\
\text{Pseudohypoparathyroidism, CKD, Pancreatitis,} \\
\text{Critical illness, TLS / Rhabdomyolysis}
\]
True hypoparathyroidism:
- mCC: I. Surgical
  a. Transient hypocalcemia: due to prolonged Hypercalcemia prior to surgery
  b. Hungry bone syndrome: due to prolonged decrease in S. Ca, S. P,
  S. Mg, loss of calcium Equilibrium
  - Post surgery, bones take up the calcium, so ↓ in S.Calcium

a. Medical causes:
  a. Autoimmune: PEA Type 1 (Poly Glandular Autoimmune Syndrome)
  b. Genetic: DiGeorge / CATCH 22 syndrome
     - microdeletions in 22q
     C - cardiac Abnormalities - TOF
     A - Abnormal Facies
     T - Thymic Hypoplasia
     C - Cleft Palate
     H - Hypocalcemia
     - It is Autosomal dominant

CKD:

\[
\begin{align*}
S. Ca^{2+} & \downarrow, S. P & \uparrow, S. PTH & \uparrow \uparrow \\
\downarrow \\
\text{2° hyper parathyroidism in CKD, it is due to increase in FGF-23} \\
\downarrow \\
\text{FGF-23 Inhibits 1α Hydroxylase} \\
\downarrow \\
\text{Decrease in calcitriol} \\
\downarrow \\
\text{↑ in PTH} \\
\downarrow \text{Ca}^{2+} \text{ absorption from intestine} \\
\downarrow \\
\text{Hypocalcemia} \\
\downarrow \\
\text{↑ in PTH}
\end{align*}
\]
In CKD, after sometime FGF resistance occurs

Decrease in number of nephrons

Hyper phosphatemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause</th>
<th>PTH</th>
<th>S.Ca</th>
<th>S.Po</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Hyperparathyroidism</td>
<td>Adenoma</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Secondary Hyperparathyroidism</td>
<td>CKD</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Tertiary Hyperparathyroidism</td>
<td>Long Standing</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

**Pseudo hypoparathyroidism**

- It is characterized by PTH resistance

**PTH resistance**

- **Type 1**
  - "αααα" subunit deficiency
  - Complete resistance when administered exogenous PTH
  - No change

- **Type 2**
  - No deficiency
  - Partial resistance
  - S.Ca, S.Po↓; no change but urine cAMP will become normal

- Pseudo hypoparathyroidism:

  a. **Type 1a:**

  - Type 1a will have bone mineral changes
  - It causes albright hereditary osteodystrophy
  - Characterised by short stature, round facies, metal retardation, Short 4th metacarpal > metatarsal
b. Type 1b:
- Type 1b will not have any bone mineral changes

**Pseudopseudohypoparathyroidism**

- Pseudopseudohypoparathyroidism is just like PHP type 1a, but biochemically it is normal (S.Ca^{2+}, S.Po₄, S.PTH will be normal in pseudopseudohypothyroidism)

<table>
<thead>
<tr>
<th>Type</th>
<th>Hypocalcemia</th>
<th>Response of urinary camp to pth</th>
<th>S.PTH</th>
<th>As a subunit deficiency</th>
<th>AHO</th>
<th>Resistance to hormones other than pth</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHP1a</td>
<td>YES</td>
<td>DECREASED</td>
<td>↑</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>PHP1b</td>
<td>YES</td>
<td>DECREASED</td>
<td>↑</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>PHP2</td>
<td>YES</td>
<td>NORMAL</td>
<td>↑</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

PHP = Pseudohypoparathyroidism  
PHP = Pseudopseudohypoparathyroidism

**Vitamin D deficiency**

- S. Ca & S. Po₄ - Both are ↓
  
  S. Ca, S. Po₄ ↓
  
  Check for 25 (OH) D₃ & 1,25 (OH)₂ D₃

  ↓

  25 (OH) D₃ ↓
  
  1,25 (OH)₂ D₃ ↓
  
  Nutritional rickets
  
  ↓

  1,25 (OH)₂ D₃ ↓
  
  Vit. D dependant Rickets (VDDR) Type 1
  
  ↓

  1α Hydroxylase deficiency
  
  ↓

  Resistant to Calcitriol
Drugs causing hypocalcemia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>mechanism causing hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate, Foscarnet</td>
<td>Chelators of calcium</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides, Amphotericin B</td>
<td>Tubular wasting</td>
</tr>
</tbody>
</table>

Symptomatology of hypocalcemia

Symptoms of acute hypocalcemia:
- Symptoms of acute hypocalcemia is characterized by neuromuscular symptoms

Acute mild:
- Characterized by circumoral paresthesias, twitching, tingling of hands & feet, carpopedal spasms

Acute severe:
- Characterized by laryngospasm or seizure

Latent tetany:
- Characterized by Trosseau sign & Chovstek’s sign
- Trosseau sign is also known as “main d’ accoucheur”
- In severe hypocalcemia, there will be ↑QT internal leading to Torsades de pointes (polymorphic VT + prolonged QT interval)
- In severe hypocalcemia, there is ↑ICT, like pseudotumor cerebri leading to seizures & papilledema along with neuropsychiatric symptoms like irritability & depression

Symptoms of chronic hypocalcemia:
- Characterised by calcification
- Calcification commonly occurs in basal ganglia
- Dry skin, Brittle Hair
- Dental problems
- Cataract
Causes of chronic hypocalcemia:
- Genetic causes of hypoparathyroidism - Digeorge
- Inherited syndromes with resistance to PTH - PHP
- Reversible impairment of PTH - like Mg++ deficiency
- Acquired hypoparathyroidism - PGA type1
- Vit D deficiency
- Vit D resistance - Type 2 VDDR
- Hyperphosphatemia / Tumor lysis
- Bisphosphonates
- Hungry bone syndrome
- Acute pancreatitis
- Drugs

Treatment of hypocalcemia

- In acute severe or symptomatic or latent tetany
  - 1g (10ml) of Calcium gluconate 10% over 10 minutes, 1g contains 93mg of elemental calcium
  - 5g in 500ml 5% Dextrose at 1-3 mg of elemental calcium/kg/hr
  - Oral calcium upto 2g daily
  - Oral calcium contains CaCO₃ contains 40% elemental calcium
  - If the patient is stable, start away treat with oral Ca²⁺ upto 2g/day
  - Vit D (25(OH)D₃) if < 30ng/ml is considered as deficiency and treated accordingly
  - Hypomagnesemia (< 0.8mg/dL) ⇒ 1IV mgSO₄
PHOSPHORUS METABOLISM

- Body elemental stores of calcium = 1000 - 1300 gm (99.3% in bone /0.7 in soft tissue /0.1% distributed between tissue & ECF)
  Phosphorus = 500 - 600 gm (85/14/1%)

  In bone : 99.3% = calcium, 85% = phosphorus

  Phosphorus = • 2/3rd organic, 1/3rd inorganic
  • 50% ionised
  • 10% is bound to albumin

  (N) serum level of phosphorus : 2.5 - 4.5 mg/dl
  - 60% absorption from intestine (regulated by vit. D)

- Phosphorus & Kidney :
  - Excreted solely by kidney.
  - In renal failure \(\Rightarrow\) Hyperphosphatemia.
  - Phosphorus reabsorption \(\Rightarrow\) Only at PCT (\(\text{Na} - P\) cotransporter)
    Fibroblast growth factor - 23 = Inhibit \(\text{Na} - P\) cotransporter

  - Fractional excretion of phosphorus : - \(\uparrow\) In proximal renal tubular acidosis (RTA)
  - (N) in Distal RTA

Hyperphosphatemia

- It is CKD - unless proved otherwise
- Other cause : Acute Kidney injury, Tumor lysis syndrome, Rhabdomyolysis.
- In CKD \(\Rightarrow\) Phosphorus converts endothelial cells to osteoblasts

  State of irreversible calcification \(\leftarrow\) trap calcium

- In CKD \(\Rightarrow\) maintain phosphorus levels < 5.5 mg/dl

Causes :

  i) \(\uparrow\) Phosphorus intake : phosphate enemas for colonoscopy.

  ii) \(\downarrow\) Phosphorus excretion : CKD, AKI, Familial tumoral calcinosi, Acromegaly

  iii) Redistribution from : Cell to blood - • Tumor lysis syndrome
  • Rhabdomyolysis
  • Hemolysis
  • Acidosis

Scanned with CamScanner
Familial tumoral calcinosis

- AR
- due to missense mutation of FGF 23 → loss of function of FGF 23
- ↑ activity of Na – P cotransporter = ↑ Phosphorus reabsorption
- This leads to calcium trapping → Ca₃(PO₄)₂ deposition (bone/soft tissue)

- Symptoms due to:
  - Hypocalcemia
  - Calcification (vascular/soft tissue)

Hyperphosphatemia - clinical features & management

- Features:
  - Formation of widespread calcification precipitates
  - Tetany/seizures due to hypocalcemia
  - Pulmonary/cardiac calcification

Treatment:
- Dialysis (if CKD)
- In other conditions → Treat hypocalcemia
  - Oral phosphate binders
    - Calcium based: Calcium acetate
    - Pure phosphate: Sevelamer, Lanthanum

Hypophosphatemia

- Leads to Cardiomyopathy, Rhabdomyolysis, Hemolysis, Insulin resistance, Neuromuscular toxicity
  - To be addressed earliest
- To be symptomatic: Phosphorus levels < 1 mg/dl
- **Cause:**
  - ↓ Phosphorus in diet
  - ↑ Excretion from kidney: Na–P cotransporter defect, PCT defect
  - Cellular shift → FGF-23 gain of function mutation
    - **Tumor induced Osteomalacia**
  - Hypophosphatemic rickets:
    - Na–P cotransporter defect
    - X-linked or AD or AR

- **mc → Phosphate-regulation neutral endopeptidase X linked gene**
  - Proximal RTA:
    - Proximal tubular defect
    - mc - Fanconi syndrome

- Transcellular shift →
  - Alkalosis
    - Hungry bone syndrome
    - Refeeding syndrome (Alcoholics)
    - DMA after insulin therapy
    - Sepsis

- Symptoms: Proximal myopathy, bone pain, myocardial function impaired, Neurological symptom - Rare.

Treatment: IV phosphorus replacement (if serum level is < 1 mg/dl)

**Tumor induced osteomalacia:**
- Mesenchymal / Fibrogenic Tumor, lymphoma secreting FGF-23.
- Paraneoplastic condition
- Ca²⁺ levels → (N)
- Phosphaturia (+)
- ↓ in bone mineralization
MAGNESIUM METABOLISM

- Normal level = 1.5 - 1.9 mcg / litre
- 2nd most abundant intracellular cations (after potassium)
  a meq / l of mg$^{2+}$ = 1 mmol / l of mg$^{2+}$ = 2.4 mg /dl

- Magnesium in kidney:

- All the ions in humans are maximally reabsorbed in PCT except
  - mg$^{2+}$

  - mg$^{2+}$ reabsorption:
    - 25% at PCT - Passive transport
    - 65% at Thick Ascending limb of loop of Henle
      - Paracellular pathway
        (via paracellulin / claudin)
    - 5 - 10% actively reabsorbed at DCT (by TRPM)
      - Active transport

Hypermagnesemia

- Pediatric cause: FHH (Familial Hypocalciuric Hypercalcemia)
- Symptoms:
  - ↑ Serum mg$^{2+}$ > 5meq /litre cause PTH impaired production
  - decrease in serum mg$^{2+}$ < 0meq/litre cause PTH resistance
  - decrease in Serum mg$^{2+}$ impaired tubular secretion of K+ ⇒ Refractory Hypokalemia
  - 4 - 6meq /l - Nausea, flushing, headache,
    drowsiness, sluggish deep tendon reflex (DTR)
System

- 6 - 10 meq/L - Hypocalcemia, ↓ DTR, Bradycardia, hypotension.
- >10 meq/L - Flaccid quadriplegia, respiratory failure, cardiac arrest
- >13 meq/L - Cardiac arrest → Block Ca²⁺ & K⁺ Channels
  - PR - Prolongation
  - QRS widening
  - QT Prolongation (rare)

Diagnosis - CHD (unless proved otherwise)
Treatment - Dialysis

Hypomagnesemia

I. Impaired intestinal absorption
   A. Hypomagnesemia with secondary hypocalcemia (TRPM6 mutations)
   B. Malabsorption syndromes
   C. Vitamin D deficiency
   D. Proton pump inhibitors
II. Increased intestinal losses
   A. Protracted vomiting/diarrhea
   B. Intestinal drainage, fistulas
III. Impaired renal tubular reabsorption
   A. Genetic magnesium-wasting syndromes
      1. Gitelman’s syndrome
      2. Bartter’s syndrome
      3. Claudin 16 or 19 mutations
      4. Potassium channel mutations (Kv1.1, Kc4.1)
   B. Acquired renal disease
      1. Tubulointerstitial disease
      2. Postobstruction, ATN (diuretic phase)
      3. Renal transplantation
C. Drugs and toxins
   1. Ethanol
   2. Duretics (loop, thiazide, osmotic)
   3. Cisplatin
   4. Pentamidine, fosarnet
   5. Cyclosporine
   6. Aminoglycosides, amphotericin B
   7. Cetuximab
D. Other
   1. Extracellular fluid volume expansion
   2. Hyperaldosteronism
   3. SIADH
   4. Diabetes mellitus
   5. Hyperparathyroidism
   6. Phosphate depletion
   7. Metabolic acidosis
   8. Hyperthyroidism

Causes:
- ↓ intake of Mg²⁺
- Drugs:
  - PPI’s
  - Cisplatin
  - Pentamidine
  - Cetuximab
- Aminoglycosides, Amphotericin B

- **↑ renal secretion of magnesium.**

**i)** Bartter’s syndrome
- Hypermagnesuria with normal serum magnesium.

**ii)** Gitelman’s syndrome
- Hypomagnesemia due to inhibition of TRPM6 in the intestine.

**Transcellular shift:**

<table>
<thead>
<tr>
<th>IV. Rapid shifts from extracellular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Intracellular redistribution</strong></td>
</tr>
<tr>
<td>1. Recovery from diabetic ketoacidosis</td>
</tr>
<tr>
<td>2. Refeeding syndrome</td>
</tr>
<tr>
<td>3. Correction of respiratory acidosis</td>
</tr>
<tr>
<td>4. Catecholamines</td>
</tr>
<tr>
<td><strong>B. Accelerated bone formation</strong></td>
</tr>
<tr>
<td>1. Post-parathyroidectomy</td>
</tr>
<tr>
<td>2. Treatment of vitamin D deficiency</td>
</tr>
<tr>
<td>3. Osteoblastic metastases</td>
</tr>
<tr>
<td><strong>C. Other</strong></td>
</tr>
<tr>
<td>1. Pancreatitis, burns, excessive sweating</td>
</tr>
<tr>
<td>2. Pregnancy (third trimester) and lactation</td>
</tr>
</tbody>
</table>

- **Symptoms:**
  - Neuromuscular hyperexcitability
  - Tetany, muscle spasms & cramps
  - Seizures
  - Vertical nystagmus.
  - Respiratory muscle involvement
    - (cardiac) inhibiting Na-K ATPase
  - Magnesium competes with Digoxin to bind with Na-K ATPase.
  - Hypomagnesemia → **↑ Digoxin binding**
    - Digoxin toxicity.

- Ventricular tachyarrhythmias.
- Widening of QRS
- **↑ QT**
- Polymorphic VT.
- Hypocalcemia
  - Hypoparathyroidism
  - Decreased bone mass.

  - Hypokalemia $\rightarrow$ ↑ tubular secretion of potassium

Management of hypomagnesemia

- Severe symptoms:
  - IV MgSO$_4$ (2g) (16 meq)
  - 10% in 10 min

  - Continue correction even after achieving normal blood level to correct intracellular depletion

  - Mild symptoms: Magnesium oxide tablets
  - Amiloride
  - Triamterine

- Associations
  - Myocardial infarction
  - Hypokalemia.
  - Hypocalcemia.
  - Insulin resistance
  - Migraine
  - Colon cancer
OSTEOPOROSIS

Osteoporosis

- Quantitative bone disorder.
- Decrease in
  1. Osteoid matrix
  2. Mineral phase
  3. Bone mineral density or
  4. Peak bone mass.
- "Micro architectural bone distortion"
  (Bone geometry is affected)
- "Pathological fractures"

- Peak bone mass:
  - Spine: 20 years
  - Long bones: 25 - 30 years.

- Pathological fracture → vertebral (mc) > Hip > Distal radius.
  - after 70 years → Hip fracture
  - Distal forearm fractures are the early & sensitive maker of bone fragility in males.
  - MC in post menopausal females (40%)
  - Secondary osteoporosis is due to metabolic causes

Risk Factors for osteoporosis

- **Modifiable causes**
  → Smoking
  → Estrogen deficiency
    [ early menopause, oophorectomy ]
  → ↓ Calcium
  → ↓ Vitamin D
  → Alcoholism

- **Non modifiable causes**
  → History of fracture
    - as an adult
    - in 1st - degree relative.
  → Female gender
  → Age
  → White race
  → Dementia
Secondary causes of osteoporosis:

→ Drugs

1. Steroids
2. Proton pump inhibitors
3. Heparin
4. Lithium
5. SSRIs
6. Cyclosporine
7. Pioglitazone
8. Eltroxin

→ Hypogonadism

- Hyperprolactinemia
- Turner’s syndrome
- Klinefelter’s syndrome

→ Endocrine disorders

- Hyperparathyroidism
- Cushing’s syndrome
- Diabetes mellitus [Type 1 & 2]
- Thyrotoxicosis
- Adrenal insufficiency (Addison’s)

→ Rheumatological disorders

- Rheumatoid arthritis
- Ankylosing spondylitis

→ Miscellaneous causes

- Multiple myeloma
- Thalassemia
- Hemochromatosis
- Marfan’s syndrome
- Ehlers-Danlos syndrome
- Sarcoidosis / Amyloidosis
- Immobilization

Pathophysiology:

1. ↑ Peak bone mass
2. ↑ Osteoclastic activity
3. ↓ Osteoblastic activity
4. Micro architectural bone changes
Diagnosis of osteoporosis

- **Dexa - Scan**: [Dual energy x-ray absorptiometry]
  - Indications:
    - Women > 65 years / men > 70 years
    - Younger males / females with risk factors
    - Prior fragility fracture
    - Family history
    - Smoking
    - Steroid
    - Alcoholic
    - Rheumatoid arthritis / Ankylosing spondylitis

- **Bone mineral density in comparison with**:
  - Young healthy adult
  - Same age
  - T Score

- **Score**: 0 to -1 → normal
  - 1 to -2.5 → osteopenia
  - 2.5 % above → osteoporosis
- "T Score -2.5 = Z score -1"

Treatment Of Osteoporosis

- Smoking cessation
- Physical activity
- Stop alcohol
- Adequate calcium - 1000 mg/day
- Vitamin D - 2000 IU/day

Drugs
  1. Inhibitors of bone resorption:
  2. Bisphosphonates: [DOC]
     - Alendronate
     - Risedronate
     - Ibandronate
     - Zolendronate
b) Calcitonin
d) SERM

2) Stimulators of bone formation.
   - Fluoride
   - Recombinant PTH - Teriparatide

3) Mixed mechanism
   - Strontium ranelate

4) Adjunctive therapy
   - Calcium
   - Vitamin D

→ Denosumab - (antibody against Rank ligand)

### Bisphosphonates, HRT & SERM

Bisphosphonates:
- Oral bisphosphonates (DOC)
- Drugs:
  - Risedronate
  - Alendronate - 70 mg once a week
  - Ibandronate - 150 mg monthly
  - IV - Zoledronate - 5mg
    - Very poor oral absorption - hence to be taken on empty stomach 30 minutes before the 1st meal & remain upright for 30 minutes.

→ Side effects:
  - Jaw necrosis
  - FSGS
    (Pamidronate → Collapsing FSGS)
  - Hypocalcemia.

HRT (hormone replacement therapy)
- Side effects:
  1. Breast cancer
  2. CHD
  3. Stroke

→ “Severe hot flushes” → Only indication for HRT.
SERM (Selective estrogen receptor modulator)

- Tamoxifen
  - antagonist → Breast & blood vessels.
  - agonist → Overall

Side effects:
- Cramps
- Hot flushes
- ↑ risk for endometrial cancer.
- Thromboembolism.

-Raloxifen.
  - antagonist on endometrium → No risk of endometrial cancer.
  - SE: Thromboembolism.

Calcitonin And rPTH

Calcitonin
- Weak anti resorptive drug
- Route: intranasal or subcutaneous.
- Tachyphylaxis or rapid tolerance
- "No effect on non-vertebral fractures"
- Drug is given preferentially in older women with multiple fractures.

Recombinant PTH
- Drugs:
  1. Teriparatide
  2. Abaloparatide.
→ Intermittent PTH exposure
  ↓
    stimulates bone formation & decreases sclerostin

→ Chronic PTH exposure
  ↓
  ↑ RANKL ↓ OPG (Osteoprortogerin, Physiological inhibitor of RANK-L)
  ↓
  Bone resorption
  ↓
  Osteoporosis

Route: Subcutaneous.
Strontium Ranelate:
- both resorptive and osteotrophic
- Side effects:
  - Diarrhoea
  - Thromboembolism
  - Seizures

Monoclonal antibody against RANK-L
- Denosumab
- Romosozumab

Radiological abnormalities:
1. Codfish spine or fish mouth vertebrae
   Osteomalacia > Osteoporosis

2. Dowager's hump
   Curvature of spine

3. Wedge compression fractures

Surgical management:
- Vertebroplasty (Poly methyl methacrylate)
HYPOKALEMIA

Potassium metabolism

- major intracellular cation
- mostly in the muscle

\[
1 \text{ mmol of } K^+ = 1 \text{ meq of } K^+ = 40 \text{ mg } K^+
\]

Normal serum $K^+ = 3.5 - 5.5 \text{ meq/l or mmol/l}$

Total body $K^+ = 50 \text{ meq x body weight}$

$= 50 \text{ meq x 60}$

$= 3000 \text{ meq}$

Conc. of $K^+$ in the cell = 145 to 150 meq/l

- The normal ratio between extracellular and intracellular concentrations is important for maintenance of resting membrane potential (RMP) and neuromuscular functioning
- Intracellularly, potassium is required for cell growth, maintenance of cell volume, DNA and protein synthesis, enzymatic function and acid-base balance

<table>
<thead>
<tr>
<th>Distribution of Total Body Potassium in organs and Body compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organs and Compartments</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Muscle 2650 mmol</td>
</tr>
<tr>
<td>Liver 250 mmol</td>
</tr>
<tr>
<td>Interstitial fluid 35 mmol</td>
</tr>
<tr>
<td>Red blood cells 35 mmol</td>
</tr>
<tr>
<td>Plasma 15 mmol</td>
</tr>
</tbody>
</table>
Renal handling

- 90% of $\text{K}^+$ excreted by kidney

Fractional excretion of $\text{K}^+$

$$Fe_{\text{K}^+} = \frac{\text{U}_{\text{K}^+}}{\text{S}_{\text{Cr}}} \times 100$$

= 10%–30% or $\sim 90$ mmol/day where $\text{Cr}$ is creatinine, $\text{S}$ is serum, and $\text{U}$ is urine

Active uptake

$\text{K}^+$ channel

$\text{Na}^+$ channel

$\text{Na}^+$-H$^+$-ATPase

$\text{Na}^+$-ATPase

$l_{\text{H}^+}$ channel

$\text{Cl}^-$ channel

Aldosterone
Hypokalemia - clinical presentation

I Muscle:
- Muscle weakness / Paralysis
- Flaccid muscle paralysis
- No sensory involvement

II Cardiac - ECG changes / Arrhythmias

III Smooth muscles
- Constipation
- Ileus
- Bladder dysfunction

IV Renal
- Nephrogenic diabetes insipidus (DI) → Polyuria.
- Structural Damage to Kidney → Chronic Tubulointerstitial Disease (Dilation and vacuolization of PCT)

Miscellaneous
- ↑ Renal NH₃ Production
  Hepatic Encephalopathy
- Decrease insulin secretion
  Carbohydrate intolerance
The ECG patterns that may be seen with hypokalemia range from slight T wave flattening to the appearance of prominent U waves, sometimes with ST segment depressions or T wave inversions. These patterns are not directly related to the specific level of serum potassium.

- 3.5-4 meq/l
- 3-3.5 meq/l: flattening of T wave
  - Prominent U wave
  - Prolonged QT interval/Qu interval

- <3 meq/l: sagging/depression of ST segment

- <2.5 meq/l: QRS widening
  - ↑ risk of arrhythmia
  - PR prolongation

**Approach to patient with hypokalemia**

1. Look for Renal (or) spot K⁺
   - Urine spot K⁺
   - >15 meq/l
   - <15 meq/l
     - Renal
     - Transcellular

** Causes of:**

- **Transcellular shift (From Blood to cell)**
  - Insulin
  - Salbutamol
  - α - Antagonist
  - Metabolic alkalosis

- **Transcellular shift (cell to blood)**
  - β -blockers
  - α - Agonist
  - Acidosis
- Hyperglycemia
- Hyperosmolarity
- Exercise
- ↑ Hormones (GH, Thyroid)

**Cellular potassium shifts**

![Diagram showing cellular potassium shifts](image)

**Renal causes for hypokalemia**

(ABG – Arterial Blood Gas)

- Acidosis
- Alkalosis

+ Renal H+ loss

→ Renal Tubular Acidosis (RTA)
  - Type 1
  - Type 2

**Renal tubular acidosis**

- Tubular Defect
  - Defective excretion of H+ (Distal Type 1 RTA)
  - Defective reabsorption of HCO3- (Proximal Type II RTA)

- Metabolic Acidosis
- Alkaline urine
RTA Type I (Distal RTA)

1. Causes:
   - Defect in α-intercalated cell of CCD (mainly)
   - β-intercalated cells (rarely)
2. Defective H⁺ ATPase or H⁺ K⁺ ATPase
3. Can be primary (majority) / secondary
4. Primary distal RTA seen in children (5-10yrs)
5. Never progresses to CKD
6. Metabolic Acidosis
   - Alkaline urine (pH > 5.5)
Severe metabolic acidosis
   - ↑ Ca²⁺ resorption from Bone
   - Hypercalcemia.
   - Hypercalciuria → Stone Formation
   - Hydropicaturia
   - Volume depletion ↑
   - ↑ RAS (Renin angiotensin system)
   - ↑ aldosterone
   - K⁺ wasting → Hypokalemia

RTA Type II (Proximal RTA)
- Generalised proximal tubular dysfunction
- Less severe acidosis

Stone formation nil Less RAAS activity less hypokalemia.

Generalised proximal tubular dysfunction
   - Glucose → Glycosuria.
   - amino acid → Aminoaciduria.
   - Bone mineral Changes
   - Phosphorous wasting
   - Rickets

Causes of hypokalemic distal (Type I) RTA

Primary
   - Idiopathic
   - Familial

Secondary
   - Autoimmune disorders
     - Hypergamma globulinemia
     (MCC of distal RTA)
   - Primary biliary cirrhosis
   - SLE
Genetic diseases:
- Autosomal dominant (AD)
  defective anion exchanger
- Autosomal recessive (AR)
  defective H+ ATPase
- Drugs and Toxins
  Amphotericin B
  Toluene
- Disorders with Nephrocalcinosis
  Hyperparathyroidism
  Vit D intoxication
  Idiopathic hypercalciuria

<table>
<thead>
<tr>
<th>Causes of proximal (Type 2)</th>
<th>Renal Tubular Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not associated with Fanconi syndrome</td>
<td>Renal Tubular Acidosis</td>
</tr>
<tr>
<td>Sporadic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Familial</td>
<td>Familial</td>
</tr>
<tr>
<td>Disorder of carbonic anhydrase</td>
<td>Disorder of carbonic anhydrase</td>
</tr>
<tr>
<td>Drugs: acetazolamide, sulfanilamide, topiramate</td>
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</tr>
<tr>
<td>Carbonic anhydrase II deficiency</td>
<td>Carbonic anhydrase II deficiency</td>
</tr>
<tr>
<td>Associated with Fanconi syndrome</td>
<td>Associated with Fanconi syndrome</td>
</tr>
<tr>
<td>Selective (no systemic disease present)</td>
<td>Selective (no systemic disease present)</td>
</tr>
<tr>
<td>1. Sporadic</td>
<td>1. Sporadic</td>
</tr>
<tr>
<td>2. Familial</td>
<td>2. Familial</td>
</tr>
<tr>
<td>Autosomal recessive proximal RTA with ocular abnormalities: Na⁺, HCO₃⁻ cotransporter (NBCe1) defect</td>
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</tr>
<tr>
<td>Autosomal recessive proximal RTA with osteoporosis and cerebral calcification carbonic anhydrase II defect</td>
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</tr>
<tr>
<td>Generalized (systemic disorder present)</td>
<td>Generalized (systemic disorder present)</td>
</tr>
<tr>
<td>Genetic disorders</td>
<td>Genetic disorders</td>
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<tr>
<td>Cystinosis</td>
<td>Cystinosis</td>
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<tr>
<td>Wilson disease</td>
<td>Wilson disease</td>
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<tr>
<td>Hereditary fructose intolerance</td>
<td>Hereditary fructose intolerance</td>
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<td>Lowe syndrome</td>
<td>Lowe syndrome</td>
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<tr>
<td>Metachromatic leukodystrophy</td>
<td>Metachromatic leukodystrophy</td>
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<tr>
<td>Dysproteinemic states</td>
<td>Dysproteinemic states</td>
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<tr>
<td>Myeloma kidney</td>
<td>Myeloma kidney</td>
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<td>Light chain deposition disease</td>
<td>Light chain deposition disease</td>
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<tr>
<td>Primary and secondary hyperparathyroidism</td>
<td>Primary and secondary hyperparathyroidism</td>
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<td>Drugs and toxins</td>
<td>Drugs and toxins</td>
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<tr>
<td>Outdated tetracycline</td>
<td>Outdated tetracycline</td>
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<tr>
<td>Rifampicin</td>
<td>Rifampicin</td>
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<tr>
<td>Gentamicin</td>
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<tr>
<td>Streptomycin</td>
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<tr>
<td>Lead</td>
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<td>Cadmium</td>
<td>Cadmium</td>
</tr>
<tr>
<td>Mercury</td>
<td>Mercury</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>Tubulointerstitial disease</td>
</tr>
<tr>
<td>Post transplantation rejection</td>
<td>Post transplantation rejection</td>
</tr>
<tr>
<td>Balkan nephropathy</td>
<td>Balkan nephropathy</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
<td>Medullary cystic disease</td>
</tr>
</tbody>
</table>

- Tubulointerstitial disease (TID)
  Obstructive uropathy
  Renal transplantation
Factors differentiating Type 1, Type 2, Type 4

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K⁺</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Renal Function</td>
<td>0/near normal</td>
<td>0/near 0</td>
<td>Stage 3, 4/5 chronic kidney disease (CKD)</td>
</tr>
<tr>
<td>Urine PH During Acidosis</td>
<td>High</td>
<td>Low</td>
<td>Low or high</td>
</tr>
<tr>
<td>Serum HCO₃⁻</td>
<td>10-20</td>
<td>16-18</td>
<td>16-22</td>
</tr>
<tr>
<td>urine pCO₂ (mm Hg)</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>&gt;70</td>
</tr>
<tr>
<td>urine Citrate</td>
<td>low</td>
<td>High</td>
<td>low</td>
</tr>
<tr>
<td>Fanconi Syndrome</td>
<td>No</td>
<td>may be present</td>
<td>No</td>
</tr>
</tbody>
</table>

Management

Non-volatile acid: 1 mg/Kg → To be excreted from the body

A. Sodium Bicarbonate  Shohl’s Solution  1 meq/ml
Or  of HCO₃⁻
sodium citrate  1 meq of citrate
5 ml → 500 mg of sodium citrate + 640 mg of citric acid

B. Potassium citrate:  5 ml → 10 meq of K⁺ (Citakka) 10 meq of citrate/HCO₃⁻

Severe hypokalemia
Serum K⁺ = 1.5 meq/l
LV Kcl infusion  1-amp Kcl = 10 ml
1 ml = 2 meq
2 amp = 20 meq → increases K⁺ by 0.25 meq/l

a amp Kcl 100 ml/hr
In 200 ml NS 1 amp/hr
Over 2 hrs 20 meq/hr x 2 hrs
40 meq → increases K⁺ by 0.5 meq/l
Example: If serum K⁺ = 1.5 mEq/l → target K⁺ = 3-3.5
max dose that can be given/day = 240 mEq/l

Hypokalemia / urine K⁺ loss (alkalosis)

- To low BP
  1) Bartter syndrome
  2) Gitelman syndrome

- High BP
  1) Conn's
  2) Liddle
  3) Cushing
  4) AME (apparent mineralocorticoid excess)
  5) GRA (glucocorticoid remediable Aldosterone)

Electrolyte transport in the thick ascending limb

- Na⁺ K⁺ 2Cl⁻ symport
  (Type 1 Bartter)

- ROMK channel
  (Type 2 Bartter)

- CLCNKB
  (Type 3 Bartter) → Survives to adulthood (classical)

- Bartter
  (Type 4 Bartter)

- Type 5 Bartter
  Hypocalcemia
  Autosomal dominant
Type 1
- Volume depletion
- Intravascular depletion
- Vomiting, Failure to thrive, polyuria
- a° Renin angiotensin system (RAS) → Hypokalemia, alkalosis → Hypercalcemia → Stones → Hypermagnesuria

Type 3
1. Intravascular volume depletion → stimulates prostaglandin (PG) → stimulates renin
2. Treatment → NSAID (indomethacin)
3. Serum Ca\(^{2+}\) & Mg\(^{2+}\) → normal

Gitelman syndrome
- Milder disease (survive into adulthood)

Defect Na\(^{+}\)-Cl\(^{-}\) symporter in DCT
- Less volume depletion
- Less vomiting
- Less hypokalemia
- Less activation of RAS
- No PG stimulation

Ca\(^{2+}\) conservation (hypercalcemia, hypercalciuria)
Mg\(^{2+}\) absorption → Hypomagnesemia

<table>
<thead>
<tr>
<th>Features Differentiating Bartter and Gitelman Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>Maternal Hydramnios</td>
</tr>
<tr>
<td>Polyuria, polydipsia</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Tetany</td>
</tr>
<tr>
<td>Growth retardation</td>
</tr>
<tr>
<td>Urinary calcium</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Serum magnesium</td>
</tr>
<tr>
<td>Urine prostaglandins</td>
</tr>
<tr>
<td>Response to indomethacin (improvement of hypokalemia and renal salt wasting)</td>
</tr>
</tbody>
</table>
HYPERKALEMIA

Introduction

medical emergency
no cardinal manifestations
ECG (to rule out arrythmia)

patients at risk - CKD or ARF (inability to excrete K+)

Presents with non specific symptoms like:
- fatigue, syncope, palpitation, giddiness

Neuromuscular manifestations:
  1) Paresthesia / weakness
  2) ↓ NH₄⁺ production
  3) ↑ insulin secretion

ECG changes in hyperkalemia

<table>
<thead>
<tr>
<th>QRS Complex</th>
<th>Approximate Serum Potassium (mmol/L)</th>
<th>ECG Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>P wave</td>
<td>-4</td>
<td>Normal</td>
</tr>
<tr>
<td>T wave</td>
<td>6-7</td>
<td>Peaked T waves</td>
</tr>
<tr>
<td></td>
<td>7-8</td>
<td>Flattened P wave, prolonged PR interval, depressed ST segment, Peaked T wave</td>
</tr>
<tr>
<td></td>
<td>8-9</td>
<td>Atrial standstill, prolonged QRS duration, further peaking T waves</td>
</tr>
<tr>
<td></td>
<td>≥9</td>
<td>Sine wave pattern</td>
</tr>
</tbody>
</table>
Approach to hyperkalemia

↑Serum K⁺

Pseudo hyperkalemia
rise is ~ 0.5
Pt can have ↑ WBC
↑ Platelet count
wrong collection technique

True hyperkalemia
is almost always associated with
Renal failure (CKD/AKI)

True hyperkalemia without
renal failure

urine spot K⁺

urine spot K⁺ reduced

Aldosterone related

TTKG
(Transtubular Potassium Gradient)

If TTKG < 8

Give 0.05mg of Fludrocortisone

TTKG
> 8 or 10
True hypoaldosteronism

TTKG still
low < 8
Aldosterone Resistance

Transcellular shift is seen in:
1) Hyperglycemia
2) α agonist, β antagonist
3) Exercise
4) ↑ Osmolality
5) Tumor lysis syndrome (TLS) / Rhabdomyolysis / Hemolysis
Trans tubular potassium gradient (TTKG)

Normal: 8-12

An indicator of aldosterone activity

\[
TTKG = \frac{\text{Urine Potassium}}{\text{Serum Potassium}} + \frac{\text{Urine Osmolarity}}{\text{Serum Osmolarity}}
\]

\[
(\frac{\text{Urine Potassium}}{\text{U. Osmolarity}} \times \frac{\text{S. Osmolarity}}{\text{Serum Potassium}})
\]

In hyperkalemia, TTKG: 10 to 12

True hypoaldosteronism

- Hyporeninemic hypoaldosteronism
  - Low Renin, Low aldosterone
    - NSAIDs
    - β blocker
    - DM

- Hyperreninemic hypoaldosteronism
  - Low Aldosterone, High renin
    - Addison’s disease
    - ACE inhibitors / ARB
    - Heparin

Aldosterone resistance

- Genetic
  - Pseudohypoaldosteronism
    - Type 1
  - Pseudohypoaldosteronism
    - Type 2
    (Both are autosomal recessive (AR))

- Acquired
  - tubulointerstitial disease
    - RTA type IV
  - Aldosterone not able to bind to the receptor
    - no K⁺ excretion & H⁺ excretion
    - Hyperkalemia & Acidosis
Renal tubular acidosis (RTA) type IV

Fibrosis or injury to the interstitial site of P cell prevents aldosterone attachment

\[ \text{Hyperkalemia & Acidosis} \]

\[ \text{H}^+ \quad \text{Na}^+ \quad \text{Aldosterone} \]

\[ \text{P cell} \]

\[ \text{K}^+ \]

Renal function test (RFT) → abnormal (mc)

Hyperkalemia is disproportionate to degree of renal failure

Causes:  
  a) Chronic tubulointerstitial disease  
  b) SLE  
  c) Reflux Nephropathy  
  d) Obstructive nephropathy  
  e) Sickle cell nephropathy

Drugs associated with RTA Type IV:
  1) Cyclosporine / Tacrolimus  
  2) Amiloride / Triamterene (ENaC blockers)  
  3) Trimethoprim  
  4) Pentamidine  
  5) Aldosterone antagonist - Spironolactone  
     Eplerenone

Factors differentiating type 1, 2 & 4 RTA

<table>
<thead>
<tr>
<th>Factors Differentiating Type 1, Type 2 and Type 4 RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 RTA</td>
</tr>
<tr>
<td>Serum K⁺</td>
</tr>
<tr>
<td>Renal function</td>
</tr>
<tr>
<td>Urine pH during acidosis</td>
</tr>
<tr>
<td>Serum HCO₃⁻ (mmol/L)</td>
</tr>
<tr>
<td>Urine pCO₂ (mmHg)</td>
</tr>
<tr>
<td>Urine citrate</td>
</tr>
<tr>
<td>Fanconi syndrome</td>
</tr>
</tbody>
</table>
In Type 4 RTA:
- Hyperkalemia
  - Renal function - Never normal
  - Urine pH - Variable
  - Acidosis
  - Hypocitraturia

Usually in alkali loading urine PCO₂ ↑ via H⁺ - ATPase
In distal RTA - urine PCO₂ fails to ↑
But in type 4: Urine PCO₂ - Normal

Pseudohypoaldosteronism

Pseudohypoaldosteronism type 1  Liddle syndrome
1. Loss of function mutation of ENaC
   (AR)
   2. Hyperkalemia
   3. Acidosis
   4. to low BP

Pseudohypoaldosteronism type 2  Gitelman’s syndrome
- AR
- also known as Gordon’s syndrome
- 3. problem in DCT
- Hyperkalemia
- Acidosis
- HTN

- Hypokalemia
  ↑ urine K⁺
- Acidosis
  ➔ to low BP
  - Gitelman syndrome
  - Opposite Pseudohypoaldosteronism Type 2
  - Opposite to pseudohypoaldosteronism Type 1

- Hypokalemia
  ↑ Urine K⁺, alkalosis
- Hypokalemia
  ↑ BP
## Drugs causing hyperkalemia

<table>
<thead>
<tr>
<th>Medications Associated with Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>Potassium-containing medicines</td>
</tr>
<tr>
<td>β-Adrenergic receptor blockers</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Angiotensin receptor blocker (ARA2)</td>
</tr>
<tr>
<td>Heparin</td>
</tr>
<tr>
<td>Aldosterone receptor antagonist</td>
</tr>
<tr>
<td>Potassium-sparing diuretic</td>
</tr>
<tr>
<td>NSAR and COX-2 inhibitors</td>
</tr>
<tr>
<td>Digitalis glycosides</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
</tr>
</tbody>
</table>

Digoxin also causes hyperkalemia.

### Treatment of hyperkalemia

- **ECG**
  - Presence of tall T waves → stabilize myocardium
  - **Calcium gluconate**
    - 10 ml 10% IV over 10 minutes
    - 10ml has 1g (≈93 mg of elemental Ca²⁺)
    - Onset of action: 1-3 minutes
    - Duration of action: 30 min-1 hr
    - Repeat one more dose in unresponsive cases
To ↑ cellular uptake of K⁺ → insulin dextrose infusion

↓

10 units of regular insulin IV followed by 500 ml of 50% dextrose slowly over 1 hr

Or

10 units of insulin in 100 ml of 25% dextrose & run it over 1 hr
(onset of action 30 min acts for 4-6 hr)

Nebulised Salbutamol

- 10-20mg
  As an adjuvant therapy (never given as monotherapy)

- onset of action 30 min & stays for 2-4 hrs

For K⁺ Removal → Sodium or Calcium (K⁺ Bind)

Polystyrene sulfonate

↓

not used due to increased risk of intestinal perforation

Dialysis - is the last option

New drugs: Patiromer, Zirconium Cyclosilicate
THYROID BASICS

Development of thyroid

- Starts at 3rd week of intrauterine life
- It is an endodermal derivative
- Endodermal cells arise from the floor of primitive pharynx

Thyroid Development

- From Foramen Caecum, it begins as a diverticulum which elongates to form Thyroglossal duct / Tract
- Thyroglossal tract usually disappears and in some patients remnants give rise to Thyroglossal cyst
- From Thyroglossal tract, it migrates towards thyroid
- Structural and functional unit of Thyroid gland

Thyroid follicle

- Adjacent to follicle, Para follicular cells are present.
- Para follicular cells are C - cells derived from the ultimobranchial body (neural crest cell)
- Para follicular cells produce Calcitonin
- Follicular cells produce $T_3, T_4$
- Hormone synthesis starts at 11 weeks of IUP
Anatomical Relations:
Anteriorly: Sternalis
Sternothyroid
Posteriorly: Carotid sheath
Medially: Recurrent laryngeal nerve
esophagus

Hormone synthesis
- Thyroid Gland has numerous Follicles
- Follicles contains follicular epithelial cells
- In the centre of the follicle, colloid Present.
- Inside the colloid, hormones are stored (2 - 3 months)
Follicular epithelial cell:
- It has two surfaces
  1. Basolateral membrane
  2. Apical membrane
- TSH receptor is present on the basolateral membrane
- TSH stimulates the gland to produce thyroid hormones
- Although TSH is required for the proper functioning of the thyroid gland, thyroid can produce thyroid hormones even in the absence of TSH.

That is why, in pituitary insufficiency or adult hypopituitarism, hypothyroidism is not prominent.

- TSH binds to TSH receptor
- Dopamine competes with TSH to bind to TSH receptor
- Steroids on binding of TSH to TSH receptor

Step - 1: Iodide uptake:
- Iodide uptake into the follicular epithelial cell through \( \text{Na}^+ - \text{I}^- \) symporter (sodium - iodide symporter).
- Na-1 Symporter can be seen in:
  - Breast
  - Salivary gland
  - Thyroid
  - Placenta

- To visualise Thyroid gland, we do Radioisotope scan.

- In Radioisotope Scan (Thyroid Scintigraphy) use isotope of Iodine $^{131}$
- $^{131}$ also enters Thyroid through Na-1 Symporter
- Now, Technetium 99 has replaced $^{131}$

Inhibitors of Na-1 Symporter:
- i) Thiocyanate
- a) perchlorate

Step - a Iodide Crossing Apical membrane:
- Iodide crosses apical membrane via Iodide - chloride antiport (also known as pendrin).
- This pendrin also present in the inner ear
- Pendred Syndrome
  - Goitre with Sensory Neural Hearing Loss (SNHL)

\[ \text{TSH} \]
\[ \text{TSH receptor} \]
\[ \text{Na-1 Symporter} \]
\[ \text{Step 1} \]
\[ \text{I}^- \text{ Iodide - chloride Antiport} \]
\[ \text{(pendrin)} \]

Step - 3 Organification of Iodine:
- Conversion of $I^- \rightarrow I_3^-$ done by enzymes present on apical membrane
  - i) Thyroid Peroxidase (TPO)
  - a) Dual Oxidase (Duox)
- Drugs inhibiting Thyroid Peroxidase
  - Thionamides
Step - 4 Iodination:
- Inside the colloid, thyroid hormone precursor molecule is present → Thyroglobulin
- It has Tyrosine residues
- Iodine is attached to the Tyrosine residue of Thyroglobulin to form MIT or DIT

Step - 5 Coupling:
- MIT Combines with DIT → T₃ 
- DIT Combines with MIT → T₄
  \{ under the control of Thyroid Peroxidase (TPO) \}
- Very small amount of DIT combines with MIT
  \( \text{DIT + MIT} \rightarrow \text{reverse } T₃ \text{ (very little)} \)
- Physiologically not significant.

Step - 6 Hormone release:
- Thyroglobulin with the hormones taken back into the epithelial cell
- Undergoes Proteolysis, T₃ & T₄ are released into blood stream
- Thyroglobulin is taken back into colloid
- Hormone release is inhibited by Iodides
- Physiologically, most important hormone is T₃

Last Step Conversion of T₄ → T₃:
- Peripherally T₄ gets converted to T₃ by enzyme Deiodinase

<table>
<thead>
<tr>
<th>Age</th>
<th>RDA of iodine (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years</td>
<td>90</td>
</tr>
<tr>
<td>6-12 years</td>
<td>120</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>150</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>250</td>
</tr>
</tbody>
</table>
Difference between $T_4$ and $T_3$:

<table>
<thead>
<tr>
<th>Variable</th>
<th>$T_4$</th>
<th>$T_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution</td>
<td>10 L</td>
<td>40 L</td>
</tr>
<tr>
<td>Extrathyroidal pool</td>
<td>800 $\mu$g</td>
<td>54 $\mu$g</td>
</tr>
<tr>
<td>Daily production</td>
<td>75 $\mu$g</td>
<td>25 $\mu$g</td>
</tr>
<tr>
<td>Fractional turnover per day</td>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>Metabolic clearance per day</td>
<td>1.1 L</td>
<td>24 L</td>
</tr>
<tr>
<td>Half-life (biologic)</td>
<td>7 days</td>
<td>1 day</td>
</tr>
<tr>
<td>Serum levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5–11 $\mu$g/dL</td>
<td>95–190 ng/dL</td>
</tr>
<tr>
<td></td>
<td>(64–132 nmol/L)</td>
<td>(1.5–2.9 nmol/L)</td>
</tr>
<tr>
<td>Free</td>
<td>0.7–1.86 ng/dL</td>
<td>0.2–0.52 ng/dL</td>
</tr>
<tr>
<td></td>
<td>(9–24 pmol/L)</td>
<td>(3–8 pmol/L)</td>
</tr>
<tr>
<td>Amount bound</td>
<td>99.96%</td>
<td>99.6%</td>
</tr>
<tr>
<td>Biologic potency</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

- Daily production of $T_4$ is 2 times more than $T_3$.
- Fractional turn over of $T_3$ is 60% but $T_4$ is 10%.
- Clearance of $T_3$ is $\gg\gg\gg$ $T_4$.
- Serum $t\frac{1}{2}$
  - $T_3$ = 1 day
  - $T_4$ = 7 days (pharmacologically important)
- Potency $\Rightarrow T_3$ is 4 times potent than $T_4$.
- Bound form
  - $T_4 \rightarrow 99.96\%$
  - $T_3 \rightarrow 99.6\%$
- Free form of $T_3$, $T_4$ is the metabolically active form.
- So, the free form
  - $T_3 = 0.4\%$
  - $T_4 = 0.04\%$

Deiodinases:
- Converts $T_4$ to $T_3$ peripherally.
- Deiodinase I - Thyroid, Liver, Kidney.
- Deiodinase II - Thyroid, pituitary, brain.
- Deiodinase II - has more affinity to $T_4$ than Deiodinase I.
- $T_4 \rightarrow T_3$ Conversion by Deiodinases is inhibited in fasting state, Systemic illness, Acute infection, Oral Contrast.

- Deiodinase III is normally seen in placenta only. It is activated in muscle and Liver in following conditions: fasting state, Systemic illness, acute infection, oral iodinated Contrast.

- Where in these conditions Deiodinase I & II are inhibited.

- So, by the action of Deiodinase III, $T_4 \rightarrow$ reverse $T_3$.

**Drugs Inhibiting Deiodinase:**
1. β - Blocker - Propranolol
2. PTU
3. Amiodarone
4. Steroids

- Don’t measure $T_3$, $T_4$ levels in fasting, Systemic illness, acute infection, oral contrast because they show false values.

- Here, reverse $T_3$ is formed in excess. But it is clinically insignificant because patient is Euthyroid.

**Thyroid Hormone Receptor:**
- TSH Receptor
  - cell membrane receptor
  - acts via cAMP
- $T_3 / T_4$
  - Intracellular receptors
- T₃ & T₄ are bound to 3 proteins
  a) Thyroid binding globulin (70%)
  b) Albumin (20%)
  c) Transthyretin (10%)
  also known as Prealbumin - also carries Vitamin A

Euthyroid hyperthyroxinemia

<p>| TABLE 405-3 CONDITIONS ASSOCIATED WITH EUTHYROID HYPERTHYROIDINEMIA |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cause</th>
<th>Transmission</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial dysalbuminemic</td>
<td>Albumin mutations, usually R218H</td>
<td>AD</td>
<td>Increased T₃</td>
</tr>
<tr>
<td>hyperthyroxinemia (FDH)</td>
<td></td>
<td></td>
<td>Normal unbound T₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rarely increased T₂</td>
</tr>
<tr>
<td>TBG</td>
<td>Increased TBG production</td>
<td>XL</td>
<td>Increased total T₃, T₂</td>
</tr>
<tr>
<td>Familiar excess</td>
<td></td>
<td></td>
<td>Normal unbound T₃, T₂</td>
</tr>
<tr>
<td>Acquired excess</td>
<td>Medications (estrogen), pregnancy, cirrhosis, hepatitis</td>
<td>Acquired</td>
<td>Increased total T₃, T₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal unbound T₃, T₂</td>
</tr>
<tr>
<td>Transthyretin *</td>
<td>Islet tumors</td>
<td>Acquired</td>
<td>Usually normal T₃, T₂</td>
</tr>
<tr>
<td>Excess</td>
<td>Increased affinity for T₃ or T₂</td>
<td>AD</td>
<td>Increased total T₃, T₂</td>
</tr>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
<td>Normal unbound T₃, T₂</td>
</tr>
<tr>
<td>Medications: propranolol, iodide, lopanic acid, amiodarone</td>
<td>Decreased T₃ → T₂ conversion</td>
<td>Acquired</td>
<td>Increased T₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased T₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal or Increased TSH</td>
</tr>
<tr>
<td>Resistance to thyroid hormone</td>
<td>Thyroid hormone receptor β mutations</td>
<td>AD</td>
<td>Increased unbound T₃, T₂</td>
</tr>
<tr>
<td>(RTH)</td>
<td></td>
<td></td>
<td>Normal or Increased TSH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some patients clinically thyrotoxic</td>
</tr>
</tbody>
</table>

*Also known as thyroxine binding prealbumin (TBPA).

Abbreviations: AD, autosomal dominant; TBG, thyroxine binding globulin; TSH, thyroid stimulating hormone; XL, X-linked.
Hyperthyroxinemia:
- $T_3$ or $T_4$ is high (may be free or bound)

$$T_3, T_4 - high$$

- Free $T_3, T_4 - high$
- Bound $T_3, T_4 - high$

**Thyrotoxicosis**
- Due to hyperfunctioning of thyroid gland
- Normal thyroid gland

**Hyperthyroidism**
- Thyrotoxicosis without hyperthyroidism

- Total $T_3, T_4$ has no value
- Only free $T_3, T_4$ is useful

So, in Euthyroid Hyperthyroxinemia:

- Total $T_3, T_4$ - high
- Bound $T_3, T_4$ - high
- Free $T_3, T_4$ - normal
- TSH - normal

**Causes of Euthyroid Hyperthyroxinemia:**

1. Thyroid Binding globulin excess:
   - It can be familial - X-linked Recessive
   - Acquired - seen in Pregnancy, estrogen, Viral hepatitis

2. Resistant to Thyroid hormones (RTH)
   - Autosomal Dominant Condition
   - Resistant to Thyroid Receptor Beta due to mutation
   - Partial resistance produces Euthyroid Hyperthyroxinemia
   - Most of the patients are Euthyroid
System

- hormones are not binding to receptor
  ↓
  TSH ↑↑
  ↓
  But, patient clinically euthyroid

- Rarely, this TSH may again stimulate hormone Synthesis
  ↓
  T₃, T₄Synthesised acts on
  α - receptors (which are sensitive)
  ↓
  Rarely, may go into Thyrotoxicosis

- TSH - may increase T₃, T₄ (free)
  ↓
  acts on α - receptor causes Thyrotoxicosis
  - heart rate increases
  - Goitre
  - Attention deficient Hyperactive disorder
  - mild reduction in IQ

Thyroid hormone actions

- maintains 'Basal Metabolic Rate'.

  1) Carbohydrate metabolism:
     1) Increases glucose uptake in tissues
     a) Increase • gluconeogenesis
genogenesis} ↑ Glucose

- That is why in Myxedema Coma, which is an Extreme Form of
  Hypothyroidism
  ↓
  myxedema coma patient
  suffers from Hypoglycemia.

  2) Protein metabolism:
     • Catabolic action → Proteolysis
     • patient get myopathy
       osteopenia
       Hypercalcemia
       Hypercalcuria / stones
3) Fat metabolism:
   • Increases Lipolysis.
   • Increases clearance of cholesterol
   • Because of this, hypothyroid patient has Hypercholesterolemia.
   • Any patient who is having Hypercholesterolemia.

   1st rule out Hypothyroidism

4) Increases O₂ Consumption Everywhere except Brain & Gonads.

5) With respect to Electron Transport chain
   → Thyroid hormones are uncouplers of oxidative phosphorylation
   → No ATP formed
   → Shift towards 'Thermogenesis'
   • That is why in a Myxedema Coma, patient has Hypothermia.

   Myxedema Coma → Extreme Hypothyroidism
   i) Hypoglycemia
   ii) Hypothermia

6) Growth:
   • for Bone growth
   • CNS - myelination

7) Heart:
   • Indirect action
   • Increases the Sensitivity to Catecholamines

   • Bone protein mobilisation due to ↑T3 / T4
   → results in osteoporosis

8) Liver:
   • It converts
     β - Carotene → Vitamin A
   • also stimulates Erythropoiesis.
TFT AND HYPOTHYROIDISM

Thyroid Function Test

- TSH → Done while fasting
- Free \( T_3/T_4 \) → no relation to food

<table>
<thead>
<tr>
<th>TSH</th>
<th>( T_4 )</th>
<th>( F_t )</th>
<th>( T_3 )</th>
<th>( FT_3 )</th>
<th>Condition</th>
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<tbody>
<tr>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Subclinical hypothyroidism; Recovery from Acute illness</td>
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<tr>
<td>↑</td>
<td>↓</td>
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<td>Primary hypothyroidism</td>
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<tr>
<td>↑</td>
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<td>↑</td>
<td>Thyroid hormone resistance / Thyroid adenoma</td>
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<td>Normal Or ↓↓</td>
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<td>↓</td>
<td>↓</td>
<td>TSH appropriately Normal; Secondary Hypothyroidism</td>
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<tr>
<td>↓</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
<td>Thyrotoxicosis / H.mole / Pregnancy</td>
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Basics of TFT interpretation

- A normal TSH excludes primary abnormality of thyroid function
- \( T_3 \) toxicosis is present in 2-5% and hence free \( T_3 \) is measured for everybody with suppressed TSH and normal free \( T_4 \)
- Serum thyroglobulin levels are increased in all types of thyrotoxicosis except thyrotoxicosis factitia
- Causes of elevated / decreased TBC can be interpreted

Primary hypothyroidism:

\[ \downarrow \text{Free } T_3, \text{ Free } T_4, \downarrow \]

\[ \text{TSH } \uparrow \uparrow \]
Primary hypothyroidism - if suspected due
↓
Exclude autoimmune causes by antibodies tests
↓
1. Thyroid peroxidase Antibody
2. Anti thyroglobulin
3. Anti microsomal
4. Anti TSH receptor

- M/C cause for autoimmune primary hypothyroidism
  is “Hashimoto's Thyroiditis”

### Drugs and TFT

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Propranolol</th>
<th>Iodine</th>
<th>Amiodarone</th>
<th>Propylthiouracil</th>
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<th>Inhibitors of Deiodinase 1 and 2</th>
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<tr>
<th>Phenytoin</th>
<th>Carbamazepine</th>
<th>Rifampicin</th>
<th>Sertaline</th>
<th>Ritonavir</th>
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<tr>
<th>Enzyme Inducers</th>
<th>↑se metabolism of free T₄</th>
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<td></td>
<td>↑se TSH (hypothyroidism)</td>
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<tr>
<th>Lithium</th>
<th>D₂ blockers</th>
<th>Clomiphene</th>
<th>Spironolactone</th>
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<th>↑se TSH</th>
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<tr>
<th>AL(OH)₃</th>
<th>Cholestyramine</th>
<th>Calcium carbonate</th>
<th>Ferrous sulfate</th>
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<th>↓se Thyroid Hormone absorption</th>
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**Antibodies:**

- Anti - TPF, TPA, and TSH antibodies or microsomal or TSH are seen or TSH are seen in 100% patients with autoimmune hypothyroidism and 80% with Grave's disease
TSH receptor antibodies

- Stimulating (80%)
  - Grave's disease

- Inhibitory (20%)
  - Hashimoto's thyroiditis

20% have TSH receptor blocking antibodies whereas Others have Thyroid stimulating immunoglobulin TSI which is responsible for Graves disease.

Excess iodide transiently inhibits thyroid hormone synthesis for 5 to 7 days followed by thyroid escape phenomenon called "Wolff chaikoff effect".

Hypothyroidism

Primary Hypothyroidism:
- Autoimmune
  - Hashimotos thyroiditis
- Iodine deficiency
- Post operative
- Congenital hypothyroidism
- Drugs [Lithium, clo miphenes, DaBlockers, Spironolactone, IFN-α]

Secondary hypothyroidism:
  - Due to pituitary

Hashimoto's thyroiditis

- Autoimmune thyroiditis/illness
- Female >> male
- Middle aged females [mean age of 60 yrs]
- m/C cause for primary hypothyroidism-Other autoimmune illness associated
  - Type 1 dm
  - Perinicious anaemia
  - Vitiligo
  - SLE
  - Addison
• HLA DR-3; HLA-DR -4; DR -5
  CTLA4 polymorphisms
  [Cytotoxic T-lymphocyte Associated Antigen]
  LIFR polymorphisms

• most of the patient presents with Goitre
  [Irregular, firm and heterogeneous enlargement of gland]

• †es risk of premalignant condition
  - Extranodal marginal zone lymphoma (B-cell)
  - Papillary carcinoma of thyroid

**Histology:**
• Lymphocytic infiltration with germinal centre formation
• Atrophy of follicles with oxyphil metaplasia or oxyptic cells
• Hurthle cell with eosinophilic cytoplasm
• Absence of colloid
• Mild fibrosis

**Symptoms of Hashimoto's thyroiditis**

Thyroid hormone maintains basal metabolic rate
Deficiency causes:
• Generalized slowing of metabolic process (m/c in both primary and secondary hypothyroidism)
• Fatigue (m/c)
• Slowing of speech
• Cold intolerance
• Constipation
• Weight gain (m/c)
• Delayed relaxation of DTR (deep tendon reflexes)
• Decreased heart rate
• Hair loss

TSH ↑↑ → Stimulate fibroblasts and Glycosaminoglycans
and ↓T<sub>3</sub>, ↓T<sub>4</sub> → Trap water
[It causes symptoms of myxedema]
Accumulation of matrix [GAGs] inside interstitial space of many tissues

- Puffiness
- Macroglossia
- Non-pitting edema
- Periorbital edema

Myxedematous symptoms in hypothyroidism are mostly due to Hypothyroidism

Excess of TSH is seen in primary hypothyroidism

These symptoms are commonly seen in primary hypothyroidism.
Complications of hypothyroidism

- m/C menstrual abnormality Oligomenorrhoea (or) Amenorrhoea/infertility
- Obstructive sleep apnea syndrome due to macroglossia
- Weight gain and unexplained constipation
- Pericardial effusion
- Decreased pulse rate
- Decreased exercise capacity
- Shortness of breath
- Hypercholesterolemia
- Rarely menorrhagia
- Dry coarse skin

Presentation:
→ Goitre → Firm and non tender
→ Tiredness / Poor concentration / Weight gain / Hair loss
→ menorrhagia / infertility
→ Dry coarse skin / Delayed DTR / myxedema / Bradycardia
→ Periorbital puffiness + Hoarse voice + Non pitting edema + macroglossia ⇒ primary hypothyroidism

Approach and subclinical hypothyroidism

1. m/C combination possible—High TSH and Low free T4 seen in excess intake of drug

\[ \text{LOW T4} \quad \text{on drugs} \quad \text{↑TSH} \quad \text{interpret disease} \]
\[ \text{↑TSH} \quad \text{(interprets disease)} \quad \text{↑T4 (excess drug)} \]

2. High TSH and high FT₄ shows that the patient was on treatment and the treatment is not correct.

3. High TSH ; Normal free T4 → Sub clinical hypothyroidism
4. Anti - TPO → Hashimotos Thyroiditis

5. Normal TSH and ↑T₄. This combination is not possible

**Subclinical hypothyroidism**

- TSH upper limit → 5 milli IU/litre
  - 5-10m IU/L → High normal

- Sub clinical hypothyroidism → ↑ cardiovascular mortality

Indications for subclinical hypothyroidism treatment:
1. TSH > 10m IU/L
2. Symptoms
3. Pregnant
4. Antibodies positive

In hypothyroidism proximal myopathy + pseudo-hypertrophy of calf seen called "Hoffman's syndrome"
Treatment

- Eltroxin 1.7 mg/kg/day
- Preferably at 7 am in the morning on an Empty stomach followed by food intake 30 min later
- In EK 25 mcg/day
- Follow up after 8 -12 weeks
  - If the patient misses the drug in between follow up the results show ↑TSH and ↑T₄
- TSH will take minimum 12 -16 weeks to normalize
- Clinical relief 3 -6 months after TSH normalizes
- For monitoring the patient → TSH is the best choice
- M.C.C For Treatment failure → “Non - compliance”

Myxedema coma

40% mortality
seen in long standing hypothyroid triggered by
↓
Infection
Extreme Non compliance
mI/Stroke

Presentation:
Reduced consciousness / seizure
  1) Hypothermia
  2) Hypoglycemia
  3) Hypoventilation [↑PCO₂]
  4) Hyponatremia [↑ADH]
  5) Bradycardia [↓ Cardiac output]

Treatment:
- IV T₄ + IV T₃
- Steroids (Hydrocortisone 100mg IV Q6h)
- Eltroxine 500 mg V followed by 50 - 100 mg/day
- IV T₃ 5 - 20 mg V → If IV is not possible- given Through Ryele’s tube
- Avoid hypotonic fluids
Treatment

- Eltroxin 1.7 mg/kg/day
- Preferably at 7 am in the morning on an empty stomach followed by food intake 30 min later
- In elderly people (> 60yrs) or cardiac disease → 25 mg/day
- Follow up after 8 -12 weeks
  if the patient misses the drug in between follow up
  the results show ↑TSH and ↑T₄
- TSH will take minimum 12 -16 weeks to normalize
- Clinical relief 3 -6 months after TSH normalizes
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- IV T₃ 5 - 20 mg, V → If IV is not possible- given Through Ryele’s tube
- Hypertor
- Avoid hypotonic fluids
Hashimoto's encephalopathy (old term)

SREAT [Steroid responsive encephalopathy with auto immune thyroid disease] [New Term]

- Auto immune vasculitis unrelated to thyroid function
- Hashimotos encephalopathy can occur with a normal TFT
- HLA - B -8 associated
- Elevated antibody titres

Presentation:
- Sub acute onset of confusion / Altered level of consciousness
  - Or
  - Seizure / myoclonus
    - Or
    - Small vessel stroke
- Good response to steroids
- Treatable condition

Other point of Hashimoto's Encephalopathy:
- Anti enolase antibody
- Can occur in euthyroid state
- Stroke like pattern or slowly progressive cognitive
  - Impairment with Dementia; confusion or Hallucinations
- Background slowing on EEG
- Steroid responsive
THYROTOKICOSIS

Introduction
- Increase in free or total T₃/T₄ is known as Hyperthyroxinemia.
- Increase in free T₃/T₄, with clinical symptoms is K/A.

Thyrotoxicosis
- Increase in total T₃/T₄, person remains euthyroid (seen in Resistance to thyroid hormone & TSH excess)

Causes for thyrotoxicosis

With Hyperthyroidism (over working thyroid gland)
  → 1° Hyperthyroidism
      - Autoimmune - Graves
      - Toxic adenoma
      - Toxic MNG
  a) 2° Hyperthyroidism
      - TSH Adenoma

Without Hyperthyroidism (normal working thyroid gland)
  → Subacute thyroiditis
  a) Thyrotoxicosis Factitia (because of ingestion of exogenous thyroid hormone)

- Cause of hyperthyroidism, thyroglobulin levels are elevated, except in Thyrotoxicosis Factitia (thyroglobulin levels are not elevated)
- Thyroglobulin levels are also checked during followup of Papillary ca. thyroid after surgery

  - Free T₃/T₄ ↑ \[ \left\{ \begin{array}{l}
  1° hyperthyroidism → Check for Autoimmune causes (Graves) \\
  TSH ↓
\end{array} \right. \\
  \]

  TPO Ab
  Tg Ab
  microsomal Ab
  TSH-R Ab

  \[ \left\{ \begin{array}{l}
  \text{Any 1 will be } +ve \text{ in } 80\% \text{ cases}
\end{array} \right. \]

  - Free T₃/T₄ ↑ \[ \left\{ \begin{array}{l}
  2° Hyperthyroidism \\
  TSH ↑
\end{array} \right. \]
- Free T<sub>4</sub> - n
- Free T<sub>3</sub> - ↑
- TSH Suppressed

\[ T_3 \text{ Thyrotoxicosis (2\% cases)} \]

**Graves disease**

- Most cause of thyrotoxicosis - 75%
- 20-50 years
- Females > males (4:1)
- Autoimmune
- Associated with HLA DR<sub>a</sub>, CTLA<sub>4</sub>, PTPN<sub>6</sub>

**Risk Factors:**
- Smoking
- Post partum
- HAART

**Jod basedow effect:**
- Iodine supplementation in deficient areas, in a patient with a nodule or TSH-R Ab causing thyrotoxicosis is called as jod basedow effect

**Antibodies:**
- Thyroid stimulating Ig
- TPO
- Thyroglobulin - 80%
- TSH - R Ab

**Difference between thyrotoxicosis and grave's disease**

- Ophthalmopathy - severe proptosis
- Dermopathy - Pretibial myxedema with nodular lesions / plaques
- Acropathy - Clubbing
Thyroid stimulating Ig/TSH-R Ab

\[ \downarrow \]

Thyrotropin receptor

\[ \downarrow \]

T-cells

\[ \downarrow \]

Inflammatory cytokines interferon gamma

\[ \downarrow \]

High T\textsubscript{3}/T\textsubscript{4}

\[ \downarrow \]

Thyrotoxicosis

\[ \downarrow \]

Infiltrate EOM

\[ \downarrow \]

Glycosaminoglycans

\[ \downarrow \]

Retro orbital fibroblasts

\[ \downarrow \]

Trap H\textsubscript{2}O - Ophthalmopathy - Dermopathy

---

- **mc clinical sign in Thyroid ophthalmopathy - lid retraction**
  1 Kocher's sign: Staring appearance on fixation
  2 von graefe sign: Eyelid Lags behind eye ball on attempted down gaze
  3 Joffroy sign: Absent forehead creases on upgaze
  4 Stellwag: Decreased blinking
  5 Dalrymple: Widening of palpebra fissure on fixation
  6 Mobius: Poor convergence
Graves disease - clinical features

- Rapid weight loss inspite of increased appetite
- Panic attack with Hyperactivity, Nervousness, tremulousness; tachycardia
- Hypokalemic periodic palsy
- Elderly with Fatigue & weightloss - Apathetic thyrotoxicosis
- Proximal myopathy without fasciculations
- New onset Atrial Afilliation / Worsening of Heart failure
- Heat intolerance; warm & moist skin
- Diarrhea, Polyuria, oligomenorrhea, Loss of Libido
- Gynecomastia
- Depression
- Impaired sexual function
- Osteopenia
- Hypercalcemia

On palpation:
- Diffusely enlarged gland, firm but not nodular
- Warm, moist skin

NO SPECS classification of thyrotoxicosis and thyroid scintigraphy

- N - No signs, only symptoms
- O - only signs
- S - Soft tissue involvement
- P - Proptosis
- E - EOM
- C - Corneal involvement
- S - Sight loss

- $T_3/T_4$ ratio >20 is absolutely in favour of graves
- Hypercalcemia, Hyperglycemia, Elevated ALP, Leucocytosis, LFT elevated

Thyroid scintigraphy:
- Previously done by $I_{131}$, now its done by Tc 99
- In graves, $I_{131}$ diffuse increased uptake
Radionuclide diagnosis

Treatment of Graves Disease

- First line - Antithyroid drugs
- 50% of cases achieve remission with Anti thyroid drugs
- Mostly used are Thionamides
  - Propylthiouracil (PTU)
  - Methimazole
  - Carbimazole
  - PTU T₄ → T₃ conversion

PTU:
- Deiodinase (Θ), TPO Inhibitor
- 75% plasma protein binding & No Transplacental passage
- In Pregnancy – DOC (PTU)
- Very short t½ – 1-2hrs – multiple doses
- Extremely Hepatotoxic
- Carbimazole commonly used
- Carbimazole has no protein binding
- Transplacental passage is high
- t½ – 6 – 8 hours – 5 mg thrice daily – K/v titration
- Methimazole can cause Aplasia cutis, choanal atresia if used in pregnancy
- Half life of Methimazole is 6hrs and is an irreversible inhibitor
- Beta blockers are given along with these – Propranolol 40mg 6th hourly
Follow-up:
- Dose titration at 4-6 weeks depending on Free T4 levels
- Approximately 30-60% achieve remission in 12-18 months
- Common S/E of carbimazole is Rash
- Most dangerous S/E of carbimazole is Agranulocytosis
- Other S/E - cholestasis/drug induced lupus

Relapse or unable to achieve remission:
- Radio iodine is used for relapse or unable to achieve remission
- Radio iodine is C/I in
  1. Child
  2. Pregnancy
  3. Active eye disease
- With Radio iodine, there is no increase in isk of cancer
- 10% risk of permanent hypothyroidism
- I131 is used for Radiotherapy
- I131 - Scintigraphy
- I125 - Brachytherapy / Radioimmuno assay
- TSH is now estimated by chemiluminescence assay; Previously by Radioimmuno assay
- I137 - Normal Iodine
- I131 - Radio Iodine

Surgery in Graves disease
- Biopsy suspicious of malignancy in nodule
- Hyper parathyroidism
- Pregnancy / Lactation
- Young children
- Compressive symptoms
- 1 month prior to Radio iodine, Antithyroid drugs to be given to achieve full euthyroidism, to prevent thyroid storm
- Severe opthalmopathy requires therapy with steroids
- Sub total thyroidectomy is the most performed surgery
Thyrotoxicosis crisis/storm

- Precipitator:
  - Acute illness
  - Radio iodine
  - Surgery
  - when pt. has not achieved Euthyroid state

- 30% mortality — mostly due to Cardiac arrhythmias / Cardiac failure

Clinical features:
- Any person with thyrotoxicosis presenting with
  - Fever + Delirium
  - Seizures
  - Loss of consciousness

Management:
- Propyl thiouracil in Large doses:
  - 1000 mg stat
  - 250 mg every 4 hours
- Iodide given — as
  1. It produces Wolff — Chaiikoff effect
  2. Inhibits proteolysis
- Oral iodides like lopanoid acid 500 mg can be used
- Steroids — hydrocortisone 100 mg Tds i.v
- Beta blocker — Propronol 60 mg 4th hourly

Differential diagnosis of graves:
- Thyrotoxicosis without hyperthyroidism — Subacute thyroiditis

Acute thyroiditis
- In Acute thyroiditis, TFT is normal
- Seen in children
- Characterised by pain in the neck
- Infectious etiology — Staph aureus — m.C
- Radiation or Trauma induced
- Focus of infection: Puriform sinus
Subacute thyroiditis

De Quervain
(or)
Unilateral Painful thyroiditis
(or)
Viral/Granulomatous thyroiditis

Always compared with Graves

De Quervain / Viral / Granulomatous thyroiditis:
- Seen in women - 30-50 yrs
- No single virus has been isolated
- Associated with HLA B - 35
- Most often it is post viral
- Fever + painful thyroid / sore throat + Pain referred to ear +
  ESR ↑↑ ⇒ Thyroiditis (most probably)
- Due to release of stored hormone initially patient presents
  with symptoms of thyrotoxicosis followed by hypothyroidism &
  finally recovery
- Clinical course of subacute thyroiditis
  1-6 wks - Free T3/T4 ↑↑
  TSH ↓
  6-12 wks - Free T3/T4 ↓
  TSH ↑
  >12 wks - Recovery
- In 131 scintigraphy - Graves - B/L increased diffuse uptake
  - Subacute thyrotoxicosis - As the gland is
    not over working there will be decreased
    uptake

Treatment:
- Aspirin / NSAIDs - 600 mg 6th hourly
- If not responding - Steroids
- Permanent hypothyroidism can develop in 15% of patients (85% recover)
Painless thyroiditis / silent thyroiditis:
- Seen in post partum females
- Most of them with underlying autoimmune illness (mc: Type 1 DM)
- Painless
- ESR - Normal
- Anti-TPO Ab - Positive
- Steroids have no role
- Spontaneous recovery
- β-blockers can be used
- High chance of recurrence in the subsequent pregnancy

Chronic thyroiditis - Riedel's thyroiditis
- In chronic thyroiditis TFT is normal
- Middle aged woman
- Painless thyroid with local symptoms
- Dense fibrosis
- Hard mass
- IgG, related disease
- Tru-cut biopsy is in 3 conditions:
  • Riedel's thyroiditis
  • Anaplastic
  • Lymphoma
- In other cases, USG-Guided FNAC

Effects of amiodarone
- Amiodarone contains 39% of iodine / weight
- Class III Antiarrhythmic drug
- Amiodarone can produce both Hypo & Hyper thyroidism /
  thyrotoxicosis
- Amiodarone induced hypothyroidism is transient & it is due to
  wolff chaikoff effect. Don't stop Amiodarone, start low doses
  of L-thyroxine
- Amiodarone induced thyrotoxicosis is a serious condition
Amiodarone induced thyrotoxicosis

- Type 1
  - It is due to Jod basedow effect
  - seen with underlying disease (graves)

- Type 2
  - Its due to Lysosomal destruction
  - There is no underlying disease

Treatment of amiodarone induced thyrotoxicosis:
- Stop amiodarone
- Sodium ipodate or trypanoate inhibit the release of hormones
- Perchlorates can be used — Na/I symport is Inhibited
- Steroids can also be used

Low $T_3$ / sick euthyroid syndrome

- Seen in acutely ill patient under the effect of IL-6
- Seen in people who are fasting or chronic systemic illness
- Deiodinase is inhibited, $\rightarrow T_4$ is not coverted to $T_3 \rightarrow$ low $T_3$
- All the excess $T_4$ is converted to $\uparrow rT_3$ (reverse $T_3$)
- There will be $\downarrow T_3 \cup T_4 \cup TSH \uparrow rT_3$ — most common pattern
- If the patient is very ill, there can be $\downarrow T_3 \ \downarrow T_4 \ \downarrow TSH$ its due to accelerated metabolism from muscle and liver due to reduced perfusion

Nodule

- With Thyrotoxicosis
- Euthyroid
Nodule with euthyroid:
- In this the IOC is USG guided FNAC or USG.

USG features of malignancy:
- Hypoechochogenicity*
- An absent halo
- Irregular margins*
- Taller than wide shape*
- Presence of micro-calcifications*
- Increased intranodular vascularity
- Extra-thyroidal extension
- Nodal disease in neck
- No findings are definitive

Nodule with thyrotoxicosis:
- IOC thyroid scintigraphy - $^{131}I$ scan

Hot nodule:
- >99% benign, <1% malignant
- Increased radionuclide concentration
- May function independent of thyroid-Pituitary axis feedback mechanism (autonomous nodules)

Cold nodule:
- Non-functioning thyroid nodule
- Large majority are benign, 15-25% malignant

A solitary "toxic" nodule with suppression of the remainder of the thyroid

Pathological diagnosis confirmed a benign adenoma in the region of cold spot (arrows)
Hyper functioning solitary nodule / toxic adenoma

**Toxic Autonomous Nodule (toxic adenoma)**

**History**
- 49-year-old woman

**LAB:**
- **T4 = 15 mg/dL**
- **T3 = 304 ng/dL**
- **TSH < 0.01 IU/mL**
- **FT4 = 1.5-6.0 ng/mL**
- **FT3 = 2.0-4.0 ng/dL**
- **TSH < 0.01 IU/mL**
- **RRAI was elevated (48/9)**

**Scan**
- Hot nodule occupies most or all of the right thyroid lobe with near-total suppression of the left lobe.
- The background activity is diminished to such an extent that the salivary glands are barely visualized.

- A nodule with increased uptake and suppression of the remaining gland
- It is due to mutation in the TSH receptor signalling pathway
- It can be differentiated from Graves by scintigraphy. Here only some part will be uptaking the radionuclide increased focal uptake
- Radio iodine is the treatment of choice

**Toxic multinodular goitre**

**Toxic Multinodular Goiter**

**History**
- 71-year-old man with anxiety and weight loss

**Laboratory values:**
- **T4 = 14.1 ng/dL**
- **T3 = 299 ng/dL**
- **TSH < 0.01 IU/mL**
- The RRAI was 17% at 6 hours and 37% at 24 hours

**Scan**
- Enlarged thyroid with overall non-uniform uptake
- Areas of both increased and decreased activity are scattered throughout the gland

- There will be areas of both increased and decreased uptake
- Toxic MNG, seen in elderly with features of thyrotoxicosis like AF, tremor, weight loss
INTRODUCTION TO MGE AND DIARRHOEA

Malabsorption

- Diminished absorption of
  - Carbohydrates
  - Fat
  - Protein

- Hallmark of malabsorption → Steatorrhea
  ↓
  Pale, fat, bulky, malodorous stool

- 72 hr fecal fat test = ≥ 7 g (steatorrhea)
  (100 gm fat x 5 days
  9 testing fecal fat for
  Last 3 days)

Diarrhoea

- Stool water content > 200 ml in 24 hrs
- Most prominent clinical symptom of a patient with malabsorption → Diarrhoea
- Fat malabsorption
  ↓
  ↑ Osmotic load delivered to colon
  ↓
  Osmotic diarrhoea

<table>
<thead>
<tr>
<th>BRISTOL STOOL CHART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
</tr>
<tr>
<td>Type 2</td>
</tr>
<tr>
<td>Type 3</td>
</tr>
<tr>
<td>Type 4</td>
</tr>
<tr>
<td>Type 5</td>
</tr>
<tr>
<td>Type 6</td>
</tr>
<tr>
<td>Type 7</td>
</tr>
</tbody>
</table>
Osmotic diarrhoea v/s secretory diarrhoea

Secretory diarrhoea can be due to:
→ Toxigenic: E. Coli, V. Cholera.
→ Tumors: VIP secreting tumor

<table>
<thead>
<tr>
<th>Fasting</th>
<th>Osmotic diarrhoea</th>
<th>Secretory diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Stool osmolar gap</td>
<td>* Improvement with fasting</td>
<td>* No improvement with fasting</td>
</tr>
<tr>
<td>↓</td>
<td>* &gt;50 mosm/kg</td>
<td>* &lt;25 mosm/kg</td>
</tr>
</tbody>
</table>

(\[\text{measured osmolarity} - \text{calculated osmolarity}\])

=300 mosm/kg - a × (stool Na⁺ + K⁺)

(\[\text{Osmolar gap} < 25 \text{ mosm/kg}\])

* Factitious diarrhoea - Reduced stool osmolality

Small intestinal v/s large intestinal diarrhoea

<table>
<thead>
<tr>
<th>Small intestinal diarrhoea</th>
<th>Large intestinal diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Tö-Ileum</td>
<td>* Ulcerative colitis, Rectum Colitis</td>
</tr>
<tr>
<td>Crohn’s disease - Ileum</td>
<td>* Small volume with ↓ frequency</td>
</tr>
<tr>
<td>Toxigenic</td>
<td>* Blood, pus, mucus + + +</td>
</tr>
<tr>
<td>* Large volume with ↓ frequency</td>
<td>* No steatorrhea</td>
</tr>
<tr>
<td>* No blood, pus mucus</td>
<td>* Less chances of abdominal pain and vomiting</td>
</tr>
<tr>
<td>* Steatorrhea</td>
<td>* Tenesmus often present</td>
</tr>
<tr>
<td>* Abdominal pain and vomiting</td>
<td>urgency often present</td>
</tr>
<tr>
<td>* Tenesmus absent</td>
<td>urgency absent</td>
</tr>
</tbody>
</table>
Acute v/s chronic diarrhoea

- Acute diarrhoea. → < 14 days
  → mostly due to infections
- Chronic diarrhoea. → > 2 weeks

Organisms involved

- N/v/c/c for viral diarrhoea in children → Rotavirus
- N/v/c/c for viral diarrhoea in adults: Norovirus
- Severe ileitis resembling appendicitis: Yersinia enterocolitis
- Diarrhoea due to Campylobacter jejuni trigger Guillain Barre syndrome
  ↓
  Large intestinal diarrhea.

- Severe inflammatory diarrhea affecting all 4 layers
  ↓
  Colitis → Shigella, Dysenteriae (10^4 organisms sufficient)

- Staph aureus
  Bacillus cereus
  Clostridium perfringes → Preformed toxin

Preformed toxin – Staphylococcus

- Incubation period: 1-6 hrs
- Pork, canned meat, custard
- Vomiting is the prominent symptom with abdominal cramps
due to preformed toxins (vagal stimulation)
- Fever
  Hypotension
  Never seen
- Diarrhoea is rare
- No role of any antibiotics
Preformed toxin – bacillus cereus

- a forms of food poisoning:

  Incubation time:
  
<table>
<thead>
<tr>
<th>1-6 hrs</th>
<th>6-12 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>• Due to uncooked fried rice</td>
<td>• Due to pudding, meat balls dried potato</td>
</tr>
<tr>
<td>• Preformed toxin</td>
<td>• Toxin formed inside small intestine</td>
</tr>
<tr>
<td>• Vomiting predominant</td>
<td>• Diarrhea predominant</td>
</tr>
</tbody>
</table>

* Requires only conservative management

Enterotoxin pathogens

- Toxigenic diarrhoea / Small intestinal diarrhoea / Secretory diarrhea (Acute)

- m/C: Enterotoxigenic E.coli (ETEC)
  
  Vibrio cholera
  ↓
  
  Small intestinal diarrhea
  ↓
  
  • Large volume
  • Dehydration

- No invasion of mucosal surface
- Intestinal fluid loss due to toxin

Cholera

- Enterotoxin activates adenyl cyclase → ↑cAMP

  Responsible for toxigenic / Secretory diarrhea

- Toxin Coregulated Pilus (TCP) mediates attachment of vibrio to intestinal mucosa

- Inflammatory cells are absent in stool
Diarrhoea

- Secretory diarrhea
  \[\text{Toxin: - } \text{ETEC, V. Cholera}\]
  \[\text{Tumori: - VIP oma.}\]
  \[\downarrow\]
  Loss of $K^+$ and $HCO_3^-$
  \[\downarrow\]
  Hypokalemia with metabolic acidosis (Normal anion gap metabolic acidosis)
  \[\leftrightarrow\]
  Renal tubular acidosis (RTA)
  \[\rightarrow\]
  GI loss
  \[\leftrightarrow\]
  Positive anion gap
  \[\rightarrow\]
  Negative anion gap

- Ringer lactate is the fluid of choice in cholera.
- DOC: Doxycycline
  - DOC in pregnancy: Azithromycin

*Warning:* Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

**ETEC (Enterotoxigenic E.coli)**

- m/C/C for:
  1. Traveller's diarrhea.
  2. Community acquired diarrhea.
  3. Toxigenic diarrhea.

- Produces heat labile toxin (LT toxin)
  \[\downarrow\]
  Acts by increasing cyclic AMP

- EHEC (Entero hemorrhagic E.Coli) produces $O_{157}:H_{7}$
  \[\downarrow\]
  (Shiga like toxin)
  Hemolytic uremic syndrome
Causative organisms

- HUS → EHEC > Shigella dysenteriae
- Reactive arthritis → m1c worldwide: Chlamydia trachomatis
  m1c India: Shigella dysenteriae
- Bone marrow suppression → Salmonella
- GBS → Campylobacter jejuni
- Toxic megacolon → Clostridium difficile
- Aortitis endovascular infection → NTS (Nontyphoidal Salmonellosis)
- Intestinal hemorrhage → Salmonella
- Right lower quadrant tenderness → Yersinia
- Small bowel lymphoproliferative disorder → Campylobacter

Incubation period

- 1 to 6 hrs: Staph aureus
  B. cereus (vomiting) \{ Preformed toxin “heat stable”
- 8 to 16 hrs: B. cereus (diarrhea) → Toxin in GIT
  Cl. Perfringens → Preformed \{ Heat labile
- > 16 hrs: All other organisms

Pseudomembranous enterocolitis

- Clostridium difficile related enterocolitis
- Antibody most implicated in pseudomembranous
- Colitis: Cephalosporins
  Clindamycin
  Amox / Ampicillin
  Fluoroquinolones
- Toxin A: Enterotoxin (small intestine)
- Toxin B: Cytotoxin (large intestine)
Vibrio parahemolyticus

- Acute diarrheal disease with hemolysis following raw fish intake
- Hemolysis phenomenon on blood agar
- No role for antibiotics

Invasive colitis

- Small volume bloody diarrhea
- Abdominal cramps
- Fecal leukocytes
- Shigella / Salmonella / Yersinia / E. Jejuni / E. Histolytica
  ↓
  m/c
- Stool with inflammatory exudate containing neutrophils, mucus and blood
- Invasion by plasmid antigen
- Shigella enterotoxin can produce toxigenic diarrhea
  Invasive colitis - Plasmid mediated
- Shiga toxin → Cytotoxin → HUS
- Invasive diarrhea v/s UC
  Fecal WBC → Infection
  Markers for UC in stool: Fecal lactoferrin, calprotectin
- Doc for shigella: Ciprofloxacin
- Non typhoid salmonellosis
  ↓
  most dreaded complication: Aortitis/ Endovascular infection
- Perforation is the commonest complication of enteric fever
- Diarrhoea is seen in 2nd week of enteric fever
MALABSORPTION

Hallmark of malabsorption **steatorrhea**.
Steatorrhea is > 7g /24 hour fecal test
most prominent clinical manifestation is diarrhea.

**Basic physiology of absorption**

Villi are for absorption
Crypts for secretion
Intestine has -

   - Epithelial cells
   - Lamina propria
   - Muscularis mucosa

2] Submucosa.

3] Muscular layer
   - Outer longitudinal
   - Inner circular

   - Continuous removal of intestinal epithelial cells occur every 48-72hrs
   - Cylindrical structures surrounding villi are called **Crypts of Lieberkühn**
   - Alpha defensins, lysozymes, phospholipase A₂ are produced by Paneth cells
   - Luminal surface of small intestine has visible mucosal folds called **plica circularis**
   - Interstitial cells of Cajal are pacemaker cells of small intestine
   - Brunner's gland are submucosal glands in duodenum which secrete bicarbonate rich alkaline juice
   - Macroscopic lymphoid aggregates in ileum - **Peyer's patches**
Fat absorption

- Long chain fatty acids are predominantly absorbed in the jejunum

1 Bile acids
- Essential for micelle formation
- Formed in cytoplasm of hepatocyte
- 1° Bile acids
  - Cholic acid
  - Chenodeoxycholic acid
- 1° Bile acids are conjugated with Glycine & Taurine to form conjugated bile acids → Bile salts
- 500mg of bile acid is formed per day
- Rate limiting enzyme 7α hydroxylase
- Bile acid pool → 4g due to Enterohepatic circulation

Liver

Conjugated Bile acid

2nd part of duodenum

Form micelles and get absorbed into jejunum

Active transport of bile acid

Reaches ileum → colon → Acted upon by colonic bacteria.
- Deoxycholic acid
- Lithocholic acid (deconjugated bile acids)

- 500 mg formed per day

500 mg excreted per day

Pool size 4g is maintained
Problems (hits)

1. Bile acids
   1) Cirrhosis No bile acid fat malabsorption
   2) Bile duct
      • Primary biliary cirrhosis (autoimmune destruction of intrahepatic bile duct)
      • Primary sclerosing cholangitis [Abrosis of IHBD
         EHBD]
   3) Small intestinal bacterial overgrowth
      Lot of bacteria in small intestine ↑↑ deconjugate bile acid
      Conjugated bile acid is needed for micelle formation leading to fat malabsorption
   4) Ileal disease (Crohn's, T6)
      Defective enterohepatic circulation

II. Pancreas
   1) ↓ Pancreatic lipase (chronic pancreatitis) → (↓) lipolysis
      ↓
      TG is not broken into FA & glycerol

III. Intact small intestinal mucosa for absorption (jejunum)

Affected by
   1) Celiac disease
   2) Whipple disease
   3) Tropical sprue

IV. Esterification and chylomicron formation

Affected by
   - Abetalipoproteinemia

V. Delivery by lymphatics to tissues

Affected by - Intestinal lymphangiectasia.
   - If integrity of small intestinal mucosa is lost, all three absorptions are affected (fat, protein carbohydrate)
Comparison of long, medium, short chain FA

I. Short chain fatty acids (<8 carbon atoms)
   - Not a part of diet
   - Formed from unabsorbed carbohydrate in colon

II. Medium chain fatty acids (8-12 carbon atoms)
   - Only in small amount (e.g., coconut oil)
   - Doesn’t require lipolysis
   - No need for micelle formation
   - Completely absorbed in SI

III. Long chain fatty acids (>12 carbon atoms)
   - Major protein in diet
   - Requires lipolysis
   - Requires micelle formation

Bile acid diarrhea v/s Fatty acid diarrhea

<table>
<thead>
<tr>
<th>Bile acid diarrhea</th>
<th>FA diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light (mild) ileal disease where EHC is only mildly affected ↓</td>
<td>Osmotic diarrhea due to extensive ileal disease ↓</td>
</tr>
<tr>
<td>Compensated by increased bile synthesis from liver ↓</td>
<td>Ileal bile acid reabsorption is defective ↓</td>
</tr>
<tr>
<td>No malabsorption ↓</td>
<td>Liver not compensating by ↑ bile acid synthesis ↓</td>
</tr>
<tr>
<td>Diarrhea due to ↑ bile acid in colon (Bile acid ↑ osmolality of the stool ↓) (No response to low fat diet)</td>
<td>No conjugated bile acids ↓</td>
</tr>
<tr>
<td></td>
<td>Defective fat absorption ↓</td>
</tr>
<tr>
<td></td>
<td>Steatorrhea, osmotic diarrhea ↓</td>
</tr>
<tr>
<td></td>
<td>(Response to low fat diet)</td>
</tr>
</tbody>
</table>
Carbohydrate absorption

mostly absorbed as monosaccharides in jejunum
disease affecting jejunal mucosal integrity will affect all 3 absorptions

- Glucose > galactose absorbed by → SGLT sodium dependent
  glucose transporter-1
  (α⁺ active transport)
  (mutation) ↓
  Familial glucose galactose malabsorption syndrome

- Fructose is absorbed by GLUT 5 [facilitated diffusion]
  [SGLT 2 is present in PCT of kidney]

Lactose intolerance

Deficiency of lactase enzyme

Primary                          secondary
- Severe                         - Acquired
- From birth, diarrhea & failure to thrive
  - Acquired
- From birth, diarrhea & failure to thrive
  - IBS like symptoms +

Diagnosed by
- stool reducing substance > 10%
- Stool acidic pH

Diagnosis of carbohydrate malabsorption

1. urine d-xylene test
   - (best non-invasive test for carbohydrate malabsorption)
     (best non-invasive test overall → 24 hr fecal fat test )
     (best non-invasive test for fat malabsorption

xylene requires only an intact small intestinal mucosa for its absorption [∗· xylene is used]
Urinary D-xylose test

25g D-xylose

[Urine D-xylose excretion]

> 5g       < 4.5-5g
Normal    Positive D-xylose test

True +ve     False +ve
- Celiac disease  - Renal failure
- Whipple's disease  - 3rd space loss (ascites)
- Tropical sprue  - Vomiting
- Transit
- SIBO

Protein malabsorption

Predominantly absorbed in jejunum as amino acids

1. Hartnup disease
   Present with features of pellagra

2. Enterokinase deficiency
   Enterokinase is needed for activation of trypsin

3. Cystinuria
   Defective absorption of Cysteine / Ornithine / Lysine / Arginine

Diagnosis of protein malabsorption

Qualitative test

1. Stool chymotrypsin
2. Stool elastase
   Deficient

Quantitative test

1. 14C egg white breath test
   if 10% absorption
2. Phenol and p-cresol levels
   in urine
Other tests for fat malabsorption

- Stool fat by sudan III stain (Qualitative test)
- Acid steatocrit test
- ¹⁴C triolein breath test
- Lactose hydrogen breath test
  - Hydrogen in breath indicates carbohydrate malabsorption

[Gold standard for diagnosis of malabsorption – Small intestine mucosal biopsy]

Only 3 conditions are 100% diagnosed with diffuse specific findings
  1) Whipple
  2) Abetalipoproteinemia
  3) Agammaglobulinemia

Schilling test

Step 1 → 1000 μg of unlabelled Vit B₁₂
  (to saturate stores)
  ↓
  with (or) soon after 1 mg of radiolabelled Vit B₁₂
  ↓
  urinary excretion in 24 hrs
  ↓
  > 10% of radiolabelled Vit B₁₂ ☑
  < 7% → Positive → Vit B₁₂ malabsorption
Step 2a → Give intrinsic factor and repeat the test

- Normal
- Deficiency of IF
  - Pernicious anemia
- Still abnormal
  - Step 2b
    - Give pancreatic enzymes and repeat the test
      - Abnormal
        - Step 2c
          - Normal 
          - Abnormal
            - Think of ileal disease
              - Give antibiotic
                - Repeat the test
                - Normal → SI60

Symptoms of malabsorption

1. GI Symptoms
   - Diarrhea
     - ↑ Osmotic load
     - Defective secretory effect of bile acid surface
       - Abdominal distension
         - Gaseous distension (due to action of bacteria on unabsorbed CHO)
         - Fluid distention (due to hypoproteinemia due to protein loss)
           - Abdominal discomfort
           - Foul smelling stools (due to malabsorption of proteins)

2. Musculoskeletal symptoms
   - Bone pain
   - Osteomalacia → Vit D deficiency
   - Fracture (#)
Clinical features

1. Acanthocytes on peripheral smear
2. Neurological features
3. 100% diagnosed by post prandial biopsy
4. Steatorrhea
5. Histology $\rightarrow$ vacuolation within enterocytes

**Intestinal lymphangiectasia**

1. Congenital $-$ multiple lymphatics involved
2. Acquired $-$ a$^o$ to infection
   
   Present as protein losing enteropathy
   $\rightarrow$ Hypoproteinemia.
   $\rightarrow$ Edema.
   $\rightarrow$ Fat malabsorption (steatorrhea).

Diagnosed by $\alpha$, antitrypsin in stool
4. Tetany
5. Paraesthesia.
6. muscle weakness → d/t deficiency of Ca, mg, P

III. Cutaneous
1. Easy bruisingability → d/t deficiency of vit K
2. Ecchymosis
3. Neuropathy
4. Ataxia
5. Night blindness
6. Follicular hyperkeratosis
7. Acrodermatitis enteropathica → d/t deficiency of Zinc
8. Hyperpigmented dermatitis → d/t deficiency of Niacin
9. Perifollicular haemorrhage → d/t deficiency of vit C

IV. Miscellaneous
1. Weight loss + fatiguability + edema + ascites + muscle wasting + d/t loss of protein [ ID - Nephrotic syndrome]
2. Anemia

   (Iron deficiency anemia) (vit B12 deficiency)
   small intestine pathology
   megaloblastic anemia

3. Oxalate stones in kidney (Oxalate not chelated with Ca^{2+} as Ca^{2+} binds to fatty acid)
4. Peripheral neuropathy (d/t vit B12 (or) E deficiency)

Abetalipoproteinemia 01:13:14
- Defect in fat absorption
- Defective chylomicon formation
  d/t absent β-lipoprotein (Apo B48)
  ↓
  Hypolipidaemia.
CELIAC DISEASE, WHIPPLE'S DISEASE & TROPICAL SPRUE

Celiac Disease:

Also known as: Celiac sprue
Non-tropical sprue
Gluten sensitive enteropathy

It affects: Proximal small intestinal mucosa (Duodenum & jejunum)

Chief antigen: Gliadin

It is completely reversible within 6 months of gluten restriction
(both clinically & histologically)

If not reversible → It is known as Refractory Celiac disease.

Celiac disease is also known as Iceberg disease

Genetic susceptibility HLA - DQα or DQβ

Intestinal mucosal abnormality

Classical celiac disease - present with malabsorption

Atypical celiac disease - presents with symptoms other than malabsorption

Silent celiac disease - asymptomatic, but serologically positive

Latent celiac disease - serologically -ve, but genetic susceptibility

(Genes associated are:
Healthy (HLA - DQα or Individuals HLA - DQβ)
Signs of malabsorption:

malabsorption

- Cutaneous
- Musculoskeletal
- Diarrhoea
- Abdominal distension
- Foul smelling stool
- Ascites

Atypical celiac disease

Patients present with symptoms other than malabsorption and can present at any age.

Atypical symptoms:
- a) Short stature & failure to thrive
- b) Unexplained Fe deficiency anemia
- c) Unexplained osteopenia
- d) Ataxia, peripheral neuropathy due to vitamin-E
- e) Associated with hypoplaspin
- f) ↑ LFT

Diagnosis of celiac disease

Diagnosis is by biopsy & serology.

Biopsy Findings: (non-specific)
1) Findings localised to mucosa.
   a) Villous atrophy
   b) Crypt hyperplasia
   c) Mucosal thickness normal
   d) Lamina propria infiltrates
   e) Vacuolar degeneration of surface epithelium may be seen

Serology:
1) Antigliadin antibodies (IgG, IgA) - non sensitive
   non specific not used now
2) Anti Endomysial antibodies (IgA)
   - done by Indirect Immunofluorescence
   - Best sensitivity & specificity
   - Labour intensive & costly

3) Anti Tissue Transglutaminase antibody (IgA)
   - done routinely
   - done by ELISA

Diagnosis flowchart:

- Positive biopsy → Celiac
- Negative biopsy → Repeat biopsy
- Negative serology → Not celiac
- Positive serology → Celiac

Disorders associated with celiac:

1) Dermatitis herpetiformis
2) Type 1 DM
3) IgA nephropathy
4) Bird fancier's lung
5) Down's syndrome
6) Hypo or hyperthyroidism
Treatment of Celiac disease:
- Gluten restriction
  ↓
  If not reversible within 6 months
  ↓
  Refractory Celiac disease
  ↓
  Treat - with steroids

3 Potential dangerous complications:
- Enteropathy associated T-cell lymphoma.
- Small intestinal adenocarcinoma.
- Esophageal Squamous cell carcinoma.

Can eat: rice, corn, maize, potato, soybean.
Must not eat: wheat, barley, rye, oats

Whipple’s Disease

Chronic multi system disease:
  Involves: Small intestine - involves (Proximal + distal)
  CNS
  CVS
  Joints.

It involves a Gram positive bacteri: Actinobacteria.
  - Tropheryma whipplei
    ↓
    Can’t be cultured, Slow doubling time

- Male > Females
- More common in 50-60 yrs of age
- Associated with HLA DRB1 13, HLA DQB1 06

1) Small intestine - Malabsorption (Distal > proximal)
   ↓
   Vit B12 deficiency
   → Lymphadenopathy

2) CNS involvement
   - More common in relapse
   - CNS involvement in relapse - Bad prognosis
   - M/C Finding - Dementia (progressive)
     and M/C finding - Progressive Supranuclear palsy
   - Opsoclonus myoclonus
   - Myorhythmias (Occulo - masticatory
     Occulo - facial)
3) CVS
   a common vs. culture negative endocarditis
   mc cause of culture negative endocarditis - HACEK

4) Joints:
   - Small joints migratory intermittent polyarthritis

Diagnosis of Whipple’s

- Upper GI endoscopy with small intestinal mucosal biopsy
- It shows gram positive organisms
  which are PAS positive inside macrophages in lamina propria.
- PCR assay to detect T. whipple

Treatment of Whipple:

Induction: Ceftriaxone
            or       + Streptomycin
            Penicillin G
Maintenance: Cotrimoxazole
            (to prevent relapse) (cotrimoxazole used due to its good CNS penetration)

Tropicalsprue

m/c cause of malabsorption in India
- Panintestinal involvement
- Toxigenic coliform organisms are involved
  - Like Ecoli
  - Klebsiella
  - Enterobacter
- Presents with features of malabsorption
  + Vit B12 deficiency
    ↓
    (Hyperpigmentation of hands)
- Biopsy is similar to Celiac disease.
- In Celiac disease - Biopsy ⊗ but serology negative

\[ \downarrow \]

Could be tropical sprue

- Treatment: Folic acid + Tetracycline.
INFLAMMATORY BOWEL DISEASE

- It includes four entities
  1) Ulcerative colitis
  2) Crohn’s Disease
  3) Microscopic colitis
  4) Diversion colitis
- Behcet’s disease in rheumatology behaves as Crohn’s Disease

Inflammatory bowel disease

- Most commonly affects Jewish
- Least commonly affects Asians
- Occurrence Crohn’s Disease > ulcerative colitis
- More common in males > females
- Usually at 15-30yr Age - 1st episode starts
- Some cases diagnosed at 70 - 90 yrs
- Always characterized by remissions and relapses
- In females
  Ulcerative colitis > Crohn’s Disease
  - Smoking
  - Appendectomy
  - Oral contraceptive pills
  - Familial concordance

Note: Smoking & Appendectomy are protective factors for UC

Causative Factor for Crohn’s Disease:
- Smoking
- Antibiotic use within 1st one year of life increases the risk of IBD by 3 times
- α-Methyl Dopa use associated with occurrence of ulcerative colitis
<table>
<thead>
<tr>
<th>TABLE</th>
<th>EPIDEMIOLOGY OF IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>Incidence (North America) per person-years</td>
<td>0.193 per 100,000</td>
</tr>
<tr>
<td>Age of onset</td>
<td>second to fourth decades and seventh to ninth decades</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Jewish &gt; non-Jewish &gt; African American &gt; White, Hispanic &gt; Asian</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>0.51-1.58</td>
</tr>
<tr>
<td>Smoking</td>
<td>May prevent disease (odds ratio 0.58)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>No increased risk</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Protective (risk reduction of 15-25%)</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>4-18% concordance</td>
</tr>
<tr>
<td>Dizygotic twins</td>
<td>0-8% concordance</td>
</tr>
<tr>
<td>Antibiotic use in the first year of life</td>
<td>2.9 x the risk of developing childhood IBD</td>
</tr>
</tbody>
</table>

Genetic disorders associated with IBD

1) Turner syndrome
   - Both ulcerative colitis and Crohn’s disease

2) Hermansky-Pudlak syndrome - Autosomal Recessive
   a) Granulomatous colitis
   b) Platelet functional defects
   c) Oculocutaneous albinism
   d) Pulmonary fibrosis

3) Glycogen storage disease type 1 (von Gierke’s Disease)

4) Wiskott-Aldrich Syndrome
   - Due to WASP gene mutation on X - Chromosome
   - Recurrent eczema
5) IPEX syndrome - Immunodysregulation Polyendocrinopathy Enteropathy X-linked

- Loss of Fox P3
  - Fox P3 \rightarrow \text{Transcription regulating factor}
  - Cell-mediated immunity
    - which mediates tolerance
- T-regulatory cells identified by
  - CD3 \rightarrow \text{Pan T-cell marker}
  - CD4 \rightarrow \text{T-helper cell marker}
  - CD25 \rightarrow \text{T-regulatory cell}
- T-regulatory cells have an antigen \rightarrow \text{Fox P3}
  - Loss of Fox P3
    - Loss of T-regulatory cells
      - Autoimmune inflammation
- It includes
  - Ulcerative colitis
  - Type 1 Diabetes mellitus
  - Dermatitis
- Most powerful anti-inflammatory cytokine \rightarrow \text{IL-10}
- Deficient IL-10 \rightarrow \text{Early onset refractory IBD}
<table>
<thead>
<tr>
<th>Name</th>
<th>Genetic Association</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner's Syndrome</td>
<td>Loss of part or all of X chromosome</td>
<td>Associated with UC and colonic CD</td>
</tr>
<tr>
<td>Hermansky-Pudlak Syndrome</td>
<td>Autosomal recessive Chromosome 10q33</td>
<td>Granulomatous colitis, ocuolocutaneous albinism, Platelet dysfunction, Pulmonary fibrosis</td>
</tr>
<tr>
<td>Wiskott Aldrich Syndrome (WAS)</td>
<td>X-linked recessive disorder, loss of WAS protein function</td>
<td>Colitis immunodeficiency, Severe platelet dysfunction, and thrombocytopenia</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>Deficiency of the Glucose-6-phosphate transport protein type B1</td>
<td>Granulomatous colitis, presents in infancy with hypoglycemia, growth failure, hepatomegaly, and neutropenia</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>Loss of FoxP3 transcription factor and T regulatory cell function</td>
<td>UC like autoimmune enteropathy, with endocrinopathy (neonatal type 1 diabetes or thyroid), dermatitis</td>
</tr>
<tr>
<td>Early onset IBD</td>
<td>Deficient IL-10 and IL-10 receptor function</td>
<td>Severe, refractory IBD in early life</td>
</tr>
</tbody>
</table>

**Etiopathogenesis of IBD**

Crohn's Disease:

- Genetically Susceptible individuals
- **NOD-2** gene on chromosome 16 mutation

1) Defective clearance of intracellular bacteria.  
   * Mycobacterium paratuberculosis

- Our innate immune system easily clears *Mycobacterium paratuberculosis*
- This explains the association of *Mycobacterium paratuberculosis* with Crohn's disease
a) Paneth cells are defective:
• Paneth cells are responsible for defence
• They secrete Lysosome, Proteases etc.,
• So, innate immunity is not acting
  Resulting in hyperactivity of adaptive immunity (Th1 response)

3) Defective Autophagy:
  Also results in hyperactivity of adaptive immunity along

---

**Ulcerative colitis**

- 50% → rectal involvement → Proctitis
- 30-40% → Rectum + sigmoid colon → Proctocolitis
- 10-20% → Complete colon → Pancolitis

- Of these 10% cases of pancolitis have ileal involvement
  ↓
  Backwash ileitis

- 'Continuous' involvement

**Gross features of ulcerative colitis**

1) Superficial inflammation of mucosa and submucosa.

2) 1st change → Erythematous mucosa with fine granular surface

3) Hemorrhage, edema, ulceration of mucosa.
   ↓
   Inflammatory polyps due to epithelial regeneration
   ↓
   Pseudo polyps

4) Atrophic featureless, short and narrow colon
   ↓
   Lead pipe or pipestem colon
   With no haustrations
Radiology:

Lead pipe colon - rigid, ahustral appearance of colon - Chronic ulcerative colitis

Lead pipe sign - describes the rigid and featureless appearance of the colon in chronic ulcerative colitis. The sign is due to a complete loss of haustral markings and usually a degree of uniform luminal narrowing due to chronic bowel wall thickening.

Microscopic features:

![Microscopic Image](image)

**FIGURE** medium-power view of colonic mucosa in ulcerative colitis showing diffuse mixed inflammation, basal lymphoplasmacytosis. Crypt atrophy and irregularity, and superficial erosion these features are typical of chronic active ulcerative colitis.
• Superficial inflammation - mucosa/submucosa
• Loss of crypt architecture
• Cryptitis - non-specific
• Basal plasma cells and lymphoid aggregates
• Paneth cell metaplasia

**Crohn's disease**

• Can involve any part of GIT
• Characterised by skip lesions
• Transmural involvement
• 30-40% has ileitis
• 40-50% has ileocolitis
• 15-20% has colitis
• Most common pattern -

**Macroscopy of Crohn's disease**

• Segmental involvement with skip lesions
• Earliest findings are Aphthous ulcers

**Aphthoid ulcers**
(target sign)

• Pathology: Mucosal ulcers with surrounding translucent mound of edema.

• Linear serpiginous ulcers
• Stellate ulcers will fuse longitudinally & transversely to leave behind areas of uninvolved mucosa.

↓
Cobble - stone appearance
• Major complications
  a) Thickening of bowel wall and fissures, fistula and abscess
     ↓
     Which will lead to strictures & fibrosis
     ↓
     Garden hose or hose pipe appearance
  b) Thickened mesentery encasing bowel wall
     ↓
     Creeping mesenteric fat

Microscopy of Crohn’s disease

1) Transmural involvement
  a) Non Caseating granuloma seen in any layer or uninvolved
     bowel or extraintestinal
  b) Mesenteric adenopathy
  c) Pyeloric metaplasia
  d) Lymphoid aggregates
  e) Cryptitis

Clinical features of ulcerative colitis

Proctitis: Fresh bleeding per rectum
     or
     Blood streaked on to the surface of hard stool

Proctocolitis:
     Large bowel diarrhoea.
     ↓
     Small volume frequent stools with blood,
     Pus, mucus and Tenesmus

Pancolitis
• Clinical examination is almost normal
• Systemic Symptoms like fever, weight loss rarely
• Velveting edematous rectal mucosa.
• 90% cases have relapsing course
• Fecal lactoferrin
• Fecal calprotectin

} Elevated in ulcerative colitis
Endoscopy of ulcerative colitis

- Symmetrical and continuous inflammation
- Erythematous mucosa with decreased vascularity
- Hemorrhage and ulcers in mucosa
- Inflammatory pseudopolyps
- Loss of hystations, shortening & narrowing of colon

↓

Lead pipe or pipestem appearance

<table>
<thead>
<tr>
<th>Endoscopic criteria for mayo score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 points</strong></td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>↓ vascularity</td>
</tr>
<tr>
<td>Mild friability</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Pseudopolyps in ulcerative colitis
Radiology of ulcerative colitis

- Fine mucosal granularities
- Serrations producing hazy margins
- Superficial ulcers
  ↓
  Deep ulcers
  Collar button ulcer
  Or
  Collar stud ulcer

- Loss of haustrations, short and narrow colon
  ↓
  LEAD PIPE
  or
  PIPESTEM Appearance

Lead pipe sign - describes the rigid and featureless appearance of the colon in chronic ulcerative colitis. The sign is due to a complete loss of haustral markings and usually a degree of uniform luminal narrowing due to chronic bowel wall thickening.
Clinical features – Crohn’s disease

- Ileocolitis along with systemic symptoms (Low grade fever, weight loss)
- Due to presence of systemic symptoms, most often this disease diagnosis is confused with Tuberculosis
- Episodes of right lower quadrant pain relieved by diarrhoea
- More of small intestinal diarrhoea
- Features of malabsorption – no bile acid absorption, enterohepatic circulation is defective
- Main complication in Crohn’s Disease
  ↓
  Due to Thickening of Bowel wall
  1) Obstruction
  a) Stricture
  3) Fissure
  4) Abscess
  5) Fistula → Extravesical
    Perianal

- On Abdominal examination
  Inflammatory mass palpable

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Endoscopy & Radiology - Crohn’s disease

Endoscopy:
- Aphthous ulcers
- Cobble stone appearance
- Fissure, fistula and fibrosis etc

Radiology :
- 1st finding – Aphthous ulcers – Target sign
Aphthoid ulcers
(target sign)

- Pathology: Mucosal ulcers with surrounding translucent mound of edema

Findings - Fissure ulcers - Rose thorn appearance

Fissure ulcer
(Rose thorn appearance)

- Pathology: Transmural ulcers

String sign
Based on degree of severity of disease (ulcerative colitis)

Truelove and Witts classification of the severity of ulcerative colitis

<table>
<thead>
<tr>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 stools/day, without or with only small amount of blood</td>
</tr>
<tr>
<td>No fever</td>
</tr>
<tr>
<td>No tachycardia</td>
</tr>
<tr>
<td>Mild anemia</td>
</tr>
<tr>
<td>ESR &lt; 30 mm/hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate between mild and severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 stools/day, with blood</td>
</tr>
<tr>
<td>Fever &gt; 37.5°C</td>
</tr>
<tr>
<td>Heart rate &gt; 90 beats/min</td>
</tr>
<tr>
<td>Anemia with hemoglobin level &lt; 75% of normal</td>
</tr>
<tr>
<td>ESR &gt; 39 mm/hr</td>
</tr>
</tbody>
</table>

ESR - erythrocyte sedimentation rate

Severe ulcerative colitis:

- Fever
- Tachycardia
- Anemia
- ↑ ESR
- >6 Bloody stools
Crohn’s Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate Crohn’s disease</td>
<td>People with mild to moderate Crohn’s are able to eat food normally without dehydration, fevers, stomach pain, blockages in their intestine, or losing more than 10% of their body weight</td>
</tr>
<tr>
<td>Moderate to severe Crohn’s disease</td>
<td>People are considered to have moderate to severe Crohn’s if they do not respond to treatment for mild to moderate Crohn’s or if they have high fever, significant weight loss, stomach pain or tenderness, occasional nausea or vomiting or significant anemia.</td>
</tr>
<tr>
<td>Severe Crohn’s disease</td>
<td>People with severe crohns have symptoms despite taking steroids, or they have high fevers, persistent vomiting, blockages in their intestine, or an abscess.</td>
</tr>
</tbody>
</table>

Severe Crohn’s Disease

- Symptoms despite taking steroids
- Fever, vomiting, obstruction and abscess

Extra intestinal manifestations – IBD

- Always more common in Crohn’s disease than ulcerative colitis
- With two exception which is more common in ulcerative colitis
  1) Pyoderma gangrenosum
  2) Primary Sclerosing cholangitis (PSC)
    - 3/4 patients of PSC will have ulcerative colitis
    - But 5% with ulcerative colitis will have PSC

1. SKIN:
   - Erythema nodosum
   - Pyoderma gangrenosum

2. Ocular:
   - Episcleritis
   - Uveitis

3. Arthritis:
   - Ankylosing Spondylitis
   - Large joint migratory Asymmetric PolyArthritis (LMPA)
IV stones:
  - Gall stones
  - Renal stones

v) Thromboembolism:
  - Dangerous complication

  - Extraintestinal manifestation which correlate with relapse in IBD
    - Erythema Nodosum
    - Episcleritis
    - LMN

Serology – IBD

In Crohn's Disease:

1) ASCA
   - Anti – Scharomyces cerevisiae Antibody
   - Used for screening
   - Linked to early complication in Crohn’s Disease
   - Also positive in Crohn’s disease

2) OMP – C
   - Outer membrane Protein

3) APA
   - Anti – pancreatic Antibody

4) Antiflagellin

5) Anti 1α → Correlates with risk for surgery

In ulcerative colitis:

1) P-ANCA → levels correlate with relapse

2) Antibody cell Antibody

[Images of Pyoderma gangrenosum and Erythema nodosum]
Treatment of ulcerative colitis

5-Amino-salicylic Acid — mainstay of treatment is sulfasalazine

- It is a combination of
  5- Amino Salicylic Acid + Sulfapyridine
    (Active moiety)          (Carrier molecule)

- 5-Amino-salicylic Acid gets absorbed in small intestine before it reaches the disease site (colon)

- To prevent its absorption, it is clubbed with the carrier molecule Sulfapyridine

- But because of complications due to sulfa molecule so, not used now

- Delayed release 5-Amino-salicylic Acid are used now
  ↓
  mesalamine (Oral & Topical)

Induction Therapy:

1) mild ulcerative colitis
   5-Amino-salicylic Acid (Topical or oral)

2) moderate ulcerative colitis
   5-Aminosalicylic Acid
   +
   Steroids

   Steroid refractory cases — Azathioprine or 6-mercaptopurine

3) Severe ulcerative colitis
   IV steroids
   +
   IV cyclosporine or infliximab
Induction therapy for ulcerative colitis based on disease severity

**Mild disease**
- 5-Aminosalicylates
  - Topical (distal colitis)
  - Oral (distal/extensive colitis)
  - Combination

**Moderate disease**
- 5-Aminosalicylates
  - Topical (distal colitis)
  - Oral (distal/extensive colitis)
  - Combination
- Glucocorticoids
  - Topical (distal colitis)
  - Oral (distal/extensive colitis)
  - Combination
- Azathioprine or 6-mercaptopurine

**Severe disease**
- IV
- Glucocorticoids
- IV cyclosporine
- IV infliximab

---

**Table: Oral 5-ASA Preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Formulation</th>
<th>Delivery</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MESALAMINE (400, 800 mg) (Delticol, Asacol HD)</td>
<td>Eudragit S (PH 7)</td>
<td>Distal ileum-colon</td>
<td>2.4-4.8 g, 6-1.8 g</td>
</tr>
<tr>
<td>MESALAMINE (1.2 g) (Lialda)</td>
<td>MMX mesalamine (SP04%)</td>
<td>Ileum-colon</td>
<td>2.4-4.8 g</td>
</tr>
<tr>
<td>Methylcellulose microgranules</td>
<td>Stomach-colon</td>
<td>0.4 g (a)</td>
<td>15-4</td>
</tr>
<tr>
<td>MESALAMINE (250, 500, 1000 mg) (Pentasa)</td>
<td>Intelicor extended-release mechanism</td>
<td>Ileum-colon</td>
<td>1.5 g (na)</td>
</tr>
</tbody>
</table>
maintenance Therapy

1) mild ulcerative colitis:
   5-Aminosalicylic Acid
   alone

2) moderate ulcerative colitis:
   5-Aminosalicylic Acid
   +
   Azathioprine
   or
   6-mercaptopterine

3) severe ulcerative colitis:
   5-Aminosalicylic Acid
   +
   Azathioprine
   +
   Infliximab

Table: Indications for surgery in patients with ulcerative colitis

   Colonic dysplasia or carcinoma
   Colonic hemorrhage, uncontrollable
   Colonic perforation
   Growth retardation
   Intolerable or unacceptable side effects of medical therapy
   Medically refractory disease
   Systemic complications that are recurrent or unmanageable
   Toxic megacolon
Surgery in ulcerative colitis:
Total proctocolectomy with ileo-anal anastomosis

- If ulcerative colitis associated with primary sclerosing cholangitis, cholangiocarcinoma can occur
- Risk of cholangiocarcinoma persists even after colectomy

On Biopsy:
Two Possibilities:
1) Dysplasia, Associated lesion or mass (DALM)
   a) Flat Dysplasia

```
DALM
  /       \
/         \   
Adenoma-like DALM  Non-adenoma-like DALM
  \   /     \       /     \
       Follow algorithm for the management of polypoid lesions (see Figure 8.2-2)
     /               \
  Colectomy          Colectomy

Low-grade dysplasia

High-grade dysplasia

mutilocal
Colectomy
unilocular
Colectomy

Repeat colonoscopy within 6 months

Indefinite dysplasia

Repeat Colonoscopy within 6 months

No dysplasia

Continued surveillance

Dysplasia?

Yes

Colectomy

No

Repeat colonoscopy at frequent intervals

* Ideal frequency has not been determined
```
Treatment of Crohn's disease

1) Mild disease:
   Oral budesonide 9mg/day
   +
   5-Aminosalicylic acid (5-ASA)

• Maintainance with 5-ASA
• Oral budesonide is delayed released preparation

So, percentage of active drug in the blood is very less
No steroid related side effects or very less

2) Moderate to severe disease:
   Steroid (Oral or iv)
   +
   Azathioprine or 6-mercaptopurine

• If remission achieved, then maintain with
  Azathioprine or 6-mercaptopurine
  +
  Low dose methotrexate

• If remission not achieved
  Start Anti-TNF-α
  ↓
  If remission achieved
  ↓
  Maintain with Azathioprine + Anti-TNF-α

• Monoclonal antibody approved against α4 integrin
  ↓
  Natalizumab

• Antibiotics are always given in Crohn's disease
• Crohn's disease has risk of carcinoma colon
• Also has risk of Leukemia / Lymphoma.
• Carcinoma colon risk is more in ulcerative colitis than Crohn's disease
### Important tables

#### Different clinical, Endoscopic, and Radiographic

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross blood in Stool</td>
<td>Yes</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Mucus</td>
<td>Yes</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Occasionally</td>
<td>Frequently</td>
</tr>
<tr>
<td>Pain</td>
<td>Occasionally</td>
<td>Frequently</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant perineal disease</td>
<td>No</td>
<td>Frequently</td>
</tr>
<tr>
<td>Fistulas</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Small intestinal Obstruction</td>
<td>No</td>
<td>Frequently</td>
</tr>
<tr>
<td>Colonic obstruction</td>
<td>Rarely</td>
<td>Frequently</td>
</tr>
<tr>
<td>Response to antibiotics</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrence after surgery</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ANCA-positive</td>
<td>Frequently</td>
<td>Rarely</td>
</tr>
<tr>
<td>ASCA-positive</td>
<td>Rarely</td>
<td>Frequently</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>Rarely</td>
<td>Frequently</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Rectal soaring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous disease</td>
<td>Yes</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Cobblestoning</td>
<td>Yes</td>
<td>Frequently</td>
</tr>
<tr>
<td>Granuloma on biopsy</td>
<td>No</td>
<td>Occasionally</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiographic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel significantly abnormal</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal terminal ileum</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Segmental colitis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Asymmetric colitis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stricture</td>
<td>Occasionally</td>
<td>Frequently</td>
</tr>
</tbody>
</table>

**Differentiating Crohn’s colitis from ulcerative colitis:**

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>CROHN’S COLITIS</th>
<th>ULCEERATIVE COLITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal lesion</td>
<td>Aphthous ulcer are Common in early disease; late disease is notable for stellate, raking, bear claw, linear, or serpiginous ulcers and cobblestoning</td>
<td>Micro ulcer are more common, but larger ulcers are possible. Pseudo polyps are more common</td>
</tr>
<tr>
<td>Distribution</td>
<td>Often discontinuous and asymmetrical with skipped segment of normal intervening mucosa, especially in early disease</td>
<td>Continuous, symmetrical and diffuse, with granularity or ulceration found in entire involved segments; however, periappendiceal inflammation (cecal patch) is common, even when the cecum is not involved</td>
</tr>
<tr>
<td>Rectum</td>
<td>Complete, or more often relative, rectal sparing</td>
<td>Typically involved with proximal distribution</td>
</tr>
<tr>
<td>Ileum</td>
<td>Often involved (approximately 75% of case)</td>
<td>Not involved except as backwash ileitis in pan ulcerative colitis</td>
</tr>
<tr>
<td>Depth of Inflammation</td>
<td>Mucosal, submucosal, and transmural</td>
<td>Mucosal, transmural only in fulminant disease</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Serosal findings</td>
<td>Marked erythema and creeping Fat (the latter is virtually pathognomonic)</td>
<td>Absent except in severe colitis or toxic megacolon</td>
</tr>
<tr>
<td>Perianal complications</td>
<td>Often prominent including large and skin tags, deep fissure, perianal fistula, that are often complex</td>
<td>Not prominent (fissure or fistula if present should be uncomplicated)</td>
</tr>
<tr>
<td>Strictures</td>
<td>Often present</td>
<td>Rarely present suggest adenomas or cancer</td>
</tr>
<tr>
<td>Fistulas</td>
<td>Perianal enterocutaneous, rectovaginal enterovesiculat and other fistula may be present</td>
<td>Absent except for rare occurrence of rectovaginal or perianal fistula</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Granulomas are present in 15%-60% of patient (higher frequency in surgical specimens than in mucosal punch biopsies)</td>
<td>Granulomas should not be present (microgranulomas may be associated with ruptured crypt abscess)</td>
</tr>
<tr>
<td></td>
<td>crypt abscesses may be present</td>
<td>crypt abscesses and ulcers are the defining lesion</td>
</tr>
<tr>
<td></td>
<td>Focally enhanced inflammation often on a normal background is The hallmark</td>
<td>Ulceration on a background of inflamed mucosa</td>
</tr>
<tr>
<td>Serology</td>
<td>pANCA in 20%-25% ASCA in 41%-76%</td>
<td>pANCA in 60%-65% ASCA in 5%</td>
</tr>
</tbody>
</table>
Short bowel syndrome

- Due to resection of varying lengths of intestine
- Which results in malabsorption
- Most common cause in children is Necrotising Enterocolitis
- In adults is
  1) Mesentric vascular disease
  2) Crohn's disease
- Manifestation depends on the part of small intestine that is removed

Classical features

1) Hyperoxaluria:

- Unabsorbed Long-Chain Fatty Acids (LCFA)
  \[ \text{Binds with Ca}^{++} \]
  \[ \text{Resulting in free oxalates} \]
  \[ \text{Oxalates absorbed and excreted by kidney} \]
  \[ \text{Results in Hyperoxaluria} \]
a) Cholesterol gall stones:
  • Seen in ileal resection
  • Which is usually done in Crohn’s disease tuberculosis
  • Defective bile acid absorption
    ↓
  • Results in defective entero hepatic circulation
    ↓
  • Formation of cholesterol gall stones

b) D-Lactic Acidosis
  • Normally, D-lactate is not formed in the body
  • Due to Presence of unabsorbed carbohydrates and proteins in colon
    ↓
  Decreases the colonic pH
    ↓
  Changes the bacterial milieu of colon
    ↓
  Normally, good bacteria like Bacteroides fragilis
    • yet killed and unnecessary coliform starts to grow
    ↓
  These coliforms result in excess D-lactate formation
    ↓
  D-lactate absorbed from colon
    ↓
  Which can cause neurological features

4) Hypergastrinemia:
  • Normally, small intestinal hormones keep a check on Gastrin secretion (inhibits)
  • Acid from parietal cell can also keep a check on Gastric secretion (inhibits)
  • In small intestinal resection, all these hormones which inhibit Gastrin are absent
  • Acid is not being secreted from parietal cell
  • So, Antrum produces lots of Gastrin → Hypergastrinemia
- Loss of duodenum → Fe absorption defective
- Loss of jejunum → Ca\(^{2+}\) / Folate / ADEK absorption defective
- Loss of ileum → Loss of Bile Acid / vit-\(B_{12}\)

- Loss of ileocecal valve
  \downarrow
  Results in bacteria migration from colon to small intestine
  \downarrow
  Results in SIBO (Small Intestinal Bacterial Overgrowth)

- Deficiency of vitamin-K is rare
  \downarrow
  Because Bacteria can Synthesize vitamin K

Management:

- Depends on colon

  Colon present
  \downarrow
  Complex carbohydrates
  35 Kcal/kg/day + fibre
  \downarrow
  Gets converted into short chain fatty acids in the colon and gets absorbed
  \- Intact Protein
  \- medium chain Triglycerides

  Colon Absent
  \- Intact Protein
  \- Long chain triglycerides
  \- But, most often
  \- Total parental Nutrition is given

- Drugs approved – GLP-1 Analogue – Teduglutide
  \downarrow
  maximally slows the transit time
  \downarrow
  more time for absorption
SIBO (Small Intestinal Bacterial Overgrowth)

- Also known as Stagnant bowel syndrome/ Blind loop Syndrome
- Jejunal Aspirate of $> 10^6$ CFU/ml
- Most common organism - Enterobacteriaceae Pseudomonas
- In case of Enterobacteriaceae Pseudomonas, jejunal aspirate of $> 10^5$ CFU is enough

Causes:
1) Altered anatomy:
   - Short bowel syndrome
   - Any surgery which results in ileocecal valve loss
   - Blind loops
   - Jejunocolic fistula
   - Diverticula

2) Dysmotility:
   - Diabetes mellitus
   - Scleroderma
   - Hypothyroidism

3) Hypochlorhydria:
   - In case of long-term acid suppression

4) Immunodeficiency Conditions:
   - HIV

5) Multifactorial:
   - Coeliac disease
   - Parkinsons disease
   - Bacterial overgrowth in small intestine
     \[ \downarrow \]
     These bacteria deconjugate the conjugated bile acids
     \[ \downarrow \]
     So, no conjugated bile acids in small intestine
     \[ \downarrow \]
     No micelle formation
     \[ \downarrow \]
     Fat malabsorption
     \[ \downarrow \]
     Patient presents with diarrhea and steatorrhea.
• Bacteria utilizes vitamin-\( \theta_{13} \)
  \[ \downarrow \]
  Patient presents with Macrocytic Anemia
  Cobalamine deficiency

• These bacteria also synthesize folate & vitamin K
  • \( \uparrow \) Folate levels
  • \( \uparrow \) Vitamin K levels

Diagnosis:
1) Jejunal Aspirate:
   • \( > 10 \text{ CFU/ml} \Rightarrow \text{Gold standard} \)

a) Lactose hydrogen breath test:
   Due to bacterial overgrowth in small intestine
   \[ \downarrow \]
   Carbohydrate are metabolised in small intestine by these bacteria
   \[ \downarrow \]
   Absorbed into blood
   \[ \downarrow \]
   \( \text{H}_2 \) is seen in breath

3) Urinary indican levels: High
   • Due to Tryptophan metabolism by intestinal bacteria.
Treatment:

- Antibiotics for 7-10 days
- Drug of choice: Rifaximin

### Antibiotic Regimens for SIBO

- Ciprofloxacin (250 mg twice daily)
- Norfloxacin (800mg once daily)
- Metronidazole (250 mg 3 times daily)
- Trimethoprim / Sulfamethoxazole (160/800 mg twice daily)
- Doxycycline (100mg 2 times daily)
- Amoxicillin-clavulanic acid (500 mg 3 times daily)
- Tetracycline (250 mg 4 times daily)
- Neomycin (500 mg 3 times daily)
- Rifaximin (800 - 1200 mg once daily)

- Macrolides are not recommended
IRRITABLE BOWEL DISEASE

- Functional bowel disorder
- Overlapping symptoms
- F >> m
- First onset before 45yrs
- Abdominal pain is the key symptom for IBS

- It is a functional disorder, not a structural disorder
- It is generally associated with Fibromyalgia, Chronic fatigue syndrome, anxiety disorders & GERD
- For IBS to be diagnosed, the symptoms should be started before 45 years of age
- It’s like the “manifestation of stress in G.I.T”

Rome IV criteria: IBS:
- Recurrent “abdominal pain”, on average of at least 1 day/week in the last 3 months associated with 2 or more of the following:
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form (appearance)

Criteria should be fulfilled for the last 3 months with symptom onset over 6 months prior to the diagnosis

Abdominal pain:
- Mostly episodic, crampy lower abdominal pain
- Exacerbated by eating / emotional stress
- Relieved by defecation
- Change in the frequency / form of stool
- Key clinical symptom in IBS: Abdominal pain
- Consistent clinical feature of IBS: Altered bowel habits
Altered bowel habits:
- Most consistent feature of IBS
- Characterised by week or months of constipation with incomplete evacuation interrupted by brief periods of diarrhea.
- It usually manifests like
  - Day time diarrhea
  - Small volume stools
  - Mucus in large amount

Other related symptoms:
- Abdominal distension / Belching
- Dyspepsia / Heart burns
- Nausea / Vomiting

Never consider following symptoms as IBS:
1. Symptoms after 45yrs
2. Nocturnal Diarrhea
3. Large volume Diarrhea.
4. Blood in stool
5. Steatorrhea / Malabsorption
6. Anemia / Wt. Loss in the patient
7. Patient with Fever / ↑ in ESR

Calprotectin (marker of inflammatory bowel disease) is
serum crp levels will absolutely be normal in case of irritable bowel symptom

Pathophysiology of IBS:
- Exact pathophysiology of IBS remains uncertain
- Visceral hypersensitivity: Enhanced pain sensitivity of the gut may play an important role in the development of chronic abdominal pain in IBS
- Graph: In normal pt's the stool distending volume of 100ml didn’t cause much pain but in IBS pt's (orange) a distending volume of 100ml causes pain. It shows the Rectal Hypersensitivity
- Increase colonic motor potentials
- In brain, central activation of the cingulate cortex
- Serotonin containing enterocromaffin cells are increased
- Vanilloid channels (TRPV1) are also implicated

Management of IBS

- Mainstay of treatment remains lifestyle & diet modification

**Fodmap diet of IBS:**
- Fermentable oligosaccharides Disaccharides Mono saccharides and Polyols
- FODMAP diet should be avoided in IBS

\[
\text{↑ in FODMAP} \quad \downarrow
\]

Not absorbed in small intestine

\[
\downarrow
\]

In colon, because of a lot of carbohydrates from FODMAP diet, the food gets fermented and produce gas

**How do Fodmaps affect people with IBS?**

- Diarrhoea
- Gas production
- Bloating, distension, flatulence, abdominal pain, constipation

Disease
Examples of FODMAP foods:
1. Fruits with lots of free fructose - Apple, Honey, Cherry
2. Milk and milk products with lactose
3. Nuts, cereals, legumes, bananas, asparagus

Drugs in the treatment of IBS:
- Usage of drugs in the treatment of IBS mainly depends upon whether the IBS is diarrhea predominant or constipation predominant

<table>
<thead>
<tr>
<th>IBS-C (constipation)</th>
<th>IBS-D (Diarrhoea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. psyllium husk</td>
<td>1. Alosetron-SHT₃ antagonist</td>
</tr>
<tr>
<td>2. peg laxatives</td>
<td>Not used now because it is associated</td>
</tr>
<tr>
<td>3. Tegaserod - SHT₄ agonist</td>
<td>with increased incidence of ischemic colitis</td>
</tr>
<tr>
<td>Not in use because of cardiotoxicity</td>
<td>a. Loperamide - used at a dose of 4gms, 45 minutes before every meal</td>
</tr>
<tr>
<td>4. Lubiprostone - bicyclic fattyacid which activates Cl⁻ channels → ↑ influx of Na⁺ &amp; Cl⁻ into bowel</td>
<td>3. Eluxadoline - New drug, opioid μ receptor agonist</td>
</tr>
<tr>
<td>5. Linaclotide - Guanyl cyclase agonist ↓</td>
<td></td>
</tr>
<tr>
<td>↑ cGMP</td>
<td></td>
</tr>
</tbody>
</table>

- Antibiotics have no role in IBS
- Antispasmodics like dicyclomine may be useful
- Prebiotics and probiotics have no role in IBS
- Antidepressants like TCA's have found to be useful in IBS
STOMACH

Stomach – Normal

- Cardia - mostly mucus & Endocrine glands
- Antrum - mostly G-cells - Produce Gastrin

Antrum
(G cells - Gastrin)

Fundus
(Parietal - acid secreting cells) +
(Chief cells - Pepsin)

Body / Corpus

- Body - All types of cells
  - Parietal cells / Oxyntic cells - Acid, Intrinsic Factor
  - Chief cells - Pepsinogen
  - ECL cells - Histamine
  - Mucus cells
  - G-cells

Gastric pit (Fundus)

Isthmus

Neck

Base (Fundus)

Surface mucus cells

Mucus neck cells

Parietal cells

Endocrine cell

Chief cells

Active space
• Gastric glands in the body of the stomach are known as oxyntic glands because they have a lot of oxyntic cells.

• In the oxyntic glands, parietal cells are seen in the neck, or, isthmus chief cells at the base of the gland. mucosal cells are seen at the surface.

- 3 layer of gastroduodenal mucosal defence
  - Pre epithelial layer
  - Epithelial layer
  - Subepithelial layer

**Gastritis and peptic ulcer disease**

1. Acute gastritis:
   - It is an acute inflammation of the gastric mucosa.

   Which is predominantly associated with upper GI symptoms and histologically there is infiltration by the neutrophils.
   - Very often, it is a superficial inflammation
   - MC cause for acute gastritis - NSAID's
   - 2nd MC is - Infection - *H. pylori* - Very often it's self-limiting
   - Serious cases are seen in Immunocompromised - CMV1, HSV are the agents

Acute phlegmonous gastritis:
   - Acute, severe, progressive inflammation of gastric wall leading to stomach wall necrosis
   - Associated with high mortality
   - Seen in immunocompromised
   - Caused by *Streptococcus*
   - Characterised by abdominal pain, vomiting, high grade fever, sepsis and septic shock
   - On CT: Thickening of gastric wall with low intensity areas and gas formation
   - This is the most fulminant form of gastritis
Chronic gastritis:
- Superficial involvement of the gastric mucosa with lymphocytes and plasma cells
- Chronic gastritis can progress to atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer
- There are 2 types of chronic gastritic - Type B is more common than type A

Chronic gastritis - type A:
- Less common than type B
- It is associated with autoimmune disease - more often with pernicious anemia
- Very strong correlation with HLA A - B and HLA DR - B
- It is characterised by antibodies predominantly against Fundus / Body Antibodies against Parietal cells; So, IF and acid are not produced
- IF - megaloblastic anemia
- Acid - Achlorhydria.
- Feedback inhibition of gastrin release from antral G-cells by acid gets affected, leading to hypergastrinemia
- Hypergastrinemia leads to carcinoid tumor

Type B gastritis:
- more common than type A
- It is associated with H. Pylori
- Starts as an antral predominant gastritis then it progresses to pangastritis
- This can lead to atrophic gastritis, intestinal metaplasia and gastric adenocarcinoma
- Maltoma is a consequence of non-atrophic pangastritis due to H. pylori

* Gastritis which presents with intestinal obstruction - Eosinophilic gastritis
* Gastritis due to involvement of plasma cells leading onto tumor like appearance with pseudotumor endoscopy appearance is - Russell body gastritis
• Commonest cause of Granulomatous gastritis – Crohn’s disease
• Gastritis associated with celiac disease – Lymphocytic gastritis

Menetrier’s disease

- Also known as Hypertrophic gastritis
- Shows large tortuous mucosal folds predominantly in the body
  & fundus sparing the antrum
- Males >> Females with age of 40-60 years
- Predominantly mediated by TGF-α
- Histological finding: Foveolar Hyperplasia
- In children, this is due to CMV infection

Clinical features:
- Patient will have Hypersecretion of mucus leading to lots of protein loss
- This is protein losing gastropathy
- Upper GI Symptoms + Hypoalbuminemia + Edema in a middle-aged man suggestive of Menetrier’s disease
- It is a Pre-malignant condition

DIAGNOSIS:
- The IOC is Endoscopy with full thickness biopsy

DOC:
- The disease is cause by TGF α which acts through EGFR pathway
- So, the DOC is EGFR inhibitor – Cetuximab
H. Pylori and Maltoma

H. Pylori
- "Gram negative"
- microaerophilic
- Rod shaped
- [Catalase +ve; Oxidase +ve; Urease +ve]

Generally, resides in the antrum, migrate proximally inside the antrum → Deeper portions of the mucosal gel

Urease neutralize gastric acid by ammonia to survive in stomach

In the Antrum migrate proximally using Flagella. →
Flagella is responsible for mobility and chemotaxis etc

To adhere onto host cell - Two Factors
1. LPS
2. OMP - Outer Membrane Protein
Colonization of H. Pylori

Colonization of gastric mucosal epithelium → Chronic superficial gastritis

It is protective against:

1. GERD
2. Barret oesphagus
3. Adeno carcinoma of esophagus
4. Adeno carcinoma of cardia of stomach

Colonization Dependent on socio economic status
- Transmitted by feco-oral Route
- 80% of our population are actually having H. pylori

Toxins produced by H. Pylori

<table>
<thead>
<tr>
<th>Vacuolating toxin (VacA)</th>
<th>2. Type IV secretion system</th>
<th>3. Effectors [capA]</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Gastric mucosal injury</td>
<td>- Pill-like structure</td>
<td>- Actin</td>
</tr>
<tr>
<td>Secretory enzymes</td>
<td>- For injections of</td>
<td>Remodelling</td>
</tr>
<tr>
<td>Mucinase, Protease, Lipase</td>
<td>effectors</td>
<td>- IL-8 induction</td>
</tr>
<tr>
<td>- Gastric mucosal injury</td>
<td></td>
<td>- Host cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apoptosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition</td>
</tr>
</tbody>
</table>

Clinical outcomes of H. Pylori infections

The clinical outcomes of Helicobacter pylori infections

> 80%
15 - 20%
< 15%

- Asymptomatic or chronic gastritis
- Chronic atrophic gastritis
- Gastric or duodenal ulcer
- Gastric cancer
- MALT lymphoma
**H. pylori predisposing factors:**
- Colonization induced chronic superficial gastritis (>80%), but only 15-20% develop peptic ulcer.
- Ammonia production and alkalization is the first step.
- 80% of population in developing countries infected by 20 yrs.
- Elevated cytokines in gastric epithelium of affected individuals (IL-1 and IL-8) has predisposition.

**Oneliner:**
- 70-80% of duodenal and 60-70% of gastric ulcers are due to H. pylori.
- Gastric adenocarcinomas are more common in body or fundus or corpus.
- Maltoma is a type of lymphoma associated.
- Biopsy urease Test is the most convenient, simple and quickest test.
- Stool antigen test is the best for follow up.
- Antral predominant gastritis leads to duodenal ulcer.
- Corpus predominant gastritis leads to gastric ulcer; adenocarcinoma.
- Non atrophic pangastritis leads to maltoma.
Investigation for H. Pylori

**IOC: Upper GI endoscopy + Biopsy Urease Test**

- **Most specific and most sensitive Test**
- **If Test result positive → The patient colonized by H. pylori**
  - Symptoms due to H. pylori → Eradicate
  - If it is asymptomatic colonization, eradication is up to physicians discretion
  - In young patients if symptoms are not due to H. pylori better not to treat
  - If it is due to H. pylori then treat the patient

**Role of histology:**
- No much role
- "Warthin stain"

**Role of culture:**
- Even, after the repeated anti H. pylori regimes if the patient is still harbouring organism
- But, for practical purpose histology and culture are not required

<table>
<thead>
<tr>
<th>TABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TESTS COMMONLY USED TO DETECT HELICOBACTER PYLORI</strong></td>
</tr>
<tr>
<td>Test</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td><strong>Tests based on Endoscopic Biopsy</strong></td>
</tr>
<tr>
<td>Biopsy urease test</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Culture</td>
</tr>
<tr>
<td><strong>Noninvasive Tests</strong></td>
</tr>
<tr>
<td>Serology</td>
</tr>
<tr>
<td>*C 13 urea breath test</td>
</tr>
<tr>
<td>Stool antigen test</td>
</tr>
</tbody>
</table>
Treatment

Standard regime:

OCA Regime:
- Omeprazole 20mg bd \(\rightarrow\) [7-14 days]
- Clarithromycin 500mg bd
- Amoxicillin 1g bd

[or]

OCM Regime:
- Omeprazole 20mg bd \(\rightarrow\) 14 days
- Clarithromycin 500mg bd
- Metronidazole 500mg bd

For clarithromycin resistance:

OBTM Regime:
- Omeprazole; Bismuth subsalicylate; 14 days
- Tetracycline; Metronidazole

First line therapies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Dose</th>
<th>Days</th>
<th>FOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>PPI [std/double dose] clarithromycin [500mg] Amoxicillin [1g] or</td>
<td>BID</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>Triple</td>
<td>metronidazole 500mg (TID)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>PPI [std dose] Bismuth subcitrate [130-300mg] or subsalicylate [300mg]</td>
<td>BID</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>[Quadraple]</td>
<td>Tetracycline [500mg] metronidazole [200-500mg]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>PPI [std dose] Clarithromycin [500mg] Amoxicillin [1g] Nitroimidazole</td>
<td>BID</td>
<td>10-14</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>[500mg]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential</td>
<td>PPI [std dose] PPI, clarithromycin (500mg) + Nitroimidazole (500mg)</td>
<td>BID</td>
<td>5-7</td>
<td>NO</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>Hybrid</td>
<td>PPI [std dose] PPI, Amox, Clarithromycin, Nitroimidazole</td>
<td>BID</td>
<td>7</td>
<td>NO</td>
</tr>
<tr>
<td>Levofoxacin Triple</td>
<td>PPI std / double dose + Amox (5g)</td>
<td>BID</td>
<td>5-7</td>
<td>NO</td>
</tr>
<tr>
<td>Levofoxacin (sequential)</td>
<td>PPI std + double dose + Amox (5g) PPI, Amox, Levofoxacin (500mg) Nitroimidazole (500mg)</td>
<td>BID</td>
<td>5-7</td>
<td>NO</td>
</tr>
</tbody>
</table>

**Warning:** Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Confirm eradication after 1 month of completion of treatment by following tests:
- Urea breath Test [Radioisotope C13]
  - Or
- Stool Antigen Test
  - Inexpensive
  - Convenient
  - Non invasive
  - Generally preferred test

Positive stool antigen test after one month implies drug resistance
Start second line treatment
If second line Regime not working → Go for culture and sensitivity
<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity/ specificity (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive (endoscopy/biopsy Required)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid urease</td>
<td>80-95/95-100</td>
<td>Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds</td>
</tr>
<tr>
<td>Histology</td>
<td>80-90/90-95</td>
<td>Requires pathologic processing and staining, provides histologic information</td>
</tr>
<tr>
<td>Culture</td>
<td>/-</td>
<td>Time-consuming, expensive, dependent on experience, allows determination of antibiotic</td>
</tr>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>&gt;80/90</td>
<td>Inexpensive, convenient, not useful for early follow-up</td>
</tr>
<tr>
<td>Urea breath test</td>
<td>&gt;80/90</td>
<td>Simple, rapid, useful for early follow-up, false negatives with recent therapy (see rapid urea low-dose radiation with 13C test)</td>
</tr>
<tr>
<td>Stool antigen</td>
<td>&gt;80/90</td>
<td>Inexpensive, convenient</td>
</tr>
</tbody>
</table>

Serology → Has no role  
Because patient will continue to remain positive even after eradication

**Oneliners:**
- Most commonly used PPI Omeprazole 20mg Bd
- Dexlansoprazole is the recent PPI approved, most potent and delayed release, useful in GERD.
- Negative effect on antiplatelet effect clopidogrel
- Tenatoprazole is a irreversible PPI
- PPI long term use  ➔ Bone Fracture; Hip Fracture  
  Short term use  ➔ Acute tubulo interstitial nephritis  
  Electrolyte Imbalance  ➔ Hypomagnesemia

**Drug Interaction:**
- Between PPI and clopidogrel
  - Clopidogrel activation requires CYP3A4, which is affected by PPI.
  - So, should be careful while using PPI with clopidogrel
PEPTIC ULCER

Ulcer:

Ulcers are defined as breaks in the mucosal surface > 5 mm in size, extending into the submucosa.

**Duodenal ulcers**

- 1st portion of duodenum (95%) with ~ 90% located within 3 cm of pylorus
- Usually < 1 cm (3-6 cm; giant ulcer)

**Gastric ulcers**

- Distal to junction between antrum and acid secretory mucosa
- Prepyloric area

<table>
<thead>
<tr>
<th>Features</th>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Less common</td>
<td>More common</td>
</tr>
<tr>
<td>Location</td>
<td>Antrum; lesser curvature</td>
<td>Anterior wall; 1st part</td>
</tr>
<tr>
<td>Age group</td>
<td>Middle age</td>
<td>Middle or old age</td>
</tr>
<tr>
<td>Male: Female</td>
<td>1:1</td>
<td>4:1</td>
</tr>
<tr>
<td>Association H. pylori</td>
<td>65%</td>
<td>85%-100%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Level of gastric acid secretion</td>
<td>Mostly Normal</td>
<td>Mostly increased</td>
</tr>
</tbody>
</table>

Cushing ulcer → Stress related
Curling ulcer → Burns
Kissing ulcer → Both anterior and posterior wall of duodenum

Perforation → Gastric ulcer → Anterior duodenal ulcer
Bleeding → Duodenal ulcer → Gastroduodenal artery (posterior)
Gastric ulcer → Left gastro epiploic artery
Dumping Syndrome:
Early (10–30min)
- Intravascular depleton
Late (2–3 hrs)
- Reactive hypoglycemia.

Types of gastric ulcer (Daintree johnson)

- Type I
  In the antrum, near lesser curvature, normal acid level
- Type II
  Combine gastric and duodenal ulcer
  High acid level
- Type III
  Prepyloric
  High acid level
- Type IV
  Ulcer in the proximal stomach and cardia
  Normal acid level

Type I most common
It is fundamental that any gastric ulcer should be regarded as being malignant no matter how classically it resembles a benign gastric ulcer.
Multiple biopsies should be taken, as many as 10 well targeted biopsies.

Malignant gastric ulcer

<table>
<thead>
<tr>
<th>mucosal folds</th>
<th>Effacing mucosal folds</th>
</tr>
</thead>
<tbody>
<tr>
<td>margin</td>
<td>Irregular margin</td>
</tr>
<tr>
<td>Floor</td>
<td>Necrotic slough in the floor</td>
</tr>
<tr>
<td>edges</td>
<td>Everted edges</td>
</tr>
<tr>
<td>surrounding</td>
<td>Shows nodules; ulcers and</td>
</tr>
<tr>
<td>area</td>
<td>Irregularities</td>
</tr>
<tr>
<td>size and extent</td>
<td>Large and deep</td>
</tr>
</tbody>
</table>
Gastric ulcers

COX – 1 Housekeeping (mucosal protection)
COX – 2 Inducible inflammation and mitogenesis under cox – 2

A major factor in duodenal ulcer
   H. pyloric
   NSAID

Malignancy risk more is gastric ulcer
Gastric ulcers have normal or decreased acid output

Zollinger ellison syndrome

Gastrinoma (Gastrin secreting tumour)
80% sporadic
20% associated MEN – 1 syndrome
30–50 years affected
Female > male
60% malignant
Neuroendocrine tumour
Express chromogranin; Synaptophysin
m/c location duodenum 1st part
20% coming from pancreas
m/c in Gastrinoma triangle / Passaro's triangle
Duodenal gastrinomas: (10 - 80%)
  Tends to be small; multiple; benign, MEN1 associated

Pancreatic gastrinoma: (60%)
  Large; Solitary and malignant

Other points in ZES:
  marker: Neuron specific enolase
  80% in gastrinoma triangle
  Duodenal lesions are smaller & less aggressive
Peptic ulceration is the m/c manifestation
Gastric carcinoids are m/c in men
Symptom abdominal pain → Peptic ulcer
Gastric hypertension → Gastric carcinoids, MEN 1 syndrome associated

Peptic ulcer
Unusual loctions (O2 and beyond)
Refractory to medical therapy
Recurrence
Diarrhoea (osmotic + secretory)
Small; multiple; duodenal; less aggressive/MEN – 1

Gastrin Radioimmunossay:
Of acids suppressing medicines for 48 hrs
< 200 pg/ml Normal
200-1000 pg/ml Confirmatory Test (70%)
> 1000 pg/ml Gastrinoma (30%)

Screening Test of choice: Serum gastrin level
Prior to screening test, patient should be off acid suppressing medicines for 1 week

200-1000 pg/ml – Secretin stimulation Test (confirmatory Test)

Secretin stimulation test

Confirmatory Test
Secretin inhibits gastrin
Secretin stimulates or ↑ gastrin level in gastrinoma, IV
Secretin over 30mins of gastrin levels ↑ by
> 200pg/ml is confirmatory

Localization of the tumour

Somatostatin receptor scintigraphy
or
Octreotide scan

18C → Gallium – Dotatate PET/CT Scan
Somatostatin receptor scintigraphy
"Octreotide scan"

- Gastrinomas have somatostatin receptors
- Radioactively labeled octreotide
- Single most sensitive study
- Misses small duodenal gastrinomas

MEN syndrome associated duodenal gastrinoma are best localized by **endoscopic ultrasound**

Few points:
- Basal acid output / Maximal acid output: **No significance**
- Endoscopic ultrasound in MEN syndrome

**Gastrinoma Treatment:**
- **High dose PPI** (Omeprazole 60 mg – 80 mg)
  +/−
- Octreotide

**Definitive treatment:** Surgery
- Whipple surgery has the best outcome
- In MEN - I → No role for surgery unless tumour > 2.5 cm

∴ High dose PPI followed by surgery
- m/c site for metastasis - Liver
Development of liver

- ventral wall of foregut
  ↓ at 3-4 weeks
  Proliferating endodermal bud
called hepatic diverticulum

- Cranial
  - Liver
  - Biliary tract

- Caudal
  - Gall bladder
  - Cystic duct
  - Ventral pancreas

- Signal for development of hepatic bud comes from cardiac mesenchyme
  - FGF: Fibroblasts growth factor
  - BMP-7: Bone morphogenetic protein

- Cords of hepatoblasts invade septum transversum
  (endoderm) (mesoderm)

  hepatocytes

  - Cholangiocytes
    - TGF-β
    - NOTCH-2

  - Alagille syndrome:
    - Autosomal dominant
    - < 6 months of age
    - NOTCH-2 pathway defect
    - Paucity of intrahepatic bile duct
    - Mental retardation / Pulmonary valvular
    - Hypoplasia / Visual field defects / Growth defects

Active space
- **Components:**
  1. Endoderm → hepatic diverticulum
     - hepatoblasts
     - hepatocyte
     - cholangiocyte
  2. Mesoderm → septum transversum
     - Stellate cells
     - Connective tissue of liver
  3. Yolk sac → Kupffer cells (macrophage)
  4. HNF-6 : Hepatocyte nuclear factor - 6
     - Biliary tree development

**Vascular development of liver**

- Superior segment
  - Left
  - Common hepatic vein
  - Right
  - Inferior segment
    - Left
    - Right
    - Portal vein

- Vitelline vein

- Umbilical vein: carry oxygenated from placenta

- Oxygenated blood bypass liver via ductus venosus

- Obliterated pre-hepatic part of left umbilical vein forms ligamentum teres hepatis
- Ductus venosus after birth → ligamentum venosum
Anatomy of liver

- Lobes of liver:
  1. Anatomical lobes
     - Falciform ligament
     - Left: II, III
     - Right: IV, V, VI, VII, VIII
  2. Surgical lobes
     - Cantlie's line from gall bladder to inferior vena cava (IVC)
     - Left: II, III, IV, I
     - Right: V, VI, VII, I

- I → caudate lobe → directly drains to IVC
- IV → quadrate lobe
- Basic structural and functional unit: Lobule

- Periportal hepatocytes - Zone I
- Midzonal hepatocytes - Zone II
- Centrilobular (zone 3) zone is most vulnerable to hypoxia.
- 70/40; 30/60 rule
  - 70% blood supply & 40% O2 supply → portal vein
  - 30% blood supply & 60% O2 supply → Hepatic artery
- Hepatic artery: anterior to portal vein, left to bile duct
- Glisson's capsule covers all structures except hepatic vein
- Cirrhosis → lobules are replaced by nodules
  → Connected by fibrous septa
Cellular anatomy of liver -

- Three membranes
  1. Contiguous membrane: tight junctions and gap junctions
  2. Canalicular membrane: bile flow
  3. Sinusoidal membrane (basolateral membrane)
- Space of Disse: between sinusoidal membrane and sinusoidal endothelial lining
  Stellate cells
- Stellate cells:
  - situated in space of Disse
  - also called Ito cell
    - Vitamin A storing cell
    - Lipocyte
- In cirrhosis, activated stellate cells
  ↓
  produce TGF-β
  ↓
  Fibrosis (key event in cirrhosis)

- NK cells in liver: pit cells
  - Expressed in liver
LIVER PHYSIOLOGY

Bilirubin pathway

- Bilirubin → Heme degradation
  80% Hb
  20% heme containing proteins
- Bilirubin → 300 mg per day
  4 mg/kg per day

Heme

  → heme oxygenase in smooth endoplasmic reticulum

Biliverdin

  → biliverdin reductase in cytoplasm

Bilirubin (Or)

  combines with albumin

  dissociates before liver

Albumin

  organic anion transport protein

  → Enters hepatocyte

Bilirubin

  diglucuronide

  is conjugated by UDP glucuronyl transferase

  binds to glutathione

  if obstruction

ATP

  mRP - 2 channel

  → Excreted into bile

  mRP - 3 channel

  → Excreted in plasma

  → Urine
- Bilirubin diglucononide
  \[ \text{Colon} \rightarrow \text{deconjugated by bacteria} \]
  \[ \text{unconjugated bilirubin} \]
  \[ \text{urolbilinogen} \]
  - 80% excreted in stool
  - 20% enters enterohepatic circulation
  - Small amounts absorbed
  - Traces present in urine normally

- Increased urolbilinogen in urine $\rightarrow$ Hemolysis
  - Cirrhosis

Absent urolbilinogen in urine $\rightarrow$ obstruction of biliary tree

**Hyperbilirubinemia**

- Bilirubin estimation
  - Classically, van den Bergh / Diaz reaction
  - More recently, HPLC (High performance liquid chromatography)

- Normal values
  - Total Bilirubin = 1 - 1.3 mg/dL
  - Indirect bilirubin = 0.2 - 0.9 mg/dL
  - Direct bilirubin = 0 - 0.3 mg/dL

- Jaundice
  (hyperbilirubinemia)
  \[ \text{Direct (conjugated)} \quad \text{Indirect (unconjugated)} \]
  - 15 - 50% of total (hepatic)
  - > 85% of direct (hemolysis)
  - > 50% of total (obstruction)

- Most proteins produced by liver are positive acute phase reactants.
  - Exception of 4 proteins that are negative acute phase reactants.
  They are:
  1) Albumin
  2) Transferrin
3) AFP (alpha fetoprotein)
4) Transthyretin

- **Delta bilirubin**: variant of direct bilirubin with long half life
  - $t_{1/2}$ of normal bilirubin = 4 hours
  - $t_{1/2}$ of delta bilirubin = 14 - 21 days
- In certain patients it may take longer time for bilirubin to return to normal following clinical recovery.

- High total serum bilirubin levels correlates with poor outcome.
LIVER FUNCTION TEST

Serum Bilirubin

- Method of estimations:
  - Van den Bergh reaction (Diazo reaction)
    - Van den Bergh reagent + Blood → Purple
      (direct / conjugated)
    - Van den Bergh + alcohol + Blood → Total bilirubin
  - Total - direct → Indirect bilirubin.

- High performance liquid chromatography (gold standard)

- Normal value:
  - Total bilirubin → 1 - 1.3 mg/dl
  - Direct bilirubin → 0 - 0.3 mg/dl
  - Indirect bilirubin → 0.2 - 0.9 mg/dl

- Variant - delta bilirubin → t_1/2 = 14 - 21 days
  may take extra time for bilirubin to come back to normal after recovery

- t_1/2 (half life) of normal bilirubin = 4 hours

Hyperbilirubinemia:

Indirect hyperbilirubinemia

- Indirect bilirubin > 85% total
- When associated with extravascular hemolysis

  Heme + globin

  Protoporphyrin + Fe

  Biliverdin → Bilirubin

  Direct hyperbilirubinemia

  Conjugated > 50%
  (obstruction)

  Conjugated 15 - 50%
  (hepatic)
- LDH +++
- haptoglobin ↓↓ Specific for hemolysis
- Coomb's test → autoimmune hemolysis

* When not associated with hemolysis

Drugs:
- Probenecid
- Rifampicin

Hereditary unconjugated hyperbilirubinemia
- Gilbert's syndrome
- Criggler Najjar type 2

* High serum total bilirubin level correlates with poor outcome

Liver Enzymes

Aminotransferases:

<table>
<thead>
<tr>
<th>ALT: Alanine amino transferase</th>
<th>AST: Aspartate amino transferase</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGPT</td>
<td>SGOT</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Cytoplasm and mitochondria</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>Liver specific</td>
<td>Skeletal muscle: rhabdomyolysis</td>
</tr>
<tr>
<td>Liver specific</td>
<td>Cardiac muscle: MI</td>
</tr>
</tbody>
</table>

* In a healthy person:
  - ALT
    - AST < 30 IU/L
  - ALT > AST
    - AST is more rapidly cleared by the reticuloendothelial system.

Acute hepatocellular injury

- Course of most liver disease
  - Acute hepatitis
  - Chronic hepatitis
  - Cirrhosis
Cirrhosis

- Decompensation
  (Portal HTN)
- Hepatocellular Carcinoma

Complications

- In acute hepatitis:
  - ALT and AST → very high → > 1000 IU/L
  - When ALT and AST → moderately high → bad prognosis
    less viable hepatocytes

- Causes:
  1. Acute hepatocellular injury
     - Virus
     - Drugs
     - Toxins
     - Ischaemia
  2. Acute bile duct obstructions
    - Usually, ALT > AST
    - When underlying chronic alcoholic liver disease → AST > ALT

- In alcoholic liver disease:
  - AST and ALT levels < 300 - 400 IU/L
  - When AST / ALT = 2 : 1 → in acute hepatitis is mostly
    suggestive of alcoholic hepatitis
  - When AST / ALT = 3 : 1 → diagnostic of alcoholic hepatitis
  - AST > ALT in alcoholics because of pyridoxal phosphate
    deficiency.
  - Acute injury on chronic liver - ALT > AST > 1000, AST > ALT

Chronic Hepatitis

- Clinically present with fatigue, usually asymptomatic
- ALT and AST are elevated up to 5 times normal < 150 IU/L

- Causes:
  1. NASH: Non-alcoholic steatohepatitis
  2. Chronic viral hepatitis (B or C)
  3. Wilson's disease
  4. Autoimmune hepatitis
  5. Hemochromatosis
• When AST > ALT in chronic hepatitis ——> Cirrhosis
  because of impaired hepatic blood flow and
decreased sinusoidal update of AST

• High ALT and AST but <150 in the absence of chronic hepatitis:
  • Celiac disease
  • Hyperthyroidism
• Isolated high AST ——> rhabdomyolysis, MI

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Alkaline Phosphatase (ALP)

• Normal value ——> 40 - 140 IU/L
• Physiological increase MI
  - less than 4 times upper limit of normal
  - can be seen in pregnancy
    - blood group O
    - elderly (>70y)
    - adolescent age
    - after heavy meal

• Sources of ALP
  1) Liver (canalicular membrane)
     a) Bone
     b) Intestine
     c) Kidney
     d) Placenta

• High ALP ——> Possible ——> Confirmation with:
  > 4 times normal
  (800 IU/L)
  > Cholestasis
  1) GGT: Gamma-glutamyl transferase
     - Specific for cholestasis
  2) S’ nucleotidase also
     - produced by liver & bone

• Reduced ALP ——> Acute hepatitis in Wilson’s disease
Conjugated Hyperbilirubinemia

- Direct bilirubin = >50% of total

Conjugated hyperbilirubinemia

**Evidence of cholestasis**
- ALP > 4 times
- GGT

**USG, Abdomen**
- Ducts are dilated
  - Extrahepatic cholestasis
    - ERCP / CT
    - Surgical management
- Ducts are not dilated
  - Intrahepatic cholestasis
    - 1. Drugs
    - 2. Sarcoidosis
    - 3. Primary biliary cirrhosis
    - 4. Cytomegalovirus infection

**No evidence of cholestasis**
- Inherited conjugated hyperbilirubinemia
- Dubin Johnson Syndrome
- Rotor syndrome

Drugs causing cholestasis

1) Simple gland Cholestasis
   - Anabolic steroids
   - Estrogen

2) Cholestatic hepatitis
   - Azathioprine
   - NSAIDS - Piroxicam

3) Granulomatous hepatitis
   - Allopurinol
   - Phenytoin
   - Procafamide
   - Sulfonamides

4) Vanishing bile duct syndrome
   - Erythromycin
   - Amoxicillin / Clavulanate
Synthetic Functions Of Liver

S. albumin, Total proteins and globulin

- Serum albumin:
  - 15g/day
  - molecular weight = 69,000

  - low albumin is a marker of chronicity
  - is a negative acute phase reactant

- globulins:
  - Polyclonal hypergammaglobulinemia → Autoimmune hepatitis
  - monoclonal hypergammaglobulinemia → Blood dyscrasias

a. PTT, PT, INR, Platelet count

  - Thrombocytopenia → One of the first markers of portal hypertension

<table>
<thead>
<tr>
<th></th>
<th>Acute hepatitis (↑)</th>
<th>DIC (↓)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT / aPTT / INR</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>S. Fibrinogen</td>
<td>normal</td>
<td>↓↓</td>
</tr>
<tr>
<td>S. Fibrin degradation products</td>
<td>normal</td>
<td>↑↑</td>
</tr>
<tr>
<td>D - dimer</td>
<td>normal</td>
<td>↑↑</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>normal</td>
<td>↓</td>
</tr>
</tbody>
</table>

- In Vit K deficiency → PT is elevated
  - aPTT is normal

- MELD Score: acute hepatitis prognosis
  - Parameters - INR
    - S. bilirubin
    - Creatinine
Fibroscan And Other Tests

- Also called transient elastography to look for cirrhosis

- Fibrosect 2: blood markers of cirrhosis
  1) Hyaluronan
  2) $\alpha_1$ - microglobulin
  3) Tissue inhibitor of metalloproteinase - I

- Quantitative liver function tests:
  - Indocyanine green clearance
  - Galactose elimination capacity
  - Caffeine clearance
  - Lidocaine metabolite formation
  - Aminopyrine breath tests

- Bile acids - quantitatively to assess hepatic reserve increased in cholestasis
INHERITED HYPERBILIRUBINEMIA

Classification of inherited hyperbilirubinemia:

- Indirect (unconjugated)
  - Gilbert's syndrome
  - Criggler Najjar syndrome (type 1 and 2)
  - All inherited hyperbilirubinemias - Autosomal recessive
- Direct (conjugated)
  - Dubin Johnson Syndrome
  - Roturs Syndrome

Gilbert's syndrome

- Due to deficiency of UDP glucuronyl transferase (10-30% of normal)
- Mild unconjugated hyperbilirubinemia.

< 3 mg/dL - 85% or above is indirect bilirubin

- Fasting and infection - deepens jaundice
- Benign condition
- Liver function test (LFT) - Normal
- Hepatic histology - Normal; Lipofuscin in hepatocyte
- Good prognosis
- Phenobarbitone (enzyme inducer) can be used for treatment

Criggler najjar syndrome type 1 and 2

Criggler Najjar Syndrome type 1
- Complete deficiency of UDP glucuronyl transferase (Therefore phenobarbitone has no role)
- Serum bilirubin > 30 mg/dL
- Death within 1-2 yrs
- C/F- Kernicterus
- Treatment - Liver transplantation
- Least common type
- Patients planned for liver transplant-phototherapy, tin protoporphyrin (Hemeoxygenase inhibitor)

Criggler Najjar Syndrome type 2
- AR
- < 10% of normal UDP glucuronyl transferase
- Serum bilirubin: 7 - 10 mg/dL (does not exceed 20 mg/dL)
- C/F – Jaundice (can present as late as 30 yrs)
- LFT – Normal
- Histology – Normal
- Good prognosis
- Good response to phenobarbital
- Pigmented bile in duodenum
- No Kernicterus

**Dubin Johnson syndrome**

- AR
- Mutation in *ABCC2* gene/ *MRP2* protein – defective
  (Present on canalicular membrane)
  
  Cannot excrete conjugated bilirubin into bile
  
  Conjugated hyperbilirubinemia.

- Conjugated hyperbilirubinemia – 4-7 mg/dl
- LFT – Normal
- Good prognosis
- Coarse pigment inside centrilobular hepatocyte
  
  due to epinephrine
  
  gives dark pigmentation to liver on gross examination

- Bromsulphathaline test (BSP) positive
  
  Normally: at – 45 mins – ↑
  120 mins – ↓
i) In Dubin Johnson Syndrome - levels are ↑ in 120 min > 45 min

iii) Urine coproporphyrin excretion - type I >> III (Normally type III > 1)
• Oral Cholecystography - non visualisation of gall bladder and biliary tree.

Rotors Syndrome

• AR
• Conjugated hyperbilirubinemia - 4-7 mg/dl
• Defect in OATP (Organic Anion Transport Protein)

• OATP is required for subsequent uptake of conjugate bilirubin
• Liver biopsy and gross examination - normal
• BSP test negative
• Oral Cholecystography - normal
• Urinary coproporphyrin - I >> III (Total high)
• Tc HIDA Scan - no visualization of liver/ Gall bladder
ACUTE VIRAL HEPATITIS

- Acute hepatitis ⇒ Hepatitis A and Hepatitis E

**Hepatitis A Virus**

- Single stranded RNA virus.
- Picornaviridae.
- Non enveloped, heat sensitive virus. (⇒ 85°C)
- Mode of transmission: feco-oral
- Very rarely sexual / parenteral
- Vertical transmission ⇒ Never
- Incubation period ⇒ 30 days.
  - 30 days ⇒ A
  - 40 days ⇒ E
  - 50 days ⇒ C
  - 60 days ⇒ B

Acute hepatitis:
- Most common cause worldwide ⇒ Hepatitis E (adults)
  - Hepatitis A (children)

**Hepatitis A:**

- Prodromal stage ⇒ 2-3 days.
  - Fever, myalgia, vomiting
  - Followed by jaundice.
- LFT: ↑ Bilirubin high
  - Hepatic Jaundice (15 - 50% conjugated)
  - Aspartate aminotransferase (AST) & Alanine aminotransferase (ALT)
    - More than 1000 ALT has to be more than AST.
- Clinically:
  - Jaundice
  - Mild Hepatomegaly in 85%.
  - Extra hepatic manifestations (rarely)
    - Rash or arthralgia.
  - Right upper quadrant tenderness.

Causes:
- Most common cause of viral hepatitis in children
  ⇒ Hepatitis A
- Most common cause of acute relapsing viral hepatitis.
  ⇒ Hepatitis A
- Incubation period of 4 weeks.
Differential diagnosis:
- virus → Hepatitis A,
  Hepatitis E, Hepatitis B
- Drug/toxin
- Ischaemia
- Autoimmune
- Wilson's disease
- Alcohol.

Investigation:
- anti HAV IgM → disappears in 12 weeks.
  → clinically → 8 weeks
- anti HAV IgG → recovered.

Note: Acute relapsing hepatitis
→ a in 1,000,000 → fulminant hepatic failure
  
  Encephalopathy ± coagulopathy
  within 7 days of onset of symptoms
→ very rarely → asymptomatic.
→ vaccine.
  • Fulminant hepatic failure → 100% mortality without transplant.
  • model for end-stage liver disease (MELD) Score → INR, serum
    bilirubin, creatinine
    → prognostic
  • Vaccine → HAVRIX Vaccine → 1 ml, I.M.
    2 doses → 0, 6–12 months

Pre exposure → more than 2 weeks prior to travel
Post exposure → within 2 weeks of exposure

Hepatitis Virus

- HepaEviridae under calcivirus
- Single stranded RNA Virus
- Non enveloped.
- Destroyed by boiling (more than 85°C)
- 4 genotypes
- mode of transmission: Feco-oral
- rarely vertical
- No sexual or parenteral transmission
- Immune mediated injury to hepatocytes
- Incubation period → 40 days.
- Clinical picture is almost same as hepatitis A

Cardinal points of difference:
1. hep E → Cholestatic phase, hep A → Relapsing Phase
2. Vaccine not available for HEV
3. risk of fulminant hepatitis in hepatitis E → 1–2% 
4. Fulminant hepatitis risk in pregnancy (E) → 20%
5. Anti HEV IgM → 16 weeks.
6. Clinical recovery → 8 weeks.
   • Most common cause of acute viral hepatitis in adults → Hepatitis E.

**Treatment of acute viral hepatitis**

- Jaundice with enzymes extremely high
- Vomiting
- Mild hepatomegaly
- Anti HRV or HEV IgM → positive
- Treatment → Hydration
  - Glucose replenishment
  - 10% dextrose (10 gm in 100 ml)
  - Target: 150 gm dextrose per day.
- NO risk for chronicity, cirrhosis, hepatocellular carcinoma.
Acute liver / Hepatic failure

- Encephalopathy +/- coagulopathy occurs within 6 months from the onset of clinical symptoms.
- Modified in 6 months → First 7 days → fulminant hyperacute.
- 7–28 days → acute
- 28 days – 6 months → subacute.

Cause:
- Viruses → mc cause of acute hepatitis- Hepatitis A(children) & hepatitis E (adults)
- Mc cause of acute liver failure - Hepatitis E (more incidence)
- Risk for fulminant hepatic failure - coinfection of hepatitis D with hepatitis B
- EBV (E ≥ D)
- CMV
- HSV
- Hemorrhagic virus
- E → 1-2%, 20% risk of hepatic failure in pregnancy
- D → coinfection with HAV → extremely high risk of hepatic failure (5-20%)

- Drugs:
  - Dose dependant
    - Acetaminophen
    - Carbon tetrachloride
    - Mushroom poisoning
  - Dose independant idiosyncratic
    - INH
    - Valproic acid
    - Phenytoin
    - Carbamazepine
    - Propylthiouracil
    - Halothane
    - Nitrofurantoin

Toxins causing acute liver failure

- Alcohol
- Rat killer poison (containing zinc phosphide)
- Metabolic causes: Wilson's disease
  - Galactosemia
  - Tyrosinemia
  - α, antitranspepsin deficiency
- Auto immune hepatitis
- Pregnancy related cause → acute fatty liver of pregnancy
  → HELLP
- Vascular causes → Budd Chiari syndrome
- Metastasis to liver → from breast and lung.
• In Asia and Africa → viral hepatitis (HEV mc in India)
• In Europe → Paracetamol is mc

**Acute hepatic failure**

Characteristic features:

• **Hepatic encephalopathy** → Cerebral edema
  \[\uparrow ICP\]

• Coagulopathy → low platelet count
  \[\downarrow PT, \downarrow INR \rightarrow\text{Elevated}\]
  • Bleeding is rare.

• Renal failure
• Sepsis → Lung related infections. (mc cause of death)
• Electrolyte abnormalities → \[\downarrow Na, \downarrow\text{glucose}\]
• Pulmonary dysfunction (mc cause of death)
• Gastrointestinal bleeding (rarely)
• Hemodynamic abnormalities:
  → Hyperdynamic circulation picture, splanchnic vasodilatation.
  → low peripheral resistance (hypotension) → increase cardiac output
  → arrhythmias

**Management of acute liver failure**

→ Definitive management - liver transplantation
• Prognostic index - MELD score → INR
  • Serum bilirubin
  • Creatinine

Paracetamol poisoning:

→ Toxic dose: **7500mg (15 tablets)**
→ Hepatocytes injury - centrilobular hypoxia.
• 1st 24 hours → Nausea and vomiting
• 24-72 hours → Right upper quadrant pain and tenderness
  → \[\uparrow ALT, \uparrow AST, \uparrow PT, \uparrow \text{Bilirubin}\]

• 72-96 hours → Hepatic necrosis.
  • Renal dysfunction
  • Coagulopathy
  • Encephalopathy
  • Lactic acidosis.
→ Death occurs.
Symptoms:
- Jaundice not very prominent
- Encephalopathy / Cerebral edema
- SIRS
- Renal failure
- Coagulopathy

Kings College Hospital Indicators of bad prognosis
- Acute liver failure → paracetamol poisoning.
- Transplantation required for:
  → PT ↑ or INR > 6.5
  → Encephalopathy
  → Serum - creatinine high.
  → pH < 7.25 after 24 hours

Management:
- N-acetyl cysteine → used in drug induced liver injury
- Repletes glutathione
  - Ionotropic
  - Anti inflammatory
- Given within 15 hours or as early as possible.
- Methionine → alternative drug
- Cerebral perfusion pressure high → > 55 mmHg.
- N-acetyl cysteine → 300mg /kg, in 3 parts
  - 1 hour - 150mg /kg
  - 4 hour - 50 mg /kg
  - 16 hour - 100mg /kg
  → 200ml 5% dextrose
AUTOIMMUNE HEPATITIS

Autoimmune hepatitis

- Acute \(\rightarrow\) chronic \(\rightarrow\) cirrhosis
- Decompensation
  - Hepatocellular

- \(\rightarrow\) 30-50 years females \(\rightarrow\) SLE

  - Thyroiditis
  - Grave's disease
  - Rheumatoid arthritis

- \(\rightarrow\) Originates in the 20's
- Type 2 Autoimmune hepatitis \(\rightarrow\) children
  - Poorer prognosis \(\rightarrow\) cirrhosis
- Good response to steroids

Type 1 AIH

- \(\rightarrow\) Anti smooth muscle antibodies

Type 2 AIH

- \(\rightarrow\) Anti LKM-1
  - (Liver Kidney microsomal)

- \(\rightarrow\) Anti LC1 (Liver cytosol type I)
- Antibodies

- Both types \(\rightarrow\) anti SLA (soluble liver antigen)

Histology findings:
1. Lymphoplasmacytic infiltrate
2. Interface hepatitis or piece meal necrosis
3. Emperipolesis
4. Rosette formation

Clinical presentation of autoimmune hepatitis

- Acute hepatitis \(\rightarrow\) chronic hepatitis \(\rightarrow\) cirrhosis
- Cardinal points:
  1. Any acute hepatitis where virus / drug / toxin has been excluded
     \(\rightarrow\) worked up for autoimmune
  2. Any acute hepatitis where jaundice fails to resolve or reappear
     (waxing and waning of jaundice)
  3. Any acute hepatitis in a patient with SLE / RA / thyroiditis
4. Any acute hepatitis with polyclonal hypergammaglobulinemia

- Chronic hepatitis:
  - Fatigue with LFT → increased ALT / AST
  - Hepatomegaly with fatigue in young female
  - Cirrhosis
  - Autoimmune hepatitis → chances for decompensation less likely

- Decompensated → Jaundice + Splenomegaly
  → Late and less common

- Thyroiditis + Grave's disease + RA
- Asymptomatic / acute / fulminant
  rarely   rarely

<table>
<thead>
<tr>
<th>Type</th>
<th>disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>LKM-1</td>
<td>AIH type II, Hepatitis C</td>
</tr>
<tr>
<td>LKM-2</td>
<td>Drug induced hepatitis</td>
</tr>
<tr>
<td>LKM-3</td>
<td>Hepatitis D</td>
</tr>
</tbody>
</table>

**Type 1 & type 2 hepatitis**

**Type 1 (Lupoid hepatitis)**
- Young females
- 30-40 years
- SLE - positive (HLA DRB103, DRB104)
- Acute or chronic
- more steroid responsive
- Suppressor T-cell deficient
- Anti smooth muscle antibody / pANCA
- insidious onset or typical attack, acute viral hepatitis → Jaundice does not resolve
- Liver palpable

**Type 2**
- Seen in children
- 8-10 years
- autoimmune conditions associated
- TI DM / vitiligo / pernicious anemia
- anti LKM - 1 antibody
- less common
- chronic hepatitis
- less steroid responsive
- DRB1 - 03
- DRB1 - 07
- Anti - SLA
- Anti LC 1 is frequently found
- p - ANCA is not found
- Also seen in adults
Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

**Treatment of autoimmune hepatitis**

→ Steroids ± Azathioprine
   (Prednisolone)
→ Overall prognosis → good if treatment is started before cirrhosis
→ S. Bilirubin and enzymes ↓
→ Histological remission → to be achieved
→ Cirrhotics → transplant
→ Recurrence post transplant → 40%
Primary biliary cirrhosis (PBC)

- Now known as primary biliary cholangitis
- Destruction of intrahepatic bile duct (Intralobular)
- Auto immune destruction \( \rightarrow \) T- lymphocyte mediated.
- Females more common than males \( \rightarrow \) 9 : 1
- 30 - 50 year
- Associated auto immune illnesses.
  - Sjogren syndrome
  - Renal tubular acidosis (RTA)
  - Gall stones
  - Small joint arthritis
- Antibody \( \rightarrow \) anti mitochondrial antibody (AMA)
  \( \rightarrow \) 95% cases, against pyruvate dehydrogenase \( E_2 \).
- Differential diagnosis \( \rightarrow \) intrahepatic cholestasis.
- Chronic progressive auto immune cholestatic disorder.
- No infections
- AMA more than 95% \( \rightarrow \) IgM. \( \rightarrow \) Presence is good enough for diagnosis.
- Directed against \( \rightarrow \) PDH - E2
- ALP and GGT \( \rightarrow \) very high.
- Hypercholesterolemia.

Clinical presentation of PBC

- Asymptomatic in 60% cases
- Routinely diagnosed \( \rightarrow \) ALP ↑↑↑
- Fatigue is the most common symptom.
- Pruritis \( \rightarrow \) due to accumulation of Lysophosphatidic acid
- Melanin deposition \( \rightarrow \) hyperpigmentation.
- Xanthelasm and Xantheomas \( \rightarrow \) hypercholesterolemia.
- Jaundice in less than 10%
- Hepatomegaly \( \rightarrow \) 25%
- Decompensation occurs late.
- Liver palpable \( \rightarrow \) right upper quadrant pain \( \rightarrow \) 25%
- Diarrhoea, Steatorrhoea, weight loss \( \rightarrow \) malabsorption
- Metabolic bone disease
- Sjogren, RTA, gall stones
- Intrahepatic cholestasis \( \rightarrow \) AMA positive.
Histopathology:
→ Biopsy
→ Earliest histological changes → loss of the canals of Hering
→ Most important diagnostic clue → Ductopenia
  ↓
  loss of intrahepatic or intralobular bile duct.
→ Florid duct lesion with non caseating granuloma.

Treatment of primary biliary cholangitis

→ Florid duct lesion or chronic non suppurative lesion of inter lobular ducts.

→ Drug → preventing progression to cirrhosis
  → Ursodeoxycholic acid (UDCA)
  → No symptomatic benefits.

New drug → Faesnoid X receptor antagonist
  ↓
  Obeticholic acid.

Primary sclerosing cholangitis (PSC)

→ Fibrosing destruction with strictures of both intra and extra hepatic bile ducts.
→ Seen in males more than females → 2 : 1.
→ Associated with ulcerative colitis (pseudocystosis)
→ 2/3rd of PSC have ulcerative colitis
→ 5 % of ulcerative cholitis have PSC.
→ Increases risk for cholangiocarcinoma.
→ Cholelithiasis (intra + extra hepatic cholelithiasis)
→ Rapidly progresses to cirrhosis
→ Very bad prognosis (management - Liver transplantation)
→ AMA negative
→ Atypical p - ANCA positive
→ Strong HLA association → DRW 52
→ PSC diagnosed by → MRCP, preferred over ERCP
→ Stricture and dilatation in between.
Histopathology → Periductal onion skin fibrosis.
   → PSC are also asymptomatic.
   → Fatigue, pruritis
   → Cholangitis is more common
      - Fever, chills, abdominal pain (right upper quadrant pain)
   → Jaundice is less than 10%.

Treatment → Transplantation.

<table>
<thead>
<tr>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune condition</td>
<td>Fibrosing</td>
</tr>
<tr>
<td>Weak HLA association</td>
<td>Strong HLA association - DR- W5a</td>
</tr>
<tr>
<td>Antibody + T cell</td>
<td>Fibrotic</td>
</tr>
<tr>
<td>mediated</td>
<td></td>
</tr>
<tr>
<td>A M A</td>
<td>A M A negative</td>
</tr>
<tr>
<td>Females</td>
<td>Atypical p - ANCA</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>males</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>AMA positivity</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>mRCP</td>
</tr>
<tr>
<td>No risk for malignancy</td>
<td>Liver transplant</td>
</tr>
<tr>
<td>Ductopenia → florid duct</td>
<td>Increase risk of malignancy</td>
</tr>
<tr>
<td>lesion → non caseating</td>
<td>Onion skin fibrosis</td>
</tr>
<tr>
<td>granuloma</td>
<td></td>
</tr>
</tbody>
</table>
Wilson’s disease- etiopathogenesis

- Autosomal recessive.
- 1st manifestation occurs < 20 years.
- Gene: ATP - 7b on chromosome 13q
- ATP 7b gene → Menke kinky hair syndrome Characterised by Calcium deficiency

Neurodegenerative condition
→ X linked recessive.
- Copper (Cu) via DMT 1 (divalent metal transporter)
  ↓ binds to
  Intestinal epithelial cells.
  ↓
  Metallothioneins
- Copper excreted in bile (90%)
- Circulating copper bound to apoceruloplasmin
  ↓
  Called as Holoceruloplasmin.
- In Wilson’s disease
  (i) copper incorporation into apoceruloplasmin is defective → Rapid ceruloplasmin degradation
  (ii) Defective biliary excretion of free copper.

- Features:
  ↑ Free copper.
  ↑ Liver copper
  ↑ Urinary copper
  ↓ Total copper
  ↓ Serum ceruloplasmin.
  → Hepatolenticular degeneration occurs

Clinical manifestation

(i) Liver manifestations.
  - 1st presentation occurs < 20 years of age.
  - Clinical presentation:
    - Fatigue, hemolysis.
    - Cirrhosis.
    - Fatty liver.
  - Hepatitis, hepatomegaly, cholestasis, can present as any kind of liver disease.
  - Asymptomatic - but with biochemical abnormality.
  - Wilson’s disease can cause severe form of Jaundice.
• Clinical features:
  ↓ Alkaline phosphatase
  ↑ serum AST /ALT
  ↓ cholinesterase.

(a) Neurological manifestations
  - 1st presentation occurs < 10 years of age
• Clinical features.
  (i) Dysarthria (mc)
  (ii) Gait abnormalities.
  (iii) Dystonia - vacuous smile
  (iv) Tremor
  (v) Parkinson like.
(ad) Neuropsychiatric symptoms
  → Tremor: wing beating tremor.
(b) Kayser - Fleischer ring (KF)
• Copper deposition in superior and inferior poles of Desemnet membrane.
• Slit lamp examination.
  • In neurological wilson disease 95% have KF ring.
  • In hepatic wilson disease 5% have KF ring
  → KF ring also seen in cholestatic conditions.
  → non specific finding.
  → Disappears with therapy.

Sunflower cataract
  → Copper deposition in centre of lens.
  → Does not affect vision.

Other manifestations.
• Endocrine → Hypoparathyroidism
• Renal → Type 2 / proximal renal tubular acidosis.
• Rheumatological → Large joint arthritis.
• GIT → Pancreatitis.
• Amenorrhea, infertility abortion.
• Hematological → Coomb's negative hemolytic anemia.
• Bone disease (India)
• Cardiac: Cardiomyopathy

Diagnosis

(1) Serum ceruloplasmin
  - Synthesised in liver.
  - Acute phase reactant protein.
  - Normal level 20-40mg/dl
  - 6 copper atoms bind to ceruloplasmin.
→ Low serum ceruloplasmin.
  < 15 mg/dl → Suggestive of Wilson's disease
  < 5 mg/dl → Diagnostic of Wilson's disease
• Normal values do not exclude diagnosis.
• False low serum ceruloplasmin seen in renal and GI loss of ceruloplasmin.
• False high serum ceruloplasmin seen in
  → Acute inflammation - Positive acute phase reactant
  → Pregnancy.

(a) Total serum copper → Non-ceruloplasmin bound copper
(TSC) +
  Ceruloplasmin bound copper
  - Majority of serum copper are bound to ceruloplasmin
• ↓ Total serum copper and ↓ ceruloplasmin bound copper → Wilson's disease.

(b) Urinary copper (24 hrs)
• High 24 hours urinary copper excretion
  → > 100mg suggestive of Wilson's disease.
  → 40-100mg → D-penicillamine challenge test
  ↓
  Increase urinary copper → Wilson's disease

(4) Hepatic tissue copper - gold standard method
• Copper concentration measured by,
  (i) Neutron activation analysis
  Atomic absorption spectrometry
• > 250 mg/g of dry weight - diagnostic

Histopathology:
• Glycogen degeneration → vacuolation
• Fatty changes
• Periportal hepatocytes affected
• Macronodular cirrhosis.

Electron microscopy findings and management of Wilson's disease

Electron microscopy:
• Tennis Racquet appearance
  Dilatation of tips of cristae and widening of intracristal space
Prognostic index
Nazer prognostic index
- Bilirubin
- AST
- Prothrombin time.

Management
1st DOC: D penicillamine
- 500mg thrice daily
- Along with pyridoxine
- Toxicity: 1 myasthenia gravis
  2 Aplastic anemia
  3 Membranous nephropathy

2nd DOC: Trientine
  ↓
given along with Zinc
- in pregnancy DOC: Zinc
  In neuro wilsion → add tetra thio molybdate.

Zinc
- Induce metallothionein on enterocytes
  ↓
  prevents copper exit from enterocytes.

MRI in Wilson's disease
T₂ hyperintensities.

- Face of giant panda sign
- Superior colliculus - low intensity
  (chin and mouth)
- tegmentum - ↑ intensity (eyes)
- Pars reticulata - preservation of signal
  intensity (ears)

Bright claustrum sign
- Thin rim of T₂ hyperintensity
  in claustrum
- In pons
  a. Hyperintensity of pons
  b. Hyperintensity bisected by line
c. Trisected hyperintensity

"mercedes benz sign"
or
"Trident sign"

Brain Stem changes: CPM like

a. Classical: Hyperintensity of whole of the central pons sparing a peripheral rim;
b. Bisected pontine signal change by a horizontal line and;
c. Trisected: Pontine hyperintensity trisected by a hypointense line like 'Mercedes Benz' sign
**HEMOCHROMATOSIS**

**Hereditary hemochromatosis**

- Hemochromatosis = Chronic-hepatitis → Cirrhosis
  → Decompensation

1) HFE gene related:
   - On chr 6p, AR
   - Males > females
   - Age = 40-60yr
   - Homozygous = disease
   - Heterozygous = carriers

2) Non HFE gene related:
   - Hemojuvelin
   - TFR-2
   - Hepcidin
   - mc in boys

- Carriers: ↑ risk for porphyria, cutanea tarda, Non alcoholic steatohepatitis

- HFE - Gene:
  - Duodenal enterocyte = iron absorption

- DMT (Divalent Metal Transporter)
- Ferroportin → regulated by Hepcidin
- Genes controlling Hepcidin = HFE gene
  - HJV
  - TFR-2
- Impaired Hepcidin synthesis
- Uncontrolled iron reaching blood stream
- Hemochromatosis

**Disease course: Hemochromatosis**

- Chronic hepatitis is the early stage
  - Liver
    - Peripoortal hepatocytes (iron accumulation site)
      - Mixed / macronodular cirrhosis - mostly asymptomatic
      - Hepatomegaly (AST < ALT < 150, ALT > AST) fatigue
  - Skin
    - Bronzing/metallic/slate grey hyperpigmentation
      (Fore arms, Dorsum of hand, Neck)
  - Pancreas
    - Pancreatic diabetes [Type 3c]

Scanned with CamScanner
- Joint → Small joint, Non erosive, Non inflammatory
  arthropathy → pseudogout (chondrocalcinosis)
- Gonads → Hypogonadism [hypogonadotrophic type]
- Heart → Diastolic dysfunction (dilated cardiomyopathy),
  Conduction blocks.

Arthropathy

- High mucosal absorption (> 4g/day)
- Hepcidin responds to signal mediated by HFE/TfR2/Hemogluvin

\[ \text{S. Ferritin} \quad \text{PSAT} = \frac{\text{S. Iron}}{\text{TIBC}} \times 100 \]

Best method: S. ferritin + PSAT

↑↑ S. ferritin (>1000ng/ml)  
↓ S. Iron → Iron bound to transferrin  
Baa prognosis.  
TIBC = Total Iron Binding capacity
TIBC = Total Iron Binding capacity

Natural history of HH

Confirmatory test: C282Y mutation
- Alcohol ↑ risk for cirrhosis in hemochromatosis
### Representative Iron Values in Normal Subjects, Patients with Hemochromatosis, and Patients with Alcoholic Liver Disease

<table>
<thead>
<tr>
<th>Determination</th>
<th>Normal</th>
<th>Symptomatic Hemochromatosis</th>
<th>Homozygotes with Early, Asymptomatic Hemochromatosis</th>
<th>Heterozygotes</th>
<th>Alcoholic Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma iron, mmol/L (mg/dL)</td>
<td></td>
<td>9-27 (50-150)</td>
<td>32-54 (180-300)</td>
<td>Elevated or normal</td>
<td>Often elevated</td>
</tr>
<tr>
<td>Total iron-binding capacity, mmol/L (mg/dL)</td>
<td>45-56 (250-370)</td>
<td>36-54 (200-300)</td>
<td>36-54 (200-300)</td>
<td>Elevated or normal</td>
<td>45-56 (250-370)</td>
</tr>
<tr>
<td>Transferrin saturation, percent</td>
<td>22-46</td>
<td>50-100</td>
<td>50-100</td>
<td>Normal or elevated</td>
<td>27-50</td>
</tr>
<tr>
<td>Serum ferritin, mg/L</td>
<td></td>
<td>900-6000</td>
<td>200-500</td>
<td>Usually &lt;500</td>
<td>10-500</td>
</tr>
<tr>
<td>Men</td>
<td>20-250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>15-150</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver iron, mg/dry wt</td>
<td>300-1400</td>
<td>6000-18,000</td>
<td>2000-4000</td>
<td>300-3000</td>
<td>300-2000</td>
</tr>
<tr>
<td>Hepatic iron index</td>
<td>&lt;1.0</td>
<td>&gt;2</td>
<td>1.5-2</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

### Treatment: Hemochromatosis

- **TOC**: Phlebotomy [if cirrhosis → efficacy ↓]
  - Cannot reverse joint & gonads changes
  - Remove: 1 unit of whole blood weekly
    - Assuming 500 ml of blood
    - Assumes 250 mg of iron
  - When S. Ferritin < 150 ng/ml → once monthly phlebotomy
- If phlebotomy is not well tolerated → s/c Desferrioxamine
  - Daily for 5 days a week
- Liver transplant is done when Cirrhosis & decompensation sets in
  - ↑ Risk of HCC - post transplant
Classification of Iron Overload States

Hereditary Hemochromatosis
- Hemochromatosis, HFE-related (type 1)
  - C282Y homozygosity
  - C282Y/H63D compound heterozygosity
- Hemochromatosis, non-HFE-related
  - Juvenile hemochromatosis (type 2A) (hemojuvelin mutations)
  - Juvenile hemochromatosis (type 2B) (hepcidin mutation)
  - Mutated transferrin receptor 2, TFR2 (type 3)
  - Mutated ferroportin 1 gene, SLC11A3 (type 4)

Acquired Iron Overload
- Iron-loading anemias
  - Thalassemia major
  - Sideroblastic anemia
  - Chronic hemolytic anemias
  - Transfusional and parenteral iron overload
  - Dietary iron overload
- Chronic liver disease
  - Hepatitis C
  - Alcoholic cirrhosis, especially when advanced
  - Nonalcoholic steatohepatitis
  - Porphyria cutanea tarda
  - Dysmetabolic iron overload syndrome
  - Post-portacaval shunting

- Prussian Blue Staining
  used for iron.
NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Definition

- NAFLD - Fat accumulation in more than 5% of hepatocytes (macrovascular steatosis)
  Alcohol intake <30 g/d males or <20 g/d in females

- In NAFLD
  
  80% → 20%
  
  Isolated fatty liver (IFL) → Fatty liver (Steatosis) + inflammation → Non Alcoholic steatohepatitis (NASH)

  Progresses to

  Occurs in zone 3 hepatocytes - Chicken wire fibrosis - Cirrhosis → Decompensated → Hepatocellular Carcinoma.

Difference between IFL and NASH, two hit hypothesis

- For difference between IFL and NASH
  
  Liver biopsy - degree of Steatosis
  - degree of Lobular inflammation
  - Ballooning of hepatocytes

  In NASH there will be - more degree of Steatosis,
  more degree of Lobular inflammation
  more ballooning of hepatocytes

<table>
<thead>
<tr>
<th>TABLE 87-1 NAFLD Activity Score on a Liver Biopsy Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
</tr>
<tr>
<td>Ballooning</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
</tr>
<tr>
<td>Total Score</td>
</tr>
</tbody>
</table>

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.
Two hit hypothesis

- Risk factors for NAFLD - **MC - Starvation**
  - Obesity
  - Sedentary lifestyle
  - Metabolic syndrome
  - Insulin resistance
  - Polycystic ovarian syndrome

- In NAFLD - in the presence of oxidative stress/ mitochondrial dysfunction/ Gut dysbiosis or endotoxins
  \[ \downarrow \]
  Can develop NASH

Causes of NAFLD, NASH

Drugs:
1) Bleomycin - **MC**
2) Tetracycline
3) Azacitidine
4) L- asparaginase
5) Estrogen and steroids
6) Valproate
7) Nitrofurantoin
8) Amiodarone

Metals
- Barium
- Chromium
- Mercury

![Fatty liver](image1)

![Ballooning of hepatocytes](image2)
Liver enzymes in NASH, IFI

- If liver enzymes (AST, ALT) - Normal + Fatty liver → likely to be IFI

- If liver enzymes (AST, ALT) - < 150 μ/l + Fatty liver → NASH

- If liver enzymes (AST, ALT) - < 150 μ/l but AST > ALT
  - likely to be NASH + cirrhosis
  - Should definitely perform a fibroscan

- Other signs - Hepatomegaly
  - Right upper quadrant pain

Associations of NASH
- Obstructive sleep apnea syndrome
- Polycystic ovarian Syndrome
- Coronary artery disease
- Colonic adenomas
- Hypothyroidism
- Vitamin D deficiency

Symptoms of NASH, NAFLD

- Common symptoms - none
- Common sign - hepatomegaly

- Uncommon symptoms - vague right upper quadrant pain
  - Fatigue
  - Malaise

- Uncommon signs - Splenomegaly
  - Spider angioma
  - Palmar erythema
  - Ascites
- Low adiponectin levels + Leptin resistance
Diagnosis -
- Fibro Scan - Transient elastography
- In NASH - Serum ferritin levels are high
- Blood markers of fibrosis - Cytokeratin 18 terminal peptide of procollagen 3

Management of NASH, NAFLD

- NAFLD - Active exercise + weight reduction
- NASH - Weight reduction
  - D.O.C. Vitamin E: 800-1000 IU/day
  - Pioglitazone, Pantoprazole
  - Regular coffee consumption
  - Omega 3 fatty acid consumption

<table>
<thead>
<tr>
<th>Option</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Improve most histopathologic features of NAFLD</td>
<td>Data is lacking for fitness improvement; only ± 20% of patients were able to achieve the goal in clinical trials</td>
</tr>
<tr>
<td>Exercise</td>
<td>Improve insulin resistance, liver enzymes, and steatosis by imaging</td>
<td>No studies have assessed the effect on NASH hepatopathy; weight loss is not associated with diabetes modification</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Improve NASH when used for 2 years; no improvement in fitness</td>
<td>Validation studies in diabetes and various effects; groups are needed to confirm a benefit, may increase risk of premature cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Pioglitazone 30-45 mg daily</td>
<td>Validation studies in diabetes and various effects; groups are needed to confirm a benefit, may increase risk of premature cancer</td>
</tr>
<tr>
<td>Oral</td>
<td>Pantoprazole 400 mg three times daily</td>
<td>Validation studies in diabetes and various effects; groups are needed to confirm a benefit, may increase risk of premature cancer</td>
</tr>
</tbody>
</table>

Active space
ALCOHOLIC LIVER DISEASE

- Male of Cirrhosis in India → Alcoholic Liver Disease (ALD)
- Cirrhogenic dose of Alcohol
  - Male = 40-80 g/day
  - Female = 20-40 g/day

### Alcohol Content of Various Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Approximate Alcohol Content</th>
<th>Serving Size</th>
<th>Amount of Alcohol</th>
<th>Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>5%</td>
<td>12 oz</td>
<td>14.02 g</td>
<td>Men: 3-5 cans, Women: 1.5-3 cans</td>
</tr>
<tr>
<td>Wine</td>
<td>12%</td>
<td>5 oz</td>
<td>14.02 g</td>
<td>Men: 3-5 glasses, Women: 1.5-3 glasses</td>
</tr>
<tr>
<td>Hard liquor</td>
<td>40%</td>
<td>1.5 oz</td>
<td>14.02 g</td>
<td>Men: 3-5 drinks, Women: 1.5-3 drinks</td>
</tr>
</tbody>
</table>

*Alcohol intake of 40-60 g/day for men and 20-40 g/day for women for 10 years.

### Standard Drink (12 gms abs.alcohol)

- One beer = 12 ounces
- 1 ounce = 30 ml
- 4 ounces = 1 ounce
- Small peg = 30 ml
- Large peg = 60 ml
Course of Disease

- Normal liver → Fatty liver
- Fatty liver → Alcoholic hepatitis
- Pericentral fibrosis in fatty liver
- Micronodular cirrhosis
- Macronodular cirrhosis with hepatocellular carcinoma

Cirrhosis starts in - Zone 3

Alcoholic hepatitis → 70% mortality

- Macro nodule → > 3mm
- Micro nodule → < 3mm

Alcohol metabolism

- Alcohol dehydrogenase (ADH)
- Cytochrome P₄₅₀ (CYP₄₅₀)
- Catalase

Product: Acetaldehyde
Acetaldehyde:
- depletes glutathione
- ↑ reactive O₂ species
- Adducts are formed in liver
- ↑ NADH/NAD ratio

In cirrhosis → Oxidative stress ↑ → mitochondrial dysfunction

Fibrosis ← Hepatocyte hypoxia.
(Zone 2 - centrlobular zone)

Best serum marker for ALD: Carbohydrate deficient Transferrin

Cause for thrombosis in ALD:

Increase in S-adenosyl homocysteine → thrombosis
Alcoholic hepatitis

- MC after binge drinking
- Presents similar to acute hepatitis
- Liver inflammation ⊕
- Mostly neutrophil mediated
  - ↑ mortality (10%) → Encephalopathy
    - Coagulopathy
- \( \frac{AST}{ALT} > 3:1 \)
- \( AST < ALT \) → <300 u/l
- Macrocytic anemia/megaloblastic anemia → due to ↓ Thiamine
- MCV ↑, TC ↑, PT ↑, Sr. Albumin ↓ (-ve acute phase reactant)

Alcoholic Hepatitis: Histopathology

- The central vein (terminal hepatic venule (THV), is encased in connective tissue (C) (central sclerosis). Fat laden hepatocytes (F) are evident in the lobule. The portal tract displays moderate chronic inflammation.
- Neutrophil mediated inflammation
- Ballooning degeneration (zone 3)
- Mallory body → made of intermediate filaments (Cytokeratin 8/18)

Other Conditions for Mallory Denk bodies:
- Wilson's disease
- Indian childhood cirrhosis
- NASH
- Cholestasis
- Alcohol / α1 Antitrypsin deficiency
- Primary Biliary Cirrhosis
- HCC
Hepatitis C → Chronic Hepatitis with fatty liver

Fatty liver in ALD:

microvesicular Steatosis

ALD: management

Alcoholic hepatitis

Hepatic encephalopathy or at least one of the following:
- $DF^* > 32$
- MELD$^+$ score $> 16$
- Glasgow score$^1$ $> 9$

Yes  No

Poor prognosis: consider specific therapy  Good prognosis: nutritional support and conservative management

Active gastrointestinal bleeding, systemic infection, or renal insufficiency

Yes  No

Pentoxifylline 400 mg three times daily for 28 days  Prednisone 40 mg for 7 days.

If serum bilirubin level decreases, continue prednisone 40 mg daily for an additional 21 days, followed by a two-week taper. If bilirubin level does not decrease, stop treatment after 7 days.

Severity markers:
- Hepato-encephalopathy
- MELD Score $> 18$
- Glasgow score $> 9$
- Discriminant Fraction $> 3.2$

$DF = 4.4 \times (PT_f - PT_c) + \text{Serum bilirubin}$

- If $DF < 3.2$ → Conservative management
  
- If $DF \geq 3.2$ → Bad prognosis = Start Steroid for 1 week (Prednisolone)

Active GI bleed → Pentoxifylline 400mg TID
• Portal Hypertension in absence of cirrhosis → Alcoholic hepatitis.

Acetaminophen intake:

In chronic alcoholic liver disease → Acetaminophen poisoning
  • ALT & AST > 1000
  • AST > ALT

Micronodular Cirrhosis: Causes -
  • Alcohol
  • Biliary cirrhosis
  • Indian childhood Cirrhosis
  • Budd Chiari Syndrome
    - Cystic fibrosis

Hemochromatosis - mixed cirrhosis

Microvesicular steatosis: Causes:
  - Pregnancy (AFLP)
    • Reyes syndrome
    • Eclampsia
    • Tetracycline
    • Valproate
    • Jamaican Sleeping sickness
    • Alcohol
    • Acid lipase deficiency

NASH & Chronic hepatitis - Macrovesicular Steatosis
Reyes Syndrome - Swollen mitochondria ↓ in numbers
Nutmeg liver - Chronic venous Congestion
HEPATITIS C

Hepatitis C virus - structure

- Single stranded RNA
- Flaviviridae family → Hepacivirus
- Positive sense single stranded RNA
- 9.7 Kb in length

- Structural proteins := Core protein
  Envelop protein E₁
  Envelop protein E₂

- Non structural proteins := NS₁, NS₂, NS₃, NS₄, NS₅, NS₆, NS₇, NS₉

- Host signal peptidase will cleave the structural proteins from non structural proteins

- E₂ := most variable region of HCV genome

- Directly acting antiviral drugs := NS₁, NS₂, NS₃, NS₅, NS₆
  → inhibitors := NS₁ → evir
  NS₂ → avir
  NS₃ → uvir

- Core protein forms viral nucleocapsid
- E₁ and E₂ proteins for viral assembly
  P₁ → ion channels for viral release
- NS₃ is the serine protease / function as serine protease is enhanced by association with NS₄A

- NSSA := RNA binding site within replication complex
- NSSB := is the RNA dependent RNA polymerase
Life cycle of hepatitis C virus

1. HCV Virus infects human
2. Binding to unidentified cell surface receptor and internalization in liver cell
3. Cytoplasmic release and uncoating of RNA genome
4. Translation and polyprotein processing by cellular and viral proteases
5. RNA replication
6. Packaging and assembly
7. Virion maturation
8. and 9. Release from host cell

→ 6 - genotypes

Epidemiology:
→ Punjab in India has highest prevalence
→ Estimated prevalence in India → 0.5 - 1.5%
→ Higher prevalence in Punjab → 5.2% (3.2%)
→ Geno 3 - Commonest genotype in India → most prone for Cirrhosis
→ Geno 1 - commonest worldwide
• No vaccines

Transmission:
• Blood transfusion incidence:
  → Hep B
  → 1 case for every 2 lakh units
  → Hep C
  → 1 case for every 15 lakh units
• Most common mode of transfusion of hepatitis C virus
  → i.v. drug abusers (sharing needles)
- Transfusion hepatitis → CMV or EBV or HCV
- Chronic hemodialysis patients - needle prick → 1.8 - 6%
- Efficient percutaneous transmission
- Transfusion related → 4% only (acute HCV)
- IVDU → 48 to 90%
- Chronic hemodialysis
- Needle stick in health-care workers Seroconversion → 1.8 - 6%
- Rare form of transmission:
  - Perinatal → 5 - 7%
  - Vaginal delivery → no risk
  - Breast feeding → negligible, advised to feed
- Percutaneous - Iv. Drug users → 1.8 - 6%

**Acute Hepatitis C**

- Acute HCV → 20% of cases
- 85% → chronicity after acute hepatitis C
- Incubation period → 50 days
- Non specific manifestations
- Anicteric hepatitis
- Jaundice → 10 - 20%
- Clinical features → Nausea, vomiting, headache
- ALT, AST → very high
- Risk for fulminant hepatic failure → 0.5 - 1%
- Rare in clinical practice → majority asymptomatic
- 20% risk for Cirrhosis in patients followed up for 20 years

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.
- Anti HCV → positive
- HCV RNA → positive
- 6 months → 85% HCV RNA positive → chronic HCV
  → 15% HCV RNA undetectable → recovered

Symptomatic patients:
→ Vomiting, enzymes high
→ Acute HCV
  HCV RNA → positive
  Anti HCV → positive

Screening:
→ Anti HCV positive → false positive
  or recovered acute HCV
  Chronic HCV
  HCV RNA → detectable
  HCV RNA → undetectable

In chronic HCV
→ ALT / AST enzyme are of no value
→ Variable and fluctuating

Chronic Hepatitis C

→ Screening → anti HCV → positive
→ HCV RNA detectable (enzymes have no value)
→ Patient with fatigue with variable enzymes, arthralgias, paraesthesias, myalgias, pruritis, sicca syndrome
→ Extrahepatic manifestations
→ Cirrhosis and its complications

Extra-hepatic manifestations:
→ Essential mixed Cryoglobulinemia.
→ Lichen planus
→ Porphyria cutanea tarda
→ Sjogren syndrome → marginal zone B-cell lymphoma
→ Auto immune thyroiditis
→ membrano proliferative glomerulo-nephritides (MPGN)
→ Diabetes mellitus

→ Anti-LKM1 → chronic HCV
  → Auto immune hepatitis type - a
→ Anti-LKM2 → Drug
→ Anti-LKM3 → chronic hepatitis D

→ Cryoglobulinemia → fatigue + arthritis + confluent
  Purpura + neuropathy + MPGN I Raynaud’s

**Diagnosis of Hepatitis C**

- Indirect
  - EIA → detects antibodies
  → Latest EIA 3 (as early as 7-8 weeks)
  → Negative → if no hemodialysis, HIV
  → Anti HCV → positive

Anti HCV positive

- False positive
  - Positive
  → HCV

- or
  → Resolved acute HCV
  → HCV RNA undetectable

→ Anti HCV negative
→ CHD patient on dialysis go for HCV RNA

**Management :-**

<table>
<thead>
<tr>
<th>Acute HCV</th>
<th>Chronic</th>
<th>Cirrhosis</th>
<th>Decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99%</td>
<td>75-80%</td>
<td>55-60%</td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>SVR</td>
<td>SVR</td>
<td></td>
</tr>
</tbody>
</table>

SVR → Sustained Viral Response
→ HCV RNA → undetectable after 12 weeks
- Directly acting anti viral drugs

- Pangenotypic drugs:
  NSSA inhibitor with NS5B inhibitor x 12 weeks
  - Velpatasvir + Sofosbuvir
    (100 mg daily) (400 mg daily)

Decompensated cirrhosis → add Ribavirin
  NSSA NS5B
  - Avir (++) ← potency ← urir
  - Low barrier to resistance ← high barrier to resistance

- WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older irrespective of disease stage.

- WHO recommends the use of pan-genotype DAA regimens for the treatment of persons with chronic HCV infection aged 18 years and above.
HEPATITIS B

Hepatitis B Virus

- DNA virus
- Hepadnaviridae
- Partially double stranded
  - Complete - Strand
  - Incomplete + Strand

42nm Dane particle
4 overlapping genes

- S
- P
- (Surface)
- (Polymerase)

- C
- (Core)
- Anti Hbc IgG
- IgM

- X
- HCC
- Development

S gene → Small
S + pre S2 → medium
S + pre S2 + pre S1 → Large

Once infected with the virus → HbsAg +

S-gene mutation (‘a’ gene)
Escape mutant
HbsAg - , HBV DNA +

Occult HepB infection

<table>
<thead>
<tr>
<th></th>
<th>Acute Hep B</th>
<th>Chronic Hep B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg</td>
<td>+ ve</td>
<td>- ve</td>
</tr>
<tr>
<td>IgG</td>
<td></td>
<td>+ ve HbsAg</td>
</tr>
<tr>
<td>anti Hbc IgM</td>
<td></td>
<td>- ve IgM</td>
</tr>
<tr>
<td>HbeAg (Qualitative factor)</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>
Precore / Basal core mutation

↓

Can't express HbeAg

Problems of Ag - Ab of HBV

| HbsAg +ve | HbsAg +ve |
| HbeAg -ve | HbeAg -ve |
| ? Precore mutant | High infectivity |
| ↓ | High replication |

↓

• HBV DNA
  (Quantitative marker)

Life cycle

Infective virion

↓

Transcription

Nucleus

Subgenomic mRNA

(Covalent closed circular DNA cccDNA) Pregenomic mRNA

↓

Reverse transcriptase

Incomplete viral Particle

DNA dependent

Replication

Complete viral particle

DNA polymerase

HBV DNA load - IU/ml or copies/ml

↓

best marker for viral load.

Natural history of HBV

Acute → Chronic → Cirrhosis

Decompensation

Hep B

Hep B

Needle Vertical also possible

Sexual

Facts

1. cccDNA - Pregenomic mRNA is not under the Control of P gene.

a. Core particles interacts with S protein to initiate viral assembly in the ER.

10 genotypes - Type A (mc)
100 times infectious as HIV
10 times infectious as HCV
↓
All body fluids except stool
↓
Prick 6%-30%

mother → Child 90/10 Risk

HbsAg +ve          HbeAg - ve - 10%
HbsAg +ve          HbeAg + ve - 90%

1 in 2,000,000 units of blood transfused (infected)
Percutaneous - 6 to 30%
Vertical 100%
Chronic
- Any other mode 5%

Interpretation of HBV serology

1. Acute Hepatitis B (incubation - 60 days)
   • HbsAg +ve
   • anti Hbc IgM +ve
   • +/- Hb & Ag

2. after 6 months

95% recovery
HbsAg = -ve
Anti Hbc Ag IgG = +ve
Anti Hbs = +ve

5% - Chronic Hepatitis B
HbsAg = +ve
Anti Hbc IgG = +ve
Hbe Ag = +ve

Low infectivity/low respiration
HBV DNA < 2,000IU/ml

3. HbsAg
   - Anti Hbc IgG = +ve
   - Anti Hbe = +ve
   - Hbe Ag = -ve

Pre-core mutant
HBV DNA < 2,000IU/ml
4. HbS Ag +ve : 2 genotypes
   Anti HbS Ag + ve

5. anti Hbc IgM +ve : Acute Hepatitis B
   Remote infection (significant if going for transplant)

6. anti Hbc Ig + ve : False positive

7. anti HbsAg + ve : Vaccination

Precore / basal core mutants

• Unable to secrete HbeAg
• Bad prognosis
  ↓
  Core promoter mutation
  ↓
  HCC

Hep A - 100% recovery
Hep B - 95%
Hep C and Chronicity - 85% Chronic
Hep E - 100% recovery

Perinatal transmission (mother HbsAg +ve)
  ↓
  Hep B immunoglobulin (Ig) soon after birth 0.5ml
  +
  First dose vaccine within 12 hrs.

percuteous exposure
  ↓
  Anti Hbs

   100
   ↓
   Nothing

   10-100
   ↓
   Booster

   40
   ↓
   Unvaccinated
   ↓
   Ig + vaccine (in 7 days)
   0.05 ml/kg

Sexual Contact - Ig within 14 days.
Adult 3 doses 0, 1, 2
>20 yrs - 1 ml = 20 μg im deltoid
<20 yrs 0.5 - ml = 10 μg im deltoid

CKD pt - 4 doses (0, 1, 2, 6)
(aml)

≤ 20 yrs CKD pt. - 4 doses (0, 1, 2, 6)
(0.5-ml)

Chronic Hepatitis

Chronic Hep B ↓
Asymptomatic
Intermitent Jaundice
ALT > AST

- Extra hepatics
  - Polyarteritis nodosa (30/1)
  - Membranous Nephropathy
  - Small joint arthritis

HbeAg +ve ↓
HBV DNA > 20,000
High Infectivity

HbeAg -ve ↓
HBV DNA

< 2000 → Carrier
> 2000 → High Infectivity

ALT
Fibroscan

Cirrhosis

No cirrhosis

ALT > 2 times upper limit
No Tx

ALT < 2 times
↓
No Tx.
Stages of Chronic Hep B

- Immune tolerance: HBV DNA ↑, ALT (N), No inflammation
- Immune clearance: ↓, ALT ↑, Inflammation
- Inactive (Carrier): ↓, ALT (N), No inflammation
- Reactivation: Acute Hepatitis B, HbsAg +ve, ALT ↑, HbeAg -ve
- HBV DNA ↑.

Chronic Hepatitis B Epidemiology

- Age of acquisition of virus: Perinatal → Chronic
- Grade of liver disease
  - Determines risk of progression
  - Degree of replication
- Replicative Phase HBV DNA > 20,000
- Spontaneous seroconversion 1 - 1.5 %
- Intrahepatocyte HbcAg is present

Clinical Features

1. Fatigue
2. Intermittent jaundice
3. Acute exacerbations
4. Complications of cirrhosis
5. Extrahepatic
   - PAN
   - Arthritis
   - Membranous Nephropathy
6. Bilirubin: 3 - 10 mg/dl

Treatment
1. Peg interferon
   - s/c
   - 30 %
   - HbsAg +ve
   - HbsAg -ve

No effect seen in:
1. Young Asians
2. HbeAg -ve
3. Cirrhosis

Side effects:
- Thyroiditis
- Psychosis
- Bone marrow suppression
2. Lamivudine (YMDD mutation)
   ±
   Adefovir (nephrotoxic)

3. DOC - Entecavir / Tenofovir
   (0.5 mg daily) (300 mg daily)
   ↓

   Tenofovir alafenamide

Advantages
1. ↓ Systemic toxicity / nephro / bone
   a. Dose . 25 mg (low dose)
   b. more stable

HbsAg → HbsAg only drug interferon α
+ve -ve 20%-30%

HPE - Ground glassing of hepatocyte

Hepatitis D

* RNA delta virus.

Super infection
\[
\begin{align*}
\text{Chronic HBV HbsAg, anti Hbc IgG} & \\
\text{Acute HDV anti HDV IgM +ve} & \\
\text{Cirrhosis (anti LKM III antibody)} & \\
\end{align*}
\]

Coinfection:
\[
\begin{align*}
\text{Acute hepatitis B anti Hbc IgM +ve} & \\
\text{2nd peak of jaundice anti HDV IgM +ve} & \\
\text{No risk for cirrhosis} & \\
\text{Risk for fulminant hepatitis (20%)} & \\
\end{align*}
\]
ASCITES

Decompensation in cirrhosis: Portal hypertension +

Introduction to Ascites

- Definition: Fluid in peritoneal cavity
- Ascites is the earliest complication of portal hypertension.
  Note - Portal hypertension and splenomegaly appears together
- Cause:

  Due to portal hypertension  
  Not due to portal hypertension

Serum Ascitic Fluid Albumin Gradient (SAAG)

\[ SAAG = \text{Serum albumin} - \text{Ascitic fluid albumin} \]

\[ \begin{align*}
\text{SAAG} \\
\downarrow \\
&\begin{array}{ll}
\text{Low SAAG (10%)} & \text{High SAAG (90% cases)} \\
\leq 1.1 \text{ g/dl} & \geq 1.1 \text{ g/dl} \\
\text{Portal hypertension} & \text{Portal hypertension} \\
\end{array}
\end{align*} \]

Low SAAG ascites
- High ascitic fluid albumin
  - Peritoneal carcinomatosis > Peritoneal TB > Peritonitis
- Low serum albumin
  - Nephrotic syndrome

High SAAG ascites
- Low protein ascites (no albumin leak via sinusoids)
  - Sinusoidal pathology
  - Proteins in ascitic fluid ↓↓
  Cause: cirrhosis with portal hypertension
- High protein ascites
  - Hepatic vein pathology
  - Proteins in ascitic fluid ↑↑
  Cause: Budd-Chiari syndrome, constrictive pericarditis
Pathophysiology of ascites in portal hypertension

Portal Hypertension $\rightarrow$ Splanchnic vasodilatation $\rightarrow$ Defective
(Nitric oxide mediated) $\rightarrow$ intravascular volume

$\downarrow$

Stimulates RAAS
(Renin Angiotensin
Aldosterone System)
and sympathetic system

$\downarrow$

$\uparrow$ Na$^+$, H$_2$O retention

$\downarrow$

$\uparrow$ Intravascular volume

Fluid leak into peritoneal cavity

$\downarrow$

Ascites $\leftarrow$ Via Hepatic vein / sinusoids

Note:
- First sign of decompensation: Splenomegaly $\rightarrow$ Portal hypertension
- First complication of decompensation (portal hypertension): Ascites
- Ascites in portal hypertension without decompensation: Alcoholic hepatitis

Diagnosis of ascites

- Ultrasound - minimum 100 ml of ascitic fluid can be detected
- Shifting dullness - 500 ml
- Fluid thrill - 1000 ml
- Neck veins +ve - Constrictive pericarditis
  - Ideal site for Ascitic fluid tap
    - Left lower quadrant 2 cm cephalad and 2 cm medial to anterior superior iliac spine

Assessment of ascitic fluid

Normal Ascitic fluid:
- WBC < 500 cells/µl
- PMN (poly morpho nuclear leucocytes) < 250 cells/µl
Hemorrhagic Ascites:
RBC > 10,000 cells / μl ⇒ Pink ascitic fluid
milky Ascitic fluid

<table>
<thead>
<tr>
<th>Chylous</th>
<th>Pseudochoylous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>sudden</td>
</tr>
<tr>
<td>Cause</td>
<td>Acute obstruction / trauma to lymphatic duct lymphocytosis</td>
</tr>
<tr>
<td>Microscopic examination</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt; 110 mg/dl chylomicrons present</td>
</tr>
<tr>
<td>Lipoprotein electrophoresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gradual</td>
</tr>
<tr>
<td></td>
<td>Neutrophils in ascitic fluid due to inflammation</td>
</tr>
<tr>
<td></td>
<td>mixed cellular reaction, cholesterol esters, neutrophils</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dl chylomicrons absent</td>
</tr>
</tbody>
</table>

Approach to a case of ascites

- Ascitic fluid
  - WBC > 500 cells / μl
  - PMN > 250 cells / μl

  - Ascitic fluid - Bile stained
    - Ascitic fluid - Bilirubin > 6 mg/dl
      - Biliary peritonitis
      - x-ray (standing)- air under diaphragm
        - 2° Bacterial peritonitis
          - mostly perforation peritonitis

SBP, MNB, CNNA

Spontaneous Bacterial Peritonitis (SBP)
- Ascitic fluid - culture positive
- PMN : > 250 cells / μl
- No evidence of intra-abdominal, surgically treatable source of infection
- Most common organism : E-Coli
Monomicrobial Non-neutrocytic Bacterascites (MNb)
- Culture positive
- PMN < 250 cells/μl
- Most common cause - Gram positive organism

Culture Negative Neutrocytic Ascites
- Culture negative
- PMN > 250 cells/μl
- Good immunity

Management
- SBP: Inj Cefotaxim 2g IV TDS x5 days
- Risk of recurrence is high
- Prophylaxis
- Prior SBP or Cirrhosis + Portal HTN: Norfloxacin 400mg OD
- Active GI bleed: Inj Ceftriaxone 1g IV x7 days

Management of Subacute Bacterial Peritonitis

- Salt restriction
  - Monitor urine sodium
  - Urine Na⁺: K⁺ ratio > 1 ⇒ require further salt restriction
  - < 1 ⇒ start drug therapy
- Diuretics
  - Spironolactone 100 mg + Furosemide 40 mg
  - Not responding
  - Add midodrine
  - Not responding
  - Therapeutic paracentesis every 2 weeks
  - Not responding
  - TIPS
    (Transjugular intrahepatic portosystemic shunt)

Refractory Ascites

Diuretic intolerant ascites

Resistant ascites
  - Not responding to Spironolactone 400mg
  - Furosemide 160mg
  - Salt restriction

HEPATIC ENCEPHALOPATHY

Definition

Hepatic Encephalopathy (HE) or Portosystemic encephalopathy (PSE) is a reversible syndrome of impaired brain function, occurring in patients with advanced liver failure.

Hepatic encephalopathy
- Complication of portal hypertension (PHTN)
- A/V/A portosystemic encephalopathy
- Reversible
- Precipitating factor present
- Predominant cell affected - Astrocyte (Alzheimer's type II astrocyte)
- Grading system - West Haven
- Major toxin involved - Ammonia.

Gut - derived neurotoxins

- Most important - Ammonia.

Produced in the intestine from

Dietary protein → deamination of glutamine via glutaminase → bacterial action in the colon
- Ammonia is absorbed by non-ionic diffusion
  ↓
  Ammonia (NH₃)
  ↓
  Enters portal circulation
  ↓
  Liver
  ↓
  Detoxification by urea cycle

- In hepatic encephalopathy
  ↓
  Liver dysfunction - No urea cycle
  ↓
  ↑ Ammonia in circulation
  ↓
  Enters brain - Astrocyte
  ↓
  In Astrocyte - Glutamate + NH₃
  ↓
  Glutamine synthetase
  ↓
  Glutamine
  ↓
  Enters neuron → Converted to Glutamate

Acts on NMDA Receptor (Post synap-
↓
Neurotoxicity
↓
1) Extra cellular and cerebrospinal
Fluid(CSF) glutamate - ↑↑
ii) Total brain glutamate - ↓↓

Endotoxins and types of hepatic encephalopathy

Other endotoxins Causing HE
1) mercaptans (degradation of methionine in the gut
a) Phenols
3) Free fatty acid
4) Gamma Amino Butyric Acid (GABA)
5) Octopamine
6) Aromatic Amino acids
7) manganese
Types of Hepatic Encephalopathy

- **Type A**
  - HE in acute liver failure (Fulminant hepatic failure)
  - High grade cerebral edema is seen
  - < 7 days
  - Fulminant

- **Type B**
  - HE post TIPSS (Transjugular intrahepatic Portosystemic Shunting)
  - 7-28 days
  - Acute

- **Type C**
  - HE in Cirrhosis
  - > portal HTN
  - 28 days - 6 months
  - Subacute

**Precipitating factors**

1. ↑ nitrogen load - due to - constipation
   - GI bleeding
   - Dietary protein
   - Azotemia (uremia)

2. Infection - sepsis
   - In vomiting → Hypovolemia, hyponatremia → Alkalosis
     \[ \text{↑} \text{NH}_3 + \text{H}^+ \rightarrow \text{NH}_4^+ \text{↑} \]

- CNS drugs
- Dehydration

**Pathogenesis**
Modified West Haven Criteria

Grading of HE

Grade 0  MHE  Grade I  Grade II  Grade III  Grade IV
Normal  • Minimal HE  • Altered sleep pattern  • Confused  • Stupor  • Coma.
  • ↓ attention span  • disoriented  • Responsive  • Unrespon
tive  • ↓ deep pain
  • ± tremors  • personality  • muscle rigidity
  • Psychometric test defective  • behaviour changes  • Astrexis or
  • test defective  • changes  • flapping  • tremors
  e.g. number connection test

Concealed HE
EEG - Normal

Overt HE
EEG - Abnormal

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Hepatic encephalopathy investigation and treatment

Electroencephalography (EEG)

Triphasic waves - HE - Grade IV
Stages of EEG and Clinical state

<table>
<thead>
<tr>
<th>Stage of EEG</th>
<th>Clinical State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alert</td>
</tr>
<tr>
<td></td>
<td>Drowsy</td>
</tr>
<tr>
<td></td>
<td>Stuporose</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Deep coma</td>
</tr>
<tr>
<td>Triphasic</td>
<td>Terminal</td>
</tr>
</tbody>
</table>

Treatment

1. Lactulose containing bowel wash
   - non-absorbable disaccharide (metabolized by intestinal bacteria)
     - reduce pH\(\rightarrow\) \(NH_3 + H^+ \rightarrow NH_4^+\)
2. Rifamixin \(\rightarrow\) 400mg TDS / 550mg BD
3. Acarbose
4. L-ornithine, L-aspartate
5. Sodium benzoate
HEPATOrenal SYNDROME

Hepatorenal Syndrome

1) Diagnosis of exclusion
   a) Structurally normal kidney
      ↓
      But functionally abnormal kidney → due to portal hypertension (PHTN)
      ↓
      Splanchnic vasodilation
      ↓
      Activates renin angiotensin system (RAS)
      ↓
      Severe intra renal vasoconstriction

3) In ultrasound - Normal kidney, urine analysis - Normal
4) Prerenal impairment - excluding - GI loss
   Diuretics use
   ↓ Albumin

Criteria, Types, Treatment of Hepatorenal system

Criteria
1) Cirrhosis + PHTN
2) Acute renal failure (acute kidney injury)
3) No structural kidney disease
4) Urinalysis - Normal
5) No GI loss / No Hypoalbuminemia
6) No diuretic overdose
Types of HRS

- Types I
  - Bad prognosis
  - Without transplant
  - Median survival: 4-6 weeks

- Types II
  - Not seen clinically
  - Presents as refractory ascites
  - Median survival without transplant: 4-6 months

Treatment
- Definitive treatment - Liver transplant
- Vasoconstrictors - for splanchnic vasoconstriction (Only in patients awaiting transplantation)

- Terlipressin
- Norepinephrine
- Midodrine + s/c Octreotide

Table 2. Vasoconstrictor Drugs for the Treatment of Hepatorenal Syndrome

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terlipressin</td>
<td>Vasopressin analogue</td>
<td>1 mg IV every 4-6 h; increase to 2 mg every 4-6 h if no improvement in Scr (decrease by 25% by day 3) up to a maximum of 12 mg/d; as long as there are no side effects; maximal treatment 14 d</td>
<td>Not available in the United States</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α-Adrenergic agonist</td>
<td>0.5-3.0 mg/h (continuous infusion); titrate to achieve a 10-15 mm Hg increase in MAP</td>
<td>Requires ICU; in countries where terlipressin is not available, norepinephrine can be used as a bridge therapy in ICU patients or as an alternative in patients in whom midodrine + octreotide has failed</td>
</tr>
<tr>
<td>Midodrine + octreotide</td>
<td>α-Adrenergic agonist (midodrine); somatostatin analogue (octreotide)</td>
<td>Midodrine: 7.5-12.5 mg orally 3 ×/d; Octreotide: 100-200 μg SC 3 ×/d</td>
<td>Requires ICU; in countries where terlipressin is not available, norepinephrine can be used as a bridge therapy in ICU patients or as an alternative in patients in whom midodrine + octreotide has failed</td>
</tr>
</tbody>
</table>

Note: All vasoconstrictors should be given in combination with 25% IV albumin.
Abbreviations: ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous; Scr, serum creatinine

Pseudohapatorenal Syndrome
- Liver failure + Renal failure
  - Eg - in leptospirosis (Weil's disease)
Hepato pulmonary Syndrome

- Clinical triad of:
  - Liver disease (usually portal hypertension with or without cirrhosis)
  - Hypoxemia
  - Intra pulmonary vascular vasodilation

Pathogenesis

- Due to nitric Oxide (NO) → Intrapulmonary vasodilation
  + Shunting alveolar capillary
  ↓ Deoxygenated blood in vein
  ↓ Affects diffusion
  ↓ Hypoxia

- ↑ (A - a) O₂ - (A - alveolar, a - artery)
- C/F - Platypnea (Dyspnea on lying down)
  Orthodeoxia (Shunting of deoxygenated blood ↑ on standing)
- Vascular abnormalities predominate in lower lung fields
- Absence of Cardiopulmonary diseases
- IODC - Bubble Echocardiography
- Treatment - Liver transplant
Budd Chiari Syndrome (BCS)

- Obstruction at any site from the efferent vein of the acinus to the entry of IVC (inferior vena cava) into right atrium
- M.C. site - hepatic vein or terminal IVC
- Females: 35 - 40 yrs
- Post partum period

Classification

1° BCS
- Occurs without a cause (Idiopathic)

2° BCS
- Inherited
  - Factor V Leiden mutation - M.C.
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
- Acquired
  - Polycythemia rubra vera
  - Paroxysmal nocturnal hemoglobinuria
  - Anti-phospholipid antibody syndrome
  - Pregnancy
  - Oral contraceptive pills (OCP)

Types of clinical presentation:

- Acute - rare
  - In acute hepatitis
  - C/F - Abdominal pain
    - Ascites
    - Hepatomegaly
  - Rarely fulminant form

- Subacute - M.C.
  - Refractory Ascites
due to transudation from hepatic veins
  - High SAPP, high protein (Serum to Ascites Albumin gradient)

- Chronic
  - Cirrhosis (decompensated)
  - Liver failure
  - Cirrhosis - involves Zone - 3
d  - Centrilobular zone
  - Sinusoidal distention
Budd Chiari Syndrome - diagnosis, treatment

- Screening test - ultrasound with hepatic venous doppler
- I.O.C - CECT
  - Caudate lobe hypertrophy - shows hyperintensity
  - Occlusion of hepatic vein
- For nodules/ hemorrhage in the liver - MRI
- Gold standard test - venography

Treatment

- Acute BCS
  - Conservative management
  - Wait for recovery
  - Angioplasty with stenting
    - if not effective
    - TIPSS (Transjugular intrahepatic Portosystemic shunt)
- Subacute BCS
- Decompensated
  - Liver transplant
- Poor prognosis - 90% die within 3yrs

Extra hepatic portal venous obstruction

- 1st order portal vein obstruction
  - due to umbilical sepsis > thrombosis
  - Seen in children (3-8 yrs)
  - C/F: massive upper GI bleeding
    +
    - massive splenomegaly
  - No ascites / no hepatomegaly
  - No cirrhosis
  - Normal liver function test (LFT)
  - Good prognosis
• Management - manage upper GI bleed
  \[\text{endoscopic variceal ligation}\]
  • Complications - growth retardation
  Portal biliopathy - due to cavernoma formation
  (collaterals - compress biliary system)
  • Screening test - ultrasound and colour doppler - shows cavernoma formation
  • I.O.C - CECT - shows leash like cavernous appearance

GROWTH RETARDATION

• Deprivation of portal blood flow leading to reduction of hepatotropic Factors needed for normal growth.
• Malabsorption secondary to portal hypertensive enteropathy.
• Early satiety due to massive splenomegaly
• Growth hormone (GH) resistance evidenced by high levels of GH and low levels of Insulin-like growth factor-1 (IGF-1)
• Anemia and Hypersplenism

USG AND COLOUR DOPPLER

• 94-100% sensitive and 96% specific in the diagnosis of EHPVO.
• Non-visualization of portal vein with multiple tortuous anechoic structures at porta representing cavernoma formation.
• Liver size and echotexture is normal.

CECT ABDOMEN

• The exact extent of portal vein thrombosis with or without extension to intrahepatic divisions, splenic and superior mesenteric vein can be visualized.
• The multiple portosystemic collaterals and thin gallbladder visible not clearly seen on USG are better depicted on CT.
• CBD and MBP dilatation seen
• The main role of CT lies in ruling out other causes

• If Refractory
  Or Failed endoscopy \[\rightarrow\] Surgical management
  \[\downarrow\]
  mesenterico - left portal vein bypass

Surgery

INDICATIONS FOR SURGERY
• Persistent Variceal Bleeding who fail endoscopic therapy
• Presence of gastric or ectopic varices not amenable to endoscopic management
• Symptomatic Portal Biliopathy
• Growth failure
• Symptomatic hypersplenism

MESENTERICO-LEFT PORTAL VEIN (RED) BYPASS
• Most physiological and the shunt of choice as it restores the hepatic blood flow.
• Besides correcting portal hypertension, it also abolishes the systemic manifestations of EHPVO
Non Cirrhotic Portal Fibrosis (NCPF)

- Idiopathic portal hypertension
- Seen in adolescents & young adults
- A/H/A Obliterative portal venopathy
  - Hepatoporal sclerosis
- 2nd or 3rd order portal vein occlusion
- C/F - Massive upper GI bleed
  - Massive splenomegaly
  - No hepatomegaly / ascites
- LFT - Normal, absence of serum markers - hepatitis B, C
- Good prognosis
- Negligible chances for cirrhosis

Diagnosis - 1st line: Doppler ultrasound - thickened portal vein
  2nd line: Biopsy - shows sclerotic portal vein with
  - Normal hepatic vein, no cirrhosis

**Thickened portal vein**

- NCPF is associated with

  **Immunological disorders**
  - Common variable immunodeficiency syndrome
  - Connective tissue disease - SLE, scleroderma
  - Crohn disease

  **Infections**
  - Umbilical/portal pyemia, diarrheal diseases,
    bacterial infection in infancy
  - HIV infection
  - Arsenic poisoning
  - E-coli
  - Hypervitaminosis A
Post sinusoidal obstruction syndrome

- Obstruction before the efferent vein
- Seen post bone marrow transplant

due to heavy conditioning with cyclophosphamide, busulfan
Before transplantation
PORTAL HYPERTENSION

- Decompensated cirrhosis → present only in case of portal hypertension
- Portal hypertension: responsible for all complications of cirrhosis of liver:
  → GI bleed
  → Ascites → SBP (spontaneous bacterial peritonitis)
  → HE (Hepatic Encephalopathy)
  → HRS (Hepatorenal syndrome)
  → HPS (Hepatopulmonary syndrome)

Definition and causes of portal hypertension

Definition:
- Hepatic sinusoidal pressure > 6 mm Hg
- Portal venous pressure > 12 mm Hg

Causes:
- Prehepatic
  - 1st order portal vein → EHPVO (Extra hepatic portal vein occlusion)
    No cirrhosis
    - Splenomegaly
    - Upper GI bleeding
- Posthepatic
  - Efferent vein → hepatic vein → IVC
  - Budd Chiari syndrome → cirrhosis
  - Chronic constrictive pericarditis
  - Tricuspid regurgitation
  - Right heart failure
- Intrahepatic
  - divided into:
    → Presinusoidal: NCPF (Non cirrhotic portal fibrosis)
      Schistosomiasis
      Sarcoidosis
      Primary Biliary cirrhosis
    → Sinusoidal
    → Postsinusoidal: After bone marrow transplant
Portal hypertension in cirrhosis

- **Portal pressure** = Flow (F) × Resistance (R)

  ![Diagram of portal hypertension in cirrhosis]

- **Portal hypertension in cirrhosis is due to:**
  1. Nodules compressing sinusoid or ↑ resistance
  2. Defenestration and constriction of sinusoids

- **Portal hypertension is manifested by:**
  → Caput meduase

- **Clinically:**
  1. Thrombocytopenia due to hypersplenism
  2. Splenomegalgy
  3. Upper GI endoscopy → to look for varices
  → most important complication → ascites
Portal cirrhosis - portal vein
- 7.5 cm long and runs dorsal to hepatic artery and bile duct
- At hilum,
  - Umbilical vein drains to Left portal vein
  - Cystic vein drains to Right portal vein
- High compliance, low resistance (hepatic arterial buffer response)
- In case of portal vein occlusion → Hepatic artery.

Hepatic venous pressure gradient (HVPG)

\[
\begin{align*}
\text{HVPG} & = \text{Wedged hepatic} - \text{Free Hepatic} \\
& = \left( \text{WHVP} \right) - \left( \text{FHVP} \right)
\end{align*}
\]

- 1-5 mm Hg: normal
- >10 mm Hg: clinically significant portal hypertension
- >12 mm Hg: high risk for bleeding
- WHVP is almost equal to sinusoidal pressure
- Use of hepatic venous pressure gradient (HVPG) in the differential diagnosis of portal hypertension:

<table>
<thead>
<tr>
<th>Type of portal Hypertension</th>
<th>WHVP</th>
<th>FHVP</th>
<th>HVPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehepatic</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hepatic</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Posthepatic</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

\begin{align*}
\text{Risk of bleeding } & \alpha \text{ HVPG} \\
\text{Implication:} & \\
\text{Patient with cirrhosis} & \\
\downarrow & \\
\text{Checked for HVPG} & \\
\downarrow & \\
\text{HVPG > 10 mm Hg} & \\
\downarrow & \\
\text{Upper GI Endoscopy} & \\
\text{Small varices} & \text{Annual endoscopy} \\
\downarrow & \\
\text{medium / Large varices} & \text{Non-selective } \beta \text{ blocker} \\
\downarrow &
\end{align*}
Drug for treatment of portal hypertension

- Portal pressure = Flow × Resistance
- Drugs that ↓ portal blood flow:
  - Non-selective β- Adrenergic blockers
  - Somatostatin and its analogues
  - Vasopressin

- Acute upper GI Hemorrhage

- Drugs that ↓ intrahepatic Resistance:
  - α₁- Adrenergic blocking agents (Eg: Prazosin)
  - Angiotensin receptor blocking agents
  - Nitrates

  no therapeutic role

Esophageal variceal hemorrhage

- Primary prophylaxis for esophageal variceal hemorrhage →
  Non- indicated therapies:
  - Variceal sclerotherapy: Not effective
  - Surgical shunt: ↑ mortality
  - TIPSS (Transjugular Intrahepatic portosystemic shunt): lack of evidence
  - Cyanoacrylate injection in gastric varies: effective, ↑ complication risk
- Vasoactive agents used in management of acute variceal hemorrhage:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding)</th>
<th>Recommended Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide (SMT analogue)</td>
<td>Continuous IV infusion of 50 μg/hr</td>
<td></td>
<td>2-5 days</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Continuous IV Infusion: 0.2-0.4 U/min can be increased to 0.8 U/min</td>
<td></td>
<td>24 hours</td>
</tr>
<tr>
<td>Terlipressin (VP analogue)</td>
<td>Initial 48 hours: 2 mg IV every 4 hours until control of bleeding</td>
<td>Maintenance: 1 mg IV every 4 hours to prevent rebleeding</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>

**Warning:** Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

- Management of acute esophageal varices:
  - Vasoactive Drugs: Terlipressin
    - or
    - Octreotide
    - or
    - Vasopressin

  Blood transfusion (7-9 g/dl) → IV Antibiotic (ceftiraxone 1g/24 hours) →

  EGD (Esophagastroduodenoscopy): done within 12 hours of admission + patient →

  Hemodynamically stable → Variceal source confirmed

  Endoscopic variceal ligation risk of re-bleeding ↑

  TIPSS
Scoring system

modified Child–Pugh scoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Numerical Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Slight/moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>None</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>None</td>
</tr>
<tr>
<td>(seconds increased)</td>
<td>Slight/moderate</td>
</tr>
<tr>
<td></td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Total Numerical Score</td>
<td>Child-Pugh Class</td>
</tr>
<tr>
<td>5-6</td>
<td>A</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
</tr>
</tbody>
</table>

- Nutritional status: was used in the conventional scoring system

Rockall risk score

- Predicts poor prognosis
  (Rebleeding and mortality → upper GI hemorrhage)
- Uses clinical criteria (↑ age, comorbidity, shock)

  + Endoscopy findings

Forrest classification

- Endoscopic
- Assesses risk for:
  → Re-bleeding
  → Surgical requirement
  → Mortality
- Classified as: Active bleed, Recent bleed, Lesion without bleeding

![Forrest classification system with predictive prognosis](image)
**INFECTION DISEASE-1**

**Staphylococci**

- **Gram positive Cocci**
  - Catalase (+ve) → micrococcaceae
  - Catalase (-ve) → Streptococcaceae
    - micrococi → Staphylococci
    - Bacitracin Sensitivity Testing
      - Sensitive → Resistant
    - Enterococci
    - Streptococci Pneumococci

- **Staphylococcus in nutrient agar → Golden yellow pigmented colonies (β-carotene)**
- Blood agar → mild positive for hemolysis
- Specific medium → Ludlam’s medium
- Staph aureus v/s CONS:
  1) Coagulase test +ve
  2) Thermonuclease +ve
  3) DNase /phosphatase +ve
  4) Mannitol fermentation ☑
  5) Potassium tellurite agar → Black colonies
- Most common method of typing → Phage typing
  (mc type -80/81)
- Resistance → β-lactamase (Phage / Plasmid mediated)
  - MRSA (Chromosomally /Genetically mediated mec A gene)
  - MRSA is identified by disk diffusion method by using Oxacillin / Cefoxitin
  - mc site of colonization of staph. aureus → Anterior nares
Virulence factors:

I. Cell wall-based Protein A - Antiphagocytic, chemotactic, Co-agglutination

II. Leucocidin (Panton Valentine toxin) + ɣ hemolytic toxin → Synergohymenotropism → Destroys macrophages

III. Enterotoxin - Preformed toxin
   - Incubation period - 6 hrs
   - Heat stable
   - Acts on vagus & vomiting centre
   - No fever
   - No role for antibiotics

IV. Toxic shock syndrome Toxin / Pyrogenic exotoxin C / Enterotoxin F
   - Superantigen
   - a/w vaginal tampons
   - MC seen in actively menstruating females
   - Presents with fever with hypotension
   - MODS
   - Rx: Clindamycin

V. Exfoliative toxin
   - Staphylococcal scalded skin syndrome (SSS)
   - Nicholsky sign (+ve)

Clinical symptoms:
1) Skin and soft tissue infections
2) Breast abscess / mastitis
3) Folliculitis / furuncle / Carbuncle
4) Septic arthritis / Osteomyelitis
5) Pneumonia
6) Endocarditis
7) Tropical pyomyositis
Treatment:

1. Skin & soft tissue infections
   - Methicillin sensitive
   - Methicillin resistant
     - Dicloxacillin
     - Cephalexin
     - Cefazolin
     - Clindamycin
     - Minocycline
     - Co-trimaxazole
     - Linezolid (600 mg bd)

2. Systemic infections
   - Methicillin sensitive
   - Methicillin Resistant
     - Oxacillin 2g IV Q6H
     - Vancomycin 1g IV bd Infusion
       - Direct IV → Redman Syndrome
       - Ototoxicity
     - Nephrotoxic (Tubulotoxic)
       - Renal failure
         - Dose - 1g once in 5 days
         - Complete Failure
           - Stop vancomycin
             - Linezolid,
             - Teicoplanin,
             - Daptomycin,
             - Quinupristin / Dalopristin

3. VRSA → Telavancin
CoNS:

- mc → Staphylococcus epidermidis
- Most abundant species on skin
- Early prosthetic valve endocarditis
- mc infection associated with implantable foreign bodies
- Staphylococcus saprophyticus → Complicated UTI in pregnancy

Streptococcus:

- Catalase negative

Streptococci

↓

Carbonylase & antigen Lancefield

↓

Group A  Group B  Group C  Group D

Streptococcus Pyogenes  Streptococcus agalactiae  Clinically insignificant  Enterococci

↓

m-protein

↓

Griﬃth typing

↓

Unclassified

S. viridans

Based on Hemolysis (5% Blood agar)

↓

Partial Hemolysis  complete Hemolysis  No Hemolysis

↓

S. viridans  S. Pyogenes  Enterococci

- Catalase test → Staph v/s strep
- Bile solubility & Inulin fermentation → Strep v/s Pneumococci
- PYR test & failure to ferment ribose → Strep. pyogenes
- CAMP test & Hippurate hydrolysis → Strep. agalactiae
Antigenic structure:
- Cell wall → m Protein
- Streptolysin O and S (ASO titres are not used now a days)
- Toxin → 1) Pyrogenic exotoxin
  a) Erythrogenic toxin
  b) Dick toxin
  c) Scarlatiniform toxin
- Pyrogenic exotoxin C → TSS / Scarlet fever / Necrotising fasciitis
- Streptokinase: DNase B

Clinical spectrum:
1) Pharyngitis     6) Necrotising fasciitis
2) Scarlet fever   7) TSS
3) Impetigo        8) Myositis
4) Erysipelas      9) Puerperal sepsis
5) Cellulitis      10) Otitis media

Scarlet fever:
- Fever with scarlatiniform rash
- Upper trunk / Day 2 / Spares palms & soles
- Sandpapper skin
- Strawberry tongue
- Pastia’s lines ☹

Impetigo:
- Superficial infection of skin
- Young children
- Painless
- Erythematous papules / vesicles
- Honeycomb like crusting
- Rx: Benzathine Penicillin
Erysipelas:
- Involves Superficial dermis
- Erythematous edematous plaques
- Tenderness ++
- Fever ++
- Almost always on face (malar area of face)
- Rx: Benzathine Penicillin

Cellulitis:
- Epidermis + Dermis + Subcutaneous tissue
- mc in Immunocompromised
- Extremely dangerous
- Necrotising fasciitis → Sepsis → Infection Related
  (Breach of deep fascia)  Glomurolonephritis (IRGN)
  ↓  RPGN

Necrotizing fasciitis:
1) Pain
a) Systemic toxicity
2) Bullae
3) Hyponatremia
4) Crepitus
5) WBC > 15,000
INFECTIONOUS DISEASES – 2

- Empirical therapy targets:
  Staph + Strep + Anaerobes
  ↓
  1. vancomycin + Penicillin + Clindamycin
  2. Augmentin + cloxacillin (oxacillin) + Clindamycin

Sepsis:
- Old definition → SIRS (Systemic Inflammatory Response Syndrome), a focus of infection in body (Any 2/4 of the following)
  1) Temp < 36°C or > 38°C
  2) TC < 4000 or > 12,000
  3) HR > 90
  4) RR > 24

- New definition:
  → Life threatening organ dysfunction caused by a dysregulated host response to infection
  → SOFA (Sepsis organ failure assessment) score - Difficult to calculate
  → qSOFA score
    1) Systolic BP ≤ 100 mmHg
    2) Altered mentation
    3) Respiratory rate ≥ 22/min
      (Score ≥ 2a Poor outcome)

Severe sepsis → 1) Hypotension
  (sepsis with 2) Hypoxemia.
  organ dys- 3) Oliguria.
  function) 4) Metabolic acidosis
  5) Thrombocytopenia.
  6) Obtundation
Septic shock

- Definition → 1) Septic shock < 90 mmHg for 1 hour despite adequate fluid resuscitation
  2) Pressor support needed to maintain
     BP - 90/70 mmHg

- Refractory septic shock → Even with Pressor support,
  BP - < 90 mmHg for 1 hour

Complications:
  1) Hypotension
  2) Hyperventilation → Respiratory failure
  3) DIC
  4) Adrenal insufficiency
  5) Septic AKI / ATN
  6) ARDS

Streptococci viridans

- Species → S. mutans / Sanguis
- Presents as normal human flora of mouth
- Causes Infective endocarditis
- Penicillin susceptible
- α - hemolytic
- a/w Dental extractions

ENTEROCOCCI:
- γ - Hemolytic
- Normal flora of large intestine
- Needs high salt medium
- a/w large bowel related sepsis
- Hospital acquired infection
- Causes infective endocarditis, meningitis, UTI
- Rx: Vancomycin + Aminoglycoside
- Enterococci are intrinsically resistant to cephalosporins
Infective endocarditis

Vegetations consisting of platelet fibrin microcolonies on

1) Native prosthetic valve
2) Low pressure side of VSD
3) Mural endocardium damaged by foreign body
4) Intracardiac devices

- AV shunt infections Arterio-arterial shunt infections are called infective endarteritis

- MCC overall → Staph. aureus
  mc community acquired native valve endocarditis → Strep. Viridans
  mc health-care associated native valve endocarditis → Staph. aureus

- Prosthetic valve endocarditis:
  1) < 2 months → CONS
  2) 2 - 12 months → CONS
  3) > 1 year → Strep. Viridans

- IV Drug abusers left side → Staph. aureus / Enterococci
  Right side → Staph. aureus

Risk factors:
1) IV drug abusers
2) CVC (central venous catheter)
3) CIED (cardiovascular implantable electronic device)
4) Prosthetic valves
5) Structural heart disease
6) Malignancy → NBTE (non bacterial thrombotic endocarditis)
Cardiac lesions

High Risk

1. Prosthetic valve
2. TOF
3. PDA
4. AR
5. PS
6. Coarctation of aorta
7. VSD
8. MR

Moderate Risk

1. MVP + MR
2. TS
3. TR
4. PS
5. Mitral stenosis

Low Risk

1. ASD
2. MVP without MR

One liners:
- S. aureus can adhere directly to endothelium without injury
- S. aureus → mec CIED associated IE
- ASD has least risk of IE among CHD
- 15% of IE have negative blood culture
  a) T. whipplei

Clinical presentation:

Infective endocarditis

Acute Presentation

1. S. aureus

Subacute Presentation

1. S. Viridans
2. CONS
3. Enterococci HACEK
   (Prevent as level of unknown etiology)

Cardinal symptoms - fever, chills, malaise also anaemia
Infected Endocarditis

Cardiac

1. New onset murmur
2. CHF
3. Worsening of heart failure
4. Perivascular abscess
   - Conduction abnormality
5. Embolization into coronary arteries
6. Pericardial extension

Non-cardiac

1. Immunological
   - Osler’s node
     - Pink
     - Painful
     - Pulp of finger
     - Pea size
2. Roth spots
   - Exudative lesion
   - Pale centre
   - Surrounded by hemorrhages
3. RF positivity
4. MPO
   - Nephritic syndrome
   - Low C1, C4

Embolic

1. Janeway lesions
   - Non-tender
   - Rash
   - Palms & soles
2. Septic emboli
3. Splinter hemorrhage
4. Stroke
5. Pulmonary infarction
6. Renal infarction
7. Mycotic aneurysm
   (mca w/s virens)

- Infective endocarditis also have:
  1. Clubbing
  2. Splenomegaly
Diagnosis:

modified Duke's criteria.

- Major criteria.
  1. Positive blood culture
  2. Echocardiogram (+ve)
     Oscillating mass/abscess
     Dehiscence/New onset-murmur

- Minor criteria.
  1. Fever
  2. Risk factors
  3. Immunological phenomenon
  4. Embolic phenomenon
  5. Culture not meeting major criteria

- Transeosophageal ECHO is needed for:
  1. Myocardial abscess
  2. Valve perforation
  3. Intracardiac fistula
  4. Vegetation < 2mm
  5. Prosthetic valve

Surgery in endocarditis:
  1. Acute heart failure secondary to AR
  2. Ruptured sinus of valsalva
  3. Perivascular extension of infection
  4. Rupture into pericarditis
  5. Fungal endocarditis

Summary of treatment:

- Streptococci: Penicillin + Gentamicin (2 weeks)
- Enterococci: Ampicillin + Gentamicin (4-6)
- Staphylococci:
  - Native valve: Vancomycin (4-6 weeks)
  - Prosthetic: Vanco + Genta + Rifampicin

Culture negative
Culture report negative: Ceftriaxone + Gentamicin
Prophylaxis:

- Needed for
  1) Prior endocarditis
  2) Prosthetic valve
  3) Post cardiac transplant
  4) Unrepaired cyanotic congenital heart disease
  5) Repaired cyanotic CHD < 6 months
     (also repaired acyanotic)

- DOC Amoxicillin 2g 1 hour before procedure
  ↓
  Allergic to Penicillin
  ↓
  Clarithromycin / Clindamycin

- Can't take orally → Ampicillin 2g IV/IM
  ↓
  Allergic to penicillin
  ↓
  Clindamycin 600 mg IV

- Prophylaxis is also needed in:
  1) Manipulation of dental tissue / Periapical region / Perforation of oral mucosa.
  2) Incision of respiratory mucosa.

- Prophylaxis is not recommended for GI / GU procedures.
- In 1982 → Centers for Disease Control (CDC) defined HIV as Gay associated virus
- In 1984 → Luc Montagnier isolated virus in Paris (Pasteur Institute) awarded Noble prize in 2008
- Old term → Lymphadenopathy associated virus

HIV - CDC definitive diagnosis (1982):
- Even without laboratory investigations, presence of one of the following itself is enough for diagnosis.
  1) Candidiasis of trachea, esophagus / Bronchi / Lungs
  2) Extrapulmonary cryptococcosis
  3) Cryptosporidiosis with diarrhea > 1 month
  4) Primary CNS lymphoma < 60
  5) Kaposi sarcoma < 60
  6) PCP Pneumonia
  7) Progressive Multiple leucoencephalopathy
  8) Toxoplasmosis in Brain
  9) CMV other than liver / spleen / LN
  10) HSV infection causing
      - mucocutaneous ulcer > 1 month
      - Bronchitis
      - Pneumonitis
      - Esophagitis
  11) MAC / M. Kansasi infections involving other than;
      - Lung
      - Skin
      - Lymph node

Staging of HIV based on CD4:

<table>
<thead>
<tr>
<th>Stage</th>
<th>CD4 count</th>
<th>CD4(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>&gt; 500 cells / μl</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Stage 2</td>
<td>200-500 cells / μl</td>
<td>14-25</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&lt; 200 cells / μl</td>
<td>&lt; 14</td>
</tr>
</tbody>
</table>
- The above classification is not applicable to children < 1 yr
- In children < 1 yr:
  - Stage 1 \( \rightarrow \) > 1500 cells / \( \mu l \)
  - Stage 2 \( \rightarrow \) 750-1500 cells / \( \mu l \)
  - Stage 3 \( \rightarrow \) < 750 cells / \( \mu l \)

India and HIV:
- First case was detected in 1986 in Chennai
- HIV prevalence in India is 0.37%
- Worst affected state \( \rightarrow \) Andhra Pradesh
- Maximum prevalence is seen in Manipur
- People living with HIV / AIDS (PLHA) in India is approximately 21 lakhs

One liners:
- AIDS can develop within 3 years in 90% with CD4 count < 200/\( \mu l \)
- Active replication occurs even when sequestered in lymphoid tissue

Structure of virus

```
  
  Retrorinidae
  
  Delta Retroviridae \[ \downarrow \]
  
  HTLV - 1

  Lenti Retroviridae \[ \downarrow \]
  
  HIV

- Structural genes
  1. GAG (P55)
  2. Pol
  3. Env

  PIT \[ \downarrow \]
  
  P24 \[ \downarrow \]
  
  Reverse \[ \downarrow \]
  Integrate \[ \downarrow \]
  Protease \[ \downarrow \]
  Transcripase

  Shell \[ \downarrow \]
  Core \[ \downarrow \]

  Antigen, Antigen

  6P30 (Spike Protein)

  6P41 (Transmembrane Pedicle Protein)
```
- Non-structural genes
  1) Tat gene (p14)
     - Transcriptional activator gene
     - Elongation of viral DNA template
  2) NEF (p27)
     - Negative effector
     - Downregulation of CD4 molecules
  3) Rev (p19)
     - Regulation of viral gene expression
  4) Vit (p34)
     - Viral infectivity factor
  5) Vpr (p15)
     - Viral protein R
  6) Vpu/Vpx
     - Viral protein U/X

Based on Envelop protein

\[
\begin{align*}
\text{HIV-1} & \quad \text{HIV-2} \\
\downarrow & \quad \downarrow \\
\downarrow & \quad \downarrow \\
\downarrow & \quad \downarrow \\
\text{(mc)} & \quad \text{Only in Africa.} \\
\text{m} & \quad \text{less infectious} \\
\text{n} & \quad \text{less virulent} \\
\text{o} & \quad \text{11 to Simian virus} \\
\text{C} & \quad \text{most common subtype worldwide}
\end{align*}
\]

- Mode of transmission $\rightarrow$ sexual $>$ parent to child $>$ blood transfusion $>$ needle stick
- Risk of transmission $\rightarrow$ blood transfusion $>$ parent to child $>$ iv drug abuses $>$ needle stick (0.3%)
- Chance of infection from female to male is half as from male to female
- Maximum risk during pregnancy is not time of delivery (20-30%)
- Exclusive breastfeeding carries low risk of transfusion
- Mastitis, low maternal CD4 count, maternal vitamin A deficiency increases the risk of transmission
- HIV is nil in urine
- Saliva can't transmit HIV because of presence of Salivary Protease inhibitor
- Delta 3a mutation → Don't express viral protease → protection from HIV infection
- DC sign → C type lectin receptor on dendritic cells → Not protective

HIV Life cycle:
- Co-receptor for Fusion of HIV
  1) CXCR 4 → T lymphocyte
  2) CCR 5 → macrophage

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow edition 4 videos.

**HIV Lifecycle And Drug Targets**

1. **Entry Inhibitors**
2. **Nukes and Non Nukes**
   - Reverse transcription
   - Viral DNA
3. **Integrate Inhibitors**
   - Integration (strand transfer)
   - Viral DNA
   - Human Genomic DNA
4. **Protease Inhibitors**

**Fusion → Uncoating → Reverse transcriptase (Viral DNA)**

↓

viral DNA integrated with host DNA ← Integrate

↓

Transcription → Translation → Viral protein assembly

(Protease)

↓

Released into circulation ← Budding

Scanned with CamScanner
Acute HIV infection:

- 1P → 3-6 weeks
- Presentation similar to infectious mononucleosis;
  1) Fever
  2) Sore throat
  3) Lymphadenopathy
  4) 10% meningoencephalitis
- No risk for opportunistic infections
- CD8 T cells upregulated

CD4 count and opportunistic infections:

< 600 - Lymphadenopathy / thrombocytopenia
< 500 - Skin infections / HSV / HZV
< 400 - Kaposi Sarcoma
< 300 - Oral Hairy leukoplakia / TB
< 200 - Mucocutaneous herpes
  Cryptosporidium / mierosporidium
  PCP
  Miliary TB
  Esophageal candidiasis
< 100 - Cerebral toxoplasmosis
  Cryptococcal meningitis
  Primary CNS lymphoma
  HIV associated dementia
  PMLE
< 50 - CMV Retinitis
  MAC infection

CMV infection:

- Retinitis > colitis > esophagitis > pneumonitis
- Retina → Asymmetric bilateral involvement with perivascular hemorrhage or white fluffy exudate
- Painless progressive visual loss
- Rx: IV Ganciclovir x 3 weeks followed by oral Ganciclovir till CD4 > 150 for 6 months
MAC disease:
- Average CD4 at diagnosis is < 10
- Organism acquired through respiratory portal
- Disseminated disease with fever, weight loss, night sweats and lymphadenopathy (pulmonary involvement is rare)
- Diagnosis → blood culture / BACTEC (1 to 10 days)
- Rx: clarithromycin + ethambutol
- Prophylaxis with azithromycin if CD4 < 50

Cerebral toxoplasmosis

- CD4 < 100
- Reactivation of T. gondii cysts in brain
- Fever, headache, focal neurological deficit, seizure or confusion
- MRI → multiple ring enhancing lesions
- Diagnosis → Elevation of both Toxoplasma IgG and IgM
- Rx: Sulfadiazine + Pyrimethamine + leucovorin x 6 weeks (or) Clindamycin + Pyrimethamine
- Prophylaxis → CD4 < 100 / HIV → Cotrimoxazole
Cryptosporidiosis

- Cryptosporidium parvum
- Contact → Oocysts in contaminated water
- CD4 < 100
- Presents with small bowel diarrhea
- Major complication → Biliary involvement & stricturing
- Stool microscopy → 4-6 micrometre
- Acid fast
- Rx: ART + Nitazoxanide

Primary CNS lymphoma:
- AIDS defining malignancy
  (example → 1) Kaposi Sarcoma
    a) Invasive Ca cancer
  3) primary CNS lymphoma
- EBV associated
- Type → Diffused large B-cell lymphoma
- Rx: Stereotactic RT + methotrexate
- MRI → Hypointense on T1,
  Hyperintense on T2

Fungal meningitis:
- Cryptococcus neoformans
- CD4 < 100 Cells / μl
- Best seen with India ink preparation
- Subacute meningitis
- Worsening of headache due to impaired CSF absorption
- CSF study → 1) Opening pressure
  a) ↑ Protein
  3) ↓ Sugars
  4) Budding yeast hyphae
- Diagnosis → Latex agglutination test / Cryptococcal antigen test
- Rx: Amphotericin B + 5 Flucytosine
- Mode of transmission → Inhalation of spores
- Angioinvasion

Scanned with CamScanner
Progressive multifocal leukoencephalopathy

- JC virus
- Demyelination of subcortical white matter
- Can occur even when counts > 100-200
- Diagnosis \(\rightarrow\) MRI + JC viral CSF
- No definitive treatment

Pneumocystis jirovecii:
- Opportunistic fungal pulmonary pathogen with no ergosterol, no fungal culture
- Diffuse infiltrates in beginning of prehilar region is seen on chest x-ray
- Beta glucan drive inflammatory response
- Presents with fever / cough / dyspnea, especially hypoxia.
- Impaired diffusion capacity
- Respiratory alkalosis
- Widened alveola = arterial \(\text{Po}_2\) final
- Can occur as a part of IRIS
- May be associated with oropharyngeal candidiasis
- Complication \(\rightarrow\) Pneumothorax
- Diagnosis \(\rightarrow\) Indirect immunofluorescence using monoclonal antibodies against Pneumocystis pneumonia.

- Histopathology \(\rightarrow\) Foamy intra alveolar exudates
- Methanamine silver stains the wall
- Giemsa wright stains the nuclei
- Doc \(\rightarrow\) Co-trimoxazole, 2\(^{nd}\) choice - Trimethoprim + Dapsone, 3\(^{rd}\) \(\rightarrow\) Atovaquone
  - 4\(^{th}\) \(\rightarrow\) Clindamycin + Primaquine
  - 5\(^{th}\) \(\rightarrow\) Pentaminidine
- Prophylaxis \(\rightarrow\) Co-trimoxazole > Dapsone > Atovaquone
Kaposi sarcoma:

- HHV 8
- May be seen with normal CD4
- Multiple vascular nodules in skin, mucous membrane and viscera.
- Biopsy → Vascular involvement
- Dermatological or visceral lesions managed by chemotherapy (IFN based)
- Milder lesions respond to ART
- Can also occur as part of IRIS

Diagnosis:

- Screening test → 4th generation ELISA
- HIV ELISA → 95% positive within 8 weeks; earliest by 22 days
- Sensitivity of HIV ELISA is 99.99%
- Supplementary tests:  
  - Western blot
  - RFLP
  - Line immunoassay
  - IF array
  - Specificity = 99.99%
- Indeterminate western blot:
  - Early HIV
  - HIV-a
  - Autoimmune illness
  - Pregnancy
  - Tetanus toxoid

- Gold standard → HIV RNA (detects as early as 12th day)

```
HIV-1 / HIV-2 ELA 4th generation screen
 Non-Reactive  Repeated Reactive
       ↓       ↓
  Report as Non-Reactive  HIV-1 / HIV-2 Discriminatory Assay (multiplex)
          HIV-1 Reactive
          HIV-2 Non-Reactive
                   ↓
  Report as HIV-1 Indeterminate
          HIV-1 Non-Reactive, HIV-2 Reactive
                   ↓
  Report as HIV-1 Positive
          HIV-1 Non-Reactive, HIV-2 Non-Reactive
                   ↓
  Report as HIV-1 Indeterminate
          Not Done
                   ↓
  Report as HIV-1 Negative
          Not Detected
                   ↓
  Report as HIV-1 positive
```
ART Eligibility: 5 Policy Scenarios

Estimated millions of people eligible for ART (2014)

1. CD4 ≤ 350
   Recommended since 2003

2. CD4 ≤ 350
   Recommended since 2010

3. CD4 ≤ 350 + TDF
   Incremental approach 2013

4. CD4 ≤ 500
   + Indications for ART at any CD4
   2015 guidelines

5. All HIV +
   Treat all
   2015 guidelines

All HIV cases are treated irrespective of CD4 count

Classes of HIV drugs:

I. Entry inhibitors → Fusion inhibitor → Enfuvirtide (only injection)
   Coreceptor blocker (CCR 5) → Maraviroc

II. Nucleoside Reverse Transcriptase Inhibitors (NRTI)
   1) Zidovudine
   2) Didanosine
   3) Stavudine
   4) Lamivudine
   5) Abacavir
   6) Emtricitabine

III. Non - Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
   1) Nevirapine
   2) Efavirenz
   3) Delavirdine
   4) Etravirine
   5) Rilpivirine

IV. Nucleotide Reverse Transcriptase Inhibitor:
   Tenofovir
V. Integrase inhibitor:
1) Raltegravir
2) Dolutegravir
3) Elvitegravir

VI. Protease inhibitor:
1) Ritonavir
2) Neefinavir
3) Indinavir
4) Saquinavir
5) Amprenavir
6) Atazanavir

- All ART regimen must include Nucleotide Reverse Transcriptase inhibitor → Tenofovir (S/E → Proximal tubular injury → salt wasting Nephropathy → AKI)

- 3rd drug in the Regimen → NRTI.
  
  First zidovudine was used
  (A/E → myopathy, Lactic acidosis,
   Ξm Suppression, Resistance)

  Changed to Didanosine
  (A/E → Pancreatitis)

  Changed to Stavudine
  (A/E → Peripheral Neuropathy)

  Drugs used now → Lamivudine, Abacavir,
  Emtricitabine

- Abacavir -- requires HLAB5701 testing prior to administration
  (due to risk of hypersensitivity & sudden MI) 3rd drug → NNRTI
  → Efavirenz (A/E: Delusions & CNS toxicity)

- NACO Protocol → Tenofovir + Lamivudine + Efavirenz

- World wide Recommended protocol → Tenofovir
  + Emtricitabine
  + Integrase inhibitor (Raltegravir)
- Protease inhibitor is not used as first-line → Metabolic Syndrome complex
- Resistance testing is mandatory
- Primary goal of therapy (viral load <20 copies /ml)
- 3 drugs from a different classes must be used

One liners:
- PCP Pneumonia → DOC --> Cotrimoxazole
- MAC infection → DOC --> Ethambutol
- Toxoplasmosis → DOC --> Sulfadiazine + Pyrimethamine
- Any patient with HIV +ve should undergo tuberculin skin test, if positive should receive Isoniazid for 9-12 months
- DOC for Cryptosporidium parvum → Nitazoxanide
- Perivascular hemorrhages and retinal exudates → CMV retinitis
- Characteristic cells of CNS involved in AIDS → microglial cells
- Mc extranodal site of lymphoma → Brain
- Commonest helminthic infection → Strongyloides stercoralis
- Microglial cells are characteristically involved
- Nevirapine → Hepatoxicity/Rash
- Delavirdine is least preferred → Because of multiple daily dosing
- Prior NNRTI resistance → Only Etravirine can be used
- Ritonavir boosting is recommended for all except Nelfinavir
- All protease inhibitor is associated with metabolic Syndrome
  Except Atazanavir
- Amprenavir → Hyperbilirubinemia
- NNRTI, are ineffective against HIV -a
HIV -2 NACO Regimen $\rightarrow$ Tenofovir
  +
  Lamivudine
  +
  Lapinavir / Ritonavir

Best Regimen $\rightarrow$ Tenofovir
  +
  Emtricitabine
  +
  Dolutegravir

**Needle stick injury prophylaxis:**
- Optimally effective if started within 72 hours
- Tenofovir + Emtricitabine + Dolutegravir $\times$ 4 weeks (2NRTI's + Integrase inhibitor)
- Abacavir and Nevirapine are always avoided
- Pre-exposure prophylaxis $\rightarrow$ Emtricitabine / Tenofovir
SLE - ETIOPATHOGENESIS

Connective tissue disorder

1) SLE
   a) APLA
   b) Sjogren
   4) Polymyositis / Dermatomyositis
   5) mixed connective tissue disorder
   6) Sarcoidosis

Rheumatoid Arthritis can be considered as Arthritis
   Vasculitis
   Connective Tissue Disorder

SLE

Systemic lupus erythematosus
Disease of females in reproductive age group

(Flm → 9:1)

Male SLE - Poor Prognosis

Childhood SLE: 100% Renal involvement

Type 3 HSR (immune complex mediated disease)

↓

Deposited in 1. Vessel wall: Vasculitis
          2. Joints: Arthritis
          3. Glomeruli: Glomerulonephritis

Other Egs. of Type 3 Hypersensitivity reaction:

1) PAN
   a) Reactive Arthritis
   3) PSEW

1. Genetic susceptibility - must to be detected
   1) Most strongest genetic risk of SLE: Early Complement deficiency
      C3, C4, C5
      (most important - C3, C4 deficiency)
[C_2b, C_9 (late complement deficiency)]
- Susceptibility to Neisseria, Toxoplasma]

a) HLA DR-3, DR-2, B8
b) TREX gene mutation (present on chromosome)

c) Environmental risk factors (a 3rd hit)
   i) EBV
   ii) OCP & HRT
   iii) Smoking (Alcohol is protective)
   iv) Deficiency of Vit D
   v) Silicosis

[UV - B rays do not trigger SLE
   it can cause flares in an SLE patient]

Genetic + environmental
↓
Immune dysregulation
↓
↑ Apoptosis & reduced clearance of
   apoptotic cell (innate immunity is activated)

Key pathogenic cytokine: IFN-α
↓

Produced by
Lymphoid dendritic cell
(plasmacytoid dendritic cell)

Genetic signature of SLE: upregulation of genes due to IFN-α

[ IFN-β - Produced by Fibroblast
  IFN-γ - Produced by TH1 (adaptive immunity)]
IFN-α
↓
upregulates myeloid dendritic cells and activates
them to present antigen to T cells
↓
Activation of T Cells

Th₁  Th₃  Th₂
↓  ↓  ↓
most important
↓
IL-4, IL-5, IL-10, IL-13
↓
Secondarily activates B cells
↓
Antibodies
↓
Immature complexes deposited in various organs

Activation of B cell

T cell activates B cell by:

1. IL-4 Pathway
2. CD40 L - CD40 interaction
   ↓  ↓
   T cell  B cell
3. IL-12/21 pathway
SLE - IMMUNOLOGICAL BASIS

Antibodies

Auto antibodies may be seen 3 year before the onset of clinical feature
Screening → ANA (Anti Nuclear Antibody)

↓

Also used for all connective tissue disorder screening

ANA positivity is only significant if done by
Indirect immunofluorescence using Hep-2 cell line
(Hep - 2 → Human epidermoid cell line)

↓

Quantitative result
(ELISA is qualitative and is not significant)

Titre ≥ 1/180 is significant (< 1/80 insignificant) can be due to

1) Infection
2) Normal (<5%)
3) Thyroid disorder
4) Inflammatory bowel disease

[SLE - 97 to 98% ANA+ve
Scleroderma - 95% ANA+ve
Sjogren - 95% ANA+ve
Mixed connective tissue disorder (MCTD) - 100% ANA+ve]

If ANA (+ve),

↓

ANA positivity

↓

1) Speckled pattern: most suggestive of connective tissue disorder
   but non-specific

Anti-Nuclear Antibody (ANA)

speckled pattern
a) Rim pattern - SLE
b) Homogenous - Drug induced SLE
c) Nucleolar pattern - Scleroderma
d) Centromere pattern - CREST syndrome

\[ \text{ANA (} + \text{ve)} \]
\[ \downarrow \]
\[ \text{ENA profile (Extractable Nuclear Antigen Profile)} \]
1) Anti ds DNA (70-75% of SLE patient)
2) Anti smith (20-25% of SLE patient)

Anti smith is more specific
But - Anti ds DNA is still preferred because:
- ⊖ in 70-75% of SLE patients
- High titre correlate with disease activity
- ↑ Chance of nephritis & vasculitis
• Anti-dsDNA, ↓ C₅, ↓ C₃ - Correlate with disease activity
  ↓
Due to activation of classical complement pathway

3) Anti U1 RNP
Overlap Syndrome: Features of SLE / Limited scleroderma / Polymyositis / Dermatomyositis ± RA

For eg: SLE/Scleroderma overlap:
- Predominant is written 1°
- In this case, SLE is predominant

Mixed connective tissue disorder
= Overlap syndrome + Anti U1 RNP

**Mixed connective tissue disorder v/s overlap**
3) Associated with Raynaud’s phenomenon
4) ILD
5) Absence of Renal involvement
6) 100% ANA +ve

4) Anti Ro (SS-A), Anti La (SS-B)
   Associated with a° Sjogren’s
   Pregnancy - Neonatal lupus with congenital heart block
   Titres correlate with ↓ risk of nephritis ↓ vasculitis associated
   with subacute cutaneous lupus (High photosensitivity skin lesion)

6) Anti histone antibody
   - Drug induced lupus

7) Anti phospholipid antibody (APLA)
   - APLA syndrome
   - 1/3rd SLE patients have APLA

8) Anti erythrocyte antibody
   - SLE patients are prone for Auto-immune hemolytic anemia (AIHA)

9) Anti platelet antibody
   - Associated with a° idiopathic thrombocytic purpura (ITP)

10) Anti neuronal (glutamate) antibody
    - M/C antibody in CNS / Neuronal lupus

11) Anti - ribosomal P antibody
    - Specific for depression / psychosis in CNS lupus

M/C CNS lesion: Decline in cognitive function
SLE: CLINICAL FEATURES

Clinical presentation

Associated symptoms with SLE:
- Fever of unknown origin
- Fatigue / tiredness / lethargy
- Irregular cycle / weight gain
- Unexplained hair loss or dryness of skin

Skin presentations are:
1) Acute cutaneous Lupus Erythematosus (malar Rash)
2) Chronic cutaneous Lupus Erythematosus (Discoid Rash)
3) Subacute cutaneous Lupus Erythematosus

Acute cutaneous lupus erythematosus

Also known as malar Rash
- MC rash SLE
- Highly photosensitive
- Erythematous Rash
- Tendency for scaling
- Non-scarring
- Spares nasolabial fold
DD: Acne Rosacea

Chronic cutaneous lupus erythematosus

Also known as Discoid Rash
- most common disfiguring rash
- erythematous rash involving face, scalp, neck & back

Biopsy findings are:
1) Keratotic scaling
2) Follicular plugging
3) Dermal atrophy
Seen as circular erythematous patches
(hyperpigmentation at borders)

5-20 Rule:
Patient with Discoid Rash → Chances of SLE: 5%
Patient with SLE → Chances of discoid rash (20%)

It’s a Premalignant Lesion → Squamous cell carcinoma of skin
(∴ biopsy is a must)

SLE generally cause Non-scarring alopecia.
But Discoid Lupus Erythematosus (DLE) → Scarring cicatricial alopecia.

Discoid lesions on back
↓
Carpet Track sign of DLE

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Subacute cutaneous lupus

In subacute cutaneous Lupus – 50% SLE

- Highly photosensitive
- Superficial
- Non-scarring
- B/L symmetrical
- Seen in forearm
- Psoriasiform pattern
- Associated with Anti Ro/La antibodies
- Precipitated by : : Hydrochlorothiazide

Lupus profundus
Also known as Lupus panniculitis
Affects the fat underlying the skin
Verrucous Lupus
Also Known as Hypertrophic Lupus

Arthritis in SLE

1) Presents as arthritis and not arthralgia
   Arthralgia - Only pain
   Arthritis - Evidence of inflammation
               (redness, edema, warmth, tenderness)

2) It is an inflammatory Arthritis
   Relieved with activity & exacerbated with rest
   ▲ ESR, CRP ▼
   ▸ CRP levels low because of anti CRP antibodies
   ▲ Synovial fluid WBC ▲ (≥500/mc)

3) B/L symmetrical
4) Small joint polyarthritis
5) Predominant upper limb arthritis
6) Non deforming, non erosive
Jaccoud Arthropathy

↓

SLE arthritis which is deforming but non-erosive

If erosive - Do anti CCP

↓

Suspecting RA

Whenever one joint swelling is out of proportion:

→ Eg: 3 days h/o fever on \& off, pain, swelling \& edema of knee joint, asymmetrical, severe tenderness

- Septic Arthritis

Patient on 3 months steroid develops progressive pain on hip movement especially on flexion \& internal rotation

↓

Suspect Avascular necrosis / Osteonecrosis
ORGAN SYSTEM MANIFESTATIONS OF SLE

Vascular manifestations

- M/C cause of death in SLE: Acute coronary syndrome
- Condition of vessel in SLE affected 30 year old resembles vessel in an 80 year old unaffected woman.
- Accelerated atherosclerosis in SLE
  = MI Equivalent
- APLA is seen in 1/3rd patient
- Also associated with small vessel vasculitis

Lung

\( \Rightarrow \) pleuritis ± effusion
- M/C Lung involvement
- Small, B/L exudative effusion

Respiratory discomfort in a patient on treatment for SLE
↓
Left sided effusion
↓
Diagnostic tap
↓
Lights criteria: → Exudate

TB  Malignancy  Pneumonia  Autoimmune
Autoimmune causes - diagnosis of exclusion

2) Lupus Pneumonitis (Diffuse alveolar hemorrhage)

30 yr female under treatment for SLE (6 months) in remission phase with minimal steroid dose. Presents acutely with 3 days fever, cough, 2-3 episodes of hemoptysis, Hemodynamically stable

D/D Could be community acquired pneumonia.

\[
\downarrow
\]

Rx with antibiotics

or

SLE relapse \(\rightarrow\) Lupus pneumonitis

\[
\downarrow
\]

Rx with immunosuppressants

Assess disease activity: ds-DNA titres

C3, C4 - in SLE

CRP ↓↓

Diffuse alveolar hemorrhage - s/o SLE

1) Hemosiderin laden macrophage in sputum

2) PFT: ↑ DLCO

3) Bronchoscopy - blood on air passage

3) Interstitial Lung Disease

- Very minimal
- Presents as Non-Specific interstitial pneumonia

4) Shrinking Lung Syndrome

- Restrictive ventilator defect
- Elevated hemidiaphragm + Shrunken lung
- Nerve involvement

Heart - manifestations

[m/C Cardiac lesion: Pericarditis without tamponade (postmortem findings)]

[m/C endocarditis: Libmann Sachs endocarditis (vegetations on the under surface of valve leaflet)]
m/C valvular: mitral regurgitation
m/C arrhythmia: ventricular tachycardia

**GIT - manifestations**

m/C manifestation: decreased peristalsis with preserved LES tone
m/C liver manifestation: raised enzymes (clinically not significant)
Autoimmune hepatitis type 1 - lupoid hepatitis

**CNS - manifestations**

m/C manifestation: ↓ cognitive function
Aggressive CNS lupus - diffuse grey matter lesions and seizures.
Antibodies: Antiglutamate antibody
Antibodies on depression or psychosis: Antiribosomal P
Increased risk of stroke/CVT in SLE associated with APLA

**Hematological - manifestations**

m/C clinical manifestation: Anemia of chronic disease
m/C lab abnormality: Lymphopenia.

i) Autoimmune hemolytic anemia:
   Any young female with a rapidly progressive anemia.

Look for features of hemolysis:
   - Reticulocyte > 2.5
   - Macrocyes
   - ↑ LDH
   - ↓ haptoglobins
   - Jaundice
   - ↑ Indirect bilirubin
   - Splenomegaly
   - ↓ do DCT

In SLE,
   Warm antibody (IgG) mediated DCT +ve AIHA (extravascular)

a) a° ITP:
   Due to antiplatelet antibody
   SLE is premalignant → DLBCL (Diffuse large B-cell lymphoma)
### TABLE: Systemic Lupus International Collaborating Clinics (SLICC) Criteria for Classification of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATIONS</th>
<th>IMMUNOLOGIC MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Acute, subacute cutaneous LE (photodistributed, malar, maculopapular, bullous)</td>
<td>ANA &gt; reference negative value</td>
</tr>
<tr>
<td>Chronic cutaneous LE (discoid lupus, panannular, ichthyosiform, planar-like, hypertrophic verrucous, chilblains)</td>
<td>Anti-dsDNA &gt; reference, if by ELISA</td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td>Ax Reference</td>
</tr>
<tr>
<td>Non-scarring alopecia</td>
<td>Anti-Sm</td>
</tr>
<tr>
<td>Synovitis involving &gt; 2 joints</td>
<td>Antiphospholipid (any lupus anticoagulant, false-positive RPR, anti-cardiolipin, anti-β 2-glycoprotein I)</td>
</tr>
<tr>
<td>Serositis (pleurisy, pericarditis)</td>
<td>Low serum complement (C3, C4, or CH50)</td>
</tr>
<tr>
<td>Renal</td>
<td>Positive direct coombs test if absence of hemolytic anemia.</td>
</tr>
<tr>
<td>Protein or red blood cell casts</td>
<td></td>
</tr>
<tr>
<td>Renal biopsy</td>
<td></td>
</tr>
</tbody>
</table>

Renal biopsy read as systemic lupus qualifies for classification as SLE if any lupus autoantibodies are present, even if total criteria are fewer than 4.

### Renal - manifestations

**Lupus Nephritis**: Glomerular involvement

- 50 to 60% SLE patients have renal involvement
- Children - 100%

**Class I: Minimal Mesangial Lupus**
- Benign
- Not associated with disease activity
- Asymptomatic
- Doesn't require treatment
- Immune complex deposition in both

**Class II: Mesangial Proliferative Lupus**
- Light microscopy: Normal
- Mesangial Proliferation
- Immunofluorescence: Mesangial immune complex deposits in both
Biopsy is done when: Proteinuria > 500 mg/day with microhematuria
Proteinuria > 1 g/day

Active Lupus Nephritis: Class III (< 50% glomerulus involved)
Class IV (> 50% glomeruli involved)

Class III: Focal Proliferative Lupus Nephritis
Class IV: Diffuse Proliferative Lupus Nephritis
Class IV: Worst prognosis

Presentation:
Acute onset rapidly progressive renal failure
Proteinuria + RBC in urine
Crescents on Biopsy - Type II RPGN
anti ds-DNA high
c3, c4 and CRP low

Class IV:
RPRF → RPGN presentation (type II)

Light microscopy
- RPGN + Crescents

Immunofluorescence:
most specific pathologic finding of SLE
Full house effect
- IgG + IgM + IgA + C3 + C4 + C1q
(wireloop lesion - class IV - subendothelial deposits - non specific)
Electron microscopy: Hematoxylin bodies

Class I & class II are treated when there is Nephrotic syndrome
Known as Lupus podocytopathy
Class V - Membranous Lupus

Adult onset nephrotic syndrome

Biopsy: Membranous nephropathy
Light microscopy: ↑ capillary wall thickness
IF: Immune complex deposits in the capillary wall
EM: Subepithelial deposits

- refractory to standard therapy

Class IV

Activity index:
1. PMN infiltrates
2. Karyorrhexis
3. Wire loop lesions
4. Endocapillary hypercellularity
5. New cellular crescents
6. Degree of interstitial inflammation

Chronicity index:
- Tubular atrophy
- Interstitial fibrosis
- Fibrous crescents

Class VI: Advanced sclerotic lupus

> 90% of glomeruli are sclerosed
MANAGEMENT OF SLE

Management based on skin & joint involvement

mild → Topical steroids
moderate/severe → Topical steroids + Hydroxychloroquine
[Antimalarial]
  ↓
S/E - Irreversible retinal toxicity [1%]
  ↓
No response
  ↓
Oral methotrexate

Second line drugs:
  Retinoids
  Thalidomide

Management based on Organ system involvement

Steroids → IV methyl prednisolone (500 mg - 1 g) followed by
  Oral prednisolone (1 mg/kg/day)
  ↓
Taper and bring to minimal 5 mg/day dose
  Over a period of 4 months [3-4]
  ↓
Plus cyclofosfamide or mmF [equally effective]

CYCLOFOSFAMIDE:
According to NIH protocol: 6 doses of IV cyclofosfamide
  monthly once - 1g IV

According to Euro-lupus protocol: [low dose]
  500mg IV every 4 weeks
  X 3 months
adverse effects:
  a) Secondary malignancy - AML
  b) gonadal toxicity - Ovum banks
  c) Haemorrhagic cystitis

Dose dependent toxicity - Bone marrow suppression

Mycophenolate mofetil:
  IMP dehydrogenase inhibitors
  Purine synthesis inhibitors

Dose: 500 mg 1-0-1 X 1 week
  1g 1-0-1 X 1 week
  1.5g 1-0-1 X 2a week
  Total: 6 months therapy

Side effects: GI side effects; Bone Marrow Suppression [less]

At the end of induction

- Remission
  - maintenance therapy
    - Low dose steroid + MMF or Azathioprine

- Not in remission
  - Cyclosporamide → MMF
    - MMF → Cyclo
    - Calcineurin Inhibitors [eg: cyclosporine / Tacrolimus]
      - Rituimab → Anti CD20

Treatment of class V lupus

- [Steroid refractory]
  mmF + Steroid [steroid refractory]

  - Respond
    - maintenance therapy

  - No Response
    - mmF + Low dose Tacrolimus
**Newer drugs for SLE**

- **Anifrolumab** - Against IFN α [Not available in India]
- **Anti CD20** - Rituximab, Ocrelizumab
- **CTLA4 -Ig** - Fusion molecule - [Abatacept]
  (Fc IgG4)
- **Anti CD22** - Epratuzumab
- **Anti BlyS** - Benlysta, [Belimumab]
  ↓
  - Atacicept [TACI -Ig]
  - [B -lymphocyte stimulation]
- **Anti IL -6** - Tocilizumab
- **Anti -INF α** - Sipalizumab

**Antiferon [Anti -IFN α vaccine]**

**Drug induced SLE**

- **C** Carbamazepine; chlorpromazine
- **H** Hydralazine
- **I** Isoniazid; Interferon; Infliximab
- **M** Methyldopa
- **P** Procainamide; Phenytoin; Propyl thiouracil

- **M : F = 1 : 1**
- Skin and joints → Always involved
- Kidney and brain never involved
- Anti ds DNA negative
- Anti histone positive
- ANA – homogenous pattern
- Most drugs causing lupus are safe in SLE patients
- On stopping drugs – very good prognosis
Anti phospholipid antibody syndrome

- Characterized by antibodies acting on Protein C \( \frac{2}{3} \) inhibiting it
- Function of protein C \( \frac{2}{3} \) Inhibits Factor \( \frac{5}{8} \)
- In APLA \( \rightarrow \) Uncontrolled activation of Factor \( \frac{5}{8} \)
- Predisposition to thrombosis
  - Abs acting on platelets
    - Thrombocytopenia
    - Platelet count < 1,00,000/ml
    - Not low enough to produce bleeding
    - Thrombocytopenia without bleed + thrombosis \( \Rightarrow \) APLA
    - DD: Heparin
  - Target Antigens in APLA - \( \beta \) glycoprotein
  - Non-specific
  - Prothrombin

Lab criteria: Any 1 out of 3 Abs twice over 12wks

1. Anti cardiolipin Ab
   - IgG, Ab - Done by ELISA
   - Most sensitive
2. Anti \( \beta \text{ glycoprotein} \) Ab
   - IgG, IgM, IgA
   - ELISA
3. Lupus Anticoagulant
   - most specific
   - Detected indirectly by the
     prolongation of:

   a. APTT
   b. DRVVT (Dilated Russeu Viper Venom Test)
   c. KCT (Kaolin Clotting Time)

Clinical criteria:

Pregnancy criteria: Any 1 out of 3 +ve
1. Before 10wks - 3 or more miscarriages
2. After 10wks - Even 1 miscarriage (2nd Trimester Abortion)
3. Premature Delivery (<34 wks) of a morphologically normal
   neonate due to Preeclampsia / Eclampsia / HELLP Syndrome

Adult criteria:

1. Episode of Thrombosis with Ab +ve – most often venous

   a. DVT (MC cause)
   b. Venous obstruction causing venular dilation - Lacy network
      pattern or Livedo reticularis
   c. Pulmonary embolism

2. Arterial Thrombosis:
   a. Stroke (MC)
   b. Cardiac - MI/Libman sacks
   c. Retinal artery thrombosis

3. Neurological Symptoms in APLA: chorea
   Migraine can occur

4. Rarely involves Renal vein / Small vessels in kidney to produce
   Thrombotic microangiopathy

5. Adrenal Vessels: Addison’s like picture if Adrenal vessels are
   involved
6. AIHA with Thrombocytopenia & no bleed

Revised sapporo classification criteria for apla

Clinical Criteria:

1. Vascular thrombosis
   One or more clinical episodes of arterial venous or small vessel thrombosis in any tissue or organ

2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
   (b) One or more premature births of a morphologically normal neonate before 34th week of gestation because of eclampsia, severe preeclampsia, or recognized features of placental insufficiency or,
   (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory Criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis

2. Anticardiolipin antibody of immunoglobulin (Ig) G or IgM isotype in serum or plasma, present in medium or high titer (>40 GPL or MPL, or > 99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay (ELISA)

3. Anti $\beta_2$ glycoprotein I antibody of IgG or IgM isotype in serum or plasma (in titer > 99th percentile) present on two or more occasions at least 12 weeks apart, measured by a standardized ELISA

Definite antiphospholipid syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria are met. Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive antiphospholipid antibody test and the clinical manifestation
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

<table>
<thead>
<tr>
<th>TABLE</th>
<th>CLASSIFICATION AND NOMENCLATURE OF ANTIPHOSPHOLIPID ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Assay for their Detection</td>
</tr>
<tr>
<td>Antibodies against cardiolipin (ACL)</td>
<td>Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid</td>
</tr>
<tr>
<td>Antibodies against B3GP1 (anti-B3GP1)</td>
<td>ELISA using as antigen affinity purified or recombinant B3GP1 in the absence of PL</td>
</tr>
<tr>
<td>Lupus anticoagulant (LA)</td>
<td>Activated partial thromboplastin time (aPTT) kaolin clotting time (KCT) Dilute Russell viper venom test (DRVVT)</td>
</tr>
</tbody>
</table>

Abbreviations: APL: antiphospholipid syndrome, B3GP1: B3 glycoprotein, PL: phospholipid

**Clinical features:**

1. DVT/BCS >> Arterial Thrombosis
2. Hepatic vein Thrombosis – Budd chiari syndrome may be seen rarely
3. Sneddon syndrome – Livedo reticularis + HTN + stroke
4. Renal site of lesion – Small vessels
5. AIHA + Thrombocytopenia without bleeding
6. Adrenal dysfunction
7. Lupus Anticoagulant positivity has the Highest risk of thrombotic events specific / +ve in 40% cases
8. ACL Ab is most sensitive
9. IgA Ab / B3 gpAb

**Catastrophic APLA syndrome**

- Occurs in patient with APLA with a trigger – most often an infection
- Defined as ≥ 3 organ systems getting involved in ≥1 week
- Histologically, small vessel occlusion with lab finding of APLA
**Treatment of APLA**

**In pregnancy**

Previous H/O Thrombosis due to APLA
  (or)
H/O miscarriage
  (or)
Preterm Delivery due to APLA
  ↓
Heparin + Low dose Aspirin through out Pregnancy
  +
Warfarin - Post partum if continued for life if documented evidence of APLA is established

**In Adults**

- APLA diagnosed due to Thrombosis
  ↓
LMW Heparin x 5 days overlapped with warfarin for life (INR 2-3)

- Recurrent thrombosis - INR 2.5-3.5

- APLA diagnosed laboratory wise but no clinical signs ⇒ no 1st prophylaxis required

- Anyone with H/O Thrombosis in 1st Pregnancy / Anyone with H/O Thrombosis ⇒ Requires Heparin + Low dose Aspirin in Pregnancy f/b Warfarin irrespective of APLA status

**Catastrophic APLA R**: Requires IV Ig + Plasmapheresis

- Steroids are useless in APLA except in catastrophic APLA where IV steroids may be tried
SJOGREN’S SYNDROME AND SYSTEMIC SCLEROSIS

Sjogren’s syndrome

\[
\begin{align*}
\text{Sjogren’s Syndrome} & \\
\text{Primary} & - DR-3 \\
& - B-B \\
& - DW-3 \\
\text{Secondary} & - Associated other \\
& - Connective tissue \\
& - Disorder
\end{align*}
\]

Sjogren’s syndrome:
- 9:1 [Female: Male]
- Middle aged and elderly females
- 40-60 years - [Peak age]

Causes for secondary Sjogren’s Syndrome:
1. Most cause → Rheumatoid arthritis*
2. Systemic lupus erythematosus (SLE)
3. Scleroderma
4. Mixed connective tissue disease (CTD) (mCTD)
5. Primary biliary cirrhosis
6. Chronic hepatitis-c [always associated]
7. Vasculitis

\[
\begin{align*}
\text{Sjogren’s syndrome} & \\
\text{Glandular} & \quad \text{Extra-glandular}
\end{align*}
\]

Glandular Sjogren’s

- Dry mouth [xerostomia] [more specific]
- Dry eye
- Fatigue; Anaemia of chronic disease
- Deep red tongue
- Dental caries
Bilateral parotid enlargement - primary sjogren's syndrome

Schirmer test:
- Detects deficient tear production in sjogren's syndrome
- Decreased tear break up time

Extraglandular sjogren's

m/c manifestation - Arthritis of SLE & Sjogren's are similar
Raynaud's phenomenon - a° Raynaud's
1) Lung involvement - small airway pathology
   Interstitial lung disease (ILD) - more common
   Non-specific interstitial pneumonia (NSIP) - m/c lung manifestation
   Most characteristic → Lymphocytic interstitial pneumonia (LIP)

a) In Kidney - Tubular involvement
   Distal renal tubular acidosis (RTR) [type-1]
   Hypokalemia

b) In liver - primary biliary cirrhosis

c) Peripheral neuropathy
   - B/L symmetrical small fiber sensory > motor
   - Lower limb > upper limb polyneuropathy

Look for:
- Persistent parotid enlargement
- Purpura
- Leukopenia
- Cryoglobulinemia
- Low C3 level

Sjogren leads to marginal zone lymphoma.
**Diagnosis**

minor salivary gland (labial) biopsy

→ CD4 + T cell infiltrate

[Anti Ro (m/c) – [SSA]
[Anti La – [SSB]] \} bad prognosis (extraglandular involvement)

**Management**

Glandular

- Dry eyes - artificial tear drops
- Dry mouth - salivary substitutes

Extraglandular:
- Arthritis - Hydroxychloroquine
- NSAIDS

Lung or other organ system involvement - Oral steroids + methotrexate/ Azathioprine / cyclofosfamide

If patients having ILD - cyclophosphamide
If patients not having ILD - methotrexate or Azathioprine

**Warning**: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.
Scleroderma

- Thickening and induration of skin

Two types:

1. Scleroderma without systemic features
   - Localized scleroderma
     - morphea
   a. Scleroderma with systemic features [systemic sclerosis]

      1. Diffuse cutaneous scleroderma
      a. Limited cutaneous scleroderma

      [Skin lesions on face and "heliotrope" elbow]

Pathophysiology:

- Fibrosis of affected organs
  + Small vessel injury [microvascular injury]

- Endothelial injury

  [Antiendothelial antibodies] → Vascular remodelling
  neo-intimal proliferation

  [Non inflammatory fibrotic proliferative obliterative arteriopathy]

  [ESR low]

  [Key pathogenic cytokine - TGF - β]

  Obliterative arteriopathy (especially in renal vessels) which is a cause for thrombotic microangiopathy (TMA)

Organs: Affected → skin, lungs; GIT; Heart and Kidneys
ROS - Reactive oxygen species

Environmental Agents and Drugs Implicated in Scleroderma-like Syndromes

<table>
<thead>
<tr>
<th>Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica</td>
</tr>
<tr>
<td>Heavy metals</td>
</tr>
<tr>
<td>Mercury</td>
</tr>
<tr>
<td>Organic chemicals</td>
</tr>
<tr>
<td>Vinyl chloride</td>
</tr>
<tr>
<td>Benzene</td>
</tr>
<tr>
<td>Toluene</td>
</tr>
<tr>
<td>Trichloroethylene</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
</tr>
<tr>
<td>Pentazocine</td>
</tr>
<tr>
<td>Taxol</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary supplement/Appetite Suppressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-tryptophan (contamination)</td>
</tr>
<tr>
<td>mazindol</td>
</tr>
<tr>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Diethylpropion</td>
</tr>
</tbody>
</table>
Raynaud's phenomenon

- Episodic vasoconstriction in response to cold, stress or vibration
- Pain, numbness and tightness of extremities
- Sometimes associated with severe ischaemia -
  Critical limb ischaemia - Gangrene
- Pallor, cyanosis; redness on rewarming

<table>
<thead>
<tr>
<th>Primary Raynauds</th>
<th>Secondary Raynauds</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Raynauds disease]</td>
<td>associated with Scleroderma(m/o)</td>
</tr>
<tr>
<td>- Not associated with CTD</td>
<td>sjogren; MCTD</td>
</tr>
<tr>
<td>- Family history [+ ]</td>
<td>- No family history</td>
</tr>
<tr>
<td>- Young females [20-45]</td>
<td>- Middle aged and elderly [40-60 years]</td>
</tr>
<tr>
<td>- Less painful; less severe/ no critical limb ischemia</td>
<td>- More painful; more severe, critical limb ischemia</td>
</tr>
<tr>
<td>- Nail fold capillary microscopy - normal</td>
<td>Areas - capillary dropout</td>
</tr>
</tbody>
</table>

Diffuse vs limited scleroderma

both present as secondary Raynauds phenomenon

<table>
<thead>
<tr>
<th>Diffuse scleroderma</th>
<th>Limited scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Short lasting secondary Raynauds [weeks to months]</td>
<td>- Long standing secondary Raynauds [months to years]</td>
</tr>
<tr>
<td>- No critical limb ischemia</td>
<td>- Critical limb ischaemia</td>
</tr>
<tr>
<td></td>
<td>- More severe</td>
</tr>
<tr>
<td></td>
<td>- More painful</td>
</tr>
<tr>
<td></td>
<td>C calcinosis cutis</td>
</tr>
<tr>
<td></td>
<td>R Raynaud's</td>
</tr>
<tr>
<td></td>
<td>E esophagitis</td>
</tr>
<tr>
<td></td>
<td>S sclerodactyly</td>
</tr>
<tr>
<td></td>
<td>T Telangiectasia</td>
</tr>
<tr>
<td></td>
<td>- Anti centromere antibody</td>
</tr>
<tr>
<td>Diffuse scleroderma:</td>
<td>Critical limb ischaemia:</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>- Skin manifestations + short lasting Raynaud's</td>
<td></td>
</tr>
<tr>
<td>- Edema / Atrophy and induration</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>↓</strong> Loss of body oil</td>
<td></td>
</tr>
<tr>
<td>Loss of body hair</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Extreme hyperpigmentation</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>↓</strong> Alternating hypo &amp; hyperpigmentation</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>[salt and pepper appearance]</td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>↓</strong> Extreme fibrosis</td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Microstomia;</td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
<tr>
<td>Puckered mouth;</td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>Pursed lip;</td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
<td>&quot;mask facies&quot;</td>
<td><img src="image10.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Joint contractures; Tendon friction rubs; Arthritis; ulcers at the site of trauma [friction ulcers]
<table>
<thead>
<tr>
<th>Diffuse scleroderma</th>
<th>Limited scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Diffuse to elbow, face</td>
</tr>
<tr>
<td></td>
<td>[less fibrosis]</td>
</tr>
<tr>
<td><strong>Raynauds</strong></td>
<td>Long standing [more severe]</td>
</tr>
<tr>
<td>short</td>
<td>RARE</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>GIT is M/C - Lax LES; GERD;</td>
</tr>
<tr>
<td>Yes</td>
<td>Gastric antral vascular</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>ectasia - watermelon</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>stomach</td>
</tr>
<tr>
<td>Yes</td>
<td>intestinal pseudo</td>
</tr>
<tr>
<td><strong>ILD</strong></td>
<td>obstruction; calcinosis</td>
</tr>
<tr>
<td>Yes</td>
<td>cutis</td>
</tr>
</tbody>
</table>

**Musculoskeletal:** Arthralgia; CTS/tendon friction rub

**Renal:** scleroderma; Renal crisis

**Cardiac:** Restrictive cardiomyopathy; pericarditis

**ILD:** Non-specific interstitial pneumonia
<table>
<thead>
<tr>
<th>Diffuse scleroderma</th>
<th>Limited scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Anti - Topoisomerase (Scl-70) antibody</td>
<td>Anti centromere Antibody</td>
</tr>
<tr>
<td>m/c cause of death in scleroderma - Fibrosis [ILD]</td>
<td></td>
</tr>
<tr>
<td>Few points</td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis: F&gt;&gt;m</td>
<td></td>
</tr>
<tr>
<td>- 5:1</td>
<td></td>
</tr>
<tr>
<td>- 30-35 years</td>
<td></td>
</tr>
</tbody>
</table>

**Lung manifestation:**

<table>
<thead>
<tr>
<th>Diffuse Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic sclero-derma-PFT + DLCO</td>
</tr>
<tr>
<td>Symptomatic scleroderma- HRCT</td>
</tr>
<tr>
<td>&quot;Diffuse Type&quot;</td>
</tr>
<tr>
<td>X-ray - B/L bibalol subpleural reticular infiltrates</td>
</tr>
</tbody>
</table>

Usual Interstitial pneumonia (UIP)
(or)
Idiopathic pulmonary fibrosis
Honey comb; Destructive lung architecture; cystic changes;
"Traction bronchiectasis"

**Limited scleroderma:**

- Pulmonary artery hypertension has poor prognosis in limited scleroderma.

- m/c death → "PAH"

When:

- \[ \frac{FEV_1}{FVC} \rightarrow N \]

- Normal
- Restrictive
- Vascular [PAH]

- FVC ↓ Or normal
- DLCO ↓↓↓
Ground glass opacification (NSIP)

[Non-specific interstitial pneumonia]

\[ \text{when } \frac{\text{FEV}}{\text{FVC}} \leq 0.7 \]

\[ \downarrow \]

Normal \quad \text{Restrictive [ILD]} \quad \text{Vascular [PAH]}

\text{FVC} \downarrow \downarrow \downarrow \downarrow \text{DLCO} \downarrow

FVC is decreased in ILD

\textbf{Renal manifestation in scleroderma.}

\textbf{Scleroderma renal crisis:} Seen only in Diffuse Type
- within first 4 years
- ACE inhibitors are DOC

Presentation: TMA; microangiopathic hemolysis; Thrombocytopenia; Renal failure

\textbf{Classical schistocytes seen}

\textbf{Anti} - topoisomerase present
\textbf{Anti} - U3 - RNP present

\textbf{Antibodies in scleroderma}

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topoisomerase I scl-70</td>
<td>Diffuse scleroderma</td>
</tr>
<tr>
<td>Centromere</td>
<td>CREST</td>
</tr>
<tr>
<td>U3RNP</td>
<td>PAH; ILD; Renal crisis</td>
</tr>
<tr>
<td>RNA polymerase III [fibrillarin]</td>
<td>Diffuse Type</td>
</tr>
<tr>
<td></td>
<td>Joint contractures; tendon</td>
</tr>
<tr>
<td></td>
<td>friction rub and renal crisis</td>
</tr>
<tr>
<td>Anti Ku</td>
<td>SLE and scleroderma overlap</td>
</tr>
</tbody>
</table>
Management of scleroderma

- ANA 95%
- Anti SCL-70 50%
- Anticentromere 75%

No single drug found to be useful
Steroid plus cyclophosphamide → ILD
Nifedipine / Anticoagulation / Bosentan → PAH
ACE inhibitors → Renal crisis
In trial: Pirfenidone - Anti TGF beta.
- d - penicillamine - Anti fibrotics

Drugs used in Raynaud's phenomenon:
- DOC - Bosentan

Ca²⁺ channel blocker → Nifedipine; Prostacyclin (Iloprost - parenteral);
α - blocker - prazosin; ARB - Lorsartan;
PDE inhibitor: Sildenafil
Surgery: sympathectomy
INFLAMMATORY MUSCLE DISORDERS

INTRODUCTION

- Also called idiopathic inflammatory myositis
- Systemic sub acute autoimmune inflammation with mononuclear cell infiltrate in muscle
  ↓
  Persistent muscle weakness
  ↓
  Polymyositis  Dermatomyositis  Inclusion body myositis  Immune mediated necrolising myopathy

Polymyositis vs Dermatomyositis

<table>
<thead>
<tr>
<th>Polymyositis</th>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only in Adults</td>
<td>Adults &amp; Children (In children juvenile dermatomyositis)</td>
</tr>
<tr>
<td>Age: 40 yrs</td>
<td>Can present alone or with other autoimmune condition</td>
</tr>
<tr>
<td>Never manifests alone</td>
<td>Skin features occur before / concurrently or after muscle involvement</td>
</tr>
<tr>
<td>Skin feature ☐</td>
<td>F &gt;&gt; m</td>
</tr>
<tr>
<td>F &gt;&gt; m</td>
<td></td>
</tr>
</tbody>
</table>

Clinical presentation

Bilateral Progressive Symmetrical Subacute presentation
Proximal LMN weakness
LL > UL
Mild myalgia ☐
Difficulty in climbing stairs
Difficulty in getting up
Difficulty in standing up from squatting position
Involvement at each level presents as:
Anterior horn cell: → Asymmetric, fasciculations ⊕, atrophy
Radical → Pain along distribution, asymmetric
Nerve → Sensory involvement ⊕
   Distal to proximal involvement
NMJ → Myasthenia like presentation
Muscle → Tendon reflex preserved,
   Sensory - Normal

Intermittent Persistent
↓
   1) Poly / Dermatomyositis
   2) Hypothyroid myopathy
   3) Drug induced myopathy

Subacute progressive symmetrical proximal (LL>UL) weakness
→ DD: Dermatomyositis / Polymyositis
Peculiarities are:
   a) Pharyngeal & neck flexor involvement
   b) Extra ocular & facial muscle always spared
   c) Respiratory muscle, involved very late

Screening : ↑↑↑ CPK
IgG : muscle biopsy

Dermatological manifestation of dermatomyositis

- Only in dermatomyositis
1) Gottron's papule: They are pathognomic  
   Violaceous, flat topped papule on extensor aspect on MCP & PIP joint
2) Gottron Rash / Sign:
3) Heliotrope Rash: Violaceous periorbital edema / erythema.
4) V sign on anterior neck
5) "Shawl sign" on posterior neck
6) Periungual erythema and Nailfold telangiectasia.
7) Calcinosi cutis
8) Linear erythema of finger
9) Holster sign - "Poikiloderma lesion on lateral aspect of thigh"

Antibodies associated with poly / dermamyositis

1. Anti Jo/Synthetase antibody
   Polymysitis > Dermatomyositis
   causes:
   1) Arthritis (similar to SLE)
   2) Interstitial lung disease (NSIP)
   3) Raynaud's phenomenon (a)
   4) mechanic hand
      Crusting of lateral aspect of index & middle finger (Seen in both polymysitis / Dermatomyositis)

2. Anti SRP (Signal Recognition peptide)
   Polymysitis >>> Dermatomyositis,
   denotes Cardiac involvement

3. Anti helicase (mi2) antibody
   Only seen in dermamyositis

<table>
<thead>
<tr>
<th>Diagnostic Features</th>
<th>Dermatomyositis</th>
<th>Polymysitis</th>
<th>Inclusion Body myositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>Children and adults</td>
<td>Adults</td>
<td>Adults &gt;50 yr</td>
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<tr>
<td>Disease onset</td>
<td>Subacute</td>
<td>Subacute</td>
<td>Chronic</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Proximal</td>
<td>Proximal</td>
<td>Selective pattern</td>
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<tr>
<td>Symmetry</td>
<td>Symmetric</td>
<td>Symmetric</td>
<td>Asymmetric</td>
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<tr>
<td>Systemic features</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Skin changes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>Yes</td>
<td>Rarely</td>
<td>No</td>
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<td>Associated connective tissue disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Associated malignancy</td>
<td>Yes</td>
<td>Yes</td>
<td>No/Yes</td>
</tr>
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<td>-----------------------</td>
<td>-----</td>
<td>-----</td>
<td>--------</td>
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<tr>
<td>Laboratory features</td>
<td></td>
<td></td>
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<tr>
<td>Serum enzymes</td>
<td>Normal to high</td>
<td>Normal to high</td>
<td>Normal to high</td>
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<td>Abnormal EMG</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal muscle biopsy</td>
<td>Perifascicular atrophy, capillary depletion, patchy MHC class I expression and microinfarcts</td>
<td>CD 8T cell invasion of non necrotic fibers and MHC class I expression on fibers</td>
<td>CD 8T cell invasion, MHC expression vacuolated fibers, and tubulofilamentous inclusions in fibers</td>
</tr>
</tbody>
</table>

Both polymyositis/Dermatomyositis can be Paraneoplastic

Ca. Ovary - most striking

Also Adenocarcinoma of stomach & Lungs

Muscle biopsy:
- Dermatomyositis
- Perifascicular atrophy
- Polymyositis
- CD 8 + T Cell invasion

Inclusion body myositis 00:18:40

- Chronic
- M > F (Age 50 yrs)
- Distal asymmetrical
- Quadriceps involvement +
  \[ \Rightarrow \text{"recurrent falls"} \]
- Paraneoplastic
- No skin changes
Management

Dermatomyositis/ Polymyositis

\[ \text{No Interstitial lung Disease} \rightarrow \text{Steroid + methotrexate + Azathioprine} \]

\[ \text{Interstitial lung Disease} \rightarrow \text{Steroid + Cyclophosphamide} \]

Maintenance: Low dose steroids + mycophenolate mofetil or Azathioprine
**SARCOIDOSIS**

**Introduction**

Presents with:

- CTD
- Arthritis
- Vasculitis

(connective tissue disorder)

Multisystem inflammatory disease

HLA Susceptibility:

- HLA B8 - No effect on prognosis
- DRBI-03
- DRBI-04
- Good Prognosis
- DQB1-02

3/4 (50-70%) → spontaneous Resolution

20% → Chronicity

↓

5% → Death (due to Interstitial Lung Disease)

- $CD_4^+ T$ Cell mediated inflammation, characterised by non-caseating granuloma.

  - Immune Paradox:
    - Enough $CD_4^+ T$ cell $\rightarrow$ infection

- Other causes of non-caseating granuloma:
  a) Berylliosis
  b) Crohn's disease
  c) HSP (Hypersensitivity Pneumonitis)
  d) Cat scratch disease

**Organs involved in sarcoidosis**

- Any age ($F > M$)
- Can involve any organ
I. Skin:
   Acute: (Good prognosis)
   - Lofgren syndrome
     - G/L Hilar adenopathy
     - Arthritis
     - Erythema Nodosum (5%)
   - Heerfordt Waldenstrom
     - Waldenstrom
     - Uveitis
     - Parotitis
     - Palsy

   Chronic: Lupus Pernio (Bad Prognosis)
   - Crusted erythematous maculopapular
   - Lesion on face or violaceous papule
   - On nose / face with dilated capillaries

Sarcoid granuloma:
   1) Asteroid body
   2) Conchoidal body
2) Eyes:
   - Chronic anterior uveitis (m/C) > Acute anterior uveitis
     Posterior uveitis > Retinitis

3) Lungs (m/C organ involved)
   - Fever, Myalgia, weight loss, Non-specific cough
     ↓
     x-ray
     ↓
     Hilar lymphadenopathy
     ↓
     Biopsy: Non caseating granuloma

Staging based on chest-xray finding

Scadding scoring System:
Stage 1: B/L Hilar Adenopathy
Stage 2: B/L Hilar Adenopathy + Infiltrates
Stage 3: Infiltrates alone
  ↓
  Ground glass opacification
  (Non specific interstitial pneumonia)
  ↓
  Involve upper lobe (only connective
tissue disorder involving upper lobe

Stage 4: Fibrosis

In Rheumatology, only 3 things involve upper lobe of lungs:
  1) Ankylosing spondylitis
  2) Sarcoidosis
  3) Psoriatic Lung disease

Other conditions involving upper lobe:
  1) Berylliosis
  2) Radiation induced Lung disease
  3) Hypersensitivity pneumonitis
  4) Langerhans cell histiocytosis

Garland Sign: Right + Left Hilar Lymphadenopathy + Right
paratracheal Adenopathy
4) Cardiac
   Conduction defects
   Restrictive cardiomyopathy > Dilated cardiomyopathy

5) Hepatic
   Intrahepatic cholestasis

6) Renal
   - Chronic Tubulointerstitial disease
   - m/C Glomerular disease: membranous nephropathy

7) Haematology
   - Lymphadenopathy
   - Splenomegaly due to hypersplenism

8) Metabolic
   - Hypercalcemia (due to production of 1,25 (OH)2 cholecalciferol)

9) Neuro:
   B/L LMN 7th Nerve Palsy
   — DD:
     1. Sarcoidosis
     2. Guillain barre syndrome
     3. Diphtheria
     4. Lyme disease

   Pituitary stalk involvement
   - Central Diabetes Insipidus
   Transverse myelitis
   Hypothalamic involvement
   Basilar meningitis

**Diagnosis**

Old method: Ga - 67 Scan
   — Panda sign / Lambda sign (outdated)

Now a days: 10C PET Scan biopsy

ACE levels normal can rule out sarcoidosis

ACE high: DD:
   1. Gaucher's disease
   2. Miliary TB
   3. Leprosy
   4. Hyperthyroidism
In BAL \( \frac{CD_8}{CD_4} \) ratio is high (↑↑) in sarcoidosis

If \( \frac{CD_8}{CD_4} \) ↑↑ \( \rightarrow \) Hypersensitivity Pneumonitis

Rare findings:
- Only in Indian patients
  - Multiple red papules over cheek & chin
- Osteolysis
  - Perthes Jungling disease

**Paradoxical response**

00:18:04

1) Immune paradox

2) Clinical paradox
   - As lung disease worsens, Nodal enlargement usually regresses
   - Can present with Anaemia & splenomegaly
   - Drug related Sarcoid like lesions: Anti TNF α therapy

Markers:
1) ACE
2) Serum Amyloid A
3) Soluble IL-2 receptor

Treatment:

Acute: No drugs required
Optional - steroids

Chronic: Steroids + Methotrexate or Azathioprine

2nd line: Anti TNF-α
CRYSTAL ARTHROPATHY

Dietary purine

< Adenine and guanine >

Endogenous purine

Hypoxanthine / Xanthine

Uricase

Other mammals

Allantoin

Homo sapiens and primates

Uric acid (Pool: 1.2 g)

Intestine

(0.3 g/day)

Excretion

(0.7 g/day)

Kidney

(0.5 g/day)

GMP

Amp

Adenosine

Inosine

Hypoxanthine

Xanthine Oxidase

Xanthine

Xanthine Oxidase

Uric acid

Uric acid → breakdown product of purine metabolism

Uric acid pool - 1.2 g/day

Daily Excretion ~ 700 mg/day

Urine Excretion ~ 500 mg/day

24 hr urine uric acid = 11 mg/kg/day
**4 Component handling of uric acid (handled by kidney)**

Renal elimination of uric acid
Operational-defined, 4-component model of renal uric acid handling

- Glomerular Filtration
  - 100% filtration
- Proximal convoluted tubule
  - S1: 100% reabsorption
  - S2: 0%-3% reabsorption, 95%-100% reabsorption
  - S3: 50% secretion, 40%-48% reabsorption, 8%-12% excretion

Net reabsorption of 90% of filtered uric acid

100% filtered
100% reabsorbed at S1 of PCT
50% secreted at S2 of PCT
40% reabsorbed at S3 of PCT

\[ \text{Net Result} = 10\% \text{ Excreted} \]

(100/50/40 rule)

**Classification of hyperuricemia**

Hyperuricemia

\[ \downarrow \]

1\(^{\circ}\) molecular defects undetected

\[ \downarrow \]

- Under Excretion (90%)
- Over production (10%)

2\(^{\circ}\) associated with specific enzyme defect
  - X linked
  - \( \uparrow \) PRPP synthetase
Secondary hyperuricemia:

a) ↑ uric acid synthesis de novo (Purine bio-synthesis)
   1) HGPRTase defect:
       - Lesch Nyhan Syndrome
         (Mental Retardation, Hyperuricemia, Self mutilation)
   2) ↓ Glucose-6-phosphatase
       - von Gierke’s disease
         Hypoglycemia, Lactic acidosis, Hyperuricemia, Hyperlipidemia,
         Doll facies, Seizures
   3) Fructose-1-phosphate aldolase defect

b) Idiopathic

c) Drugs
   1) Thiazides
   2) Pyrazinamide
   3) Nicotinic acid
   4) Salicylate
   5) Alcohol
   6) Cyclosporine
   7) Loop diuretics
   8) Ethambutol

d) ↑ ATP degeneration

Losartan → increased uric acid excretion
preferred in HTN with hyperuricemia.

Clinical presentation

Hyperuricemia: (> 6.8mg/dl - male
         > 6mg/dl - Female)
can be: asymptomatic or affect joints (gouty arthritis) or present
with renal manifestations

Asymptomatic hyperuricemia:
- Considered as a part of Insulin resistance and is included in
  metabolic syndrome
- Correlate directly with Sugars/Cholesterol/Creatinine/BP
- ↑ risk for developing gout (first attack after 20 yrs)
- Alcohol/Sea food/Red meat - ↑ uric acid level
Renal disease due to uric acid

1. Uric acid Nephropathy
   - Tumour lysis syndrome

2. Urate Nephropathy
   - Chronic long standing hyperuricemia related tubulo-interstitial damage

Other causes:
1. Hyper Oxaluria
2. ↑ Uric acid
3. Hyper Ca²⁺
4. Hypo Kalemia

Can lead to chronic long standing hyperuricemia related tubulo-interstitial damage

Lead Poisoning: ↑ uric acid CTID

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Joint manifestation

1. Acute Gouty Arthritis
   - Fluctuations in the level of uric acid triggers it
   - Alcohol & Sudden lowering of uric acid by drugs trigger it
   - m>40 (40-60yr)
   - Asymmetrical onset
   - Clinically - MTP of great toe affected
   - Rarely ankle/wrist/knee
   - acute on chronic presentation maybe seen
   - Explosive onset (Extreme pain)
   - Hot red dusky swollen joint & Signs of inflammation
   - X-ray ⇒ ↑ Soft tissue density
   - Polarised light microscopy
     - Negatively bi-refringent needle shaped Crystals containing MSUM (monosodium urate monohydrate)
Polarized light microscopy of urate crystals. Illustrated are extracellular birefringent needle-shaped urate crystals.

Polarized light microscopy of urate crystals. Illustrated are intracellular birefringent needle-shaped urate crystals.

Treatment

**Acute Gout**

- Confirmed diagnosis known
- Not diagnosed
  - **DOC:** NSAID (Naproxen or Indomethacin)
  - Colchicine 0.5 mg - 0.6 mg hrly for 10 dose
  - No response
    - Intra articular steroid
    - Or Single intra muscular ACTH

**New drugs:**
- IL-1β antagonist
  - Anakinra / Canakinumab / Rilonacept

**Chronic tophaceous gout**

- "Tophi" - marker of chronic gout
- Irregular asymmetric moderately discrete tumescence that we see on hands / Feet / Olecranon / Forearm / Antihelix of ear
- Painless

↓

Acute inflammation around tophi makes it painful

1\textsuperscript{st} episode of acute gout

↓ 12 yrs

Chronic gout

Rate of tophus formation correlates with degree and duration of hyperuricemia.

X-ray finding of chronic tophaceous gout

- Asymmetrical
- Punched out erosion
- Lytic lesions
- Overhanging edges
- Sclerotic borders
- Differ from rheumatoid arthritis
  - maintenance of the joint space
  - Absence of periarticular
  - Osteopenia
  - Location outside the joint capsule

RA vs Chronic tophaceous gout

In chronic gout: maintenance of joint space, absence of peri-articular osteopenia.

"martell Sign or G sign" - Overhanging edges

Treatment:
Chronic tophaceous gout (on assymetric hyperuricemia)

Aim: To control hyperuricemia

I Drugs which inhibit xanthine Oxidase

- Allopurinol
- Oxypurinol
- Febuxostat

II Uricosuric drugs

- Probenecid (Sulfapyrazone)
- Benzbromarone (Lesinurad)
Recombinant Uricase
(Specifically used for tumor lysis syndrome)
- Rasburicase
- Pegloticase

(Infusion reaction can occur and are dangerous)

Xanthine oxidase

1) Allopurinol
   - No role in acute gout
   - Sudden lowering with drug can trigger attack

HLA B1502, B5801 → Sudden hypersensitivity to drug (SJS)

S/E: GI intolerance, Bone marrow Suppression, Alopecia, Hepatitis
   \[\uparrow\] T½ of warfarin, Theophylline
   Starting dose: 300mg / day (if renal failure: 100mg / day)

2) Febuxostat
   Safe in Renal Failure
   Less side effects

Uricosuric drugs

Severe Gastrointestinal distress
Hypersensitivity ⊕
\[\downarrow\] Renal excretion of penicillin / Salicylate
Benzbromarone is safe in renal failure

Food grouping acc. To purine content
- Group 1 high purine content
  (100 to 1000mg of purine nitrogen per 100gms of food)
  - Anchovies
  - Bouillon
  - Brains
  - Broth
  - Consommé
  - Goose
  - Gravy
  - mackerel
  - meat extracts
  - mince meat
  - mussels
  - Partridge
  - Roe
  - Sardines
Food in this list should be omitted from the diet of patients who have gout (acute and remission stages)

Associations of hyperuricemia:
1) Atherosclerosis
   a) Type 2 DM
   b) Systemic hypertension
   c) Hyper triglyceridemia.
   d) Hypothyroidism

Pseudogout
- Seen in elderly males (65 - 75 yrs)
- Due to calcium pyrophosphate deposition
- Painless
- Mostly involve knee joint
- Non inflammatory arthritis
- ANKH gene mutation
- Wrist/Shoulder may be involved
- X-ray ⇒ Chondrocalcinosis
- Positively birefringent Rhomboid crystals prove diagnosis
- Always do synovial study
- Fever

- Rx: NSAIDS / Steroids

- Associated with:
  1) 1st hyperparathyroidism
  2) Hemochromatosis
  3) Hypophosphatasia
  4) Hypomagnesemia (Gitelman syndrome)

Calcium apatite deposition disease
- In areas of tissue damage / CKD / hypercalcemia
- Shoulder joint involvement
  - Milwaukee shoulder
  - Mostly asymptomatic or can cause destruction
- Intra articular calcification
- Non-inflammatory (Synovial fluid WBC count - low)

**Calcium oxalate deposition disease**

Envelope shaped - Ca Oxalate dihydrate
Dumbbell shaped - Ca Oxalate monohydrate
Positive birefringement crystals
Non-inflammatory
Involves bone / Articular cartilage
m/C: Finger, wrist, elbow
INTRODUCTION TO INFLAMMATORY ARTHRITIS

Arthritis (Two types)

Inflammatory

Non inflammatory

e.g: Rheumatoid Arthritis

Oska Arthritis

Diagnostic approach:

1) Arthralgia or Arthritis

Arthralgia

Pain around joint

Arthritis

Inflammation (redness, warmth)

or

Pain

or

Tenderness

or

Edema

a) Inflammatory or Non inflammatory

a) History

morning stiffness

- All inflammatory arthritis → morning stiffness is relieved by activity & exacerbated by rest

- Duration:
  Peripheral arthropathy > 45 min
  Axial arthropathy > 30 min

b) Clinical finding

Features of inflammation at joint

c) Lab markers:

ESR, CRP

Serum ferritin, platelet count
d) X-rays:
   Rarefaction or erosion of inflammatory arthritis

e) Best Test
   Synovial fluid WBC count > 5000/ml

3) Unilateral or bilateral
4) Involving - lower limb
   Or
   upper limb
   Or
   Combined

5) Mono arthritis
   Or
   Oligoarthritis
   Or
   Polyarthritis

6) Involving small joints
   or
   Large joints
   or
   Combined

* In case of Rheumatoid Arthritis
  1) Arthritis
  2) Inflammatory
  3) Bilaterally symmetrical
  4) Predominantly upper limb
  5) Small joint
  6) Polyarthritis

Additional findings in RA:

1) On x-ray
   ↓
   If erosions present → Rheumatoid Arthritis

2) Markers
   • Anti-CCP (Anti-Cyclic citrullinated peptide)
   • Rheumatoid factor (RF)
Rheumatoid arthritis (RA)

- Most common chronic inflammatory, symmetrical involving small joint (upper limb) Peripheral erosive polyarthritis
- Risk of Rheumatoid Arthritis ↑ > 40 yrs Age
- F > m, F : m ratio 3 : 1

Pre – RA

1) Genetic and environmental susceptibility
2) Antibodies positive for RA
3) Clinical evidence without the evidence of arthritis
4) Early undifferentiated arthritis also known as palindromic rheumatism

1) Genetic and environmental susceptibility:
   - Genetic:
     - Females > males
     - HLA DRB104 - Causative
     - HLA DRB1 01
       - Certain alleles are protective
         - 03
         - 05
         - 07
     - 15% concordance in identical twins
- Environmental risk factors
  - Strongest risk factor → Smoking
  - No single causative infectious agent is established
  - Chronic periodontitis is also risk factor

a) Auto antibodies

For eg: A 50 year old female complains of
Pain in small joints in both upper limb right side > left side with early morning stiffness relieved with activity

On examination → Normal

Differential diagnosis: Undifferentiated Arthritis

- Evaluate: ESR and CRP

---

Risk factor score for RA

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<th>Variables</th>
<th>Score</th>
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<tbody>
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<td>Age (years)</td>
<td>x0.02</td>
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<tr>
<td>Female</td>
<td>1</td>
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<td>Joint distribution</td>
<td></td>
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<tr>
<td>Small joints of hand / Feet</td>
<td>0.5</td>
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<tr>
<td>Symmetry</td>
<td>0.5</td>
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<tr>
<td>Upper limb</td>
<td>1.0</td>
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<tr>
<td>Upper &amp; lower limb</td>
<td>1.5</td>
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### Inflammatory Arthritis

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<td>Morning stiffness (on 100mm VAS)</td>
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<tr>
<td>2.6-90mm</td>
<td>1.0</td>
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<tr>
<td>&gt;90mm</td>
<td>2.0</td>
</tr>
<tr>
<td>Tender joints (n)</td>
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<tr>
<td>4-10</td>
<td>0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.0</td>
</tr>
<tr>
<td>Swollen joints</td>
<td></td>
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<tr>
<td>4-10</td>
<td>0.5</td>
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<tr>
<td>&gt;10</td>
<td>1.0</td>
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<tr>
<td>CRP (mg/L)</td>
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<tr>
<td>5-50</td>
<td>0.5</td>
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<tr>
<td>&gt;50</td>
<td>1.5</td>
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<tr>
<td>RF positivity</td>
<td>1</td>
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<tr>
<td>ACPA positivity</td>
<td>2</td>
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</table>

#### Serology

- In early undifferentiated Arthritis
  - 1) CRP +ve
  - 2) Anti-CCP +ve
  - 3) RF +ve
  \[ \uparrow \text{risk for development of RA} \]
- a out of 3 Positive → high risk of progression to RA

Rheumatoid Factor (RF):
- IgM Antibody → Against Fc portion of IgG
- Seen in 75-80% cases of RA
- Increased risk for progression from undifferentiated Arthritis
- Increased risk for articular complications in RA
- ‘no role in follow up’
**Anti-CCP**
- CCP → Cyclic citrullinated polypeptide
  - or
  - mutated citrullinated vimentin (anti-MCV)
- Anti-CCP Antibody is seen in 85-90% of RA cases
- more specific than Rheumatoid Factor (RF)
- ↑ risk for extraarticular features
- ↑ risk for progression from undifferentiated arthritis

From established RA → Progress to chronic stabilized RA after 2 years

- Pre-RA → 1st 3 months duration
- Established RA → 3-24 months
- Chronic stabilized RA → After 24 months

**Indian Rheumatology Association - Classification of RA:**
- VERA - Very Early Rheumatoid Arthritis → within 1st 3 months
- Early established RA → within 1 year
- Late established RA → 1-2 years
- Chronic stabilised RA > 2 yrs

**Pathogenesis**

- Inflammation - Arthritis
  - Tendinitis
  - Bursitis
- Inflammation starts at 'DRUJ' (Distal Radio Ulnar Junction)
- Tcell + B cell mediated
- Key pathogenetic cytokine in RA → TNF-α
- Osteoclasts are activated
  - Bone resorption
    - Genetic + Environmental Factors
      - Activates
        - Antigen Presenting cells (APC)
APA. Presents the Antigen to T-cell which activates T-cell
Activated T-cell
3 responses
\( Th_1 \gg Th_n > Th_a \)

Activated T-cell

\( Th_1 \) response \( Th_2 \) response

Releases IFN-\( \gamma \) Releases IL-4

Activates Macrophage Activates B-cell
to produce TNF-\( \gamma \) to produce Antibodies
TNF-α

- TNF-α inhibits osteoblasts by DMK-1 pathway also known as Dickkopf pathway
- Activates osteoclast - By RANK-L/RANK interaction
- RANK receptor present on the inactive Osteoclast
- osteoprotogelin prevents binding of RANK-L to RANK Receptor
- In Rheumatoid Arthritis
  
  **TNF-α Blocks Osteoprotogelin**
  
  ** Releases RANK-L from Activated macrophage**
  
  **Facilitates RANK-L-RANK interaction**
  
  **Activates osteoclast**
RHEUMATOID ARTHRITIS – ARTICULAR & EXTRA ARTICULAR MANIFESTATIONS

- It’s an inflammatory arthritis starting at the Distal Radio Ulnar joint (DRUJ)
- Main inflammatory cytokine
  ↓
  TNF-α – which is released from activated macrophage
  - As a part of Th1 response
- Three joints are involved at the same time
  - Wrist joint
  - Metacarpophalangeal (MCP) joint
  - Proximal interphalangeal (PIP) joint
- Distal interphalangeal joint (DIP) is not involved in Rheumatoid arthritis

Pathology

Inflammation of synovium
  ↓ results in
  Synovial Hypertrophy
- Inflammatory granulation tissue that causes hypertrophy of joint space is called pannus
- Changes in joint due to synovial hypertrophy

1) Zig-Zag Deformity:
- It’s not a true deformity
- Earliest change in Rheumatoid Arthritis
- Radial deviation at the wrist joint
- Ulnar deviation at metacarpophalangeal (MCP) joint
2) Piano key deformity of the ulnar styloid:
   • This is also not a true deformity
   • It is due to rupture of Extensor Carpi ulnaris Tendon

3) Subluxation of metacarpophalangeal (MCP) joint:
   Due to Synovial Hypertrophy
   
   There is subluxation of MCP joint

True deformities in rheumatoid arthritis

As the disease progresses, true deformities occur

1) Buttonhole or Boutonniere deformity:
   • Flexion of PIP (proximal interphalangeal) joint
   • Hyperextended DIP (distal interphalangeal) joint
   • This is due to synovitis of PIP joint and subluxation of lateral band

2) Swan neck deformity:
   • Hyperextended PIP (proximal interphalangeal) joint
   • Flexion of DIP (distal interphalangeal) joint
• Swan neck deformity is due to rupture of flexor digitorum superficialis tendon

So, no flexion of PIP joint
PIP joint goes into hyperextension
And secondary flexion of DIP joint

3) Hitchhiker thumb deformity:
• Abduction of thumb
• Hyperextension of interphalangeal joint of thumb
• This is known as Hitchhiker thumb deformity

4) Vaughan Jackson syndrome:
(deformity)
• Due to rupture of extensor tendons of III, IV, V

Only extensor indices tendon is intact

5) Intrinsic plus deformity:
• Due to chronic tightness of intrinsic muscles

Causes subluxation of MCP joint
resulting in
Flexion of MCP joint
Extension of interphalangeal joint
Causing intrinsic plus deformity
6) Opera glass hand deformity:
   - It’s an arthritis mutilans of hand
   - Shortening of fingers

   Due to destruction of
   phalanges

   Excessive skin gets folded
   transversely resembling
   ‘Opera glass’.

DIP deformities in Rheumatoid Arthritis

   - DIP joint arthritis is not seen in Rheumatoid Arthritis

DIP deformities in RA

mallet finger

   - Hyperflexion of DIP joint
   - Which can be seen in
     1) Swan neck deformity
     2) loss of central slip of
        extensor tendon

   - DIP deformity in Rheumatoid arthritis is mallet finger

Gamekeeper’s Thumb/skier’s Thumb:

   - Ulnar collateral ligaments
     of MCP joints are
     destroyed due to synovitis

   Resulting in laxity of
   the ulnar collateral
   ligament of MCP joint

Lower limb in rheumatoid arthritis (RA)

   - In lower limb, first joint to be affected
     ↓

   Metatarsophalangeal (MTP) joint
Classical deformities
- Pes planus
- Forefoot varus
- Ankle valgus

Triad
- Cock up toe deformity
  - Hallux valgus
  - Hyperflexed digits

- Rarely knee joint may be involved

3. Striking joints involved in Rheumatoid Arthritis
   - Temporomandibular joint
   - C1 - C2 → Atlanto - Axial joint
     The axial joints are not involved in Rheumatoid Arthritis except C1 - C2
   - Crico - Arytenoid Arthritis

Extra-articular manifestations of RA
- Most common cause of death in RA
  - MI
  - Due to Accelerated atherosclerosis

- So, RA is also known as MI equivalent

1. Neuro-ocular
   - RA doesn't involve brain parenchyma so, cognitive dysfunction is extremely rare
     - C1 - C2 Atlanto - Axial joint involvement
       - Cervical myopathy
       - Entrapment neuropathy
         - Due to synovial hypertrophy resulting in compression of nerve
         - Carpal Tunnel syndrome

- Most common ocular manifestation is dry eye
most common cause of secondary Sjogren’s syndrome

Episcleritis → Acute painful red eye

Scleritis → most characteristic manifestation associated with long term RA

Can lead to visual loss

• Uveitis is not seen in RA

a) Cutaneous manifestation:

• RA nodule or Rheumatoid node

Painless nodule

• Occurs mostly on pressure areas:
  Elbow (most common)
  Finger
  Olecranon

• Associated with ↑ RF Titres

Bad prognosis

Rheumatoid nodules in olecranon bursa and along proximal ulna.

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

• It is also associated with more extraarticular features

• Only 10% of RA cases develops nodules in the 1st year

• It’s a late manifestation

• Palpable purpura
  • Petechiae
  • Vesicles
  • Bulla
  • Ulcers (rare)

  \{ Small vessel vasculitis \}

• Erythema nodosum

• Pyoderma Gangrenosum \{ very rare \}

3) Hematological manifestation:

• Anaemia of chronic disease (most common)
Inflammation

\[ \text{\textdownarrow} \]

↑ hepcidin

\[ \text{\textdownarrow} \]

Inhibits ferroportin

\[ \text{\textdownarrow} \]

Iron cannot come into circulation

\[ \text{\textdownarrow\textdownarrow} \]

Serum iron

- most sensitive & specific indicator is ↓↓ Serum iron
- Warm antibody (IgG) Autoimmune hemolytic anaemia

\[ \text{\textdownarrow} \]

Coombs Test +ve

- In late stages of RA

RA + Neutropenia + Splenomegaly

Felty's syndrome (very rare)

- Felty's syndrome has to be always differentiated from Leukemia & Lymphoma.
- Large Granular Lymphocytic Leukemia (LGL) can behave very similar to Felty's syndrome
- So, Felty's Syndrome is a diagnosis of exclusion
- RA is a premalignant condition → ↑ ed risk of DLBCL (Diffuse large B-cell lymphoma)

4) Cardiac manifestation

- Pericarditis without Tamponade - most common
- Endocarditis is very rare
- Most common valvular lesion → Mitral Regurgitation
- Most common Arrhythmia → Ventricular Tachycardia

5) Endocrine manifestation: → Hypoandrogenism

6) Skeletal manifestation:

Because of ↑ TNF - α

\[ \text{RANK - L} \ & \text{RANK Interaction} \]

↓ Osteoclastic activity

Osteoporosis
1) Renal manifestation:
- most common association of RA
  ↓
  Secondary membranous nephropathy

- Long standing RA produces \( \text{a}^\circ \) Amyloidosis
  \( \downarrow \)
  RA Amyloidosis

2) Gastrointestinal manifestation:
- GI vasculitis
  ↓
  mesenteric artery vasculitis (medium vessel vasculitis)
  ↓
  mesenteric ischemia

**Lung involvement**

- most common lung manifestation
  \( \downarrow \)
  Pleuritis ± effusion

- Pleural effusion in RA
  - Lymphocytic exudative effusion
  - Unilateral >> Bilateral
  - ↑ Protein
  - ↑ LDH
    - Low pleural fluid glucose (<30g/L) - diagnostic of RA

- High LDH also seen in Empyema
  ↓
  To differentiate it from RA
  ↓
  Pleural fluid pH < 7.2 - Suggestive of empyema

**Interstitial lung disease in RA**

- most dangerous complication in RA with respect to lung
  \( \rightarrow \)
  Interstitial lung disease (ILD)
ILD in RA

- IdiopathicILD
- UIP (usual interstitial pneumonia)
  - Or
  - Idiopathic Pulmonary Fibrosis (IPF)
    - Characterized by
      - Loss of lung architecture
      - Honey combing
      - Traction bronchiectasis
      - Steroid unresponsive

- NSIP
  - Non specific interstitial pneumonia
  - Associated with connective tissue disease & drugs
    - Ground glass opacities
    - Steroid Responsive

- UIP - universal interstitial pneumonia is the most common ILD in RA
- All the connective tissue disorders causes
  - Lower lobe ILD's

Caplans syndrome

Nodules + Pneumoconiosis + RA \{ Caplans syndrome \}

- Indicates high disease activity
**Immunology**

- ILD with decreased DLCO and \( \frac{FEV_1}{FVC} \) Normal
- ILD can cause pulmonary Hypertension
- Two conditions that can produce nodules in the lung other than ILD
  \( \text{wegener's silicosis} \)

**Symptoms in ILD:**
- Dry cough
- Exertional dyspnea
- RA patient

- Asymptomatic
- Symptomatic

\[ \text{Screen for ILD} \quad \text{Do HRCT} \]
- PFT (Pulmonary function test)
- DLCO (Diffusion capacity using CD)

- Now, in Rheumatoid Arthritis → UIP (Universal Interstitial pneumonia)

- Response to treatment in ILD is poor

**Bilateral, peripheral, and subpleural reticular infiltrates are evident. The presence of advanced fibrosis is indicated by honeycomb changes (arrowheads) and traction bronchiectasis (arrow).**
* NSIP - Nonspecific interstitial pneumonia
  ↓
* Lung architecture is maintained
* Ground glass opacities
* NSIP is seen in other connective tissue disorders

Rheumatoid vasculitis

- Long standing disease
- RF Positivity
- Mononeuritis multiplex
- Vasculitic ulcers
- Petechiae
- Purpura & gangrene
- Systemic features are uncommon
- RA patient came with Acute Abdominal pain
  - Proteinuria
  - Ascites

Here acute abdominal pain could be due to
  - Superior mesenteric Artery vasculitis
  ↓
  - But there is no proteinuria
So, presence of proteinuria
  ↓
  - Indicates 2° Amyloidosis
- Long standing disease
- It has a very bad prognosis
- Methotrexate causes remission
- Cyclophosphamide in glomerular disease
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning Stiffness</td>
<td>morning stiffness in and around the joints lasting at least 1 hr before maximal improvement</td>
</tr>
<tr>
<td>2. Arthritis of ≥ 5 joint areas</td>
<td>At least 5 joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by physicians (the 14 possible joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 joint area swollen as above in wrist, MCP, or PIP joint</td>
</tr>
<tr>
<td>4. Symmetric Arthritis</td>
<td>Simultaneous involvement of same joint areas (as in criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum Rheumatoid Factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive</td>
</tr>
<tr>
<td>7. Radiographic Changes</td>
<td>Changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
</tbody>
</table>
RA Patients

VERA
Very Early Rheumatoid Arthritis
Look for serology

Established RA
Features of Arthritis Present clinically

RF
CCP
As a prognostic marker

Chronic stabilized RA

Anti - CCP
RF
CRP
ESR

2 out of 3 is enough for diagnosis

In India, 2/4 is enough

Repeating RF & CCP → No value in follow up
Repeat CRP → For follow up

X-ray: Periarticular Osteopenias → Erosions
Management

In VERA patient

**DMARD’S - Disease modifying Anti Rheumatoid Drugs**
- Gold
- D - Pencillamine
- Azathioprine
- Hydroxychloroquine
- methotrexate
- Sulfasalazine
- Leflunomide

**DMARD of choice → methotrexate**

Treatment

- using single Agent
  - methotrexate

- Combination of drugs
  - Ideal combination
    - methotrexate
    - Hydroxychloroquine
    - Sulfasalazine

- Leflunomide is a reserve drug

- Dose of methotrexate
  - 2.5 mg on Saturday & Sunday
  - up to 25 mg weekly dose

- Remaining Sdays → Folic Acid

methotrexate

- Dihydrofolate reductase inhibitor
- Dose dependent toxicity
  - Bone marrow Suppression
- Mucositis - most common toxicity
Long-term methotrexate use → Dangerous complication
   In Liver - Hepatic cirrhosis
   In Lungs - ILD (Interstitial lung Disease)

2) Hydroxychloroquine (HCQ) - Dose of 200mg BD
   • Causes irreversible retinal toxicity in 1% of cases

3) Sulfasalazine - 2g/day

4) Leflunomide -
   • It is a Dihydro orotate dehydrogenase inhibitor
   • Leflunomide also causes hepatotoxicity

So, in a VERA patient,
   methotrexate 2.5mg on Saturday & Sunday
   Or
   methotrexate 2.5mg on Saturday & Sunday
   +
   Hydroxychloroquine 200mg BD
   +
   Sulfasalazine 2g/day

• Disease activity is followed up by → CRP (marker for follow up)

In case of established RA with clinical evidence of
   Synovitis / Arthritis
   ↓
   As DMARDs takes 6 - 8 weeks to achieve target therapeutic level
   ↓
   Start steroids
   ↓
   This is known as Bridge therapy
Early diagnosis & treatment

- window of opportunity is 4 yrs
  ↓
  To be specific - 3 months i.e., Pre-RA
- 1/3rd of undifferentiated arthritis → RA
- RF, CCP, CRP are used

IRA guidelines

- Never diagnose RA in the presence of monoarthritis
- Don't diagnose RA unless hands are involved
- If DIP joint is involved consider alternate diagnosis
- Lumbar spine is never involved
- RF (Rheumatoid Factor) never needs to be repeated
  ↓
  Because it poorly correlates with Treatment

Biologics in RA

- Rheumatoid arthritis disease activity is high despite being on 2 or more DMARD'S
- Biologics are used
- But Biologics have ↑ risk of infections
  Contraindicated in pregnancy
  (Hydroxychloroquine is the safest DMARD in Pregnancy)
- Biologics → Never use it alone
  Always given along with DMARD’S

1. Anti-TNF-α -
   - Infliximab
   - Etanercept
   - Adalimumab
   - Golimumab
   - Certolizumab

- Anti-TNF α → risk of Drug induced SLE
  - Hepatitis & Flare
- Never start Anti-TNF - α with out ruling out latent TB
- Dose of infliximab - 2mg/kg IV once every 2 weeks
  a) Anti - CD20 - Rituximab
  b) Anti - IL-1 - Anakinra
  c) Anti - IL-6 - Tocilizumab
  d) CTLA4 - IgG Fusion molecule → Abatacept
     CTLA4 - Cytotoxic T - cell Lymphocyte Associated Antigen -4
  e) JAK - 3 inhibitor - Tofacitinib

<table>
<thead>
<tr>
<th>Table 1</th>
<th>DMARDs used for the treatment of rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dosage</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4-8mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>monthly or</td>
</tr>
<tr>
<td></td>
<td>16mg SQ</td>
</tr>
<tr>
<td></td>
<td>Every other week (100mg weekly)</td>
</tr>
<tr>
<td></td>
<td>16mg SQ every week (6-100g weight)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>5mg orally BID</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>weight based</td>
</tr>
<tr>
<td></td>
<td>&lt;40kg/500mg</td>
</tr>
<tr>
<td></td>
<td>60-100kg/750mg</td>
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<tr>
<td></td>
<td>&gt;100kg/1000mg IV dose</td>
</tr>
<tr>
<td></td>
<td>at weeks 0,2, and 4</td>
</tr>
<tr>
<td></td>
<td>And then every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>13mg SQ weekly</td>
</tr>
<tr>
<td>Anakinra</td>
<td>100mg SQ daily</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>100mg IV* 4 days</td>
</tr>
<tr>
<td></td>
<td>0 and 4</td>
</tr>
<tr>
<td></td>
<td>May repeat course every 24 weeks or more</td>
</tr>
<tr>
<td></td>
<td>Premedicate with methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>100mg to decrease infusion reaction</td>
</tr>
</tbody>
</table>
SPONDYLOARTHITIDES

Seronegative spondyloarthropathy

- Ankylosing spondylitis or Bechterew's disease or Marie - Strumpell disease
- Reactive arthritis or Reiter's syndrome
- Psoriatic arthritis
- IBD or enteropathic arthritis
- Juvenile Idiopathic Arthritis (JIA)

Common binding features

- All of them are seen under 40 years (< 40 yrs)
- Axial predominant arthropathy
- Rheumatoid Factor RF Negative
- HLA B27 - Positive
- Males > Females
- Most common extra articular manifestation → uveitis
- Pathology: Enthesitis
  Enthesis - site where ligament/ligament/tendon/joint capsule attaches to bone

Ankylosing spondylitis

- Male to female ratio is 3:1
- Generally diagnosed between 15-30 yrs
- HLA B27 positive in 90-95% of adults
- Axial inflammatory arthropathy
- Sacroiliitis is the earliest manifestation with enthesitis (Achilles Tendinitis) with varying degree of peripheral joint involvement
  +
  Extra articular manifestations
- Key cytokine in ankylosing spondylitis is TNF-α
Immunology

- Inflammatory granulation tissue (TNF-α) erodes the annulus fibrosus.
  - One disc glides over the other.
  - Resulting in syndesmophyte formation.
  - Which predisposes to bony ankylosis.
  - Bamboo spine.

- Most common complication → spinal fracture.
  - TNF-α
  - Activates osteoclast
  - Resulting in bone resorption
  - Square wave vertebra.

- Approach to the patient
  - E.g., 20 year old boy complains of back pain since 3 months.
- Mostly it is buttock pain
  - Alternative buttock pain
    - Morning stiffness for > 30 minutes
    - Relieved with activity
    - Maximum pain in the early morning hours, disturbing sleep
  - And ESR
    - Elevated
    - CRP
  - Sacroiliitis is the earliest manifestation
    - It can be asymmetrical.
### Table: Criteria for ankylosing spondylitis

Rome, 1961

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low back pain and stiffness for more than 3 months, not relieved by</td>
</tr>
<tr>
<td>2. Pain and stiffness in thoracic region</td>
</tr>
<tr>
<td>3. Limited motion in lumbar spine</td>
</tr>
<tr>
<td>4. Limited chest expansion</td>
</tr>
<tr>
<td>5. History or evidence of iritis or its sequelae</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiographic Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Radiograph showing bilateral sacroiliac changes characteristic of ankylosing spondylitis (this excludes bilateral osteoarthritis of sacroiliac joints)</td>
</tr>
</tbody>
</table>

**Define Ankylosing Spondylitis**

Grade 3 or 4 bilateral sacroilitis with at least one clinical criterion  

or  

At least four clinical criteria.

---

**ASAS classification criteria for axial SpA**  
(in patients with back pain ≥ 3 months and age at onset ≤ 45 years)

- Sacroiliitis on imaging:  
  - Active (acute) inflammation on MRI highly suggestive of sacroilitis associated with SpA  
  - Definite radiographic sacroilitis according to modified New York criteria  

- Or  

- HLA-B27  
  - Plus ≥ 2 other SpA features**

**SpA features:**  
- Inflammatory back pain  
- Arthritis  
- Enthesitis (heel)  
- Uveitis  
- Dactylitis  
- Psoriasis  
- Crohn’s disease / ulcerative colitis  
- Good response to NSAIDS  
- Family history for SpA  
- HLA-B27  
- Elevated CRP
• To qualify as the criterion for inflammatory back pain of axial spine the chronic (3 months) back pain should have four or more of these characteristic features
  (i) Age of onset below 40 years
  (ii) Insidious onset
  (iii) Improvement with exercise
  (iv) No improvement with rest and
  (v) Pain at night with improvement upon getting up

Earliest signs can be detected by 3-6 months after the onset

Sacroiliac Joints:
Early patches osteoporosis develop around the distal third of both the bones. Joint margins become illdefined and joint intervals become widened. Subchondral erosions starts and when there is multiple erosions, produces Rosary effect

Investigation of choice → MRI of spine
Bamboo spine

Radiology

- Earliest x-ray finding → Blurring of cortical margins of Subchondral Bone

- Sacroiliitis
- Bony erosions
- Bony ankylosis
- Calcification of Anterior interspinous ligament
  ↓
  Dagger sign

- Calcification of Apophyseal Joint capsule (pointed by black arrows in diagram)
  ↓
  Trolley Track sign

- Shiny corner sign or
  Romanus sign

Shiny corner sign / Romanus sign
modified Schober's Test:
- Palpate Posterior superior iliac spine (PSIS)
- Between the two PSIS → Sacral dimple

- In this test marks are made 5 cm below and 10 cm above the sacral dimples
- The distance between these marks should increase from 15 cm to at least 20 cm with lumbar flexion
- The distance less than 5 cm is abnormal

Extra articular features & peripheral joint involvement

- Involvement predicts poor prognosis

Extra articular features
- Most common - uveitis → acute anterior uveitis
- Cardiac manifestations → acute aortic regurgitation
  - Heart Blocks
- Lungs → Interstitial lung diseases (ILD)
  - Involves upper lobe

- Bronchiolitis obliterans
- Most common ILD in ankylosis spondylitis → NSIP
  (Non Specific Interstitial pneumonitis)
- BOOP - Bronchiolitis Obliterans Organising Pneumonia
  - Pattern of ILD strongly associated with Ankylosing spondylitis
• In axial skeleton involvement →
  Cervical joints
  • Asymmetrical joint inflammation
  • Syndesmophytes → more marginal & delicate

• Most characteristic or diagnostic of
  Psoriatic Arthropathy
  ↓
  Ray pattern
• Most often 2nd digit is involved

Extra articular manifestations in psoriatic arthritis

1) Most common - uveitis
  ↓
  Bilateral chronic posterior uveitis

2) Lungs
  • Upper lobe ILD → Nonspecific interstitial pneumonia

3) Kidney
  • a" IgA nephropathy

4) Heart
  • Aortic regurgitation
  • AV Blocks
  • It is 100% clinical diagnosis

Ray pattern PA Hand note the erosive changes are present at the three joints of the second digit (arrows). This pattern of arthritis is virtually diagnostic of psoriasis.
- Renal manifestations → a**n**a**g** IgA nephropathy
- Skin manifestation → may have psoriatic lesions
- GIT → Inflammatory bowel disease like pathology

**Management – AS**

- mainstay of treatment → physiotherapy
- 1st line management → **NSAID**
  
  Reverses the natural history of disease

- Intra articular steroids for pain relief
- Sulfasalazine for peripheral arthritis
- Drug of choice → TNF-α Blockers

**Warning:** Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

**Reactive arthritis / Reiter’s syndrome**

- Occurs after 1–4 weeks after infection

  **Enteric infection**  **Urethritis**  **URTI**

  **Enteric infection**

  **Urethritis**

  **URTI** – upper respiratory tract infection

- most common cause in India **Shigella Dysenteriae**
- most common cause of urethritis worldwide

  **Chlamydia trachomatis**

- Enteric infection caused by all the enteric bacteria except E.coli
- Urethritis except **N. gonorrhoea** can cause reactive arthritis
- **URTI** – upper respiratory tract infection

  **β- hemolytic streptococci Chlamydia pneumonia**

  Can cause reactive arthritis
### Table: Microbial Infections Associated with Reactive Arthritis

<table>
<thead>
<tr>
<th>Enteric Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella: various serovars</td>
</tr>
<tr>
<td>Shigella</td>
</tr>
<tr>
<td>S. Flexneri</td>
</tr>
<tr>
<td>S. dysenteriae</td>
</tr>
<tr>
<td>S. sonnei</td>
</tr>
<tr>
<td>Yersinia</td>
</tr>
<tr>
<td>Y. enterocolitica (especially O:3 and O:9)</td>
</tr>
<tr>
<td>Y. pseudotuberculosis</td>
</tr>
<tr>
<td>Campylobacter</td>
</tr>
<tr>
<td>C. jejuni</td>
</tr>
<tr>
<td>C. coli</td>
</tr>
<tr>
<td>Clostridium difficile</td>
</tr>
</tbody>
</table>

**Bacteria Causing urethritis**

- Chlamydia trachomatis
- Mycoplasma genitalium [-]
- Ureaplasma urealyticum [-]

**Bacteria Causing upper Respiratory Infection**

- Beta-hemolytic streptococcus[-]
- Chlamydia pneumonia

---

- **Reactive arthritis following enteric infection**
  
  - Male to female ratio 1:1

- **Reactive arthritis following urethritis**
  
  - Male to female ratio is 9:1

- **Age of onset 15 – 30 yrs**
  
  - Male > Female

- **1 - 4 week before, there is history of infection**

  ![Diagram](https://via.placeholder.com/150)
• Presents with mono or OligoArthritis
  - Asymmetrical
  - Additive arthritis
  - Painful arthritis

• Starts predominantly in lower limb → knee
  + ankle
  + Subtalar
  + metatarsophalangeal

• Risk for chronicity → 60%

<table>
<thead>
<tr>
<th></th>
<th>Ankylosing Spondylitis</th>
<th>Reactive Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B27</td>
<td>In 90% cases doesn’t correlate with prognosis</td>
<td>In 70% cases Correlates with poor prognosis</td>
</tr>
<tr>
<td>Pain at Presentation</td>
<td>Doesn’t correlate with bone fusion Pain is due to spasm Enthesitis (++++)</td>
<td>Doesn’t correlate with chronicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enthesitis (+)</td>
</tr>
</tbody>
</table>

Other features – reactive arthritis

• Inflammation of fingers & toes
  ↓
  Dactylitis
  ↓
  Sausage digit

![Image of foot with marked area]
Keratoderma blenorrhagica:

- Hyperkeratotic vesicles on the palms & soles which crusts
- Seen in 25% of patients
- Most important differential diagnosis is pustular psoriasis

Circinate balanitis:

- Painless shallow erythematous ulcer on glans penis
- Seen in 25% of patients
- Rarely upper limb involvement in reactive arthritis
- Because in gonococcal arthritis → There is upper limb & lower limb involvement

Extraarticular features – Reactive arthritis

1) Acute Anterior Uveitis
2) Cervicitis / Salpingitis / Urethritis
3) No risk of ILD
4) No axial Arthropathy
5) Cardiac → Aortic regurgitation due to aortic root dilatation → Heart blocks
6) a hemorrhage

- Reactive arthritis is completely clinical diagnosis
- ESR, CRP → High
- NSAIDS → Indomethacin - Drug of choice
- Reverses the disease course
- 60% of patients can go into chronicity
- HLA B27 → poor prognosis / chronicity
- If the disease goes into chronicity (Chronic reactive arthritis / Persistent Arthritis)

Drug of choice – Sulfasalazine
- Steroids are used only for intraarticular injection for pain relief
- No benefit of initiating antibiotic therapy after development of arthritis

**Enteropathic arthritis or IBD arthritis**

- Male to female ratio 1:1
- <30 yr of age
- Most common in Crohn's disease > ulcerative colitis
- It can be of two types

  - Ankylosing spondylitis-like form
    - Seen in 10%
    - HLA B27 +ve in 50%
    - Do not correlate with relapse of IBD
  - Peripheral Arthritis-like form
    - Seen in 50%
    - HLA B27 -ve
    - It may be
      - Pauciarticular
      - Polyarticular

**Peripheral arthritis**

- Pauciarticular
  - Most common in knee joint
  - Acute self-limiting attacks
  - Correlates with relapse or disease activity in IBD

- Polyarticular
  - Most common in MCP joint
  - Chronic long standing attacks
  - Do not correlate with relapse

- Enthesitis/dactylitis are very rare
- Polyarticular arthritis is less common
- Infliximab is most effective
Psoriatic arthritis

- 5-30% of patients with psoriasis develops arthritis
- Association
  - HLA CW6 > HLA B27
  - HLA B57
  - HLA DR7
  - HLA DQ-3
- Seen in 40-50 years males > Females
- 50/30/20 rule
  - 50% of patients
  - 1st psoriasis then Arthropathy
  - in 30% of patients psoriasis & arthropathy at the same time
  - in 20% of patients 1st arthropathy then Psoriasis
- Dactylitis / enthesitis / nail changes are seen in every patients
- Nail changes are seen in 90%

Nail changes
1) Nail pitting (most common)
2) Onycholysis
3) Horizontal ridging
4) Yellow nail changes
5) Dystrophic hyperkeratosis
Pattern of arthritis in psoriasis
1) Pure DIP joint arthritis
   a) Symmetrical polyarthitis (2nd most common)
2) Asymmetrical mono & oligoarthritis (most common)
3) Axial arthropathy - Cervical joints

X-ray findings:
- Pencil in cup deformity
  ↓
  Due to
  Distal interphalangeal (DIP)
  Joint involvement

Telescoping of digits

- Marginal proliferative erosions
- Small-joint ankylosis
- Osteolysis of phalangeal and metacarpal bone, with telescoping of digits
- Periostitis and proliferative new bone at sites of enthesitis

- Marginal erosions with adjacent bony proliferation (Whiskering)

Arthritis mutilans
Severe joint destruction, especially at the metatarsophalangeal articulations, has resulted in fibular deviation and dorsal dislocation of the digits (Lanois’ deformity). The presence of a pencil-in-cup deformity (arrow) at the interphalangeal joint of the big toe and osseous ankylosis of the first metatarsophalangeal and second and third proximal interphalangeal articulations (arrowheads) makes the diagnosis of psoriatic arthritis most likely.
• In axial skeleton involvement →
  Cervical joints
  • Asymmetrical joint inflammation
  • Syndesmophytes → more marginal & delicate

• Most characteristic or diagnostic of
  Psoriatic Arthropathy
  ↓
  Ray pattern
• Most often 2nd digit is involved

Extra articular manifestations in psoriatic arthritis

1) Most common — uveitis
  ↓
  Bilateral chronic posterior uveitis

2) Lungs
  • Upper lobe ILD → Nonspecific interstitial pneumonia.

3) Kidney
  • a1Gn nephropathy

4) Heart
  • Aortic regurgitation
  • AV Blocks

• It is 100% clinical diagnosis
VASCULITIS: CLASSIFICATION & LARGE VESSEL

Introduction

vasculitis: Inflammation within the vessel wall
- Modified Chapel - Hill classification is used for vasculitis. It is based on the predominant size of the vessel involved.

Large vessel vasculitis
- It is a granulomatous inflammation within the vessel wall
- Predominantly CD4+ T Helper cell mediated
  i. Bechets
  ii. Temporal arteritis (TA)
  iii. Takayasu
  iv. Cogan's (triad) - Aortitis + Vestibulitis + Interstitial Keratitis

Temporal arteritis
- It is also called as Giant cell / Cranial / Granulomatous Arteritis
- Although giant cells are seen, it is not diagnostic of this condition
- Although called as cranial arteritis, extracranial vessels are also involved
- Along with this condition, Takayasu is also a granulomatous arteritis
- Full name: temporal arteritis polymyalgia rheumatica syndrome
- Seen only in > 50 years
- mean age: 72 years
- F > M: 2:1
- 2/3 of the patients are having associated polymyalgia rheumatica (PMR)
- HLA DRB, DQ - important for TA vs PMR
- mc vessel involved: superficial temporal artery
- 2nd mc: vertebral artery
- 3rd mc: ophthalmic artery
- 4th mc: posterior ciliary artery

Polymyalgia rheumatica (PMR): Pain & stiffness especially in early in the morning in shoulder, neck & pelvis/girdle
- ↑ in ESR >50mm/hr
- Excellent response to low dose steroids (10mg/day)

Clinical manifestations:
- 25% patients have non-specific symptoms. They may present with
  - Pyrexia of unknown origin
  - Fatigue, weight loss
  - Jaw claudication - Specific
- 75% of patients present with headache - mc
  - New onset headache in >50 years with ↑ in ESR (>100mm/hr)
  - 10% of patients are characterized by tenderness of temporal artery or ↓ pulsations
- It is associated with visual loss - unilateral or bilateral, temporary/Permanent- So, start the patient with steroids immediately after diagnosis of temporal Arteritis
### American College of Rheumatology Classification Criteria for Giant Cell Arteritis

<table>
<thead>
<tr>
<th>Criterion (*)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset ≥ 50yr</td>
<td>Development of symptoms or findings beginning at age of 50 or older</td>
</tr>
<tr>
<td>New headache</td>
<td>New onset or new type of localized pain in the head</td>
</tr>
<tr>
<td>Temporal artery abnormality</td>
<td>Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries</td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate (ESR)</td>
<td>ESR ≥ 50mm/hr by the Westergren method</td>
</tr>
<tr>
<td>Abnormal artery biopsy</td>
<td>Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

**IOC: Temporal artery biopsy**

- Transmural inflammation with mononuclear \& giant cells

- Temporal arteritis is characterized by skip lesions so, if first biopsy is negative, it cannot eliminate TA completely

- Some patients may have visual field defects (VFD). When the posterior ciliary artery is involved, characteristic VFD is Altitudinal hemianopia. Very often associated with Anterior Ischemic Optic Neuropathy (AION) — characterized by the presence of pale swollen optic disc
AION

Management: 1mg/kg oral steroid + Low dose Aspirin
New drug: IL-6 Antagonist - tocilizumab

- Giant cell arteritis suspected
  - Temporal artery biopsy
    - Positive biopsy: GCA proven
    - Negative biopsy: GCA still strongly suspected
      - Perform second biopsy of temporal artery or occipital artery or perform imaging study if large artery involvement suspected
      - GCA suspicion low
    - No further biopsy

Takayasu arteritis

- Also k/a Pulseless Disease / non Specific aortoarteritis /
  Occlusive thromboaortopathy
- mc vessel involved: Subclavian Artery > Common carotid > Aorta > Renal > Superior mesenteric > Pulmonary > coronary
- Pulmonary & Renal are never involved in Temporal arteritis, but they can be involved in takayasu
- Coronary - in 10% of cases
- Seen only in <50 years
- mean age: 24 years
- Young female with upper limb claudication → Check for pulse
  ↓
  Asymmetry in pulse
  ↓
  Check B.P (Asymmetry in B.P > 10 mmHg)

- Carotid / Subclavian / Aortic bruit
- IOC: CT Angiogram - shows occlusion / Stenosis / Aneurysm (rare)
- Associated aortic root dilation & aortic regurgitation may be seen
- As Renal artery is involved - Renovascular HTN is seen
- As Pulmonary artery is involved - Pulmonary artery HTN can be seen

Treatment:
- Steroids, Tocilizumab, Aspirin
- Poor prognosis as it is a progressive disease
- Renal involved - PTRA must be done (Percutaneous Transluminal Renal Angioplasty)

<table>
<thead>
<tr>
<th>Comparison of Giant Cell Arteritis and Takayasu's Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>Female-male ratio</td>
</tr>
<tr>
<td>Age range (yr)</td>
</tr>
<tr>
<td>Average age of onset (yr)</td>
</tr>
<tr>
<td>Visual loss</td>
</tr>
<tr>
<td>Involvement of aorta or its major branches</td>
</tr>
<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Pulmonary artery involvement</td>
</tr>
<tr>
<td>Renal hypertension</td>
</tr>
<tr>
<td>Claudication</td>
</tr>
<tr>
<td>Ethnic groups with highest incidence</td>
</tr>
<tr>
<td>Corticosteroid responsive</td>
</tr>
<tr>
<td>Bruits present</td>
</tr>
<tr>
<td>Surgical intervention needed</td>
</tr>
</tbody>
</table>
Behcet’s disease

- It is called as occult oro genital Syndrome
- Most important manifestations: Oral cavity manifestations
  +
  2 out of 4
- 2 out of 4 - Genital
  - Skin
  - Occular
  - Pathergy test
- Most often diagnosed by dermatologists as 80% cases have skin manifestations
- Biopsy shows: Systemic perivasculitis with neutrophilic infiltration
- M:F - 1:1 - but males have severe disease
- HLA B5, B51
- Anti-saccharomyces cerevisiae antibodies (ASCA) - because of which bechets shows a lot of features similar to crohns with respect to bowel involvement
- Anti selenium binding protein & Anti endothelium Ab (also seen in Kawasaki)

Oral cavity lesions:
- Characterised by recurrent painful aphthous ulcers with shallow necrotic base & can be seen anywhere in the oral cavity & heals without scarring
- Also known as canker sores

Genital ulcers:
- Not so recurrent
- More painful & heals with scarring
- Can be seen anywhere except glans penis & urethra

Eye:
- Acute anterior / posterior uveitis
- Retinitis
Pethergy test:
- Hypersensitivity to scratch / intra dermal saline

Systemic features:
- The most striking feature seen in Bechets Diseases is thrombosis of venous > arterial
  ↓
  (Both superficial & deep)
- It can involve CNS - k/a CNS bechets - characterized by venous strokes, brainstem arterial strokes
- Iliocolitis similar to crohns
- Small joint non erosive arthritis

Treatment:
- Muco cutaneous Disease - Topical steroids
- Arthritis - Hydroxychloroquine
- Severe mucocutaneous disease - Thalidomide / methotrexate
- Systemic Disease: Oral steroids + Azathioprine
- Bilateral panuveitis is very dangerous complication leading to blindness
**VASCULITIS - MEDIUM & SMALL VESSEL**

**Small vessel vasculitis**

- **ANCA associated vasculitis:**
  - Wegener's: Granulomatosis with polyangitis (EPA)
  - Necrotising vasculitis with Fibrinoid Necrosis (NVFN) +
    - Granuloma + C-ANCA (70%) + P-ANCA (25%)
  - Churg - Strauss: Allergic/
    - Eosinophilic GPA (AGPA/EGPA)
      - NVFN + Eosinophilis
      - Tissue eosinophilic infiltrate
      - Extra vascular granuloma
      - C - ANCA (5%) + P - ANCA (40%)

- m - PAN (microscopic PAN): NVFN without Granuloma.
  - P - ANCA (50%) + C - ANCA (40%)

- Renal Limited Vasculitis
  - Masson's trichrome stain is used in the image above to stain NVFN
  - Red colour - Fibrinoid necrosis

**Differentiating small vessel vasculitis based on anca studies 00:03:40**

- ANCA - Anti Neutropil Cytoplasmic Ab
- Screening ANCA is by Immunofluorescence
  - i. Cytoplasmic pattern (C - ANCA)
  - ii. Nuclear pattern or perinuclear pattern (P - ANCA)
- Confirmation is by ELISA
  - For cytoplasmic pattern - Proteinase 3 Ag is checked. It is seen in granules of neutrophils
  - For perinuclear pattern - MPO is checked. It is seen in the lysosomes of monocytes

**Conditions with predominant C-ANCA positive**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Proteinase 3 (PR3, usually c-ANCA)</th>
<th>Frequency (%) myeloperoxidase (MPO, usually p-ANCA)</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with polyangitis (wegener)</td>
<td>70</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td>40</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangitis (Churg-Strauss)</td>
<td>5</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>Renal - limited Pauci-immune Crescentic GN</td>
<td>80</td>
<td>70</td>
<td>10</td>
</tr>
</tbody>
</table>

1. Wegener’s - 70% +ve
2. m-PAN - 40% +ve
3. Renal limited vasculitis - 20% +ve
4. Churg - Strauss - 5% cases +ve
- ANCA titers do not correlate with relapse

**Conditions with predominant P-ANCA positive**

1. m-PAN - 50%
2. Renal limited vasculitis - 70% P-ANCA +ve
3. Churg Strauss - 40%
4. Wegener's - 25%
- Drugs induced P-ANCA +ve - Hydralazine, Propylthiouracil

**False +ve P-ANCA:**
- Target antigen is not MPO
- Seen in
  a. Rheumatoid Arthritis
  b. IBD
  c. Infective Endocarditis
d. Autoimmune Hepatitis

e. Goodpasture Syndrome

f. Primary Sclerosing cholangitis

- Goodpasture may produce ANCA even due to P-ANCA

Wegener’s GPA

- NVFN + Granuloma + C > P-ANCA
- HLA DP B 104
- > 40 years, m : F = 1 : 1

manifestations

↓ major
95% Upper Respiratory tract involvement
90% Lung involvement
60% Renal

↓ minor
Skin
Neuropathy
Acute anterior uveitis

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow edition 4 videos.

i. 95% Upper respiratory tract involvement:
- Can be seen in 4 forms
  a. B/L serous otitis media with deafness
  b. Midline nasal deformity
  c. Recurrent sinusitis due to staph aureus
  d. Subglottic stenosis

ii. 90% Lung involvement
- Can be seen in 2 forms
  - Diffuse Alveolar Hemorrhage (DAH)
  - Cavitating Nodules with Thick walls

![X-ray images of lung involvement](image_url)
iii. Renal Involvement

\[ \text{DPN} + \text{crescents} \rightarrow \text{RPGN} \]

Minor manifestations:
1. Small Fiber Neuropathy - Similar to D.M
2. Acute anterior uveitis
3. Skin lesions - Petechiae or purpura/vesicae or bullae

Pathological features of Wegener's:
- Geographical necrosis
- Palisading histiocytes

\[ \text{M-PAN} \]

- > 40 years
- M > F
- No granuloma is seen
- \( \text{P-ANCA} = 50\% \), \( \text{C-ANCA} = 40\% \)

Major manifestations:
1. Kidney: Gets involved in 100% of patients - Type III RPGN
   \[ \downarrow \]
   On biopsy: DPN + crescents

2. Lung: 50% of patients - Only DAH, no nodules
3. URT: 30% - Sinusitis due to Staph aureus
4. Fever & Constitutional symptoms are more common

Minor manifestations:
1. Cutaneous manifestations are more common when compared with Wegener's
2. Neuropathy is less severe
3. Uveitis - not seen
4. Mesenteric artery involvement - may be seen leading to bowel ischemia.
Churg–Strauss syndrome

- EGPA or A/GPA
- NVFN with Extravascular Granuloma
- It has 3 phases

i. Allergic/Asthmatic phase/Prodromic phase:
   - Behaves just like Bronchial asthma with allergic rhinitis.

ii. Eosinophilic Phase:
   - Repeated episodes of bronchial asthma
   - B/L Fleeting lung infiltrates
   - Disproportionate Eosinophilia

iii. Vasculitis phase:
   - Skin lesions suggestive of vasculitis
   - Cardiac involvement – MCC of death
   - Severe neuropathy
   - Renal: RPGN type III but very mild

Differential diagnostic features of the antineutrophil cytoplasmic antibody – associated vasculitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Wegener's Granulomatosis</th>
<th>Microscopic Polyangitis</th>
<th>Polyarteritis Nodosa</th>
<th>Churg–Strauss Syndrome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary infiltrates or nODULES</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>Asthma and eosinophilia in CSS</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>++</td>
<td>Progressive renal failure uncommon in CSS</td>
</tr>
<tr>
<td>Upper airway disease</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>E/M disease usually favours</td>
</tr>
<tr>
<td>Skin, Purpura</td>
<td>+</td>
<td>+++</td>
<td>–</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Peripheral nervous system involvement</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>Often a prominent feature of CSS</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of anca associated vasculitis:

i. High dose IV steroids for 3days + Oral steroids tapered over 4-6 wks
   Oral cyclophosphamide - 6 months

Relapse: rituximab

maintenance: Low dose steroids + Azathioprine or MMF

ii. For mild disease: methotrexate may be used

iii. For severe lung hemorrhage or CNS vasculitis - plasma exchange

**Poly Arteritis Nodosa (PAN)**

- Involves only medium sized vessels
- Seen in 5th - 6th Decade
- M > F
- BAD prognosis

- Commonly associated with Hep B & Hairy cell leukemia
  30/1 rule: 30% of patients with PAN are HBsAg positive but 1% of patients with HBsAg are having PAN

- It produces micro aneurysms than occlusion of medium sized vessels

- Glomerular/pulmonary capillaries are not involved - So, DAH / Glomerular nephritis not seen in PAN

- Classically it causes Renal Artery microaneurysms So, it produces typical features of Renovascular HTN

- It can produce mesenteric & testicular artery occlusion - Testicular Pain

- Patients presents with HTN with disproportionate target organ damage because of renovascular HTN

- Skin lesions: Nodules, Ulcers, Gangrenous, Mononeuritis multiplex

- MR/CT Angiogram: microaneurysms are seen

- Constitutional symptoms: +++ with fever & weight loss

**ACR criteria for PAN**: (ACR)

1. Weight loss > 4Kg
2. Livido reticularis
3. Testicular pain
4. Mononeuropathy
5. Systemic HTN
6. HBsAg
7. Aneurysm on arteriogram
8. Biopsy: necrotising vasculitis with granulocyte & monocytes in arterial wall
   - It is steroid refractory

Other medium vessel vasculitis:
- Kawasaki
- Thromboangitis obliterans/Euerger’s disease.

**Immune complex mediated small vessel vasculitis** 00:32:17

1. Goodpasture syndrome
2. HSP
3. Cryoglobulinemia
4. Hypersensitivity vasculitis / Cutaneous leukocytoclastic angiitis

**Henoch Schönlein Purpura (HSP)** 00:33:14

- It is now called as Henoch – Schönlein Vasculitis / IgA vasculitis
- MC vasculitis in children
- Seen in < 20yrs, M > F
- Peak age: 4 - 7 years

4 Systems involved:
1. Skin — 100% involved
2. Joints — 50%
3. G.I.T — 70%
4. Kidney — < 10% of patients

i. Skin: Non - thrombocytopenic palpable purpura,
   predominantly in lower limb extensor aspect

ii. Joint: LMN Arthritis (large joint migratory Non deforming)

iii. G.I.T: Acute Abdominal pain (Abd. angina) - Blood in stool, vomiting,
   Intussusception (rare), Erosive Hemorrhagic Duodenitis

iv. Kidney: IgA nephropathy, Seen in adult HSP Glomerulonephritis
Biopsy from skin lesions: Only for Arthralgia & Abdominal Pain - Steroids are used

vessel wall granulocytes & IGA predominant on IF

**Essential mixed cryoglobulinemia**

- Cryoglobulins are cold precipitated immunoglobulin. It is classified as Type 1, 2, & 3.
- 70% of patients are having Hepatitis C. It is closely associated with Hep C.
- It is immune complex mediated small vessel vasculitis.
- 40 - 60y, M > F

**Type 1:** Purely monoclonal, it is plasma cell disorder; - monoclonal IgM/IgG

**Type 2:** Combined polyclonal IgG, Ig monoclonal IgM

**Type 3:** Purely Polyclonal

- Hep C
- Sjogren
- SLE

### Types of Cryoglobulins

<table>
<thead>
<tr>
<th>Cryoglobulin</th>
<th>RF Positivity</th>
<th>Monoclonality</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>No</td>
<td>Yes (IgG or IgM)</td>
<td>Hematopoietic malignancy (multiple myeloma, waldenstrom’s)</td>
</tr>
<tr>
<td>Type II</td>
<td>Yes</td>
<td>Yes (polyclonal IgG, monoclonal IgM)</td>
<td>Hepatitis C, Other infection</td>
</tr>
<tr>
<td>Type III</td>
<td>Yes</td>
<td>No (polyclonal IgG and IgM)</td>
<td>SLE, Sjogren’s syndrome, Other infection</td>
</tr>
</tbody>
</table>

**Clinical Manifestations:**

**Skin:** Non - Thrombocytopenic
- Palpable Purpura
- Confluent purpura
- Extremity ulcers
Joint: small joint, upper limb - non erosive arthritis
Kidney: MPGN
GIT: Hep-C & peripheral neuropathy
Treatment: treat hepatitis -C

Secondary vasculitis

1. Drugs: ANCA +ve: Hydralazine, PTU
2. Rheumatological: SLE, RA, Sarcoid
3. Infectious: Histoplasmosis, Rickettsiae,
   HepB - PAN
   HepC - Cryoglobulinemia
MINERAL DEFICIENCIES

Copper deficiency:
- Microcytic hypochromic anemia
- Hair defects - Defective keratinisation and pigmentation
- Growth retardation
- Defective elastin
- Mental retardation
- Osteoporosis

Copper toxicity: Hepatotoxicity
    - Hemolytic anemia

Chromium deficiency: Impaired glucose tolerance.

Phosphorus deficiency:
- Rhabdomyolysis
- Hemolysis
- Ataxia
- Seizure

Zinc deficiency:
- Growth retardation
- Alopecia
- Ageusia
- Anosmia
- Gonadal dysfunction
- Dermatitis
- Immune dysfunction
Zinc toxicity: Pulmonary fibrosis

Manganese deficiency:
- Lipid + Carbohydrate metabolism - altered
- Growth and skeletal developmental retardation
- Upper body rash

Iron deficiency:
- Impaired cognition
- Poor work performance
- Premature labor
- Increased perinatal deaths
Deficiency

Selenium deficiency:

Seen in Keshan disease
Causes Hypothyroidism in Sub himalayan zone

Molybdenum deficiency:

- Neurological Symptoms + oesophageal cancer

Toxicity / overdose

- Manganese overdose: Parkinsonism like features.
- Boron overdose: Developmental defects
  - male sterility
  - Testicular atrophy
- Iron toxicity: Increased susceptibility to malaria
- Lead toxicity: Gout, tubulointerstitial disease
  - Saturnine gout / Lead nephropat - hyperuricemia
- Cadmium toxicity: Nephrotoxicity with severe bone pain
  - (Ouch Ouch nephropathy)
- Chromium toxicity: Renal failure + lung cancer
- Arsenic toxicity: Peripheral neuropathy
  - Garlic like odour
  - Lung and nasal cancers
- Fluorine toxicity: Calcification of tendon / ligament
  - Exostoses
ACID BASE REGULATION - 1

Chemical buffer system

- Bicarbonate buffer system ← most efficient
- Phosphate buffer system

  $\text{pK}_a$ of $\text{HCO}_3^- = 6.1$ (weak acid)
  
  $\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3$
  
  $\text{H}_2\text{O} \quad \text{CO}_2$

  $\text{pK}_a$ of $\text{HPO}_4^{2-} = 6.8$ (weak acid)
  
  $\text{HPO}_4^{2-} + \text{H}^+ \rightarrow \text{H}_2\text{PO}_4^-$

- When a molecule has got a $\text{pK}_a$ which is close to the physiological pH it will be an effective buffer

- Intracellular buffer
  - Proteins $\rightarrow$ Hb
  - Phosphate

Respiratory buffer system

- Exhaling or retaining of $\text{CO}_2$ in response to extracellular pH
  
  $\text{HCO}_3^- + \text{H}^+ \rightarrow \text{H}_2\text{CO}_3$
  
  $\text{H}_2\text{O} \quad \text{CO}_2$
  
  Exhaled out of lungs

Renal buffer system

- 80 meq of non volatile acids are produced per day, excreted by kidney

- 4320 meq of $\text{HCO}_3^-$ filtered / day at glomerulus

- For every molecule of $\text{HCO}_3^-$ reabsorbed, one $\text{H}^+$ is excreted

- Total $\text{H}^+$ excreted / day $\rightarrow 4320 + 80 = 4400$ meq
- For excretion of 4400 meq $H^+$ → >2500 lts of urine /day
- .:: The management of $H^+$ excretion done by urinary buffers

- Ammonia buffer ($NH_4^+$)
- Phosphate buffer

- $pK_a = \text{pH at which associated form } = \text{dissociated form}$
  \[ HA = A \]

- Henderson equation:
  \[ pH = pK_a + \log \frac{A}{HA} \]

- Bicarbonate generation = net acid excretion in urine = 70-80 meq /day

- Acid is getting excreted in the form of:
  - Ammonium ($NH_4^+$)
  - Titratable acid (phosphate / creatinine / butyrate)

- .::. $\text{NRE} = NH_4^+ + \text{Titratable acid} = 70-80$ meq / day

**Bicarbonate at the proximal tubule**

![Diagram of bicarbonate at the proximal tubule](image)
Acidification of urine

- Acidifying machinery → Cortical collecting tubule
  → α intercalated cells

Ammonia recycling

- Ammonium synthesis & excretion is the most important way kidneys eliminate non volatile acid

- Formation of ammonia:
  - Glutamine → Glutamate → α Kg

    \[
    \begin{align*}
    \text{NH}_3^+ & \quad \text{NH}_3^+ \\
    \text{Na}^+ - \text{H}^+ \text{ exchanger in PCT} \\
    \text{NH}_4^+ & \text{secreted into lumen of PCT} \\
    \text{NH}_3 & \quad \text{H}^+
    \end{align*}
    \]

- In response to ↑ acid load kidney compensates by
  → ↑ Ammonia excretion

- Stimuli of ammonia production → * metabolic acidosis
  * Hypokalemia
• $NH_4^+$ at thick ascending limb $\rightarrow$ Na$^+$K$^+$2Cl$^-$ $\rightarrow$ reach the interstitium $\downarrow$
  $NH_4^+$ $\leftarrow$ Urine $\leftarrow$ Collecting duct

• pKa of ammonia $\rightarrow$ 9.2 $\therefore$ at physiological pH 98% is $NH_4^+$
• Ammonia generated in the kidney $\rightarrow$ $NH_4^+$

**Acids in the body**

• $\alpha$ types
  • Volatile acids
    • Formed by metabolism of $\bullet$ carbohydrates
      • Fat
      • Proteins
    • Excreted as $CO_2$ from lungs

• Non volatile acids (fixed acids)
  • Formed by metabolism of $\bullet$ phospholipid
    • Nucleic acids
  • Ex: Sulphuric acid, phosphoric acid, organic acids
  • Excreted by kidneys

• According to Henderson Hasselbach's equation, important
determinants of $H^+$ $\rightarrow$ Bicarbonate (22.26 meq/L)
  - $PCO_2$ (40 mmHg)

• $1^{st}$ defence $\rightarrow$ Chemical buffer
• $2^{nd}$ defence $\rightarrow$ Respiratory buffer
• $3^{rd}$ defence $\rightarrow$ Renal buffer

**Metabolic acidosis**

• Heart:
  • ↓ myocardial contractility
  • Sympathetic overactivity

• CNS
  • Lethargy, disorientation, stupor, coma.
- Hyperventilation
- Hyperkalemia

- measured cations + unmeasured = measured + unmeasured
  cations  anions  anions
  \[ MC + UC = MA + UA \]
  \[ MC - MA = UA - UC \]
  \[ Na^+ - (Cl^- + HCO_3^-) = UA - UC \]
  \[ \text{Anion gap} = UA - UC \]
  \[ = 8-12 \text{ meq/L} \]

- Corrected anion gap = Anion gap + 2.5 (4.5 - S. Albumin)

- Classification of metabolic acidosis:
  - High anion gap MA:
    - Ketoacidosis → DM
    - Alcohol
    - Starvation
  - Lactic acidosis
  - Uremic acidosis
  - Methanol / ethylene glycol
  - Salicylate / paraldehyde

- Normal anion gap MA:
  - Renal acidification defect → RTA
  - GI loss of HCO_3^- → Diarrhoea
    - Small bowel tumor
    - Ureterosigmoidostomy
    - Anion exchange resins

- Hyperchloremic metabolic acidosis

**Metabolic alkalosis**

- Heart:
  - Cardiac arrhythmias

- Brain
  - Cerebral insufficiency
- Hypocalcemia.
- Hypokalemia.
- Hypomagnesemia.

- Classification of m. alkalosis:
  - Chloride or Saline sensitive/ responsive:
    - Urinary Cl^- < 15 meq/L
    - Vomiting
    - Nasogastric succioning
    - Long term diuretic use
    - Cystic fibrosis
    - Post hypercapnia
    - Pyloric stenosis

- Chloride unresponsive: saline resistant
  - Urinary Cl^- > 15 meq/L
  - With HTN → RAS activation
    - Aldosterone tumors
      - Liddle syndrome

- Without HTN → * Recent diuretic use
  - Bartter syndrome
  - Gitelman syndrome
ACID BASE REGULATION - 2

ABG - Arterial blood gas precautions

- Abnormal modified Allen test
- Local infection / distorted anatomy at the puncture site
- Severe peripheral vascular disease of the artery
- Active Raynaud’s syndrome

ABG - Procedure and precautions

- Preferred artery → Radial A
  - Femoral A
- 21 gauge needle
- Flush the syringe with 0.5 ml of 1:1000 heparin
- Don’t leave excess heparin in the syringe → ↓ HCO₃⁻, ↓ PCO₂
- Ensure no air bubbles
- Early analysis & transported via cold chain

Estimation of H⁺ from pH

- As the pH ↑ → H⁺ ↓
- pH 7.4 → H⁺ → 40
  - 7.3 → 50
  - 7.5 → 32

Normal values of ABG

- pH → 7.36 - 7.44 (7.40)
- HCO₃⁻ → 24-36 meq/L (24)
- PCO₂ → 35-45 (40)
- H⁺ → 24-44 meq/L (40 meq/L)
- pH < 7.2 → Severe acidosis
- pH > 7.6 → Severe alkalosis
Calculation of bicarbonate

- Obtain ABG & serum electrolytes simultaneously
- \( \text{HCO}_3^- = 24 \times \frac{\text{PCO}_2}{\text{H}^+} \)
- Measured \( \text{HCO}_3^- \) is compared with \( \text{HCO}_3^- \) of venous blood
- For ABG to be compatible
  The measured \( \text{HCO}_3^- \) should be within \( \pm 2 \) values compared to \( \text{HCO}_3^- \) of venous blood

Interpretation of ABG

- \( \text{pH} \rightarrow > 7.40 \rightarrow \text{Alkalosis} \)
  \(< 7.40 \rightarrow \text{Acidosis} \)
  \( 7.40 \rightarrow \text{Normal / mixed ABG} \)

- Respiratory or metabolic component has changed in the direction of pH
  - Ex: \( \text{pH} = 7.32 \downarrow (7.40) \text{ Acidosis} \)
    \( \text{HCO}_3^- = 16 \downarrow (24) \text{ Acidosis} \)
    \( \text{PCO}_2 = 35 \downarrow (40) \text{ Alkalosis} \)
  - Metabolic acidosis
    \( \text{pH} = 7.46 \uparrow (7.40) \text{ Alkalosis} \)
    \( \text{PCO}_2 = 25 \downarrow (40) \text{ Alkalosis} \)
    \( \text{HCO}_3^- = 20 \downarrow (24) \text{ Acidosis} \)
  - Respiratory alkalosis

- Compensation for metabolic acidosis
  - By respiratory alkalosis
    \( \text{HCO}_3^- \downarrow \text{ by } 1 \text{ meq/L } = \text{PCO}_2 \downarrow \text{ by } 1 \text{ A mmHg} \)
  - Ex: \( \text{pH} = 7.10 \)
    \( \text{PCO}_2 = 32 \)
    \( \text{HCO}_3^- = 10 \)
  - Metabolic acidosis

\( \text{HCO}_3^- \) fall from 24 \( \rightarrow 10 = 14 \) meq/L fall
\( \therefore \) compensation \( = 14 \times 1 \text{A} \)
\( = 17 \)
\[ \therefore \text{The expected PCO}_2 = 40 - 17 \]
\[ = 23 \]

\[ \therefore \text{It is uncompensated or partially compensated metabolic acidosis} \]
\[ \because \text{In the given problem PCO}_2 \text{ is 32} \quad \text{and the expected PCO}_2 \text{ is 23} \]
\[ \text{hence there is uncompensation} \]

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.
ACID BASE REGULATION - 3

Compensation

- metabolic acidosis:
  - $\text{HCO}_3^- \downarrow$ by 1 meq /L = $\text{PCO}_2 \downarrow$ by 1.2 mmHg

- metabolic alkalosis:
  - $\text{HCO}_3^- \uparrow$ by 1 meq /L = $\text{PCO}_2 \uparrow$ by 0.7 mmHg
  - Ex:
    - $\text{pH} = 7.43$ - Alkalosis
    - $\text{HCO}_3^- = 33$ - Alkalosis
    - $\text{PCO}_2 = 40$ - \( \nabla \)
      = metabolic alkalosis
    - Increase in $\text{HCO}_3^- = 33 - 24 = 8$
    - Expected $\uparrow$ in $\text{PCO}_2 = 8 \times 0.7$
      = 5.6
    - Expected $\text{PCO}_2 = 40 + 5.6 = 45.6$ mmHg
  - \( \therefore \) it is uncompensated metabolic alkalosis

- $\text{pH} = 7.30$
  - $\text{HCO}_3^- = 14$

  $\text{PCO}_2 = 20 \downarrow$ $\text{PCO}_2 = 28 \downarrow$ $\text{PCO}_2 = 35 \downarrow$ $\text{PCO}_2 = 42 \downarrow$
  - met. Acidosis
  - met. Acidosis
  - met. Acidosis
  - met + Resp
  - fully compensated
  - partially compensated
  - or
  - Simple metabolic acidosis

- Winters Formula for metabolic acidosis:
  - $\text{PCO}_2 = 1.5 \times \text{HCO}_3^- + 8 \pm 2$

- Active space
Compensation for respiratory acidosis & alkalosis

- **Respiratory**
  - 1 4 → Resp. Acidosis
  - 2 4 → Resp. Alkalosis

- **Respiratory acidosis:**
  - Acute resp. Acidosis → \( PCO_2 \uparrow \) = \( HCO_3 \uparrow \)
    - 10 mmHg 1 meq/L
  - Chronic resp. Acidosis → \( PCO_2 \uparrow \) = \( HCO_3 \uparrow \)
    - 10 mmHg 4 meq/L

- **Respiratory alkalosis:**
  - Acute resp. Alkalosis → \( PCO_2 \downarrow \) = \( HCO_3 \downarrow \)
    - 10 mmHg 2 meq/L
  - Chronic resp. Alkalosis → \( PCO_2 \downarrow \) = \( HCO_3 \downarrow \)
    - 10 mmHg 4 meq/L

- **Ex:** pH = 7.25
  - Acidity
  - \( PCO_2 = 55 \)
  - Res. Acidosis
  - \( HCO_3^- = 30 \)
  - met. Alkalosis
  - = Respiratory acidosis
  - \( PCO_2 \uparrow = 55-40 = 15 \)
  - ∴ For \( 10 \uparrow \rightarrow HCO_3 \uparrow \) by 1
  - \( 15 \uparrow \rightarrow = 1.5 \)
  - ∴ \( HCO_3^- = 24 + 1.5 = 25.5 \)
  - ∴ It is respiratory acidosis + metabolic alkalosis

**Calculation of anion gap**

- Serum anion gap = Na\(^+\) - (Cl\(^-\) + HCO\(_3^-\) )
- Normal SAG = 8-12 meq/L
- Metabolic acidosis → *Loss of HCO\(_3^-\)*
  - If loss of HCO\(_3^-\) compensated by Cl\(^-\)
  - Na\(^+\) = (Cl\(^-\) \uparrow + HCO\(_3^-\) \downarrow)
- Normal anion gap metabolic acidosis
• When loss of $\text{HCO}_3^-$ is compensated by an ion other than $\text{Cl}^-$ (unmeasured anion) $\rightarrow$ High anion gap metabolic acidosis

• In high anion gap metabolic acidosis calculate delta ratio

$$\text{Delta ratio} = \frac{\Delta \text{AE}_{\text{aq}}}{\Delta \text{HCO}_3^-} = \frac{\Delta \text{AE}_{\text{aq}}}{\Delta \text{HCO}_3^-} = \frac{\text{AE}_{\text{aq}} - \text{Ia}}{\text{Aa} - \text{HCO}_3^-}$$

• Normal = 1-2 $\rightarrow$ High anion gap metacidosis

• Delta ratio <1 $\rightarrow$ High anion gap + Normal anion gap
  Met. Acidosis         Met. Acidosis

• Delta ratio >2 $\rightarrow$ High anion gap + met. Alkalosis
  Met. Acidosis         Met. Acidosis
Urine anion gap

- To differentiate normal AG, met. Acidosis due to RTA or GI loss, urine AG is done
  \[\text{urine AG} = \text{urine Na}^+ + \text{urine K}^+ - \text{urine Cl}^-\]
- Positive urine AG → RTA
- Negative urine AG → GI loss of HCO$_3^-$

Example 7
- pH = 7.24
- pCO$_2$ = 42
- pO$_2$ = 99
- Na = 143
  \[\begin{array}{|c|c|c|c|c|c|c|}
  \hline
  & \text{pH} & \text{pCO$_2$} & \text{pO$_2$} & \text{HCO$_3^-$} & \text{AG} & \text{Delta ratio} \\
  \hline
  \text{Normal range} & 7.4 & 35 - 45 & 80 - 100 & 22 - 26 & 8 - 16 & 4 - \text{NAGMA} + \text{HAGMA} \\
  \hline
  \end{array}\]

NAGMA - Normal Anion Gap Metabolic Acidosis
HAGMA - High Anion Gap Metabolic Acidosis

Answer
- 1. pH = 7.24 → pH < 7.4 - Acidosis
- 2. pCO$_2$ = 42 → > 40 - respiratory acidosis
- 3. HCO$_3^-$ = 21 → < 24 - metabolic acidosis

metabolic acidosis with respiratory acidosis
- For metabolic acidosis, always calculate AG
  - Anion Gap = 143 - (100 + 21)
  - = 22
  - High anion gap metabolic acidosis
- Calculating delta ratio
  - Delta ratio = \[\frac{\text{AG} - 1a}{24 - \text{HCO}_3^-}\]
  - = 10/3
  - = >2
* Diagnosis = High anion gap metabolic acidosis + metabolic alkalosis + Respiratory acidosis

### Strong ion difference

Strong ion difference = \((Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + Lactate^-)\)

* Difference between measured strong cations & anions
* Normal SID → 40 meq/L

![Strong ion difference diagram]

* SID = \(HCO_3^- +\) albumin + phosphate
* met. Alkalosis → SID ↑
* met. Acidosis → SID ↓
* Dehydration → SID ↑
* Lactic acidosis → SID ↓
* Hypoalbuminemia → SID ↓

Saline cause acidosis by decreasing [SID] due to the hyperchloremic

![Saline solution diagram]

\([SID] = 19\)  → pH↓  → more acidosis
Osmolarity

- Calculated osmolarity = 2Na⁺ + \frac{8 \text{ Glucose}}{18} + \frac{8 \text{ UN}}{a.8} = 285-290

- Measured osmolarity → Osmometer

- Osmolal gap → * measured − calculated > 10
  
  Osmolarity  osmolarity

  * methanol poisoning

  * Ethylene glycol poisoning

- Diagnosis = High anion gap metabolic acidosis + metabolic alka-
  losis + Respiratory acidosis