



# **MEDICINE**

Susmit Islam

# Medicine

Susmit

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# Preface

What follows are my own notes on various topics in medicine, mostly based off of the following sources:

- ▶ *Davidson's Principles and Practice of Medicine* 23rd ed.,
- ▶ *Oxford Handbook of Clinical Medicine* 10th ed.,
- ▶ *Long Cases in Clinical Medicine* 2nd ed.,
- ▶ *Short Cases in Clinical Medicine* 6th ed.

The date below tells you the last time when I edited this document, so refer to that if you're worried about the temporal validity of the contents. The chapters are arranged somewhat at random, partly reflecting the order in which I studied them. These notes are, first and foremost, for my personal use, so pardon the inconvenience. Over time I will try tidying things up more. There's probably plenty of mistakes, all my own. **Use at your own peril.**

Susmit Islam

2022-07-28

# Chapter 1

## Respiratory medicine

### 1.1 Tuberculosis

#### Side effects of anti-TB drugs

► **Isoniazid:**

- Hepatitis
- Rash
- B<sub>6</sub> deficiency → peripheral neuropathy (so pyridoxine supplement required during therapy)

► **Rifampicin:**

- Hepatitis
- Rash

► **Pyrazinamide:**

- Hepatitis
- Hyperuricaemia (rarely turns into gout)

► **Ethambutol:**

- Retrobulbar neuritis (reversible)
- Arthralgia

► **Streptomycin:**

- Ototoxicity (8th nerve palsy)
- Rash

# Chapter 2

## Cardiology

### 2.1 Anatomy and physiology

#### Coronary circulation

- ▶ **RCA** → RA, RV, SA node (in 60% individuals), AV node (90%)
  - **Posterior descending artery** → posteroinferior part of interventricular septum and posterior LV
    - Branch of RCA (in 90%) or LCX (in 10%)
- ▶ **LAD** → anterosuperior part of interventricular septum, anterior wall of LV
  - LAD is called the *widowmaker* artery, for almost the entirety of LV is supplied by it, and so infarctions involving this have high fatality.
- ▶ **LCX** → lateral, posterior and inferior LV
- ▶ See also: [table 2.2](#)

#### Electrophysiology of the heart

##### Sinoatrial node

- ▶ Spontaneous depolarization = *pacemaker potential* (details: [Fig. 2.1](#))
  - Due to small influx of  $\text{Na}^+$  ions, with 2 components
  - Background inward current  $I_b$
  - “Funny” current  $I_f$ 
    - “Funny” as the channels are activated in hyperpolarized cells, as opposed to most other voltage-gated channels, which activate upon depolarization
- ▶ Atrial tissue is activated like a “forest fire”, but by the time the potential reaches the insulating annulus fibrosus at the AV junction, it peters out (which is why we need the AV node to act as a “repeater”)

## Action potentials in the conductive system and the myocytes

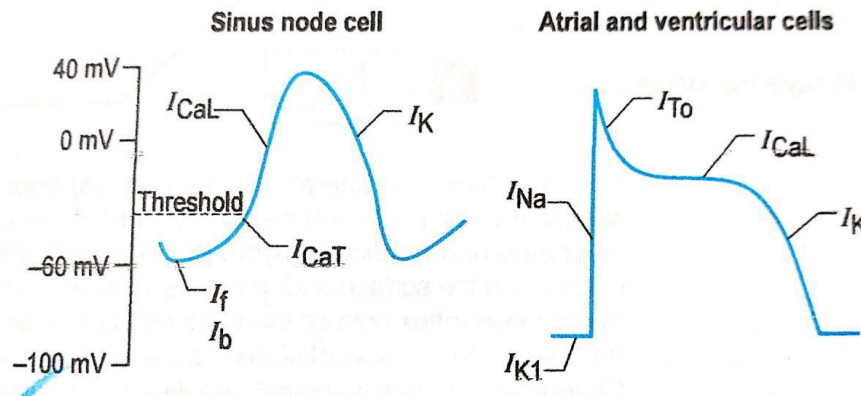


Figure 2.1: Cardiac action potentials. CaL: L-type (long-lasting)  $\text{Ca}^{2+}$  channel, CaT: T-type (transient)  $\text{Ca}^{2+}$  channel.  $\text{I}_{\text{K1}}$ : inward rectifier  $\text{K}^{+}$  current,  $\text{I}_{\text{Na}}$ : inward  $\text{Na}^{+}$  current,  $\text{I}_{\text{To}}$ : transient outward  $\text{K}^{+}$  current,  $\text{I}_{\text{CaL}}$ : inward  $\text{Ca}^{2+}$  current,  $\text{I}_{\text{K}}$ : delayed rectifier (outward)  $\text{K}^{+}$  current.

## Effects of the autonomic nervous system on the heart

- $\beta_1$ -adrenergic stimulation  $\rightarrow$   $\uparrow$ force of contraction, heart rate (+ve inotropic and chronotropic)
  - $\beta_1$  stimulation  $\rightarrow$   $\oplus$  adenylyl cyclase-cAMP system  $\rightarrow$   $\oplus$  intracellular protein kinases  $\rightarrow$   $\uparrow$ phosphorylation of proteins including L-type  $\text{Ca}^{2+}$  channels  $\rightarrow$  **enhanced  $\text{Ca}^{2+}$  influx**  $\rightarrow$   $\uparrow$  FoC
  - Return of  $\text{Ca}^{2+}$  to sarcoplasmic reticulum from the myocyte is mediated by phospholamban, which enhances  $\text{Ca}^{2+}$  reuptake into the SR in its phosphorylated state. So  $\beta_1$  stimulation also promotes  $\text{Ca}^{2+}$  removal from the myocyte, thereby enhancing myocardial relaxation. Enhanced relaxation  $\rightarrow$   $\uparrow\uparrow$ ventricular filling, and the  $\uparrow$ FoC helps the heart to pump that extra blood out properly.

## Cardiac peptides

- ANP (atrial natriuretic peptide)
  - Released by atrial myocytes upon being stretched
  - Vasodilator  $\rightarrow$   $\downarrow$ BP
  - Diuretic ( $\uparrow\text{Na}^{+}$  and  $\text{H}_2\text{O}$  excretion)
- BNP (brain/B-type natriuretic peptide)
  - Called so because first discovered in porcine brain extracts
  - Released by ventricular myocytes upon being stretched
  - Diuretic
- Neprilysin:
  - NOT a cardiac peptide (made by the kidney and other tissues)
  - Breaks down ANP, BNP  $\rightarrow$  vasoconstrictor
  - Therapeutic target in heart failure



## Haemodynamic effects of respiration

### Effects

|   | Inspiration      | Expiration |
|---|------------------|------------|
| JVP   | ↓                | ↑          |
| BP  | ↓ (upto 10 mmHg) | ↑          |
| HR  | ↑                | ↓          |
| 2nd heart sound (S <sub>2</sub> ) splitting | ↑                | ↓          |

Table 2.1: Haemodynamic effects of respiration

### Mechanisms

#### ► BP:

- Inspiration → -ve intrathoracic pressure → ↑ venous return to RA → ↑ RV output
- Inspiration → ↑ pulmonary vascular capacitance → ↓ venous return to LA → ↓ LV output → ↓ BP

#### ► S<sub>2</sub> splitting (i.e. delay between A<sub>2</sub> and P<sub>2</sub>):

- Inspiration → ↑ RV filling → ↑ prolonged ejection from RV → ↑ delayed P<sub>2</sub>
- Inspiration → ↓ LV filling → ↓ faster ejection from LV → ↓ faster A<sub>2</sub>

## 2.2 Presenting problems in CVS disease

### Features of benign murmur

- Soft
- Midsystolic
- Heard at left sternal edge
- No radiation
- No other cardiac abnormalities

## 2.3 ECG

### Anatomy of an ECG

### Abnormalities of components

#### Pathological Q

- Depth > 2mm
- Height > 1mm
- Present in ≥ 2 leads

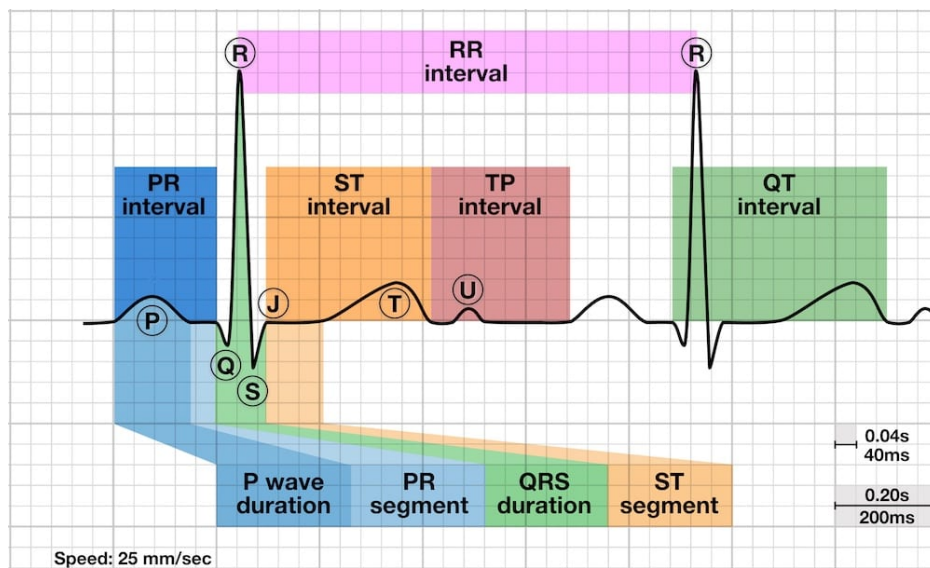


Figure 2.2: Parts of a normal ECG

- ▶ Assocd with loss of R height ( $Q > R/4$ ; normally  $Q \leq R/4$ )
- ▶ Indicates *transmural* myocardial necrosis

### Segments vs intervals

- ▶ e.g. ST segment = end of S → start of T
- ▶ PR interval = start of P → start of R

### ST segment elevation

- ▶ Normal: upto 1mm in limb leads, upto 2mm in chest leads
- ▶ Causes
  - STEMI: convexity upwards
  - Acute periCarditis: conCAvity upwards
- ▶ Indicates ongoing myocardial injury

### Myocardial infarction

A somewhat interesting physiological explanation on how the changes arise

### Sites of infarction based on lead

- ▶ Septal:  $V_1, V_2$
- ▶ Anterior:  $V_3, V_4$
- ▶ Lateral: I, aVL,  $V_5, V_6$
- ▶ Extensive anterior:  $V_1-V_6$
- ▶ Anterolateral: I, aVL,  $V_1-V_6$
- ▶ Further details: table 2.2 and section 2.1

| Location  | Leads  | Coronary artery |
|-----------|--|-----------------|
| Anterior  | V <sub>2</sub> -V <sub>4</sub>               | LAD             |
| Lateral   | V <sub>5</sub> -V <sub>6</sub>               | LCX > LAD       |
| Inferior  | II, III, aVF                                 | RCA ≫ LCX       |
| Posterior | V <sub>1</sub> , V <sub>2</sub> (depression) | RCA ≫ LCX       |

Table 2.2: ECG leads and arteries involved according to anatomical location of infarct

**Reciprocal changes**

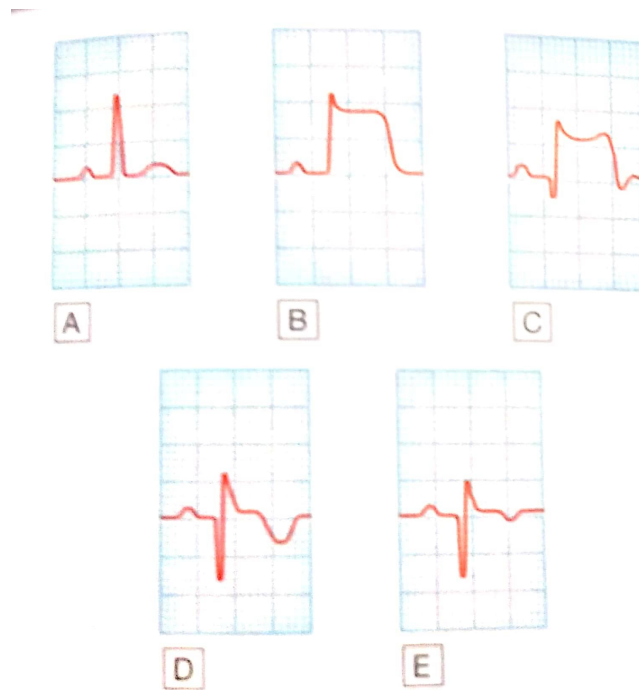
- Acute STEMI in some surface of the heart → ST elevation in corresponding leads, and ST depression in reciprocal leads

| Site      | Facing                                  | Reciprocal                      |
|-----------|---|---------------------------------|
| Septal    | V <sub>1</sub> , V <sub>2</sub>         | V <sub>7</sub> -V <sub>9</sub>  |
| Anterior  | V <sub>3</sub> , V <sub>4</sub>         | None                            |
| Lateral   | I, aVL, V <sub>5</sub> , V <sub>6</sub> | II, III, aVF                    |
| Inferior  | II, III, aVF                            | I, aVF                          |
| Posterior | V <sub>7</sub> -V <sub>9</sub>          | V <sub>1</sub> , V <sub>2</sub> |

Table 2.3: Reciprocal changes according to location of infarct

**Evolution over time of the ECG appearance of STEMI**

- STEMI = complete proximal occlusion of major coronary artery



A. Before the onset of infarction



B. In acute phase, ST elevation



C. Progressive loss of R and deepening Q



D. Resolution of ST elevation; fully developed pathological Q; T inversion



E. In old infarcts, T-wave inversion may or may not persist

- ST elevation resolves after a few days

**NSTEMI**

- ▶ **Partial occlusion of major or complete occlusion of minor** coronary artery
- ▶ *Subendocardial/partial-thickness MI* → **no pathological Q**
- ▶ **ST depression + T inversion** in chest leads

## 2.4 Coronary Artery Disease

- ▶ Diseases arising due to narrowing of the lumen of one or more coronary arteries and the resulting ischaemia/infarction of the myocardium or the conductive system.
- ▶ **Types:**
  - Stable angina: Fixed atheromatous stenosis
  - Unstable angina:
    - dynamic obstruction
    - due to plaque rupture/erosion with thrombosis
  - MI
  - Heart failure
  - Arrhythmia
  - Sudden cardiac death
    - ventricular arrhythmia
    - asystole
    - massive MI

## 2.5 Arrhythmias

### Classification according to ECG morphology

- ▶ **Narrow complex:** QRS < 120ms (3 small sqs)
  - Sinus tachycardia
  - Atrial fibrillation (irregular narrow complex tachycardia)
  - Atrial flutter
  - AV Nodal Re-entry Tachycardia (AVNRT aka SVT)
- ▶ **Broad complex:** QRS > 120ms (3 small sqs)
  - Ventricular tachycardia
  - AV Re-entry Tachycardia (AVRT e.g. Wolff-Parkinson-White syndrome)
    - Abnormal band of conductive tissue connecting atria and ventricles (accessory pathway)

### Management of SVT

- ▶ Carotid sinus massage or
- ▶ Valsalva manoeuvre
- ▶ If the manoeuvre fails,

- Adenosine (3-12mg IV) or
- Rate-limiting CCB (Verapamil 5mg IV) or
- $\beta$ -blocker
- ▶ If haemodynamic state compromised, DC cardioversion
- ▶ Recurrent SVT → catheter ablation

## 2.6 Atrial fibrillation

### Causes

- ▶ **Cardiac**
  - CAD (including acute MI)
  - Mitral stenosis (MS; rheumatic mitral valve disease)
  - Hypertension
  - Cardiomyopathy
- ▶ **Non-cardiac**
  - Thyrotoxicosis
  - Pulmonary embolism
  - Pneumonia
  - Alcoholism

### Investigations

- ▶ ECG
- ▶ Echo: to see valvular condition
- ▶ Thyroid function test: to exclude thyrotoxicosis

### Management of AF

- ▶ **Rhythm control:**
  - Pharmacological cardioversion
    - Pt stable + no history of heart disease → IV flecainide
    - Structural / ischaemic heart disease → IV amiodarone
  - DC cardioversion if drugs fail
- ▶ **Rate control**
  - $\beta$ -blockers
  - Digoxin
  - Rate-limiting CCB: verapamil / diltiazem
- ▶ **Thromboprophylaxis:**
  - Oral Warfarin
  - Target INR: 2.0-3.0

- Reduces risk of stroke by  $\frac{2}{3}$
- Start 4wks before cardioversion, continue till 3mo after successful cardioversion

## 2.7 Myocardial Infarction

### Management

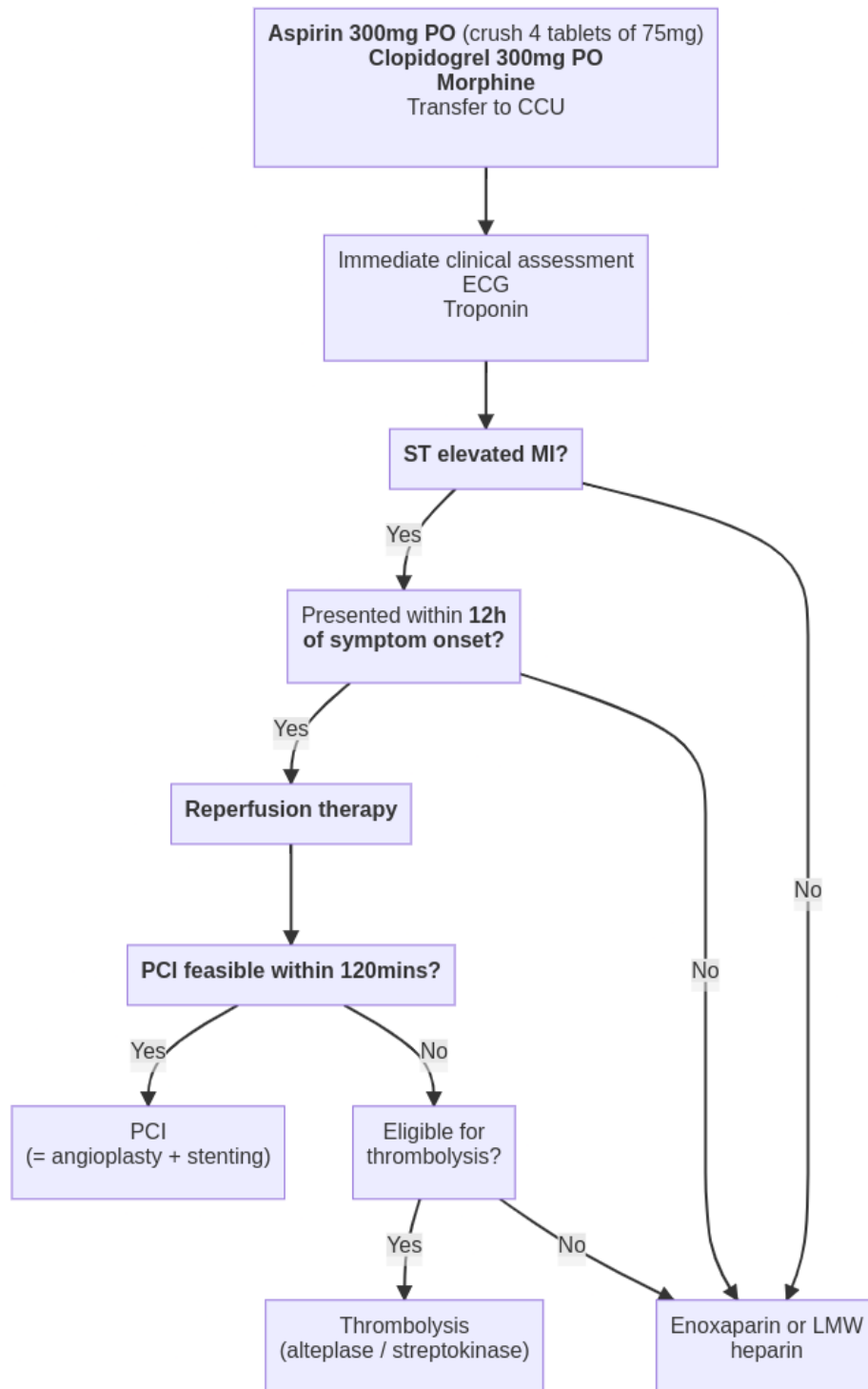


Figure 2.3: Management of acute MI



# Chapter 3

## Dermatology

### 3.1 Anatomy and physiology

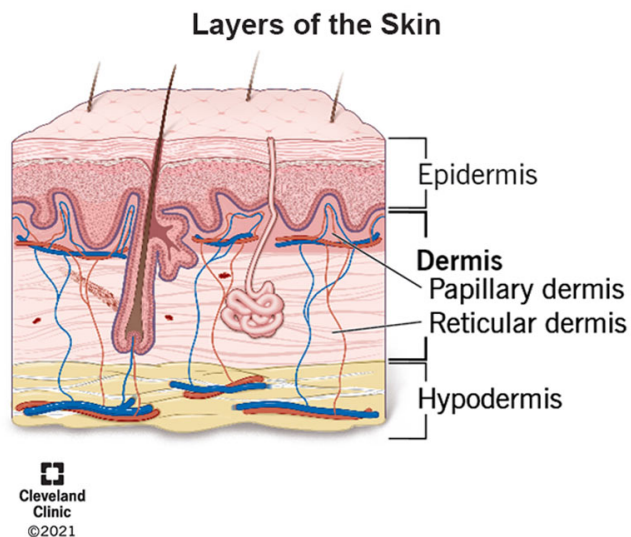


Figure 3.1: Layers of the skin

#### ► Layers of skin:

- **Epidermis:** further layered into (from out→in)
  - corneum
  - lucidum: *only in thick skin* i.e. palm and sole
  - granulosum
  - spinosum
  - basale
- **Dermis:**
  - **Papillary dermis:** more superficial part, containing
    - loose areolar tissue
    - subpapillary vascular plexus

- **Reticular dermis:** deeper part, containing
  - collagen
  - deep vascular plexus
  - nerves
  - pilosebaceous units (hair follicle + sebaceous gland)
  - sweat glands
  - some keratinocytes around the hair follicles and sweat glands (important for wound healing - these are the reasons behind healing without scarring in upto partial-thickness skin wounds)
- Subcutis / subcutaneous tissue: (technically not part of the skin) adipose tissue

## Epidermal appendages

- ▶ Hair follicles:
  - phases of growth
    - anagen:
      - active growth
      - lasts years in scalp hairs
    - catagen:
      - transitional
      - lasts days (in scalp)
    - telogen:
      - resting
      - lasts months (in scalp)
- ▶ Sebaceous glands
  - usually associated with a hair follicle (called a *pilosebaceous unit*)
  - androgens → ↑ sebum
  - oestrogen → ↓ sebum
- ▶ Sweat glands
  - innervated by *sympathetic cholinergic* fibres

## 3.2 Principles of management of skin disease

### Topical treatments

- ▶ Ointments vs Creams
  - Ointments preferred to creams for dry skin (e.g. chronic eczema) as
    - more hydrating
      - 80% oil + 20% water in ointments (vs 50-50 for creams) → prevent water loss from skin by oil layer
    - less preservatives → less risk of allergy

- ▶ Emollients
  - Moisturise, lubricate, protect skin
  - *Vehicles without active drug*
- ▶ Glucocorticoids

## Phototherapy

- ▶ UVB
- ▶ Psoralen UVA
  - Psoralen:
    - natural photosensitiser from plant source
    - cross-link DNA strands on excitation with UVA
  - Cumulative exposure to PUVA → ↑ risk of SCC, so reserved for UVB resistance
- ▶ Uses
  - Psoriasis
  - Atopic eczema
  - Vitiligo
  - Chronic urticaria

## Systemics

- ▶ Antihistamines
- ▶ Retinoids
  - *Anti-inflammatory*
  - Promote *differentiation of skin cells*
  - **Teratogenic**
    - must be prescribed with robust contraception
    - females must have negative pregnancy test before, during, and after therapy
- ▶ Immunosuppressants
  - Glucocorticoids e.g. prednisolone
  - Methotrexate
  - Azathioprine

## Biologics

- ▶ Biological *inhibitors of proinflammatory cytokines*
- ▶ **TNF- $\alpha$  inhibitors**
  - Infliximab
  - Etanercept
- ▶ **Interleukin inhibitors**
  - Ustekinumab: IL-12, 23

- Guselkumab: IL-23
- Secukinumab: IL-17
- ▶ *Rituximab*:
  - Binds to CD20 → cause ADCC of B cells
  - As terminally differentiated plasma cells don't have CD20 they're safe
  - Use: pemphigus vulgaris

## Non-surgical therapy

- ▶ Cryo
  - *Liquid N<sub>2</sub>*
  - Causes cell membrane destruction → death
- ▶ Laser
- ▶ PDT / photodynamic therapy

## 3.3 Skin cancers

### Classification

- ▶ Non-melanoma skin cancer (NMSC): most common
  - SCC
  - BCC
- ▶ Melanoma
  - Less common
  - More metastatic risk → cause of most skin cancer deaths

## 3.4 Fungal infections

### Types

- ▶ Superficial
  - Dermatophytes: aka **ringworm / tineasis**
    - *Trichophyton*
    - *Epidermophyton*
    - *Microsporum*
  - Yeast
- ▶ Deep: less common
  - Chromomycosis
  - Sporotrichosis

## 3.5 Scabies

### Agent

Caused by the mite *Sarcoptes scabies hominis*

### Diagnosis

- ▶ Identify the skin burrow
- ▶ Visualize the mite by dermatoscope / extracting with a needle

### Treatment

- ▶ Affected + all asymptomatic family members / physical contacts
- ▶ Topical permethrin / malathion
  - 2 applications
  - 1 wk apart
  - Whole body, except head
- ▶ Oral Ivermectin:
  - Single dose
  - For poor adherence, immunosuppression or heavy infestation

## 3.6 Acne

- ▶ *Chronic inflammation of pilosebaceous units*

### Pathogenesis

Key components are:

- ▶ ↑ Sebum production
- ▶ Colonisation of pilosebaceous ducts by *Propionibacterium acnes*
- ▶ Occlusion of pilosebaceous ducts

### Features

- ▶ Hallmark: **comedone**
- ▶ Greasiness of skin

### Management

- ▶ **Mild disease**
  - Topical Benzoyl peroxide
  - Topical Retinoids
  - Topical antibiotics

- Erythromycin
- Clindamycin
- ▶ **Moderate disease:** topical *plus*
  - Systemic tetracycline
  - Oestrogen containing OCP
  - Isotretinoin: if inadequate response to topical+systemic therapy for 6 months
- ▶ **Severe disease**
  - Isotretinoin 0.5-1 mg/kg for 4 months:
    - Reduce sebum secretion and follicle colonisation
    - Teratogen
    - Pregnancy must be avoided during treatment *and* within 2 mo of drug cessation
  - Systemic glucocorticoid (with isotretinoin)
  - If unable to use isotretinoin
    - UVB phototherapy
    - PDT

### 3.7 Eczemas

- ▶ Seborrhoeic dermatitis is associated with *Malassezia* yeasts

#### Features

Most types have the following clinical features:

##### Acute

- ▶ Ill-defined erythema, oedema
- ▶ Papules, vesicles, bullae
- ▶ Exudation
- ▶ Scaling

##### Chronic

- ▶ Above features
- ▶ Lichenification
  - Skin thickening with pronounced skin markings, 2° to chronic scratching
  - Fissures
  - Dyspigmentation

#### Management

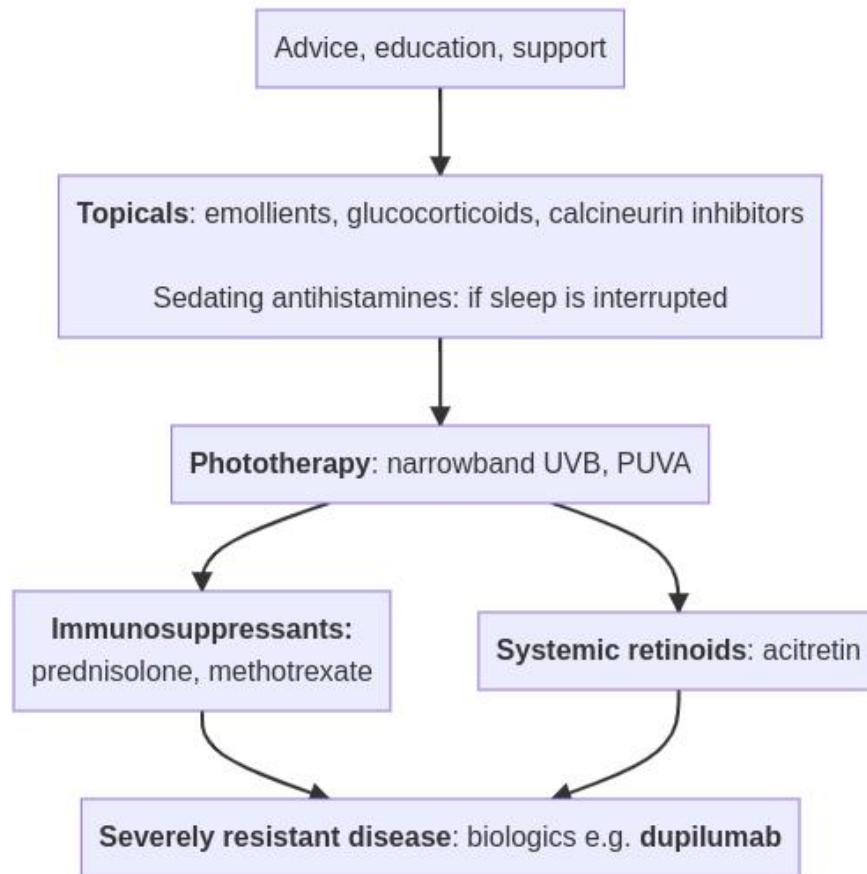


Figure 3.2: Management of eczema

### 3.8 Psoriasis

- ▶ Chronic inflammatory hyperproliferative skin disease
- ▶ **Characteristics**
  - **Well-defined erythematous scaly plaques**
  - Affecting **extensor surfaces, scalp, nails**

#### Histological features

- ▶ Keratinocyte hyperproliferation + abnormal differentiation → nucleated stratum corneum cells (transit time from basale to corneum reduced to 5 from 28 → keratinocytes reach the surface while immature)
- ▶ Inflammation with Th-1 and Th-17 infiltration
- ▶ Tortuosity of dermal capillaries and release of VEGF

#### Exacerbating factors

- ▶ **Sunlight**

- ▶ **Trauma**
- ▶ **Infection**
  - $\beta$ -haemolytic strep  $\uparrow$  guttate psoriasis
  - HIV may initially present with severe psoriasis
- ▶ **Drugs**
  - Antimalarials
  - $\beta$ -blockers
  - Lithium
  - NSAIDs
- ▶ **Stress and anxiety**

## Clinical types

- ▶ **Plaque psoriasis:**
  - most common
  - well-demarcated erythematous plaques
  - silver-white scales in untreated
    - bleed on scraping (due to dilated vessels underneath)  $\rightarrow$  **Auspitz sign**
  - **Sites**
    - extensor surfaces
      - elbows
      - knees
      - lower back
    - scalp
    - nails
- ▶ **Guttate psoriasis:**
  - follows *Strep* throat
  - common in children/adolescent
  - UVB highly effective
  - may herald the onset of plaque psoriasis in adulthood
- ▶ **Erythrodermic psoriasis:** generalised  $\rightarrow$  medical emergency
- ▶ **Pustular psoriasis**



## Management

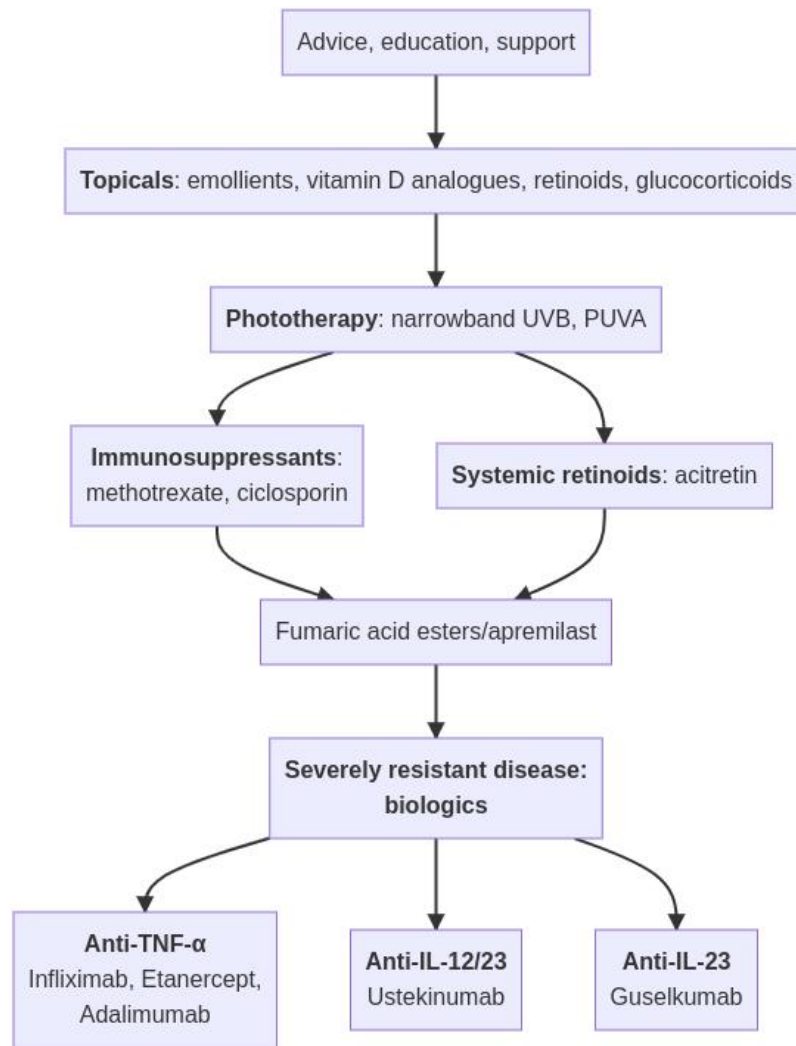


Figure 3.3: Management of psoriasis

## Complications

- ▶ Psoriatic arthropathy
- ▶ Exfoliative dermatitis
- ▶ Secondary infection
- ▶ Hyperuricaemia and gout

## 3.9 Hypopigmentation

### Causes

- ▶ Vitiligo
- ▶ Albinism
- ▶ Pityriasis alba
- ▶ Pityriasis versicolor

### Vitiligo

- ▶ **Acquired**
- ▶ Cell-mediated **autoimmune destruction of melanocytes**
- ▶ Loss of melanocytes → hypopigmented patches

### Albinism

- ▶ **Autosomal recessive**
- ▶ **Reduced melanin production by normal number of melanocytes**
- ▶ ↑↑ risk of sunburn, skin cancer

## 3.10 Hyperpigmentation

### Causes

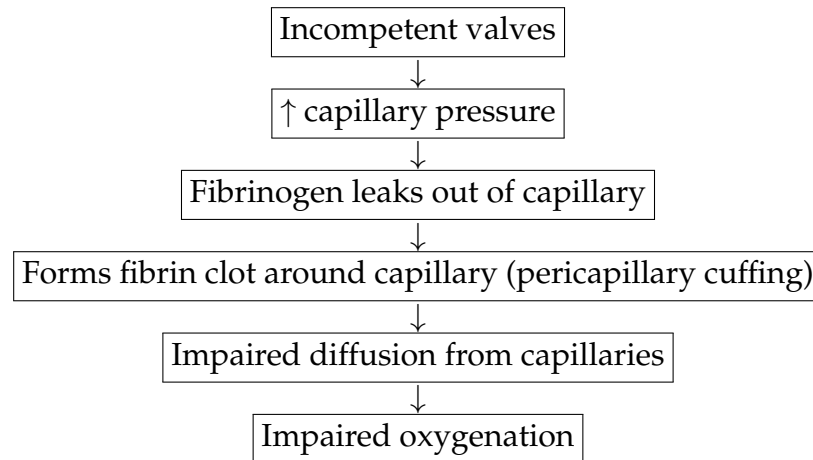
- ▶ **Endocrine**
  - Melasma/chloasma:
    - in pregnancy / some OCP users
    - discrete patches of facial pigmentation
  - Addison's disease
  - Cushing's syndrome
  - Nelson's syndrome
    - hyper-ACTH 2° to bilateral adrenalectomy for Cushing's
    - due to loss of -ve feedback from plasma cortisol
  - CKD
- ▶ **Drugs**
  - Amiodarone
  - Anti-cancers:
    - Bleomycin: Hodgkin's
    - Busulfan: CML
  - Choroquine
  - Psoralens

## 3.11 Stuff not large enough to devote a section to

### SPF (sun protection factor)

- $\frac{\text{UV dose for producing erythema with sunscreen}}{\text{UV dose for producing erythema without sunscreen}}$

### Mechanism of venous ulceration



# Chapter 4

## Nephrology

### 4.1 Anatomy and Physiology

#### Nephron

► **Glomerulus** (fig. 4.1)

- Glomerular capillaries enclosed by Bowman's membrane
- Space between adjacent capillaries occupied by *mesangial cells*
- **Glomerular capillaries:**
  - Endothelial cells with
    - fenestrations ( $\approx 70\text{nm}$ )
    - charged glycocalyx (mostly -ve)
  - GBM (glomerular basement membrane) made of *type IV collagen* etc
- **Podocytes / visceral epithelial layer:** interdigitating foot processes cover up the fenestrations, making the filtration barrier tighter
- **Mesangial cells:** contract and relax to control capillary diameter  $\rightarrow$  GFR

► **Renal tubules**

- Lining different according to location and function
- **Interstitial fibroblasts** produce **erythropoietin**

#### Juxtaglomerular (JG) apparatus

- **Macula densa** around the distal tubules: Sense Na concentration in distal tubule filtrate, controlling the **tubuloglomerular feedback** mechanism
- If low GFR, release PGE2  $\rightarrow$  dilate afferent arteriole  $\rightarrow$   $\uparrow$ GFR
  - If high GFR, make adenosine from ATP  $\rightarrow$  afferent arteriolar constriction  $\rightarrow$   $\downarrow$ GFR
    - Aside: this is the mechanism behind the mild diuresis produced by caffeine. Adenosine carries the signal for tiredness in the brain, and caffeine blocks adenosine receptors. In the brain, the blocking means you feel less tired. In the afferent arterioles, blocking means you can't reduce your GFR.
  - If high GFR, stimulate **JG cells** to secrete renin

## Glomerular Capillary Membrane-

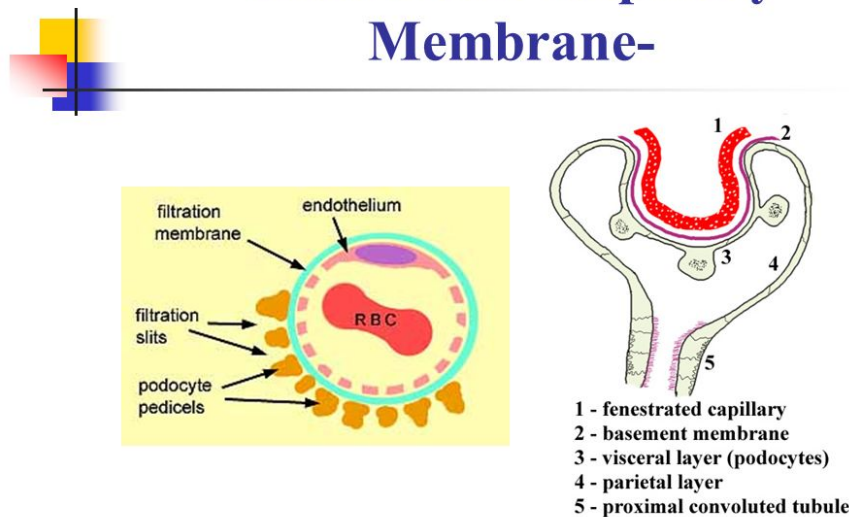


Figure 4.1: Microstructure of the glomerulus

## 4.2 Presenting problems in urinary disease

► **Oliguria:** < 400mL/day

► **Anuria:** < 100mL/day

► **Haematuria:**

■ Healthy individuals may have upto 12,500 RBCs/mL

■ Macroscopic or microscopic-dipstick+ haematuria indicates significant pathology

■ **Types:**

• Initial:

- blood during the start of micturition
- cause: penile urethral pathology

• Terminal:

- blood at the end of micturition
- cause: bladder / prostatic urethral pathology

• Intermittent:

- cause: IgA nephropathy, Alport's, PKD, renal tumour

► **Proteinuria:**

■ Very small amounts of high molecular weight and moderate amounts of low molecular weight proteins pass through the healthy GBM (glomerular basement membrane)

■ Whatever passes is **almost completely reabsorbed** by receptors on tubular cells

■ So in healthy individuals, < 150mg/day protein excreted through urine

■ Transient proteinuria

- Causes
  - Vigorous exercise
  - Fever
  - Heart failure
  - UTI
- Retest after trigger has resolved to verify if persistent proteinuria
- Proteinuria best tested on early morning sample, as some have orthostatic proteinuria (benign, < 1g/day, associated with upright posture)
- Dipstick positive when > 0.5 g/day
  - If persistent dipstick proteinuria, 24h urinary protein must be quantified. > 1g/day → likely glomerular disease
  - PCR (Protein:Creatinine ratio) in spot sample might give better estimates than 24h protein as 24h urine collection is often inaccurate
  - Renal biopsy to confirm dx in significant proteinuria

## 4.3 Glomerular diseases (“Glomerulonephritides”)

### Introduction

- ▶ Though strictly means inflammation of the glomeruli, used to describe all glomerular disease (even if non-inflammatory e.g. minimal change disease)
- ▶ Lie on a *spectrum*, from *nephrosis* (podocyte pathology → proteinuria) to *nephritis* (inflammation + GBM damage → haematuria)

### Types

#### Nephrotic presentation

- ▶ **Minimal change disease**
  - Normal except on electron microscopy
  - Electron microscopy shows fusion of podocyte foot processes
- ▶ Focal segmental glomerulosclerosis (FSGS)
- ▶ **Membranous nephropathy**

#### Mild glomerulonephritic presentation

- ▶ IgA nephropathy
- ▶ Mesangiocapillary glomerulonephritis

#### Rapidly progressive glomerulonephritic presentation

- ▶ Focal necrotising glomerulonephritis
- ▶ Diffuse proliferative glomerulonephritis
- ▶ Anti-GBM disease (aka Goodpasture’s syndrome)

## 4.4 Nephrotic syndrome<sup>1</sup>

### Features

- ▶ Massive **proteinuria** (> 3.5 g/day (medicine) or 1 g/m<sup>2</sup>/day (paediatrics))
  - **Hypoalbuminaemia** (< 3 g/dL)
  - Generalised **oedema** (pitting)
  - “Effusions”: Ascites, pleural effusion, pericardial effusion
- ▶ Features of reduced circulatory volume
  - Scanty urination (colour normal)
  - Pulse: weak
  - BP: low
  - Capillary refill: prolonged (> 3s)
- ▶ Hyperlipidaemia & lipiduria
  - due to ↑ lipoprotein production by liver
- ▶ **Recurrent infections**
  - due to loss of immunoglobulins with urine
- ▶ Features of **complications**
  - Shiny abdominal wall, rigidity and tenderness, absent bowel sounds → **peritonitis**, likely by *Strep pneumo*
  - Loin pain ± palpable kidney + haematuria → **renal vein thrombosis**
  - Alterations of consciousness, hemiplegia → **stroke**

### Histopathology

- ▶ Histological types include
  - **Minimal change disease:**
    - no pathology visible with light microscope, visible pathology only under electron microscope.
    - most common type in **children** (2-8y)
  - **Membranous nephropathy:** most common type in **adults**

### Aetiopathogenesis

#### Minimal change disease

- ▶ **Effacement of podocyte foot processes**

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<sup>1</sup>Most parts of this section, unless specifically mentioned to be for membranous nephropathy, refers to minimal change disease i.e. (most cases of) paediatric nephrotic syndrome

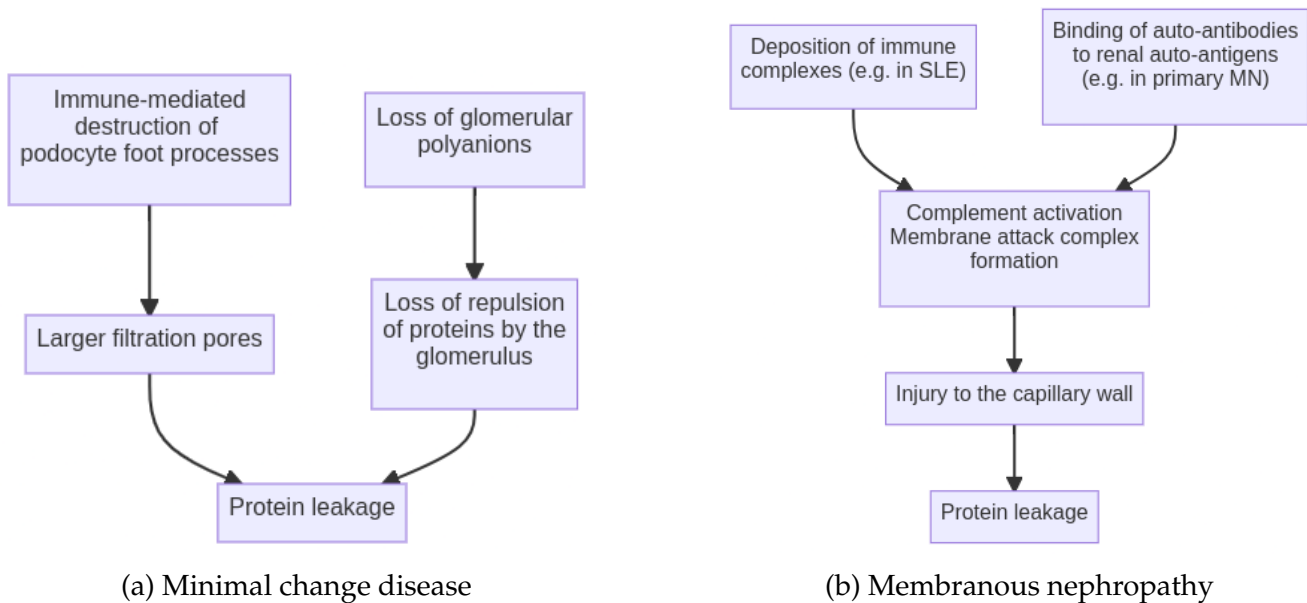


Figure 4.2: Pathogenesis of nephrotic syndrome

### Membranous nephropathy

- ▶ **Autoantibodies to podocyte surface antigens** (e.g. M-type phospholipase A<sub>2</sub> receptor 1) → **MAC-mediated glomerular capillary injury**
  - Antibodies to phospholipase A<sub>2</sub> (PLA2Rab), thus, can be used for diagnosis without biopsy (but may be absent in early disease so biopsy might still be needed)
- ▶ **Aetiology:**
  - Primary / Idiopathic: HLA-DQA1
  - Secondary:
    - Drugs e.g. NSAIDs, penicillamine (treatment for Wilson's)
    - Heavy metal poisoning
    - Hep-B
    - Malignancy
    - SLE
- ▶ **Fates:**
  - 1/3 spontaneous remission
  - 1/3 remain nephrotic
  - 1/3 progressive CKD

### Investigations

- ▶ **Urine RME**
  - Albuminuria
  - Granular & hyaline casts



- Pus cells if associated with UTI
- ▶ Diagnostic
  - 24h total protein:  $> 1\text{g/m}^2/\text{day}$
  - PCR (Protein-Creatinine ratio)  $> 2$
  - Serum albumin  $< 25\text{ g/L}$
  - Serum cholesterol  $> 220\text{ mg/dL}$
- ▶ Renal biopsy: if nonresponsive to corticosteroid therapy

## Treatment

### Minimal Change Nephropathy

- ▶ Specific:<sup>2</sup>
  - **High dose glucocorticoid for 6wks**
  - Prednisolone  $1\text{ mg/kg/day}$
  - KDIGO guidelines: (4wks daily + 4wks alternate day) or (6wks daily + 6wks alternate day)
  - Incomplete response to steroid: Cyclophosphamide ( $1.5\text{-}2\text{ mg/kg/day}$ ) or Cyclosporin ( $3\text{-}5\text{ mg/kg/day}$ ) for 8-12wks with prednisolone  $7.5\text{-}15\text{ mg/day}$  (i.e. low dose)
- ▶ Supportive:
  - Diet:
    - normal with adequate protein
    - salt restriction
  - Oedema: if severe,
    - restrict salt and fluid intake
    - loop diuretics
  - Hypovolaemia: infuse albumin
  - Infections: treat & prevent (pneumococcus, meningococcus vaccine)
  - Hypercoagulability:
    - due to loss of coagulation inhibitors (antithrombin III, protein C, protein S) +  $\uparrow$  liver production of procoagulants
    - consider LMW heparin / warfarin if severe NS

### Membranous Nephropathy

- ▶ Specific:<sup>3</sup>
  - **High-dose glucocorticoids + cyclophosphamide (Ponticelli regimen)**
    - Reserved for severe cases for risk of toxicity of this regimen

<sup>2</sup><https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GD-Guideline-Key-Takeaways-for-Clinicians-Nephrotic-Syndrome-in-Children.pdf>

<sup>3</sup><https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GD-Guideline-Key-Takeaways-for-Clinicians-Membranous-Nephropathy.pdf>

- If secondary, **treat the underlying cause**
- ▶ **Supportive:** same as above

## Complications

- ▶ Hypercoagulability → **renal vein thrombosis, pulmonary embolism**
  - Dx of RVT: Doppler, CT, or MRI
  - Rx: Heparin 6 days (5-7d), Warfarin 6 months (3-6m)
- ▶ Infections: due to loss of immunoglobulins
  - **Pneumococcal infection** → peritonitis, septicaemia
  - Cellulitis
  - Strep infection
- ▶ Hyperlipidaemia → **atherosclerosis**
- ▶ **Pleural effusion**
- ▶ **Pericardial effusion**

## 4.5 Acute post-streptococcal glomerulonephritis

### Pathogenesis

- ▶ Occurs following sore throat or skin infection by **group-A  $\beta$ -haemolytic streptococcus** (nephritogenic strains: 12, 49)
- ▶ **Antibodies against streptococcal M protein cross-react** with glomerular antigens because of molecular mimicry
- ▶ Complement activation, inflammatory cell infiltration. Net effects:
  - **Oliguria**
  - **Haematuria**
  - Hypervolaemia, **hypertension**, hyperkalaemia
  - **Oedema**
  - ↓ **Renal function**  $\Rightarrow$ 
    - Azotaemia
    - Acidosis
- ▶ **Complications** (due mostly to acute hypertension)
  - Acute LVF
  - Hypertensive encephalopathy
  - Acute kidney injury

### Features

- ▶ Age: 5-12y; history of strep throat/skin infection a few wks prior
- ▶ **Scanty, smoky urine**
- ▶ **Puffy face**

► **Hypertension**

► Features of *complications*

- **ALVF**:
  - cough
  - respiratory distress
  - orthopnoea
  - gallop rhythm
  - bilateral basal crepitations
- **Hypertensive encephalopathy**:
  - headache
  - blurred vision
  - convulsion
  - delirium
  - papilloedema
- **AKI**: anuria

## Investigations

► **Evidence of nephritis**

- Urine RME:
  - RBC, RBC casts
  - Mild proteinuria
  - Leucocytes
- Serum C3: ↓
- Serum C4: normal

► **Evidence of prior strep infection**

- ASO titre: ↑
- Anti-DNAse B: ↑

► **Evidence of complications**

- Serum electrolytes: may show hyperkalaemia and acidosis
- Serum creatinine
- X-ray chest

## Treatment

- **Rest**
- **Diet**: restrict fluid, salt, protein.
- **Diuretics**: furosemide
- **Antibiotics**: phenoxymethyl penicillin PO to prevent spread of remaining strep within the body
- **Antihypertensive**

## 4.6 Alport's syndrome

- ▶ Mutation / deletion of COL4A5 on chr-X → **defect of collagen type IV**
- ▶ **X-linked recessive**
- ▶ Deposition of abnormal collagen → progressive degeneration of GBM
  - Haematuria starts in early infancy
  - ESRD by late teens / twenties
  - Female carriers usually have haematuria, rarely significant renal disease
- ▶ Other basement membranes with collagen IV are also involved
  - cochlear BM → **SNHL** (sensorineural hearing loss; especially in high-frequencies)
  - **ocular abnormalities:**
    - lenticonus
    - keratoconus
    - cataracts
    - corneal erosions
- ▶ ACEi may slow (but not prevent) loss of renal function
- ▶ Might require RRT (renal replacement therapy)

## 4.7 Adult Polycystic Kidney Disease

### Introduction

- ▶ Better known as Autosomal Dominant PKD (ADPKD)
  - There's a much rarer (1:20,000) autosomal recessive PKD (ARPKD)
- ▶ Prevalence 1:1000
- ▶ **Autosomal dominant**
- ▶ Small cysts lined by tubular epithelium develop from childhood, enlarge slowly
- ▶ Surrounding normal kidney tissue compressed and progressively damaged
- ▶ Mutations: PKD1 (in 85%), PKD2 (15%) (code for polycystin 1 and 2, respectively)

### Features

- ▶ Asymptomatic initially
- ▶ **Hypertension** from around 20 yrs of age
- ▶ Either (or both) kidney may be palpable, nodular
- ▶ Vague **loin discomfort** due to **enlarging mass**
- ▶ Acute loin pain due to haemorrhage into a cyst
- ▶ **Haematuria** with little / no proteinuria
- ▶ About 30% have **hepatic cysts** (mostly with no liver function impairment)
- ▶ **Berry aneurysms** of cerebral vessels in  $\approx 5\%$  (may lead to SAH)
- ▶ **Renal failure** → features of CKD
- ▶ Mitral / aortic regurgitation (frequent, rarely severe)

## Investigations

- ▶ Dx is based on family history, clinical features, and USG
- ▶ Criteria for dx in patients with +ve family history
  - 15-39y:  $\geq 3$  unilateral or bilateral cysts
  - 40-59y:  $\geq 2$  cysts in each kidney (total:  $\geq 4$ )
  - $\geq 60$ y:  $\geq 4$  cysts in each kidney (total:  $\geq 8$ )

## Management

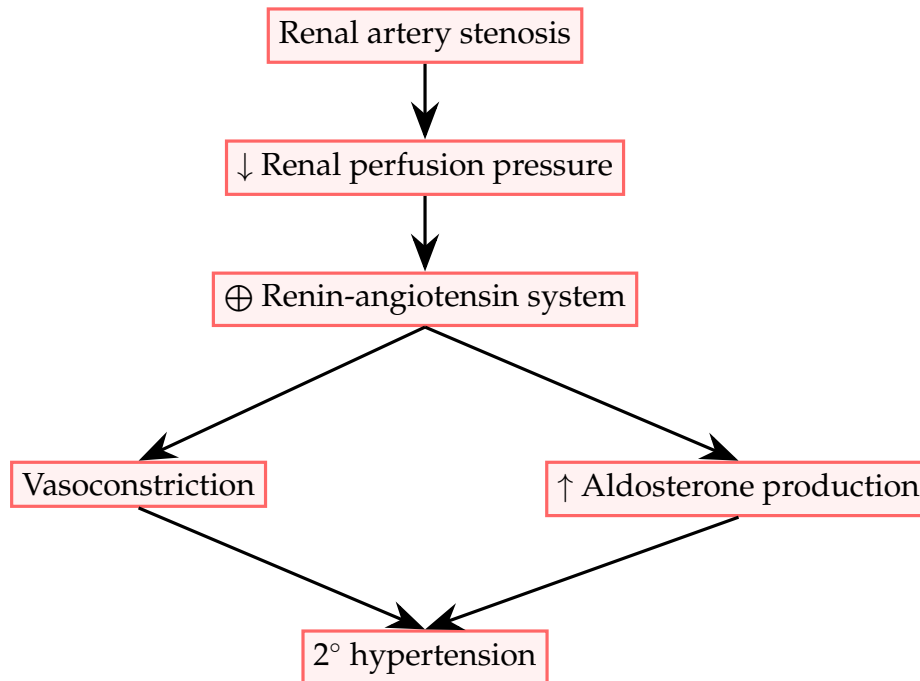
- ▶ **BP control:** 1st choice ACEi / ARBs
- ▶ **Tolvaptan:** Vasopressin V2 receptor antagonist
  - Reduce cyst growth
  - Slow rate of GFR decline
- ▶ **Octreotide:** Long acting somatostatin (aka growth hormone inhibiting hormone) analog
  - Reduces rate of growth of liver and renal cysts
- ▶ **Large cyst:** US-guided aspiration / laproscopic cystectomy
- ▶ **RRT** (renal replacement therapy) : dialysis / transplantation

## 4.8 Renal artery stenosis

### Introduction

- ▶ **Most common cause of 2° hypertension**
- ▶ Most cases are due to **atherosclerosis**
- ▶ Younger ( $\leq 40$ ) cases mostly non-atheromatous, due to *fibromuscular dysplasia*

### Pathophysiology



### Features

- ▶ Hypertension: may be severe and difficult to control
- ▶ Acute pulmonary oedema: associated with severe hypertension
- ▶ Progressive renal failure
- ▶ Worsened renal function with ACEi or ARB administration ( $\geq 30\%$  increase in serum creatinine raises possibility of renal artery stenosis)
- ▶ Peripheral vascular disease: associated, but not caused by the stenosis
  - In older patients with atherosclerotic renal artery stenosis (due to generalised atherosclerosis)
  - Especially in legs

### Investigations

- ▶ CT / MR angiogram of renal vasculature: confirmatory
- ▶ Serum creatinine: to see if worsening renal function
- ▶ Plasma renin: may be elevated
- ▶ Serum electrolytes: may be hypokalaemia due to hyperaldosteronism

- ▶ USG: asymmetrically sized kidneys

## Treatment

### Medical

- ▶ Antihypertensives: not ACEi or ARB
- ▶ Lipid-lowering agents: Statins
- ▶ Anti-platelets: Low-dose aspirin

### Surgical

- ▶ Angioplasty
- ▶ Indications:
  - $\leq 40$ y age
  - BP not controlled by antihypertensive / history of malignant htn
  - History of flash pulmonary oedema
  - Deteriorating renal function

## 4.9 Thrombotic microangiopathies (HUS, TTP)

### Introduction

- ▶ Thrombotic occlusion of arterioles and capillaries especially in the kidneys or brain
- ▶ Common feature of these is **microangiopathic haemolytic anaemia (MAHA)**
  - Haemolysis due to passage of RBCs through abnormal vessels
  - **Schistocytes** (fragmented RBC) may be seen on PBF
  - **Reticulocytosis**
  - **↑ unconjugated bilirubin, serum LDH**
  - **↓ serum haptoglobin**
    - Lysed RBCs release free Hb into the bloodstream. This can enter into tissues and trigger the inflammatory cascade, leading to tissue damage. To protect from this, the body comes equipped with a plasma protein called *haptoglobin*, which binds to free Hb. When there's intravascular haemolysis, free Hb is released, and haptoglobin is used up, leading to its decreased serum levels.

### Haemolytic uraemic syndrome

- ▶ Thrombotic microangiopathy predominantly involving renal microcirculation
- ▶ Cause: **shiga-like toxin producing bacteria**
  - Enterohaemorrhagic *Escherichia coli*
  - *Shigella dysenteriae*
- ▶ Most common cause of AKI in children
- ▶ If no bloody diarrhoea, atypical causes of HUS (e.g. complement system abnormalities - familial HUS) should be considered

## Thrombotic thrombocytopenic purpura

- ▶ Thrombotic microangiopathy predominantly involving cerebral microcirculation
- ▶ MAHA + thrombocytopenia
- ▶ Autoimmune: antibodies to ADAMTS-13
  - aka vWF cleaving protease
    - functions of vWF: haemostasis (thrombus + clot)
      - bind to and stabilize Factor VIII (unbound half-life: 1h, bound to vWF: 12h)
      - help platelet aggregation
  - destruction of ADAMTS-13 → ↑ vWF → thrombosis

## 4.10 Acute kidney injury (AKI)

### Definition

- ▶ Sudden, (usually) reversible loss of renal function, developing over days or weeks (< 3 months), evidenced by rising serum creatinine and / or falling GFR.
- ▶ KDIGO criteria<sup>4</sup>: presence of any of the following
  - $\Delta \text{SCr} \geq +0.3 \text{ mg/dL}$  over 48h
  - $\Delta \text{SCr} \geq +0.5 \times \text{baseline}$  (or  $\text{SCr} \geq 1.5 \times \text{baseline}$ ) over 7d
  - Urine volume  $\leq 0.5 \text{ mL/kg/h}$  for  $\geq 6\text{h}$

### Causes

#### Pre-renal

- ▶ Cardiac failure
- ▶ Blood loss
- ▶ Dehydration
- ▶ Burns
- ▶ Sepsis

#### Renal

- ▶ AGN (acute glomerulonephritis)
- ▶ AIN (acute interstitial nephritis)
  - Drugs (more in [Features](#))
  - Toxins
  - Inflammatory disease
  - Infection
- ▶ ATN (acute tubular necrosis)
  - Drugs
  - Toxins
  - Prolonged hypotension

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<sup>4</sup><https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf>



**Post-renal**

- ▶ Bilateral renal stone
- ▶ BEP (benign enlargement of prostate)
- ▶ Bladder / prostate / cervical cancer
- ▶ Urethral stricture
- ▶ Meatal stenosis
- ▶ Phimosis

**Features**

- ▶ Pre-renal: features of shock
- ▶ Renal:
  - AGN: haematuria, mild proteinuria, oedema, htn
  - AIN: worsened renal function following drugs (*NSAIDs*, PPIs, penicillins)
    - NSAIDs → ↓ prostaglandins → ↓ afferent arteriolar vasodilation → ↓ GFR
  - ATN: dense granular (“muddy brown”) casts
- ▶ Post-renal: bladder distension, hydronephrosis on USG

**Management**

- ▶ Assess **fluid status**
  - If hypovolaemic, fluid resuscitation and inotropes as needed
  - Once euvolaemic, fluid intake = urine output + 500mL (for covering insensible loss)
  - If hypervolaemic, diuretics
- ▶ Manage **hyperkalaemia**
  - If  $K^+ > 6.5$  mmol/L
    - **Calcium resonium** to *stabilize myocardium*
    - **Glucose + Insulin** to *reduce K*
- ▶ Manage **acidosis**
  - $NaHCO_3$  if pH < 7
- ▶ **Treat the cause**
- ▶ Discontinue nephrotoxic drugs
- ▶ Reduce doses of other drugs according to renal function
- ▶ Diet: sufficient energy and protein while avoiding high protein intake (as renal function is poor, metabolic wastes from protein i.e. urea will accumulate in blood leading to uraemia)
- ▶ **Renal replacement therapy**: if not improving with the above measures

## 4.11 Chronic kidney disease (CKD)<sup>5</sup>

### Definition

- ▶ Irreversible loss of renal function developing over years (Davidson)
- ▶ Abnormalities of kidney structure or function, present for > 3 months, with implications for health (KDIGO)<sup>6</sup>
- ▶ End-stage renal disease (ESRD): death likely without RRT (CKD stage 5)

### Staging

| Stage | Definition   | Description            | Features  |
|-------|--|------------------------|---|
| 1     | GFR $\geq$ 90 mL/min/1.73m <sup>2</sup> with evidence of kidney damage | Normal function        | Asymptomatic  |
| 2     | GFR 60-89  | Mild CKD               | Asymptomatic  |
| 3A    | GFR 45-59  | Mild to moderate CKD   | Usually asymptomatic  |
| 3B    | GFR 30-44  | Moderate to severe CKD | Anaemia in some patients  |
| 4     | GFR 15-29  | Severe CKD             | First symptoms often at GFR < 20. Electrolyte disorders             |
| 5     | GFR < 15   | Kidney failure         | Significant symptoms and complications. Dialysis initiated if < 10. |

Table 4.1: Stages of CKD

### Causes

- ▶ Diabetes mellitus
- ▶ Hypertension
- ▶ Glomerular diseases (IgA nephropathy most common)
- ▶ Tubulointerstitial diseases
- ▶ Systemic inflammatory diseases (SLE, vasculitis)
- ▶ Renal artery stenosis
- ▶ Congenital / inherited (Alport's, PKD)

### Features

- ▶ Typically detected incidentally (by raised urea & creatinine) during routine tests, especially in high-risk patients (e.g. DM, Htn)

<sup>5</sup>Here's an awesome [video by Ninja Nerd](#) that discusses CKD in detail with its pathophys, features, dx, and rx.

<sup>6</sup>[https://kdigo.org/wp-content/uploads/2017/02/KDIGO\\_2012\\_CKD\\_GL.pdf](https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf)

- ▶ Most cases asymptomatic until  $\text{GFR} \geq 30 \text{ mL/min}$
- ▶ *Nocturia* is an early symptom, due to loss of concentrating ability.
- ▶ When GFR falls to 15-20, symptoms and signs are common.
  - Tiredness, breathlessness (due to anaemia, fluid overload)
  - Pruritus
  - Anorexia, nausea, vomiting, hiccups
  - Wt loss
  - Kussmaul breathing if profound metabolic acidosis

### Features according to systems

- ▶ *Bone* (**renal osteodystrophy**; mechanism Fig. 4.3)
  - Osteomalacia (renal rickets; due to  $\downarrow$  vit-D)
  - Osteoporosis
  - Osteosclerosis ( $\uparrow$  PTH  $\rightarrow$  rugger jersey spine)
  - Osteitis fibrosa cystica
- ▶ *Skin*
  - Pruritus
- ▶ *Gastrointestinal*
  - Anorexia
  - Nausea
  - Vomiting
- ▶ *Metabolic*
  - **Hyponatraemia, hyperkalaemia** (due to failure of RAAS system)
  - **Hypocalcaemia, hyperphosphataemia** (mechanism Fig. 4.3)
  - **Metabolic acidosis**
  - **Hyperuricaemia**, gout
  - **Hypercholesterolaemia**
- ▶ *Endocrine*
  - 2° hyperparathyroidism
  - Hyperprolactinaemia
- ▶ *Cardiovascular*
  - **Hypertension** ( $\downarrow$ GFR  $\rightarrow$   $\uparrow$ Renin  $\rightarrow$   $\uparrow$ Angiotensin )
  - Heart failure
  - LVH (2° to anaemia or htn)
  - Arrhythmias
  - Pericardial tamponade (uraemic pericarditis)  $\rightarrow$   $\uparrow$  JVP, pulsus paradoxus
- ▶ *Respiratory*
  - Pulmonary oedema

- ▶ *Nervous*: due to uraemic encephalopathy (azotaemia = elevated urea *without symptoms* i.e. no organ damage yet, uraemia = elevated urea *with symptoms*)
  - Fatigue, drowsiness
  - Restless leg syndrome
  - Asterixis (flapping tremor)
  - Seizures
  - Coma
- ▶ *Muscular*

## Investigations

- ▶ Urea and creatinine: to assess stability / progression; compare to previous results
- ▶ CBC: to see Hb%
- ▶ RBS and HbA1c: to see DM
- ▶ Urinalysis: if haematuria / proteinuria indicate glomerular cause
- ▶ Serum electrolytes: to see Na, K, acidosis
- ▶ Ca,  $\text{PO}_4^{3-}$ , PTH, vit-D
- ▶ Lipid profile

## Management

### Monitoring renal function

- ▶ GFR at least every 6 months for stage  $\geq 3$
- ▶ Plot GFR against time

### Reducing rate of progression

- ▶ **Antihypertensive** therapy: Slows rate of decline irrespective of the medication
- ▶ **Glycaemic control**: if DM present
- ▶ **Proteinuria reduction**:
  - Protein
  - $\downarrow$  Proteinuria  $\rightarrow$  risk of progression
    - As protein in the tubules trigger inflammatory damage
  - **ACEi / ARBs** can both reduce BP and reduce proteinuria
    - Reduce perfusion pressure by dilating efferent arterioles  $\rightarrow \downarrow$  proteinuria
    - Should be prescribed even if no htn
    - Reduce risk of cardiovascular events and all-cause mortality in CKD
    - Angiotensin-II critical for GFR autoregulation in case of low renal perfusion, so may exacerbate, e.g., pre-renal AKI. So should be warned to stop taking the meds if fever, diarrhoea, vomiting (and other potential causes of dehydration / pre-renal AKI) arise, and restart after getting better.
    - Should not be commenced if baseline  $\text{K}^+ > 5.5 \text{ mmol/L}$ , as they cause hyperkalaemia

## Treatment of complications

### ► Fluid & electrolyte balance

- **Limit protein intake**, especially in stages 4 and 5, as urea will accumulate.
- **Limit potassium intake**
- **Limit salt intake if oedema and htn**

### ► Acid-base balance

- ↓ excretion of acids → HAGMA (high anion gap metabolic acidosis)
- $\text{NaHCO}_3^-$  supplements

### ► Renal osteodystrophy

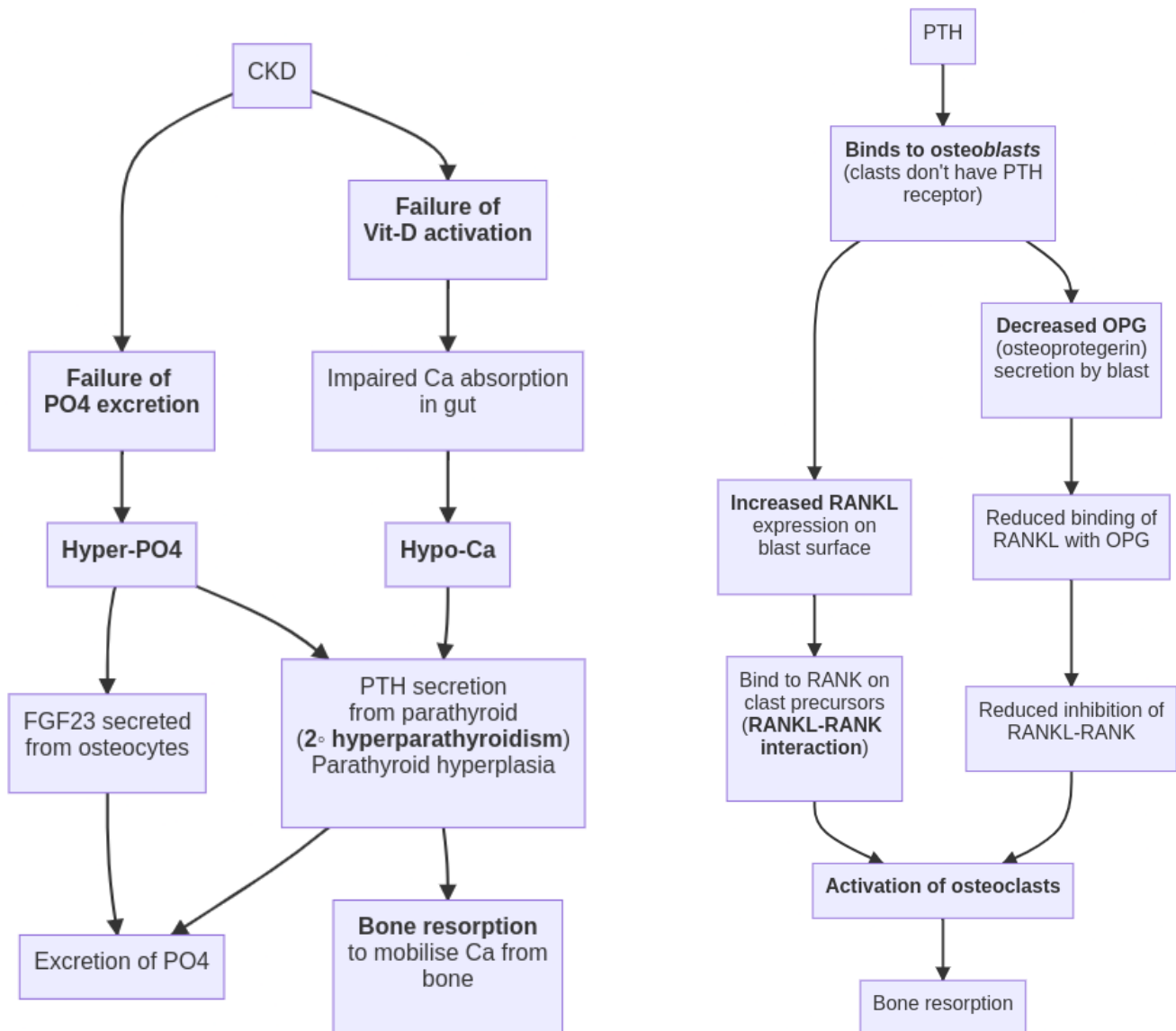
- Primary factors: ↓  $\text{PO}_4^{3-}$  excretion & vit-D activation (details: Figure 4.3)
- Phosphate correction:
  - **Limit high phosphate food** e.g. milk, cheese, eggs, protein-rich food
  - **Phosphate-binding drugs** e.g.  $\text{CaCO}_3$ ,  $\text{Al}(\text{OH})_3$
- Vit-D correction:
  - **Vit-D supplements**

### ► Anaemia

- Causes:
  - ↓ **erythropoietin**
  - Toxic effects of **uraemia** on RBCs
  - ↓ **RBC survival**
  - ↑ **capillary fragility** → blood loss
  - ↓ intake, uptake, and utilisation of dietary Fe
- **Treatment:** recombinant human **erythropoietin**
- Target Hb value: 10 g/dL

### ► Cardiovascular risk factors

- Mechanism of ↑ CV disease risk in CKD
  - ↑ BP
  - Vascular tunica media calcification → stiffness
  - Inflammation, oxidative stress
  - Abnormal endothelial function
- Treatment:
  - Regular exercise
  - Weight loss
  - Smoking cessation
  - Statins, low-dose aspirin



(a) Mechanism of renal osteodystrophy

(b) Mechanism of PTH-induced bone resorption

Figure 4.3: PTH and renal osteodystrophy

## 4.12 UTI

### Definition

- ▶ Presence of  $> 10^5$  organisms/mL in a mid-stream sample of urine (if asymptomatic).

### Features

- ▶ LUTI: cystitis/urethritis
  - Frequency
  - Urgency
  - Dysuria (burning urethral pain during micturition)
  - Haematuria
  - Strangury (intense desire to pass more urine after voiding, due to spasm of inflamed bladder wall)
- ▶ UUTI: acute pyelonephritis
  - Fever with chills and rigor
  - Vomiting
  - Loin pain
  - Renal angle tenderness

### Commonly involved pathogens

- ▶ *E. coli*: 75%
- ▶ *Proteus*
- ▶ *Pseudomonas*
- ▶ *Streptococci*
- ▶ *Staph. epidermidis*

### Investigations

- ▶ Dipstick test for nitrites, leucocyte esterase, and glucose
  - Most urinary pathogens (e.g. *E. coli*, *Proteus* etc) reduce nitrate to nitrite
  - UTI → Neutrophils in urine → leucocyte esterase
- ▶ Microscopy for WBC and organisms
- ▶ Urine culture

### Treatment

#### Cystitis

- ▶ 1st choice
  - Trimethoprim (200mg bds 3 days)
  - Nitrofurantoin (50mg qds 3 days)
- ▶ Pregnancy

- Nitrofurantoin (50mg qds 7 days)
- Cefalexin (250mg qds 7 days)
- ▶ Avoid trimethoprim during pregnancy, and nitrofurantoin at term

### Pyelonephritis

- ▶ 1st choice
  - Cefalexin (1g qds 14 days)
  - Ciprofloxacin (500mg bds 7 days)
- ▶ Hospitalise if no response within 24h

### Epididymo-orchitis

- ▶ 1st choice: Ciprofloxacin

### Acute prostatitis

- ▶ 1st choice: Trimethoprim

## Prophylactic measures in women with recurrent UTI

- ▶ Fluid intake  $\geq 2\text{L/day}$
- ▶ Regular complete bladder evacuation
- ▶ Emptying the bladder before and after intercourse
- ▶ Good personal hygiene
- ▶ Continuous prophylactic trimethoprim (100mg) and nitrofurantoin (50 mg) at night

## 4.13 Renal cell cancer

### Introduction

- ▶ Peak incidence: 65-75y
- ▶ Arises from *renal tubular cells*
- ▶ Histological types:
  - Clear cell (most common; 85%)
  - Papillary
  - Chromophobe
  - Collecting duct

### Features

- ▶  $\approx 50\%$  found incidentally (i.e. asymptomatic when diagnosed)
- ▶  $\approx 10\%$  present with the **classic triad** (especially if advanced disease)
  - Haematuria ( $\approx 60\%$  of symptomatics)
  - Loin pain ( $\approx 40\%$  of symptomatics)



- **Loin mass** ( $\approx 25\%$  of symptomatics)
- ▶ Pyrexia of unknown origin (PUO)
- ▶ Anorexia, malaise, wt loss
- ▶ **Metastasis:** ( $\approx \frac{1}{4}$ th have mets at presentation)
  - Lymphatic: to *para-aortic nodes*
  - Blood-borne: to *lungs, bones, brain*

## Investigations

- ▶ USG: to differentiate solid tumour and cyst
- ▶ CECT (contrast-enhanced CT) of abdomen and chest: for staging ( “cannon-ball” opacities in chest)
- ▶ CBC: polycythaemia (due to  $\uparrow$  erythropoietin)
- ▶ ALP: to check bony mets

## Management

- ▶ **Radical nephrectomy**
- ▶ **Partial nephrectomy:** If tumour  $\leq 4\text{cm}$
- ▶ If high operative risk / patient doesn't want surgery:
  - **Cryotherapy**
  - **Radiofrequency ablation**
- ▶ If unresectable / metastatic:
  - RCC is radio-resistant and also resistant to most chemo agents
  - Current drugs of choice:
    - **Tyrosine kinase inhibitors:**
      - pazopanib, sunitinib
      - inhibit angiogenesis
    - **mTOR inhibitors** (mammalian target of rapamycin):
      - temsirolimus, everolimus
  - High-dose IL-2

#### **4.14 Stuff not large enough to devote a section to**

# Chapter 5

## Rheumatology

### 5.1 Investigations of musculoskeletal disease

#### Joint fluid aspiration

- ▶ Normal:
  - Amount small
  - Viscosity high
  - Colourless / pale yellow
- ▶ Inflammation:
  - Amount raised
  - Viscosity lowered (due to enzymatic degradation of hyaluronan & aggrecan)
  - Turbid (due to neutrophils)
- ▶ Crystal-induced arthropathies
  - Crystals seen by polarised light microscopy
  - Urate crystals → long, needle shaped, -ve birefringence
  - Ca pyrophosphate crystals → small, rhomboid, +ve birefringence

#### Bone scintigraphy

- ▶ Dx of metastatic bone disease and Paget's
- ▶ <sup>99</sup>Tc radiolabelled bisphosphonate used

#### DEXA (Dual Emission X-ray Absorptiometry)

- ▶ Measure BMD (bone mineral density)
  - < -2.5 → osteoporosis
  - Between -2.5 and -1 → osteopenia
  - > 2.5 → high bone mass (most common cause osteoarthritis)

## Immunology

### ► RF

- Antibody to Fc fragment of human Ig
- 70% sensitive for RA (if nodules & extra-articular manifestations then 100% sensitive); specificity poor
- **RF +ve diseases**
  - Rheumatoid arthritis
  - Sjogren's syndrome
  - SLE
  - Old age (> 65)

### ► ACPA

- Antibody to peptides in which arginine has been converted to citrulline by peptidyl-arginine deiminase, an enzyme abundant in inflamed synovium.
- 70% sensitive, >95% specific for RA

### ► ANA (antinuclear antibodies)

- 100% sensitive for SLE but poor specificity
- **ANA +ve diseases**
  - SLE
  - Sjogren's
  - Systemic sclerosis
  - Rheumatoid arthritis

### ► Complement C3

- Active SLE → ↓ C3 (due to consumption of C3 by immune complexes)

## 5.2 Seropositive vs Seronegative arthritis

### ► Seropositive: RF+ inflammatory arthritis

- Rheumatoid arthritis
- SLE

### ► Seronegative: RF- inflammatory arthritis

- Ankylosing spondylitis
- Reactive arthritis
- Psoriatic arthropathy

## 5.3 Osteoarthritis

### ► Characterised by

- degeneration of articular cartilage
- subchondral osteosclerosis

- osteophyte formation at joint margin
- enlargement of affected joint

► Sites

- hips
- knees
- PIPs
- DIPs
- cervical and lumbar spine

► Investigations:

- X-ray of affected joint: findings described above in characteristics
- MRI spine if spine OA + suspected root compression / spinal stenosis

► Treatment

- Conservative:
  - Wt loss
  - Exercise
  - NSAIDs
  - Intraarticular glucocorticoids
- Surgical: if refractory
  - Total joint replacement
  - Osteotomy

## 5.4 Spondyloarthropathies

- Asymmetrical oligoarthritis associated with HLA-B27 and typically involving the spine
  - Ankylosing spondylitis
  - Reactive arthritis
  - Psoriatic arthropathy
  - Axial spondyloarthritis
  - Entropathic spondyloarthritis (arthritis associated with IBD)
- Common features:
  - Asymmetric oligoarthritis
  - Sacroilitis
  - Enthesitis (inflammation where tendon attaches to bone)

### Reactive arthritis

- “Reactive” to certain infections e.g. *Chlamydia*, *Campylobacter*, *Salmonella*, *Shigella*.
- **Reiter’s syndrome:**
  - Triad of *can’t see, can’t pee, can’t bend the knee*
    - **Conjunctivitis**

- Urethritis
- Reactive arthritis
- Due to *Chlamydia*

# Chapter 6

## Neurology

### 6.1 Raised ICP

- ▶ Normal ICP = 5-15 mmHg

#### Causes

- ▶ ICSOL
  - Intracranial haemorrhage
  - Tumours e.g. glioma
  - Brain abscess
- ▶ Hydrocephalus: blockade of CSF circulation
  - Obstructive / non-communicating
  - Communicating
- ▶ Cerebral oedema e.g. meningoencephalitis
- ▶ Venous sinus obstruction e.g. cerebral venous thrombosis

#### Features

- ▶ Headache
- ▶ Vomiting
- ▶ Diplopia / blurred vision: Due to 6th nerve palsy
  - 6th nerve palsy due to
    - stretching of the long, slender nerve
    - compression against petrous temporal bone
  - This palsy of the 6th nerve secondary to raised ICP is known as a *false localisation sign*. If the patient presented only with visible features of 6th nerve palsy, (e.g. diplopia, medial squint) we would falsely localise the primary defect to the 6th nerve. So in 6th nerve palsy always exclude RICP by looking for papilloedema.
- ▶ Depressed consciousness
- ▶ Papilloedema

- ▶ **Bradycardia**
- ▶ **Hypertension**

## Management

- ▶ According to cause:
  - Mass lesion → surgical decompression
  - Hydrocephalus → *ventriculoperitoneal shunt* operation
  - Oedema → glucocorticoids
- ▶ Supportive:
  - Head elevation
  - Fluid balance
  - BP control
  - Diuretics: mannitol

## 6.2 Neurological emergencies

- ▶ **Status epilepticus**
- ▶ **Stroke** (if thrombo)
- ▶ **Subarachnoid haemorrhage**
- ▶ **Cord compression**
- ▶ **GBS**
- ▶ **Myasthenia gravis** (if bulbar and/or respiratory)



## 6.3 Status epilepticus

### Definition

- ▶ Continuous or recurrent **seizures** for  $\geq 30$  mins **without gain of consciousness** in between.
- ▶ Clinically we assume SE after 5mins of seizure activity.

### Management

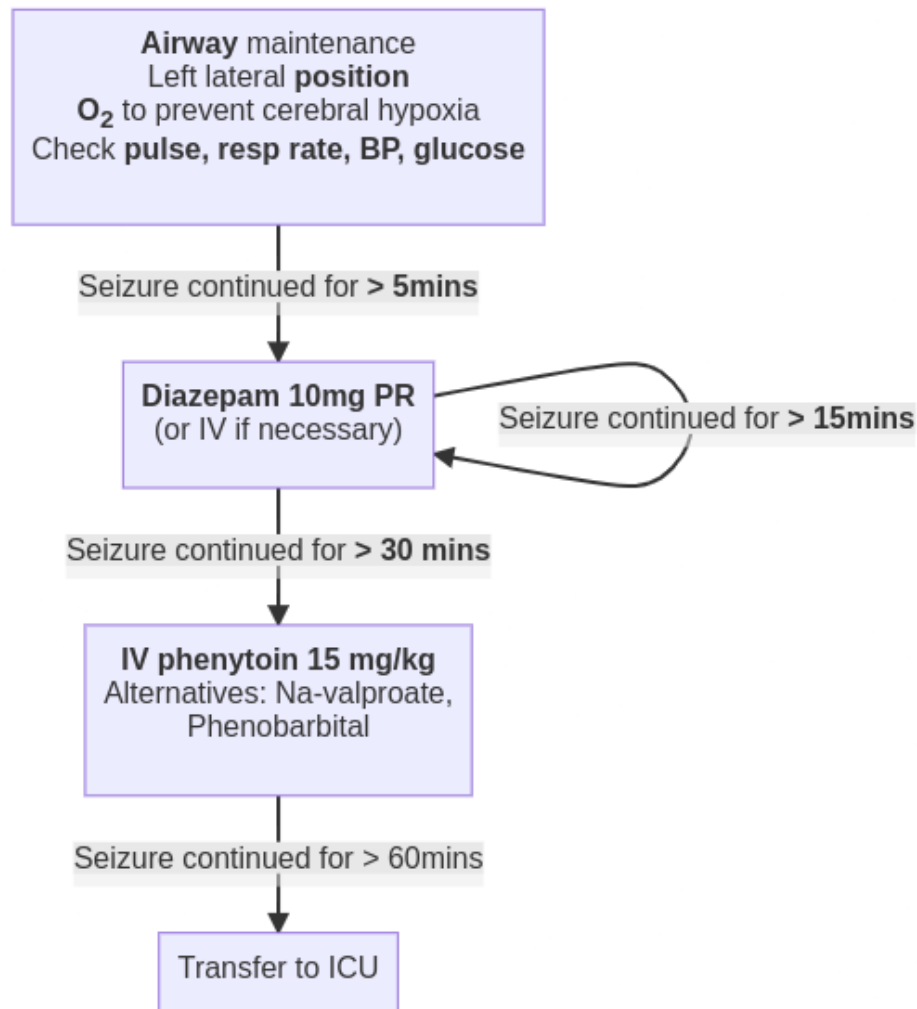


Figure 6.1: Management algorithm for status epilepticus

## 6.4 All jerks root values

- ▶ Biceps: C5
- ▶ Supinator: C6
- ▶ Triceps: C7

- ▶ Finger (aka Hoffmann test): C8
- ▶ Knee: L3, L4
- ▶ Ankle: S1, S2
- ▶ Plantar: S1 (technically not a jerk since it's a superficial reflex)

## 6.5 Subarachnoid haemorrhage

### Causes

- ▶ Ruptured berry aneurysm (85%)
- ▶ Arterio-venous malformations

### Features

- ▶ Sudden severe “thunderclap” headache (often occipital)
- ▶ Vomiting
- ▶ High BP
- ▶ Neck stiffness
- ▶ May be loss of consciousness
- ▶ Photophobia

### Investigations

- ▶ CT scan: hyperdense material in the subarachnoid space
- ▶ Lumbar puncture: blood, xanthochromia

### Management

- ▶ **Nimodipine** 30-60mg IV for 5-14d, followed by 360mg oral for 7d
  - *prevents delayed ischaemia*
- ▶ Insertion of **Pt coils** into aneurysm
- ▶ **Surgical clipping** of the neck of the aneurysm
- ▶ Surgical removal if AVM

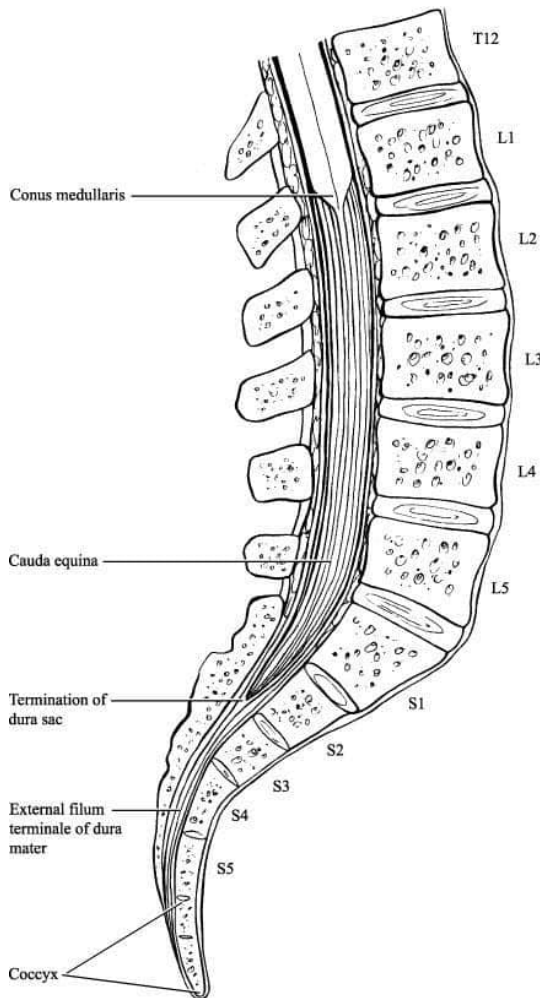
## 6.6 Subacute combined degeneration

### Features

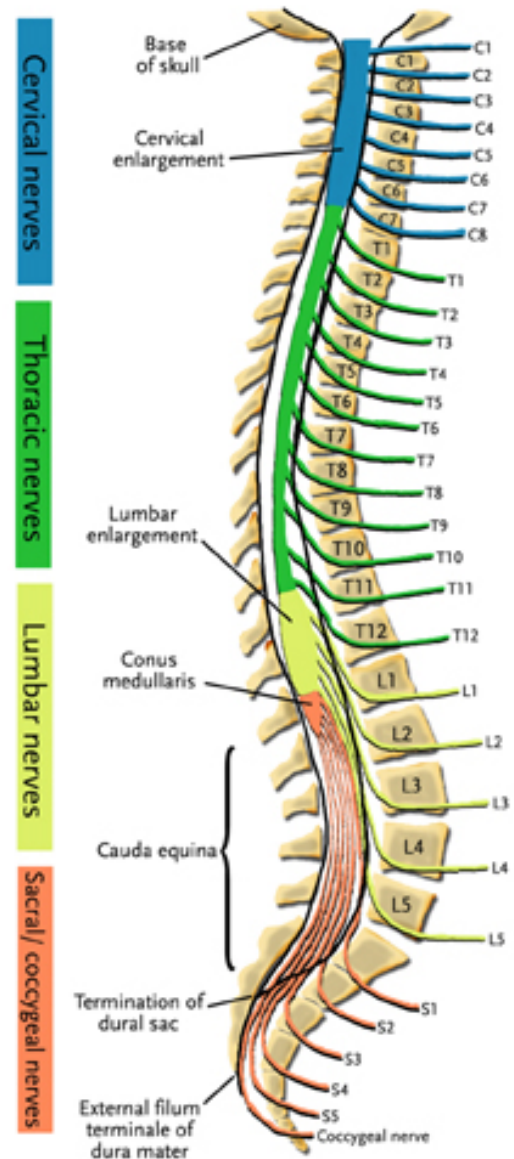
- ▶ **Peripheral neuropathy**: due to **demyelination**
- ▶ Signs of **dorsal column lesion**: **position and vibration sense lost**
- ▶ Signs of **pyramidal lesion**:
  - **plantar extensor**
  - **knee jerk brisk**
  - **ankle jerk absent**: as peripheral neuropathy affects longer nerves first, the afferent pathway for ankle jerk is damaged by the PN while the same for knee jerk is not. Combined with the corticospinal tract lesion, this makes knee jerks brisk and ankle jerks absent.
- ▶ **Optic atrophy**: death of retinal ganglion cell axons

## 6.7 Cauda equina and Conus medullaris lesions

### Anatomy



(a) The Conus and the Cauda



(b) Vertebrae with corresponding spinal cord segments

- ▶ During development, the spine grows faster than the spinal cord, which is why the spinal nerves exit the spinal column at increasingly oblique angles.
- ▶ The spinal cord ends as the tapered conus medullaris at around L1.

## Relevant physiology

- ▶ S2-4:
  - Parasympathetic fibres for bladder sphincter (activation causes emptying)
  - Somatic fibres for pudendal nerves (activation causes relaxation of urethral and anal sphincters → emptying).
- ▶ Conus is surrounded by spinal nerve roots bundled up together around it, so injury / compression in this region leads to a combination of UMN and LMN lesion features.
- ▶ Lesion in the cauda region leads only to LMN lesion features as there's no cord there.

## Features of Cauda Equina syndrome vs Conus Medullaris syndrome

| Features                       | Cauda Equina Syndrome  | Conus Medullaris   |
|--------------------------------|--|--|
| Vertebral level                | L2-sacrum  | L1-L2  |
| Spinal level                   | Injury to the lumbosacral nerve roots  | Injury of the sacral cord segment (conus and epiconus) and roots   |
| Severity of symptoms and signs | Usually severe   | Usually not severe   |
| Symmetry of symptoms and signs | Usually asymmetric   | Usually symmetric  |
| Pain                           | Prominent, asymmetric, and radicular   | Usually bilateral and in the perineal area   |
| Motor                          | Weakness to flaccid paralysis  | Normal motor function to mild or moderate weakness   |
| Sensory                        | Saddle anesthesia, may be asymmetric   | Symmetric saddle distribution, sensory loss of pin prick, and temperature sensations (Tactile sensation is spared.)                            |
| Reflexes                       | Areflexic lower extremities; bulbocavernosus reflex is absent in low CE (sacral) lesions | Areflexic lower extremities<br><br>(If the epiconus is involved, patellar reflex may be absent, whereas bulbocavernosus reflex may be spared.) |

|                               |  |  |
|-------------------------------|--|--|
| Reflexes                      | Areflexic lower extremities;<br>bulbocavernosus reflex is absent in low CE (sacral) lesions                                  | Areflexic lower extremities<br><br>(If the epiconus is involved, patellar reflex may be absent, whereas bulbocavernosus reflex may be spared.) |
| Sphincter and sexual function | Usually late and of lesser magnitude;<br><br>lower sacral roots involvement can cause bladder, bowel, and sexual dysfunction | Early and severe bowel, bladder, and sexual dysfunction that results in a reflexic bowel and bladder with impaired erection in males           |
| EMG                           | Multiple root level involvement; sphincters may also be involved   | Mostly normal lower extremity with external anal sphincter involvement   |
| Outcome                       | May be favorable compared with conus medullaris syndrome   | The outcome may be less favorable than in patients with CES  |

## 6.8 Neurogenic Bladder

### Physiological control of micturition: the Micturition Reflex

#### “Components”

##### ► Detrusor muscle

- Muscles of the bladder wall
- Innervated by
  - **Parasympathetic:**
    - cholinergic  $M_3$  receptors
    - pelvic nerve from **S2-4**
    - causes **contraction** → **urination**
  - **Sympathetic:**
    - $\beta_3$  receptors
    - hypogastric nerve from **T10-L2**
    - causes **relaxation** → **storage** / retention

##### ► Internal urethral sphincter

- Innervated by **only sympathetic**
  - hypogastric nerve from **T10-L2**

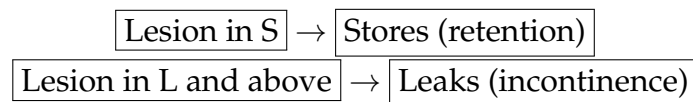
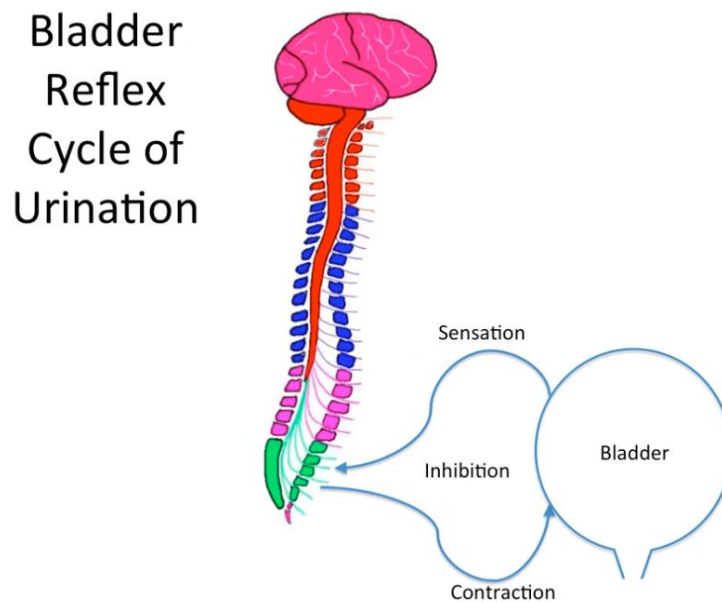
- causes storage / retention

► **External urethral sphincter**

■ **Voluntary control**

- UMN from pontine micturition centre
- LMN from S2-4 (pudendal nerve)
- causes retention

**The big picture (highest yield for clinical interpretation)**



- The reflex spontaneously tries to void the bladder upon being filled even by small amounts. The only thing holding it back is the pontine micturition centre which always inhibits the circuit, unless we voluntarily signal it not to. We can't signal the bladder to empty itself. We can only signal the micturition reflex to not hold back.
- The reflex circuit is composed of afferents and efferents from S2-4. So any **lesion above S2-4** will leave the circuit intact, while damaging the telephone lines from the pontine centre. The end result is that we lose the inhibition of the reflex (which fires every few mins after storing some tens of millilitres of urine), and without anything holding it back, there's urinary **incontinence**.
- On the other hand, any **lesion at S2-4** will damage the circuit elements themselves. That means that the reflex will be lost. This means we no longer have access to the bladder emptying circuit. So there will be urinary **retention**.

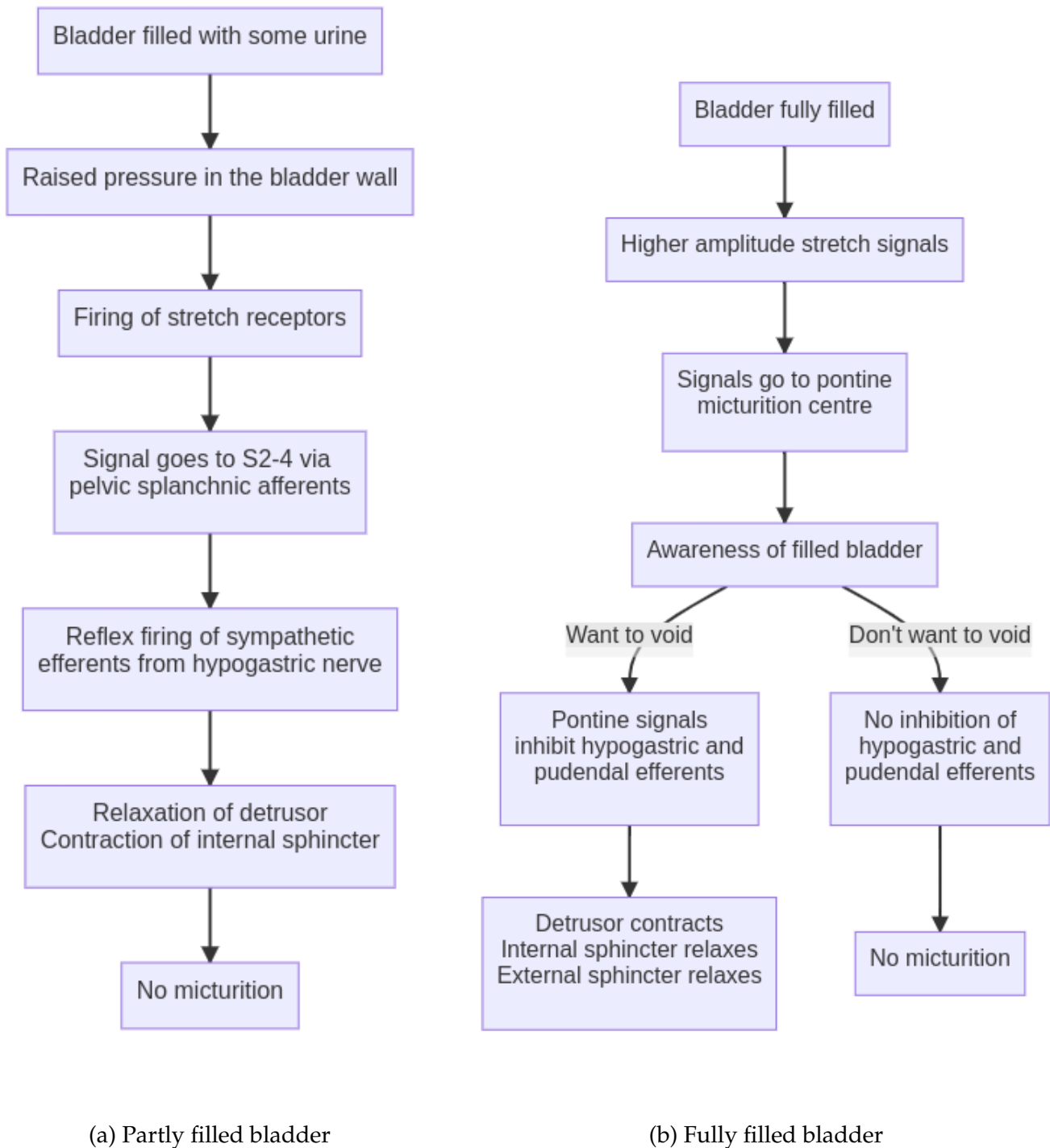
**The details**

Figure 6.3: Neural control of micturition



## 6.9 Parkinson's disease

### Parkinsonism

- ▶ Triad of **TRH**: tremor, rigidity, hypokinesia (bradykinesia)
- ▶ **Causes**
  - Idiopathic → Parkinson's disease
  - Cerebrovascular disease
  - Drugs:
    - Antipsychotics (older)
    - Metoclopramide (D<sub>2</sub> blocker → undo D<sub>2</sub> mediated inhibition of cholinergic stimulation in GIT → ↑GI motility → antiemesis)
      - Domperidone, which is also a D<sub>2</sub> blocker, selectively acts on D<sub>2</sub>s in the GIT, so no parkinsonism
      - Metoclopramide is nonselective
    - Na-valproate, Lithium
  - Other neurodegenerative diseases
    - Lewy body dementia
    - Multiple system atrophy
    - Alzheimer's
  - Genetic
    - Huntington's
    - Wilson's

### Pathophysiology

- ▶ Loss of pigmented dopaminergic neurons in substantia nigra
- ▶ **Lewy bodies in nigral cells**: pathological hallmark
  - Eosinophilic cytoplasmic inclusions
  - Lewy body = aggregation of  $\alpha$ -synuclein (hence the alternative name  $\alpha$ -synucleinopathy)
  - Other  $\alpha$ -synucleinopathies (diseases associated with Lewy body deposition (differ in the initial site of deposition and hence initial features)):
    - Lewy body dementia
    - Multiple system atrophy

### Features

- ▶ Average age of onset: 60y
- ▶ First degreee relative with PD → 2-3x risk
- ▶ Progressive, incurable
- ▶ Initially motor symptoms dominate, but eventually nonmotor symptoms (e.g. depression, anxiety, cognitive impairment) become increasingly prominent
- ▶ Motor symptoms **initially asymmetrical**
- ▶ The hallmark is **bradykinesia**, which leads to

- Micrographia (small handwriting)
- Difficulty tying shoelaces / buttoning clothes
- Difficulty rolling over in bed
- ▶ **Resting tremor** affecting limbs, chin and jaw but not the head
- ▶ **Rigidity**
- ▶ Soft, indistinct speech

## Signs

- ▶ General:
  - Hypomimia (expressionless / mask-like face)
  - Dysphonia (soft, indistinct speech)
  - Flexed (stooped) posture with impaired postural reflexes
  - Bradykinesia
  - **Glabella tap:**
    - tapping on glabella (above bridge of nose) → blink
    - normal → blinking stops after 3-5 times
    - Parkinson's → sustained blinking
- ▶ Gait: **Festinating gait**
  - Slow to start
  - Short, shuffling steps (festination)
  - Reduced arm swing
  - Impaired balance on turning (fractionated turn)
- ▶ Tremor:
  - First in arm/hand (**pill-rolling** tremor)
- ▶ Rigidity:
  - **Leadpipe rigidity:**
    - better seen in elbow / knee
    - uniform throughout movement
  - **Cogwheel rigidity** (= tremor superimposed on rigidity) better seen in wrist
  - Rigidity vs Spasticity:
    - Rigidity:
      - uniform resistance throughout range of motion
      - due to *extrapyramidal* lesion
    - Spasticity:
      - initially increased resistance, followed by lessening
      - due to *pyramidal* lesion
- ▶ The following will be normal (if abnormal, consider other causes)
  - Power, jerks, plantar
  - Eye movements
  - Sensory exam
  - Cerebellar exam

## Investigations

- ▶ Dx is clinical
- ▶ CT / MRI normal
- ▶ Functional dopaminergic imaging (SPECT / PET) abnormal even early
- ▶ In younger, exclude Huntington's and Wilson's

## Treatment

- ▶ **Only symptomatic, no cure**
- ▶ **Physiotherapy ± drugs** (drugs not given if mild)
- ▶ **Surgical:** on failure of medical therapy

## Drugs

### ▶ Levodopa + carbidopa

- Most effective in reducing **rigidity and bradykinesia**
- **Role of dietary protein:** amino acids in dietary protein compete with levodopa for intestinal absorption and transport across BBB → ↓ efficacy of levodopa
- Side effects:
  - Postural hypotension
  - Nausea, vomiting
  - Hallucinations
- Fluctuating response after 3-5y of use
  - *End of dose dyskinesia:* due to progressive loss of dopamine, duration of action of levodopa becomes shorter. Freezing and rigidity before next dose of levodopa.
    - Management: smaller, frequent dosage
  - *On-off phenomenon:* periods of severe parkinsonism (freezing and immobility - *off period*) alternating with periods of dopamine-induced dyskinesia / chorea (*on period*).
    - Management: lower levodopa dose, add selegiline with levodopa
- Contraindications:
  - Psychosis
  - Narrow angle glaucoma
  - Malignant melanoma
  - PUD

### ▶ Anticholinergics

- Benzhexol, bztropine, trihexyphenidyl
- Reduce **tremor and rigidity**, not bradykinesia
- Side effects:
  - Urinary retention, constipation, dry mouth
  - Worsening of glaucoma
- Contraindications:
  - BEP

- Narrow angle glaucoma

► **Dopamine receptor agonists**

- Ergot-derived (e.g. bromocriptine) or non-ergot-derived (e.g. ropinirole)
- Compared to levodopa, less therapeutic effect, more side effects
- Side effects:
  - Postural hypotension
  - Nausea, vomiting
  - Hallucination
  - Confusion

► **MAO-B inhibitors**

- Selegiline, rasagiline
- MAO-B facilitates dopamine breakdown → MAO-Bi potentiates the action of levodopa by inhibiting breakdown

► **COMT inhibitors**

- Tolcapone, entacapone
- COMT → peripheral breakdown of levodopa

► **Amantadine:**

- Rarely used unless patient unable to tolerate other drugs.
- Mild, short-lived effect.

## **Surgery**

► **Deep brain stimulation**

- Replaced destructive surgery
- Targets: thalamus, globus pallidus, subthalamic nuclei
- Thalamic stimulation → reduce tremor

# Chapter 7

## Diabetes Mellitus

### 7.1 Mechanism of insulin secretion

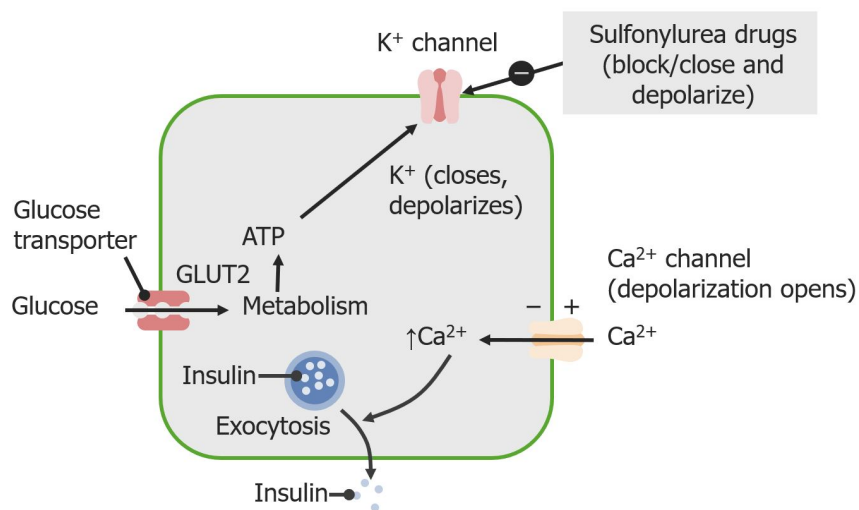


Figure 7.1: Mechanism of insulin secretion

### 7.2 Incretin effect

For the same glucose load applied orally and IV, the **oral load stimulates more insulin secretion** (because oral load  $\rightarrow$  release of gut peptides GLP-1 and GIP  $\rightarrow$   $\uparrow$  insulin secretion).

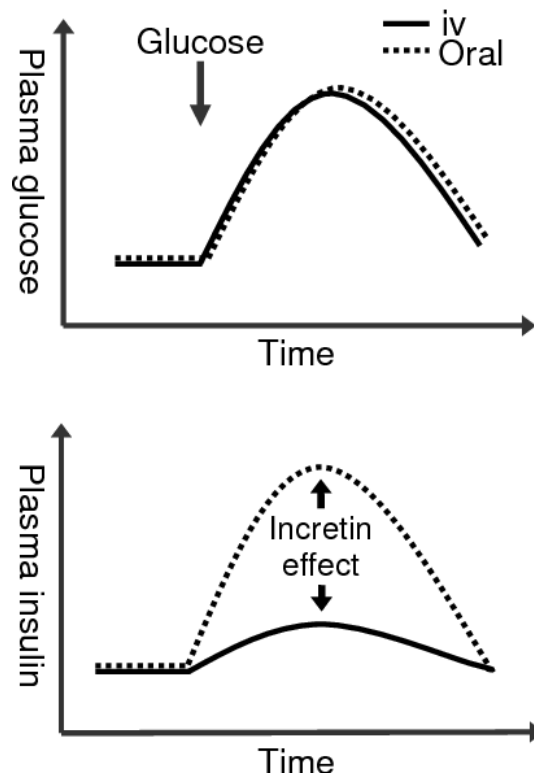


Figure 7.2: The incretin effect

### 7.3 Diagnostic criteria

- ▶ If *symptomatic*, any one of the following
  - FBS  $\geq 7.0$  mmol/L
  - RBS / 2h after OGTT  $\geq 11.1$  mmol/L
  - HbA1c  $> 6.5\%$
- ▶ If *asymptomatic*, two positives needed for dx.
- ▶ IFG:
  - FBS between 6.1-6.9 mmol/L, 2h after OGTT  $< 7.8$  mmol/L (WHO)
  - FBS between 5.6-6.9 mmol/L (American diabetes association (ADA))
- ▶ IGT:
  - FBS  $< 7.0$  mmol/L, 2h after 7.8-11 mmol/L

## 7.4 Diabetic ketoacidosis (DKA)

- ▶ **Medical emergency**
- ▶ Cause of death
  - Children: cerebral oedema
  - Adults:
    - **Hypokalaemia**
    - ARDS
    - Comorbidities: acute MI, sepsis, pneumonia
- ▶ **Cardinal biochemical features**
  - Hyperglycaemia → osmotic diuresis → dehydration, dyselectrolytaemia
  - Hyperketonaemia:
    - Insulin deficiency + elevated catecholamines → unrestrained lipolysis to make FFA → hepatic ketogenesis
  - Metabolic acidosis

### Clinical features

- ▶ **Symptoms**
  - Polyuria, thirst
  - Weakness
  - Nausea, vomiting
  - Abdominal pain
  - Blurred vision
- ▶ **Signs**
  - Dehydration
  - Hypotension
  - Tachycardia
  - Air hunger / Kussmaul breathing (deep and sighing breathing)
  - Acetone breath
  - Delirium, drowsiness, coma

### Management

- ▶ **Establish IV access**
- ▶ **Volume replacement: 0.9% NaCl**
  - If systolic BP  $\geq$  90mmHg: 1L over 1h
  - Else:  $\frac{1}{2}$ L over 15mins → reassess. If BP still  $<$  90mmHg, repeat.
- ▶ **Insulin therapy: IV 0.1 U/kg/h**
  - Corrects hyperglycaemia & acidosis
- ▶ **Monitor**

- Every 1h:
    - capillary blood glucose and ketone
    - vitals: pulse, BP, resp rate, O<sub>2</sub> sat, urine output
  - Every 2h: Venous HCO<sub>3</sub><sup>-</sup> and K<sup>+</sup>
  - Every 4h: Serum electrolytes
- ▶ If K<sup>+</sup> is low, 40mmol/L KCl with normal saline

## 7.5 Hypoglycaemia

### Features

- ▶ **Autonomic**
- Sweating
  - Trembling
  - Palpitations
- ▶ **Neuroglycopenic**
- Delirium
  - Drowsiness
  - Speech difficulty
  - Incoordination

### Management

- ▶ Oral fast-acting carbohydrate (10-15g) e.g. glucose drink / confectionery / honey to buccal mucosa
- ▶ Repeat capillary glucose measurement 10-15mins later
- If still hypo, repeat upto 3 cycles
  - Still hypo after 3 cycles → glucagon 1mg IM



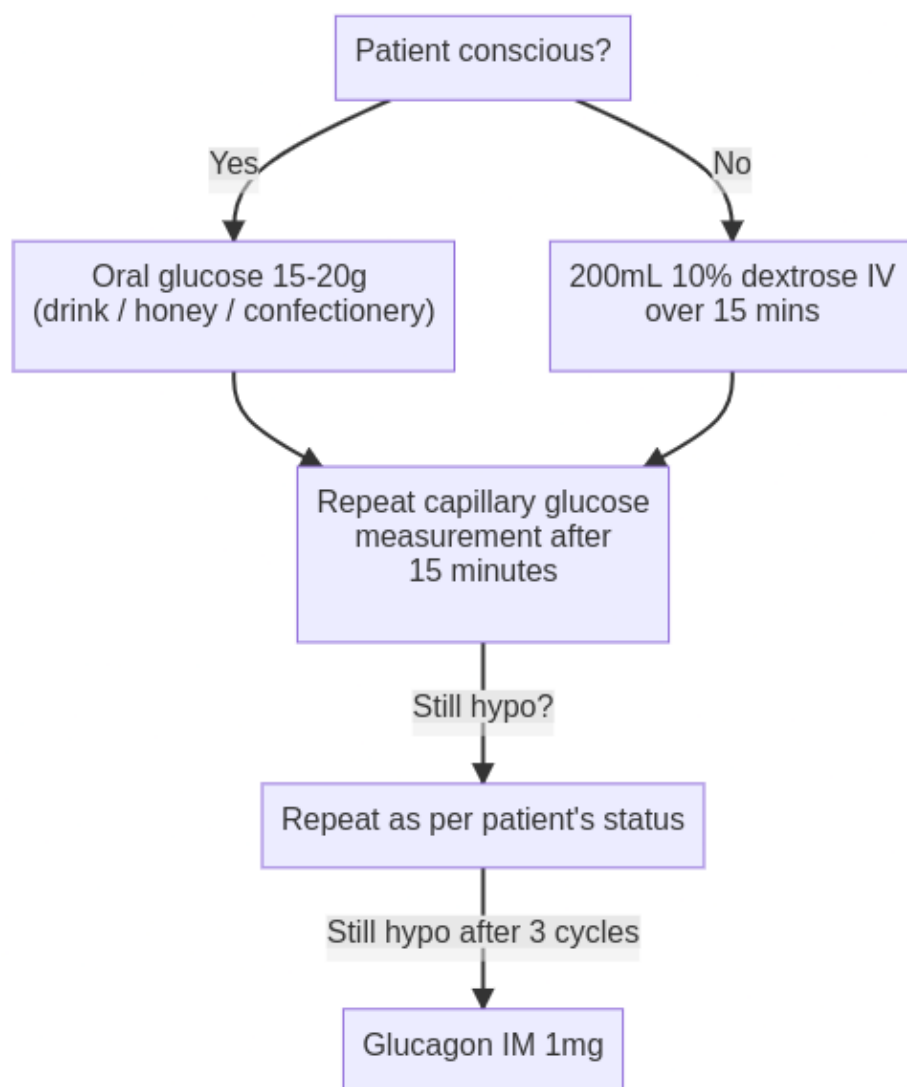


Figure 7.3: Managing hypoglycaemia

## 7.6 Insulin therapy

### Indications

- ▶ Type I DM
- ▶ Type II DM not controlled by OHA
- ▶ DIP / GDM
- ▶ DKA
- ▶ Hyperkalaemia

### Preparations

- ▶ **Rapid-acting** (rapid=LAG-less)
  - Lispro

- Aspart
- Glulisine
- ▶ **Short-acting:** soluble/regular insulin
- ▶ **Intermediate-acting:** Isophane (I for I)
- ▶ **Long-acting**
  - Glargine (gLARGE-in)
  - Detemir Route of administration: **subcutaneous**

## 7.7 Oral Hypoglycaemic Agents

- ▶ **Biguanides:** Metformin
  - Insulin *sensitiser*
  - **Mechanism of action**
    - ↓ hepatic glucose production (gluconeogenesis and glycogenolysis)
    - ↑ gut glucose uptake & utilisation
    - weak inhibitor of mitochondrial respiration → ↑ AMP, ↓ ATP → ↑ glucose uptake utilisation etc.
  - **Side effects profile**
    - Weight neutral
    - Non-hypoglycaemic
    - *Lactic acidosis*
- ▶ **Sulphonylureas:** Glibenclamide, Gliclazide, Glimepiride
  - Insulin *secretagogue*
  - **Mechanism of action:** Block  $K^+$  channel in  $\beta$ -cells → ↑ insulin secretion
  - **Side effects profile**
    - Wt gain
    - Hypoglycaemia
- ▶  **$\alpha$ -glucosidase inhibitors:** Acarbose
  - **Mechanism of action:** delay absorption of carbs
  - **Side effects profile**
    - Non-hypoglycaemic
    - Flatulence
    - Bloating
    - Diarrhoea
- ▶ **Incretin-based therapies:**
  - **DPP-4 inhibitors:** Gliptins
    - **MoA**
      - DPP-4: breaks down GLP-1 & GIP → inhibit incretin effect
  - **GLP-1 receptor agonists:** Exenatide, liraglutide
- ▶ **Thiazolidinediones:** Pioglitazone

- **Mechanism of action**

- PPAR- $\gamma$  agonist  $\rightarrow$  enhance action of insulin

- **Side effects profile**

- Non-hypoglycaemic
  - Wt gain (increase fat cells)

- ▶ **SGLT-2 inhibitors:** empagliflozin, dapagliflozin

- **MoA:** inhibit reabsorption of glucose in renal tubules  $\rightarrow$  25% of filtered glucose excreted
  - Resulting glycosuria can lead to genital fungal infections
  - Empagliflozin  $\rightarrow$  35% reduced mortality in heart failure

## 7.8 Complications of DM

### Acute complications

- ▶ Hypoglycaemia
- ▶ Diabetic ketoacidosis
- ▶ Hyperglycaemic hyperosmolar state (HHS)
- ▶ Lactic acidosis

### Long-term complications

#### Microvascular

- ▶ Diabetic **neuropathy**: peripheral neuropathy (sensory, motor or mixed), mononeuritis multiplex, autonomic neuropathy
- ▶ Diabetic **nephropathy**
- ▶ Ocular complications:
  - Diabetic **retinopathy**
  - **Cataract**
- ▶ Foot complications: ulcer, gangrene
  - Causes of diabetic ulcer:
    - ischaemia
    - neuropathy
    - combined ischaemia and neuropathy
    - trauma
    - infection

#### Macrovascular

- ▶ **Coronary**: myocardial ischaemia, infarction
- ▶ **Cerebral**: Cerebrovascular disease
- ▶ **Peripheral**: ischaemia, claudication

## 7.9 Pathogenesis of chronic complications

- ▶ **Thickened basement membrane** and **↑ vascular permeability** are the pathophysiological hallmarks

### Mechanisms

- ▶ Formation of **advanced glycation end-products (AGEs)**
  - Nonenzymatic addition of glucose to proteins
  - Exert effects by both binding to receptors (RAGE) on endothelial, inflammatory and smooth muscle cells, and by direct (non-receptor) cross-linking of collagen in the basement membrane, mediated chiefly by **VEGF** and **TGF- $\beta$**  (details: fig. 7.4)
- ▶ Excess activation of **protein kinase C (PKC)**
  - Mechanism:  $\uparrow$ intracellular glucose  $\rightarrow$   $\uparrow$ DAG synthesis (diacyl glycerol)  $\rightarrow$   $\uparrow \oplus$ PKC  $\rightarrow$   $\uparrow$ VEGF, TGF- $\beta$ , PAI-1 (plasminogen activator inhibitor-1) production by the vascular endothelium
- ▶ **Oxidative stress and sorbitol accumulation**
  - Mechanism:  $\uparrow$ intracellular glucose  $\rightarrow$   $\uparrow$ metabolism to sorbitol (by aldose reductase)  $\rightarrow$  fructose using *NADPH*  $\rightarrow$  *NADPH* used up  $\rightarrow$   $\downarrow$ availability for use in antioxidant pathway  $\rightarrow$   $\uparrow$ ROS-mediated damage
  - Accumulation of sorbitol in the lens  $\rightarrow$  cataract

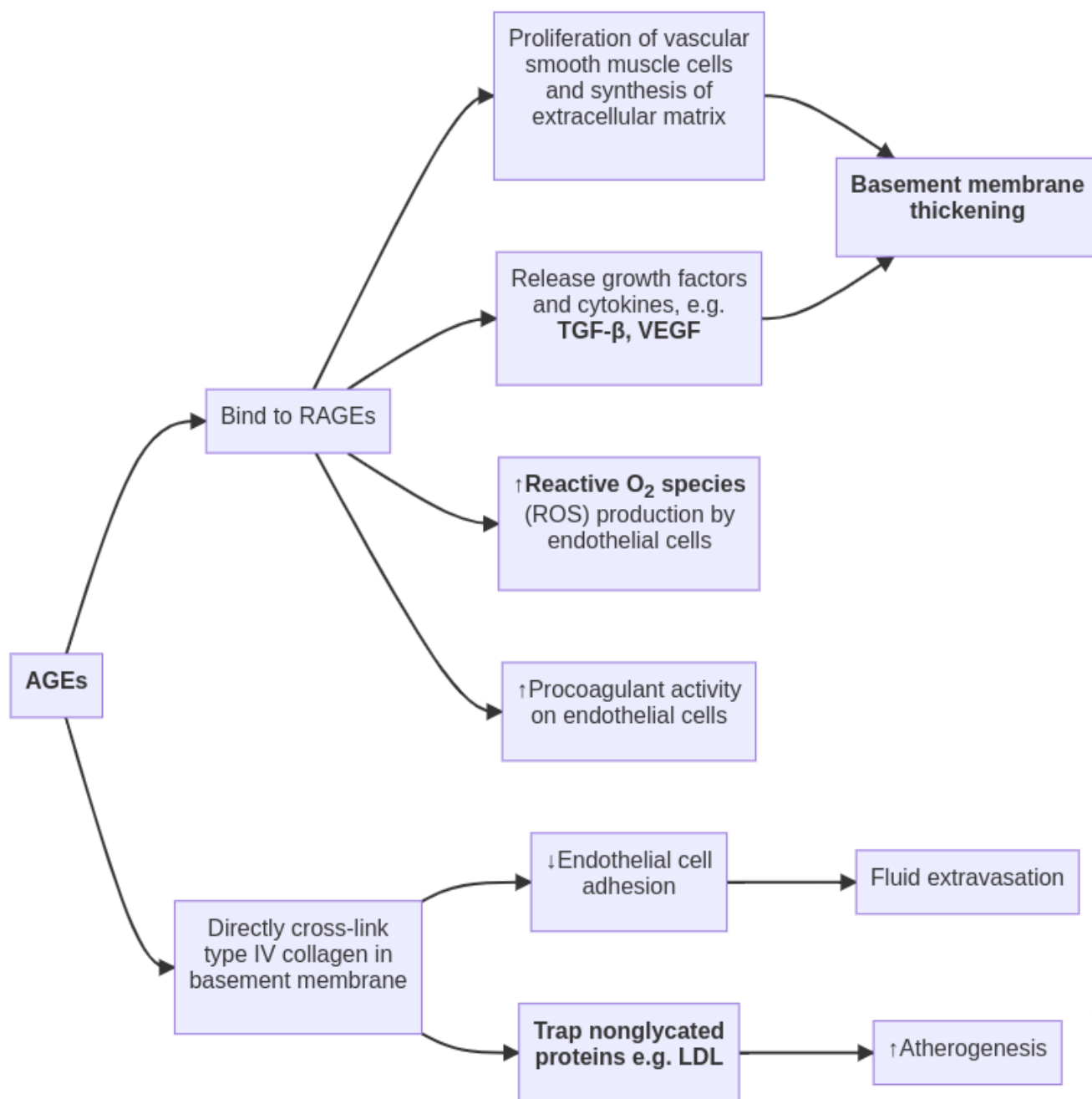


Figure 7.4: Mechanisms of AGE-induced microvascular pathology

## 7.10 Stuff not large enough to devote a section to

### Metabolic syndrome

- ▶ AKA **insulin resistance syndrome** or **syndrome X**
- ▶ Type 2 DM associated with central obesity + htn + dyslipidaemia (high TGs/LDLs and/or low HDL)
- ▶ Often associated with
  - Nonalcoholic fatty liver disease (NAFLD)
  - PCOS
- ▶ ↑risk of stroke, CAD

# Chapter 8

## Gastrointestinal diseases

### 8.1 Weight loss

#### Causes

##### ► Endocrine

- DM (more in type I)
- Thyrotoxicosis
- Addison's

##### ► GI

- Any cause of dysphagia e.g.
  - Stroke
  - MS
  - Ca oesophagus
  - Achalasia cardia
  - Plummer-Vinson syndrome (oesophageal webs+IDA)
- Malabsorption syndrome
  - IBD
  - Chronic pancreatitis (due to enzyme insufficiency)
  - Coeliac disease

##### ► Malignancies

##### ► Chronic infection

- TB
- AIDS

##### ► Psychological

- Depression
- Anorexia nervosa
- Bulimia nervosa
- Alcoholism

# Chapter 9

## Haematology

### 9.1 Chronic myeloid leukaemia (CML)

Defining characteristic: **Philadelphia chromosome**

- ▶ Shortened **chr22** by *reciprocal translocation* with **chr9**
- ▶ Results in **BCR-ABL fusion gene**
- ▶ BCR-ABL codes for a **tyrosine kinase** which influences cell proliferation and survival

#### Features

- ▶ Wt loss
- ▶ Lethargy
- ▶ Abdominal discomfort
- ▶ Splenomegaly
- ▶ Hepatomegaly

#### Phases

- ▶ Chronic
- ▶ Accelerated
- ▶ Blastic crisis

#### Investigations

- ▶ **CBC:** anaemia, leucocytosis
- ▶ **PBF:**
  - Full range of granulocytic precursors, from *myeloblasts* to *mature neutrophils*.
  - Predominant: neutrophils and myelocytes.
  - Myeloblasts < 10%.
- ▶ **Bone marrow examination:**
  - Hypercellular marrow
  - ↑ M/E ratio



- ↓ erythropoiesis
- ↑ leucopoiesis

► **Chromosome analysis** to detect Ph chromosome

## Management

### Chronic phase

► **1st line: Tyrosine kinase inhibitors (TKIs):**

- Imatinib
- Dasatinib
- Nilotinib
- normalise blood count within a month, complete cytogenetic response (disappearance of Ph chr) within 6 months in 90% patients. Resample bone marrow at 6mo to confirm. Thereafter monitor 3-monthly by RT-PCR for BCR-ABL mRNA transcripts.

► **Allogeneic HSC transplant:** if TKI fails

► **Hydroxycarbamide**

► **Interferon:** in pregnancy

# Chapter 10

## Nutritional diseases

### 10.1 Vitamins

#### B<sub>1</sub> (thiamin) deficiency

##### Functions of thiamin

- ▶ Cofactor in different pathways of aerobic metabolism of glucose
  - decarboxylation of pyruvate to acetyl-coA (so bridge between glycolysis and Krebs)
  - decarboxylation of  $\alpha$ -ketoglutarate to succinate in Krebs

##### Features

- ▶ For its pivotal role in aerobic glucose meta, the largest blow is dealt to the tissues most dependent on glucose - the **brain** and the **heart**.
- ▶ **Beri-beri**
  - **Dry:** Neurological beri-beri
    - Peripheral neuropathy
    - Wrist/foot drop
    - **Korsakoff's psychosis**
    - **Wernicke's encephalopathy**
  - **Wet:** Cardiac beri-beri (wet as it causes generalised oedema)
    - Biventricular failure
    - Generalised oedema
    - Pulmonary oedema

##### Treatment

- ▶ Wet and Wernicke's should be treated by IV vit-B and C mixture
- ▶ Korsakoff's: irreversible, nonresponsive to thiamin

## **B<sub>12</sub> deficiency**

### **Functions of B<sub>12</sub>**

- ▶ Recycles folate → essential for **cell division** (especially in RBC)
- ▶ **Myelination**

### **Features**

- ▶ **Megaloblastic anaemia**
- ▶ **Glossitis**
- ▶ **Neurologic features**
  - Peripheral neuropathy
  - Autonomic neuropathy
  - Optic atrophy
  - Subacute combined degeneration of spinal cord

### **Treatment**

- ▶ Vit-B<sub>12</sub> IM
- ▶ If combined folate and B<sub>12</sub> deficiency, only folate should not be given without B<sub>12</sub>, as B<sub>12</sub> gets used up in folate recycling, deteriorating the B<sub>12</sub> deficiency symptoms. Always give both together.