MEDICINE

Susmit Islam

Medicine

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Contents

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.
- *Kumar and Clark's Clinical Medicine* 10th 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. Inform me whenever you find one.

Use at your own peril.

Susmit Islam

2022-07-30

Chapter 1

Respiratory medicine

1.1 Tuberculosis

Side effects of anti-TB drugs

- **Isoniazid:**
  - Hepatitis
  - Rash
  - B_6 deficiency $\rightarrow$ 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** → anteriorsuperior 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 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

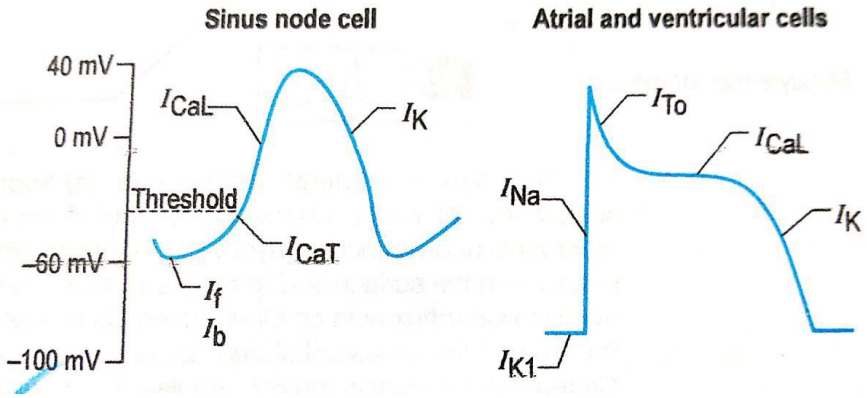


Figure 2.1: Cardiac action potentials. CaL: L-type (long-lasting) Ca^{2+} channel, CaT: T-type (transient) Ca^{2+} channel. I_{K1}: inward rectifier K^+ current, I_{Na}: inward Na^+ current, I_{To}: transient outward K^+ current, I_{CaL}: inward Ca^{2+} current, I_K: delayed rectifier (outward) K^+ current.

Effects of the autonomic nervous system on the heart

- **β_1-adrenergic stimulation $\rightarrow$ $\uparrow$force of contraction, heart rate** (+ve inotropic and chronotropic)
  - β_1 stimulation $\rightarrow$ $\oplus$ adenlylyl cyclase-cAMP system $\rightarrow$ $\oplus$ intracellular protein kinases $\rightarrow$ $\uparrow$phosphorylation of proteins including L-type Ca^{2+} channels $\rightarrow$ **enhanced Ca^{2+} influx** $\rightarrow$ $\uparrow$ FoC
  - Return of Ca^{2+} to sarcoplasmic reticulum from the myocyte is mediated by phospholamban, which enhances Ca^{2+} reuptake into the SR in its phosphorylated state. So β_1 stimulation also promotes 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 ($\uparrow Na^+$ and H_2O 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_2) splitting	↑	↓
Right sided murmurs	↑	↓
Left sided murmurs	↓	↑

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_2 splitting (i.e. delay between A_2 and P_2):
  - Inspiration → ↑ RV filling → ↑ prolonged ejection from RV → ↑ delayed P_2
  - Inspiration → ↓ LV filling → ↓ faster ejection from LV → ↓ faster A_2

2.2 Investigations of CVS disease

ECG

- Discussed in Sec. 2.4

Chest X-ray[1]

- Cardiomegaly: if cardiothoracic ratio (CTR) > 0.5
- Findings according to the chamber enlarged:
  - Left atrial enlargement:
    - Straight left heart border
    - Double cardiac shadow to the right of sternum
    - Widened carinal angle
  - Right atrial enlargement:

[1] A very nice intro to CXR interpretation from Axis Medical School

        - Projects from right heart border to right lower lung field
    - Left ventricular enlargement: may be due to dilation or hypertrophy
        - Cardiomegaly
        - Rounding of left heart border if hypertrophy
    - Right ventricular enlargement: dilation or hypertrophy
        - Cardiomegaly
        - Upwards displacement of apex
        - Straight left heart border

2.3 Presenting problems in CVS disease

Heart sounds[2]

Heart sounds

S_1

- Due to closure of atrioventricular valves (mitral and tricuspid)
- During *onset of ventricular systole*
- **Best heard at the *apex***
-

Splitting of S_2

- Normally splits as $S_2 = A_2 + P_2$, because the left ventricle contracts more forcefully and so the aortic valve closes earlier than the pulmonic valve (*"physiological splitting"*)
- During inspiration, the right heart receives more blood and the left heart receives less blood, and so A_2 happens even earlier and P_2 even later, leading to increased split.

Murmur[3]

Basics

- Points to assess: SCRIPT
    - Site: aortic, pulmonary, tricuspid or mitral area
    - Character: soft / blowing / decrescendo / crescendo-decrescendo
    - Radiation: MR $\rightarrow$ axilla, AS $\rightarrow$ neck (carotid)
    - Intensity / grading:
        - 1: very soft (audible in ideal conditions)
        - 2: soft
        - 3: moderate

[2]This video by Dirty medicine discusses heart sounds and murmurs together with detailed explanations. This playlist by Medzcool contains audio recordings of normal heart sounds and the most important abnormal heart sounds.

[3]Here's some awesome reviews by ZeroToFinals and DirtyMedicine on murmurs. This one by Strong Medicine covers the topic at a slightly deeper level with 5/6 exercises with actual recordings of murmurs.

        - 4: loud, with thrill
        - 5: very loud
        - 6: heard without stetho
    - Pitch: low (caused by low velocity blood flow) / high (high velocity blood flow)
    - Timing: systolic / diastolic

- Right heart murmurs → louder during inspiration (**RINspiration**)
- Left heart murmurs → louder during expiration (**LEXpiration**)

Features of benign murmur

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

Systolic murmurs

- **Ejection systolic murmurs**
    - Causes: **ventricular outflow obstruction**
        - AS (aortic stenosis)
        - PS (pulmonary stenosis)
    - Occur during **mid-systole** with **crescendo-decrescendo pattern** (i.e. gradual rise followed by gradual fall)
- **Pansystolic murmurs**
    - Causes: **leakage of blood into low pressure chamber** from a ventricle
        - MR (mitral regurgitation)
        - TR (tricuspid regurgitation)
        - VSD (ventricular septal defect)

Diastolic murmurs

- Low-pitched, often difficult to hear so should be examined with the bell
- **Mid-diastolic murmur**
    - Causes:
        - MS (mitral stenosis): at the mitral area and radiated to the axilla
        - TS (tricuspid stenosis): at the left sternal edge
- **Early diastolic murmur**
    - Soft, blowing, decrescendo pattern (gradual fall)
    - Causes:
        - AR (aortic regurgitation)
        - PR (pulmonary regurgitation)

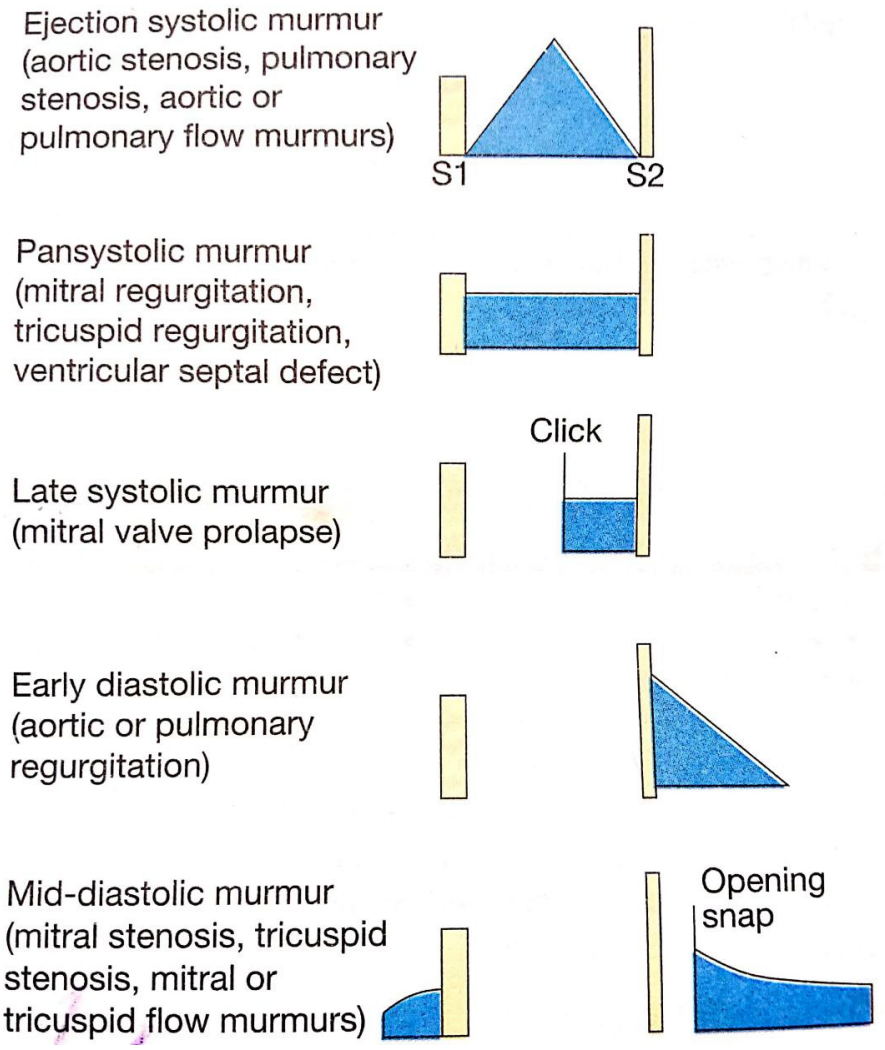


Figure 2.2: The timing and pattern of heart murmurs

- In case of "systolic regurgitations" i.e. MR/TR, due to the high flow throughout systole, the murmur is pansystolic. In case of "diastolic regurgitations", the blood has already mostly flown out of the aorta or the pumonary trunk, leaving little blood for backflow. So in this case, it's early diastolic.

Continuous murmurs

- Cause: **PDA (persistent ductus arteriosus)**

2.4 ECG

Anatomy of an ECG

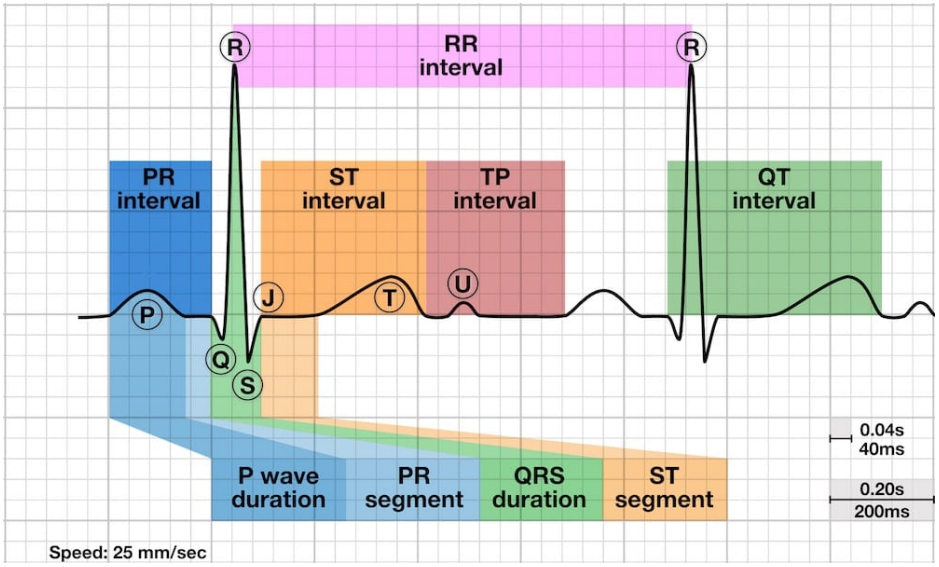


Figure 2.3: Parts of a normal ECG

Abnormalities of components

Pathological Q

- Depth > 2mm
- Height > 1mm
- Present in $\geq$ 2 leads
- 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 $\rightarrow$ start of T
- PR interval = start of P $\rightarrow$ 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 subsection 2.1

Location	Leads	Coronary artery
Anterior	V_2-V_4	LAD
Lateral	V_5-V_6	LCX > LAD
Inferior	II, III, aVF	RCA $\gg$ LCX
Posterior	V_1, V_2 (depression)	RCA $\gg$ LCX

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

Reciprocal changes

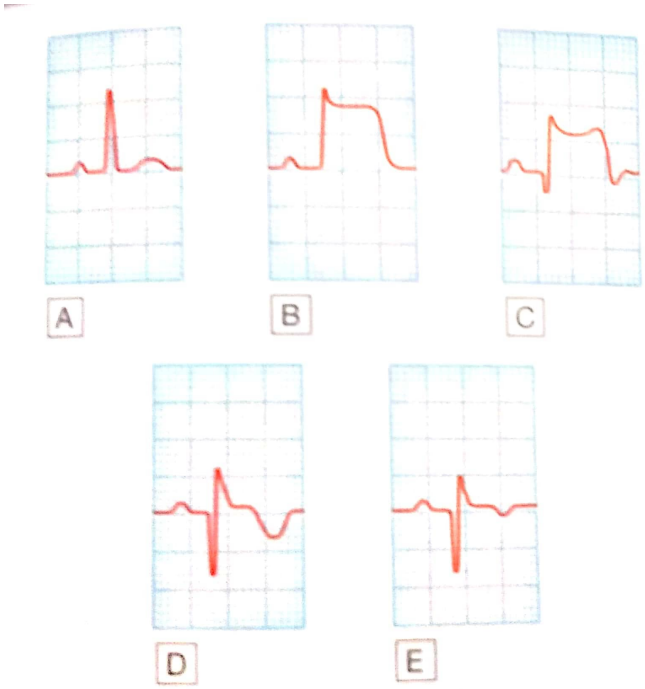
- Acute STEMI in some surface of the heart $\rightarrow$ ST elevation in corresponding leads, and ST depression in reciprocal leads

Site	Facing	Reciprocal
Septal	V_1, V_2	V_7-V_9
Anterior	V_3, V_4	None
Lateral	I, aVL, V_5, V_6	II, III, aVF
Inferior	II, III, aVF	I, aVF
Posterior	V_7-V_9	V_1, V_2

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

2.5 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

2.6 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
  - β-blocker
- If haemodynamic state compromised, DC cardioversion
- Recurrent SVT $\rightarrow$ catheter ablation

2.7 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 $\rightarrow$ IV flecainide
    - Structural / ischaemic heart disease $\rightarrow$ IV amiodarone
  - DC cardioversion if drugs fail
- **Rate control**
  - β-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

2.8 Myocardial Infarction

Management

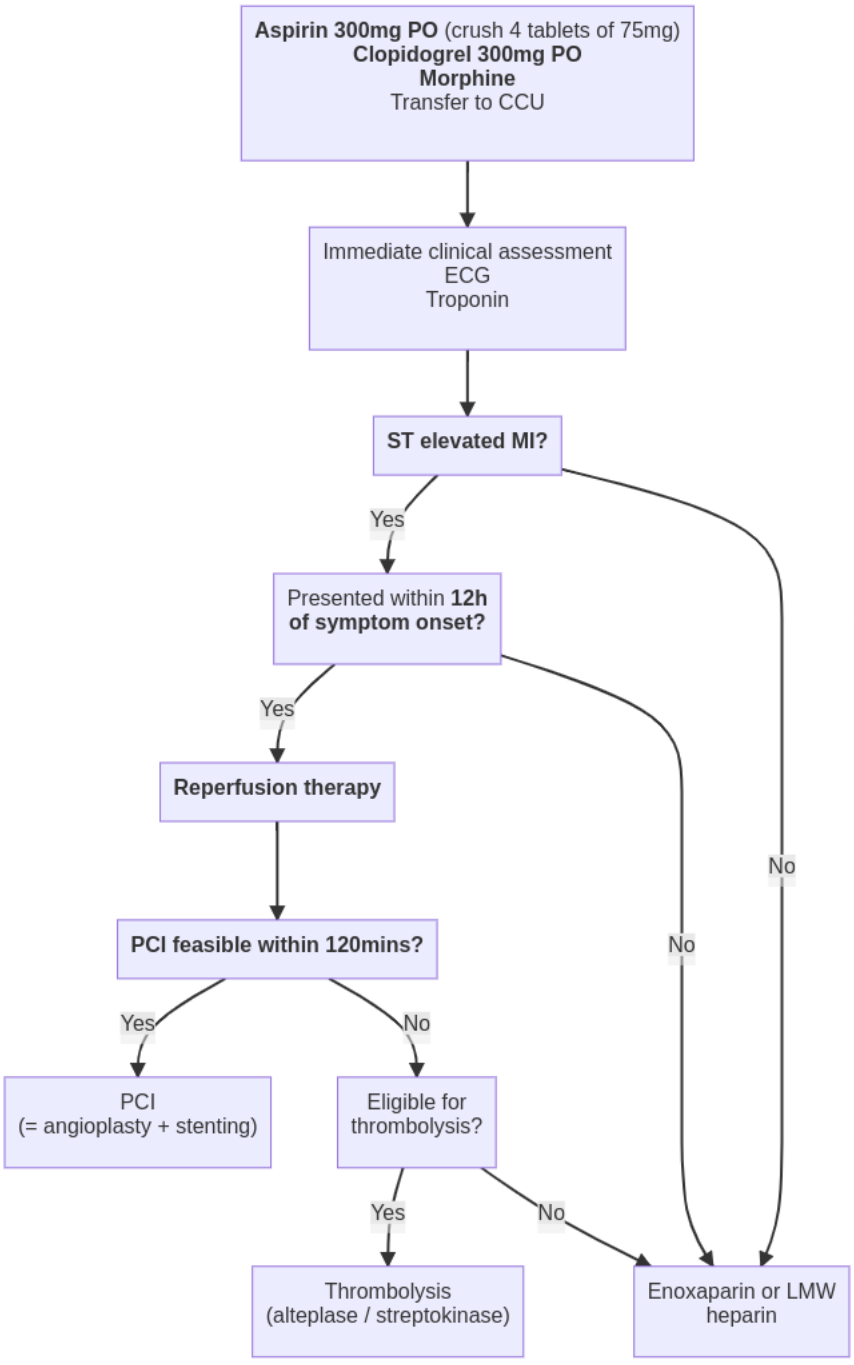


Figure 2.4: Management of acute MI

2.9 Heart failure

Pathophysiology

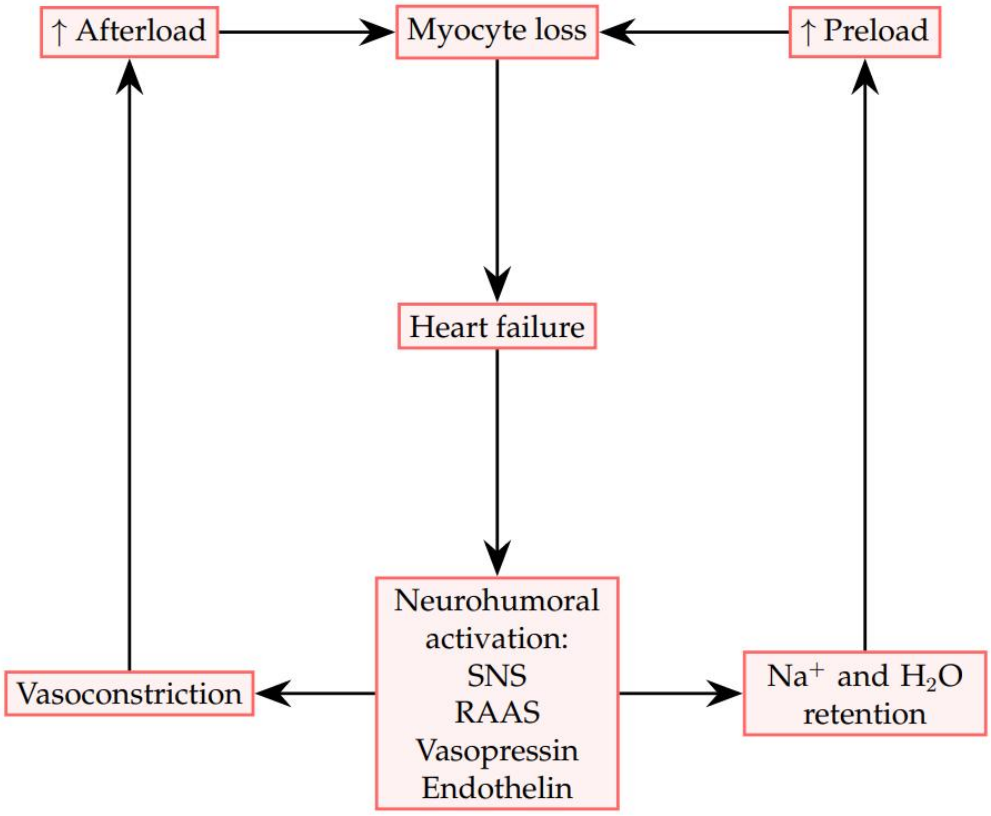


Figure 2.5: Neurohumoral activation and compensatory mechanisms in HF

- Hazards of prolonged sympathetic stimulation
  - Cardiomyocyte apoptosis
  - Hypertrophy
  - Focal myocardial necrosis
  - Predispose to arrhythmias

Features

Acute LVF

- Sudden onset **dyspnoea** at rest
  - Progresses rapidly to respiratory distress, orthopnoea
- **Cool peripheries**
- **Rapid pulse**

- ↑ **BP** (due to SNS activation)
  - May be low or normal if goes into cardiogenic shock
- ↑ JVP esp. if associated with fluid overload / RVF
- **Gallop rhythm** (tachycardia + 3 heart sounds (addition of S_3))
- **Bilateral basal crepitations** if pulmonary oedema

Chapter 3

Dermatology

3.1 Anatomy and physiology

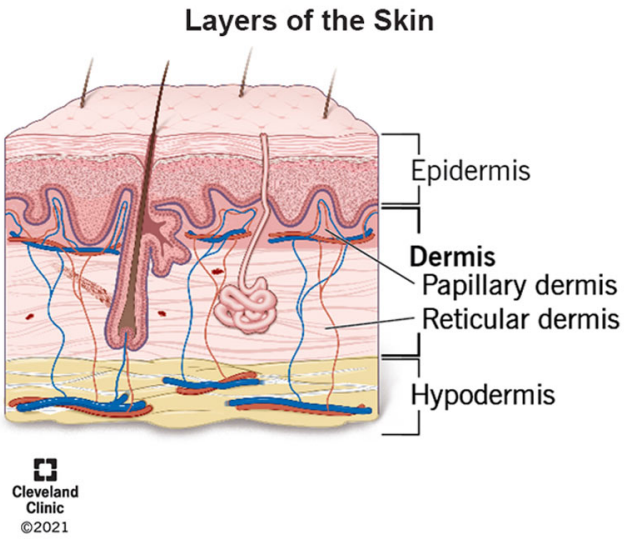


Figure 3.1: Layers of the skin

- **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 $\rightarrow \uparrow$ sebum
  - oestrogen $\rightarrow \downarrow$ sebum
- Sweat glands
  - innerved 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) $\rightarrow$ prevent water loss from skin by oil layer
    - less preservatives $\rightarrow$ less risk of allergy

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

Phototherapy

- **UVB**
- **Psoralen UVA**
  - Psoralen:
    - natural photosensitiser from plant source
    - cross-link DNA strands on excitation with UVA
  - Cumulative exposure to PUVA $\rightarrow$ $\uparrow$ 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-α 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_2
  - 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 *Sarcoptis 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, immunosuppresion 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

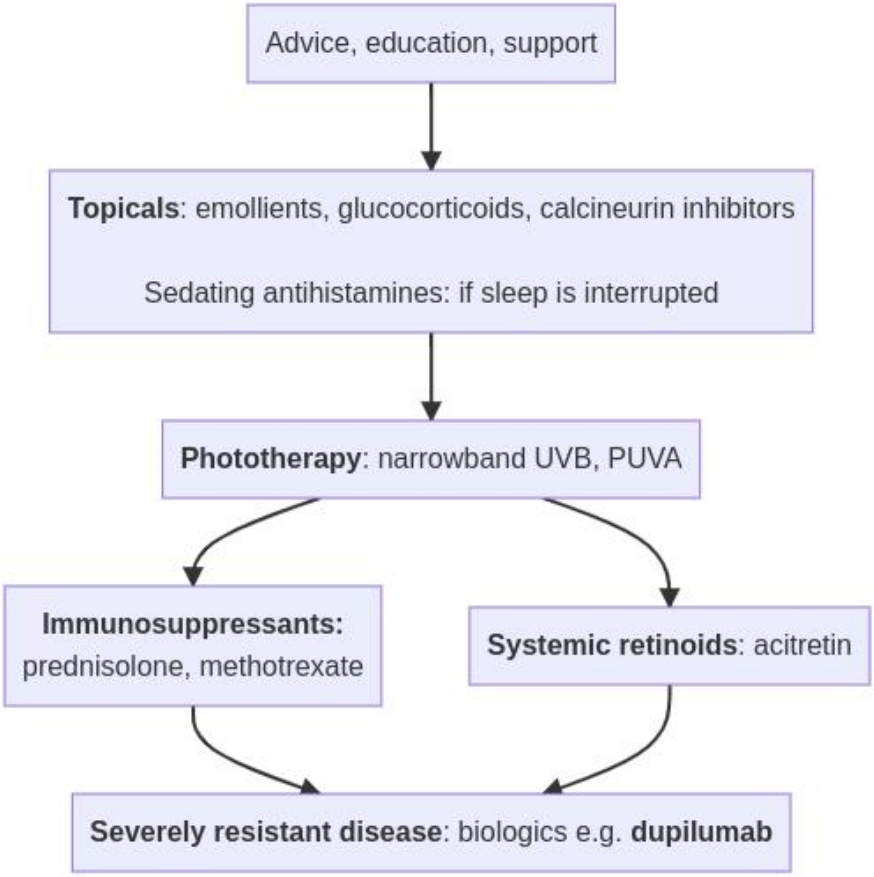


Figure 3.2: Management of eczema

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**
  - β-haemolytic strep ↑ guttate psoriasis
  - HIV may initally present with severe psoriasis
- **Drugs**
  - Antimalarials
  - β-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) → **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** sporiasis: generalised → medical emergency
- **Pustular** psoriasis

Management

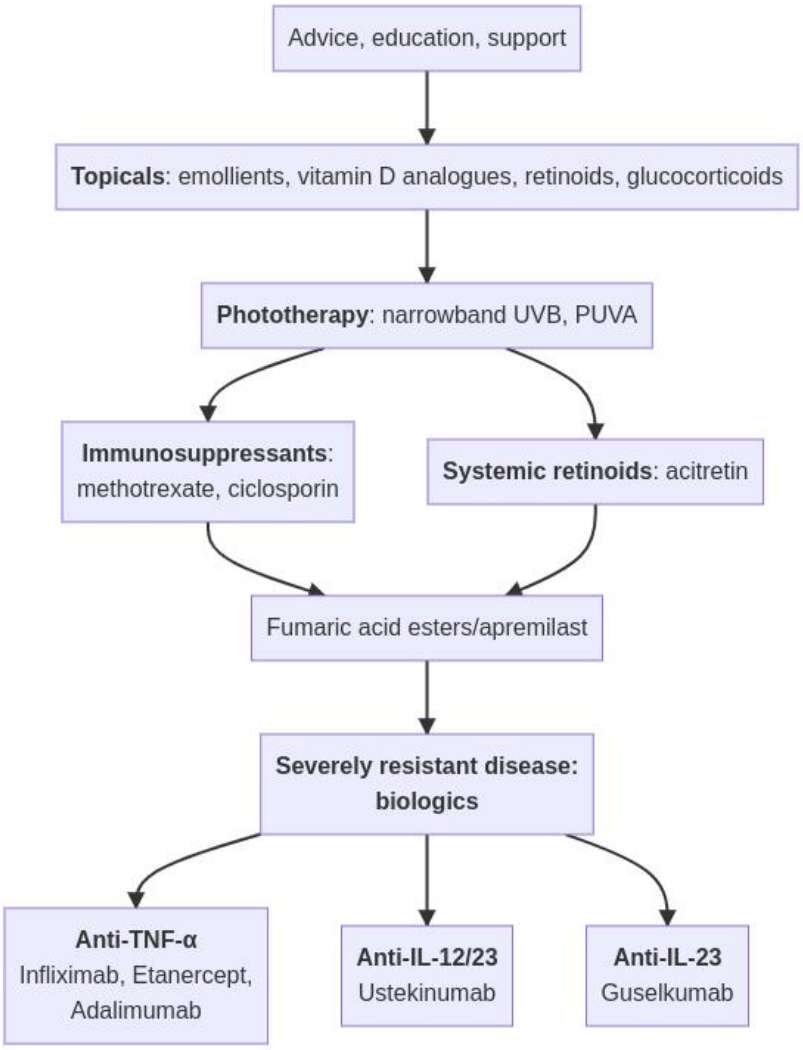


Figure 3.3: Management of psoriasis

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

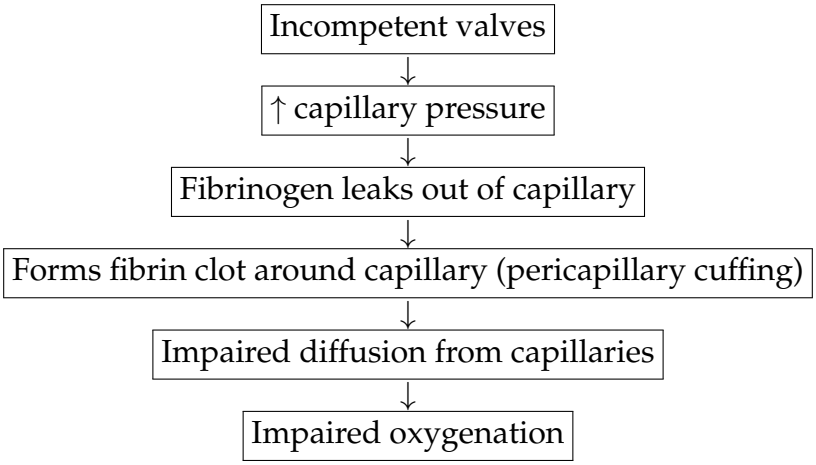
- **Endocrine**
  - Melasma/chloasma:
    - in pregnancy / some OCP users
    - discrete patches of facial pigmentation
  - Addison's disease
  - Cushing's syndrome
  - Nelson's syndrome
    - hyper-ACTH 2° to bilateral adrenalectomy for Cushing's
    - due to loss of -ve feedback from plasma cortisol
  - 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 ($\approx$ 70nm)
      - 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

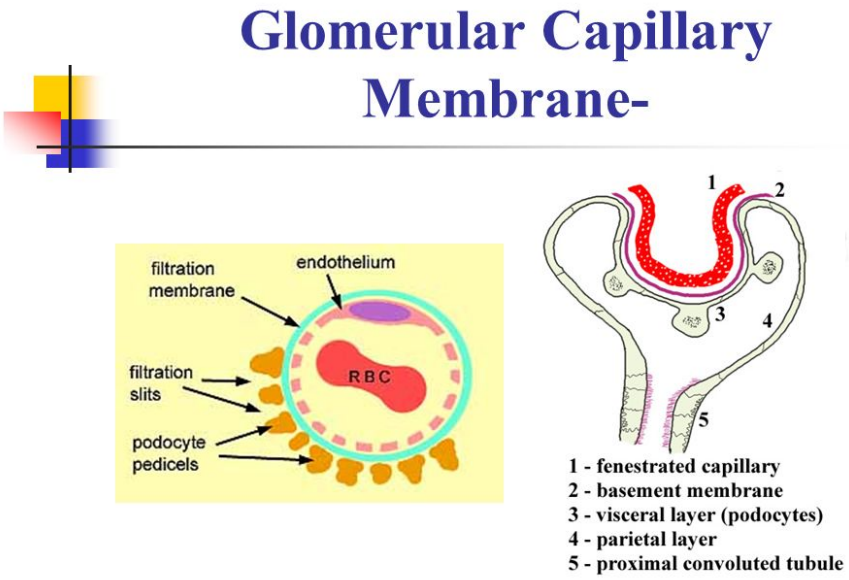


Figure 4.1: Microstructure of the glomerulus

4.2 Presenting problems in urinary disease

- **Oliguria:** < 400mL/day
- **Anuria:** < 100mL/day
- **Haematuria:**
  - Healthy indiviuals 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 [1]

Features

- Massive **proteinuria** (> 3.5 g/day (medicine) or 1 g/m^2/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

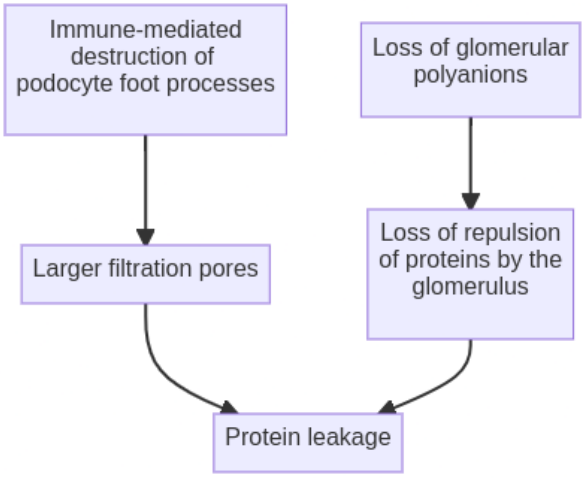
- Histological types include
  - **Minimal change disease:**
    - no pathology visible with light microscope, visible pathology only under electron microscope.
    - most common type in **children** (2-8y)
  - **Membranous nephropathy:** most common type in **adults**

Aetiopathogenesis

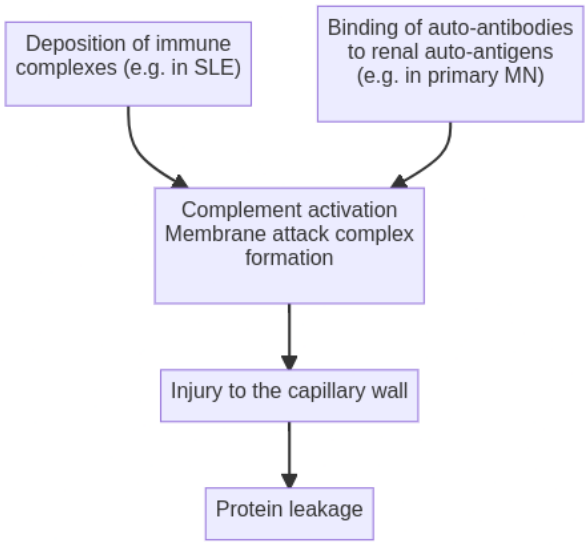
Minimal change disease

- **Effacement of podocyte foot processes**

[1] 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



(a) Minimal change disease



(b) Membranous nephropathy

Figure 4.2: Pathogenesis of nephrotic syndrome

Membranous nephropathy

- **Autoantibodies to podocyte surface antigens** (e.g. M-type phospholipase A_2 receptor 1)$\rightarrow$ **MAC-mediated glomerular capillary injury**
  - Antibodies to phospholipase A_2 (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: > $1g/m^2/day$
  - PCR (Protein-Creatinine ratio) > 2
  - Serum albumin < 25 g/L
  - Serum cholesterol > 220 mg/dL

- Renal biopsy: if nonresponsive to corticosteroid therapy

Treatment

Minimal Change Nephropathy

- **Specific:**[2]
  - **High dose glucocorticoid for 6wks**
  - Prednisolone 1 mg/kg/day
  - KDIGO guidelines: (4wks daily + 4wks alternate day) or (6wks daily + 6wks alternate day)
  - Incomplete response to steroid: Cyclophosphamide (1.5-2 mg/kg/day) or Ciclosporin (3-5 mg/kg/day) for 8-12wks with prednisolone 7.5-15 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) + ↑ liver production of procoagulants
    - consider LMW heparin / warfarin if severe NS

Membranous Nephropathy

- **Specific:**[3]
  - **High-dose glucocorticoids + cyclophosphamide** (Ponticelli regimen)
    - Reserved for severe cases for risk of toxicity of this regimen

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

[3] 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 β-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**
  - $\downarrow$ **Renal function** $\implies$
    - 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)
  - $\geq$ 60y: $\geq$ 4 cysts in each kidney (total: ge 8)

Management

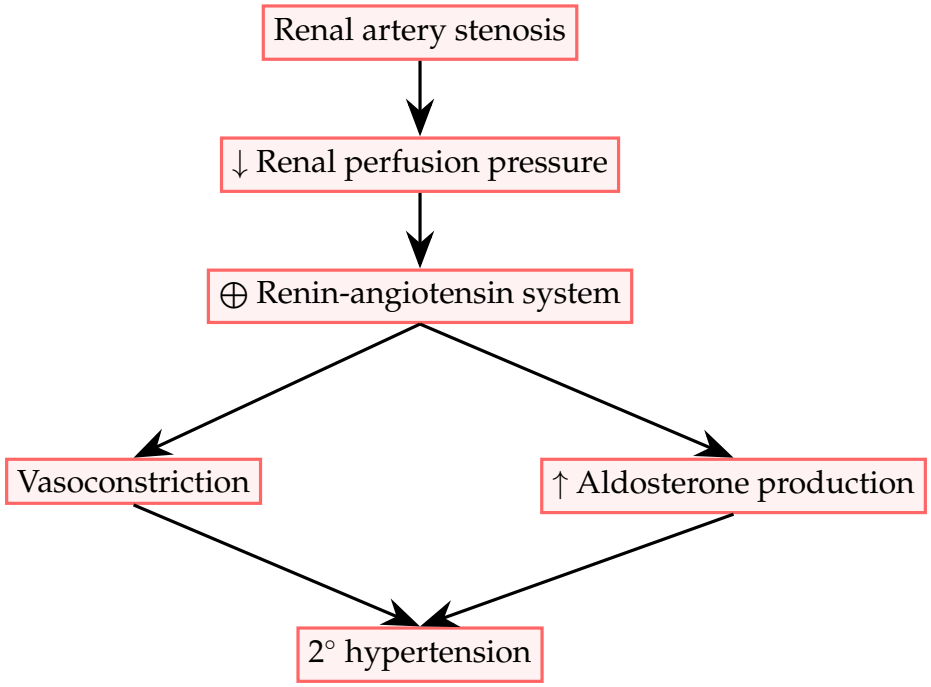
- **BP control:** 1st choice ACEi / ARBs
- **Tolvaptan:** Vasopressin V2 receptor antagonist
  - Reduce cyst growth
  - Slow rate of GFR decline
- **Octreotide:** Long acting somatostatin (aka growth hormone inhibiting hormone) analog
  - Reduces rate of growth of liver and renal cysts
- **Large cyst: 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:
  - $\leq$ 40y 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**
  - $\uparrow$ **unconjugated bilirubin, serum LDH**
  - $\downarrow$ **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 thrombocytopoenic purpura

- Thrombotic microangiopathy predominantly involving cerebral microcirculation
- MAHA + thrombocytopoenia
- 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 $\rightarrow$ $\uparrow$ vWF $\rightarrow$ 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[4]: presence of any of the following
  - $\Delta SCr \geq$ *+0.3 mg/dL over 48h*
  - $\Delta SCr \geq$ *+0.5x baseline* (or SCr $\geq$ 1.5x baseline) *over 7d*
  - *Urine volume* $\leq$ *0.5 mL/kg/h for* $\geq$ *6h*

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

[4] 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 $\rightarrow$ $\downarrow$ prostaglandins $\rightarrow$ $\downarrow$ afferent arteriolar vasodilation $\rightarrow$ $\downarrow$ 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)[5]

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)[6]
- 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^2 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)

[5] Here's an awesome video by Ninja Nerd that discusses CKD in detail with its pathophys, features, dx, and rx.

[6] https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

- Most cases asymptomatic until GFR $\geq$ 30 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, PO_4^{3-}, PTH, vit-D
- Lipid profile

Management

Monitoring renal function

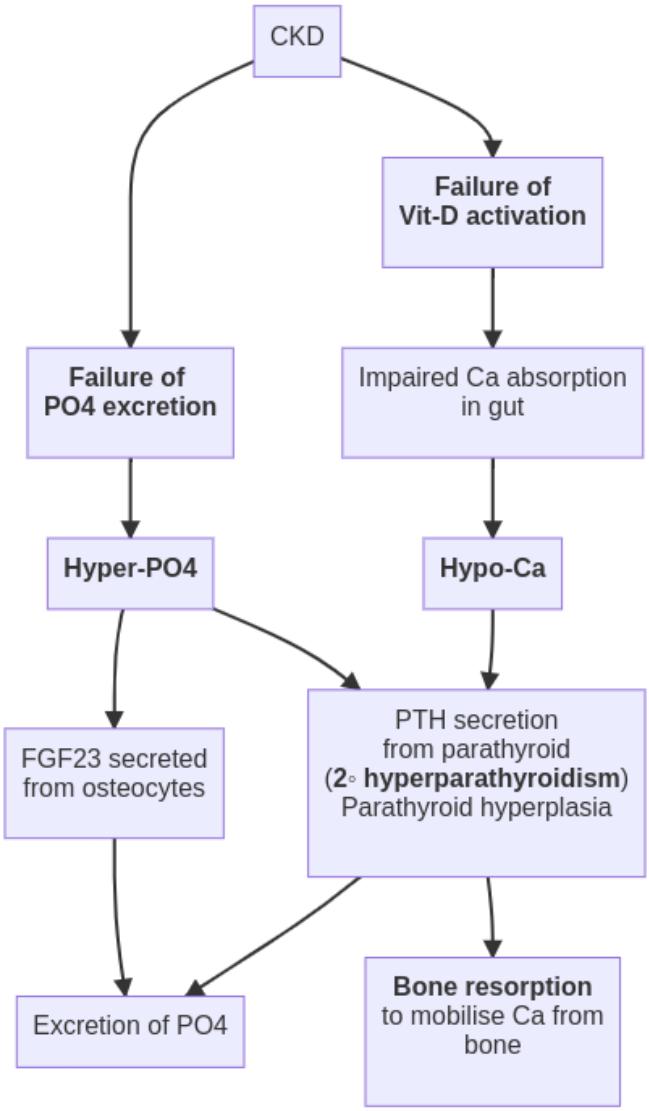
- GFR at least every 6 months for stage ≥ 3
- Plot GFR against time

Reducing rate of progression

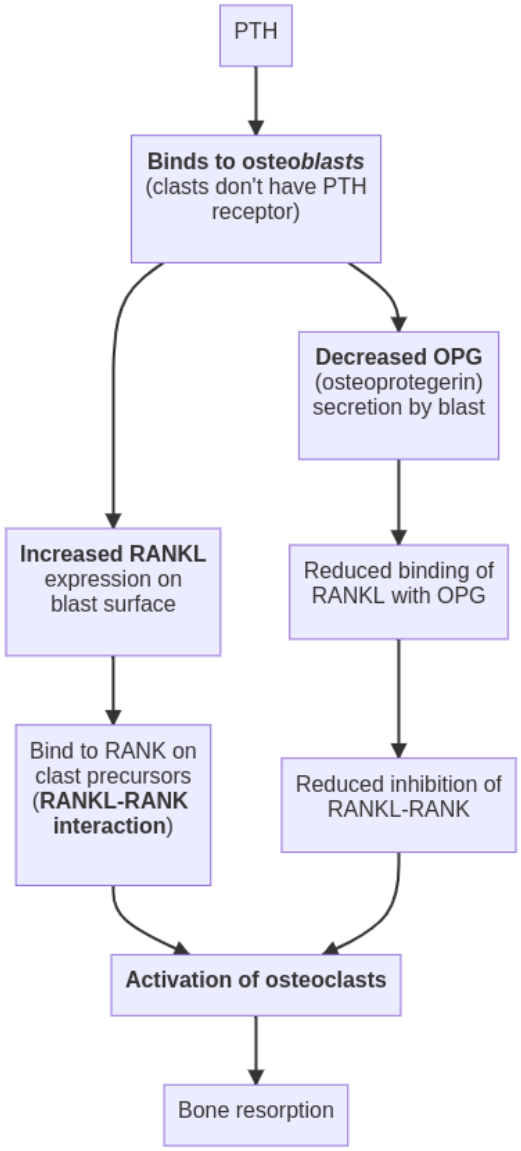
- **Antihypertensive** therapy: Slows rate of decline irrespective of the medication
- **Glycaemic control:** if DM present
- **Proteinuria reduction:**
  - Protein
  - $\downarrow$ Proteinuria $\rightarrow$ risk of progression
    - As protein in the tubules trigger inflammatory damage
  - **ACEi / 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 $K^+ > 5.5$ 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)
  - $NaHCO_3^-$ supplements
- **Renal osteodystrophy**
  - Primary factors: ↓ **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. $CaCO_3$, $Al(OH)_3$
  - 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 $\rightarrow$ Neutrophils in urine $\rightarrow$ 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 $\geq$ 2L/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 $\leq$ 4cm
- 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 $\rightarrow$ long, needle shaped, -ve birefringence
  - Ca pyrophosphate crystals $\rightarrow$ small, rhomboid, +ve birefringence

Bone scintigraphy

- Dx of metastatic bone disease and Paget's
- ^{99}Tc radiolabelled bisphosphonate used

DEXA (Dual Emission X-ray Absorptiometry)

- Measure BMD (bone mineral density)
  - < -2.5 $\rightarrow$ osteoporosis
  - Between -2.5 and -1 $\rightarrow$ osteopoenia
  - > 2.5 $\rightarrow$ 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 peptidylarginine 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 $\rightarrow \downarrow$ 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 oligoarthrites 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. meningoencephilitis
- **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

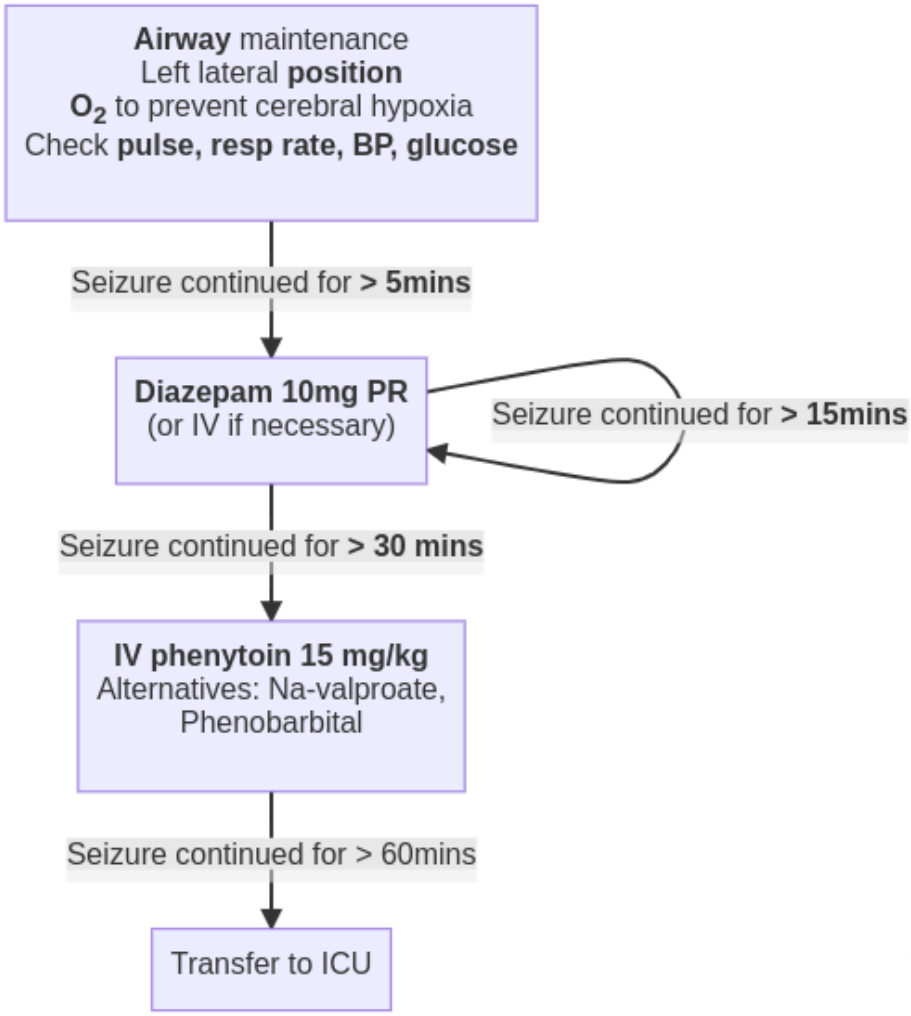


Figure 6.1: Management algorithm for status epilepticus

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

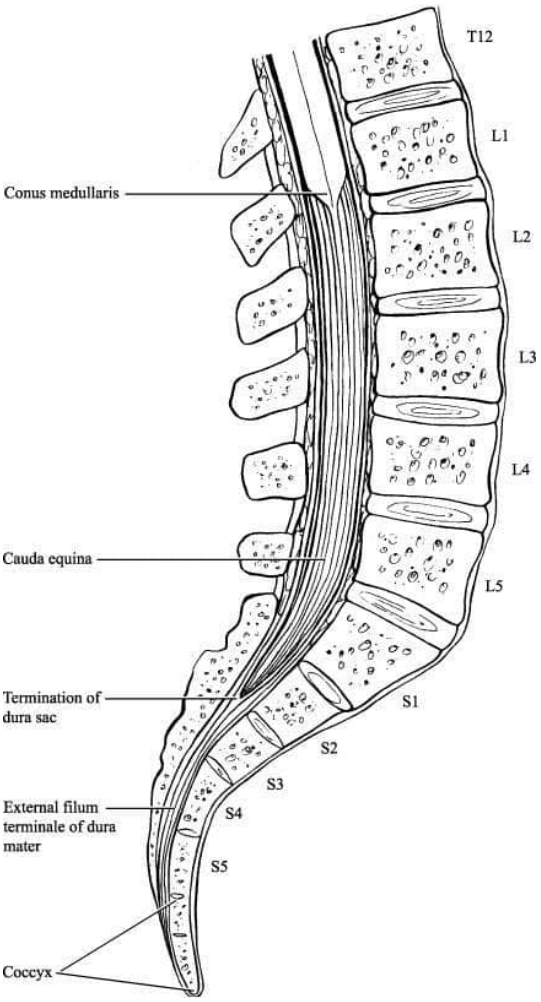
6.6 Subacute combined degeneration

Features

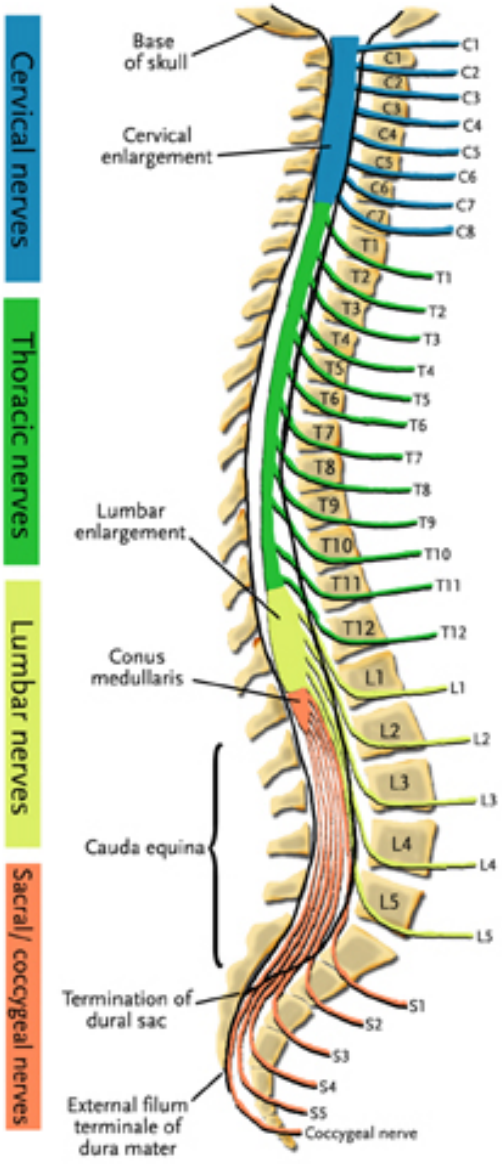
- **Peripheral neuropathy**: due to **demyelination**
- Signs of **dorsal column lesion**: **position and vibration sense lost**
- Signs of **pyramidal lesion**:
    - **plantar extensor**
    - **knee jerk brisk**
    - **ankle jerk absent**: as peripheral neuropathy affects longer nerves first, the 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 (If the epiconus is involved, patellar reflex may be absent, whereas bulbocavernosus reflex may be spared.)

Reflexes	Areflexic lower extremities; bulbocavernosus reflex is absent in low CE (sacral) lesions	Areflexic lower extremities (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; 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

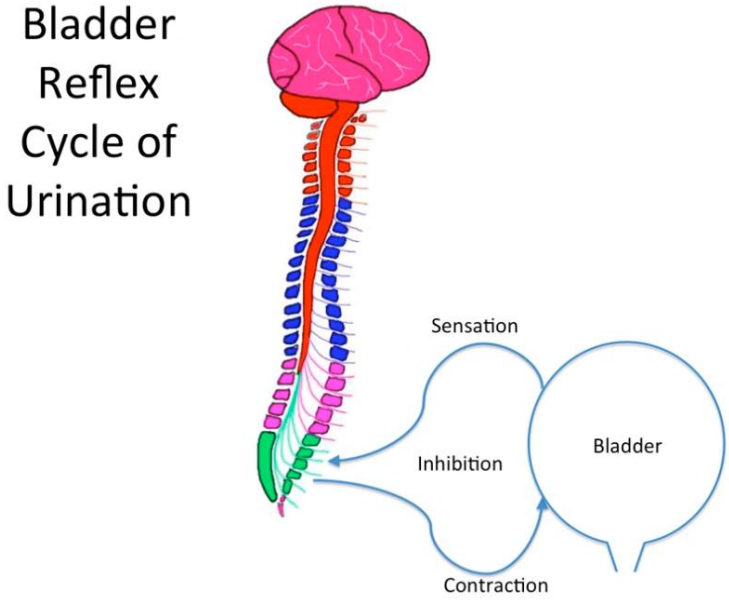
"Components"

- **Detrusor muscle**
  - Muscles of the bladder wall
  - Innervated by
    - **Parasympathetic:**
      - cholinergic M_3 receptors
      - pelvic nerve from **S2-4**
      - causes **contraction** $\rightarrow$ **urination**
    - **Sympathetic:**
      - β_3 receptors
      - hypogastric nerve from **T10-L2**
      - causes **relaxation** $\rightarrow$ **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

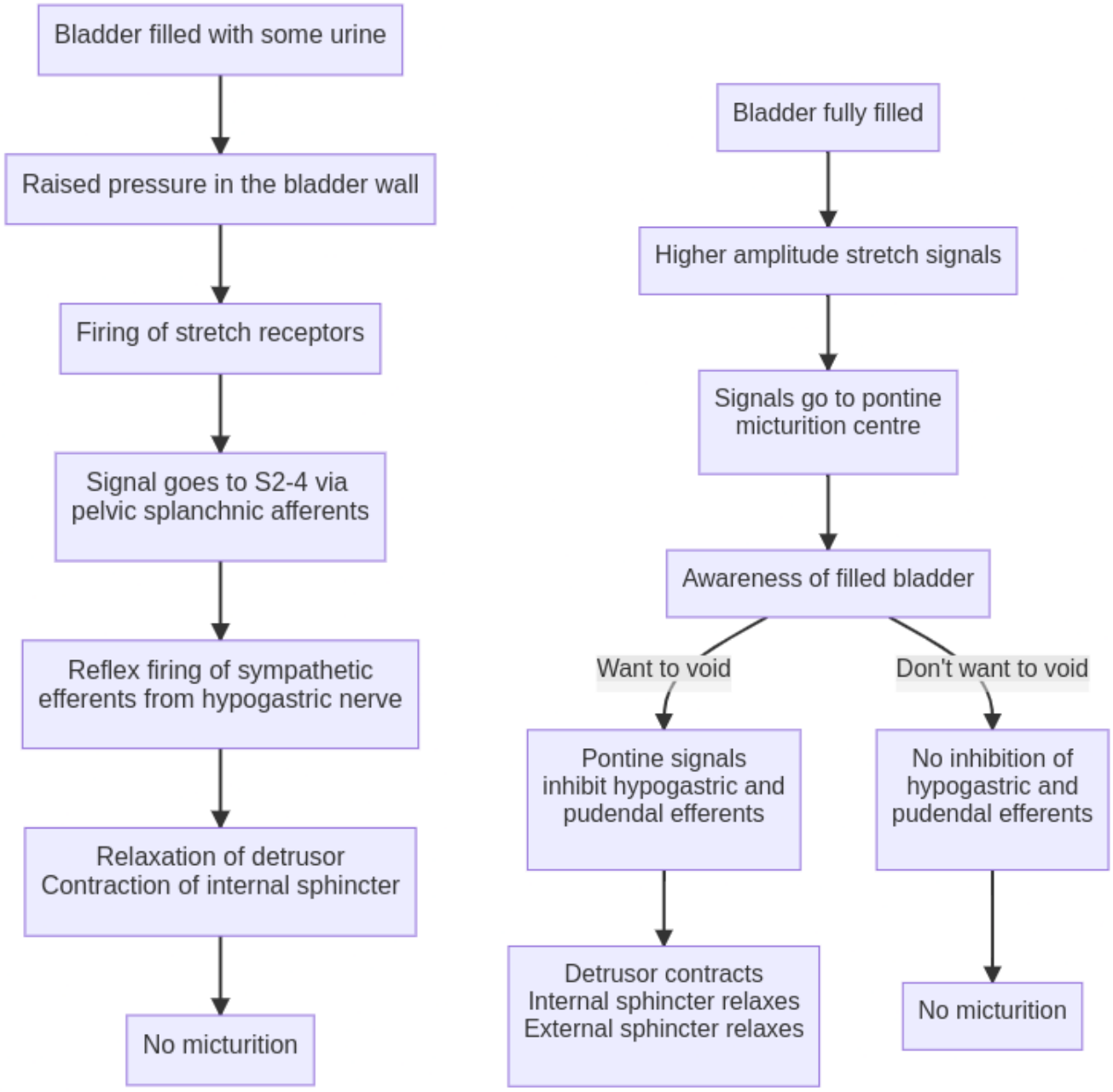
The big picture (highest yield for clinical interpretation)



Lesion in S → Stores (retention)
Lesion in L and above → Leaks (incontinence)

- 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



(a) Partly filled bladder

(b) Fully filled bladder

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_2 blocker → undo D_2 mediated inhibition of cholinergic stimulation in GIT → ↑GI motility → antiemesis)
      - Domperidone, which is also a D_2 blocker, selectively acts on D_2s 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 α-synuclein (hence the alternative name α-synucleinopathy)
  - Other α-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
  - **Glabellar 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** $\pm$ **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 $\rightarrow \downarrow$ 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, benztropine, 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 $\rightarrow$ MAO-Bi potentiates the action of levodopa by inhibiting breakdown

- **COMT inhibitors**
    - Tolcapone, entacapone
    - COMT $\rightarrow$ 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 $\rightarrow$ reduce tremor

Chapter 7

Diabetes Mellitus

7.1 Mechanism of insulin secretion

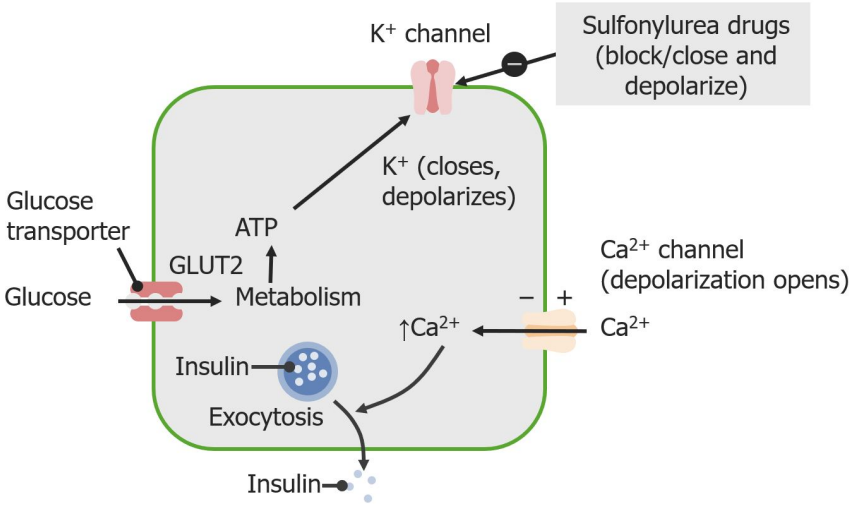


Figure 7.1: Mechanism of insulin secretion

7.2 Incretin effect

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

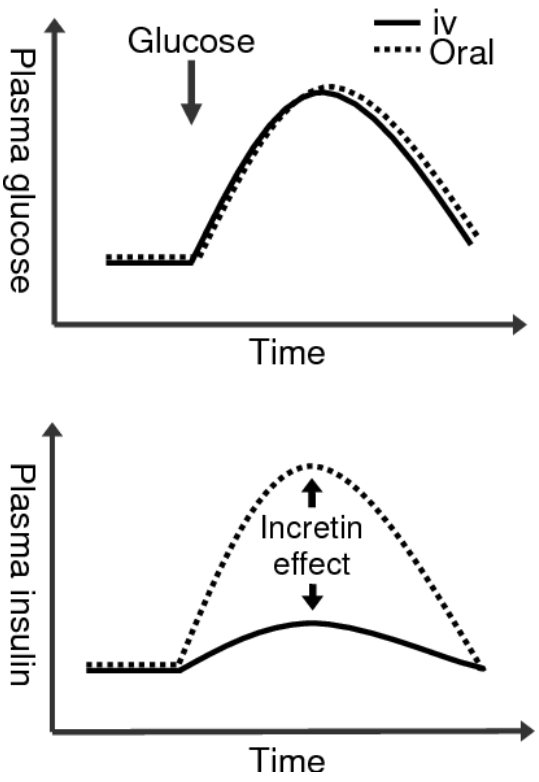


Figure 7.2: The incretin effect

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_2 sat, urine output
- Every 2h: Venous HCO_3^- and K^+
- Every 4h: Serum electrolytes

- If K^+ is low, 40mmol/L KCl with normal saline

7.5 Hypoglycaemia

Features

- **Autonomic**
  - Sweating
  - Trembling
  - Palpitations
- **Neuroglycopoenic**
  - 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 $\rightarrow$ glucagon 1mg IM

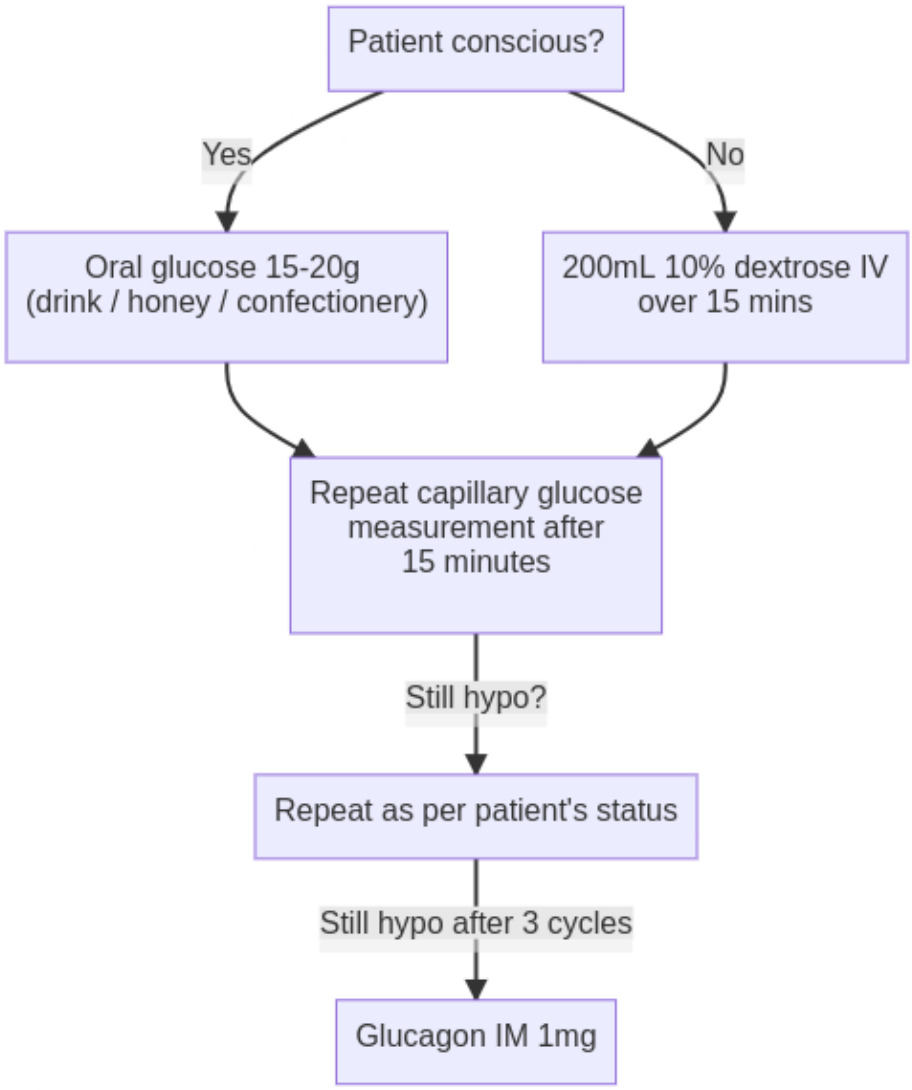


Figure 7.3: Managing hypoglycaemia

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**
    - $\downarrow$ hepatic glucose production (gluconeogenesis and glycogenolysis)
    - $\uparrow$ gut glucose uptake & utilisation
    - weak inhibitor of mitochondrial respiration $\rightarrow$ $\uparrow$ AMP, $\downarrow$ ATP $\rightarrow$ $\uparrow$ 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 β-cells $\rightarrow$ $\uparrow$ insulin secretion
  - **Side effects profile**
    - Wt gain
    - Hypoglycaemia
- **α-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 $\rightarrow$ inhibit incretin effect
  - **GLP-1 receptor agonists:** Exenatide, liraglutide
- **Thiazolidinediones:** Pioglitazone

- **Mechanism of action**
  - PPAR-γ 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-β** (details: fig. 7.4)
- Excess activation of **protein kinase C (PKC)**
  - Mechanism: ↑intracellular glucose → ↑DAG synthesis (diacyl glycerol) → ↑ ⊕PKC → ↑VEGF, TGF-β, PAI-1 (plasminogen activator inhibitor-1) production by the vascular endothelium
- **Oxidative stress** and **sorbitol accumulation**
  - Mechanism: ↑intracellular glucose → ↑metabolism to sorbitol (by aldose reductase) → fructose using *NADPH* → NADPH used up → ↓availability for use in antioxidant pathway → ↑ROS-mediated damage
  - Accumulation of sorbitol in the lens → cataract

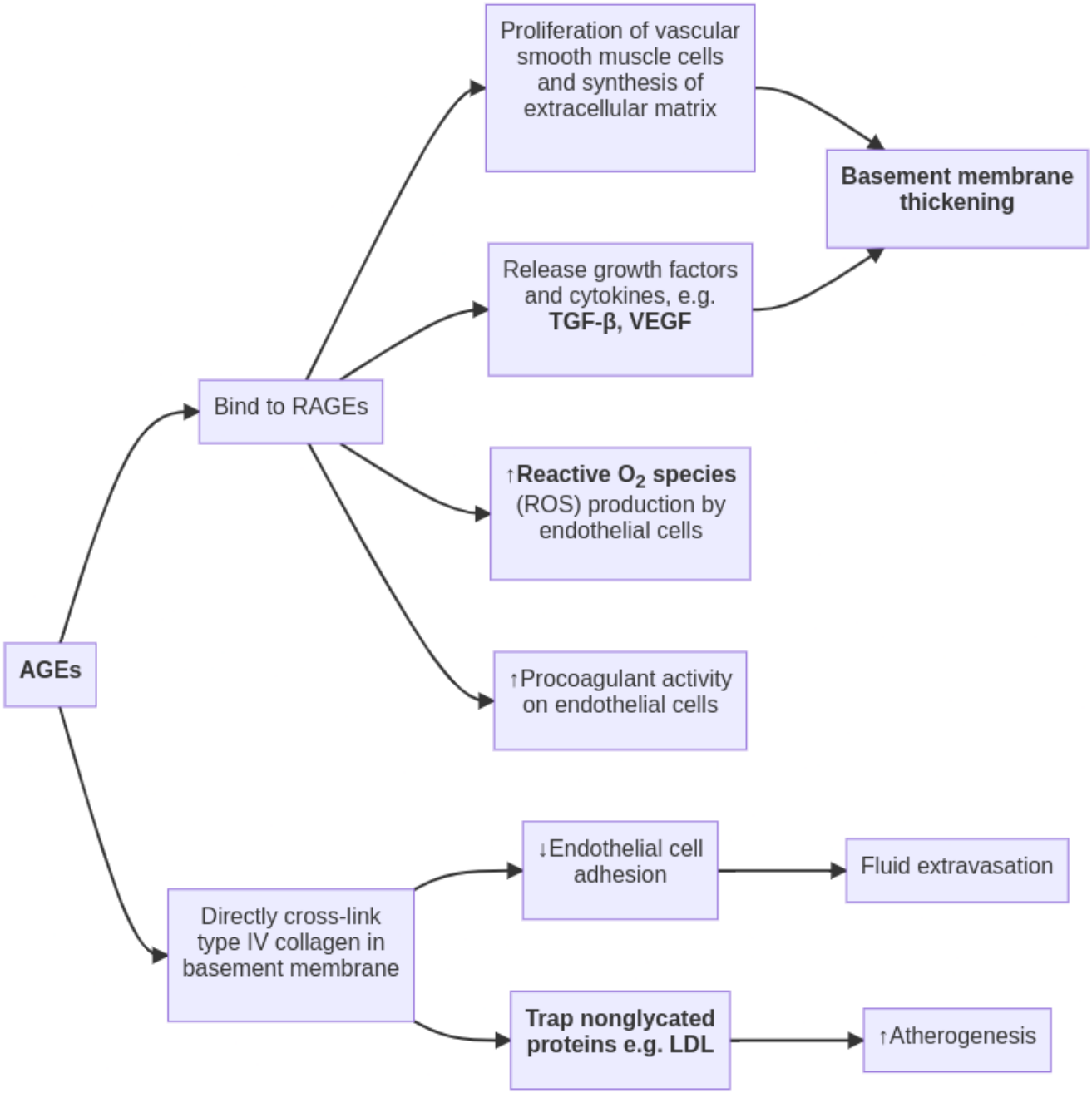


Figure 7.4: Mechanisms of AGE-induced microvascular pathology

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

- ↓ erythrpoiesis
- ↑ 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_1 (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 α-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_{12} deficiency

Functions of B_{12}

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

Features

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

Treatment

- Vit-B_{12} IM
- If combined folate and B_{12} deficiency, only folate should not be given without B_{12}, as B_{12} gets used up in folate recycling, deteriorating the B_{12} deficiency symptoms. Always give both together.