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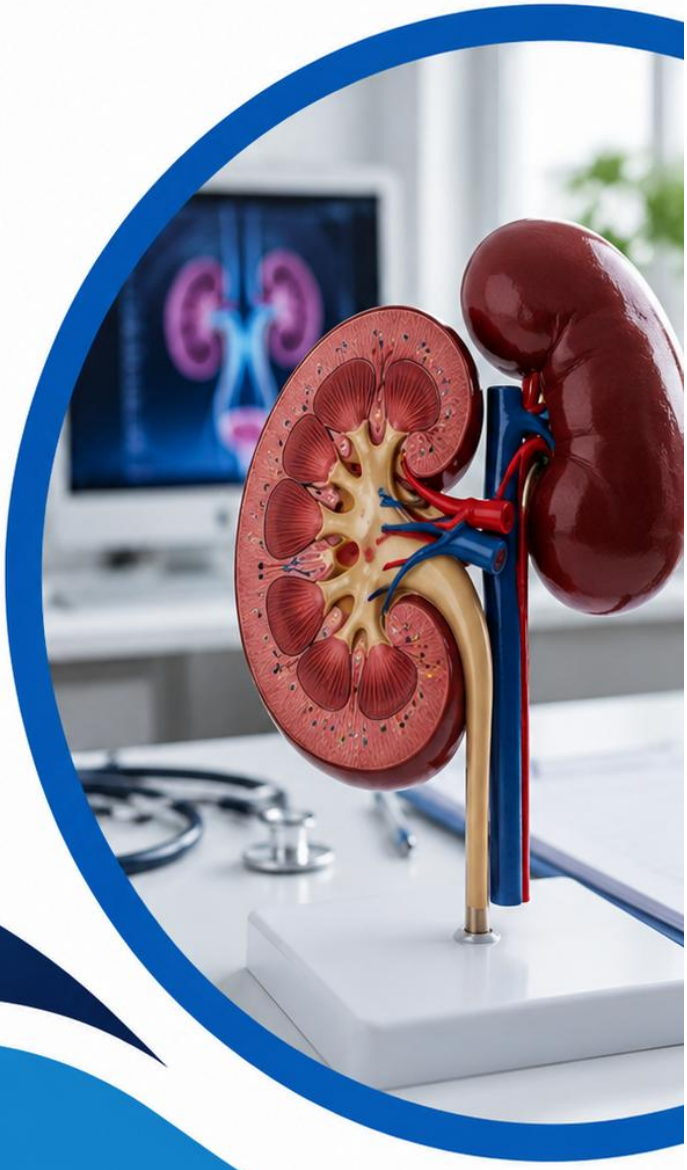
MED 407

NEPHROLOGY I



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Course code: MED 407

Course title: Nephrology I

Course credit load: 2 Units

Series 1: Fundamentals of Nephrology and Clinical Skills

- **Part 1.1: Overview of Renal Anatomy and Physiology**
    - Sub Part 1.1.1: Gross anatomy and microstructure of the kidney
    - Sub Part 1.1.2: Glomerular filtration and tubular function
    - Sub Part 1.1.3: Renal regulation of fluid, electrolyte, and acid-base balance
- **Part 1.2: Assessment of Renal Function**
    - Sub Part 1.2.1: Glomerular filtration rate and its estimation
    - Sub Part 1.2.2: Urinalysis and urine microscopy in renal disease
    - Sub Part 1.2.3: Blood tests and imaging in renal evaluation
- **Part 1.3: The Clinical Approach to the Patient with Renal Disease**
    - Sub Part 1.3.1: Renal history taking
    - Sub Part 1.3.2: Physical examination in renal disease
    - Sub Part 1.3.3: Clinical syndromes in nephrology
- **Part 1.4: Acute Kidney Injury and Chronic Kidney Disease — An Introduction**
    - Sub Part 1.4.1: Definition and classification of acute kidney injury

- Sub Part 1.4.2: Definition and staging of chronic kidney disease
- Sub Part 1.4.3: Overview of the clinical consequences of kidney disease

Introduction

The kidneys perform functions of fundamental importance to homeostasis: filtering the blood to remove metabolic waste products, regulating the volume and composition of body fluids, maintaining acid-base balance, and producing hormones including erythropoietin and activated vitamin D. Renal disease is prevalent in Nigeria and sub-Saharan Africa, where conditions such as hypertension, diabetes mellitus, glomerulonephritis, and infections contribute to a high burden of both acute and chronic kidney disease.

This Series provides the foundational knowledge required for all subsequent study of nephrology. It covers the anatomy and physiology of the kidney, the assessment of renal function through laboratory and imaging investigations, the clinical approach to history taking and examination in a patient with suspected renal disease, and the clinical syndromes that define the major presentations of kidney disease. It concludes with an introduction to acute kidney injury and chronic kidney disease as the two overarching clinical frameworks within which most renal disease is managed.

A solid understanding of these fundamentals is the prerequisite for recognising, investigating, and managing the specific renal conditions covered in subsequent Series of this course.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 1.1** describe the gross anatomy, microstructure, and major physiological functions of the kidney (Linked to Part 1.1),

- **SLO 1.2** explain glomerular filtration and the tubular mechanisms regulating fluid, electrolyte, and acid-base balance (Linked to Part 1.1),
- **SLO 1.3** describe the investigations used to assess renal function including GFR estimation, urinalysis, urine microscopy, blood tests, and imaging (Linked to Part 1.2),
- **SLO 1.4** conduct a focused clinical assessment of a patient with suspected renal disease and identify the major clinical syndromes of nephrology (Linked to Part 1.3), and
- **SLO 1.5** define acute kidney injury and chronic kidney disease, state their classification systems, and describe the clinical consequences of kidney disease (Linked to Part 1.4).

1.1 Overview of Renal Anatomy and Physiology

1.1.1 Gross anatomy and microstructure of the kidney

The kidneys are paired retroperitoneal organs, each weighing approximately 150 g and measuring 11 to 12 cm in length. Each kidney is composed of an outer **cortex** (containing the glomeruli, proximal and distal tubules) and an inner **medulla** (containing the loops of Henle and collecting ducts). The medulla is organised into **renal pyramids** whose apices (papillae) drain urine into the minor calyces, major calyces, renal pelvis, and ureter.

The functional unit of the kidney is the **nephron**, of which there are approximately one million per kidney. Each nephron consists of a **glomerulus** (a tuft of capillaries enclosed in Bowman's capsule, responsible for ultrafiltration), a **proximal convoluted tubule**, the **loop of Henle** (descending and ascending limbs; generates the medullary osmotic gradient), a **distal convoluted tubule**, and a **collecting duct**. The glomerular filtration barrier consists of fenestrated endothelium, glomerular basement membrane, and podocyte foot processes (visceral epithelium).

Fill in the blank: Each kidney contains approximately one million nephrons; the nephron consists of the glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting duct; the glomerular filtration barrier comprises endothelium, basement membrane, and _____ foot processes.

1.1.2 Glomerular filtration and tubular function

Glomerular filtration produces approximately 180 litres of ultrafiltrate per day by driving plasma water and solutes across the filtration barrier; large proteins and blood cells are normally retained. The filtrate is then modified by the tubules: the **proximal tubule** reabsorbs approximately 65 percent of filtered sodium, water, glucose, amino acids, bicarbonate, and phosphate; the **loop of Henle** creates the medullary osmotic gradient essential for urine concentration; and the **distal tubule and collecting duct** perform fine regulation of sodium, potassium, and water under the control of aldosterone and antidiuretic hormone (ADH).

The kidneys produce approximately 1 to 2 litres of urine per day from 180 litres of filtrate, concentrating urine up to a maximum osmolality of approximately 1200 mOsm/kg. The kidneys also perform important **endocrine functions**: producing **erythropoietin** (stimulating red cell production), **renin** (activating the RAAS to regulate blood pressure and sodium balance), and converting vitamin D to its active form **1,25-dihydroxycholecalciferol (calcitriol)** (essential for calcium absorption and bone mineralisation).

Fill in the blank: The proximal tubule reabsorbs 65 percent of filtered sodium, glucose, and bicarbonate; the loop of Henle creates the medullary osmotic gradient; the collecting duct regulates water under the control of _____; the kidneys produce erythropoietin, renin, and calcitriol.

1.1.3 Renal regulation of fluid, electrolyte, and acid-base balance

Fluid balance is regulated by the kidney through sodium and water handling: aldosterone promotes sodium reabsorption in the distal tubule and collecting duct; ADH promotes water reabsorption in the collecting duct; and atrial natriuretic peptide (ANP) promotes sodium excretion. These hormones collectively maintain intravascular volume and plasma osmolality within narrow physiological ranges.

Acid-base balance is maintained by the kidney through three mechanisms: **bicarbonate reabsorption** in the proximal tubule (regenerating consumed buffer), **ammonium excretion** (the kidneys generate ammonium from glutamine, providing an additional proton-accepting

mechanism), and **titratable acid excretion** (phosphate buffers in the tubular fluid accept protons). In renal failure, all three mechanisms are impaired, resulting in **metabolic acidosis** — one of the most important complications of advanced kidney disease.

Fill in the blank: The kidney maintains acid-base balance through bicarbonate reabsorption, ammonium excretion, and titratable acid excretion; in renal failure these mechanisms fail, resulting in metabolic _____.

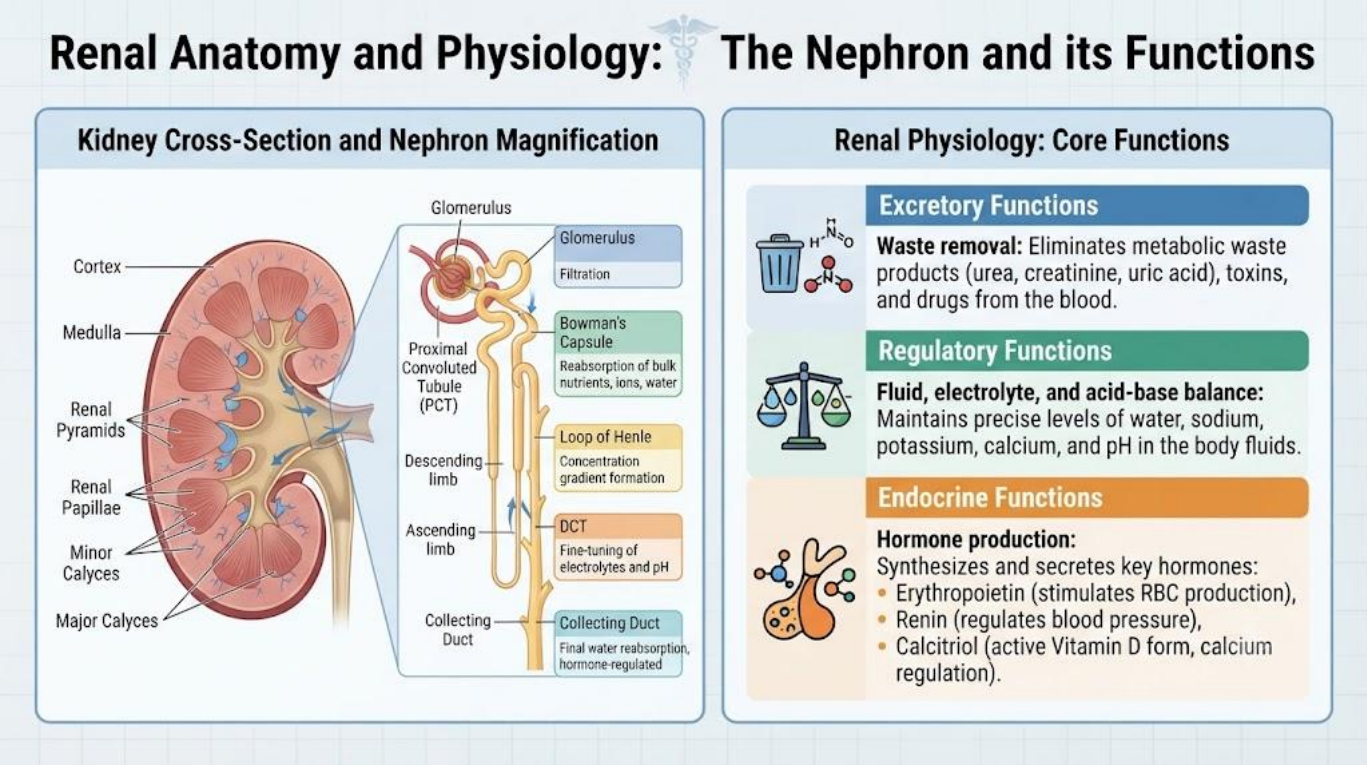

Figure 1.1: Renal anatomy, nephron structure, and the major functions of the kidney

Pilot questions 1.1

1. Describe the gross anatomy and internal structure of the kidney. (Linked to SLO 1.1)
2. Describe the components of the nephron and the function of each segment. (Linked to SLO 1.1)
3. Explain glomerular filtration, including the structure of the filtration barrier. (Linked to SLO 1.2)

4. Describe the endocrine functions of the kidney. (Linked to SLO 1.2)
5. Explain how the kidney maintains acid-base balance. (Linked to SLO 1.2)

1.2 Assessment of Renal Function

1.2.1 Glomerular filtration rate and its estimation

Glomerular filtration rate (GFR) is the volume of plasma filtered by the glomeruli per unit time, normally 90 to 120 mL/min per 1.73 m² in adults. GFR is the best single measure of overall kidney function; as nephrons are lost, GFR falls proportionally. True GFR is measured by inulin clearance (gold standard) or radiolabelled markers, but these are impractical for routine clinical use.

Estimated GFR (eGFR) is calculated from serum creatinine using equations such as the **CKD-EPI equation** or the older **MDRD equation**, which incorporate age, sex, and ethnicity to account for variation in muscle mass (creatinine is a product of creatinine phosphate metabolism in muscle). **Serum creatinine alone** is a poor indicator of early renal impairment: due to tubular secretion and the fact that serum creatinine does not rise above the normal range until approximately 50 percent of GFR is lost. **Serum cystatin C** is an alternative marker less dependent on muscle mass, useful in elderly, malnourished, or amputee patients.

Fill in the blank: GFR is normally 90 to 120 mL/min per 1.73 m²; eGFR is estimated from serum _____ using the CKD-EPI or MDRD equation; serum creatinine does not rise above normal until approximately 50 percent of GFR is lost.

1.2.2 Urinalysis and urine microscopy in renal disease

Urinalysis provides rapid diagnostic information about renal and urinary tract disease. Key dipstick findings in renal disease include: **proteinuria** (glomerular damage, nephrotic syndrome, or tubular dysfunction), **haematuria** (glomerulonephritis, urinary tract infection, calculi, malignancy), **leucocyte esterase and nitrites** (urinary tract infection), and **glucosuria without hyperglycaemia** (proximal tubular dysfunction, Fanconi syndrome). Urine protein quantification

is performed by the **urine albumin-to-creatinine ratio (uACR)** or 24-hour urine protein collection.

Urine microscopy provides critical diagnostic information in renal disease. **Red blood cell casts** (dysmorphic red cells aggregated in a cylindrical cast formed in the tubule lumen) are pathognomonic of glomerulonephritis. **Granular casts** indicate tubular injury. **Waxy or broad casts** indicate advanced chronic kidney disease with dilated tubules. Dysmorphic red blood cells (acanthocytes) suggest glomerular origin of haematuria, distinguishing it from lower urinary tract bleeding.

Fill in the blank: Red blood cell casts on urine microscopy are pathognomonic of _____; granular casts indicate tubular injury; waxy or broad casts indicate advanced CKD; dysmorphic red cells suggest glomerular origin of haematuria.

1.2.3 Blood tests and imaging in renal evaluation

Routine blood tests in renal evaluation include: serum creatinine and urea (glomerular function), serum electrolytes (sodium, potassium, bicarbonate, calcium, phosphate), **full blood count** (anaemia of CKD), and **parathyroid hormone (PTH)** (secondary hyperparathyroidism from CKD-mineral bone disease). Specialised tests for specific renal diseases include **anti-GBM antibody** (Goodpasture syndrome), **ANCA** (ANCA-associated vasculitis), **complement levels C3 and C4** (low in post-streptococcal GN, lupus nephritis, MPGN), and **ANA and anti-dsDNA** (systemic lupus erythematosus).

Renal imaging begins with **renal ultrasound**, which assesses kidney size (small kidneys in CKD; enlarged kidneys in infiltrative disease, polycystic kidney disease), echogenicity (increased in CKD), and the presence of obstruction, calculi, or cysts. **CT urography** is used for urolithiasis and urothelial malignancy. **Renal biopsy** is the definitive investigation for parenchymal renal disease when non-invasive tests are insufficient to establish a histological diagnosis; it guides treatment in glomerulonephritis, vasculitis, and transplant rejection.

Fill in the blank: Renal ultrasound assesses kidney size, echogenicity, obstruction, and cysts; renal _____ is the definitive investigation for parenchymal disease, guiding treatment in glomerulonephritis, vasculitis, and transplant rejection.

Investigation	Clinical Significance
eGFR **(CKD-EPI, MDRD; normal 90–120)**	Detects renal impairment; creatinine rises late, so eGFR is more sensitive
Urinalysis	Proteinuria (glomerular disease), haematuria, leucocyte esterase (infection), glucosuria (diabetes)
Urine Microscopy	RBC casts: glomerulonephritis; granular casts: tubular injury; waxy casts: chronic kidney disease

Investigation	Clinical Significance
Creatinine, Urea, Electrolytes	Assess renal function, detect electrolyte disturbances (e.g., hyperkalaemia)
Specialised Immunology **(Complement, ANCA, ANA, anti-GBM)**	Identifies autoimmune or vasculitic causes of renal disease
Ultrasound	Detects obstruction, kidney size, cysts, masses
CT Urography	Detailed imaging for stones, tumours, structural abnormalities
Biopsy	Definitive diagnosis of glomerular or interstitial disease

Table 1.1: Key investigations for the assessment of renal function and kidney disease

Pilot questions 1.2

1. Define GFR and explain why serum creatinine is a poor early indicator of renal impairment. (Linked to SLO 1.3)

2. Describe the urinalysis findings that suggest glomerulonephritis. (Linked to SLO 1.3)
3. Explain the significance of red blood cell casts on urine microscopy. (Linked to SLO 1.3)
4. List four specialised blood tests used in the investigation of glomerular disease and state what each detects. (Linked to SLO 1.3)
5. Describe the information provided by renal ultrasound in the evaluation of kidney disease. (Linked to SLO 1.3)

1.3 The Clinical Approach to the Patient with Renal Disease

1.3.1 Renal history taking

The renal history covers the presenting symptoms of kidney disease: **oedema** (facial, especially periorbital in the morning: suggests heavy proteinuria; ankle and leg: suggests fluid overload from reduced GFR or hypoalbuminaemia), **oliguria or anuria** (urine output below 400 mL or below 50 mL per 24 hours respectively), **haematuria** (visible or non-visible), **loin pain** (renal colic, pyelonephritis), **lower urinary tract symptoms** (dysuria, frequency, urgency, haematuria: UTI or outflow obstruction), and general symptoms of uraemia (nausea, anorexia, fatigue, confusion).

The past medical history in renal disease must include: previous renal disease or abnormal urinalysis, hypertension, diabetes mellitus, systemic lupus erythematosus, recurrent UTIs, renal calculi, obstructive uropathy, and family history of renal disease (polycystic kidney disease, Alport syndrome, familial nephritis). The **drug history** is critical: many drugs cause nephrotoxicity or interstitial nephritis, including NSAIDs, aminoglycosides, contrast agents, calcineurin inhibitors, and lithium.

Fill in the blank: Renal symptoms include oedema, oliguria or anuria, haematuria, loin pain, and lower urinary tract symptoms; the drug history must identify nephrotoxic agents including NSAIDs, aminoglycosides, _____ agents, and lithium.

1.3.2 Physical examination in renal disease

Volume status assessment is the first priority: features of **fluid overload** (elevated JVP, pulmonary oedema, peripheral oedema, hypertension) and **volume depletion** (low JVP, tachycardia, postural hypotension, dry mucous membranes) are critical to differentiate, as they determine the immediate management approach in AKI.

Relevant examination findings in renal disease include: **blood pressure measurement** (hypertension in CKD, renovascular disease, and glomerulonephritis), **periorbital oedema** (nephrotic syndrome), **xanthochromic or uraemic skin changes** (uraemia), **pallor** (anaemia of CKD), **palpable kidneys** (polycystic kidney disease, hydronephrosis), **renal bruit** (renovascular disease), **bladder distension** (urinary retention), and fundoscopic changes of **hypertensive or diabetic retinopathy** (as markers of end-organ damage).

Fill in the blank: Volume status assessment distinguishes fluid overload from volume depletion; examination findings include hypertension, periorbital oedema (nephrotic syndrome), pallor (anaemia of CKD), palpable kidneys, renal bruit (renovascular disease), and _____ distension.

1.3.3 Clinical syndromes in nephrology

The major clinical syndromes of nephrology provide diagnostic frameworks that guide investigation and management. **Nephritic syndrome** (haematuria, proteinuria, hypertension, oliguria, and oedema) results from glomerular inflammation; it indicates glomerulonephritis. **Nephrotic syndrome** (heavy proteinuria above 3.5 g per day, hypoalbuminaemia, oedema, and hyperlipidaemia) results from glomerular permeability defects without significant haematuria.

Asymptomatic urinary abnormalities (isolated haematuria or proteinuria detected incidentally on urinalysis without symptoms or oedema) are a common presentation of glomerular disease. **Acute kidney injury (AKI)** is a sudden reduction in GFR, presenting with rising creatinine and oliguria. **Chronic kidney disease (CKD)** is persistent reduction in GFR for more than three months. **Renal tubular syndromes** (e.g., Fanconi syndrome with glucosuria, aminoaciduria,

phosphaturia) indicate proximal tubular dysfunction. **Urinary tract infection syndrome** encompasses lower tract (cystitis) and upper tract (pyelonephritis) presentations.

Fill in the blank: Major nephrology syndromes include nephritic (haematuria, proteinuria, hypertension), nephrotic (heavy proteinuria, hypoalbuminaemia, oedema), asymptomatic urinary abnormalities, AKI, CKD, renal tubular syndromes, and _____ tract infection.

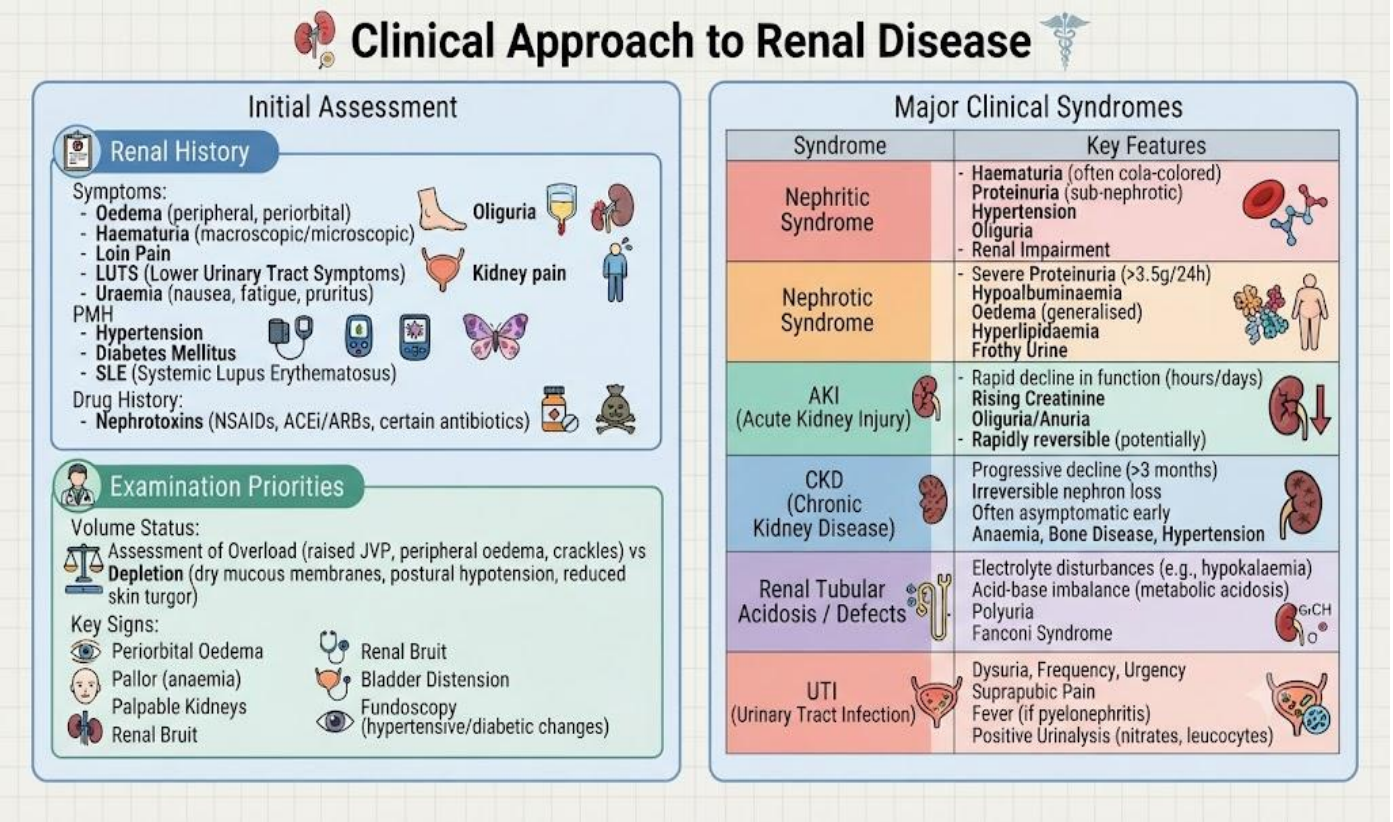

Figure 1.2: Clinical history, examination priorities, and the major clinical syndromes of nephrology

Pilot questions 1.3

1. Describe the major symptoms of renal disease and explain the mechanism of each. (Linked to SLO 1.4)
2. Explain why the drug history is particularly important in a patient with renal disease. (Linked to SLO 1.4)

3. Describe the examination findings in a patient with nephrotic syndrome. (Linked to SLO 1.4)
4. Distinguish between nephritic syndrome and nephrotic syndrome. (Linked to SLO 1.4)
5. Name the major clinical syndromes of nephrology and briefly define each. (Linked to SLO 1.4)

1.4 Acute Kidney Injury and Chronic Kidney Disease — An Introduction

1.4.1 Definition and classification of acute kidney injury

Acute kidney injury (AKI) is defined by the **KDIGO criteria** as any of: a rise in serum creatinine of 26.5 micromol/L or more within 48 hours, a rise in serum creatinine to 1.5 times or more the baseline within 7 days, or urine output below 0.5 mL/kg/hour for 6 hours or more. AKI is staged 1 to 3 by the degree of creatinine rise or urine output reduction, with Stage 3 representing the most severe impairment.

AKI is classified by cause into three categories: **pre-renal AKI** (reduced renal perfusion from hypovolaemia, low cardiac output, or renal vasoconstriction; accounts for 55 to 60 percent of hospital AKI; kidneys are intrinsically normal and recover promptly with restoration of perfusion), **intrinsic renal AKI** (direct damage to renal parenchyma; most commonly acute tubular necrosis from ischaemia or nephrotoxins; also glomerulonephritis, vasculitis, interstitial nephritis), and **post-renal AKI** (urinary tract obstruction; causes rising back pressure and tubular injury if prolonged).

Fill in the blank: AKI is classified as pre-renal (reduced perfusion, 55 to 60 percent of hospital AKI), intrinsic (tubular necrosis, glomerulonephritis, interstitial nephritis), and post-renal (urinary tract _____); KDIGO defines AKI as creatinine rise above 26.5 micromol/L within 48 hours.

1.4.2 Definition and staging of chronic kidney disease

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health. It is staged by the **KDIGO GFR categories**: G1 (GFR above 90; kidney damage with normal or high GFR), G2 (GFR 60 to 89; mildly reduced), G3a (GFR 45 to 59; mildly to moderately reduced), G3b (GFR 30 to 44; moderately to severely reduced), G4 (GFR 15 to 29; severely reduced), and G5 (GFR below 15; kidney failure). Albuminuria categories (A1: below 30 mg/g; A2: 30 to 300; A3: above 300) are combined with GFR stage to assess prognosis.

In Nigeria, CKD is predominantly caused by hypertensive nephrosclerosis, diabetic nephropathy, chronic glomerulonephritis, and HIV nephropathy. End-stage kidney disease (ESKD, CKD G5) requires **renal replacement therapy** (haemodialysis, peritoneal dialysis, or kidney transplantation) to sustain life. Access to renal replacement therapy in Nigeria remains severely limited by cost and infrastructure, making primary prevention of CKD through blood pressure and diabetes control a critical public health priority.

Fill in the blank: CKD is staged G1 (GFR above 90) to G5 (GFR below 15; kidney failure); in Nigeria the main causes are hypertensive nephrosclerosis, diabetic nephropathy, and chronic _____; ESKD requires renal replacement therapy.

1.4.3 Overview of the clinical consequences of kidney disease

Kidney disease causes multi-system complications that reflect the kidney's central role in homeostasis. **Anaemia** results from reduced erythropoietin production (normochromic, normocytic, treated with erythropoiesis-stimulating agents). **CKD-mineral bone disease (CKD-MBD)** results from reduced calcitriol production causing hypocalcaemia, secondary hyperparathyroidism, and renal osteodystrophy.

Cardiovascular disease is the leading cause of death in CKD patients, driven by hypertension, fluid overload, dyslipidaemia, uraemic toxins, and accelerated atherosclerosis. **Uraemia** (the toxic syndrome of renal failure) causes nausea, vomiting, anorexia, fatigue, pruritus, encephalopathy, and pericarditis. **Metabolic acidosis** (from impaired acid excretion) worsens

bone disease and muscle wasting. **Hyperkalaemia** (from impaired potassium excretion) risks fatal cardiac arrhythmias and requires urgent management.

Fill in the blank: Complications of kidney disease include anaemia (reduced erythropoietin), CKD-MBD (reduced calcitriol), cardiovascular disease (leading cause of death in CKD), uraemia, metabolic acidosis, and _____ (risking cardiac arrhythmias).

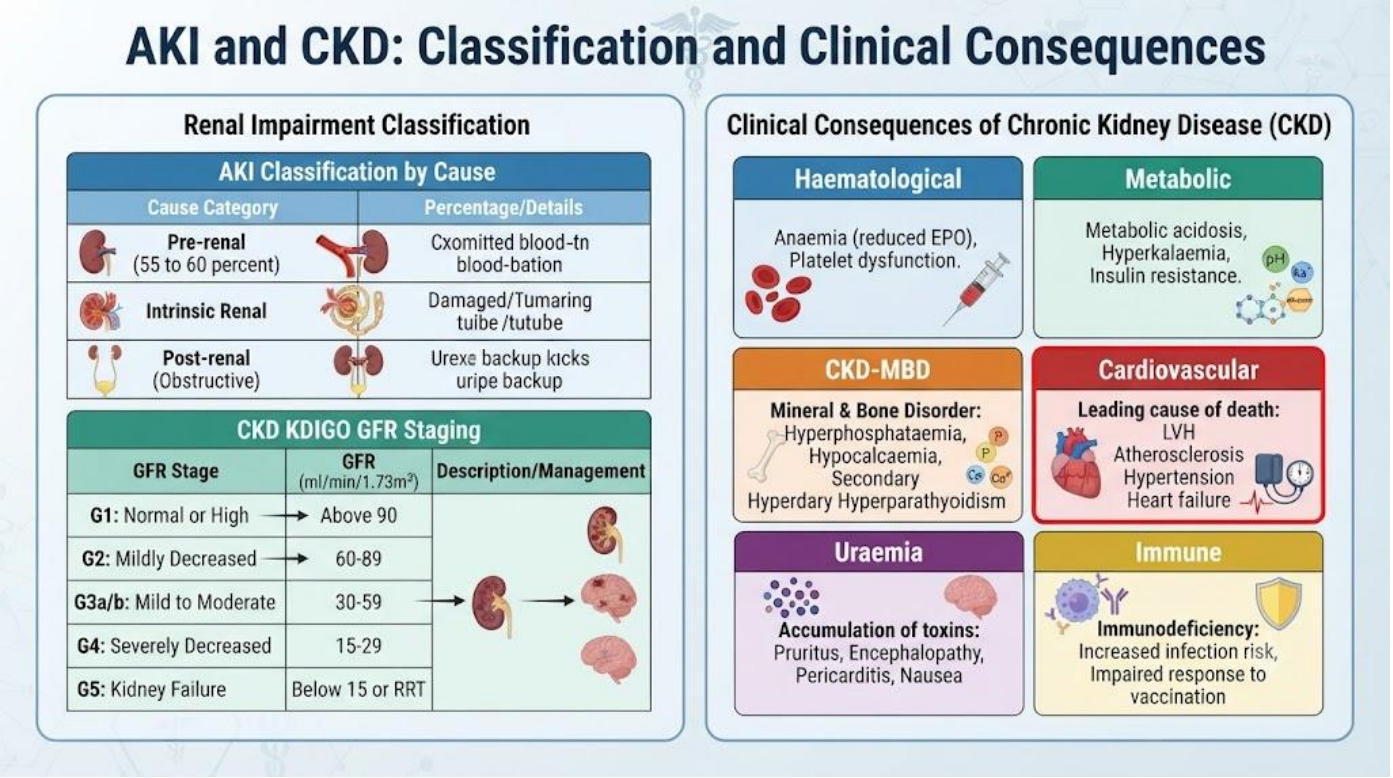

Figure 1.3: AKI classification, CKD staging, and the major clinical consequences of kidney disease

Pilot questions 1.4

1. State the KDIGO definition of AKI and describe its three-category classification. (Linked to SLO 1.5)
2. Describe the KDIGO staging of CKD by GFR category. (Linked to SLO 1.5)
3. List the major causes of CKD in Nigeria. (Linked to SLO 1.5)

4. Describe the haematological complications of CKD. (Linked to SLO 1.5)
5. Explain why cardiovascular disease is the leading cause of death in CKD patients. (Linked to SLO 1.5)

Series Summary

This Series established the foundations of nephrology. The kidney is a retroperitoneal organ containing approximately one million nephrons, each consisting of a glomerulus (ultrafiltration), proximal tubule (65 percent reabsorption of sodium, glucose, water, bicarbonate), loop of Henle (medullary concentration gradient), distal tubule and collecting duct (fine regulation under aldosterone and ADH); glomerular filtration produces 180 litres of ultrafiltrate daily; the kidneys perform excretory, regulatory, and endocrine functions (erythropoietin, renin, calcitriol). Renal function is assessed by eGFR (CKD-EPI or MDRD equations, from serum creatinine); creatinine does not rise above normal until 50 percent of GFR is lost; urinalysis detects proteinuria, haematuria, and infection; red blood cell casts on microscopy are pathognomonic of glomerulonephritis; granular casts indicate tubular injury; specialised blood tests (complement, ANCA, ANA, anti-GBM) identify specific diseases; renal biopsy provides definitive histological diagnosis.

The clinical approach includes history of oedema, oliguria, haematuria, loin pain, and lower urinary tract symptoms with attention to the drug history for nephrotoxins; examination focuses on volume status, blood pressure, periorbital oedema, pallor, palpable kidneys, and renal bruit. Major clinical syndromes are nephritic (haematuria, proteinuria, hypertension, oliguria), nephrotic (heavy proteinuria, hypoalbuminaemia, oedema, hyperlipidaemia), AKI (sudden GFR reduction), CKD (persistent over three months), tubular syndromes, and UTI. AKI is classified as pre-renal, intrinsic, and post-renal; KDIGO criteria define AKI by creatinine rise or oliguria; CKD is staged G1 to G5 by GFR; in Nigeria, hypertensive nephrosclerosis, diabetic nephropathy, and chronic glomerulonephritis are the leading causes; complications include

anaemia, CKD-MBD, cardiovascular disease (leading cause of death), uraemia, metabolic acidosis, and hyperkalaemia.

Glossary of Terms

- **Nephron:** the functional unit of the kidney; each kidney contains approximately one million nephrons, each consisting of a glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct.
- **Glomerular filtration rate (GFR):** the volume of plasma filtered by the glomeruli per unit time; normal 90 to 120 mL/min per 1.73 m^2; the best single measure of kidney function.
- **eGFR:** estimated GFR calculated from serum creatinine using the CKD-EPI or MDRD equation; used to stage CKD.
- **Red blood cell cast:** a cylindrical structure containing dysmorphic red blood cells formed in the tubule lumen; pathognomonic of glomerulonephritis.
- **Nephritic syndrome:** the clinical syndrome of haematuria, proteinuria, hypertension, oliguria, and oedema resulting from glomerular inflammation.
- **Nephrotic syndrome:** the clinical syndrome of heavy proteinuria (above 3.5 g per day), hypoalbuminaemia, oedema, and hyperlipidaemia from glomerular permeability defects.
- **Acute kidney injury (AKI):** a sudden reduction in GFR defined by KDIGO as a rise in serum creatinine of 26.5 micromol/L or more within 48 hours, or oliguria below 0.5 mL/kg/hour for 6 hours or more.
- **Chronic kidney disease (CKD):** abnormalities of kidney structure or function persisting for more than three months; staged G1 to G5 by GFR.
- **CKD-mineral bone disease (CKD-MBD):** the triad of reduced calcitriol production, hypocalcaemia, secondary hyperparathyroidism, and renal osteodystrophy complicating CKD.

- **Uraemia:** the toxic syndrome of advanced renal failure causing nausea, vomiting, fatigue, pruritus, encephalopathy, and pericarditis.
- **Renal biopsy:** the definitive investigation for parenchymal renal disease, providing histological diagnosis of glomerulonephritis, vasculitis, and interstitial nephritis.
- **Calcitriol:** 1,25-dihydroxycholecalciferol; the active form of vitamin D produced by the kidney; essential for calcium absorption and bone mineralisation.

Concept Check Questions [Series 1]

Objective Questions

1. Each kidney contains approximately one million nephrons; the glomerular filtration barrier consists of fenestrated endothelium, glomerular basement membrane, and podocyte _____ processes. (Linked to SLO 1.1)
2. Normal GFR is 90 to 120 mL/min per 1.73 m^2; eGFR is estimated from serum _____ using the CKD-EPI or MDRD equation. (Linked to SLO 1.3)
3. _____ blood cell casts on urine microscopy are pathognomonic of glomerulonephritis. (Linked to SLO 1.3)
4. The KDIGO definition of AKI includes a rise in serum creatinine of 26.5 micromol/L or more within _____ hours or oliguria below 0.5 mL/kg/hour for 6 hours. (Linked to SLO 1.5)
5. CKD G5 (GFR below 15 mL/min) represents kidney _____; it requires renal replacement therapy to sustain life. (Linked to SLO 1.5)
6. The leading cause of death in CKD patients is _____ disease, driven by hypertension, fluid overload, and accelerated atherosclerosis. (Linked to SLO 1.5)

Short-Answer Questions

7. Describe the endocrine functions of the kidney. (Linked to SLO 1.2)
8. Distinguish between nephritic syndrome and nephrotic syndrome. (Linked to SLO 1.4)
9. Classify AKI by cause and give an example of each category. (Linked to SLO 1.5)

Long-Answer Questions

10. Describe the investigations used to assess renal function, including eGFR, urinalysis, urine microscopy, blood tests, and imaging. (Linked to SLO 1.3)
11. Describe the clinical consequences of chronic kidney disease across major organ systems. (Linked to SLO 1.5)

Answers to Concept Check Questions [Series 1]

Objective Questions

1. Foot.
2. Creatinine.
3. Red.
4. 48.
5. Failure.
6. Cardiovascular.

Short-Answer Questions

7. Erythropoietin: stimulates red blood cell production in bone marrow; deficiency causes anaemia of CKD. Renin: activates the RAAS, regulating blood pressure and sodium balance. Calcitriol (1,25-dihydroxycholecalciferol): the active form of vitamin D; essential for calcium absorption from the gut and bone mineralisation; deficiency causes CKD-MBD.
8. Nephritic: haematuria (often macroscopic), proteinuria (sub-nephrotic, below 3.5 g per day), hypertension, oliguria, and oedema; caused by glomerular inflammation. Nephrotic: heavy proteinuria (above 3.5 g per day), hypoalbuminaemia (below 25 g/L), oedema (periorbital, peripheral, ascites), and hyperlipidaemia; caused by glomerular permeability defects; haematuria is absent or mild.
9. Pre-renal: reduced renal perfusion (example: hypovolaemia from diarrhoea and vomiting, septic shock, heart failure). Intrinsic: direct parenchymal damage (example: acute tubular necrosis from aminoglycoside nephrotoxicity or ischaemia). Post-renal: urinary tract obstruction (example: bilateral ureteric obstruction from pelvic malignancy or bladder outflow obstruction from BPH).

Long-Answer Questions

10. **Basic response:** eGFR: calculated from serum creatinine using CKD-EPI or MDRD equation; normal 90 to 120 mL/min; creatinine does not rise above normal until 50 percent of GFR lost; cystatin C alternative in muscle-wasting states. Urinalysis: dipstick for proteinuria (glomerular damage), haematuria (GN, UTI, calculi, malignancy),

leucocyte esterase and nitrites (UTI), glucosuria without hyperglycaemia (tubular dysfunction); uACR or 24-hour urine for protein quantification. Urine microscopy: RBC casts (pathognomonic of GN), granular casts (tubular injury), waxy/broad casts (advanced CKD), dysmorphic red cells (glomerular origin). Blood tests: creatinine, urea, electrolytes, FBC (anaemia), PTH, complement C3/C4 (low in post-streptococcal GN, lupus), ANCA (vasculitis), ANA/anti-dsDNA (SLE), anti-GBM (Goodpasture). Imaging: renal ultrasound (size, echogenicity, obstruction, cysts); CT urography (calculi, urothelial malignancy); renal biopsy (definitive histological diagnosis for parenchymal disease).

Value-added response: The integration of these investigations is what makes nephrology diagnostically elegant: the combination of RBC casts (on microscopy), low complement (on blood tests), and post-streptococcal history (on clinical evaluation) together make a diagnosis of post-streptococcal GN without the need for biopsy, while isolated proteinuria above 3.5 g per day with hypoalbuminaemia establishes nephrotic syndrome and guides the choice between empirical treatment and biopsy based on age and likely aetiology.

11. **Basic response:** Haematological: anaemia (normochromic, normocytic; from reduced erythropoietin; treated with ESAs and iron); bleeding tendency (platelet dysfunction from uraemia). Metabolic: metabolic acidosis (impaired bicarbonate reabsorption and acid excretion); hyperkalaemia (impaired potassium excretion; risk of fatal arrhythmias); CKD-MBD (reduced calcitriol, hypocalcaemia, secondary hyperparathyroidism, renal osteodystrophy). Cardiovascular: leading cause of death in CKD; hypertension (fluid overload, RAAS activation), accelerated atherosclerosis (dyslipidaemia, uraemic toxins, inflammation), LVH and heart failure, increased risk of arrhythmia. Neurological: uraemic encephalopathy (confusion, seizures), peripheral neuropathy. Gastrointestinal: nausea, vomiting, anorexia, uraemic gastritis. Dermatological: pruritus (uraemic toxins, phosphate), pallor, uraemic frost (rare). Immune: impaired immune function (increased susceptibility to infection: the second leading cause of death in CKD after cardiovascular disease).

    Value-added response: The multi-system impact of CKD reflects the kidney's irreplaceable role in homeostasis: when GFR falls below 15 mL/min, every major organ system is affected, and the clinical challenge is not merely to manage each complication individually but to understand how interventions targeting one complication (such as

treating acidosis with bicarbonate) may affect others (metabolic alkalosis, volume overload from sodium bicarbonate).

Answers to Pilot Questions [Series 1]

Part 1.1

1. The kidneys are paired retroperitoneal organs each weighing approximately 150 g and measuring 11 to 12 cm in length; the outer cortex contains glomeruli, proximal, and distal tubules; the inner medulla contains loops of Henle and collecting ducts organised into renal pyramids; papillae drain into minor calyces, major calyces, renal pelvis, and ureter.
2. Glomerulus: ultrafiltration of plasma. Proximal convoluted tubule: reabsorbs 65 percent of filtered sodium, water, glucose, amino acids, bicarbonate, and phosphate. Loop of Henle: creates the medullary osmotic concentration gradient. Distal convoluted tubule: fine regulation of electrolytes. Collecting duct: water reabsorption under ADH; sodium reabsorption under aldosterone.
3. Glomerular filtration drives plasma water and solutes across the filtration barrier by net filtration pressure (glomerular capillary hydrostatic pressure minus oncotic pressure minus Bowman's capsule pressure); normal GFR produces 180 litres of ultrafiltrate daily. The filtration barrier consists of three layers: fenestrated glomerular capillary endothelium, glomerular basement membrane (type IV collagen; negatively charged, repelling proteins), and podocyte foot processes with slit diaphragms.
4. Erythropoietin: produced by peritubular interstitial cells in the renal cortex; stimulates erythroid progenitor differentiation in bone marrow; deficiency in CKD causes normochromic normocytic anaemia. Renin: produced by juxtaglomerular cells; activates the RAAS (angiotensin I to II to aldosterone), regulating blood pressure and sodium balance. Calcitriol (1,25-dihydroxycholecalciferol): active vitamin D; essential for intestinal calcium and phosphate absorption and bone mineralisation; deficiency in CKD causes hypocalcaemia, secondary hyperparathyroidism, and renal osteodystrophy.

5. The kidney maintains acid-base balance through three mechanisms: proximal tubular bicarbonate reabsorption (regenerates consumed buffer, accounting for 85 to 90 percent of bicarbonate reabsorption); ammonium excretion (kidneys produce ammonium from glutamine via glutaminase; ammonium provides an additional proton-accepting pathway in the tubular fluid); titratable acid excretion (inorganic phosphate and other buffers in the tubular fluid accept protons, allowing continued acid excretion). All three are impaired in renal failure, resulting in metabolic acidosis.

Part 1.2

1. GFR is the volume of plasma filtered per unit time; normal 90 to 120 mL/min per 1.73 m^2. Serum creatinine is a poor early indicator because: creatinine is secreted by proximal tubular cells (overestimating GFR); its serum level depends on muscle mass (low in elderly and malnourished: creatinine may appear normal despite significantly reduced GFR); and it does not rise above the normal range until approximately 50 percent of nephron mass is lost, by which time CKD is already significantly advanced.
2. Urinalysis findings suggesting glomerulonephritis: dipstick haematuria and proteinuria together; microscopy showing red blood cell casts (pathognomonic) and dysmorphic red blood cells (acanthocytes), confirming glomerular origin of haematuria rather than lower urinary tract bleeding. Protein quantification by uACR or 24-hour urine collection documents the degree of glomerular protein loss.
3. Red blood cell casts are cylindrical structures containing dysmorphic red cells formed in the renal tubule lumen; they are pathognomonic of glomerulonephritis, meaning that their presence on urine microscopy virtually confirms glomerular inflammation as the cause of haematuria and proteinuria; the differential diagnosis of haematuria with RBC casts is limited to active glomerulonephritis.
4. Anti-GBM antibody: detects antibodies against glomerular basement membrane; positive in Goodpasture syndrome (rapidly progressive GN with pulmonary haemorrhage). ANCA (anti-neutrophil cytoplasmic antibody): detects antibodies in ANCA-associated vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis). Complement C3 and C4: low levels indicate complement consumption in immune complex-mediated GN (post-

streptococcal GN, lupus nephritis, MPGN). ANA and anti-dsDNA: positive in systemic lupus erythematosus with lupus nephritis.

5. Renal ultrasound assesses kidney size (small and echogenic in CKD; enlarged in polycystic kidney disease, infiltrative disease, or acute GN); echogenicity (increased in CKD from fibrosis); presence of obstruction (hydronephrosis: dilated pelvicalyceal system); renal calculi; cysts (simple or complex: polycystic kidney disease); renal masses; and peri-renal collections. Duplex Doppler ultrasound can also assess renal artery flow for renovascular disease.

Part 1.3

1. Oedema: reduced GFR causes sodium and water retention (fluid overload); heavy proteinuria causes hypoalbuminaemia, reducing oncotic pressure and promoting fluid shift into interstitium. Oliguria or anuria: reduced GFR reduces urine output; threshold for oliguria is below 400 mL per 24 hours. Haematuria: glomerular inflammation or lower urinary tract pathology. Loin pain: renal colic from calculi or ureteric obstruction; pyelonephritis causing renal capsule distension. Lower urinary tract symptoms (LUTS): dysuria, frequency, urgency suggest UTI or outflow obstruction.
2. Many drugs cause nephrotoxicity or interstitial nephritis: NSAIDs cause renal vasoconstriction (pre-renal AKI) and interstitial nephritis; aminoglycosides cause direct tubular toxicity (acute tubular necrosis); radiocontrast agents cause contrast-induced nephropathy in susceptible patients; calcineurin inhibitors (ciclosporin, tacrolimus) cause vasoconstriction and chronic nephrotoxicity; lithium causes nephrogenic diabetes insipidus and chronic interstitial nephritis. Identifying and stopping nephrotoxic drugs is often the most impactful intervention in drug-induced AKI.
3. Periorbital oedema (most prominent in the morning from overnight recumbency of head; suggests heavy proteinuria causing hypoalbuminaemia), generalised pitting oedema (ankles, legs, thighs, sacrum in severe cases), ascites, pleural effusions (in severe hypoalbuminaemia), hypertension (from sodium retention and RAAS activation), pallor (anaemia from urinary protein loss stimulating secondary anaemia), xanthomas (hyperlipidaemia).

4. Nephritic: haematuria (often macroscopic), sub-nephrotic proteinuria (typically below 3.5 g per day), hypertension, oliguria, and oedema; caused by glomerular inflammation (GN); RBC casts on microscopy. Nephrotic: heavy proteinuria (above 3.5 g per day), hypoalbuminaemia (below 25 g/L), oedema (periorbital, peripheral, ascites), hyperlipidaemia, lipiduria; no significant haematuria (or microscopic only); caused by increased glomerular permeability to protein without significant inflammation.
5. Nephritic syndrome (GN), nephrotic syndrome (glomerular permeability defects), asymptomatic urinary abnormalities (isolated haematuria or proteinuria on urinalysis), AKI (sudden GFR reduction), CKD (persistent above three months), renal tubular syndromes (Fanconi syndrome, renal tubular acidosis), UTI syndrome (cystitis: lower tract; pyelonephritis: upper tract).

Part 1.4

1. KDIGO AKI definition: rise in serum creatinine of 26.5 micromol/L or more within 48 hours; or rise in creatinine to 1.5 times or more the baseline within 7 days; or urine output below 0.5 mL/kg/hour for 6 hours or more. Pre-renal: reduced renal perfusion (hypovolaemia, low cardiac output, vasoconstriction); kidneys intrinsically normal; recovers with perfusion restoration. Intrinsic: direct parenchymal damage (acute tubular necrosis from ischaemia or nephrotoxins; glomerulonephritis; vasculitis; interstitial nephritis). Post-renal: urinary tract obstruction causing back pressure and tubular injury.
2. G1: GFR above 90 mL/min (kidney damage with normal or high GFR). G2: GFR 60 to 89 (mildly reduced). G3a: GFR 45 to 59 (mildly to moderately reduced). G3b: GFR 30 to 44 (moderately to severely reduced). G4: GFR 15 to 29 (severely reduced; preparation for renal replacement therapy). G5: GFR below 15 (kidney failure; renal replacement therapy required).
3. Hypertensive nephrosclerosis (most common in Nigeria; hypertension causing arteriolar damage and glomerular ischaemia), diabetic nephropathy (from diabetes mellitus), chronic glomerulonephritis (post-infectious, IgA nephropathy, lupus nephritis), HIV nephropathy (HIV-associated nephropathy: HIVAN, common in HIV-endemic sub-Saharan Africa), and sickle cell nephropathy.

4. Anaemia of CKD: normochromic normocytic anaemia from reduced erythropoietin production; worsened by iron deficiency, haemolysis, and blood loss; treated with erythropoiesis-stimulating agents (ESAs: epoetin, darbepoetin) plus iron supplementation (IV iron preferred in haemodialysis patients). Bleeding tendency from uraemic platelet dysfunction (reduced platelet aggregation). Haemolytic anaemia may occur in thrombotic microangiopathy (rare CKD complication).
5. Cardiovascular disease is the leading cause of death in CKD because: hypertension is near-universal in CKD from fluid overload and RAAS activation; LVH develops from pressure and volume overload; accelerated atherosclerosis is driven by dyslipidaemia, inflammation, oxidative stress, and uraemic toxins; vascular calcification (from CKD-MBD: elevated phosphate promotes medial arterial calcification); and increased prevalence of atrial fibrillation and other arrhythmias; all these factors compound to give CKD patients a cardiovascular mortality risk 10 to 30 times higher than the general population.

References and Attributions [Series 1]

Textual References

- Kidney Disease: Improving Global Outcomes (KDIGO). (2012). KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements, 2(1), 1 to 138.
- Kidney Disease: Improving Global Outcomes (KDIGO). (2013). KDIGO Clinical Practice Guideline for CKD Evaluation and Management. Kidney International Supplements, 3(1), 1 to 150.
- Kumar, P. and Clark, M. (2017). Kumar and Clark's Clinical Medicine (9th ed.). Edinburgh: Elsevier.
- Ulasi, I. I. and Ijoma, C. K. (2010). The Enormity of Chronic Kidney Disease in Nigeria: The Situation in a Teaching Hospital in South-East Nigeria. Journal of Tropical Medicine, 2010, Article 501957.

Figures, Plates, Tables, and Boxes

- Figure 1.1: Renal anatomy, nephron structure, and kidney functions. AI prompt: "Two-panel diagram: left panel cross-section of kidney (cortex, medulla, pyramids, papillae, calyces) with magnified nephron (Glomerulus, Bowman's capsule, PCT, Loop of Henle, DCT, Collecting Duct) labelled with functions; right panel three-section list: Excretory, Regulatory, Endocrine; clean professional infographic." OER search: "kidney nephron anatomy physiology diagram glomerulus tubule functions".
- Table 1.1: Key investigations for renal function assessment. AI prompt: "Two-section table: Functional Tests (eGFR, urinalysis, urine microscopy) and Blood Tests and Imaging (electrolytes, immunology, ultrasound, biopsy); alternating shading." OER search: "renal function investigations eGFR urinalysis urine microscopy blood tests ultrasound biopsy table".
- Figure 1.2: Clinical approach and nephrology syndromes. AI prompt: "Two-panel diagram: left (renal history and examination priorities); right (six-row clinical syndromes table: nephritic, nephrotic, AKI, CKD, tubular, UTI); clean professional infographic." OER search: "clinical approach renal disease history examination syndromes nephritic nephrotic AKI CKD diagram".
- Figure 1.3: AKI classification, CKD staging, and clinical consequences. AI prompt: "Two-panel diagram: left (AKI cause table: pre-renal, intrinsic, post-renal; CKD KDIGO G1 to G5); right (six-cell consequences grid: haematological, metabolic, CKD-MBD, cardiovascular, uraemia, immune); clean professional infographic." OER search: "AKI classification pre-renal intrinsic post-renal CKD staging KDIGO consequences diagram".

Series 2: Electrolyte Imbalance and Clinical Evaluation

- **Part 2.1: Sodium Disorders**
  - Sub Part 2.1.1: Hyponatraemia — causes and clinical features
  - Sub Part 2.1.2: Hyponatraemia — investigations and management
  - Sub Part 2.1.3: Hypernatraemia — causes, features, and management
- **Part 2.2: Potassium Disorders**
  - Sub Part 2.2.1: Hypokalaemia — causes, features, and management
  - Sub Part 2.2.2: Hyperkalaemia — causes and clinical features
  - Sub Part 2.2.3: Hyperkalaemia — management
- **Part 2.3: Acid-Base Disorders**
  - Sub Part 2.3.1: Principles of acid-base physiology
  - Sub Part 2.3.2: Metabolic acidosis and metabolic alkalosis
  - Sub Part 2.3.3: Respiratory acidosis and respiratory alkalosis
- **Part 2.4: Calcium, Phosphate, and Magnesium Disorders**
  - Sub Part 2.4.1: Calcium disorders: hypocalcaemia and hypercalcaemia
  - Sub Part 2.4.2: Phosphate and magnesium disorders
  - Sub Part 2.4.3: CKD-mineral bone disease

Introduction

Electrolyte imbalances are among the most common and potentially life-threatening problems encountered in clinical medicine. The kidneys play a central role in maintaining the narrow physiological ranges within which sodium, potassium, calcium, phosphate, and magnesium must be maintained, and derangements in these electrolytes arise from a wide variety of causes including renal disease, gastrointestinal losses, endocrine disorders, and iatrogenic sources.

This Series covers the major electrolyte disorders in systematic detail: sodium disorders (hyponatraemia and hypernatraemia), potassium disorders (hypokalaemia and hyperkalaemia), acid-base disorders (metabolic and respiratory acidosis and alkalosis), and disorders of calcium, phosphate, and magnesium, including the specific syndrome of CKD-mineral bone disease. For each disorder the causes, clinical features, diagnostic approach, and management are examined.

Competence in recognising and managing electrolyte imbalances is an essential clinical skill that applies across all specialties and is tested in every emergency clinical encounter. The systematic approach developed in this Series equips the student to identify, investigate, and treat these conditions safely.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 2.1** describe the causes, clinical features, investigation, and management of hyponatraemia and hypernatraemia (Linked to Part 2.1),
- **SLO 2.2** describe the causes, clinical features, and management of hypokalaemia and hyperkalaemia (Linked to Part 2.2),
- **SLO 2.3** explain the principles of acid-base physiology and describe the four primary acid-base disorders (Linked to Part 2.3),
- **SLO 2.4** describe the causes and management of hypocalcaemia and hypercalcaemia (Linked to Part 2.4), and

- **SLO 2.5** describe the electrolyte and mineral disorders of CKD including CKD-mineral bone disease (Linked to Part 2.4).

2.1 Sodium Disorders

2.1.1 Hyponatraemia — causes and clinical features

Hyponatraemia is defined as serum sodium below 135 mmol/L. It is the most common electrolyte disturbance in hospitalised patients. Hyponatraemia is classified by the patient's volume status: **hypovolaemic hyponatraemia** (total body sodium depleted but water loss is relatively less; causes: vomiting, diarrhoea, diuretics, adrenal insufficiency), **euvolaemic hyponatraemia** (normal total body sodium, excess water; most commonly **SIADH** — syndrome of inappropriate ADH secretion, from CNS disease, pulmonary disease, drugs, malignancy), and **hypervolaemic hyponatraemia** (excess of both sodium and water, with water excess greater; causes: heart failure, cirrhosis, nephrotic syndrome, advanced CKD).

Clinical features of hyponatraemia depend on the severity and rate of development. Mild hyponatraemia (above 130 mmol/L) is often asymptomatic. Moderate hyponatraemia (125 to 130 mmol/L) causes nausea, malaise, and headache. Severe hyponatraemia (below 125 mmol/L) causes **confusion, seizures, and coma** from cerebral oedema, which can be life-threatening. Chronic hyponatraemia is better tolerated neurologically than acute hyponatraemia.

Fill in the blank: Hyponatraemia is classified as hypovolaemic (sodium and water depletion), euvolaemic (SIADH, excess water with normal sodium), or hypervolaemic (heart failure, cirrhosis, nephrotic syndrome); severe hyponatraemia (below 125 mmol/L) causes confusion, _____, and coma.

2.1.2 Hyponatraemia — investigations and management

Investigation of hyponatraemia begins with confirming true hyponatraemia (exclude pseudohyponatraemia from hyperlipidaemia or hyperproteinaemia). Key investigations include: **serum osmolality** (low in true hyponatraemia; normal or high in pseudohyponatraemia or

hyperglycaemia-related hyponatraemia), **urine osmolality** (above 100 mOsm/kg indicates ADH activity; below 100 suggests primary polydipsia or low solute intake), and **urine sodium** (below 20 mmol/L suggests hypovolaemia or hypervolaemic states; above 40 mmol/L suggests SIADH or salt-wasting nephropathy).

Management is guided by volume status and severity. In **hypovolaemic hyponatraemia**: IV normal saline to restore volume. In **euvolaemic hyponatraemia (SIADH)**: fluid restriction (500 to 1000 mL/day); vasopressin receptor antagonists (vaptans) in selected cases; treat the underlying cause. In **hypervolaemic hyponatraemia**: fluid and sodium restriction; treat the underlying condition. In **severe symptomatic hyponatraemia** (seizures, coma): IV hypertonic saline (3 percent NaCl) with close monitoring; sodium should be corrected at no more than 10 to 12 mmol/L per day to avoid osmotic demyelination syndrome.

Fill in the blank: Severe symptomatic hyponatraemia is treated with IV _____ saline (3 percent NaCl); correction must not exceed 10 to 12 mmol/L per day to prevent osmotic demyelination syndrome.

2.1.3 Hypernatraemia — causes, features, and management

Hypernatraemia is defined as serum sodium above 145 mmol/L. It always indicates a deficit of water relative to sodium and is almost always associated with **impaired thirst or inability to access water**. Causes include: **insensible water losses** (fever, sweating, burns, mechanical ventilation), **renal water losses** from diabetes insipidus (failure of ADH: central DI from hypothalamic or pituitary disease; or nephrogenic DI from renal resistance to ADH — caused by lithium, hypercalcaemia, or genetic mutations), and **inadequate water intake** in patients unable to drink (elderly, obtunded, or infants).

Clinical features include thirst, lethargy, irritability, muscle weakness, confusion, and in severe cases seizures and coma from brain cell shrinkage. **Management** involves identifying and treating the underlying cause; replacing the water deficit with oral water (preferred) or IV 5 percent dextrose or 0.45 percent saline; sodium correction should not exceed 10 to 12 mmol/L per day to prevent cerebral oedema from overly rapid rehydration.

Fill in the blank: Hypernatraemia indicates a water deficit relative to sodium; causes include insensible water losses, diabetes insipidus (central: ADH failure; nephrogenic: ADH _____), and inadequate water intake; correction should not exceed 10 to 12 mmol/L per day.

Hyponatraemia (Na <135 mmol/L)	**Hypernatraemia (Na >145 mmol/L)**
Hypovolaemic – Causes: GI loss, renal loss; urine Na <20 mmol/L	**Causes** – Insensible losses, diabetes insipidus (central vs nephrogenic), inadequate intake
Euvolaemic – SIADH; urine Na >40 mmol/L	**Features** – Thirst, confusion, seizures
Hypervolaemic – Heart failure, cirrhosis, nephrotic syndrome	**Management** – Water replacement, correction ≤10–12 mmol/L per day
Clinical Features – Mild: nausea, headache; Severe: seizures, coma	
Management – Treat underlying cause; hypovolaemic: fluids; SIADH: fluid restriction; hypervolaemic: diuretics; severe: hypertonic saline	

Table 2.1: Sodium disorders — hyponatraemia classification, features, and management; and hypernatraemia

Pilot questions 2.1

1. Define hyponatraemia and describe its classification by volume status. (Linked to SLO 2.1)
2. Describe the clinical features of hyponatraemia and explain why severe hyponatraemia is life-threatening. (Linked to SLO 2.1)
3. Describe the investigation of hyponatraemia including urine sodium and urine osmolality. (Linked to SLO 2.1)
4. Define SIADH and describe its causes and management. (Linked to SLO 2.1)

5. Define hypernatraemia and distinguish between central and nephrogenic diabetes insipidus. (Linked to SLO 2.1)

2.2 Potassium Disorders

2.2.1 Hypokalaemia — causes, features, and management

Hypokalaemia is defined as serum potassium below 3.5 mmol/L. Causes are classified as: **reduced intake** (rare as the sole cause), **increased renal losses** (diuretics — the most common cause in clinical practice; hyperaldosteronism; hypomagnesaemia, which impairs renal potassium conservation; renal tubular acidosis), **increased gastrointestinal losses** (vomiting — loss of HCl stimulates aldosterone via volume depletion and metabolic alkalosis drives intracellular K shift; diarrhoea — direct K loss), and **transcellular shift** (potassium moves into cells in alkalosis, with insulin administration, and with beta-2 agonist excess).

Clinical features include muscle weakness and cramps (from impaired membrane excitability), constipation, polyuria (hypokalaemic nephropathy), and cardiac arrhythmias. ECG changes include **flattened T waves, prominent U waves**, and ST depression; severe hypokalaemia (below 2.5 mmol/L) risks ventricular arrhythmias. Management: oral or IV potassium supplementation; treat the underlying cause; correct hypomagnesaemia (refractory hypokalaemia until Mg is replaced).

Fill in the blank: Hypokalaemia ECG changes include flattened T waves, prominent _____ waves, and ST depression; refractory hypokalaemia should prompt correction of hypomagnesaemia; diuretics are the most common cause.

2.2.2 Hyperkalaemia — causes and clinical features

Hyperkalaemia is defined as serum potassium above 5.5 mmol/L. It is potentially fatal from cardiac arrhythmia. Causes include: **reduced renal excretion** (CKD or AKI — the most important cause in renal practice; adrenal insufficiency; drugs: ACE inhibitors, ARBs, potassium-sparing diuretics, NSAIDs, trimethoprim), **transcellular shift from cells to plasma**

(acidosis: for every 0.1 fall in pH, serum K rises by 0.3 to 0.6 mmol/L; tissue destruction: rhabdomyolysis, tumour lysis syndrome, haemolysis), and **increased intake** (dietary or IV supplementation in patients with impaired excretion). Pseudohyperkalaemia from haemolysed samples must be excluded.

Clinical features are primarily cardiac: **ECG changes in sequence** include peaked (tall, narrow, symmetrical) T waves (earliest change), PR interval prolongation, P wave flattening, QRS widening, and ultimately sine wave pattern and ventricular fibrillation. Muscle weakness and ascending paralysis may occur. Serum potassium above 6.5 mmol/L or any ECG changes constitute a **medical emergency**.

Fill in the blank: Hyperkalaemia ECG changes progress from peaked T waves through PR prolongation, P wave flattening, QRS widening to _____ wave pattern and ventricular fibrillation; potassium above 6.5 mmol/L is a medical emergency.

2.2.3 Hyperkalaemia — management

Hyperkalaemia management follows three sequential steps targeting membrane stabilisation, potassium redistribution, and potassium removal. First, **membrane stabilisation**: IV calcium gluconate (10 mL of 10 percent solution) given immediately if ECG changes are present; it protects the myocardium against arrhythmia within minutes but does not lower serum potassium.

Second, **potassium redistribution into cells**: IV insulin (10 units) with 50 mL of 50 percent glucose (to prevent hypoglycaemia) shifts potassium into cells within 15 to 30 minutes; IV sodium bicarbonate (if metabolic acidosis is present) and nebulised salbutamol (beta-2 agonist) also redistribute potassium. Third, **potassium removal from the body**: loop diuretics (if urine output is present), oral or rectal calcium resonium (ion exchange resin), sodium zirconium cyclosilicate or patiromer (newer binding agents), and haemodialysis (most rapid and effective removal in patients with AKI or ESKD).

Fill in the blank: Hyperkalaemia management: membrane stabilisation with IV calcium gluconate (protects myocardium); redistribution with IV insulin-glucose and sodium bicarbonate; removal with diuretics, ion exchange resins, or _____ (most effective).

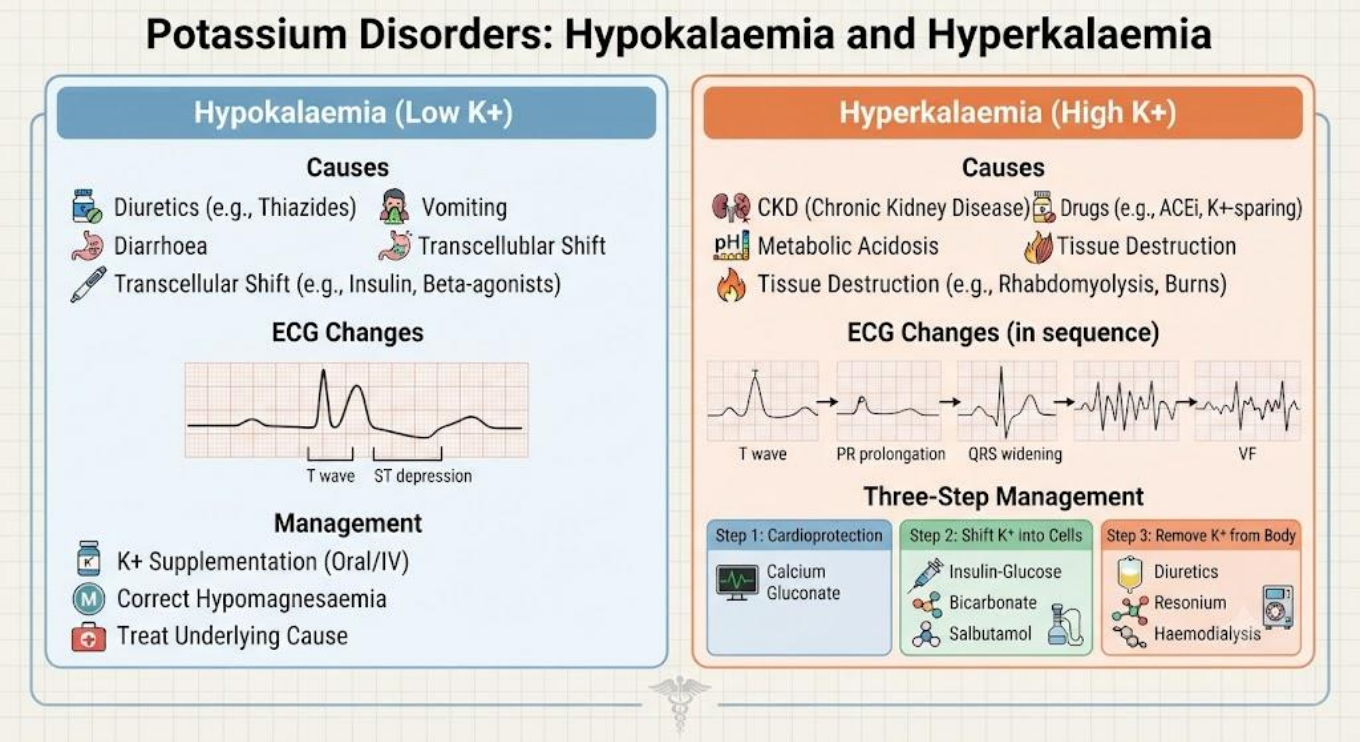

Figure 2.2: Potassium disorders — hypokalaemia and hyperkalaemia: causes, ECG changes, and management

Pilot questions 2.2

1. List the major causes of hypokalaemia and describe the mechanism by which diuretics cause potassium depletion. (Linked to SLO 2.2)
2. Describe the ECG changes of hypokalaemia and explain their clinical significance. (Linked to SLO 2.2)
3. Describe the causes of hyperkalaemia in a patient with chronic kidney disease. (Linked to SLO 2.2)
4. Describe the ECG changes of hyperkalaemia in sequence from earliest to most severe. (Linked to SLO 2.2)
5. Describe the three-step management of severe hyperkalaemia. (Linked to SLO 2.2)

2.3 Acid-Base Disorders

2.3.1 Principles of acid-base physiology

Normal blood pH is maintained between 7.35 and 7.45 by three systems acting in concert: **chemical buffers** (bicarbonate-carbonic acid system, haemoglobin, proteins; respond within seconds to minutes), **respiratory regulation** of PaCO2 (hyperventilation reduces CO2 and raises pH; hypoventilation raises CO2 and lowers pH; responds within minutes), and **renal regulation** of bicarbonate (bicarbonate reabsorption and acid excretion; responds over hours to days).

The Henderson-Hasselbalch equation describes the relationship: pH is proportional to bicarbonate divided by PaCO2. A primary change in one component is followed by **compensatory changes** in the other to minimise pH deviation: metabolic acidosis (low bicarbonate) is compensated by hyperventilation (reducing PaCO2); metabolic alkalosis by hypoventilation; respiratory acidosis by renal bicarbonate retention; respiratory alkalosis by renal bicarbonate excretion. Compensation is never complete and does not return pH to normal.

Fill in the blank: pH is maintained by chemical buffers (immediate), respiratory regulation of PaCO2 (minutes), and renal regulation of bicarbonate (hours to days); metabolic acidosis is compensated by _____ (lowering PaCO2).

2.3.2 Metabolic acidosis and metabolic alkalosis

Metabolic acidosis (pH below 7.35, bicarbonate below 22 mmol/L) is evaluated using the **anion gap (AG)** = Na minus (Cl plus HCO3); normal AG is 8 to 12 mmol/L. A **high AG metabolic acidosis** (AG above 12: unmeasured anions replacing bicarbonate) is caused by MUDPILES: Methanol, Uraemia (renal failure), Diabetic ketoacidosis, Propylene glycol or Paracetamol, Isoniazid or Iron, Lactic acidosis, Ethanol or Ethylene glycol, Salicylates. A **normal AG (hyperchloraemic) metabolic acidosis** results from bicarbonate loss (diarrhoea, renal tubular acidosis, urinary diversion).

Metabolic alkalosis (pH above 7.45, bicarbonate above 26 mmol/L) is most commonly caused by **vomiting or nasogastric suction** (loss of HCl), **diuretics** (chloride and volume depletion stimulating aldosterone-driven bicarbonate retention), and **exogenous alkali administration**. It is maintained by chloride depletion and volume depletion (both stimulate bicarbonate

reabsorption). Urine chloride below 25 mmol/L indicates chloride-responsive metabolic alkalosis (treat with normal saline).

Fill in the blank: High anion gap metabolic acidosis causes include uraemia, DKA, lactic acidosis (MUDPILES); normal anion gap metabolic acidosis results from bicarbonate loss (diarrhoea, renal _____ acidosis); metabolic alkalosis is most commonly from vomiting or diuretics.

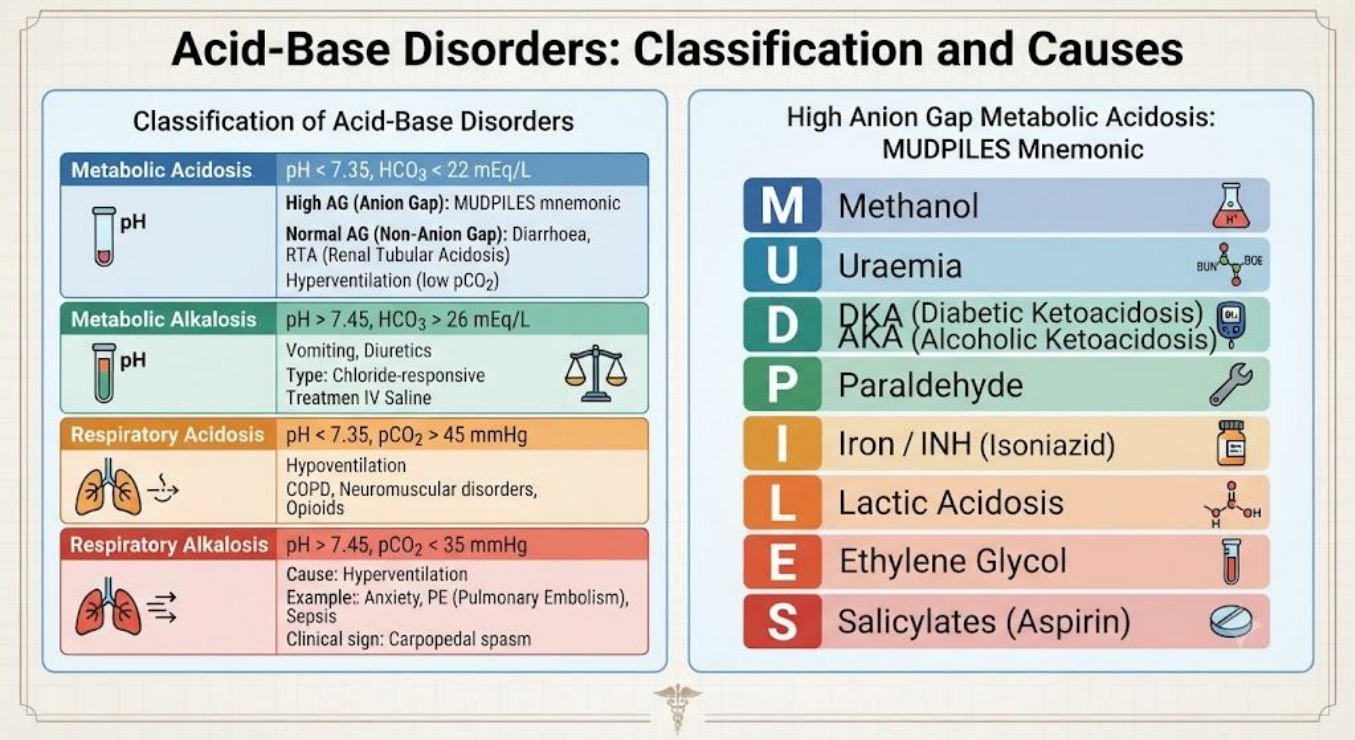

Figure 2.3: Acid-base disorders — the four primary disorders and the MUDPILES mnemonic for high anion gap metabolic acidosis

2.3.3 Respiratory acidosis and respiratory alkalosis

Respiratory acidosis (pH below 7.35, PaCO2 above 45 mmHg) results from **alveolar hypoventilation**: causes include COPD, neuromuscular disease (GBS, MND, myasthenia gravis), opioid or sedative overdose, and central respiratory depression. Acute respiratory acidosis causes confusion and coma (CO2 narcosis); chronic respiratory acidosis (as in COPD) is compensated by renal bicarbonate retention (elevated HCO3 and relatively preserved pH).

Respiratory alkalosis (pH above 7.45, PaCO2 below 35 mmHg) results from **alveolar hyperventilation**: causes include anxiety, pain, pulmonary embolism (stimulating J receptors), pneumonia, sepsis, hepatic encephalopathy, and mechanical ventilation with excessive tidal volume or rate. Features include perioral tingling, carpopedal spasm (Trousseau's sign: hypocalcaemia from alkalosis reducing ionised calcium), and tetany. Treatment is directed at the underlying cause.

Fill in the blank: Respiratory acidosis results from hypoventilation (COPD, opioids, neuromuscular disease); respiratory alkalosis results from hyperventilation (anxiety, PE, sepsis, hepatic encephalopathy); alkalosis reduces ionised calcium causing _____ and carpopedal spasm.

Pilot questions 2.3

1. Describe the three systems maintaining acid-base homeostasis and state the time course of each. (Linked to SLO 2.3)
2. Explain the anion gap and describe how it distinguishes between causes of metabolic acidosis. (Linked to SLO 2.3)
3. List the causes of high anion gap metabolic acidosis using the MUDPILES mnemonic. (Linked to SLO 2.3)
4. Describe the causes and clinical features of respiratory acidosis. (Linked to SLO 2.3)
5. Describe the causes and management of metabolic alkalosis. (Linked to SLO 2.3)

2.4 Calcium, Phosphate, and Magnesium Disorders

2.4.1 Calcium disorders: hypocalcaemia and hypercalcaemia

Hypocalcaemia (corrected serum calcium below 2.2 mmol/L; ionised calcium below 1.1 mmol/L) is caused by **hypoparathyroidism** (post-thyroid or parathyroid surgery; autoimmune), **vitamin D deficiency** (rickets, osteomalacia, malabsorption, CKD), **hypomagnesaemia** (impairs PTH release and action), and pancreatitis. Clinical features: perioral paraesthesia, muscle cramps, tetany, Chvostek's sign (facial muscle twitch on tapping the facial nerve), Trousseau's sign (carpopedal spasm on inflating BP cuff), and in severe cases seizures and laryngospasm. Treatment: IV calcium gluconate for acute symptomatic hypocalcaemia; oral calcium and vitamin D for chronic.

Hypercalcaemia (corrected calcium above 2.6 mmol/L) is caused most commonly by **primary hyperparathyroidism** (parathyroid adenoma; most common cause in outpatients) and **malignancy** (most common cause in inpatients: from PTH-related protein secretion, osteolytic metastases, or lymphoma producing calcitriol). Other causes: sarcoidosis, vitamin D toxicity, thiazide diuretics, milk-alkali syndrome. Clinical features: 'bones, moans, groans, and psychic overtones' (bone pain, abdominal pain and constipation, polyuria and polydipsia, confusion and depression). Management: IV fluids (saline); IV bisphosphonates; calcitonin; treat underlying cause.

Fill in the blank: Hypercalcaemia is most commonly caused by primary hyperparathyroidism (outpatients) and malignancy (inpatients); clinical features are 'bones, moans, groans, and psychic _____'; treatment includes IV fluids and bisphosphonates.

2.4.2 Phosphate and magnesium disorders

Hypophosphataemia (serum phosphate below 0.8 mmol/L) is caused by poor intake, malabsorption, refeeding syndrome (phosphate driven into cells by insulin when nutrition is reinstituted after starvation), and hyperparathyroidism. Severe hypophosphataemia (below 0.3 mmol/L) causes muscle weakness, haemolytic anaemia, rhabdomyolysis, respiratory failure, and impaired cardiac function. Treatment: phosphate supplementation (oral or IV in severe cases).

Hyperphosphataemia (above 1.5 mmol/L) is most commonly caused by CKD (the kidney is the primary route of phosphate excretion). It drives down ionised calcium (causing hypocalcaemia), stimulates PTH secretion, and promotes vascular calcification (combined with elevated calcium-phosphate product). Management: dietary phosphate restriction, phosphate binders (calcium carbonate, sevelamer, lanthanum). Magnesium disorders: **hypomagnesaemia** (caused by chronic diarrhoea, loop diuretics, alcohol excess, and PPIs) causes neuromuscular irritability and refractory hypokalaemia; treated with IV or oral magnesium. **Hypermagnesaemia** (usually from excessive Mg intake in renal failure) causes neuromuscular depression and cardiac arrest at very high levels.

Fill in the blank: Hyperphosphataemia in CKD drives hypocalcaemia, stimulates PTH secretion, and promotes vascular calcification; treated with dietary restriction and phosphate _____; hypomagnesaemia causes refractory hypokalaemia.

2.4.3 CKD-mineral bone disease

CKD-mineral bone disease (CKD-MBD) is a systemic disorder of mineral metabolism that develops progressively as GFR declines. The sequence of events is: reduced renal calcitriol production causes **hypocalcaemia**; hypocalcaemia and phosphate retention (from reduced renal phosphate excretion) together stimulate **parathyroid hyperplasia and PTH secretion** (secondary hyperparathyroidism). Elevated PTH mobilises calcium from bone (osteitis fibrosa cystica), demineralises the skeleton, and promotes renal phosphate excretion (but this is ineffective at GFR below 30 mL/min).

The consequences of CKD-MBD include **renal osteodystrophy** (a mixed bone disease: osteitis fibrosa cystica from high PTH, osteomalacia from vitamin D deficiency, and adynamic bone disease from low turnover), **vascular calcification** (elevated calcium-phosphate product deposits calcium in vessel walls, accelerating cardiovascular mortality), and **pathological fractures**. Management: dietary phosphate restriction, phosphate binders, activated vitamin D (alfacalcidol or calcitriol) to suppress PTH, and parathyroidectomy in refractory cases.

Fill in the blank: CKD-MBD results from reduced calcitriol causing hypocalcaemia, phosphate retention, and secondary _____ (PTH hypersecretion); consequences include renal osteodystrophy, vascular calcification, and pathological fractures.

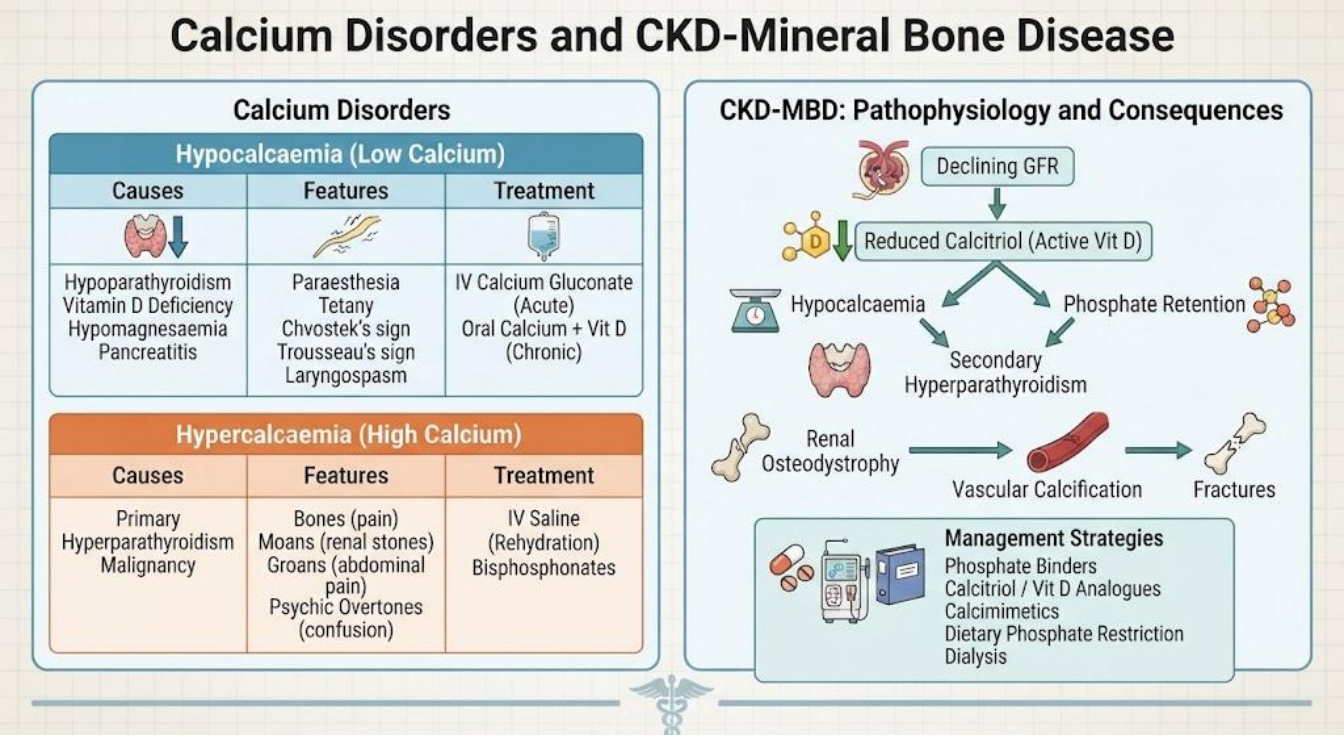

Figure 2.4: Calcium disorders and the pathogenesis and management of CKD-mineral bone disease

Pilot questions 2.4

1. Describe the causes and clinical features of hypocalcaemia. (Linked to SLO 2.4)
2. Describe the causes and management of hypercalcaemia. (Linked to SLO 2.4)
3. Explain why hyperphosphataemia in CKD promotes vascular calcification. (Linked to SLO 2.5)
4. Describe the pathogenesis and consequences of CKD-mineral bone disease. (Linked to SLO 2.5)
5. Describe the management of CKD-MBD. (Linked to SLO 2.5)

Series Summary

This Series covered the major electrolyte and acid-base disorders. Hyponatraemia (sodium below 135 mmol/L) is classified by volume status: hypovolaemic (GI or renal sodium losses), euvolaemic (SIADH: most common cause; urine sodium above 40, urine osmolality above 100), and hypervolaemic (heart failure, cirrhosis, nephrotic syndrome); severe hyponatraemia (below 125 mmol/L) causes cerebral oedema, seizures, and coma; managed with hypertonic saline at a maximum correction rate of 10 to 12 mmol/L per day. Hypernatraemia (sodium above 145 mmol/L) results from water deficit; causes include insensible losses, diabetes insipidus (central: no ADH production; nephrogenic: ADH resistance from lithium or hypercalcaemia), and inability to drink; treated with oral water or IV hypotonic fluids at a maximum rate of 10 to 12 mmol/L per day. Hypokalaemia (below 3.5 mmol/L) commonly from diuretics, vomiting, or diarrhoea; ECG shows flat T waves and prominent U waves; severe cases risk arrhythmia; treated with potassium supplementation and correction of hypomagnesaemia.

Hyperkalaemia (above 5.5 mmol/L) in CKD from impaired renal excretion, acidosis, or drugs; ECG shows peaked T waves progressing to QRS widening and sine wave; managed in three steps: IV calcium gluconate (membrane stabilisation), IV insulin-glucose (redistribution), and haemodialysis or ion exchange resins (removal). Acid-base: pH 7.35 to 7.45 maintained by buffers, respiratory regulation, and renal regulation; metabolic acidosis classified by anion gap (high AG: MUDPILES; normal AG: diarrhoea, RTA); metabolic alkalosis from vomiting or diuretics; respiratory acidosis from hypoventilation; respiratory alkalosis from hyperventilation. Hypocalcaemia from hypoparathyroidism, vitamin D deficiency, or CKD; features include Chvostek's and Trousseau's signs, tetany; treated with calcium and vitamin D. Hypercalcaemia from primary hyperparathyroidism (outpatients) or malignancy (inpatients); features: bones, moans, groans, psychic overtones; treated with IV saline and bisphosphonates. CKD-MBD: reduced calcitriol, hypocalcaemia, phosphate retention, secondary hyperparathyroidism, renal osteodystrophy, and vascular calcification; managed with phosphate binders, active vitamin D, and parathyroidectomy if refractory.

Glossary of Terms

- **Hyponatraemia:** serum sodium below 135 mmol/L; classified by volume status as hypovolaemic, euvolaemic (SIADH), or hypervolaemic.
- **SIADH:** syndrome of inappropriate antidiuretic hormone secretion; euvolaemic hyponatraemia with urine osmolality above 100 and urine sodium above 40 mmol/L.
- **Osmotic demyelination syndrome:** a neurological complication of overly rapid correction of hyponatraemia; prevented by correcting sodium at no more than 10 to 12 mmol/L per day.
- **Diabetes insipidus (DI):** a condition of excessive dilute urine from deficient ADH production (central DI) or renal resistance to ADH (nephrogenic DI).
- **Hypokalaemia:** serum potassium below 3.5 mmol/L; causes include diuretics, vomiting, diarrhoea, and transcellular shifts in alkalosis.
- **Hyperkalaemia:** serum potassium above 5.5 mmol/L; causes include CKD, acidosis, and drugs (ACEi, ARBs, potassium-sparing diuretics); potentially fatal from cardiac arrhythmia.
- **Anion gap:** serum sodium minus the sum of chloride and bicarbonate; normal 8 to 12 mmol/L; elevated in high AG metabolic acidosis from unmeasured anions (MUDPILES).
- **MUDPILES:** a mnemonic for causes of high anion gap metabolic acidosis: Methanol, Uraemia, DKA, Propylene glycol, Isoniazid or Iron, Lactic acidosis, Ethylene glycol, Salicylates.
- **CKD-mineral bone disease (CKD-MBD):** a systemic disorder of mineral metabolism in CKD: reduced calcitriol, hypocalcaemia, phosphate retention, secondary hyperparathyroidism, renal osteodystrophy, and vascular calcification.
- **Chvostek's sign:** twitching of facial muscles on tapping the facial nerve anterior to the ear; a clinical sign of hypocalcaemia.
- **Trousseau's sign:** carpopedal spasm on inflating a blood pressure cuff above systolic for 3 minutes; a clinical sign of hypocalcaemia.
- **Renal osteodystrophy:** a mixed bone disease in CKD comprising osteitis fibrosa cystica (from high PTH), osteomalacia (from vitamin D deficiency), and adynamic bone disease.

Concept Check Questions [Series 2]

Objective Questions

1. The most common cause of euvolaemic hyponatraemia is _____ (syndrome of inappropriate ADH secretion). (Linked to SLO 2.1)
2. Severe symptomatic hyponatraemia is treated with IV _____ saline; correction must not exceed 10 to 12 mmol/L per day to prevent osmotic demyelination. (Linked to SLO 2.1)
3. The earliest ECG change in hyperkalaemia is peaked _____ T waves; the most dangerous change is ventricular fibrillation. (Linked to SLO 2.2)
4. IV calcium gluconate in hyperkalaemia _____ the myocardium against arrhythmia but does not lower serum potassium. (Linked to SLO 2.2)
5. High anion gap metabolic acidosis causes include MUDPILES; normal anion gap metabolic acidosis results from _____ loss such as diarrhoea or renal tubular acidosis. (Linked to SLO 2.3)
6. CKD-MBD results from reduced calcitriol, hypocalcaemia, phosphate retention, and secondary _____ with PTH hypersecretion. (Linked to SLO 2.5)

Short-Answer Questions

7. Describe the three-step management of severe hyperkalaemia. (Linked to SLO 2.2)
8. Explain the anion gap and list four causes of high anion gap metabolic acidosis. (Linked to SLO 2.3)
9. Describe the clinical features of hypocalcaemia including Chvostek's and Trousseau's signs. (Linked to SLO 2.4)

Long-Answer Questions

10. Describe the classification, causes, clinical features, investigation, and management of hyponatraemia. (Linked to SLO 2.1)
11. Describe the pathogenesis, consequences, and management of CKD-mineral bone disease. (Linked to SLO 2.5)

Answers to Concept Check Questions [Series 2]

Objective Questions

1. SIADH.
2. Hypertonic.
3. Symmetrical.
4. Protects.
5. Bicarbonate.
6. Hyperparathyroidism.

Short-Answer Questions

7. Step 1 Membrane stabilisation: IV 10 mL of 10 percent calcium gluconate immediately if ECG changes present; protects myocardium against arrhythmia within minutes; does not lower potassium. Step 2 Redistribution: IV 10 units insulin with 50 mL 50 percent glucose; shifts potassium into cells within 15 to 30 minutes; also sodium bicarbonate (if acidosis) and nebulised salbutamol. Step 3 Removal: loop diuretics (if urine output); calcium resonium or patiromer (oral or rectal); haemodialysis (most rapid, used in AKI or ESKD).
8. Anion gap equals sodium minus (chloride plus bicarbonate); normal 8 to 12 mmol/L; elevated when unmeasured anions replace bicarbonate in metabolic acidosis. Four causes of high AG: uraemia (renal failure: accumulation of sulphate, phosphate), DKA (ketoacids), lactic acidosis (sepsis, shock, metformin), salicylate poisoning.
9. Perioral paraesthesia and tingling, muscle cramps, tetany (involuntary muscular spasm). Chvostek's sign: twitching of facial muscles on tapping the facial nerve anterior to the ear. Trousseau's sign: carpopedal spasm (wrist and hand flexion, finger extension) on inflating a BP cuff above systolic pressure for 3 minutes. Severe cases: seizures and laryngospasm.

Long-Answer Questions

10. **Basic response:** Classification: by volume status. Hypovolaemic: total body sodium depleted, water loss less; causes: vomiting, diarrhoea, diuretics, adrenal insufficiency; urine Na below 20. Euvolaemic: SIADH (CNS disease, pulmonary disease, drugs,

malignancy); urine Na above 40, urine osmolality above 100. Hypervolaemic: heart failure, cirrhosis, nephrotic syndrome, advanced CKD; urine Na below 20. Clinical features: mild (above 130): asymptomatic; moderate (125 to 130): nausea, headache; severe (below 125): confusion, seizures, coma from cerebral oedema. Investigations: serum osmolality (low in true hyponatraemia), urine osmolality (high in SIADH), urine sodium (low in hypovolaemia and hypervolaemia; high in SIADH). Management: hypovolaemic: IV normal saline; euvolaemic (SIADH): fluid restriction 500 to 1000 mL per day; treat cause; vaptans if needed; hypervolaemic: fluid and sodium restriction; treat cause; severe symptomatic: hypertonic 3 percent saline at maximum 10 to 12 mmol/L per day to prevent osmotic demyelination.

Value-added response: The most dangerous error in hyponatraemia management is treating chronic hyponatraemia too rapidly: patients with chronic hyponatraemia have adapted their brain osmolality to the low sodium environment, and rapid correction causes the brain to shrink within its now hypertonic plasma, causing osmotic demyelination (central pontine myelinolysis) with potentially irreversible neurological injury; the 10 to 12 mmol/L per day correction limit is therefore not a target but a ceiling.

11. **Basic response:** Pathogenesis: declining GFR reduces calcitriol production; hypocalcaemia and phosphate retention stimulate parathyroid hyperplasia and PTH hypersecretion (secondary hyperparathyroidism). Elevated PTH mobilises calcium from bone, demineralises the skeleton, and attempts to excrete phosphate (ineffective at GFR below 30). Consequences: Renal osteodystrophy (osteitis fibrosa cystica from high PTH; osteomalacia from vitamin D deficiency; adynamic bone disease from low turnover); pathological fractures; vascular calcification (elevated calcium-phosphate product deposits calcium in vessel walls and cardiac valves, dramatically increasing cardiovascular mortality; the leading cause of death in dialysis patients). Management: dietary phosphate restriction; phosphate binders (calcium carbonate: inexpensive but adds calcium load; sevelamer: calcium-free, reduces vascular calcification; lanthanum carbonate); activated vitamin D (alfacalcidol or calcitriol: suppresses PTH but may worsen hypercalcaemia and hyperphosphataemia); calcimimetics (cinacalcet: reduces PTH by increasing calcium receptor sensitivity); parathyroidectomy in refractory hyperparathyroidism.

Value-added response: CKD-MBD illustrates a fundamental principle of medicine: that a condition driven by a deficiency (calcitriol) and two accumulated toxins (phosphate and uraemic compounds) interacts with a hormonal response (PTH elevation) that is initially adaptive (maintaining calcium) but ultimately harmful (bone destruction and vascular calcification), and that treatment must address the deficiency, reduce the toxins, and simultaneously modulate the hormonal response.

Answers to Pilot Questions [Series 2]

Part 2.1

1. Hyponatraemia is serum sodium below 135 mmol/L. By volume status: Hypovolaemic (sodium depleted more than water; causes: vomiting, diarrhoea, diuretics, adrenal insufficiency), Euvolaemic (water excess with normal body sodium; most commonly SIADH), Hypervolaemic (both sodium and water excess, water greater; causes: heart failure, cirrhosis, nephrotic syndrome, CKD).
2. Mild (above 130 mmol/L): often asymptomatic. Moderate (125 to 130): nausea, malaise, headache. Severe (below 125): confusion, seizures, and coma from cerebral oedema; brain cells swell because the extracellular fluid is hypotonic relative to the intracellular compartment; this is life-threatening from herniation or respiratory arrest and requires urgent treatment with hypertonic saline.
3. Serum osmolality: low (below 280 mOsm/kg) confirms true hypotonic hyponatraemia. Urine osmolality: above 100 mOsm/kg indicates ADH activity (SIADH, hypovolaemia, heart failure); below 100 suggests primary polydipsia or low solute intake (tea and toast). Urine sodium: below 20 mmol/L suggests hypovolaemia or hypervolaemic states with avid sodium retention; above 40 mmol/L suggests SIADH or salt-wasting nephropathy.
4. SIADH is inappropriately elevated ADH secretion causing water retention and dilutional hyponatraemia despite normal or high plasma volume; it is the most common cause of euvolaemic hyponatraemia. Causes: CNS disease (stroke, meningitis, tumour), pulmonary disease (pneumonia, TB, COPD), drugs (SSRIs, carbamazepine,

cyclophosphamide, opioids), and malignancy (small cell lung cancer secreting ADH). Management: treat underlying cause; fluid restriction 500 to 1000 mL per day; vasopressin receptor antagonists (vaptans) for refractory cases.

5. Hypernatraemia is serum sodium above 145 mmol/L, always indicating water deficit relative to sodium. Central DI: failure of ADH production from the posterior pituitary due to head injury, tumour, surgery, or sarcoidosis; treated with intranasal desmopressin (synthetic ADH). Nephrogenic DI: renal resistance to ADH due to lithium toxicity, hypercalcaemia, or genetic mutations in the ADH receptor or aquaporin-2; treated by correcting the underlying cause, low-sodium diet, and thiazide diuretics (paradoxically reduce free water excretion).

Part 2.2

1. Causes: diuretics (most common in clinical practice: loop diuretics increase tubular flow and sodium delivery, activating RAAS and increasing aldosterone-driven K excretion; thiazides increase sodium delivery to aldosterone-sensitive segments), vomiting (HCl loss causes metabolic alkalosis; alkalosis drives K into cells; volume depletion activates aldosterone), diarrhoea (direct K loss), hyperaldosteronism (primary: Conn's syndrome; secondary: renin-driven), and transcellular shifts in alkalosis or with insulin or beta-agonists.
2. ECG changes: flattened or inverted T waves (reduced repolarisation); prominent U waves (abnormal repolarisation wave after T wave, best seen in precordial leads V3 to V5); ST depression; QT interval prolongation. Clinical significance: severe hypokalaemia (below 2.5 mmol/L) predisposes to ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease or receiving digoxin (hypokalaemia potentiates digoxin toxicity).
3. In CKD the kidney cannot excrete the normal daily potassium load (approximately 70 to 100 mmol/day); additionally: acidosis in CKD drives potassium out of cells (each 0.1 fall in pH raises serum K by 0.3 to 0.6 mmol/L); drugs commonly used in CKD (ACEi, ARBs: block aldosterone-driven K excretion; potassium-sparing diuretics; NSAIDs: reduce renal prostaglandin-mediated K excretion; trimethoprim: blocks K secretory channels); dietary K intake in the setting of impaired excretion.

4. In sequence from earliest to most severe: (1) peaked (tall, narrow, symmetrical) T waves; (2) PR interval prolongation; (3) P wave flattening and eventual disappearance; (4) QRS complex widening; (5) sine wave pattern (QRS merges with T wave); (6) ventricular fibrillation or asystole. The sequence reflects progressive impairment of membrane depolarisation and repolarisation.
5. Step 1 Membrane stabilisation: IV 10 mL of 10 percent calcium gluconate immediately; protects myocardium by raising threshold for arrhythmia; works within minutes; does not lower serum potassium. Step 2 Redistribution: IV 10 units insulin plus 50 mL 50 percent glucose (lowers K by 0.5 to 1.0 mmol/L within 15 to 30 minutes); IV sodium bicarbonate if metabolic acidosis; nebulised salbutamol 10 to 20 mg. Step 3 Removal: loop diuretics (furosemide) if adequate urine output; calcium resonium, sodium zirconium cyclosilicate (Lokelma), or patiromer (oral K binders); haemodialysis (most effective and immediate, used in AKI or ESKD or very severe K).

Part 2.3

1. Chemical buffers (bicarbonate-carbonic acid: primary extracellular buffer; haemoglobin: intracellular; proteins: intracellular and extracellular): respond within seconds to minutes. Respiratory regulation (adjust PaCO2 by changing ventilation rate): responds within minutes to hours; hyperventilation lowers CO2, raises pH; hypoventilation raises CO2, lowers pH. Renal regulation (adjust bicarbonate reabsorption and acid excretion): responds over hours to days; most powerful and precise system.
2. Anion gap (AG) equals sodium minus (chloride plus bicarbonate); normal 8 to 12 mmol/L. In high AG metabolic acidosis, an accumulation of unmeasured anions (lactate, ketoacids, uraemic acids, toxin metabolites) replaces bicarbonate, raising the AG; chloride remains normal. In normal AG (hyperchloraemic) metabolic acidosis, bicarbonate is lost and replaced by chloride; the AG remains normal.
3. MUDPILES: M (Methanol: metabolised to formate), U (Uraemia: accumulation of sulphate, phosphate, hippurate), D (Diabetic ketoacidosis: beta-hydroxybutyrate, acetoacetate), P (Propylene glycol or Paracetamol overdose), I (Isoniazid or Iron overdose), L (Lactic acidosis: sepsis, shock, ischaemia, metformin), E (Ethylene glycol: metabolised to oxalate; or Ethanol), S (Salicylate poisoning: salicylic acid).

4. Causes: COPD (most common chronic cause; CO2 retention from ventilation-perfusion mismatch), neuromuscular disease (Guillain-Barre syndrome, myasthenia gravis, motor neurone disease: respiratory muscle failure), opioid or sedative overdose (central respiratory depression), and obesity hypoventilation syndrome. Features: acute (confusion, CO2 narcosis, coma from cerebral vasodilation); chronic (renal bicarbonate compensation maintains relatively normal pH with elevated HCO3).
5. Causes: vomiting or nasogastric suction (HCl loss, volume depletion activating RAAS, bicarbonate retention); diuretics (chloride and volume depletion stimulating bicarbonate reabsorption); exogenous alkali (bicarbonate infusion, antacids). Maintenance: chloride depletion and volume depletion both stimulate proximal tubular bicarbonate reabsorption. Diagnosis: urine chloride below 25 mmol/L indicates chloride-responsive alkalosis. Management: IV normal saline (restores chloride and volume, allowing bicarbonate excretion); stop diuretics; correct hypokalaemia.

Part 2.4

1. Causes: hypoparathyroidism (post-thyroid or parathyroid surgery: most common cause; autoimmune hypoparathyroidism), vitamin D deficiency (dietary, malabsorption, lack of sunlight, CKD reducing calcitriol synthesis), hypomagnesaemia (impairs PTH release and end-organ responsiveness), and pancreatitis (calcium saponification in fat necrosis). Features: perioral paraesthesia, muscle cramps, tetany, Chvostek's sign (facial muscle twitch), Trousseau's sign (carpopedal spasm on inflating BP cuff), laryngospasm, and seizures in severe cases.
2. Causes: primary hyperparathyroidism (parathyroid adenoma: most common in outpatients; elevated PTH and calcium), malignancy (most common in inpatients: PTHrP secretion, osteolytic metastases, lymphoma producing calcitriol), sarcoidosis (macrophage calcitriol production), vitamin D toxicity, thiazide diuretics. Management: IV normal saline (rehydration and promotes calcium excretion); IV bisphosphonates (zoledronic acid or pamidronate: inhibit osteoclast-mediated calcium release; onset 2 to 4 days; used for malignancy-related hypercalcaemia); calcitonin (rapid but short-lived reduction); treat underlying cause.

3. In CKD, hyperphosphataemia occurs because the failing kidney cannot excrete the normal daily phosphate load; elevated serum phosphate binds ionised calcium, reducing free calcium (driving hypocalcaemia and PTH secretion); phosphate and calcium combine in the circulation and vessel walls when the calcium-phosphate product exceeds 4.4 mmol2/L2 (approximately 55 mg2/dL2); calcium-phosphate deposits in the media of arterial walls (medial arterial calcification), cardiac valves, and soft tissues; this accelerates cardiovascular disease and is the major contributor to the extremely high cardiovascular mortality in ESKD patients.
4. Pathogenesis: declining calcitriol production causes hypocalcaemia; phosphate retention (from reduced renal excretion) worsens hypocalcaemia; both stimulate parathyroid hyperplasia and PTH hypersecretion. PTH mobilises calcium from bone (osteitis fibrosa cystica), reduces tubular phosphate reabsorption (ineffective at GFR below 30), and raises vitamin D metabolite activation (blunted in CKD). Consequences: renal osteodystrophy (bone pain, deformity, fractures), vascular and soft tissue calcification (accelerated cardiovascular mortality), pathological fractures.
5. Dietary phosphate restriction (limit high-phosphate foods: dairy, cola drinks, nuts, processed foods); phosphate binders (with meals: calcium carbonate, calcium acetate: inexpensive; sevelamer: calcium-free, reduces vascular calcification; lanthanum carbonate); active vitamin D analogues (alfacalcidol or calcitriol: suppress PTH but may worsen hypercalcaemia and hyperphosphataemia if doses are excessive; use with monitoring); calcimimetics (cinacalcet: allosteric activator of calcium-sensing receptor in parathyroid; reduces PTH without raising calcium; used in secondary hyperparathyroidism with high calcium); parathyroidectomy (for refractory secondary or tertiary hyperparathyroidism).

References and Attributions [Series 2]

Textual References

- Spasovski, G. et al. (2014). Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia. European Journal of Endocrinology, 170(3), G1 to G47.
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- Kumar, P. and Clark, M. (2017). Kumar and Clark's Clinical Medicine (9th ed.). Edinburgh: Elsevier.
- Rose, B. D. and Post, T. W. (2001). Clinical Physiology of Acid-Base and Electrolyte Disorders (5th ed.). New York: McGraw-Hill.

Figures, Plates, Tables, and Boxes

- Table 2.1: Sodium disorders — hyponatraemia and hypernatraemia. AI prompt: "Two-panel table: Hyponatraemia (three-type classification by volume status, clinical features by severity, management); Hypernatraemia (causes including central and nephrogenic DI, features, management); alternating shading." OER search: "sodium disorders hyponatraemia hypernatraemia classification management table".
- Figure 2.2: Potassium disorders — hypokalaemia and hyperkalaemia. AI prompt: "Two-panel diagram: Hypokalaemia (causes, ECG changes, management) and Hyperkalaemia (causes, ECG sequence, three-step management); clean professional infographic." OER search: "potassium disorders hypokalaemia hyperkalaemia ECG changes management three step diagram".
- Figure 2.3: Acid-base disorders and MUDPILES mnemonic. AI prompt: "Two-panel diagram: four-row acid-base table (metabolic acidosis and alkalosis, respiratory acidosis and alkalosis) and MUDPILES mnemonic box; clean professional infographic." OER search: "acid base disorders metabolic acidosis anion gap MUDPILES mnemonic diagram".
- Figure 2.4: Calcium disorders and CKD-MBD. AI prompt: "Two-panel diagram: left two-section table (hypocalcaemia causes/features/treatment; hypercalcaemia causes/features/treatment); right CKD-MBD pathogenesis flow diagram with

management; clean professional infographic." OER search: "hypocalcaemia hypercalcaemia CKD mineral bone disease pathogenesis management diagram".

Series 3: Glomerular Diseases and Glomerulonephritis

- **Part 3.1: Introduction to Glomerular Disease**
    - Sub Part 3.1.1: Anatomy and function of the glomerulus
    - Sub Part 3.1.2: Mechanisms of glomerular injury
    - Sub Part 3.1.3: Classification of glomerular disease
- **Part 3.2: Post-Streptococcal Glomerulonephritis**
    - Sub Part 3.2.1: Epidemiology, pathogenesis, and pathology
    - Sub Part 3.2.2: Clinical features and investigations
    - Sub Part 3.2.3: Management and prognosis
- **Part 3.3: IgA Nephropathy**
    - Sub Part 3.3.1: Pathogenesis and pathology
    - Sub Part 3.3.2: Clinical features and diagnosis
    - Sub Part 3.3.3: Management and prognosis
- **Part 3.4: Rapidly Progressive Glomerulonephritis and Lupus Nephritis**
    - Sub Part 3.4.1: Rapidly progressive glomerulonephritis
    - Sub Part 3.4.2: Lupus nephritis
    - Sub Part 3.4.3: Management of RPGN and lupus nephritis

Introduction

Glomerular diseases are among the most important causes of chronic kidney disease worldwide and in Nigeria. The glomerulus, as the primary site of renal filtration, is vulnerable to immunological injury from circulating immune complexes, anti-GBM antibodies, ANCA-mediated vasculitis, and haemodynamic stress. Understanding the mechanisms of glomerular injury, the clinicopathological patterns they produce, and the specific diseases that arise from them is fundamental to nephrology practice.

This Series covers the anatomy and physiology of the glomerulus, the major mechanisms of glomerular injury, and the classification of glomerular disease. It then examines four major glomerulonephritides in clinical detail: post-streptococcal glomerulonephritis (the most common GN in Nigeria and sub-Saharan Africa), IgA nephropathy (the most common GN worldwide), rapidly progressive glomerulonephritis (the most urgent), and lupus nephritis (a systemic immune complex GN).

For each condition the pathogenesis, pathological findings, clinical presentation, investigations, management, and prognosis are covered in the detail required for clinical practice.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 3.1** describe the structure of the glomerulus and the mechanisms of glomerular injury (Linked to Part 3.1),
- **SLO 3.2** classify glomerular disease and explain the major histological patterns on light and immunofluorescence microscopy (Linked to Part 3.1),
- **SLO 3.3** describe the epidemiology, pathogenesis, clinical features, investigations, management, and prognosis of post-streptococcal glomerulonephritis (Linked to Part 3.2),

- **SLO 3.4** describe the pathogenesis, clinical features, management, and prognosis of IgA nephropathy (Linked to Part 3.3), and
- **SLO 3.5** describe rapidly progressive glomerulonephritis and lupus nephritis including their clinical features and management (Linked to Part 3.4).

3.1 Introduction to Glomerular Disease

3.1.1 Anatomy and function of the glomerulus

The glomerulus is a specialised capillary tuft enclosed within Bowman's capsule. The filtration barrier has three layers: **fenestrated endothelium** (allows free passage of water and small solutes; the fenestrae are too small to allow red cells to pass under normal conditions), **glomerular basement membrane (GBM)** (type IV collagen; negatively charged — repels anionic proteins such as albumin), and **podocyte foot processes** with slit diaphragms (the final size-selective barrier; podocyte injury disrupts the slit diaphragm and allows protein leakage).

Normal glomerular function permits filtration of water and small solutes while retaining proteins and blood cells. Loss of the GBM charge barrier allows **proteinuria** (particularly albumin); disruption of podocyte slit diaphragms causes heavy **nephrotic-range proteinuria**; glomerular inflammation allows **haematuria** and red cell casts. The mesangium (a matrix supporting the capillary loops, containing mesangial cells) provides structural support and participates in immune complex deposition and phagocytosis.

Fill in the blank: The glomerular filtration barrier has three layers: fenestrated endothelium, GBM (negatively charged, repels albumin), and podocyte _____ processes with slit diaphragms; podocyte injury causes nephrotic-range proteinuria.

3.1.2 Mechanisms of glomerular injury

Glomerular injury occurs through four main mechanisms. **Immune complex deposition** is the most common: circulating antigen-antibody complexes deposit in the glomerulus (mesangium,

subendothelial, or subepithelial space) and activate complement, attracting inflammatory cells. Examples: post-streptococcal GN (subepithelial humps), lupus nephritis, IgA nephropathy.

Anti-GBM antibody disease (Goodpasture syndrome): antibodies against the alpha-3 chain of type IV collagen bind to the GBM, causing linear IgG deposition on immunofluorescence and rapidly progressive nephritis with pulmonary haemorrhage. **ANCA-associated vasculitis** (granulomatosis with polyangiitis, microscopic polyangiitis): ANCA activate neutrophils causing pauci-immune necrotising GN (minimal or no immunoglobulin on immunofluorescence). **Haemodynamic and metabolic injury** (as in diabetic nephropathy and hypertensive nephrosclerosis) causes glomerulosclerosis without significant inflammation.

Fill in the blank: Glomerular injury mechanisms include immune complex deposition (most common), anti-GBM antibody disease (linear IgG on IF), ANCA-associated vasculitis (_____ immune GN), and haemodynamic injury (glomerulosclerosis).

3.1.3 Classification of glomerular disease

Glomerular diseases are classified by their predominant clinical syndrome (nephritic or nephrotic) and by the **histological pattern on renal biopsy** using light microscopy, immunofluorescence, and electron microscopy. Major histological patterns include: **diffuse proliferative GN** (post-streptococcal GN: mesangial and endocapillary proliferation, subepithelial humps on EM), **focal segmental glomerulosclerosis (FSGS)** (segmental scarring affecting some glomeruli: nephrotic syndrome with haematuria), **membranous nephropathy** (subepithelial immune complex deposits producing a thickened GBM: nephrotic syndrome), **minimal change disease (MCD)** (normal on light microscopy; podocyte foot process effacement on EM: nephrotic syndrome, especially in children), and **crescentic GN** (cellular or fibrous crescents filling Bowman's space: rapidly progressive GN).

Fill in the blank: Histological patterns include diffuse proliferative GN (post-streptococcal), FSGS, membranous nephropathy, minimal change disease (podocyte _____ effacement on EM), and crescentic GN (rapidly progressive GN).

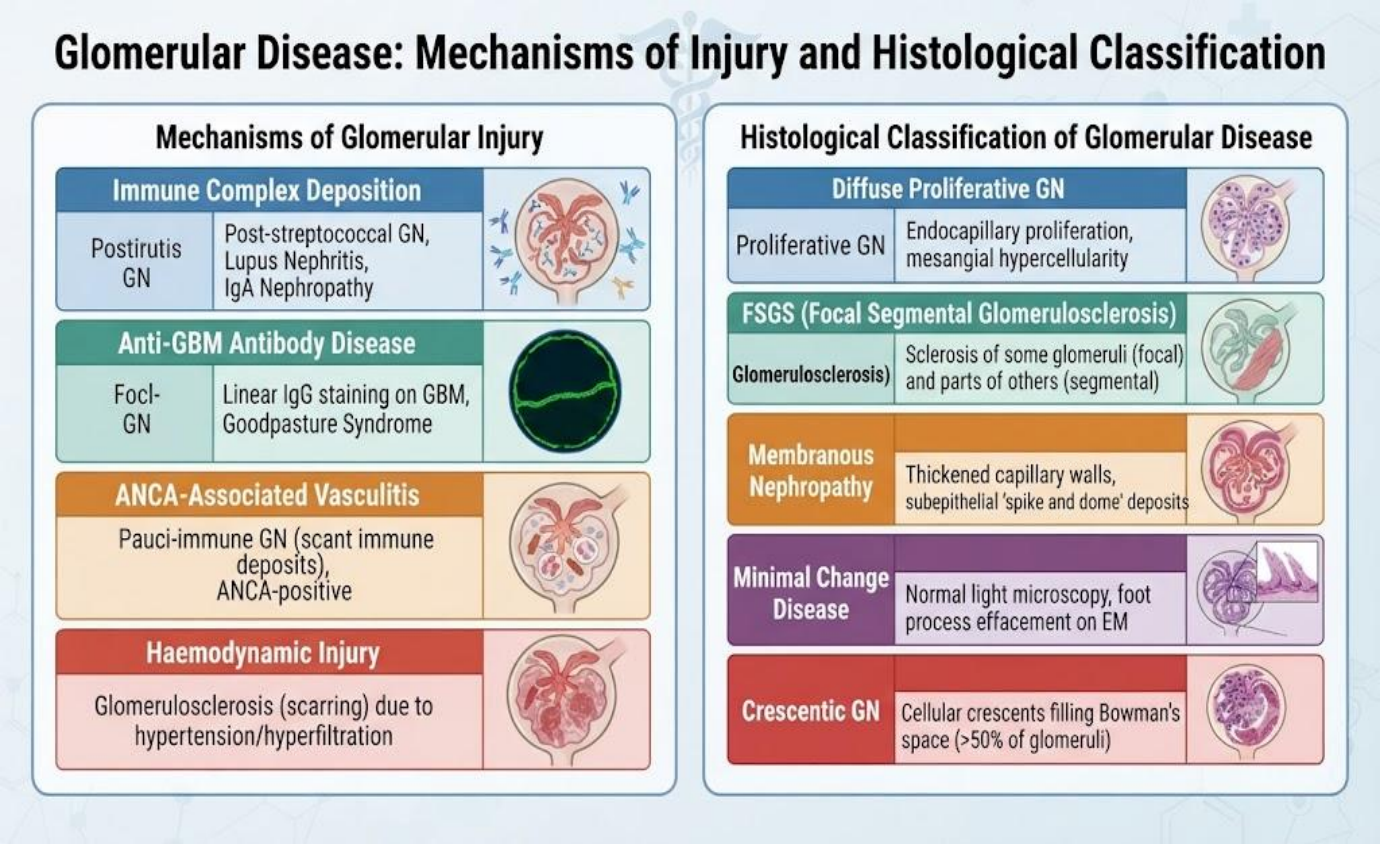

Figure 3.1: Mechanisms of glomerular injury and the major histological patterns of glomerulonephritis

Pilot questions 3.1

1. Describe the three layers of the glomerular filtration barrier and the consequence of injury to each. (Linked to SLO 3.1)
2. Explain the mechanism of immune complex-mediated glomerular injury. (Linked to SLO 3.1)
3. Distinguish between anti-GBM antibody disease and ANCA-associated vasculitis. (Linked to SLO 3.1)
4. Describe the histological features of minimal change disease on light microscopy and electron microscopy. (Linked to SLO 3.2)
5. Define crescentic GN and explain what it signifies clinically. (Linked to SLO 3.2)

3.2 Post-Streptococcal Glomerulonephritis

3.2.1 Epidemiology, pathogenesis, and pathology

Post-streptococcal glomerulonephritis (PSGN) is the most common GN in Nigeria and sub-Saharan Africa, predominantly affecting children aged 5 to 15 years. It follows infection with **nephritogenic strains of Group A beta-haemolytic Streptococcus** (S. pyogenes), most commonly pharyngitis (1 to 3 weeks before GN onset) and skin infection or impetigo (2 to 6 weeks before onset).

Pathogenesis involves deposition of streptococcal antigens (particularly SPEB and NAPlr) in the glomerulus with subsequent complement activation and inflammatory cell recruitment. On renal biopsy, **light microscopy** shows diffuse mesangial and endocapillary proliferation; **immunofluorescence** shows granular deposits of IgG and C3 ('starry sky' pattern); and **electron microscopy** shows large subepithelial immune complex deposits called 'humps' — the hallmark of PSGN.

Fill in the blank: PSGN follows nephritogenic Group A streptococcal infection; biopsy shows diffuse proliferative GN on LM, granular IgG and C3 on IF ('starry sky'), and subepithelial _____ ('humps') on EM.

3.2.2 Clinical features and investigations

PSGN presents as **acute nephritic syndrome** 1 to 3 weeks after streptococcal pharyngitis or 2 to 6 weeks after impetigo: sudden onset of haematuria (smoky or cola-coloured urine), proteinuria, hypertension, periorbital oedema, and oliguria. Systemic features include malaise, headache, and abdominal pain.

Investigations show: haematuria and proteinuria on urinalysis (red cell casts on microscopy), elevated serum creatinine (indicating AKI in severe cases), **elevated ASO titre** (anti-streptolysin O: positive in 60 to 80 percent of pharyngitis-related cases; less sensitive for skin infections), **elevated anti-DNase B titre** (more sensitive for skin infections), **low serum C3** (complement consumption in the acute phase; normalises within 8 weeks), and C4 is normal or mildly

reduced. Low C3 persisting beyond 8 weeks should prompt consideration of MPGN or lupus nephritis.

Fill in the blank: PSGN investigation shows elevated ASO titre, low serum _____ (normalises within 8 weeks), and red cell casts on urine microscopy; C3 persistently low after 8 weeks suggests an alternative diagnosis.

3.2.3 Management and prognosis

Management of PSGN is primarily supportive: **sodium and fluid restriction** (for hypertension and oedema), **antihypertensive therapy** (loop diuretics for volume-dependent hypertension; calcium channel blockers or hydralazine for resistant cases), **loop diuretics** (furosemide for oedema), and **antibiotic treatment** of any ongoing streptococcal infection (penicillin V or amoxicillin for 10 days; does not alter the course of established GN but eliminates the organism and prevents spread).

Prognosis in children is excellent: more than 95 percent achieve complete recovery of renal function within weeks to months. Dialysis may be required in the minority with severe AKI. In adults, the prognosis is somewhat less favourable, with 20 to 40 percent developing chronic renal impairment. Risk factors for poor outcome include severe AKI at presentation, persistent heavy proteinuria beyond 3 to 6 months, and crescentic change on biopsy.

Fill in the blank: PSGN management is supportive: sodium restriction, loop diuretics, antihypertensives, and antibiotics to eliminate streptococcal infection; prognosis in children is excellent (above 95 percent _____); adults have a higher risk of chronic impairment.

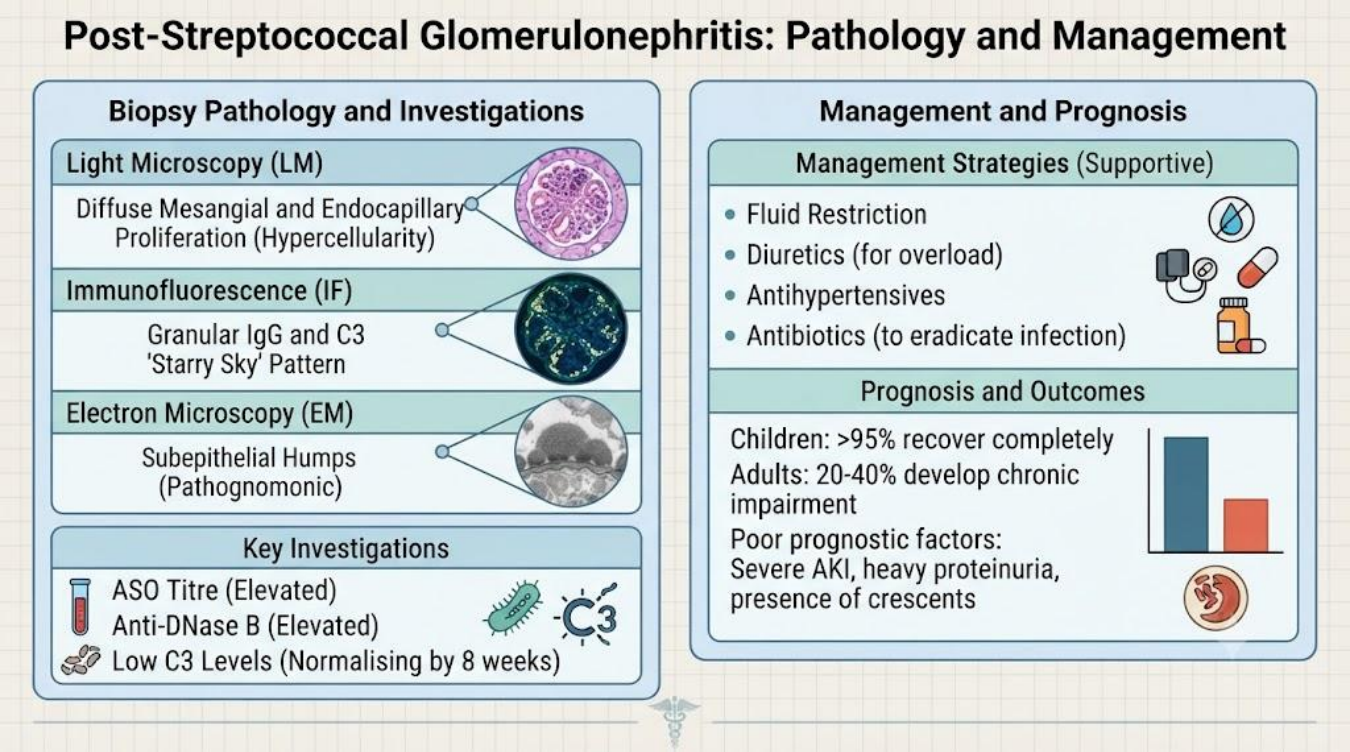

Figure 3.2: PSGN biopsy findings, investigations, management, and prognosis

Pilot questions 3.2

1. Describe the epidemiology and pathogenesis of post-streptococcal glomerulonephritis. (Linked to SLO 3.3)
2. Describe the renal biopsy findings in PSGN on light microscopy, immunofluorescence, and electron microscopy. (Linked to SLO 3.3)
3. Describe the clinical presentation of PSGN. (Linked to SLO 3.3)
4. Describe the investigations in PSGN and explain the significance of serum C3. (Linked to SLO 3.3)
5. Describe the management and prognosis of PSGN in children and adults. (Linked to SLO 3.3)

3.3 IgA Nephropathy

3.3.1 Pathogenesis and pathology

IgA nephropathy (Berger's disease) is the most common primary GN worldwide, characterised by mesangial deposition of **IgA1** (galactose-deficient IgA1) with secondary mesangial inflammation and complement activation. The pathogenesis involves four hits: aberrant O-glycosylation of IgA1, production of anti-glycan antibodies, formation of circulating immune complexes, and mesangial deposition triggering inflammation.

Renal biopsy is required for definitive diagnosis: **light microscopy** shows mesangial hypercellularity and matrix expansion; **immunofluorescence** shows mesangial IgA deposits (the defining feature) with variable C3 and IgG; **electron microscopy** shows mesangial electron-dense deposits. The Oxford Classification (MEST-C score) grades mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C) to guide prognosis and treatment.

Fill in the blank: IgA nephropathy is defined by mesangial IgA deposits on immunofluorescence; the Oxford MEST-C score grades mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, tubular _____, and crescents.

3.3.2 Clinical features and diagnosis

IgA nephropathy most commonly presents in young adults (peak age 20 to 40 years) with one of three patterns: **episodic macroscopic haematuria** (gross haematuria occurring 1 to 3 days after an upper respiratory tract infection or exercise: 'synpharyngitic haematuria' — distinguishing it from PSGN where haematuria is delayed by 1 to 3 weeks), **persistent microscopic haematuria with variable proteinuria** (asymptomatic urinary abnormalities on routine testing), or less commonly **nephrotic syndrome or hypertension** with progressive renal impairment. Rarely, IgA nephropathy presents as rapidly progressive GN.

Diagnosis requires renal biopsy (no reliable non-invasive serum test for IgA nephropathy). Serum IgA levels are elevated in approximately 50 percent of patients but are non-specific. Secondary causes of mesangial IgA deposition must be excluded: **Henoch-Schonlein Purpura**

(IgA vasculitis) (IgA nephropathy with systemic vasculitis: palpable purpura, arthritis, abdominal pain, GN), liver cirrhosis (reduced hepatic IgA clearance), and coeliac disease.

Fill in the blank: IgA nephropathy classically presents as episodic macroscopic haematuria 1 to 3 days after URTI (synpharyngitic haematuria); secondary causes of mesangial IgA deposition include Henoch-Schonlein Purpura, _____, and coeliac disease.

3.3.3 Management and prognosis

Management is stratified by risk of progression. All patients: **optimise blood pressure** (target below 130/80 mmHg), **maximise RAS blockade with ACEi or ARB** (reduces proteinuria and slows progression), and **lifestyle modification**. High-risk patients (proteinuria persistently above 1 g per day despite optimised RAS blockade): **immunosuppression** with corticosteroids (prednisolone) and in severe or crescentic disease, cyclophosphamide.

Newer therapies include **targeted-release budesonide (Nefecon/Tarpeyo)** — a gut-targeted corticosteroid with minimal systemic side effects targeting IgA1 production in the gastrointestinal lymphoid tissue — and **SGLT2 inhibitors** (dapagliflozin, empagliflozin: reduce proteinuria and slow CKD progression). Prognosis: approximately 30 to 40 percent of patients with IgA nephropathy reach end-stage kidney disease over 20 to 30 years. Poor prognostic factors include heavy proteinuria (above 1 g per day), hypertension, impaired GFR at presentation, and MEST-C scores with high T or C.

Fill in the blank: IgA nephropathy management includes RAS blockade (ACEi or ARB) for all; corticosteroids for high-risk; SGLT2 inhibitors reduce proteinuria; approximately 30 to 40 percent reach ESKD over _____ years.

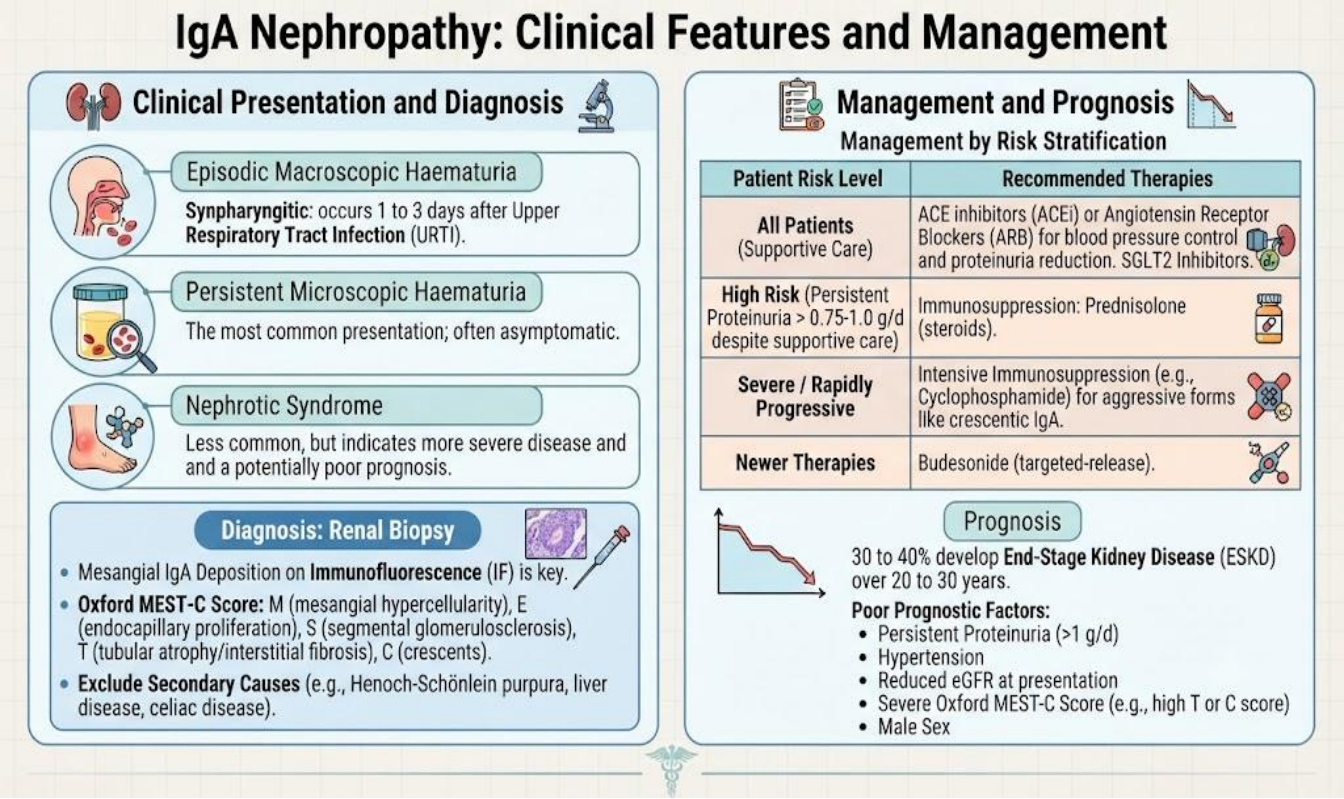

Figure 3.3: IgA nephropathy — clinical presentations, diagnosis, management, and prognosis

Pilot questions 3.3

1. Describe the pathogenesis of IgA nephropathy using the four-hit model. (Linked to SLO 3.4)
2. Describe the renal biopsy findings in IgA nephropathy. (Linked to SLO 3.4)
3. Describe the clinical presentations of IgA nephropathy. (Linked to SLO 3.4)
4. Distinguish between IgA nephropathy and Henoch-Schonlein Purpura. (Linked to SLO 3.4)
5. Describe the management and prognosis of IgA nephropathy. (Linked to SLO 3.4)

3.4 Rapidly Progressive Glomerulonephritis and Lupus Nephritis

3.4.1 Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome of rapidly deteriorating renal function (loss of 50 percent or more of GFR within weeks to months) with active urine sediment, caused by **crescentic GN** on biopsy. Crescents are formed by proliferating parietal epithelial cells and infiltrating macrophages filling Bowman's space, compressing the glomerular tuft and destroying the filtration unit.

RPGN is classified into three types by immunofluorescence pattern: **Type I (anti-GBM disease / Goodpasture syndrome)** — linear IgG deposits; presents with GN and pulmonary haemorrhage; anti-GBM antibody positive; **Type II (immune complex RPGN)** — granular immunoglobulin deposits; causes include lupus nephritis, post-infectious GN, IgA nephropathy; **Type III (pauci-immune RPGN / ANCA-associated vasculitis)** — minimal or no Ig on IF; ANCA positive (c-ANCA: granulomatosis with polyangiitis; p-ANCA: microscopic polyangiitis); most common type in adults.

Fill in the blank: RPGN types: Type I (anti-GBM: linear IgG, Goodpasture), Type II (immune complex: granular Ig, lupus or post-infectious), Type III (_____ immune: no Ig, ANCA-positive vasculitis); all cause crescentic GN and rapid GFR loss.

3.4.2 Lupus nephritis

Lupus nephritis (LN) occurs in 40 to 60 percent of patients with systemic lupus erythematosus (SLE), resulting from deposition of **anti-dsDNA immune complexes** in the glomerulus. It is the most common serious complication of SLE and a major cause of morbidity and mortality. LN is classified by the **ISN/RPS classification** (Classes I to VI) based on renal biopsy: Class I (minimal mesangial), Class II (mesangial proliferative), Class III (focal proliferative: less than 50 percent of glomeruli), **Class IV (diffuse proliferative: above 50 percent of glomeruli — most severe, most common to progress to ESKD)**, Class V (membranous), and Class VI (advanced sclerosis).

Clinical features depend on class: Class III and IV present with active nephritic syndrome (haematuria, proteinuria, hypertension, AKI); Class V presents with nephrotic syndrome. Full-house immunofluorescence pattern (IgG, IgA, IgM, C3, C4, C1q all deposited) is characteristic. Serology: **low complement C3 and C4**, elevated **anti-dsDNA antibodies** correlate with disease activity.

Fill in the blank: Lupus nephritis Class IV (diffuse proliferative) is the most severe; immunofluorescence shows 'full-house' pattern (IgG, IgA, IgM, C3, C4, C1q); serology shows low _____ C3 and C4 and elevated anti-dsDNA.

3.4.3 Management of RPGN and lupus nephritis

RPGN management is a nephrology emergency requiring immediate diagnosis and treatment to preserve renal function. General approach: **pulse IV methylprednisolone** followed by high-dose oral prednisolone, combined with an additional immunosuppressant agent according to type. Type I (anti-GBM): cyclophosphamide plus prednisolone plus **plasmapheresis** (to remove circulating anti-GBM antibodies rapidly). Type III (ANCA): cyclophosphamide plus prednisolone (or rituximab as an alternative). Renal function at presentation and time to treatment are the strongest predictors of outcome; dialysis may be required.

Lupus nephritis management for Class III and IV: induction with **high-dose corticosteroids** plus **cyclophosphamide (Euro-Lupus or NIH protocol) or mycophenolate mofetil (MMF)** (preferred in Africa due to lower gonadotoxicity); maintenance with **MMF or azathioprine** plus low-dose prednisolone for at least 3 years. **Hydroxychloroquine** is given to all SLE patients with renal disease (reduces flares). Newer agents: **belimumab** (anti-BAFF monoclonal antibody) and **voclosporin** (calcineurin inhibitor) are approved for LN. Class V: ACEi or ARB plus immunosuppression.

Fill in the blank: RPGN Type I (anti-GBM) is treated with cyclophosphamide, prednisolone, and plasmapheresis; lupus nephritis Class IV induction uses corticosteroids plus cyclophosphamide or _____ mofetil; maintenance with MMF or azathioprine.

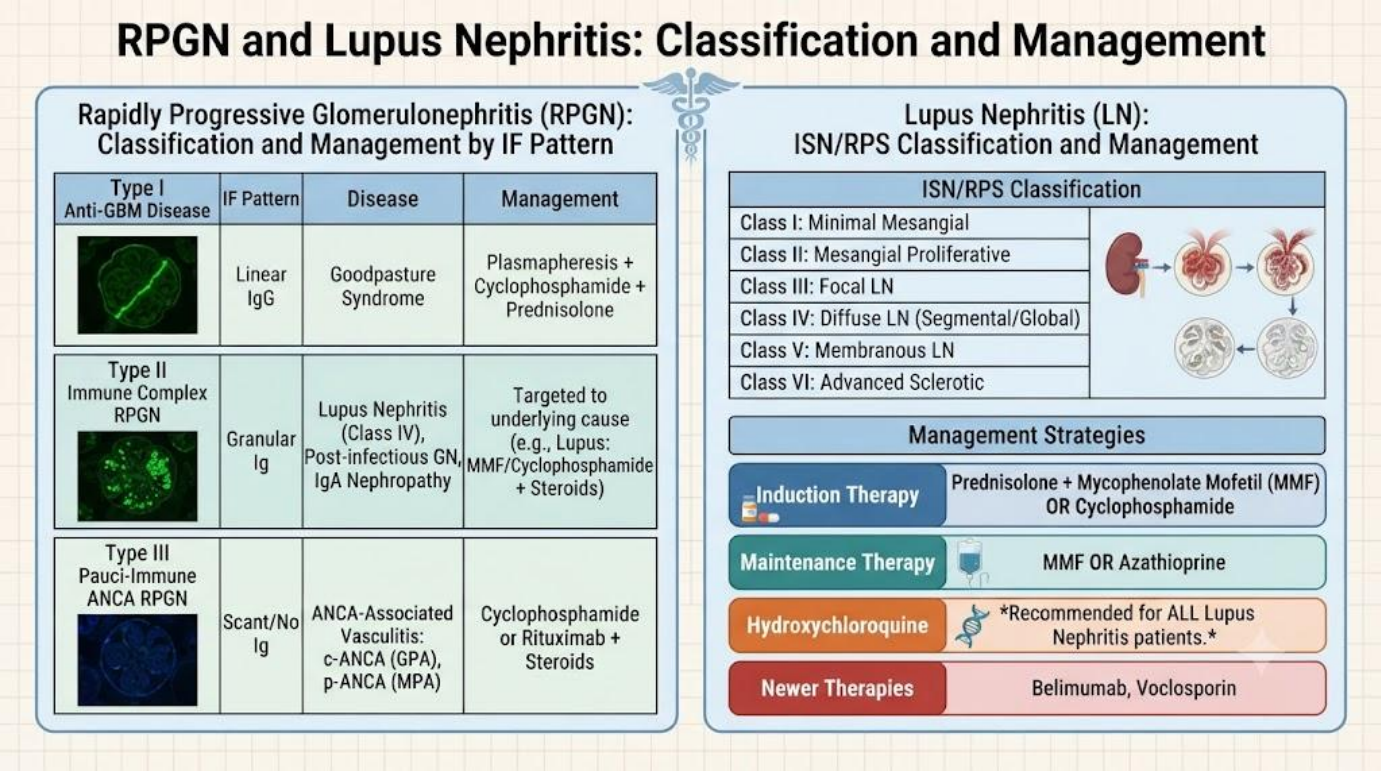

Figure 3.4: RPGN classification by immunofluorescence and lupus nephritis ISN/RPS classification and management

Pilot questions 3.4

1. Define RPGN and describe the histological finding that defines it on renal biopsy. (Linked to SLO 3.5)
2. Classify RPGN into three types and describe the immunofluorescence pattern and cause of each. (Linked to SLO 3.5)
3. Describe the ISN/RPS classification of lupus nephritis and state which class carries the worst prognosis. (Linked to SLO 3.5)
4. Describe the investigations used to diagnose and monitor lupus nephritis. (Linked to SLO 3.5)
5. Describe the induction and maintenance treatment of Class IV lupus nephritis. (Linked to SLO 3.5)

Series Summary

This Series examined glomerular diseases. The glomerular filtration barrier has three layers: fenestrated endothelium, GBM (negatively charged), and podocyte foot processes with slit diaphragms; injury to each causes distinct abnormalities (haematuria, proteinuria). Mechanisms of injury: immune complex deposition (post-streptococcal GN, lupus, IgA nephropathy), anti-GBM antibody disease (linear IgG: Goodpasture), ANCA-associated vasculitis (pauci-immune), and haemodynamic injury (glomerulosclerosis). Histological patterns: diffuse proliferative GN (PSGN), FSGS, membranous nephropathy, minimal change disease (foot process effacement on EM), and crescentic GN (RPGN). PSGN follows nephritogenic Group A streptococcal infection 1 to 3 weeks (pharyngitis) or 2 to 6 weeks (impetigo); biopsy shows diffuse proliferative GN, granular IgG/C3 ('starry sky'), and subepithelial humps on EM; presents as acute nephritic syndrome; low C3 normalising within 8 weeks; treatment is supportive (fluid restriction, antihypertensives, diuretics, antibiotics); prognosis in children is excellent (above 95 percent full recovery).

IgA nephropathy (most common GN worldwide) results from mesangial IgA1 deposition; presents as synpharyngitic haematuria (1 to 3 days after URTI), persistent microscopic haematuria, or nephrotic syndrome; biopsy shows mesangial IgA on IF and Oxford MEST-C scoring; management: ACEi or ARB for all, corticosteroids for high-risk, SGLT2 inhibitors, newer agents (budesonide); 30 to 40 percent reach ESKD over 20 to 30 years. RPGN is crescentic GN with rapid GFR loss; classified as Type I (anti-GBM: linear IgG), Type II (immune complex: granular), and Type III (pauci-immune: ANCA-associated); treatment is urgent. Lupus nephritis affects 40 to 60 percent of SLE patients; classified I to VI by ISN/RPS; Class IV (diffuse proliferative) is most severe; full-house IF; low C3 and C4, high anti-dsDNA; induction with corticosteroids plus MMF or cyclophosphamide; maintenance with MMF or azathioprine; hydroxychloroquine for all.

Glossary of Terms

- **Glomerulonephritis (GN):** inflammation of the glomeruli, typically immune-mediated, presenting as nephritic or nephrotic syndrome.
- **Post-streptococcal glomerulonephritis (PSGN):** immune complex GN following nephritogenic Group A streptococcal infection; the most common GN in Nigeria.
- **IgA nephropathy:** the most common primary GN worldwide; defined by mesangial IgA1 deposits causing episodic haematuria and proteinuria.
- **Synpharyngitic haematuria:** gross haematuria occurring 1 to 3 days after an upper respiratory tract infection; characteristic of IgA nephropathy.
- **Rapidly progressive GN (RPGN):** a clinical syndrome of rapidly deteriorating renal function caused by crescentic GN on biopsy.
- **Crescent:** a proliferating mass of parietal epithelial cells and macrophages filling Bowman's space in crescentic GN; destroys the glomerular tuft.
- **Anti-GBM disease (Goodpasture syndrome):** antibodies against alpha-3 type IV collagen causing linear IgG on IF, RPGN, and pulmonary haemorrhage.
- **ANCA-associated vasculitis:** ANCA-mediated pauci-immune necrotising GN; types include granulomatosis with polyangiitis (c-ANCA) and microscopic polyangiitis (p-ANCA).
- **Lupus nephritis:** renal involvement in SLE from anti-dsDNA immune complex deposition; classified I to VI by ISN/RPS; Class IV carries worst prognosis.
- **Full-house immunofluorescence:** simultaneous deposition of IgG, IgA, IgM, C3, C4, and C1q in the glomerulus; characteristic of lupus nephritis.
- **Oxford MEST-C score:** a scoring system for IgA nephropathy grading mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, tubular atrophy, and crescents.
- **Plasmapheresis:** therapeutic plasma exchange used in anti-GBM disease and severe ANCA vasculitis to rapidly remove pathological antibodies.

Concept Check Questions [Series 3]

Objective Questions

1. The glomerular filtration barrier consists of fenestrated endothelium, GBM, and podocyte foot processes; podocyte injury causes _____-range proteinuria. (Linked to SLO 3.1)
2. RPGN Type III (ANCA-associated vasculitis) shows _____ immune GN with minimal or no immunoglobulin on immunofluorescence. (Linked to SLO 3.2)
3. PSGN biopsy shows granular IgG and C3 ('starry sky') on IF and subepithelial _____ on electron microscopy. (Linked to SLO 3.3)
4. IgA nephropathy presents with synpharyngitic haematuria 1 to 3 days after URTI; PSGN haematuria is delayed by _____ to 3 weeks after pharyngitis. (Linked to SLO 3.4)
5. Lupus nephritis Class _____ (diffuse proliferative) is the most severe and carries the worst risk of progression to ESKD. (Linked to SLO 3.5)
6. RPGN Type I (anti-GBM disease) is treated with cyclophosphamide, prednisolone, and _____ to remove circulating anti-GBM antibodies. (Linked to SLO 3.5)

Short-Answer Questions

7. Describe the four mechanisms of glomerular injury with one example of each. (Linked to SLO 3.1)
8. Describe the clinical presentation and investigations of PSGN. (Linked to SLO 3.3)
9. Classify RPGN by immunofluorescence pattern and state the cause of each type. (Linked to SLO 3.5)

Long-Answer Questions

10. Describe the pathogenesis, clinical features, investigations, management, and prognosis of IgA nephropathy. (Linked to SLO 3.4)
11. Describe the classification, clinical features, investigations, and management of lupus nephritis. (Linked to SLO 3.5)

Answers to Concept Check Questions [Series 3]

Objective Questions

1. Nephrotic.
2. Pauci.
3. Humps.
4. One.
5. IV.
6. Plasmapheresis.

Short-Answer Questions

7. Immune complex deposition (example: PSGN; subepithelial humps; granular IF). Anti-GBM antibody disease (example: Goodpasture syndrome; linear IgG on IF; GN and pulmonary haemorrhage). ANCA-associated vasculitis (example: granulomatosis with polyangiitis; pauci-immune crescentic GN). Haemodynamic and metabolic injury (example: diabetic nephropathy; glomerulosclerosis without significant inflammation).
8. PSGN presents 1 to 3 weeks after streptococcal pharyngitis (or 2 to 6 weeks after impetigo) with acute nephritic syndrome: haematuria (cola-coloured urine), proteinuria, hypertension, periorbital oedema, and oliguria. Investigations: elevated ASO titre; low serum C3 (normalises within 8 weeks); red cell casts on urine microscopy; elevated serum creatinine in severe cases.
9. Type I (anti-GBM): linear IgG on IF; Goodpasture syndrome (GN plus pulmonary haemorrhage); anti-GBM antibody positive. Type II (immune complex): granular Ig on IF; causes: lupus nephritis, post-infectious GN, IgA nephropathy. Type III (pauci-immune): minimal or no Ig on IF; ANCA positive; c-ANCA: granulomatosis with polyangiitis; p-ANCA: microscopic polyangiitis.

Long-Answer Questions

10. **Basic response:** Pathogenesis (four hits): aberrant O-glycosylation of IgA1; production of anti-glycan antibodies; immune complex formation; mesangial deposition with complement activation and inflammation. Biopsy: LM: mesangial hypercellularity and matrix expansion; IF: mesangial IgA deposits (defining feature) with variable C3 and

IgG; EM: mesangial electron-dense deposits; Oxford MEST-C scoring. Clinical: episodic macroscopic haematuria 1 to 3 days after URTI (synpharyngitic), persistent microscopic haematuria, or nephrotic syndrome; serum IgA elevated in 50 percent; secondary causes excluded (HSP, cirrhosis, coeliac). Management: ACEi or ARB for all (proteinuria below 0.5 g per day target); corticosteroids for high-risk (proteinuria above 1 g per day despite RAS blockade); SGLT2 inhibitors; targeted budesonide (Nefecon). Prognosis: 30 to 40 percent reach ESKD over 20 to 30 years; poor factors: heavy proteinuria, hypertension, impaired GFR, high MEST-C T or C score.

Value-added response: IgA nephropathy illustrates how a ubiquitous mucosal immune response (IgA is the dominant mucosal immunoglobulin) can cause organ-specific disease when qualitatively abnormal IgA1 escapes into the systemic circulation and deposits in the glomerulus; the synpharyngitic haematuria reflects the same mucosal immune activation that would normally clear the infection — in IgA nephropathy this response simultaneously injures the kidney.

11. **Basic response:** Classification (ISN/RPS): Class I (minimal mesangial LN: normal LM, mesangial Ig on IF), Class II (mesangial proliferative), Class III (focal: under 50 percent glomeruli affected), Class IV (diffuse: over 50 percent: most severe, highest ESKD risk), Class V (membranous: nephrotic syndrome), Class VI (advanced sclerosis: above 90 percent globally sclerosed). Clinical: Class III and IV: active nephritic syndrome (haematuria, proteinuria, hypertension, AKI); Class V: nephrotic syndrome; full-house IF (IgG, IgA, IgM, C3, C4, C1q). Investigations: urinalysis (haematuria, proteinuria, red cell casts), serum creatinine, complement (low C3 and C4), anti-dsDNA (elevated correlates with activity), ANA positive, renal biopsy for definitive class. Management: Class III and IV induction: high-dose prednisolone plus MMF (preferred in Africa: less gonadotoxic than cyclophosphamide) or Euro-Lupus cyclophosphamide; maintenance: MMF or azathioprine plus low-dose prednisolone for at least 3 years; hydroxychloroquine for all; newer agents: belimumab, voclosporin.

    Value-added response: Class IV lupus nephritis illustrates why renal biopsy is mandatory in SLE with renal involvement: the clinical presentation (haematuria, proteinuria) does not reliably distinguish Class II from Class IV, and the treatment difference is profound — Class II requires minimal or no immunosuppression while

Class IV requires high-dose cyclophosphamide or MMF with significant toxicity, making the histological diagnosis the essential guide to appropriate therapy.

Answers to Pilot Questions [Series 3]

Part 3.1

1. Three layers: fenestrated glomerular capillary endothelium (injury causes haematuria from RBC passage), glomerular basement membrane (type IV collagen; negatively charged: loss allows proteinuria), podocyte foot processes with slit diaphragms (injury causes nephrotic-range proteinuria). Mesangium: supporting matrix; participates in immune complex deposition and phagocytosis.
2. Circulating antigen-antibody complexes deposit in the glomerulus (mesangium, subendothelial, or subepithelial space); they activate the complement cascade (C3a and C5a attract neutrophils and monocytes); inflammatory cells release proteases, reactive oxygen species, and cytokines causing glomerular injury; the result is nephritic syndrome (haematuria, proteinuria, hypertension, oliguria).
3. Anti-GBM: antibodies target alpha-3 chain of type IV collagen in GBM; linear IgG on IF; presents with RPGN and pulmonary haemorrhage (Goodpasture syndrome); anti-GBM antibody positive; treated with plasmapheresis, cyclophosphamide, prednisolone. ANCA: antibodies activate neutrophils; pauci-immune crescentic GN (minimal or no Ig on IF); c-ANCA: granulomatosis with polyangiitis; p-ANCA: microscopic polyangiitis; treated with cyclophosphamide or rituximab plus prednisolone.
4. Light microscopy: normal (no change on LM in MCD). Electron microscopy: diffuse effacement (fusion) of podocyte foot processes — the defining ultrastructural lesion of MCD. Immunofluorescence: negative (no immune deposits). MCD is the most common cause of nephrotic syndrome in children and is characteristically steroid-responsive.
5. Crescentic GN is defined by the presence of cellular or fibrous crescents filling Bowman's space in 50 percent or more of glomeruli on renal biopsy; crescents consist of

proliferating parietal epithelial cells and infiltrating macrophages; they compress and destroy the glomerular tuft; clinically it signifies RPGN — a nephrology emergency with rapid loss of renal function requiring immediate diagnosis and aggressive immunosuppressive treatment.

Part 3.2

1. PSGN is the most common GN in Nigeria and sub-Saharan Africa; it predominantly affects children aged 5 to 15 years; pathogenesis: nephritogenic strains of Group A beta-haemolytic Streptococcus (S. pyogenes) release antigens (SPEB, NAPlr) that deposit in the glomerulus, activate complement, and recruit inflammatory cells; the kidney itself is not infected.
2. Light microscopy: diffuse mesangial and endocapillary proliferation with neutrophil infiltration in the acute phase. Immunofluorescence: granular deposits of IgG and C3 in a 'starry sky' pattern along capillary loops and mesangium. Electron microscopy: large subepithelial electron-dense immune complex deposits called 'humps' — the pathognomonic ultrastructural finding of PSGN.
3. Acute nephritic syndrome: sudden onset of haematuria (smoky, cola-coloured, or brown urine), proteinuria (sub-nephrotic usually), hypertension, periorbital oedema (morning facial swelling), oliguria; occurring 1 to 3 weeks after streptococcal pharyngitis or 2 to 6 weeks after impetigo. Systemic features: malaise, fatigue, headache, abdominal pain.
4. Elevated ASO titre (confirms recent streptococcal pharyngitis; positive in 60 to 80 percent); elevated anti-DNase B (more sensitive for streptococcal skin infection); low serum C3 (complement consumption; low C3 persisting beyond 8 weeks suggests an alternative diagnosis: MPGN or lupus); C4 normal or mildly reduced; urinalysis: haematuria, proteinuria, red cell casts on microscopy; serum creatinine elevated in AKI.
5. Children (above 95 percent recover fully): supportive treatment — sodium and fluid restriction for hypertension and oedema; loop diuretics (furosemide) for oedema; antihypertensives (loop diuretics as first-line; calcium channel blockers or hydralazine); antibiotics for ongoing streptococcal infection (penicillin V or amoxicillin 10 days); dialysis for severe AKI. Adults: 20 to 40 percent develop chronic renal impairment; risk

factors for poor outcome: severe AKI, persistent heavy proteinuria beyond 3 to 6 months, crescentic change on biopsy.

Part 3.3

1. Four hits: (1) Aberrant O-glycosylation of IgA1 (galactose-deficient IgA1 not properly processed in the liver or mucosa); (2) Production of anti-glycan IgG and IgA antibodies against the aberrant IgA1; (3) Formation of circulating immune complexes between galactose-deficient IgA1 and anti-glycan antibodies; (4) Mesangial deposition of these immune complexes triggering complement activation and mesangial cell proliferation and injury.
2. Light microscopy: mesangial hypercellularity and matrix expansion (the degree scored by Oxford M score). Immunofluorescence: mesangial IgA deposits (the defining diagnostic feature; dominant over IgG and IgM) with variable C3 and IgG co-deposits. Electron microscopy: electron-dense deposits in the mesangium. Oxford MEST-C score grades M (mesangial hypercellularity), E (endocapillary proliferation), S (segmental glomerulosclerosis), T (tubular atrophy and interstitial fibrosis), C (crescents) to guide prognosis.
3. Episodic macroscopic haematuria (gross haematuria 1 to 3 days after URTI or exercise: synpharyngitic haematuria; the close temporal relationship distinguishes it from PSGN where haematuria is delayed by 1 to 3 weeks); persistent microscopic haematuria with variable proteinuria (found incidentally on routine urinalysis); nephrotic syndrome with or without hypertension and renal impairment; rarely, RPGN with crescentic GN.
4. IgA nephropathy: isolated renal disease; mesangial IgA deposition; no systemic vasculitis; occurs in young adults; managed with RAS blockade and targeted immunosuppression. Henoch-Schonlein Purpura (IgA vasculitis): systemic small vessel vasculitis with identical mesangial IgA deposits on renal biopsy but also palpable purpura on buttocks and lower extremities, arthritis or arthralgia, abdominal pain (GI vasculitis), and GN; considered the systemic form of IgA nephropathy; common in children; mostly resolves without treatment.
5. All patients: optimise BP below 130/80 mmHg; maximise RAS blockade with ACEi or ARB (reduces proteinuria); lifestyle modification; SGLT2 inhibitors (dapagliflozin:

reduces proteinuria and slows CKD progression). High-risk (proteinuria persistently above 1 g per day): oral corticosteroids (prednisolone); severe or crescentic: cyclophosphamide plus prednisolone. Newer: targeted-release budesonide (gut-targeted, minimal systemic effects). Prognosis: 30 to 40 percent reach ESKD over 20 to 30 years; poor prognosis: heavy proteinuria, hypertension, impaired GFR at presentation, high T or C on MEST-C.

Part 3.4

1. RPGN is a clinical syndrome of rapidly deteriorating renal function (loss of 50 percent or more of GFR within weeks to months) with active urine sediment (haematuria, red cell casts, proteinuria); defined histologically by crescentic GN with crescents in 50 percent or more of glomeruli on renal biopsy; crescents consist of proliferating parietal epithelial cells and infiltrating macrophages compressing and destroying the glomerular tuft.
2. Type I (anti-GBM): linear IgG deposition on IF; anti-GBM antibody positive; cause: Goodpasture syndrome (GN plus pulmonary haemorrhage) or isolated anti-GBM GN. Type II (immune complex): granular immunoglobulin deposition on IF; causes: lupus nephritis, post-infectious GN, IgA nephropathy, mixed cryoglobulinaemia. Type III (pauci-immune): minimal or no Ig on IF; ANCA positive; c-ANCA (PR3-ANCA): granulomatosis with polyangiitis; p-ANCA (MPO-ANCA): microscopic polyangiitis; most common type in adults over 60.
3. ISN/RPS Classes: I (minimal mesangial), II (mesangial proliferative), III (focal proliferative: under 50 percent of glomeruli), IV (diffuse proliferative: over 50 percent of glomeruli — most common to progress to ESKD), V (membranous), VI (advanced sclerosis: above 90 percent sclerosed). Class IV carries the worst prognosis with highest risk of ESKD without treatment.
4. Urinalysis: haematuria, proteinuria, red cell casts. Serum creatinine and eGFR. Complement: low C3 and C4 (complement consumption by immune complexes). Anti-dsDNA: elevated during active disease; correlates with disease activity and may predict flares. ANA: positive in SLE. Full blood count: cytopenias (part of SLE criteria). Renal biopsy: essential to classify and guide treatment. Disease activity scores: SLEDAI (Systemic Lupus Erythematosus Disease Activity Index).

5. Induction: high-dose oral prednisolone (1 mg/kg per day, maximum 60 to 80 mg) plus either mycophenolate mofetil (MMF: 2 to 3 g per day, preferred in Africa due to lower gonadotoxicity) or Euro-Lupus cyclophosphamide (500 mg IV every 2 weeks for 6 doses); severe disease: pulse IV methylprednisolone 500 to 1000 mg for 3 days before oral prednisolone. Maintenance (from 6 months): MMF 1 to 2 g per day or azathioprine 2 mg/kg per day plus low-dose prednisolone 5 to 10 mg per day for at least 3 years. Hydroxychloroquine 200 to 400 mg per day for all SLE patients. Newer: belimumab (anti-BAFF) and voclosporin (calcineurin inhibitor).

References and Attributions [Series 3]

Textual References

- Kidney Disease: Improving Global Outcomes (KDIGO). (2021). KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International, 100(4S), S1 to S276.
- Okonkwo, U. et al. (2018). Renal Disease in Nigeria: A Biopsy-Based Study. Kidney International Reports, 3(4), 828 to 836.
- Kumar, P. and Clark, M. (2017). Kumar and Clark's Clinical Medicine (9th ed.). Edinburgh: Elsevier.
- Bomback, A. S. and Appel, G. B. (2010). Updates on the Treatment of Lupus Nephritis. Journal of the American Society of Nephrology, 21(12), 2028 to 2035.

Figures, Plates, Tables, and Boxes

- Figure 3.1: Mechanisms of glomerular injury and histological patterns. AI prompt: "Two-panel diagram: left four-row table (immune complex, anti-GBM, ANCA, haemodynamic); right five-row table (diffuse proliferative, FSGS, membranous, MCD foot process effacement, crescentic GN); clean professional infographic." OER search: "glomerular injury mechanisms histological patterns GN immune complex ANCA anti-GBM diagram".
- Figure 3.2: PSGN biopsy findings and management. AI prompt: "Two-panel diagram: PSGN biopsy (LM, IF starry sky, EM humps; investigations) and management plus prognosis; clean infographic." OER search: "post-streptococcal glomerulonephritis biopsy findings management prognosis diagram".
- Figure 3.3: IgA nephropathy presentations and management. AI prompt: "Two-panel diagram: clinical presentations (synpharyngitic haematuria, microscopic haematuria, nephrotic) and management (ACEi/ARB, SGLT2, steroids) plus prognosis; clean infographic." OER search: "IgA nephropathy clinical presentations management prognosis MEST-C Oxford classification diagram".
- Figure 3.4: RPGN classification and lupus nephritis management. AI prompt: "Two-panel diagram: RPGN three-type table by IF (anti-GBM, immune complex, pauci-immune ANCA) and lupus nephritis ISN/RPS classification plus management; clean infographic."

OER search: "RPGN classification immunofluorescence lupus nephritis ISN RPS management diagram".

Series 4: Nephrotic Syndrome and Urinary Tract Infections

- **Part 4.1: Nephrotic Syndrome — Pathophysiology and Causes**
  - Sub Part 4.1.1: Definition, pathophysiology, and clinical features
  - Sub Part 4.1.2: Minimal change disease
  - Sub Part 4.1.3: Focal segmental glomerulosclerosis and membranous nephropathy
- **Part 4.2: Nephrotic Syndrome — Complications and Management**
  - Sub Part 4.2.1: Complications of nephrotic syndrome
  - Sub Part 4.2.2: Investigations and general management
  - Sub Part 4.2.3: Specific treatment of the major nephrotic diseases
- **Part 4.3: Urinary Tract Infections — Uncomplicated**
  - Sub Part 4.3.1: Epidemiology and pathogenesis
  - Sub Part 4.3.2: Clinical features, diagnosis, and management of uncomplicated UTI
  - Sub Part 4.3.3: Recurrent UTI
- **Part 4.4: Complicated Urinary Tract Infections**
  - Sub Part 4.4.1: Pyelonephritis
  - Sub Part 4.4.2: UTI in special populations
  - Sub Part 4.4.3: Catheter-associated UTI and antimicrobial resistance

Introduction

Nephrotic syndrome and urinary tract infections are two of the most clinically important renal conditions encountered in everyday medical practice in Nigeria. Nephrotic syndrome, defined by heavy proteinuria, hypoalbuminaemia, oedema, and hyperlipidaemia, has multiple causes and life-threatening complications including thromboembolic disease and infection. Urinary tract infections range from uncomplicated lower urinary tract infections in otherwise healthy women to severe pyelonephritis and urosepsis requiring hospitalisation.

This Series covers nephrotic syndrome in systematic detail: its pathophysiology, the major causative conditions (minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy), its complications, and its management. It then examines urinary tract infections from uncomplicated lower UTI through pyelonephritis to UTI in special populations including pregnancy, diabetes, and recurrent infection, with attention to the growing problem of antimicrobial resistance.

Both conditions are highly prevalent in Nigeria, and clinical competence in their recognition and management is an immediate and practical clinical priority.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 4.1** define nephrotic syndrome and describe its pathophysiology and clinical features (Linked to Part 4.1),
- **SLO 4.2** describe the pathology and clinical features of minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy (Linked to Part 4.1),
- **SLO 4.3** describe the complications and management of nephrotic syndrome (Linked to Part 4.2),

- **SLO 4.4** describe the epidemiology, pathogenesis, clinical features, diagnosis, and management of uncomplicated and recurrent urinary tract infections (Linked to Part 4.3), and
- **SLO 4.5** describe the management of pyelonephritis and UTI in special populations including pregnancy and diabetes (Linked to Part 4.4).

4.1 Nephrotic Syndrome — Pathophysiology and Causes

4.1.1 Definition, pathophysiology, and clinical features

Nephrotic syndrome is defined by the tetrad of: **proteinuria above 3.5 g per 24 hours** (or urine ACR above 300 mg/mmol), **hypoalbuminaemia below 25 g/L**, **peripheral oedema**, and **hyperlipidaemia** (elevated LDL and total cholesterol from increased hepatic lipoprotein synthesis in response to reduced oncotic pressure).

The pathophysiology centres on loss of the glomerular charge and size barrier, allowing albumin to pass freely into the filtrate. Hypoalbuminaemia reduces plasma oncotic pressure, promoting fluid shift from intravascular to interstitial spaces. The resulting **effective volume depletion** activates the RAAS and SNS, causing sodium and water retention, which worsens oedema. **Lipiduria** (fatty casts and oval fat bodies on urine microscopy) results from lipoprotein leakage through the damaged glomerulus.

Fill in the blank: Nephrotic syndrome is defined by proteinuria above 3.5 g per day, hypoalbuminaemia below 25 g/L, peripheral _____, and hyperlipidaemia; reduced plasma oncotic pressure promotes fluid shift and activates RAAS causing sodium retention.

4.1.2 Minimal change disease

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children (75 to 80 percent of paediatric cases) and accounts for approximately 15 percent of adult nephrotic syndrome. On **light microscopy** the glomeruli appear normal; **electron microscopy** shows diffuse podocyte foot process effacement (the defining lesion); **immunofluorescence** is

negative. The pathogenesis involves a circulating permeability factor (possibly a T-cell-derived cytokine such as IL-13) that disrupts podocyte function.

MCD typically presents with sudden onset of nephrotic syndrome in a child (peak age 2 to 5 years) with massive periorbital oedema, hypoalbuminaemia, and heavy proteinuria. Haematuria and hypertension are typically absent or mild. In adults, MCD is associated with **NSAIDs**, **lymphoma (especially Hodgkin's)**, and **atopy**. MCD is characteristically **steroid-responsive**: more than 90 percent of children achieve remission with corticosteroids.

Fill in the blank: MCD is the most common nephrotic cause in children; light microscopy is normal; EM shows podocyte foot process _____; it is characteristically steroid-responsive with above 90 percent of children achieving remission.

4.1.3 Focal segmental glomerulosclerosis and membranous nephropathy

Focal segmental glomerulosclerosis (FSGS) is characterised by scarring affecting some glomeruli (focal) and only part of the glomerular tuft (segmental) on light microscopy. FSGS is the most common primary cause of nephrotic syndrome in adults in many populations, and is particularly prevalent among Black African patients due to genetic variants in the **APOL1 gene**. FSGS presents with nephrotic syndrome, often with haematuria and hypertension, and a significant proportion progress to ESKD.

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in White adults over 50. It is caused by antibodies against **phospholipase A2 receptor (PLA2R)** on podocytes (primary MN, approximately 70 percent) or associated with malignancy, hepatitis B, SLE, or drugs (secondary MN). Biopsy shows subepithelial immune complex deposits producing a thickened 'spike and dome' GBM on silver stain and EM. **Anti-PLA2R antibodies** are diagnostic for primary MN (sensitivity approximately 70 percent, specificity above 95 percent) and correlate with disease activity.

Fill in the blank: FSGS is the most common primary nephrotic syndrome in Black African adults, linked to APOL1 gene variants; membranous nephropathy is caused by anti-_____ antibodies in primary disease and is associated with malignancy in secondary disease.

Pathology	Population	Key Features
Minimal Change Disease	Children aged 2–5 years	Normal LM, foot process effacement on EM, IF negative; steroid-responsive >90%
Focal Segmental Glomerulosclerosis (FSGS)	Adults; common in Black Africans (APOL1 variants)	Focal segmental scarring; most common primary adult nephrotic; progression to ESKD
Membranous Nephropathy	White adults >50 years	Subepithelial deposits, spike-and-dome on silver stain; anti-PLA2R antibodies (primary); malignancy (secondary); spontaneous remission 30–40%

Table 4.1: Major causes of nephrotic syndrome — pathology, population affected, and key clinical features

Pilot questions 4.1

1. Define nephrotic syndrome and describe the pathophysiological mechanism by which oedema develops. (Linked to SLO 4.1)
2. Describe the light microscopy, electron microscopy, and immunofluorescence findings in minimal change disease. (Linked to SLO 4.2)
3. Describe the typical clinical presentation of MCD in a child. (Linked to SLO 4.2)
4. Describe the pathogenesis of primary membranous nephropathy. (Linked to SLO 4.2)
5. Explain why Black African patients are at increased risk of FSGS. (Linked to SLO 4.2)

4.2 Nephrotic Syndrome — Complications and Management

4.2.1 Complications of nephrotic syndrome

Thromboembolic disease is the most dangerous complication: loss of anticoagulant proteins (protein C, protein S, antithrombin III) in the urine, combined with increased hepatic synthesis of

procoagulant factors and platelet hyperaggregability, creates a markedly pro-thrombotic state. Deep vein thrombosis, pulmonary embolism, and **renal vein thrombosis** (presenting with flank pain, haematuria, and sudden worsening of proteinuria) are the most important thrombotic events.

Infection risk is elevated due to urinary loss of immunoglobulins (particularly IgG) and complement components. **Spontaneous bacterial peritonitis** (caused by Streptococcus pneumoniae: ascitic fluid infection without an obvious source) is a characteristic and potentially fatal complication. **Acute kidney injury** may complicate severe hypoalbuminaemia (from renal underperfusion), diuretic overtreatment, or renal vein thrombosis. **Hyperlipidaemia** accelerates atherosclerosis: long-standing nephrotic syndrome with persistent hyperlipidaemia increases cardiovascular risk.

Fill in the blank: Complications of nephrotic syndrome include thromboembolic disease (loss of anticoagulant proteins), spontaneous bacterial peritonitis (pneumococcal), AKI from underperfusion, and hyperlipidaemia accelerating _____.

4.2.2 Investigations and general management

Investigations in nephrotic syndrome include: urine ACR or 24-hour urine protein (to quantify proteinuria), urine microscopy (lipiduria: oval fat bodies, fatty casts), serum albumin, renal function, lipid profile, complement (C3/C4 — low in lupus and MPGN; normal in MCD and MN), anti-PLA2R antibody (primary MN), ANA and anti-dsDNA (lupus), hepatitis B and C serology (secondary MN), and in adults aged over 40 with MN a screen for occult malignancy. Renal biopsy is essential in adults (to establish the specific cause), in steroid-resistant children (above 8 weeks of steroids), and in children with atypical features.

General management applies to all causes of nephrotic syndrome: **ACEi or ARB** (to reduce proteinuria and slow GFR decline), **diuretics** (loop diuretics for oedema; caution to avoid volume depletion), **dietary sodium restriction** (below 2 g per day), **statins** (for hyperlipidaemia), and **anticoagulation** with low molecular weight heparin or warfarin when albumin is below 20 g/L or thromboembolic risk is high. Pneumococcal vaccination is essential given the risk of spontaneous bacterial peritonitis.

Fill in the blank: General nephrotic management includes ACEi or ARB (reduce proteinuria), loop diuretics (oedema), sodium restriction, statins (hyperlipidaemia), anticoagulation when albumin below 20 g/L, and _____ vaccination (pneumococcal peritonitis risk).

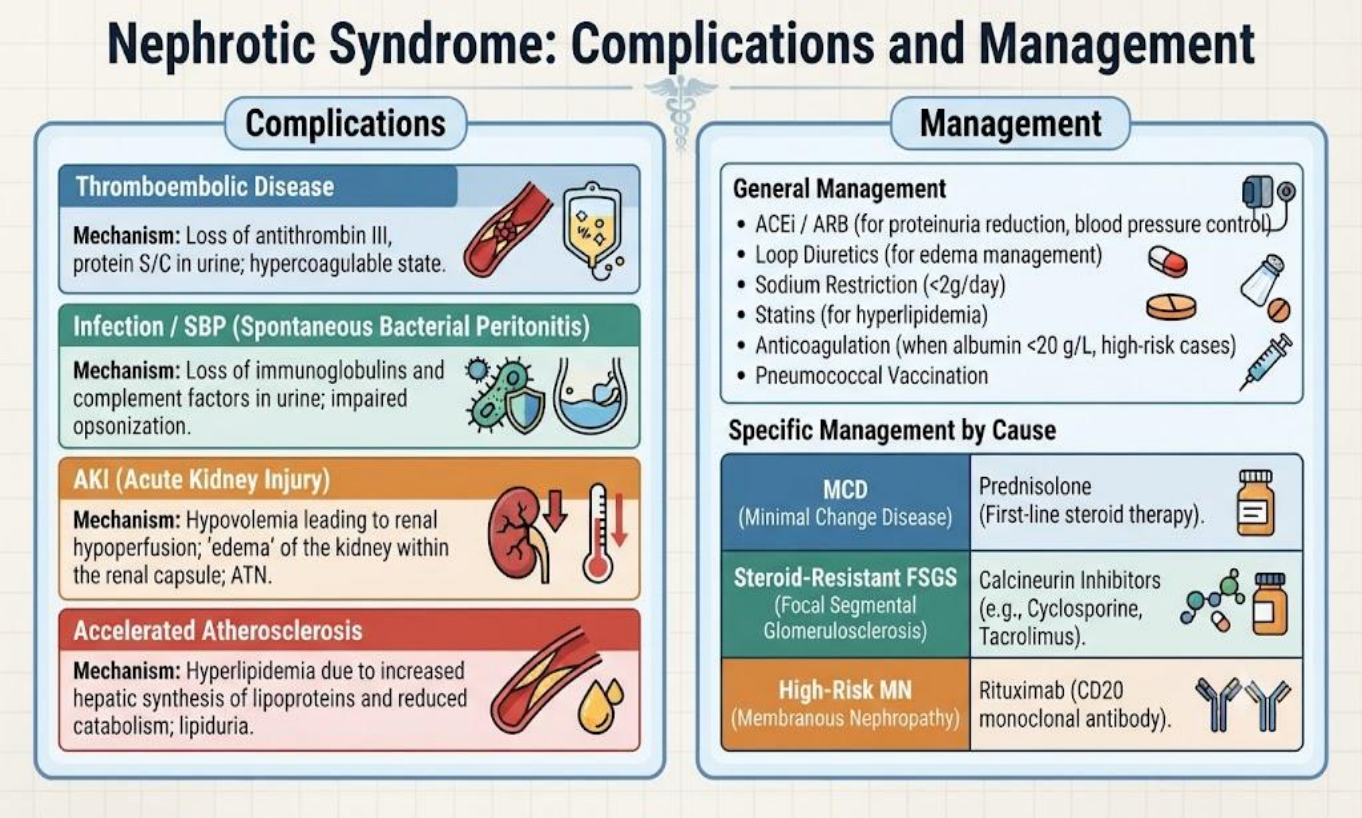

Figure 4.2: Complications of nephrotic syndrome and the general and specific management framework

4.2.3 Specific treatment of the major nephrotic diseases

MCD in children: oral prednisolone 2 mg/kg per day (maximum 60 mg) for 6 weeks, then alternate-day dosing for 6 weeks. Above 90 percent achieve remission. Frequent relapses (more than 2 per year) or steroid dependence: add **cyclophosphamide, mycophenolate mofetil, or tacrolimus** to achieve sustained remission. **FSGS**: high-dose prednisolone (1 mg/kg per day) for 16 to 24 weeks as first-line; steroid-resistant FSGS (no response after 16 weeks): **calcineurin inhibitors (tacrolimus or cyclosporin)**; rituximab and SGLT2 inhibitors as adjuncts. **Membranous nephropathy**: patients with low-risk disease (proteinuria below 4 g per day,

stable GFR, no anti-PLA2R) may be managed conservatively with RAS blockade awaiting spontaneous remission (occurs in 30 to 40 percent); high-risk disease (proteinuria above 8 g per day, rising creatinine, or anti-PLA2R above 150 RU/mL): rituximab (now first-line) or cyclophosphamide-based therapy.

Fill in the blank: MCD in children is treated with prednisolone; steroid-resistant FSGS uses calcineurin inhibitors; primary membranous nephropathy is treated with _____ (now first-line) or cyclophosphamide for high-risk disease.

Pilot questions 4.2

1. Explain why nephrotic syndrome is associated with a markedly pro-thrombotic state. (Linked to SLO 4.3)
2. Describe the risk of infection in nephrotic syndrome and explain the mechanism. (Linked to SLO 4.3)
3. Describe the investigations required in a patient presenting with nephrotic syndrome. (Linked to SLO 4.3)
4. Describe the general management measures applicable to all causes of nephrotic syndrome. (Linked to SLO 4.3)
5. Describe the specific treatment of MCD in children. (Linked to SLO 4.3)

4.3 Urinary Tract Infections — Uncomplicated

4.3.1 Epidemiology and pathogenesis

Urinary tract infections (UTIs) are the most common bacterial infections in women, affecting approximately 50 percent of women at least once in their lifetime. The most common causative organism is **Escherichia coli** (accounts for 70 to 80 percent of uncomplicated UTIs), which ascends from the periurethral area via the urethra to the bladder. Other organisms include **Staphylococcus saprophyticus** (young sexually active women), Klebsiella pneumoniae, Proteus mirabilis, and Enterococcus faecalis.

Risk factors for UTI in women include sexual activity, diaphragm and spermicide use, prior UTI, post-menopausal urogenital atrophy (reduced lactobacillary protection), and genetic susceptibility. Virulence factors of uropathogenic E. coli include **type 1 and P fimbriae** (adhesion to uroepithelium), **haemolysin** (epithelial cytotoxicity), **aerobactin** (iron acquisition), and **urease** (urea hydrolysis promoting stone formation, particularly in Proteus infections).

Fill in the blank: The most common UTI organism is E. coli (70 to 80 percent of uncomplicated UTIs); virulence factors include type 1 and P _____ (adhesion to uroepithelium), haemolysin, aerobactin, and urease.

4.3.2 Clinical features, diagnosis, and management of uncomplicated UTI

Uncomplicated lower UTI (acute cystitis) presents with dysuria (pain or burning on urination), urinary frequency, urgency, suprapubic discomfort, and sometimes haematuria. Systemic features (fever, rigors, loin pain) are absent; their presence suggests upper tract infection (pyelonephritis). Uncomplicated UTI is defined as lower tract infection in a non-pregnant adult woman without structural or functional abnormality of the urinary tract.

Diagnosis is clinical in typical presentations; dipstick urinalysis showing leucocyte esterase and nitrites supports the diagnosis. **Urine culture and sensitivity** is required for: atypical symptoms, treatment failure, recurrent UTI, complicated UTI, pregnancy, and men (all male UTIs are complicated by definition). **Management**: first-line oral antibiotics for uncomplicated cystitis in Nigeria: nitrofurantoin (5 days), trimethoprim (7 days), or fosfomycin (single dose); increased trimethoprim resistance locally may prompt use of nitrofurantoin or fosfomycin based on local sensitivity patterns.

Fill in the blank: Uncomplicated cystitis presents with dysuria, frequency, urgency, and suprapubic pain without fever; diagnosis is clinical; urine culture is required for _____ UTI, treatment failure, pregnancy, and men; first-line treatment includes nitrofurantoin or trimethoprim.

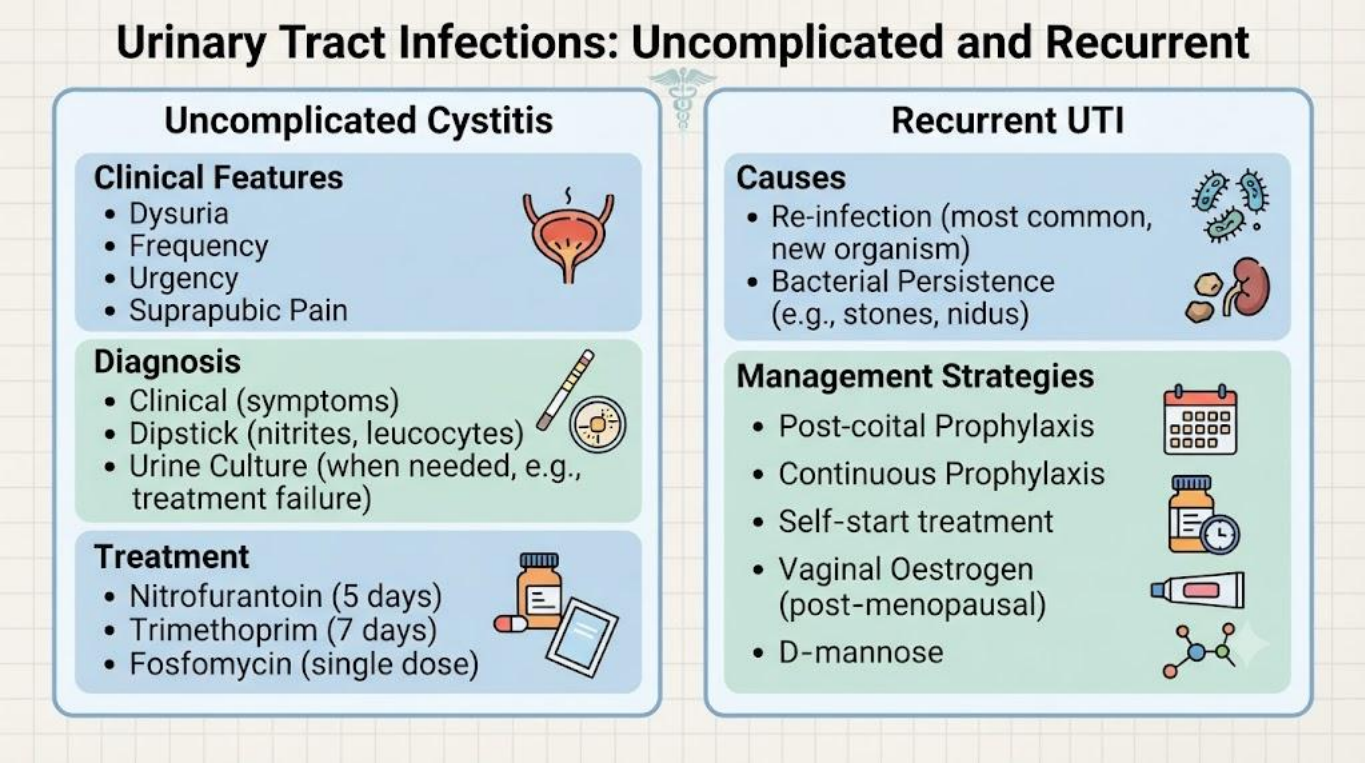

Figure 4.3: Uncomplicated cystitis — clinical features and management; and recurrent UTI — causes and management options

4.3.3 Recurrent UTI

Recurrent UTI is defined as three or more episodes per year or two or more episodes in six months. It is common in women and rarely indicates structural abnormality in premenopausal women. Causes include **re-infection with the same or different organism** (most common) or **bacterial persistence** (same organism from a focus such as a renal calculus or biofilm on a catheter).

Management of recurrent UTI options include: **post-coital prophylaxis** (single dose of nitrofurantoin or trimethoprim immediately after intercourse: if episodes are coitally related), **continuous low-dose prophylaxis** (nitrofurantoin 50 to 100 mg at night for 3 to 6 months), **self-start therapy** (patient initiates a short antibiotic course at onset of symptoms), **oestrogen vaginal cream** (for postmenopausal women: restores vaginal lactobacilli flora), and **D-mannose supplements** (reduces E. coli adhesion to uroepithelium).

Fill in the blank: Recurrent UTI (3 or more per year) management options include post-coital prophylaxis, continuous low-dose _____ prophylaxis, self-start therapy, vaginal oestrogen (postmenopausal), and D-mannose supplements.

Pilot questions 4.3

1. Describe the epidemiology and major causative organisms of UTI. (Linked to SLO 4.4)
2. Describe the clinical features of uncomplicated lower UTI and explain how it is distinguished from pyelonephritis. (Linked to SLO 4.4)
3. Describe when urine culture and sensitivity is required in the investigation of UTI. (Linked to SLO 4.4)
4. Describe the first-line antibiotic treatment of uncomplicated cystitis. (Linked to SLO 4.4)
5. Describe the management options for recurrent UTI in women. (Linked to SLO 4.4)

4.4 Complicated Urinary Tract Infections

4.4.1 Pyelonephritis

Acute pyelonephritis is infection of the renal parenchyma and pelvis, typically presenting with the **triad of fever (above 38 degrees C), loin pain, and dysuria or other lower urinary tract symptoms**. Nausea, vomiting, rigors, and systemic signs of infection are common. It results most commonly from ascending infection from the bladder.

Investigations include urine culture and sensitivity (essential: guides antibiotic choice), blood cultures (if systemically unwell or septic), full blood count (leucocytosis), CRP (elevated), and renal imaging (ultrasound to exclude obstruction: hydronephrosis) in all cases not responding promptly to treatment or in those with recurrent pyelonephritis. CT urography may be required to exclude perinephric abscess. **Management**: oral ciprofloxacin or co-amoxiclav for 10 to 14 days in mild to moderate cases; IV antibiotics (ceftriaxone or gentamicin) for severe pyelonephritis, vomiting, sepsis, or failed oral treatment; drainage of any obstructed infected system is urgent (urosepsis from obstructed pyelonephritis is a surgical emergency).

Fill in the blank: Pyelonephritis presents with fever, loin pain, and lower urinary tract symptoms; management is oral ciprofloxacin or co-amoxiclav for mild cases; IV antibiotics for severe disease; _____ of any obstructed system is urgent.

4.4.2 UTI in special populations

UTI in pregnancy carries significant risks: asymptomatic bacteriuria (ASB) occurs in 2 to 10 percent of pregnancies; if untreated, 30 percent progress to pyelonephritis, which is associated with preterm labour, low birthweight, and maternal sepsis. **Screening for and treating ASB in pregnancy is mandatory**. Safe antibiotics in pregnancy: nitrofurantoin (avoid in third trimester and near term: risk of neonatal haemolysis), cefalexin, and amoxicillin-clavulanate; avoid trimethoprim (folate antagonist, especially first trimester) and fluoroquinolones.

UTI in men is uncommon under 50 years and always considered complicated; causes include prostatitis (perineal pain, obstructive LUTS, tender prostate on rectal examination), epididymo-orchitis, and structural abnormality; requires urine culture, longer antibiotic courses (7 to 14 days), and investigation for an underlying structural cause. **UTI in diabetes** is more severe (impaired phagocytosis and neutrophil function), more likely to involve unusual organisms (Candida, gas-forming bacteria causing emphysematous pyelonephritis), and more likely to result in complications; aggressive management with culture-guided antibiotics is required.

Fill in the blank: Asymptomatic bacteriuria in pregnancy must be _____ and treated; UTI in men is always complicated and requires urine culture and investigation for structural cause; UTI in diabetes is more severe and may involve Candida or gas-forming bacteria.

4.4.3 Catheter-associated UTI and antimicrobial resistance

Catheter-associated UTI (CAUTI) is the most common healthcare-associated infection. Most patients with indwelling urinary catheters develop bacteriuria within 30 days; the catheter provides a surface for **biofilm formation** by organisms including E. coli, Klebsiella, Pseudomonas, Enterococcus, and Candida. Bacteriuria without symptoms (asymptomatic CAUTI) should not be treated with antibiotics in most patients; treatment is reserved for patients with systemic signs of infection.

Antimicrobial resistance is a major and growing challenge in UTI management in Nigeria and globally. **Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae** (most commonly ESBL-producing E. coli and Klebsiella) are increasingly resistant to cephalosporins and fluoroquinolones and require treatment with carbapenems (imipenem, meropenem) or temocillin. Prevention: remove catheters as soon as possible, use antibiotic-lock therapy for high-risk patients, and apply strict hand hygiene and infection control. Antibiotic stewardship — using narrow-spectrum agents and guided by culture sensitivities — is the cornerstone of resistance containment.

Fill in the blank: CAUTI is caused by biofilm formation on catheters; asymptomatic CAUTI should not be treated with antibiotics; ESBL-producing organisms require _____ (imipenem, meropenem); antibiotic stewardship is the cornerstone of resistance containment.

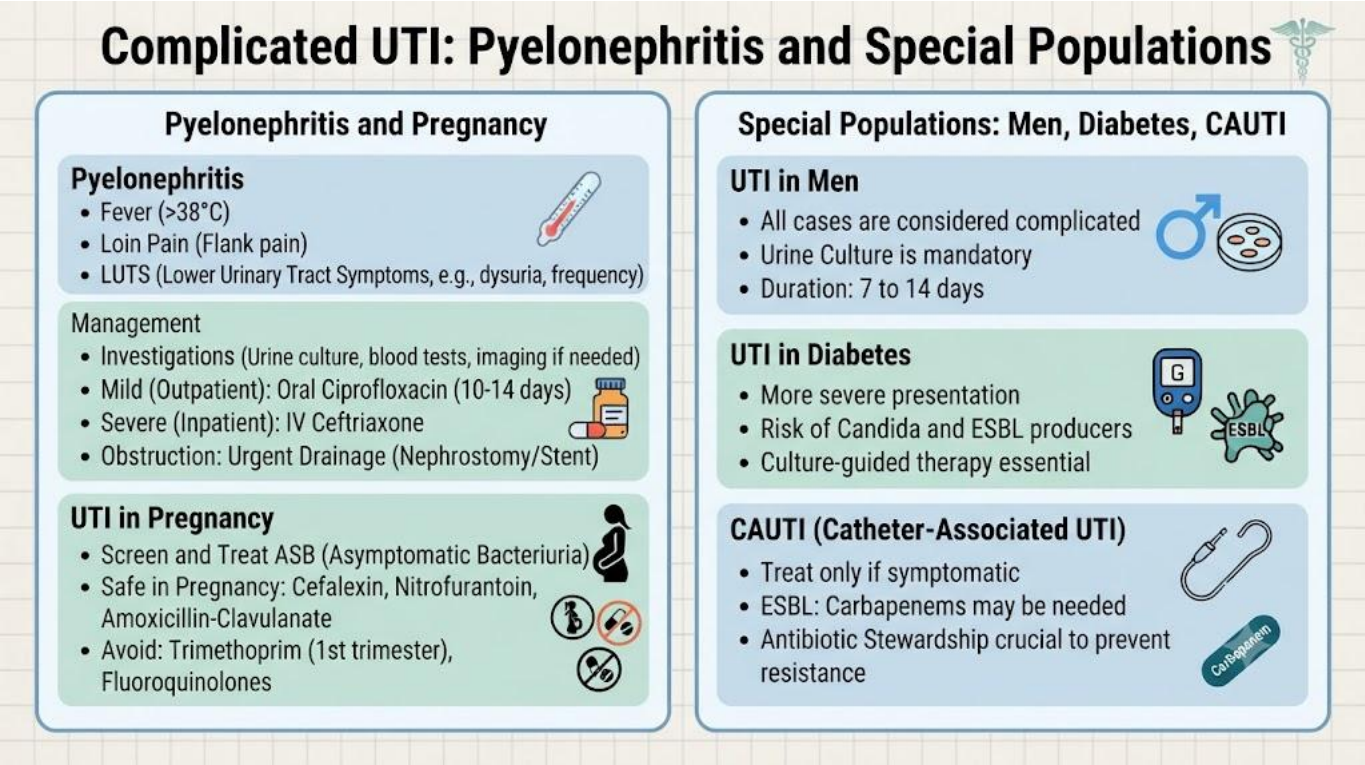

Figure 4.4: Complicated UTI — pyelonephritis, UTI in special populations, CAUTI, and antimicrobial resistance

Pilot questions 4.4

1. Describe the clinical features and management of acute pyelonephritis. (Linked to SLO 4.5)
2. Explain why asymptomatic bacteriuria in pregnancy must be screened for and treated. (Linked to SLO 4.5)
3. Describe the safe antibiotic choices for UTI in pregnancy. (Linked to SLO 4.5)
4. Explain why all UTIs in men are considered complicated. (Linked to SLO 4.5)
5. Describe the management of catheter-associated UTI and the approach to ESBL-producing organisms. (Linked to SLO 4.5)

Series Summary

This Series covered nephrotic syndrome and urinary tract infections. Nephrotic syndrome (proteinuria above 3.5 g per day, hypoalbuminaemia below 25 g/L, oedema, hyperlipidaemia) results from loss of glomerular permeability; oedema develops from reduced oncotic pressure and RAAS activation. Major causes: MCD (children; normal LM; foot process effacement on EM; steroid-responsive above 90 percent), FSGS (adults, Black African patients with APOL1 variants; focal segmental scarring; steroid-resistant cases use calcineurin inhibitors or rituximab), and membranous nephropathy (anti-PLA2R antibodies in primary disease; malignancy, hepatitis B in secondary; rituximab first-line for high-risk). Complications: thromboembolic disease (loss of anticoagulant proteins), spontaneous bacterial peritonitis (pneumococcal), AKI, and accelerated atherosclerosis. General management: ACEi or ARB, loop diuretics, sodium restriction, statins, anticoagulation when albumin below 20 g/L, and pneumococcal vaccination.

Uncomplicated UTI (E. coli 70 to 80 percent) presents as acute cystitis (dysuria, frequency, urgency, suprapubic pain; no fever); diagnosis is clinical; urine culture required for complicated UTI, recurrent UTI, pregnancy, and men; treatment: nitrofurantoin or trimethoprim. Recurrent UTI (3 or more per year) is managed with post-coital prophylaxis, continuous prophylaxis, self-start therapy, vaginal oestrogen, or D-mannose. Pyelonephritis presents with fever, loin pain, and LUTS; mild cases: oral ciprofloxacin or co-amoxiclav 10 to 14 days; severe: IV antibiotics; drainage urgently for obstructed infected system. Asymptomatic bacteriuria in pregnancy must be screened and treated (cefalexin or nitrofurantoin; avoid trimethoprim and fluoroquinolones); all male UTIs are complicated; UTI in diabetes is severe and may involve Candida or ESBL organisms. CAUTI: treat only if symptomatic; ESBL organisms require carbapenems; antibiotic stewardship is essential.

Glossary of Terms

- **Nephrotic syndrome:** the clinical syndrome of proteinuria above 3.5 g per day, hypoalbuminaemia below 25 g/L, peripheral oedema, and hyperlipidaemia from glomerular permeability defects.

- **Minimal change disease (MCD):** the most common cause of nephrotic syndrome in children; characterised by normal light microscopy and diffuse podocyte foot process effacement on EM; steroid-responsive.
- **Focal segmental glomerulosclerosis (FSGS):** nephrotic syndrome caused by focal and segmental glomerulosclerosis; more common in Black African patients with APOL1 gene variants; significant risk of ESKD.
- **Membranous nephropathy (MN):** nephrotic syndrome caused by subepithelial immune complex deposits; primary MN is caused by anti-PLA2R antibodies; secondary MN is associated with malignancy, hepatitis B, or SLE.
- **Anti-PLA2R antibody:** antibodies against phospholipase A2 receptor on podocytes; diagnostic of primary membranous nephropathy with 70 percent sensitivity and above 95 percent specificity.
- **Renal vein thrombosis:** thrombosis of the renal vein; a complication of nephrotic syndrome presenting with flank pain, haematuria, and worsening proteinuria.
- **Spontaneous bacterial peritonitis (SBP):** bacterial infection of ascitic fluid without an obvious source; characteristic complication of nephrotic syndrome, commonly caused by Streptococcus pneumoniae.
- **Uncomplicated UTI:** lower urinary tract infection in a non-pregnant adult woman without structural or functional urinary tract abnormality.
- **Asymptomatic bacteriuria:** significant bacteriuria on urine culture without symptoms; requires treatment in pregnancy (risk of pyelonephritis, preterm labour) but not in most other populations.
- **ESBL-producing organism:** a bacterium producing extended-spectrum beta-lactamase enzymes, conferring resistance to cephalosporins and penicillins; requires carbapenem treatment.
- **CAUTI:** catheter-associated urinary tract infection; the most common healthcare-associated infection; caused by biofilm formation on the catheter surface.
- **Pyelonephritis:** bacterial infection of the renal parenchyma and pelvis; presents with fever, loin pain, and lower urinary tract symptoms; requires 10 to 14 days of antibiotic treatment.

Concept Check Questions [Series 4]

Objective Questions

1. Nephrotic syndrome is defined by proteinuria above 3.5 g per day, hypoalbuminaemia below 25 g/L, peripheral oedema, and _____. (Linked to SLO 4.1)
2. Minimal change disease is normal on light microscopy; electron microscopy shows podocyte foot process _____. (Linked to SLO 4.2)
3. FSGS is more common in Black African patients due to variants in the _____ gene. (Linked to SLO 4.2)
4. Primary membranous nephropathy is caused by antibodies against phospholipase A2 _____ (PLA2R) on podocytes. (Linked to SLO 4.2)
5. The most common causative organism of uncomplicated UTI is E. _____. (Linked to SLO 4.4)
6. ESBL-producing organisms causing UTI require treatment with _____ such as imipenem or meropenem. (Linked to SLO 4.5)

Short-Answer Questions

7. Describe the complications of nephrotic syndrome. (Linked to SLO 4.3)
8. Describe the general management measures applicable to all causes of nephrotic syndrome. (Linked to SLO 4.3)
9. Describe when urine culture is required in UTI and state the first-line treatment for uncomplicated cystitis. (Linked to SLO 4.4)

Long-Answer Questions

10. Describe the definition, pathophysiology, major causes, complications, and general management of nephrotic syndrome. (Linked to SLOs 4.1 to 4.3)
11. Describe the management of UTI in pregnancy and pyelonephritis. (Linked to SLO 4.5)

Answers to Concept Check Questions [Series 4]

Objective Questions

1. Hyperlipidaemia.
2. Effacement.
3. APOL1.
4. Receptor.
5. Coli.
6. Carbapenems.

Short-Answer Questions

7. Thromboembolic disease (loss of anticoagulant proteins; risk of DVT, PE, renal vein thrombosis). Spontaneous bacterial peritonitis (pneumococcal; due to urinary loss of IgG and complement). Acute kidney injury (from renal underperfusion or renal vein thrombosis). Accelerated atherosclerosis and cardiovascular disease from persistent hyperlipidaemia.
8. ACEi or ARB (reduce proteinuria and slow GFR decline). Loop diuretics for oedema (avoid overdiuresis). Dietary sodium restriction below 2 g per day. Statins for hyperlipidaemia. Anticoagulation when albumin below 20 g/L or thromboembolic risk is high. Pneumococcal vaccination.
9. Urine culture is required for: complicated UTI, recurrent UTI (3 or more per year), treatment failure, pregnancy, and men (all UTIs in men are complicated). First-line treatment of uncomplicated cystitis: nitrofurantoin (5 days), trimethoprim (7 days), or fosfomycin (single dose); choice guided by local resistance patterns.

Long-Answer Questions

10. **Basic response:** Definition: proteinuria above 3.5 g per day, hypoalbuminaemia below 25 g/L, oedema, hyperlipidaemia. Pathophysiology: loss of glomerular charge and size barrier; hypoalbuminaemia reduces plasma oncotic pressure; fluid shifts to interstitium; effective volume depletion activates RAAS causing sodium and water retention worsening oedema; hepatic lipoprotein synthesis increases causing hyperlipidaemia. Major causes: MCD (children: foot process effacement on EM; steroid-responsive),

FSGS (adults: focal segmental scarring; APOL1 in Black Africans; ESKD risk), membranous nephropathy (anti-PLA2R primary; malignancy or hepatitis B secondary). Complications: thromboembolic disease (loss of anticoagulant proteins), spontaneous bacterial peritonitis (pneumococcal), AKI (underperfusion), accelerated atherosclerosis. General management: ACEi or ARB; loop diuretics; sodium restriction below 2 g per day; statins; anticoagulation when albumin below 20 g/L; pneumococcal vaccination.

Value-added response: Nephrotic syndrome illustrates how a single pathophysiological mechanism (loss of glomerular protein barrier) produces the full clinical syndrome: the hypoalbuminaemia from urinary protein loss explains the oedema, the RAAS activation, and the increased infection risk; the hepatic response to hypoalbuminaemia explains the hyperlipidaemia; and the loss of anticoagulant proteins alongside increased clotting factor synthesis explains the thrombophilia, making each feature of nephrotic syndrome logically derivable from the first principle of glomerular permeability failure.

11. **Basic response:** UTI in pregnancy: asymptomatic bacteriuria (ASB) occurs in 2 to 10 percent of pregnancies; untreated ASB progresses to pyelonephritis in 30 percent; pyelonephritis in pregnancy causes preterm labour, low birthweight, and maternal sepsis; therefore ASB in pregnancy must be screened for (urine culture at first antenatal visit) and treated. Safe antibiotics: cefalexin (7 days), nitrofurantoin (avoid at term due to neonatal haemolysis risk), amoxicillin-clavulanate; avoid trimethoprim (folate antagonist, especially first trimester) and fluoroquinolones (cartilage toxicity). Pyelonephritis: acute infection of renal parenchyma and pelvis; presents with fever above 38 degrees C, loin pain, and LUTS (nausea, vomiting, rigors); investigations: urine culture and sensitivity (essential), blood cultures (if septic), FBC, CRP, renal ultrasound (exclude obstruction). Management: mild to moderate: oral ciprofloxacin or co-amoxiclav for 10 to 14 days; severe (sepsis, vomiting): IV ceftriaxone or gentamicin; obstructed infected system: urgent ureteric drainage or nephrostomy (urosepsis from obstruction is a surgical emergency).

    Value-added response: The treatment of obstructed pyelonephritis (pyonephrosis) illustrates the principle that antibiotics alone cannot cure infection in the presence of obstruction: pus under pressure in the renal pelvis cannot be sterilised by any antibiotic regimen without drainage, just as an abscess cannot be cured without incision, and the

delay of drainage in favour of escalating antibiotics in pyonephrosis is a preventable cause of septic death.

Answers to Pilot Questions [Series 4]

Part 4.1

1. Nephrotic syndrome is defined by: proteinuria above 3.5 g per 24 hours, hypoalbuminaemia below 25 g/L, peripheral oedema, and hyperlipidaemia. Mechanism of oedema: loss of the glomerular protein barrier reduces serum albumin; hypoalbuminaemia reduces plasma oncotic pressure; fluid shifts from the intravascular compartment to the interstitium (Starling forces disrupted); the effective volume depletion triggers RAAS and SNS activation, causing renal sodium and water retention that worsens oedema.
2. Light microscopy: glomeruli appear completely normal; no proliferation or scarring. Electron microscopy: diffuse effacement (fusion) of podocyte foot processes — the defining ultrastructural lesion; the podocyte cytoskeleton is disrupted, abolishing the slit diaphragm. Immunofluorescence: negative (no immune deposits in the glomerulus).
3. Typical presentation: sudden onset of massive periorbital oedema (most noticeable in the morning, particularly around the eyes) in a child aged 2 to 5 years; frothy urine (proteinuria); ascites in severe cases; normal or minimally elevated blood pressure; no macroscopic haematuria; serum albumin severely reduced (often below 15 g/L); urine dipstick showing heavy proteinuria (3+ to 4+).
4. Primary membranous nephropathy is caused by IgG4 antibodies directed against phospholipase A2 receptor (PLA2R) expressed on the surface of podocytes; binding of anti-PLA2R IgG4 to podocyte PLA2R activates complement via the lectin pathway, forming the membrane attack complex that damages the podocyte and disrupts the slit diaphragm, leading to proteinuria; subepithelial immune complex deposits form, producing the characteristic spike and dome pattern on silver stain and EM.
5. APOL1 (apolipoprotein L1) gene variants (G1 and G2 alleles) are found at high frequency in individuals of West African ancestry; these variants evolved to confer

resistance to Trypanosoma brucei rhodesiense (sleeping sickness); however, when present in the homozygous or compound heterozygous state, APOL1 high-risk genotypes are strongly associated with susceptibility to FSGS, hypertension-associated ESKD, and HIV-associated nephropathy, explaining the disproportionately high burden of FSGS and ESKD in Black African patients.

Part 4.2

1. Nephrotic syndrome causes a markedly pro-thrombotic state through multiple mechanisms: urinary loss of anticoagulant proteins (antithrombin III, protein C, protein S) reduces anticoagulant defences; increased hepatic synthesis of procoagulant factors (fibrinogen, factors V, VIII, X) in response to hypoalbuminaemia increases clotting tendency; platelet hyperaggregability from hypoalbuminaemia; and increased blood viscosity from hyperlipidaemia. The combination produces a 5 to 6-fold increased risk of thromboembolism.
2. Risk of infection is elevated because: urinary loss of IgG (the most abundant circulating antibody providing humoral immunity against encapsulated bacteria) impairs opsonisation; urinary loss of complement components reduces the complement-mediated bactericidal pathway; oedematous skin provides a portal for bacterial entry. Spontaneous bacterial peritonitis from Streptococcus pneumoniae occurs in nephrotic patients with ascites; pneumococcal vaccination and high vigilance for fever in nephrotic patients are essential.
3. Urine ACR or 24-hour urine protein (quantify proteinuria); urine microscopy (lipiduria: oval fat bodies, fatty casts); serum albumin; renal function (creatinine, eGFR); lipid profile; complement C3 and C4 (low in lupus nephritis and MPGN; normal in MCD and primary MN); anti-PLA2R antibody (primary membranous nephropathy); ANA and anti-dsDNA (SLE); hepatitis B surface antigen and hepatitis C antibody (secondary MN); renal biopsy (essential in adults to establish specific cause; in steroid-resistant children).
4. ACEi or ARB: reduce intraglomerular pressure and proteinuria, slow CKD progression. Loop diuretics (furosemide): relieve oedema; caution against overdiuresis and volume depletion causing AKI. Dietary sodium restriction below 2 g per day: reduces fluid retention. Statins (simvastatin or atorvastatin): treat hyperlipidaemia; reduce

cardiovascular risk. Anticoagulation with LMWH or warfarin when albumin below 20 g/L or prior thromboembolic event. Pneumococcal vaccination: protects against spontaneous bacterial peritonitis.

5. Oral prednisolone 2 mg/kg per day (maximum 60 mg per day) for 6 weeks, followed by alternate-day prednisolone (1.5 mg/kg every other day) for a further 6 weeks; total initial course 12 weeks. Above 90 percent of children achieve remission (proteinuria below 0.3 g per day) within 4 to 8 weeks. Frequent relapses (more than 2 per year) or steroid dependence: add second-line agent (cyclophosphamide for remission consolidation; mycophenolate mofetil or tacrolimus for maintenance of remission while minimising steroid exposure).

Part 4.3

1. UTI affects approximately 50 percent of women at least once. Most common organisms: E. coli (70 to 80 percent), Staphylococcus saprophyticus (young sexually active women), Klebsiella pneumoniae, Proteus mirabilis (stone-forming, urease-positive), Enterococcus faecalis. Risk factors: sexual activity, diaphragm or spermicide use, prior UTI, post-menopausal urogenital atrophy, genetic susceptibility (P blood group antigen expression on uroepithelium).
2. Uncomplicated cystitis: dysuria, urinary frequency, urgency, suprapubic discomfort, occasional haematuria; no fever, no rigors, no loin pain, no systemic symptoms. Pyelonephritis: all the above plus fever (above 38 degrees C), loin or flank pain, nausea and vomiting, rigors, and systemic signs of infection; the presence of fever and loin pain distinguishes pyelonephritis from cystitis.
3. Urine culture and sensitivity is required for: complicated UTI (structural or functional abnormality, pregnancy, males, immunosuppression, diabetes, catheter), recurrent UTI (to identify the organism, confirm sensitivity, and detect resistant strains or bacterial persistence), treatment failure, and all UTIs in men (to determine the organism, sensitivity, and duration of treatment).
4. First-line oral antibiotics for uncomplicated cystitis: nitrofurantoin 100 mg modified-release twice daily for 5 days (active against most uropathogens including E. coli; avoid in significant renal impairment: eGFR below 30); trimethoprim 200 mg twice daily for 7

days (check local resistance rates; high trimethoprim resistance in many Nigerian centres); fosfomycin 3 g single oral dose (effective against ESBL-producing E. coli; useful when other agents are not tolerated or resistant); avoid fluoroquinolones for uncomplicated UTI to preserve efficacy for serious infections.

5. Post-coital prophylaxis: single dose of nitrofurantoin or trimethoprim immediately after intercourse (for women whose UTIs are temporally related to sexual activity). Continuous low-dose prophylaxis: nitrofurantoin 50 to 100 mg at night for 3 to 6 months; reduces UTI frequency by 95 percent. Self-start therapy: patient initiates a short antibiotic course at onset of symptoms. Vaginal oestrogen cream (postmenopausal women): restores vaginal lactobacilli, reducing E. coli colonisation. D-mannose: competes with E. coli type 1 fimbriae for uroepithelial binding, reducing adhesion.

Part 4.4

1. Clinical features: fever above 38 degrees C, unilateral or bilateral loin or flank pain (costovertebral angle tenderness on examination), dysuria, frequency, nausea, vomiting, rigors. Management: urine culture before starting antibiotics; blood cultures if systemically unwell; renal ultrasound to exclude obstruction; mild to moderate: oral ciprofloxacin 500 mg twice daily or co-amoxiclav for 10 to 14 days; severe (sepsis, vomiting, failed oral treatment): IV ceftriaxone 1 to 2 g daily or gentamicin with dose adjustment for renal function; obstructed infected system: urgent ureteric stenting or percutaneous nephrostomy is a surgical emergency.
2. Asymptomatic bacteriuria in pregnancy must be screened and treated because: 30 percent of untreated ASB progresses to pyelonephritis; pyelonephritis in pregnancy is associated with preterm labour, low birthweight, perinatal mortality, and maternal sepsis (the most common non-obstetric cause of maternal septic shock); treatment of ASB prevents these outcomes; screening is by urine culture at the first antenatal visit and at intervals thereafter.
3. Safe antibiotics in pregnancy: cefalexin 500 mg twice daily for 7 days (first-line; safe in all trimesters); nitrofurantoin 100 mg modified-release for 5 days (safe in first and second trimesters; avoid at term: risk of neonatal haemolytic anaemia from G6PD-sensitive erythrocytes exposed to nitrofurantoin metabolites); amoxicillin-clavulanate (if

sensitivity confirmed; safe in pregnancy). Avoid: trimethoprim (folate antagonist: especially avoid in the first trimester when neural tube formation is occurring); fluoroquinolones (potential cartilage toxicity; not recommended in pregnancy).

4. All UTIs in men are considered complicated because: the male urethra is 20 cm long (a natural anatomical barrier), so UTI in men rarely occurs without an underlying structural or functional abnormality (prostatic hypertrophy causing urinary stasis, renal calculi, neurogenic bladder, or urethral stricture); prostatitis and epididymo-orchitis must be considered and excluded; longer antibiotic courses (7 to 14 days) are required; urine culture and sensitivity is always needed; further investigation of the urinary tract (ultrasound, urological referral) is usually indicated.
5. CAUTI management: asymptomatic bacteriuria should not be treated in catheterised patients without systemic signs; symptomatic CAUTI: remove or change the catheter, obtain urine culture, treat with antibiotics guided by sensitivity results; remove catheter as soon as clinically possible. ESBL-producing organisms: resistant to most penicillins and cephalosporins; treatment requires carbapenems (imipenem, meropenem, ertapenem) or alternatives where susceptible (temocillin, pivmecillinam); antibiotic stewardship: prescribe based on culture results, use the narrowest effective spectrum, limit antibiotic duration, and avoid prophylactic antibiotics in catheterised patients to prevent resistance selection.

References and Attributions [Series 4]

Textual References

- Kidney Disease: Improving Global Outcomes (KDIGO). (2021). KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International, 100(4S), S1 to S276.
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- Kumar, P. and Clark, M. (2017). Kumar and Clark's Clinical Medicine (9th ed.). Edinburgh: Elsevier.
- Beck, L. H. et al. (2009). M-type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy. New England Journal of Medicine, 361(1), 11 to 21.

Figures, Plates, Tables, and Boxes

- Table 4.1: Major causes of nephrotic syndrome. AI prompt: "Three-column table: Pathology, Population, Key Features; rows: MCD (normal LM, foot process effacement EM, children, steroid-responsive), FSGS (focal segmental scarring, APOL1 Black Africans, ESKD risk), Membranous Nephropathy (subepithelial deposits, anti-PLA2R primary, malignancy secondary, rituximab); alternating shading." OER search: "nephrotic syndrome causes minimal change disease FSGS membranous nephropathy table".
- Figure 4.2: Nephrotic syndrome complications and management. AI prompt: "Two-panel diagram: left complications table (thromboembolic, infection, AKI, atherosclerosis); right management (general: ACEi/ARB, diuretics, statins, anticoagulation, vaccination; specific: MCD prednisolone, FSGS calcineurin inhibitors, MN rituximab); clean infographic." OER search: "nephrotic syndrome complications management thromboembolic peritonitis treatment diagram".
- Figure 4.3: Uncomplicated cystitis and recurrent UTI. AI prompt: "Two-panel table: uncomplicated cystitis (clinical features, diagnosis, treatment) and recurrent UTI (causes, management: post-coital prophylaxis, continuous prophylaxis, self-start, vaginal oestrogen, D-mannose); alternating shading." OER search: "uncomplicated cystitis recurrent UTI management prophylaxis nitrofurantoin trimethoprim table".

- Figure 4.4: Complicated UTI — pyelonephritis, special populations, CAUTI. AI prompt: "Two-panel table: pyelonephritis (features, management) and UTI in pregnancy (screen and treat ASB; safe antibiotics); UTI in men (all complicated) and diabetes; CAUTI (ESBL: carbapenems; stewardship); alternating section shading." OER search: "pyelonephritis UTI pregnancy special populations CAUTI antimicrobial resistance management table".

Series 5: Immune-Complex and Malarial Nephropathy

- **Part 5.1: Immune-Complex Nephropathies — An Overview**
  - Sub Part 5.1.1: Pathogenesis of immune-complex nephropathy
  - Sub Part 5.1.2: Membranoproliferative glomerulonephritis
  - Sub Part 5.1.3: Cryoglobulinaemic nephropathy
- **Part 5.2: Hepatitis B and C Nephropathy**
  - Sub Part 5.2.1: Hepatitis B-associated nephropathy
  - Sub Part 5.2.2: Hepatitis C-associated nephropathy
  - Sub Part 5.2.3: Management of hepatitis-related nephropathy
- **Part 5.3: Malarial Nephropathy**
  - Sub Part 5.3.1: Epidemiology and pathogenesis of malarial nephropathy
  - Sub Part 5.3.2: Clinical syndromes of malarial nephropathy
  - Sub Part 5.3.3: Management of malarial nephropathy
- **Part 5.4: HIV Nephropathy and Other Infection-Related Nephropathies**
  - Sub Part 5.4.1: HIV-associated nephropathy
  - Sub Part 5.4.2: Other infection-related nephropathies in Nigeria
  - Sub Part 5.4.3: Prevention and general principles of infection-related nephropathy

Introduction

Infection-related nephropathies are a major and distinctive cause of kidney disease in Nigeria and sub-Saharan Africa, reflecting the region's high burden of malaria, HIV, hepatitis B and C, schistosomiasis, and other endemic infections. These conditions differ fundamentally from the glomerulonephritides of high-income countries, where autoimmune and genetic conditions predominate, and understanding them is essential for clinical practice in the Nigerian context.

This final Series examines immune-complex nephropathies including membranoproliferative glomerulonephritis and cryoglobulinaemic nephropathy; the renal manifestations of hepatitis B and C; malarial nephropathy in detail including its distinct clinical syndromes in adults and children; and HIV-associated nephropathy, with additional coverage of other infection-related nephropathies prevalent in Nigeria including schistosomiasis and sickle cell nephropathy.

The unifying theme is that renal damage in these conditions is driven by immunological mechanisms — immune complex deposition, direct viral cytopathic effect, or haemodynamic injury — and that treatment must address both the renal consequences and the underlying infection.

Series Learning Outcomes

Upon completing this Series, you should be able to:

- **SLO 5.1** describe the pathogenesis of immune-complex nephropathy and the clinicopathological features of membranoproliferative glomerulonephritis (Linked to Part 5.1),
- **SLO 5.2** describe the renal manifestations of hepatitis B and hepatitis C and their management (Linked to Part 5.2),
- **SLO 5.3** describe the epidemiology, pathogenesis, clinical syndromes, and management of malarial nephropathy in Nigeria (Linked to Part 5.3), and

- **SLO 5.4** describe HIV-associated nephropathy and other infection-related nephropathies in Nigeria, and explain the principles of prevention (Linked to Part 5.4).

5.1 Immune-Complex Nephropathies — An Overview

5.1.1 Pathogenesis of immune-complex nephropathy

Immune-complex nephropathy results from the deposition of antigen-antibody complexes within the glomerulus, triggering complement activation and inflammatory injury. Complexes may be **pre-formed in the circulation** and deposited (as in post-streptococcal GN and lupus nephritis) or **formed in situ** within the glomerulus when a planted antigen (such as a viral or bacterial antigen) binds a circulating antibody at the glomerular site. The location of immune complex deposition determines the histological and clinical pattern: **subepithelial deposits** cause nephrotic syndrome (as in membranous nephropathy); **subendothelial deposits** cause nephritic syndrome (endocapillary proliferation and complement activation); **mesangial deposits** cause milder disease (IgA nephropathy).

Complement activation by immune complexes (via the classical pathway) generates C3a and C5a (anaphylatoxins attracting neutrophils and monocytes), the membrane attack complex (C5b-9: direct glomerular injury), and stimulates mesangial cell proliferation. The degree of complement consumption is reflected by **low serum C3**; measuring C3, C4, and the CH50 (total haemolytic complement) helps classify complement-mediated nephropathies.

Fill in the blank: Immune complex deposition in the subepithelial space causes _____ syndrome; subendothelial deposits cause nephritic syndrome; mesangial deposits cause mild disease; complement activation lowers serum C3.

5.1.2 Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) is characterised histologically by mesangial hypercellularity and basement membrane thickening with splitting (the 'tram-track'

appearance from GBM duplication on silver stain), and endocapillary proliferation. It presents as a mixed nephritic-nephrotic picture: haematuria, proteinuria (often heavy), hypertension, and reduced GFR, with persistently low C3.

MPGN is classified by immunofluorescence into: **immune complex MPGN (IC-MPGN)** (granular Ig and C3 deposits: caused by infections — hepatitis C most commonly, hepatitis B, HIV; autoimmune: lupus; monoclonal immunoglobulin deposition), and **C3 glomerulopathy** (C3-dominant deposits with minimal or no Ig: caused by complement dysregulation — factor H deficiency, factor I deficiency, C3 nephritic factor; includes dense deposit disease and C3 GN). Persistent low C3 lasting beyond 8 weeks (unlike PSGN where C3 normalises within 8 weeks) should prompt consideration of MPGN.

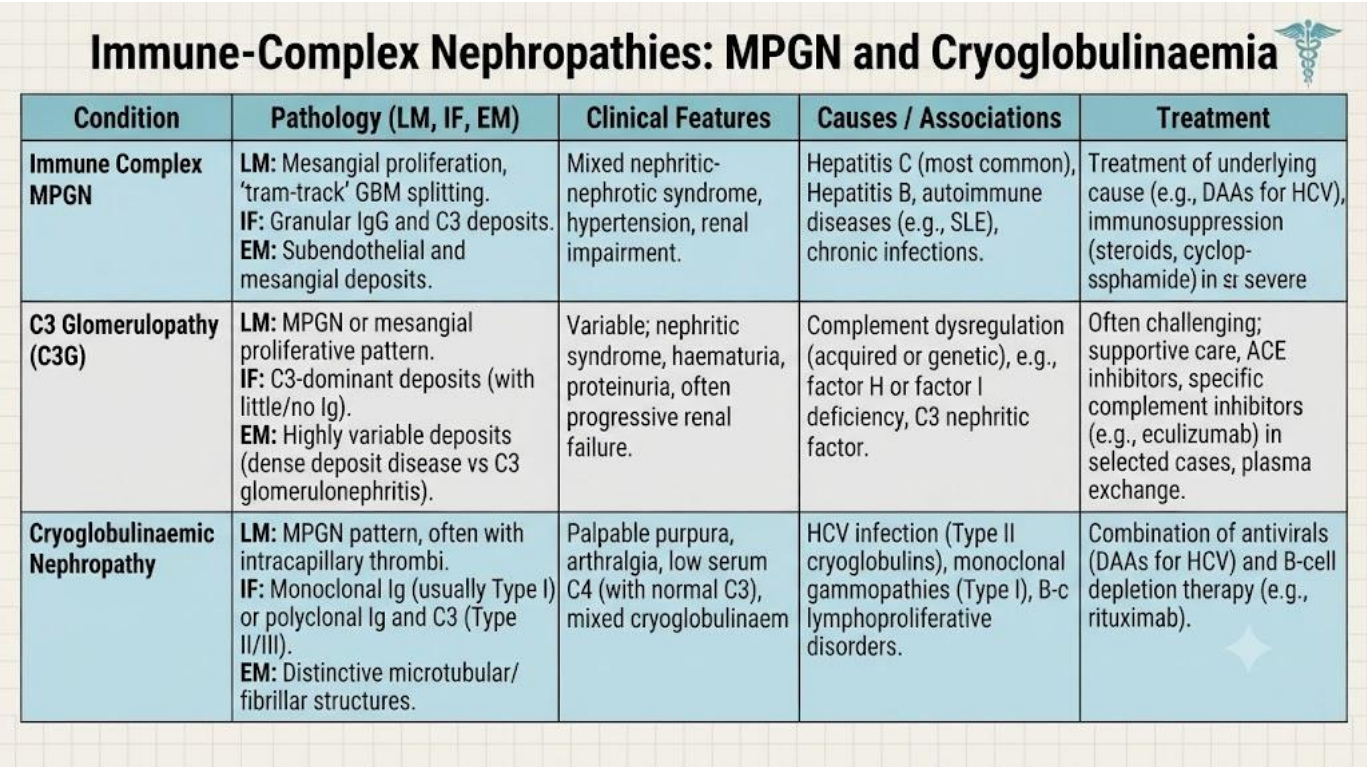
Fill in the blank: MPGN shows tram-track GBM duplication on LM and persistent low C3; it is classified as immune complex MPGN (hepatitis C, B, HIV, lupus) or C3 glomerulopathy (complement _____: factor H deficiency, C3 nephritic factor).

5.1.3 Cryoglobulinaemic nephropathy

Cryoglobulins are immunoglobulins that precipitate in the cold and re-dissolve on warming. **Cryoglobulinaemic nephropathy** occurs when cryoglobulins deposit in glomerular capillaries, causing an immune complex-mediated GN. It is classified: Type I (monoclonal IgM or IgG: associated with multiple myeloma and Waldenstrom's macroglobulinaemia), **Type II (mixed: monoclonal IgM with polyclonal IgG: strongly associated with hepatitis C virus — HCV is the most common cause)**, Type III (mixed polyclonal: associated with autoimmune diseases).

Clinical features include palpable purpura (the most characteristic feature: non-thrombocytopenic purpura from cutaneous vessel inflammation), arthralgia, Raynaud's phenomenon, and GN (nephritic or nephrotic syndrome). Laboratory: low C4 (cryoglobulins consume C4 via classical pathway; C3 may be low or normal), positive rheumatoid factor (cryoglobulin IgM has rheumatoid factor activity), positive HCV serology and HCV RNA. Treatment: treat the underlying hepatitis C with direct-acting antivirals; plasma exchange and rituximab for severe vasculitis.

Fill in the blank: Cryoglobulinaemic nephropathy Type II (mixed monoclonal IgM and polyclonal IgG) is strongly associated with _____; clinical features include palpable purpura, arthralgia, and GN; low C4 is characteristic.



Immune-Complex Nephropathies: MPGN and Cryoglobulinaemia

Condition	Pathology (LM, IF, EM)	Clinical Features	Causes / Associations	Treatment
Immune Complex MPGN	**LM:** Mesangial proliferation, 'tram-track' GBM splitting. **IF:** Granular IgG and C3 deposits. **EM:** Subendothelial and mesangial deposits.	Mixed nephritic-nephrotic syndrome, hypertension, renal impairment.	Hepatitis C (most common), Hepatitis B, autoimmune diseases (e.g., SLE), chronic infections.	Treatment of underlying cause (e.g., DAAs for HCV), immunosuppression (steroids, cyclop-ssphamide) in sı severe
C3 Glomerulopathy (C3G)	**LM:** MPGN or mesangial proliferative pattern. **IF:** C3-dominant deposits (with little/no Ig). **EM:** Highly variable deposits (dense deposit disease vs C3 glomerulonephritis).	Variable; nephritic syndrome, haematuria, proteinuria, often progressive renal failure.	Complement dysregulation (acquired or genetic), e.g., factor H or factor I deficiency, C3 nephritic factor.	Often challenging; supportive care, ACE inhibitors, specific complement inhibitors (e.g., eculizumab) in selected cases, plasma exchange.
Cryoglobulinaemic Nephropathy	**LM:** MPGN pattern, often with intracapillary thrombi. **IF:** Monoclonal Ig (usually Type I) or polyclonal Ig and C3 (Type II/III). **EM:** Distinctive microtubular/ fibrillar structures.	Palpable purpura, arthralgia, low serum C4 (with normal C3), mixed cryoglobulinaem	HCV infection (Type II cryoglobulins), monoclonal gammopathies (Type I), B-c lymphoproliferative disorders.	Combination of antivirals (DAAs for HCV) and B-cell depletion therapy (e.g., rituximab).

Figure 5.1: Immune-complex nephropathies — MPGN, C3 glomerulopathy, and cryoglobulinaemic nephropathy

Pilot questions 5.1

1. Describe how the site of immune complex deposition determines the clinical syndrome. (Linked to SLO 5.1)
2. Describe the histological features of MPGN on light microscopy and immunofluorescence. (Linked to SLO 5.1)
3. Distinguish between immune complex MPGN and C3 glomerulopathy. (Linked to SLO 5.1)
4. Describe the clinical features and causes of cryoglobulinaemic nephropathy. (Linked to SLO 5.1)

5. Explain why persistently low C3 beyond 8 weeks should prompt investigation for MPGN. (Linked to SLO 5.1)

5.2 Hepatitis B and C Nephropathy

5.2.1 Hepatitis B-associated nephropathy

Hepatitis B virus (HBV) causes renal disease through deposition of viral antigens (HBsAg, HBeAg) and their corresponding antibodies as immune complexes in the glomerulus. In Nigeria, where HBV is hyperendemic (carrier rate approximately 8 to 10 percent), HBV-associated nephropathy is an important cause of GN.

The most common HBV-associated nephropathy pattern is **membranous nephropathy** (MN): HBV antigen-antibody complexes deposit in the subepithelial space producing the typical MN biopsy pattern; HBeAg is the antigen most consistently associated with HBV-MN. This is distinguished from primary MN by **positive HBeAg or HBsAg serology** and **negative anti-PLA2R antibodies**. Other patterns include MPGN (subendothelial immune complex deposits; presents as nephritic-nephrotic syndrome with low complement) and IgA nephropathy. HBV-associated MN in children often resolves spontaneously with HBeAg seroconversion.

Fill in the blank: HBV-associated nephropathy most commonly causes _____ nephropathy; distinguished from primary MN by positive HBsAg or HBeAg and negative anti-PLA2R antibodies; childhood HBV-MN often resolves spontaneously with HBeAg seroconversion.

5.2.2 Hepatitis C-associated nephropathy

Hepatitis C virus (HCV) causes renal disease primarily through cryoglobulinaemia (Type II mixed cryoglobulins containing HCV RNA and anti-HCV antibodies) and direct immune complex deposition. HCV is the most common cause of Type II cryoglobulinaemia and MPGN in many populations. Renal biopsy in HCV-associated nephropathy typically shows an **MPGN pattern** with subendothelial immune complex deposits, low C3 and C4 (cryoglobulin-mediated complement consumption), and intracapillary cryoglobulin plugs.

HCV-associated nephropathy may also present without cryoglobulinaemia, through direct immune complex deposition of HCV antigens and antibodies causing MPGN. Clinical features: mixed nephritic-nephrotic syndrome, palpable purpura, arthralgia, Raynaud's phenomenon, peripheral neuropathy, and systemic vasculitis. **HCV RNA**, anti-HCV antibody, cryoglobulins, and complement (low C3 and C4) are the key investigations. Treatment: **direct-acting antivirals (DAAs)** achieve HCV eradication in above 95 percent of patients with a significant improvement in renal function and cryoglobulinaemic vasculitis.

Fill in the blank: HCV causes nephropathy primarily through Type II cryoglobulinaemia producing MPGN; treatment with direct-acting antivirals achieves HCV eradication in above 95 percent with significant improvement in renal function and _____ vasculitis.

5.2.3 Management of hepatitis-related nephropathy

HBV-associated nephropathy management requires treatment of the underlying HBV infection. **Tenofovir (TDF or TAF) or entecavir** are the preferred antiviral agents for HBV-associated nephropathy: they achieve viral suppression, reduce immune complex formation, and in many patients lead to stabilisation or improvement of renal function. Interferon-alpha is no longer recommended due to its nephrotoxicity and inferior efficacy. Children with HBV-MN may be managed conservatively with monitoring, as spontaneous remission with HBeAg seroconversion occurs in a significant proportion.

HCV-associated nephropathy management: **direct-acting antiviral regimens (DAAs)** — sofosbuvir-based or glecaprevir/pibrentasvir — are the treatment of choice and achieve sustained virological response (SVR: cure) in above 95 percent of patients; renal function should be monitored during DAA therapy as sofosbuvir requires dose adjustment or avoidance in severe renal impairment (eGFR below 30 mL/min). For severe active cryoglobulinaemic vasculitis or rapidly progressive nephritis, **rituximab** and short-course **plasma exchange** may be needed while awaiting the effect of antiviral therapy.

Fill in the blank: HBV nephropathy is treated with tenofovir or _____; HCV nephropathy is treated with direct-acting antivirals achieving SVR (cure) in above 95 percent; rituximab and plasma exchange for severe cryoglobulinaemic vasculitis.

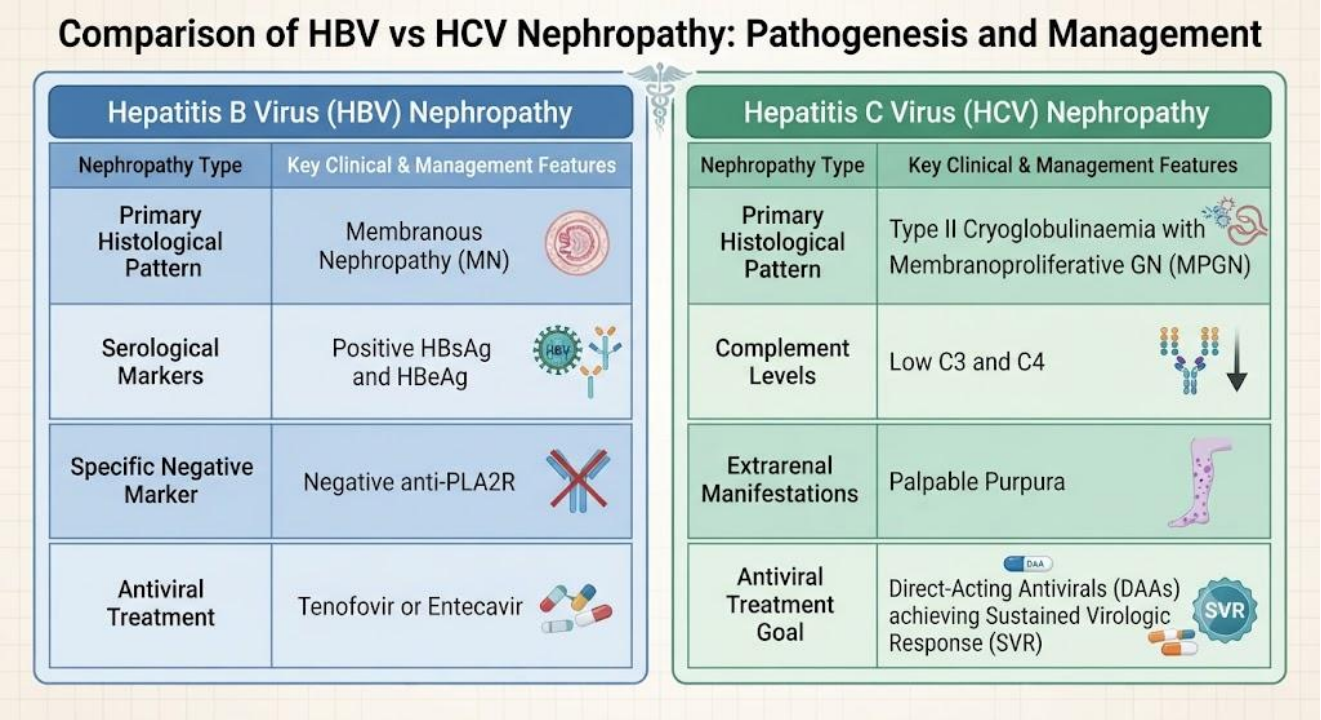


Figure 5.2: Hepatitis B and C nephropathy — pathogenesis, features, and management

Pilot questions 5.2

1. Describe the pathogenesis and most common histological pattern of HBV-associated nephropathy. (Linked to SLO 5.2)
2. Explain how HBV-associated membranous nephropathy is distinguished from primary membranous nephropathy. (Linked to SLO 5.2)
3. Describe the pathogenesis and clinical features of HCV-associated nephropathy. (Linked to SLO 5.2)
4. Describe the role of direct-acting antivirals in the treatment of HCV-associated nephropathy. (Linked to SLO 5.2)
5. Describe the management of HBV-associated nephropathy. (Linked to SLO 5.2)

5.3 Malarial Nephropathy

5.3.1 Epidemiology and pathogenesis of malarial nephropathy

Malaria (caused by Plasmodium falciparum and Plasmodium malariae) is the most important cause of tropical nephropathy in sub-Saharan Africa, including Nigeria. Malarial nephropathy develops through two main mechanisms: **immune complex deposition** (malarial antigens released during red cell lysis form immune complexes with specific antibodies that deposit in the glomerulus, activating complement and triggering glomerular inflammation) and **direct haemodynamic and cytokine-mediated injury** (severe falciparum malaria causes profound haemolysis, haemoglobinuria, microvascular sludging, and cytokine storm that reduces renal perfusion and can cause acute tubular necrosis).

P. malariae is the species most associated with chronic immune complex nephropathy in Africa (quartan malarial nephropathy), while **P. falciparum** is most associated with acute kidney injury in the context of severe malaria. The renal pathology in quartan malarial nephropathy consists of **mesangial and subendothelial immune complex deposits** with a progressive sclerosing pattern; immunofluorescence shows IgG, IgM, and complement deposits.

Fill in the blank: P. malariae causes chronic immune complex nephropathy (quartan malarial nephropathy) with mesangial deposits; P. falciparum causes AKI in severe malaria through haemolysis, haemoglobinuria, and cytokine-mediated _____ injury.

5.3.2 Clinical syndromes of malarial nephropathy

Quartan malarial nephropathy (QMN) caused by P. malariae presents as a **progressive nephrotic syndrome** predominantly in children in malaria-endemic regions of Nigeria. It typically begins with heavy proteinuria and peripheral oedema in childhood and progresses to end-stage kidney disease over years. The pattern on biopsy is a sclerosing glomerulonephritis. QMN is poorly responsive to corticosteroids and progresses despite antimalarial treatment, reflecting the chronic immune complex-mediated injury rather than active infection.

Acute malarial nephropathy (caused by P. falciparum) presents as **acute kidney injury** in the context of severe malaria, contributing to the high mortality of severe falciparum malaria in

Nigeria. It results from **intravascular haemolysis** causing haemoglobinuria (blackwater fever: massive haemolysis and haemoglobinuria causing dark urine), **microvascular obstruction** from parasitised red cell sequestration in renal vessels, cytokine-mediated vasoconstriction, and volume depletion. **Urinalysis** shows haematuria, haemoglobinuria, and proteinuria; the AKI may be oliguric or non-oliguric.

Fill in the blank: Quartan malarial nephropathy (P. malariae) presents as progressive nephrotic syndrome in children, poorly responsive to steroids; P. falciparum causes AKI through haemolysis, haemoglobinuria (_____ fever), and microvascular obstruction.

5.3.3 Management of malarial nephropathy

Management of quartan malarial nephropathy is largely supportive since the nephropathy progresses despite antimalarial therapy. Antimalarial treatment (chloroquine for P. malariae: it remains chloroquine-sensitive) is given to eliminate the active infection but does not reverse established glomerular damage. Supportive care includes management of oedema (loop diuretics), hypertension (antihypertensives), and proteinuria (ACEi or ARB). Patients who progress to ESKD require renal replacement therapy.

Management of acute malarial AKI from P. falciparum requires urgent **antimalarial treatment** (IV artesunate: the drug of choice for severe malaria in Nigeria and globally), **fluid resuscitation** (cautious IV fluids to restore renal perfusion without causing pulmonary oedema), **blood transfusion** (for severe haemolytic anaemia), and **dialysis** for AKI that does not recover spontaneously (continuous renal replacement therapy or intermittent haemodialysis). With appropriate treatment most patients with acute malarial AKI recover renal function.

Fill in the blank: Acute malarial AKI is managed with IV artesunate (antimalarial), cautious fluid resuscitation, blood transfusion for haemolytic anaemia, and _____ if AKI does not recover spontaneously; most patients recover renal function with treatment.

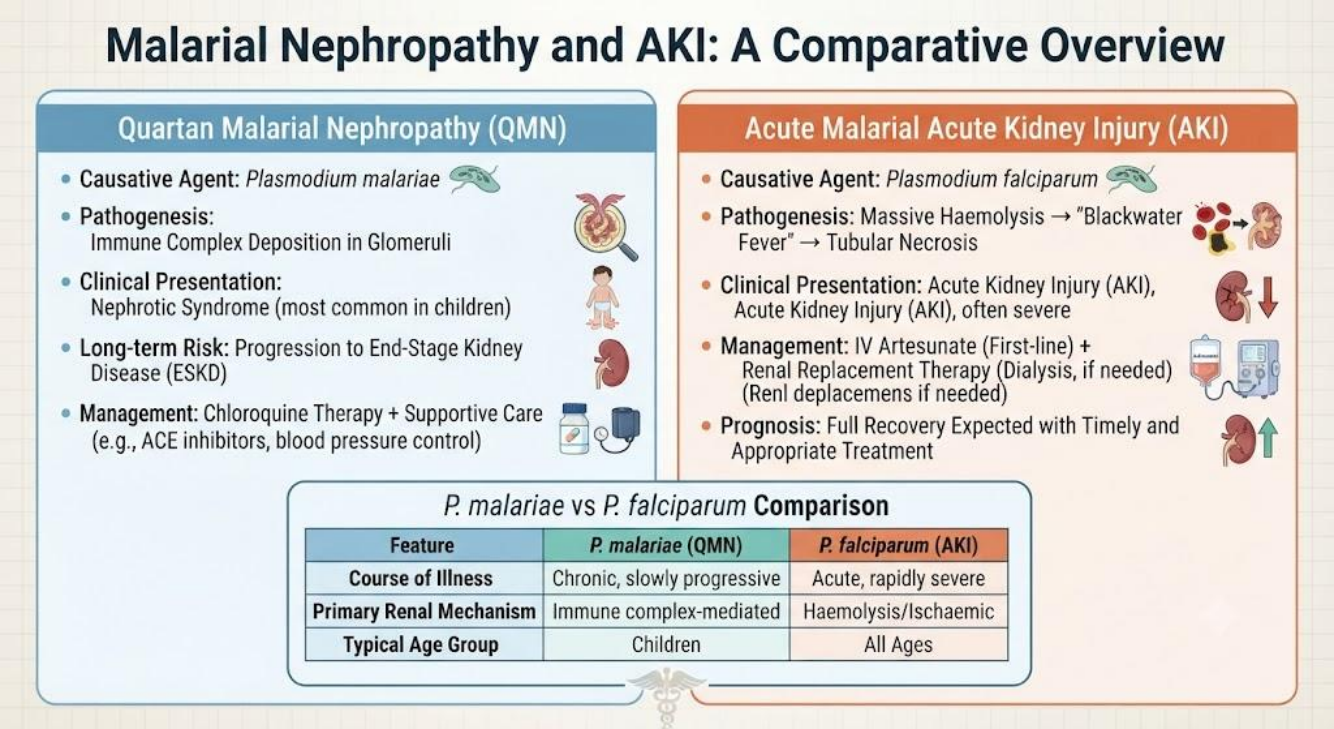


Figure 5.3: Malarial nephropathy — quartan nephropathy versus acute AKI: pathogenesis and management

Pilot questions 5.3

1. Describe the two main mechanisms of renal injury in malaria. (Linked to SLO 5.3)
2. Describe the clinical features of quartan malarial nephropathy. (Linked to SLO 5.3)
3. Explain the pathogenesis of acute kidney injury in severe Plasmodium falciparum malaria. (Linked to SLO 5.3)
4. Describe the urinary findings in acute malarial nephropathy. (Linked to SLO 5.3)
5. Describe the management of acute malarial AKI caused by P. falciparum. (Linked to SLO 5.3)

5.4 HIV Nephropathy and Other Infection-Related Nephropathies

5.4.1 HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is the most common cause of ESKD in HIV-positive individuals in sub-Saharan Africa and a leading cause of renal disease in Nigeria. It is caused by **direct infection of renal tubular epithelial cells and podocytes by HIV-1**, causing a distinctive clinicopathological syndrome. HIVAN occurs almost exclusively in patients of **Black African ancestry** (strongly linked to APOL1 high-risk genotype, as in FSGS), and typically presents in patients with **advanced HIV (low CD4 count)**.

Clinically, HIVAN presents with heavy proteinuria (often nephrotic-range), rapid decline in GFR, and ultrasound showing **enlarged, echogenic kidneys** (in contrast to CKD from other causes, where kidneys are small). On renal biopsy, the hallmark is **collapsing FSGS** (collapse and sclerosis of the glomerular tuft with overlying podocyte hypertrophy and proliferation), combined with severe tubular microcystic dilatation. **Antiretroviral therapy (ART)** is the most important treatment: effective ART with viral suppression prevents and can partially reverse HIVAN.

Fill in the blank: HIVAN occurs in Black African patients with advanced HIV, presents with heavy proteinuria and enlarged echogenic kidneys, shows collapsing _____ on biopsy, and is treated primarily with antiretroviral therapy.

5.4.2 Other infection-related nephropathies in Nigeria

Schistosomiasis (Schistosoma mansoni, S. haematobium): hepatosplenic schistosomiasis with portal hypertension can cause an MPGN-pattern nephropathy from chronic immune complex deposition. S. haematobium directly infects the urinary tract, causing haematuria, bladder wall thickening, ureteric obstruction, and obstructive nephropathy. Nigeria has a significant schistosomiasis burden in rural communities, particularly in the Niger Delta and middle belt regions.

Sickle cell nephropathy occurs in patients with homozygous sickle cell disease (HbSS): sickling of red cells in the hypoxic, hypertonic renal medulla causes papillary necrosis, haematuria,

impaired urine concentration (hyposthenuria), and glomerular hyperfiltration that over time leads to progressive CKD. **Leptospirosis** (Weil's disease) causes a triad of AKI, jaundice, and bleeding (Weil's disease) with hepatic and renal failure; treated with penicillin or doxycycline. **Streptococcal endocarditis** causes immune complex GN (embolic or immune complex-mediated) presenting as haematuria, proteinuria, and AKI.

Fill in the blank: Schistosomiasis S. haematobium causes urinary tract infection and obstructive nephropathy; sickle cell nephropathy causes papillary necrosis, hyposthenuria, and progressive CKD; leptospirosis causes AKI, _____, and bleeding (Weil's disease).

5.4.3 Prevention and general principles of infection-related nephropathy

Prevention of infection-related nephropathy rests on the control of the underlying infection. For malaria: **insecticide-treated bed nets**, indoor residual spraying, artemisinin-based combination therapy for prompt treatment, and chemoprevention in vulnerable populations (pregnant women and children). For HIV: **universal antiretroviral therapy** (UNAIDS 95-95-95 targets: 95 percent diagnosed, 95 percent on ART, 95 percent virally suppressed). For hepatitis B: **universal HBV vaccination** (expanded programme on immunisation: three-dose infant vaccination). For hepatitis C: **harm reduction programmes** and DAA treatment of all infected individuals.

General principles of managing infection-related nephropathy: **treat the underlying infection first and optimally** (most infection-related nephropathies improve or stabilise with effective treatment of the causative infection); provide **renoprotective therapy** (ACEi or ARB for proteinuria and hypertension); avoid **nephrotoxic drugs** (many antivirals, antimalarials, and antibiotics require dose adjustment or avoidance in renal impairment); and monitor renal function regularly in all patients with chronic infections.

Fill in the blank: Prevention of infection-related nephropathy targets the underlying infection: bed nets and ACT for malaria, universal ART for HIV, HBV _____ for hepatitis B; general principles include treating the infection, renoprotective therapy, and avoiding nephrotoxins.

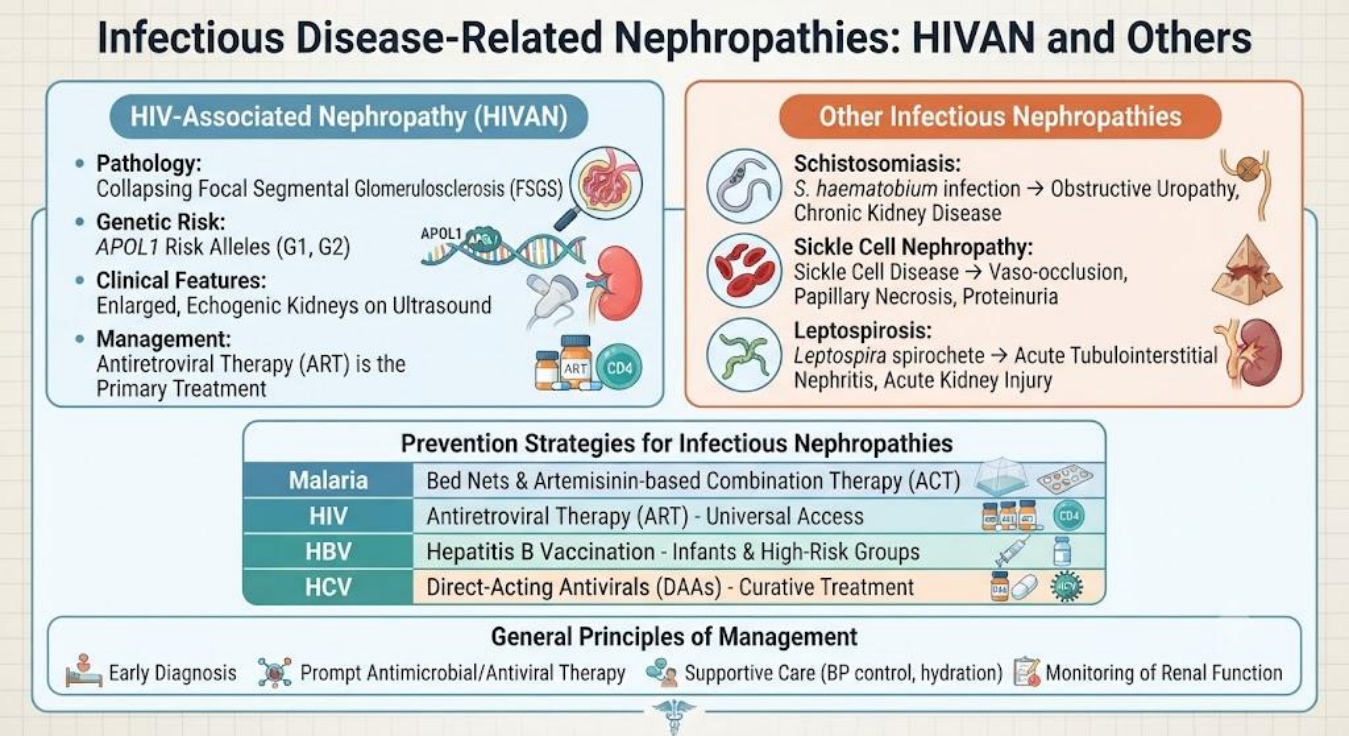


Figure 5.4: HIVAN, other infection-related nephropathies in Nigeria, and prevention strategies

Pilot questions 5.4

1. Describe the clinical features and renal biopsy findings of HIV-associated nephropathy. (Linked to SLO 5.4)
2. Explain why HIVAN occurs predominantly in patients of Black African ancestry. (Linked to SLO 5.4)
3. Describe the renal manifestations of schistosomiasis in Nigeria. (Linked to SLO 5.4)
4. Describe the renal manifestations of sickle cell disease. (Linked to SLO 5.4)
5. Describe the general principles of prevention and management of infection-related nephropathy. (Linked to SLO 5.4)

Series Summary

This final Series examined immune-complex and infection-related nephropathies. Immune complex deposition in the subepithelial space causes nephrotic syndrome; subendothelial deposits cause nephritic syndrome; mesangial deposits cause mild disease; complement activation lowers C3. MPGN shows tram-track GBM duplication, endocapillary proliferation, and persistent low C3; classified as immune complex MPGN (hepatitis C most common cause) or C3 glomerulopathy (complement dysregulation: factor H deficiency, C3 nephritic factor). Cryoglobulinaemic nephropathy Type II (HCV-driven) causes palpable purpura, arthralgia, and GN with low C4; treated with direct-acting antivirals (DAAs). HBV-associated nephropathy most commonly causes membranous nephropathy (HBsAg/HBeAg positive, anti-PLA2R negative); treated with tenofovir or entecavir. HCV-associated nephropathy causes MPGN via cryoglobulinaemia; DAAs achieve SVR (cure) in above 95 percent with significant renal improvement; rituximab and plasma exchange for severe vasculitis.

Malarial nephropathy: P. malariae causes quartan malarial nephropathy (progressive nephrotic syndrome in children; sclerosing GN; poorly steroid-responsive; progresses to ESKD); P. falciparum causes AKI in severe malaria through haemolysis, haemoglobinuria (blackwater fever), and microvascular obstruction; treated with IV artesunate, fluids, and dialysis if needed (recovery usually occurs). HIVAN (HIV-associated nephropathy) occurs in Black African patients with advanced HIV and APOL1 high-risk genotype; presents with heavy proteinuria and enlarged echogenic kidneys; biopsy shows collapsing FSGS; treated with ART. Other nephropathies: schistosomiasis (MPGN or obstructive), sickle cell nephropathy (papillary necrosis, hyposthenuria, progressive CKD), leptospirosis (AKI, jaundice, bleeding). Prevention: bed nets and ACT (malaria), ART (HIV), HBV vaccination (hepatitis B), DAAs (hepatitis C); general principles: treat the underlying infection, use renoprotective therapy, avoid nephrotoxins.

Glossary of Terms

- **Immune-complex nephropathy:** renal disease caused by deposition of antigen-antibody complexes in the glomerulus with complement activation and inflammatory injury.

- **Membranoproliferative GN (MPGN):** a GN pattern characterised by tram-track GBM duplication, mesangial hypercellularity, and endocapillary proliferation; presents as mixed nephritic-nephrotic syndrome with persistent low C3.
- **C3 glomerulopathy:** MPGN caused by complement dysregulation with C3-dominant glomerular deposits; includes dense deposit disease and C3 GN.
- **Cryoglobulins:** immunoglobulins that precipitate in the cold; Type II cryoglobulinaemia is strongly associated with hepatitis C virus.
- **Quartan malarial nephropathy (QMN):** a progressive sclerosing nephropathy caused by P. malariae immune complex deposition; presents as nephrotic syndrome in children; poorly steroid-responsive.
- **Blackwater fever:** massive intravascular haemolysis and haemoglobinuria in severe falciparum malaria causing dark urine and AKI.
- **IV artesunate:** the drug of choice for severe malaria in Nigeria and globally; administered intravenously for acute malarial AKI.
- **HIVAN:** HIV-associated nephropathy; collapsing FSGS caused by direct HIV infection of podocytes; occurs predominantly in Black African patients with advanced HIV and APOL1 high-risk genotype.
- **Collapsing FSGS:** a severe histological variant of FSGS with glomerular tuft collapse and overlying podocyte hypertrophy and proliferation; the hallmark of HIVAN.
- **Direct-acting antivirals (DAAs):** oral antiviral agents achieving sustained virological response (cure) in above 95 percent of HCV-infected patients; the primary treatment for HCV-associated nephropathy.
- **Sickle cell nephropathy:** progressive renal disease in HbSS patients from sickling in the renal medulla; manifestations include papillary necrosis, hyposthenuria, haematuria, and CKD.
- **Hyposthenuria:** inability to concentrate urine beyond 300 to 400 mOsm/kg; a characteristic finding of sickle cell nephropathy from medullary damage.

Concept Check Questions [Series 5]

Objective Questions

1. Subepithelial immune complex deposits cause nephrotic syndrome; subendothelial deposits cause _____ syndrome; complement activation lowers serum C3. (Linked to SLO 5.1)
2. MPGN shows tram-track GBM duplication on silver stain; persistent low _____ (lasting beyond 8 weeks) distinguishes it from PSGN. (Linked to SLO 5.1)
3. HCV-associated nephropathy Type II cryoglobulinaemia characteristically shows low C4 and positive _____ factor. (Linked to SLO 5.1)
4. HBV-associated membranous nephropathy is distinguished from primary MN by positive HBsAg or HBeAg and _____ anti-PLA2R antibodies. (Linked to SLO 5.2)
5. Quartan malarial nephropathy caused by P. malariae presents as progressive _____ syndrome in children and is poorly responsive to corticosteroids. (Linked to SLO 5.3)
6. HIVAN shows _____ FSGS on biopsy and occurs in Black African patients with advanced HIV; treated with antiretroviral therapy. (Linked to SLO 5.4)

Short-Answer Questions

7. Describe the clinical features and management of cryoglobulinaemic nephropathy. (Linked to SLO 5.1)
8. Describe the pathogenesis of acute kidney injury in severe falciparum malaria. (Linked to SLO 5.3)
9. Describe the renal manifestations of sickle cell disease. (Linked to SLO 5.4)

Long-Answer Questions

10. Describe the pathogenesis, clinical syndromes, and management of malarial nephropathy. (Linked to SLO 5.3)
11. Describe HIV-associated nephropathy including its pathogenesis, clinical features, biopsy findings, and management. (Linked to SLO 5.4)

Answers to Concept Check Questions [Series 5]

Objective Questions

1. Nephritic.
2. C3.
3. Rheumatoid.
4. Negative.
5. Nephrotic.
6. Collapsing.

Short-Answer Questions

7. Clinical features: palpable purpura (non-thrombocytopenic), arthralgia, Raynaud's phenomenon, GN (nephritic or nephrotic); low C4; positive rheumatoid factor; HCV RNA positive. Management: direct-acting antivirals (sofosbuvir-based or glecaprevir/pibrentasvir) to eradicate HCV; plasma exchange and rituximab for severe cryoglobulinaemic vasculitis or rapidly progressive nephritis.
8. Severe falciparum malaria causes AKI through: intravascular haemolysis releasing haemoglobin (haemoglobinuria: blackwater fever, direct tubular toxicity); microvascular obstruction from sequestration of parasitised rigid red cells in renal capillaries; cytokine storm (TNF-alpha, IL-1) causing renal vasoconstriction; volume depletion from fever, sweating, vomiting; all leading to reduced renal perfusion and acute tubular necrosis.
9. Papillary necrosis (sickling in the hypoxic renal medulla causes infarction of the papillae; presents with haematuria, renal colic, and passage of papillary tissue in urine). Hyposthenuria (inability to concentrate urine from medullary damage; fixed urinary osmolality around 300 mOsm/kg). Haematuria (from papillary necrosis or glomerular hyperfiltration injury). Glomerular hyperfiltration progressing to glomerulosclerosis and CKD. Renal tubular acidosis.

Long-Answer Questions

10. **Basic response:** Pathogenesis: P. malariae causes chronic immune complex nephropathy through deposition of malarial antigens with specific antibodies in the mesangium and subendothelial space, activating complement and causing progressive sclerosing GN. P.

falciparum causes AKI through haemolysis, haemoglobinuria, microvascular obstruction, cytokine-mediated vasoconstriction, and volume depletion. Clinical syndromes: Quartan malarial nephropathy (P. malariae): progressive nephrotic syndrome in children in malaria-endemic Nigeria; heavy proteinuria, hypoalbuminaemia, oedema; biopsy: sclerosing GN with mesangial and subendothelial IgG, IgM, and C3; poorly steroid-responsive; progresses to ESKD over years. Acute malarial AKI (P. falciparum): acute nephritic or AKI picture; haematuria, haemoglobinuria, proteinuria; blackwater fever (dark urine from haemoglobinuria). Management: Quartan MN: chloroquine (P. malariae is chloroquine-sensitive) to eliminate infection; supportive care (diuretics, antihypertensives, ACEi or ARB); renal replacement therapy for ESKD. Acute AKI: IV artesunate (severe malaria); cautious fluid resuscitation; blood transfusion for haemolysis; dialysis if AKI does not recover.

Value-added response: The distinction between quartan malarial nephropathy and acute malarial AKI is clinically important because their management differs fundamentally: QMN is a chronic fibrotic process not amenable to immunosuppression or antimalarial therapy after the damage is established, while acute falciparum AKI requires urgent artesunate treatment and supportive care, and renal function recovery is the expected outcome with appropriate management.

11. **Basic response:** Pathogenesis: HIV-1 directly infects renal tubular epithelial cells and podocytes (not through immune complex deposition); viral proteins Vpr and Nef induce podocyte proliferation, dedifferentiation, and collapse; APOL1 G1 and G2 high-risk genotypes in Black African patients dramatically amplify susceptibility (over 20-fold increased risk of HIVAN compared to APOL1 low-risk genotype). Clinical features: heavy proteinuria (often nephrotic-range); rapid GFR decline; ultrasound: enlarged echogenic kidneys (unlike CKD from other causes); occurs in patients with advanced HIV (CD4 count typically below 200 cells/microlitre). Biopsy: collapsing FSGS (glomerular tuft collapse, podocyte hypertrophy and proliferation overlying collapsed tufts) combined with severe tubular microcystic dilatation and interstitial oedema. Management: antiretroviral therapy (ART) is the primary treatment; effective viral suppression prevents HIVAN progression and can improve GFR and reduce proteinuria;

ACEi or ARB for renoprotection and proteinuria reduction; renal replacement therapy for ESKD from HIVAN.

Value-added response: HIVAN illustrates the intersection of infection, genetics, and social determinants of renal disease: a virus that primarily targets immune cells causes devastating kidney injury in a genetically susceptible population because the same APOL1 variants that protect West Africans from Trypanosoma brucei rhodesiense create exquisite susceptibility to HIV-mediated podocyte injury, making HIVAN an almost exclusively Black African disease with a pathogenesis that integrates microbiology, genetics, and immunology.

Answers to Pilot Questions [Series 5]

Part 5.1

1. Subepithelial deposits (between GBM and podocyte): loss of glomerular charge barrier; albumin leaks through into filtrate; nephrotic syndrome (heavy proteinuria, hypoalbuminaemia, oedema, hyperlipidaemia); example: membranous nephropathy, post-streptococcal GN humps. Subendothelial deposits (between endothelium and GBM): complement activation; endocapillary inflammation; nephritic syndrome (haematuria, sub-nephrotic proteinuria, hypertension, oliguria); example: MPGN, lupus Class IV. Mesangial deposits: mild complement activation; minimal clinical disease; example: IgA nephropathy, Class I and II lupus nephritis.
2. Light microscopy: mesangial hypercellularity and endocapillary proliferation; thickening and splitting of the GBM producing the tram-track or double-contour appearance on silver stain (GBM duplication from mesangial interposition into the capillary wall). Immunofluorescence: granular deposits of IgG, IgM, and C3 in the mesangium and along capillary walls; the distribution pattern distinguishes IC-MPGN (granular Ig and C3) from C3 glomerulopathy (C3 dominant with minimal or no Ig).
3. IC-MPGN: granular deposits of IgG, IgA, IgM, and C3 on IF; caused by exogenous antigens (hepatitis C, B, HIV, infective endocarditis) or autoimmune disease; complement

activated via classical pathway by immune complexes; responds to treating the underlying infection or immunosuppression. C3 glomerulopathy: C3-dominant deposits with minimal or no Ig on IF; caused by endogenous complement pathway dysregulation (factor H deficiency, factor I deficiency, C3 nephritic factor stabilising C3 convertase; not by immune complexes); may require eculizumab (anti-C5 monoclonal antibody) for treatment in complement-driven cases.

4. Clinical features: palpable purpura (the most characteristic feature: non-thrombocytopenic purpura on lower extremities and buttocks from cutaneous small vessel vasculitis); arthralgia and arthritis; Raynaud's phenomenon; GN (haematuria, proteinuria, reduced GFR). Causes: Type I (monoclonal Ig: myeloma, Waldenstrom's), Type II (mixed: HCV most common cause; also HBV, HIV, SLE), Type III (polyclonal: autoimmune diseases). Laboratory: low C4 (complement consumption via classical pathway by cryoglobulin complexes); positive rheumatoid factor (cryoglobulin IgM has rheumatoid factor activity); HCV antibody and RNA positive in Type II.
5. In PSGN, complement is consumed transiently during the acute immune complex-mediated injury; C3 returns to normal within 6 to 8 weeks as the offending streptococcal antigen is cleared and immune complexes are removed. In MPGN, complement is consumed continuously — either because the source of antigens persists (chronic hepatitis C or B infection) or because of intrinsic complement pathway dysregulation (C3 glomerulopathy) — so C3 remains persistently low beyond 8 weeks; this persistence distinguishes MPGN from PSGN and should trigger further investigation.

Part 5.2

1. Pathogenesis: HBV releases viral antigens (HBsAg, HBeAg) into the circulation; these form immune complexes with corresponding antibodies; immune complexes deposit in the glomerular subepithelial space (and sometimes mesangium and subendothelial space); complement activation causes glomerular injury. Most common pattern: membranous nephropathy (HBV-MN) from subepithelial immune complex deposition producing the typical thickened GBM with spike and dome pattern on EM.
2. HBV-associated MN: HBsAg or HBeAg positive on serology; anti-PLA2R antibodies negative (primary MN is caused by anti-PLA2R antibodies; HBV-MN does not involve

PLA2R); HBV DNA elevated; liver function tests may be abnormal; biopsy shows typical MN pattern but with evidence of viral antigen in the deposits on immunostaining in some cases; complement C3 may be mildly low (from immune complex activation).

3. HCV causes nephropathy primarily through Type II mixed cryoglobulinaemia: HCV RNA and anti-HCV antibodies form cryoglobulin complexes that deposit in glomerular capillaries causing an MPGN pattern; complement consumption lowers C3 and C4; clinical features include mixed nephritic-nephrotic syndrome, palpable purpura, arthralgia, peripheral neuropathy, and systemic vasculitis; investigations: HCV RNA, anti-HCV, cryoglobulins, low C3 and C4, positive rheumatoid factor.
4. DAAs achieve HCV eradication (SVR: sustained virological response, equivalent to cure) in above 95 percent of patients; after SVR, cryoglobulin levels fall as the antigen driving cryoglobulin production is eliminated; proteinuria reduces, renal function stabilises or improves, and cryoglobulinaemic vasculitis resolves; sofosbuvir-based regimens require dose adjustment or avoidance in severe renal impairment (eGFR below 30); glecaprevir/pibrentasvir is safe across all GFR categories.
5. HBV nephropathy: first-line antivirals are tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) (TAF preferred in renal impairment: less nephrotoxic than TDF) or entecavir; antiviral treatment suppresses HBV DNA, reduces immune complex formation, and stabilises or improves renal function; interferon-alpha is no longer recommended (nephrotoxic and less effective); children with HBV-MN may be monitored for spontaneous remission with HBeAg seroconversion.

Part 5.3

1. Two mechanisms: (1) Immune complex deposition: malarial antigens released during red cell lysis combine with specific antibodies, forming immune complexes that deposit in the glomerulus (mesangium and subendothelial space), activate complement via the classical pathway, and cause glomerular inflammation and progressive sclerosis; this mechanism underlies quartan malarial nephropathy from P. malariae. (2) Direct haemodynamic and cytokine-mediated injury: severe falciparum malaria causes massive haemolysis, haemoglobinuria, microvascular obstruction from parasitised red cell

sequestration, cytokine storm (TNF-alpha), and volume depletion causing acute tubular necrosis and AKI.

2. Quartan malarial nephropathy presents predominantly in children (peak age 5 to 10 years) in malaria-endemic regions of Nigeria; clinical features: progressive nephrotic syndrome (heavy proteinuria, hypoalbuminaemia, peripheral and facial oedema, ascites); biopsy: sclerosing GN with mesangial and subendothelial deposits of IgG, IgM, and complement; poorly responsive to corticosteroids; progresses inexorably to ESKD over years despite antimalarial treatment; natural history is of progressive renal failure.
3. Severe P. falciparum malaria causes AKI through: massive intravascular haemolysis releasing haemoglobin (which precipitates in renal tubules as haemoglobin casts causing tubular obstruction and direct toxicity; produces haemoglobinuria: dark brown or black urine: blackwater fever); sequestration of parasitised rigid red cells in renal microvascular beds causing obstruction and ischaemia; cytokine storm (TNF-alpha, IL-1) causing renal vasoconstriction and reduced GFR; volume depletion from fever, vomiting, and reduced intake.
4. Dipstick urinalysis: haematuria (blood positive from haemoglobin or haemoglobinuric AKI); proteinuria (may reflect tubular damage or glomerular injury). Urine microscopy: haemoglobin casts (from haemoglobinuria in blackwater fever), granular casts (tubular injury), red blood cells. Gross appearance: dark brown, red, or black urine in blackwater fever (haemoglobinuria); concentrated oligouric urine or dilute non-oliguric urine in AKI. Quantified proteinuria: by uACR or 24-hour collection.
5. IV artesunate (2.4 mg/kg IV at 0, 12, and 24 hours, then every 24 hours): the drug of choice for severe malaria in Nigeria; switches to oral ACT (artemisinin-based combination therapy) when patient can tolerate oral medication. Cautious fluid resuscitation: IV crystalloid (0.9 percent sodium chloride) to restore renal perfusion without causing pulmonary oedema (which is a complication of severe malaria). Blood transfusion: for severe haemolytic anaemia (Hb below 7 g/dL). Dialysis (haemodialysis or peritoneal dialysis): for AKI that does not recover spontaneously or for severe electrolyte and acid-base complications; renal function recovery is expected with appropriate treatment in most patients.

Part 5.4

1. Clinical features: heavy proteinuria (often nephrotic-range: above 3.5 g per day); rapid progressive decline in GFR; enlarged and echogenic kidneys on ultrasound (in contrast to CKD from other causes where kidneys shrink); occurs in patients with advanced HIV (CD4 count typically below 200 cells/microlitre); predominantly in patients of Black African ancestry. Biopsy findings: collapsing FSGS (collapse and global sclerosis of the glomerular tuft with overlying podocyte hypertrophy and proliferation — distinguishes HIVAN from classic FSGS); severe tubular microcystic dilatation; interstitial oedema and inflammation.
2. HIVAN occurs predominantly in Black African patients because APOL1 high-risk genotypes (G1 and G2 alleles) are found at high frequency in West African ancestry populations; HIV-1 Vpr protein activates APOL1 expression in podocytes; high-risk APOL1 variants (G1 or G2 in a homozygous or compound heterozygous state) produce APOL1 protein isoforms that cause podocyte injury and apoptosis when expressed at high levels; the combination of HIV-induced APOL1 upregulation and APOL1 high-risk genotype creates over 20-fold increased susceptibility to HIVAN in Black African patients compared to those with APOL1 low-risk genotype.
3. Schistosoma mansoni: hepatosplenic schistosomiasis with portal hypertension and splenomegaly causes chronic antigen release; immune complexes deposit in the glomerulus causing an MPGN pattern nephropathy; presents with proteinuria, haematuria, and progressive CKD in patients with chronic mansoni infection. Schistosoma haematobium: direct urinary tract tropism; infects the bladder wall causing granulomatous inflammation, haematuria, and urinary tract obstruction; ureteric involvement causes hydronephrosis and obstructive nephropathy; chronic infection is associated with bladder squamous cell carcinoma.
4. Papillary necrosis: sickling in the hypoxic, hypertonic, hyposmotic renal medulla causes ischaemic necrosis of the renal papillae; manifests as haematuria (sometimes gross), renal colic, and passage of papillary tissue in urine; diagnosis by CT urography showing papillary cavitation or ring shadows. Hyposthenuria: medullary damage from sickling impairs the counter-current concentrating mechanism; inability to concentrate urine beyond 300 to 400 mOsm/kg regardless of water intake (fixed isosthenuria); a very early

renal manifestation of sickle cell disease. Progressive CKD: glomerular hyperfiltration from increased GFR in sickle cell disease (anaemia-driven high cardiac output) causes glomerulosclerosis over time; proteinuria is an early marker; treated with ACEi or ARB.

5. Prevention: malaria (insecticide-treated bed nets, indoor residual spraying, prompt ACT treatment, intermittent preventive therapy in pregnancy); HIV (universal ART: UNAIDS 95-95-95 targets); hepatitis B (universal infant HBV vaccination: three-dose EPI schedule); hepatitis C (harm reduction, screening, DAA treatment of all infected). General management principles: treat the underlying infection optimally (most infection-related nephropathies stabilise or improve with pathogen eradication or suppression); renoprotective therapy with ACEi or ARB for proteinuria and hypertension; avoid nephrotoxins (adjust antiviral, antimalarial, and antibiotic doses for eGFR); regular renal function monitoring in all patients with chronic infections.

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Figures, Plates, Tables, and Boxes

- Figure 5.1: Immune-complex nephropathies: MPGN, C3 glomerulopathy, and cryoglobulinaemia. AI prompt: "Three-row table: IC-MPGN (tram-track, granular IgG and C3, low C3, hepatitis C), C3 glomerulopathy (C3-dominant, complement dysregulation), Cryoglobulinaemia Type II (HCV, purpura, low C4, DAAs); alternating row shading." OER search: "MPGN membranoproliferative glomerulonephritis cryoglobulinaemia hepatitis C nephropathy table".
- Figure 5.2: Hepatitis B and C nephropathy. AI prompt: "Two-panel table: HBV nephropathy (MN, positive HBsAg/HBeAg, negative anti-PLA2R, tenofovir or entecavir) and HCV nephropathy (MPGN via cryoglobulinaemia, low C3 and C4, DAAs); HBV vs HCV comparison; alternating shading." OER search: "hepatitis B C nephropathy membranous MPGN cryoglobulinaemia tenofovir DAA table".
- Figure 5.3: Malarial nephropathy syndromes and management. AI prompt: "Two-panel diagram: quartan MN (P. malariae: immune complex, nephrotic, ESKD; chloroquine and supportive) and acute malarial AKI (P. falciparum: haemolysis, blackwater fever; IV artesunate, dialysis); comparison box; clean infographic." OER search: "malarial nephropathy quartan nephrotic P falciparum AKI blackwater fever management diagram".

- Figure 5.4: HIVAN and infection-related nephropathies in Nigeria. AI prompt: "Two-panel diagram: HIVAN (collapsing FSGS, APOL1, ART) and other nephropathies (schistosomiasis, sickle cell, leptospirosis); prevention table (malaria, HIV, HBV, HCV) and general principles; clean infographic." OER search: "HIVAN HIV nephropathy collapsing FSGS APOL1 infection Nigeria prevention diagram".