

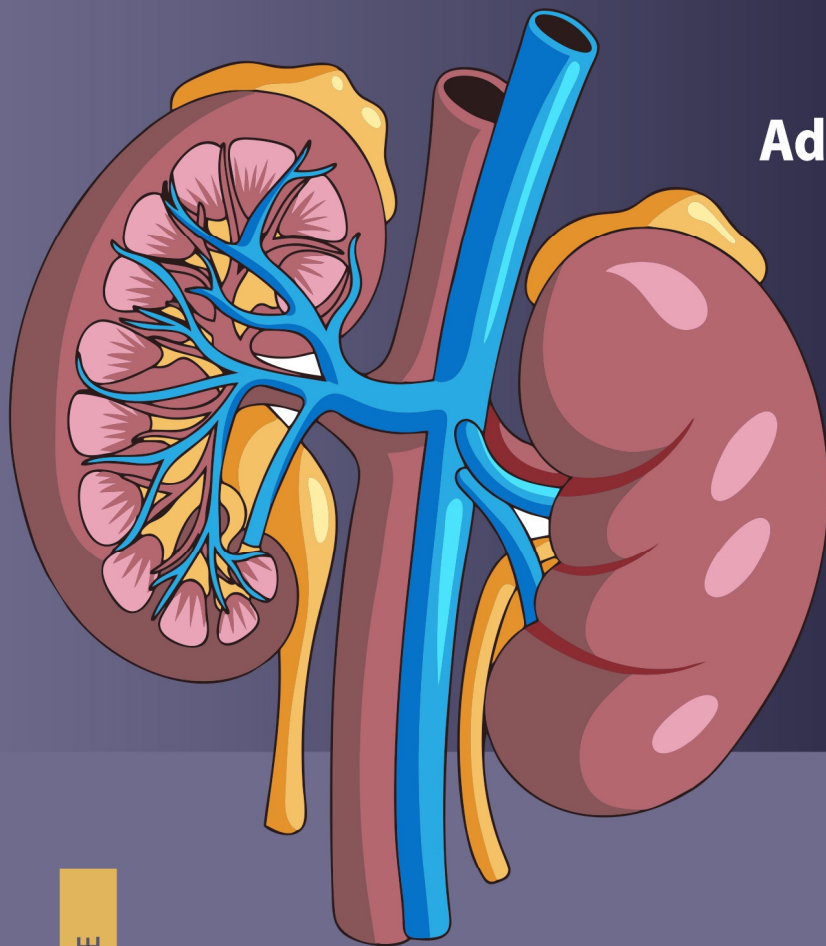


„VICTOR BABEȘ” UNIVERSITY
OF MEDICINE AND PHARMACY
FROM TIMIȘOARA

Clinical Nephrology for Medical Students

From physiology to safe bedside decisions

A CLINICALLY ORIENTED TEXTBOOK



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Preface

Kidney disease is common, clinically consequential and frequently under-recognized. Yet students often experience nephrology as a collection of formulas, uncommon histological entities and difficult electrolyte problems. This book takes a different approach. It begins with the decisions a doctor must make: Is kidney function truly abnormal? Is the process acute or chronic? Is the patient depleted or congested? Does this urine result suggest glomerular disease? Is there an emergency that requires treatment before the diagnosis is complete?

The intended reader is a fifth-year medical student who already knows general physiology and internal medicine but needs a reliable framework for clinical practice. The book therefore explains physiology when it changes interpretation or management. It deliberately distinguishes what every graduate should be able to do independently from what requires specialist input.

Treatment recommendations are anchored primarily in Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, supplemented by major nephrology journals, landmark trials and contemporary reference texts. Recommendations that are still in public-review drafts are identified as provisional rather than presented as settled guidance.

EDUCATIONAL PROMISE

Every chapter should help the reader recognize a clinical pattern, choose the first investigations, make safe initial decisions, avoid a common error and know when nephrology involvement is urgent.

How to use this book

- Start with the opening case and commit to an initial hypothesis before reading the explanation.
- Use the learning objectives as an examination checklist.
- Read the physiology sections for causal understanding; return to the algorithms for ward practice.
- Treat red emergency boxes as minimum safe-practice knowledge.
- Use the end-of-chapter questions for retrieval practice rather than passive review.
- Check the evidence-cutoff date in chapters where therapies evolve rapidly.

Editorial and evidence policy

The hierarchy of evidence for this book is: current published international guidelines; high-quality systematic reviews and major randomized trials; authoritative contemporary nephrology textbooks; and expert reviews in established journals. Local protocols, antimicrobial resistance and medicine availability must still be considered in practice.

Source type	Primary role in the book	Examples
Guidelines	Definitions, thresholds and management recommendations	KDIGO; relevant cardiology, diabetes, hypertension and infectious-disease guidance
Major trials	Benefits, harms and treatment effect estimates	Kidney and cardiorenal outcome trials
Nephrology journals	Controversies, implementation and emerging evidence	Kidney International, JASN, CJASN, AJKD, Nephrology Dialysis Transplantation
Reference texts	Integrated physiology, pathology and clinical context	Brenner & Rector; Comprehensive Clinical Nephrology

Scientific evidence reviewed through 17 September 2026. Recommendations should be interpreted with current national regulations, local protocols, antimicrobial-resistance data, medicine availability and transplant-center procedures.

IMPORTANT

This textbook supports education and supervised clinical reasoning. It does not replace current local protocols, full prescribing information or specialist assessment of an individual patient.

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PART I.

Understanding and evaluating kidney function

CHAPTER 1

Why the Kidneys Matter

*The kidneys as regulators, endocrine organs and guardians of internal stability***LEARNING OBJECTIVES**

After studying this chapter, the student should be able to:

- Describe the major excretory, regulatory and endocrine functions of the kidneys.
- Explain why serum creatinine alone is an incomplete description of kidney health.
- Relate loss of kidney function to volume, electrolyte, acid-base, hematologic, skeletal and cardiovascular complications.
- Recognize kidney disease as both a cause and a consequence of multisystem illness.
- Identify the clinical questions that should be asked whenever kidney dysfunction is suspected.

Opening case

CLINICAL CASE

A 72-year-old man with diabetes, hypertension and heart failure presents with increasing breathlessness and ankle swelling. Blood pressure is 158/86 mmHg. Jugular venous pressure is elevated, bilateral basal crackles are present and there is pitting edema to the knees. Serum creatinine is 1.8 mg/dL; six months earlier it was 1.4 mg/dL. Potassium is 5.3 mmol/L and bicarbonate is 19 mmol/L. Urine dipstick shows 2+ protein. Is this simply a laboratory problem, or is the kidney central to the entire presentation?

This patient illustrates why kidney disease cannot be reduced to creatinine. He has impaired filtration, probable albuminuric chronic kidney disease, sodium and water retention, hyperkalemia, metabolic acidosis and a strong bidirectional interaction between heart failure and kidney dysfunction. The first clinical task is not to choose a single renal diagnosis. It is to identify the immediate threats, establish chronicity, assess congestion and perfusion, review medicines and define the pattern of kidney injury.

1.1 The kidneys maintain the internal environment

Every day, the kidneys receive approximately one fifth of cardiac output and filter a very large volume of plasma water. Most filtered water and solutes are then selectively reabsorbed. This apparent inefficiency is physiologically powerful: high-volume filtration followed by precisely regulated tubular reclamation allows rapid adjustment of sodium, water, potassium, hydrogen ions and many other substances.

A healthy kidney does not merely remove waste. It continuously matches excretion to intake and endogenous production. When intake changes, the urinary composition changes; the plasma composition should remain relatively stable. This is the essence of renal homeostasis.

CORE CONCEPT

Kidney function is best understood as regulated excretion, not simple filtration. Filtration delivers substances to the tubule; reabsorption and secretion determine the final urine.

1.2 Excretory function

The kidneys eliminate endogenous waste products such as urea, creatinine, uric acid and metabolites of hormones. They also contribute to removal of many medicines and toxins. Reduced kidney function therefore has two distinct consequences: substances generated by the body accumulate, and medicines that are normally cleared by the kidneys may reach toxic concentrations.

Uremia is the clinical syndrome produced by advanced kidney failure. It is not synonymous with an increased urea concentration. Uremia may include anorexia, nausea, pruritus, cognitive change, sleep disturbance, pericarditis, platelet dysfunction, neuropathy and a general decline in functional state. No single laboratory value proves or excludes the syndrome.

1.3 Regulation of extracellular volume and blood pressure

Total-body sodium is the major determinant of extracellular fluid volume. The kidneys regulate sodium balance over time and therefore strongly influence blood pressure, edema and congestion. Water follows retained sodium, but water balance is also regulated independently through thirst and vasopressin.

A crucial distinction is that total extracellular volume and effective arterial blood volume are not identical. A patient with heart failure, cirrhosis or nephrotic syndrome may have excess total-body sodium and visible edema while the arterial circulation is sensed as underfilled. Neurohormonal responses then promote further sodium retention. Giving additional fluid solely because creatinine has increased may worsen pulmonary and venous congestion.

COMMON MISTAKE

Do not equate increased creatinine with dehydration. First assess the full circulation: history, blood pressure trend, orthostatic symptoms, jugular venous pressure, edema, lung findings, weight, urine output and the clinical context.

1.4 Electrolyte regulation

The kidneys maintain potassium, sodium, chloride, calcium, phosphate and magnesium balance. The clinical consequences of failure differ. Hyperkalemia can become immediately fatal through cardiac conduction disturbance. Sodium disorders primarily reflect water balance and may cause cerebral edema or osmotic injury. Phosphate retention and disordered vitamin D metabolism contribute to secondary hyperparathyroidism, bone disease and vascular calcification.

Plasma concentrations do not always represent total-body stores. A patient with diabetic ketoacidosis may present with a normal or high serum potassium despite substantial total-body potassium depletion. Interpretation therefore requires physiology and clinical context, not merely comparison with a reference range.

1.5 Acid-base homeostasis

The kidneys reclaim filtered bicarbonate, excrete daily nonvolatile acid and generate new bicarbonate. They accomplish this through hydrogen secretion, ammonium production and titratable acid excretion. When kidney function is substantially reduced, net acid excretion may become inadequate and metabolic acidosis develops.

Acidosis contributes to dyspnea, impaired cardiac function, hyperkalemia, muscle catabolism and bone buffering. In chronic kidney disease, even a modest reduction in serum bicarbonate may indicate a clinically relevant failure of acid excretion.

1.6 Endocrine and metabolic functions

Function	Renal contribution	Clinical consequence of dysfunction
Erythropoiesis	Production of erythropoietin by renal interstitial cells in response to tissue oxygen signaling	Normocytic anemia, reduced exercise capacity and fatigue
Mineral metabolism	1-alpha hydroxylation of vitamin D and phosphate excretion	Secondary hyperparathyroidism, bone disease and vascular calcification
Blood pressure	Renin release and interaction with the RAAS	Hypertension or maladaptive neurohormonal activation
Gluconeogenesis	Renal glucose production, especially during fasting	Altered glucose handling in advanced kidney disease
Drug and hormone metabolism	Clearance or degradation of multiple bioactive substances	Accumulation, prolonged drug effect and adverse events

1.7 The kidney as a cardiovascular organ

Cardiovascular disease is the leading major complication of chronic kidney disease. Risk rises as GFR falls and albuminuria increases. Traditional risk factors such as diabetes, hypertension, smoking and dyslipidemia coexist with nontraditional factors including inflammation, anemia, mineral-bone disorder, vascular calcification, oxidative stress and volume overload.

Albuminuria is not only a renal measurement. It is a marker of glomerular and systemic vascular injury and predicts kidney and cardiovascular outcomes. Consequently, two patients with the same eGFR may have very different prognoses if their albuminuria categories differ.

The heart and kidney influence each other through hemodynamic, venous, neurohormonal and inflammatory pathways. Low cardiac output may reduce renal perfusion, but venous congestion can also reduce effective filtration pressure and worsen kidney function. Conversely, sodium retention, anemia, hypertension and uremic toxins increase cardiac workload and injury.

1.8 Kidney disease is more than a low GFR

Chronic kidney disease is defined by abnormalities of kidney structure or function present for more than three months with implications for health. A person may therefore have CKD with a normal or high GFR if persistent albuminuria, abnormal urine sediment, structural abnormalities or another accepted marker of kidney damage is present. Conversely, a single low eGFR does not establish chronicity.

CLINICAL TRANSLATION

Always describe kidney health using at least four questions: What is the likely cause? Is the abnormality acute or chronic? What is the GFR category? What is the albuminuria category?

1.9 A five-question approach to suspected kidney disease

1. Is there an immediate threat? Look for severe hyperkalemia, pulmonary edema, severe acidosis, uremic complications, hypertensive emergency, rapidly progressive glomerulonephritis or an infected obstructed urinary tract.
2. Is the process acute, chronic or acute-on-chronic? Review previous creatinine values, urine findings, imaging, comorbidities and the time course.
3. What is the clinical syndrome? Consider AKI, CKD, nephritic syndrome, nephrotic syndrome, tubular disorder, obstruction, stone disease or electrolyte/acid-base disorder.
4. What caused it? Integrate hemodynamics, medicines, infection, systemic disease, urinary tract pathology, family history and exposure history.
5. What must be done today? Stabilize first, remove reversible causes, choose targeted tests, adjust medicines and decide whether nephrology input is urgent.

Case resolution

The patient is congested rather than clinically volume depleted. His previous creatinine suggests underlying CKD, but the rise may represent acute-on-chronic dysfunction related to decompensated heart failure, medicines or another superimposed process. Immediate priorities include ECG assessment because of hyperkalemia, confirmation of potassium, careful medication review, assessment of urine output and obstruction risk, quantification of albuminuria and treatment of congestion. The creatinine change must be interpreted alongside symptoms, perfusion, venous congestion and response to therapy.

Take-home messages

- The kidneys regulate the composition and volume of the internal environment; filtration is only one part of this work.
- Kidney disease produces multisystem consequences through volume, electrolyte, acid-base, endocrine and cardiovascular pathways.
- Creatinine is a useful filtration marker but not a complete description of kidney health.
- Albuminuria and GFR provide complementary prognostic information.
- In every patient, identify emergencies, chronicity, clinical syndrome, cause and the action required today.

Self-assessment

1. Why can a patient with heart failure be edematous yet activate sodium-retaining neurohormonal systems?
2. Name three endocrine or metabolic functions of the kidney.
3. Why does a single eGFR of 55 mL/min/1.73 m² not necessarily establish CKD?
4. Give two examples in which a plasma concentration does not accurately reflect total-body stores.
5. What are the five questions that structure the initial assessment of suspected kidney disease?

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CHAPTER 2

Functional Anatomy and Clinically Relevant Physiology

A map for understanding filtration, tubular transport and common drug effects

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Trace blood and filtrate through the kidney and nephron.
- Explain the determinants of GFR and renal autoregulation.
- Describe the principal transport functions of each nephron segment.
- Predict the renal effects of NSAIDs, RAAS inhibitors, SGLT2 inhibitors and diuretics.
- Use renal physiology to interpret common clinical changes in creatinine, sodium, potassium and acid-base status.

Opening case

CLINICAL CASE

A 66-year-old woman with CKD G3b, hypertension and osteoarthritis develops vomiting and poor oral intake. She continues ramipril and takes ibuprofen for three days. Creatinine rises from 1.5 to 2.6 mg/dL. Why did this combination place glomerular filtration at risk?

The answer requires an understanding of intraglomerular hemodynamics. Reduced effective circulating volume activates mechanisms that preserve filtration, including prostaglandin-mediated afferent arteriolar vasodilation and angiotensin II-mediated efferent arteriolar constriction. Ibuprofen impairs the afferent response; ramipril reduces efferent constriction. In a vulnerable patient, filtration pressure falls. Neither medicine is intrinsically 'poisonous' to every kidney, but the physiological context changes the risk.

HOW TO READ THE NUMBERS

Unless stated otherwise, numerical values in this chapter are approximate teaching ranges for a healthy, resting young adult. They vary with age, sex, body size, diet, pregnancy, posture, medications and disease.

KEY PHYSIOLOGICAL VALUES

Renal blood flow: 1.0–1.2 L/min (20–25% of cardiac output); renal plasma flow: 600–700 mL/min. GFR: 100–125 mL/min/1.73 m², equivalent to approximately 150–180 L/day; filtration fraction: 15–20%. Final urine: usually 1–2 L/day; urine osmolality can vary from about 50 to 1,200 mOsm/kg H₂O.

2.1 Gross organization

In adults, each kidney is usually approximately 10–12 cm long and weighs about 120–170 g, although size depends on body habitus, sex and age. Each kidney contains cortex, medulla, collecting system, blood vessels, interstitium and a highly variable nephron population. The often-quoted value is approximately 0.9–1.0 million nephrons per kidney, but measured numbers range from fewer than 0.3 million to more than 2 million. New nephrons are not generated after birth.

About 85% of nephrons are cortical and approximately 15% are juxtamedullary. All glomeruli lie in the cortex. Juxtamedullary nephrons have long loops of Henle that descend deep into the medulla and are particularly important for generating the corticomedullary osmotic gradient.

At rest, both kidneys receive approximately 1.0–1.2 L of blood each minute—about 20–25% of cardiac output. Because hematocrit occupies part of the blood volume, renal plasma flow is approximately 600–700 mL/min. Blood reaches each glomerulus through an afferent arteriole and exits through an efferent arteriole, which then forms peritubular capillaries or, for juxtamedullary nephrons, the vasa recta.

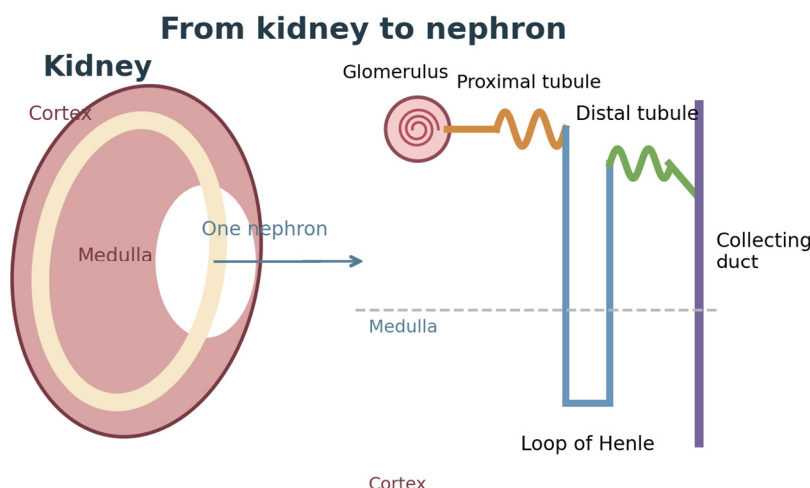


Figure 2.1. *From kidney to nephron. Cortical glomeruli initiate filtration; tubular segments extend through cortex and medulla before draining into the collecting system.*

2.2 The filtration barrier

The glomerular filtration barrier has three interacting components: fenestrated endothelium, glomerular basement membrane and podocyte slit diaphragm. It permits water and small solutes to cross while largely retaining blood cells and most circulating proteins. Barrier injury can therefore present as hematuria, albuminuria or both.

Proteinuria is not explained solely by a mechanical 'hole.' Charge and size selectivity, endothelial glycocalyx, podocyte structure, basement membrane properties and proximal tubular retrieval all contribute. This is why different glomerular diseases generate different urinary patterns.

The glomerular filtration barrier

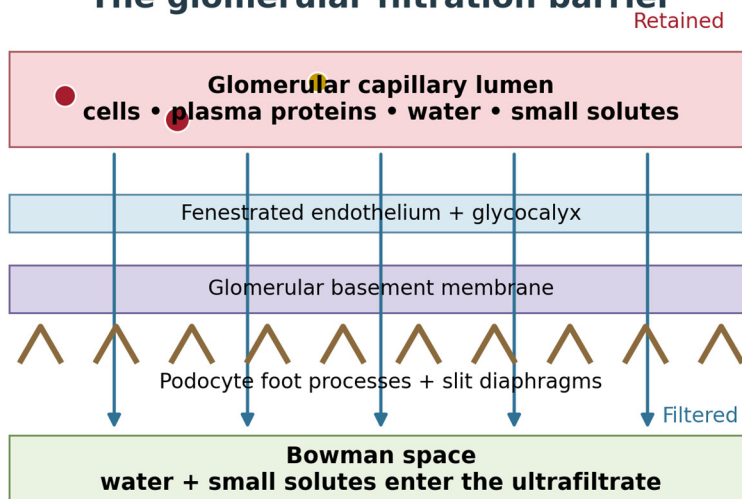


Figure 2.2. *The three-layer glomerular filtration barrier. Water and small solutes cross into Bowman space, while blood cells and most circulating proteins are retained.*

2.3 Determinants of GFR

In a healthy young adult, measured GFR is commonly approximately 100–125 mL/min/1.73 m². This corresponds to roughly 150–180 L of ultrafiltrate each day. With a renal plasma flow near 600–700 mL/min, the filtration fraction—GFR divided by renal plasma flow—is usually approximately 15–20%. More than 99% of the filtrate is subsequently reabsorbed, leaving only about 1–2 L/day as final urine under usual conditions.

GFR is the product of the filtration coefficient and net filtration pressure. Typical teaching values are a glomerular capillary hydrostatic pressure of approximately 50–60 mmHg, Bowman space hydrostatic pressure of 10–15 mmHg and average glomerular capillary oncotic pressure of 25–30 mmHg, producing a net filtration pressure near 10 mmHg. These are conceptual averages rather than bedside measurements. Clinically, changes in afferent tone, efferent tone, systemic pressure, urinary obstruction and plasma protein concentration can alter filtration.

Change	Effect on intraglomerular dynamics	Typical clinical context
Afferent constriction	Reduces renal blood flow and glomerular pressure	NSAID effect in prostaglandin-dependent states; intense sympathetic activation
Afferent dilation	Tends to increase flow and preserve glomerular pressure	Prostaglandin response; reduced tubuloglomerular feedback
Moderate efferent constriction	Raises glomerular pressure and helps preserve GFR	Angiotensin II effect during reduced perfusion
Efferent dilation	Lowers intraglomerular pressure	ACE inhibitor or ARB; therapeutically useful in proteinuric CKD
Urinary obstruction	Raises pressure beyond the filtration barrier	Stone, prostate enlargement or pelvic mass

2.4 Autoregulation

Across an approximate mean arterial pressure range of 80–180 mmHg, healthy kidneys can keep renal blood flow and GFR relatively stable. This plateau is not a rigid boundary and differs between individuals. The myogenic response begins within seconds: increased afferent arteriolar wall stretch triggers smooth-muscle contraction, whereas reduced pressure promotes relaxation.

Tubuloglomerular feedback operates over seconds to minutes. Increased NaCl delivery to the macula densa—sensed principally through NKCC2—promotes ATP/adenosine signaling, afferent constriction and reduced renin release. Reduced NaCl delivery has the opposite effect. Autoregulation has limits: severe hypotension, advanced vascular disease, sepsis and combinations of hemodynamically active drugs can move the patient outside the plateau. Chronic hypertension may shift the range rightward, making abrupt blood-pressure reductions poorly tolerated.

Renal autoregulation

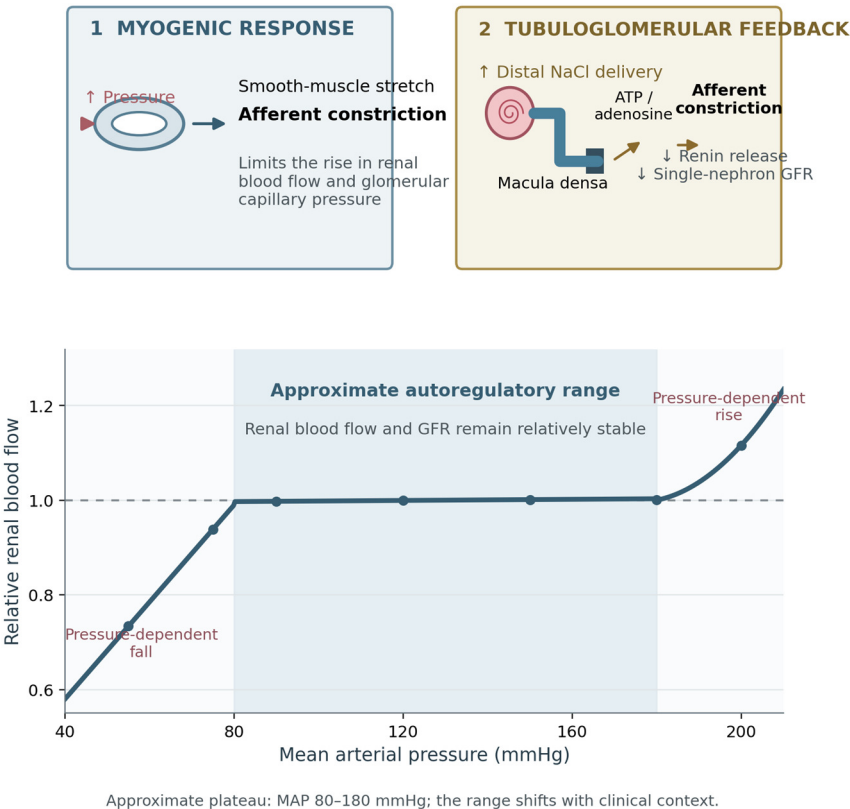
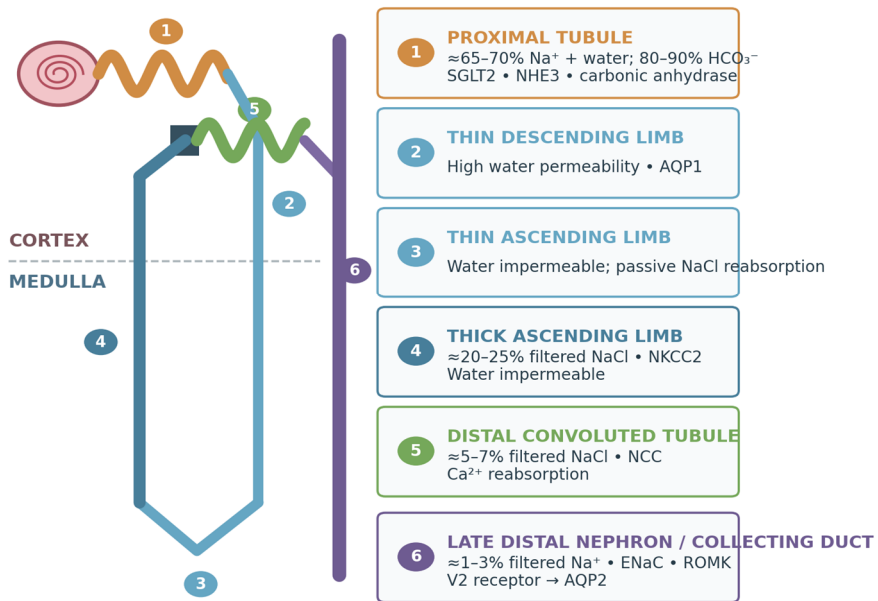


Figure 2.3. *The myogenic response and tubuloglomerular feedback stabilize renal blood flow and GFR across an approximate autoregulatory pressure range.*

2.5 The nephron segment by segment

Segment	Main functions	Clinical connections
Proximal tubule	Reabsorbs about 65–70% of filtered Na ⁺ and water, 80–90% of HCO ₃ ⁻ , and nearly all filtered glucose and amino acids	SGLT2 and carbonic anhydrase inhibitors; Fanconi syndrome; proximal RTA
Loop of Henle	Thin descending limb is water permeable; thick ascending limb reabsorbs about 20–25% of filtered NaCl through NKCC2	Loop diuretics; Ca ²⁺ /Mg ²⁺ handling; impaired concentrating ability
Distal convoluted tubule	Reabsorbs about 5–7% of filtered NaCl through NCC; regulates Ca ²⁺	Thiazide diuretics; Gitelman physiology
Late distal nephron / collecting duct	Handles roughly 1–3% of filtered Na ⁺ ; ENaC, K ⁺ /H ⁺ secretion and vasopressin-regulated water transport	K ⁺ -sparing agents, vaptans, distal RTA and diabetes insipidus

Nephron transport segments



Numbers identify physiological segments; arrows are omitted to keep the map uncluttered.

Figure 2.4. Anatomically ordered nephron segments with principal transport pathways and approximate fractions of filtered solute reabsorbed.

Major diuretic and aquaretic targets

Proximal tubule SGLT2 • NHE3 • carbonic anhydrase	SGLT2 inhibitors Carbonic anhydrase inhibitors Mannitol*
Thin descending limb AQP1; water permeable	Mannitol* (osmotic effect)
Thick ascending limb NKCC2; lumen-positive voltage	Loop diuretics
Distal convoluted tubule NCC; Ca^{2+} reabsorption	Thiazide and thiazide-like diuretics
Collecting tubule / duct ENaC • mineralocorticoid receptor • V2–AQP2	K^+-sparing agents† Vaptans (aquaretics)‡

* Freely filtered; greatest osmotic effect in water-permeable segments. † ENaC blockers and mineralocorticoid-receptor antagonists.
 ‡ V2-receptor antagonists reduce AQP2 insertion and increase electrolyte-free water excretion.

Figure 2.5. Sites of action of SGLT2 inhibitors, carbonic anhydrase inhibitors, mannitol, loop and thiazide diuretics, potassium-sparing agents and V2-receptor antagonists (vaptans).

2.6 Sodium, water and the medullary gradient

At a GFR of 125 mL/min and plasma sodium of 140 mmol/L, approximately 25,000 mmol of sodium is filtered each day. Normally more than 99% is reabsorbed, while daily urinary excretion—often around 100–200 mmol—adjusts to dietary intake. Sodium excretion determines long-term extracellular volume, whereas water excretion determines plasma tonicity; the two are related but not interchangeable.

Approximately 150–180 L of water enters the filtrate each day, but usual urine volume is only 1–2 L/day. Vasopressin acting at collecting-duct V2 receptors increases aquaporin-2 insertion and water permeability. The human kidney can generally vary urine osmolality from approximately 50–100 mOsm/kg H₂O during maximal dilution to about 1,000–1,200 mOsm/kg H₂O during maximal concentration.

The loop of Henle establishes a corticomedullary gradient through countercurrent multiplication; medullary interstitial osmolality can approach 1,200 mOsm/kg H₂O near the papillary tip during antidiuresis. The vasa recta preserve this gradient through countercurrent exchange. Loop diuretics block NKCC2 in the thick ascending limb, which normally reabsorbs 20–25% of filtered NaCl; this explains both their natriuretic potency and their impairment of urinary concentration.

2.7 Potassium handling

At a plasma potassium concentration of 4 mmol/L and a GFR of 125 mL/min, approximately 720 mmol of potassium is filtered each day. About 65–70% is reabsorbed in the proximal tubule and a further 20–25% in the thick ascending limb. Final urinary excretion is determined mainly by variable secretion in the connecting tubule and cortical collecting duct; in ordinary diets it often approximates 40–120 mmol/day.

Aldosterone, distal sodium delivery and tubular flow promote potassium secretion through ENaC-dependent lumen negativity and apical potassium channels. Insulin and beta-adrenergic activity can shift potassium into cells within minutes, whereas insulin deficiency, tissue breakdown and selected acid-base disturbances may shift potassium out of cells.

CLINICAL REASONING

Hyperkalemia often reflects more than reduced GFR. Ask about RAAS blockade, potassium-sparing diuretics, trimethoprim, NSAIDs, heparin, tissue breakdown, insulin deficiency, acidosis and impaired distal sodium delivery.

2.8 Acid secretion and bicarbonate

At a plasma bicarbonate concentration of 24 mmol/L and GFR of 125 mL/min, the kidneys filter approximately 4,300 mmol of bicarbonate each day. About 80–90% is reclaimed in the proximal tubule, approximately 10% in the thick ascending limb and the small remainder in distal segments.

The typical net nonvolatile acid load is approximately 50–100 mEq/day, depending especially on diet and catabolism. Net acid excretion equals urinary ammonium plus titratable acid minus bicarbonate excretion. The minimum achievable urine pH is approximately 4.5, but urinary pH alone does not quantify total acid excretion because most hydrogen is buffered and excreted as ammonium or titratable acid. Distinct tubular defects can therefore cause renal tubular acidosis even when GFR is relatively preserved.

2.9 The physiological logic of common medicines

Medicine/class	Primary renal action	Expected clinical observation
ACE inhibitor/ARB	Reduces angiotensin II effect and efferent arteriolar tone	Small early eGFR reduction may occur; lowers albuminuria and intraglomerular pressure
NSAID	Inhibits prostaglandin synthesis and may impair afferent vasodilation	AKI risk rises with reduced effective circulating volume
SGLT2 inhibitor	Reduces proximal sodium-glucose reabsorption; restores distal NaCl signaling	Early reversible eGFR dip followed by long-term kidney protection
Loop diuretic	Blocks NKCC2 in the thick ascending limb	Potent natriuresis; hypokalemic, hypochloremic metabolic alkalosis may occur
Thiazide	Blocks Na-Cl cotransport in the distal convoluted tubule	Natriuresis; hyponatremia, hypokalemia and increased calcium reabsorption
Mineralocorticoid antagonist	Reduces aldosterone-mediated distal sodium uptake	Reduced potassium secretion and hyperkalemia risk

DO NOT MISINTERPRET THE EARLY EGFR DIP

A modest early fall in eGFR after starting RAAS blockade or an SGLT2 inhibitor can reflect the intended reduction in intraglomerular pressure rather than structural injury. KDIGO advises continuing an ACE inhibitor or ARB unless serum creatinine rises by more than 30% within 4 weeks after initiation or dose escalation. For SGLT2 inhibitors, an early reversible eGFR dip is usually not an indication to stop therapy. In either case, assess magnitude, timing, volume status, potassium, interacting medicines and the clinical state.

Case resolution

Vomiting reduced effective circulating volume. Ibuprofen limited prostaglandin-dependent afferent vasodilation, while ramipril reduced angiotensin II-mediated efferent constriction. The combined fall in filtration pressure caused hemodynamic AKI. Management includes stopping the NSAID, assessing severity and complications, correcting volume depletion carefully and temporarily withholding selected blood-pressure medicines when clinically necessary. Kidney-protective therapy should be reconsidered and restarted after recovery when safe; an episode of AKI should not automatically lead to permanent loss of indicated RAAS inhibition.

Take-home messages

- Afferent and efferent arteriolar tone allow rapid regulation of glomerular pressure.
- Autoregulation protects filtration only within physiological limits.
- The final urine is produced by segment-specific reabsorption and secretion.
- Drug effects become understandable when mapped to the nephron and intraglomerular circulation.
- A change in creatinine may represent altered filtration hemodynamics, structural injury or both.

Self-assessment

1. What are the three principal components of the glomerular filtration barrier?
2. How do the myogenic response and tubuloglomerular feedback differ?
3. Why can NSAIDs precipitate AKI during vomiting or decompensated heart failure?
4. Where do loop and thiazide diuretics act?
5. Why can an SGLT2 inhibitor cause an early eGFR dip while improving long-term renal outcomes?

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CHAPTER 3

How Kidney Function Is Measured

Creatinine, eGFR, cystatin C and the interpretation of change

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Distinguish measured GFR, estimated GFR and creatinine clearance.
- Explain the major non-GFR determinants of serum creatinine and cystatin C.
- Interpret eGFR appropriately in stable and unstable clinical states.
- Recognize situations in which creatinine-based eGFR is unreliable.
- Use changes in creatinine and eGFR to guide, but not replace, clinical reasoning.

Opening case

CLINICAL CASE

Two patients have serum creatinine of 1.1 mg/dL. One is a frail 84-year-old woman weighing 45 kg; the other is a muscular 25-year-old man. Do they have the same kidney function?

No. Creatinine concentration reflects both production and renal elimination. Muscle mass, diet, medicines and the time required to reach steady state all influence the result. An apparently 'normal' creatinine can coexist with substantially reduced GFR in a person with low muscle mass.

3.1 What is GFR?

Glomerular filtration rate is the volume of plasma ultrafiltrate formed by all functioning nephrons per unit time. It is the most useful overall index of filtration, but it does not measure every kidney function. Tubular secretion, concentrating ability, endocrine function and structural kidney damage may be abnormal despite a preserved GFR.

GFR is commonly indexed to a body surface area of 1.73 m² to permit comparison between individuals. Indexed eGFR is used for CKD classification. For some drug-dosing decisions, particularly at extremes of body size, an absolute rather than indexed estimate may be required.

3.2 Serum creatinine

Creatinine is generated from creatine in skeletal muscle, enters the circulation at a relatively steady rate and is removed predominantly by glomerular filtration, with some tubular secretion. Because production varies with muscle mass, age, sex, diet and illness, the same creatinine concentration can represent different GFR values.

Factor	Likely effect on creatinine independent of true GFR	Example
Low muscle mass	Lower creatinine; GFR may be overestimated	Frailty, amputation, neuromuscular disease
High muscle mass	Higher creatinine; GFR may be underestimated	Muscular athlete
Cooked meat/creatine	Transient increase	Recent meal or supplement
Reduced tubular secretion	Increase without proportional GFR fall	Trimethoprim, cobicistat
Large fluid accumulation	Dilution may blunt the rise	Critical illness with positive fluid balance
Rapidly changing GFR	Creatinine lags behind the current state	Early AKI or early recovery

3.3 Why creatinine lags in AKI

Estimating equations assume a steady state: creatinine production and elimination are approximately balanced. During AKI, GFR may fall abruptly while serum creatinine rises over

hours to days. The reported eGFR is then not a valid measurement of current GFR. Conversely, during recovery creatinine may remain elevated after filtration has improved.

EMERGENCY PRINCIPLE

Do not use a laboratory-reported eGFR to stage AKI or to reassure yourself during a rapidly changing creatinine. AKI is identified and staged using changes in serum creatinine and urine output within defined time windows.

3.4 Estimated GFR

eGFR equations combine a filtration marker with demographic variables that partly account for marker generation. Contemporary practice favors validated race-free equations. KDIGO 2024 recommends using creatinine-based eGFR for initial assessment in most people and, when cystatin C is available and added precision is clinically important, estimating GFR from the combination of creatinine and cystatin C.

An equation provides an estimate, not a precise measurement. Uncertainty becomes especially important near a decision threshold: drug eligibility, kidney donation assessment, chemotherapy dosing or CKD confirmation in a person without other markers of kidney damage.

3.5 Cystatin C

Cystatin C is produced by nucleated cells, filtered by the glomerulus and metabolized after proximal tubular uptake. It is less dependent on muscle mass than creatinine, but it is not free of non-GFR determinants. Inflammation, thyroid dysfunction, glucocorticoid exposure, smoking and adiposity may affect concentration.

The combined creatinine-cystatin C equation is often more accurate because the two markers have different sources of error. Cystatin C is particularly useful when creatinine generation is unusual or when confirmation would change an important decision.

3.6 Measured GFR and creatinine clearance

Measured GFR uses the clearance of an exogenous filtration marker. It can provide greater accuracy but is resource-intensive and unnecessary for routine care. Creatinine clearance can be calculated from a timed urine collection, but collection errors are common and tubular secretion causes creatinine clearance to exceed true GFR.

A 24-hour urine collection may still be useful for selected questions, including assessment of creatinine excretion, quantification of some solutes or evaluation when estimates are discordant. The result should be checked for biological plausibility rather than accepted automatically.

3.7 Interpreting a change in creatinine

1. Confirm the value and the units. Exclude sample or transcription error and compare with previous results.
2. Define the time course. A change over 48 hours has a different meaning from a change over six months.
3. Assess urine output and clinical severity. A small creatinine rise does not exclude dangerous oliguria, hyperkalemia or pulmonary edema.
4. Review hemodynamics and volume status. Consider depletion, shock, heart failure and venous congestion.
5. Review medicines and procedures. Include NSAIDs, RAAS inhibitors, diuretics, antimicrobials, contrast exposure and obstruction risk.
6. Examine urine and image when indicated. Proteinuria, hematuria, casts or hydronephrosis can redirect the diagnosis.
7. Interpret the change in context. Decide whether it represents hemodynamic adaptation, structural injury, laboratory interference or progression.

3.8 When eGFR is less reliable

- Rapidly changing kidney function, including AKI and early recovery.
- Very low or very high muscle mass, amputation, paralysis or severe malnutrition.

- Unusual diet, creatine supplementation or medicines affecting creatinine secretion.
- Extremes of body size when an absolute GFR is needed for dosing.
- Pregnancy, where physiological changes and population-specific methods must be considered.
- Situations requiring high precision, such as living kidney donor assessment or narrow-therapeutic-index drug dosing.

3.9 Drug dosing

Drug labels and dosing studies may use different kidney-function metrics. Some rely on creatinine clearance estimated by the Cockcroft-Gault equation, whereas modern practice and electronic systems often report eGFR. The safest approach is to check the metric used in the medicine's prescribing information, consider body size and clinical stability, and monitor drug effect or concentration when appropriate.

PRESCRIBING SAFELY

A calculated number does not replace medication review. Ask whether kidney function is stable, which equation the dosing recommendation used, whether the drug has active metabolites, whether dialysis removes it and whether toxicity can be monitored.

3.10 GFR is not the whole kidney

A person with preserved eGFR may have significant albuminuria, glomerular hematuria, a hereditary structural disorder or a tubular defect. Conversely, a reduced eGFR in an older adult must be interpreted alongside albuminuria, cause, trajectory and absolute risk. Kidney assessment is multidimensional.

Case resolution

The frail older woman is likely to generate much less creatinine than the young muscular man. Her creatinine-based eGFR may therefore overestimate filtration. If the result affects a major diagnosis or treatment decision, cystatin C and a combined estimate can improve assessment. The young man may have a higher creatinine because of muscle mass despite normal filtration. Neither creatinine value should be interpreted in isolation.

Take-home messages

- Serum creatinine reflects generation, distribution and elimination—not GFR alone.
- Creatinine-based eGFR is appropriate for initial assessment in most stable adults.
- Creatinine-cystatin C eGFR can improve accuracy when precision matters or muscle mass is unusual.
- eGFR equations are unreliable during rapidly changing kidney function.
- Kidney health must also include albuminuria, urine findings, structure, cause and trajectory.

Self-assessment

1. Why may a frail patient have important kidney dysfunction despite a creatinine within the laboratory reference interval?
2. Name four non-GFR determinants of serum creatinine.
3. Why is the reported eGFR misleading during early AKI?
4. When can cystatin C add useful information?
5. What is the difference between indexed eGFR and an absolute filtration estimate?

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CHAPTER 4

Urinalysis and Urinary Microscopy*Turning a low-cost test into a diagnostic map***LEARNING OBJECTIVES**

After studying this chapter, the student should be able to:

- Collect and assess a urine specimen correctly.
- Interpret the major dipstick components and recognize common interferences.
- Distinguish glomerular, tubulointerstitial and lower urinary tract patterns.
- Recognize high-yield urinary casts, cells and crystals.
- Use urine microscopy to guide urgent clinical decisions.

Opening case**CLINICAL CASE**

A 28-year-old woman presents with edema and dark urine two weeks after an upper respiratory infection. Creatinine is 1.6 mg/dL. Dipstick shows 3+ blood and 2+ protein. Microscopy demonstrates more than 50 RBCs/high-power field, 12% acanthocytes and several RBC casts. What does each layer of testing add?

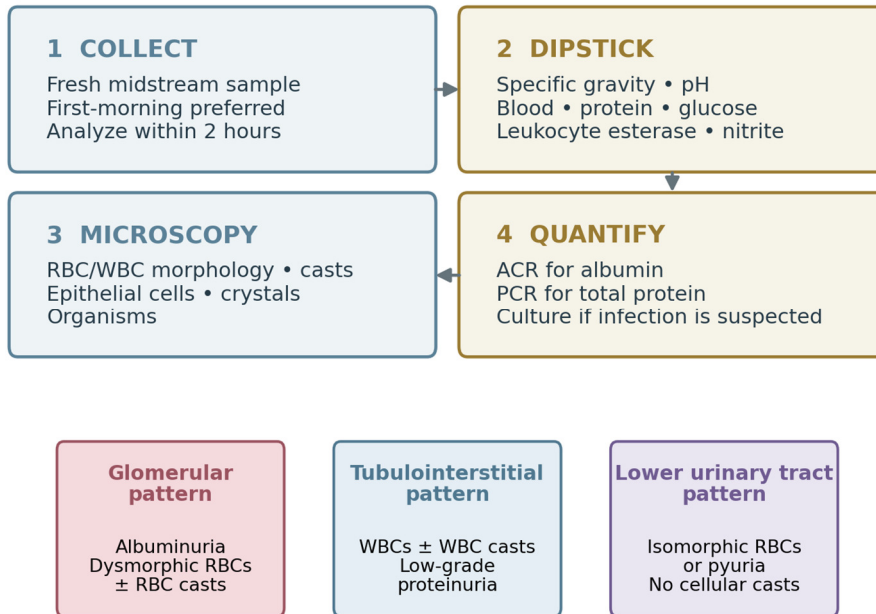
The dipstick establishes that heme and protein are present; microscopy confirms true hematuria and localizes bleeding to the glomerulus. Dysmorphic RBCs—particularly acanthocytes—and RBC casts create an active nephritic sediment. The result is not merely 'blood in urine': it is a pattern that requires prompt evaluation for glomerulonephritis.

4.1 Obtaining a useful specimen

Urine findings are only as reliable as the sample. A clean-catch midstream specimen reduces contamination. First-morning urine is preferred for ACR because it is less affected by posture and exercise. Fresh urine should ideally be examined within 2 hours; if delayed, refrigeration slows cell lysis and bacterial proliferation, but the specimen should be returned to room temperature before analysis.

Menstruation, vigorous exercise, fever, dehydration, sexual activity and urinary tract instrumentation can produce transient abnormalities. A result that is unexpected and not clinically urgent should usually be repeated under standardized conditions.

From urine sample to clinical interpretation



Always interpret urine findings together with symptoms, kidney function and chronicity.

Figure 4.1. A structured approach to urine testing: collect correctly, screen by dipstick, localize by microscopy and quantify albumin or protein.

4.2 Dipstick examination

Pad	What it detects	Important interpretation
Specific gravity	Ionic concentration; usual random range ~1.005–1.030	Affected by glucose, protein and contrast; refractometry is more accurate
pH	Usually 4.5–8.0	Persistent alkaline urine suggests urease-producing bacteria, diet or distal acidification defect
Blood	Peroxidase activity of RBCs, hemoglobin or myoglobin	Positive dipstick with no RBCs suggests hemoglobinuria or myoglobinuria
Protein	Predominantly albumin	Insensitive to low-level albumin and many nonalbumin proteins, including light chains
Leukocyte esterase	Neutrophil enzyme activity	Supports pyuria; contamination and vaginal leukocytes can confuse interpretation
Nitrite	Bacterial nitrate reduction	Specific but not sensitive; requires dietary nitrate and bladder dwell time
Glucose	Glucose above tubular reabsorptive capacity	May occur at lower plasma glucose during SGLT2 inhibition
Ketones	Mainly acetoacetate	May underestimate beta-hydroxybutyrate in ketoacidosis

The heme pad is highly sensitive but does not prove hematuria. Microscopic confirmation is essential. Conversely, vitamin C, very concentrated urine or technical factors can produce false-negative reactions. A urine dipstick is a screening instrument, not a final diagnosis.

4.3 Defining hematuria

Visible hematuria is urine that appears pink, red or brown because of RBCs. Microscopic hematuria is defined by the 2025 AUA/SUFU guideline as more than 3 RBCs per high-power field in a single properly collected specimen. Dipstick positivity alone is insufficient.

Glomerular hematuria is supported by albuminuria, RBC casts and dysmorphic RBCs. Acanthocytes—ring forms with one or more membrane blebs—are particularly specific; a proportion of approximately 5% or more strongly supports a glomerular source when assessed by experienced microscopy. Isomorphic RBCs without casts favor bleeding from the collecting system or lower urinary tract, although patterns can overlap.

DO NOT MISS

Hematuria with rapidly increasing creatinine, substantial proteinuria, RBC casts, systemic vasculitic features or pulmonary hemorrhage requires urgent nephrology assessment. Visible hematuria with clots, urinary retention or hemodynamic instability is a urological emergency.

4.4 Pyuria and bacteriuria

Pyuria generally means more than 5–10 WBCs/high-power field, although laboratory thresholds vary. Leukocyte esterase supports the finding. WBC casts localize inflammation to the kidney and occur in pyelonephritis and tubulointerstitial inflammation. 'Sterile pyuria' may occur with prior antibiotics, interstitial nephritis, stones, genitourinary tuberculosis, sexually transmitted infection or contamination.

Nitrite positivity increases the probability of bacteriuria but a negative result does not exclude infection. Some organisms do not reduce nitrate, frequent voiding limits bladder incubation and dietary nitrate may be insufficient. Urine culture should be obtained when infection is complicated, recurrent, associated with pyelonephritis, pregnancy, sepsis or resistant organisms.

4.5 Casts: why their shape matters

Casts form in distal tubules and collecting ducts from uromodulin, previously called Tamm–Horsfall protein. Their contents therefore provide a biopsy-like clue to events within the nephron. Cellular casts are more informative than free cells because they localize the process to the kidney.

Urinary sediment: high-yield patterns

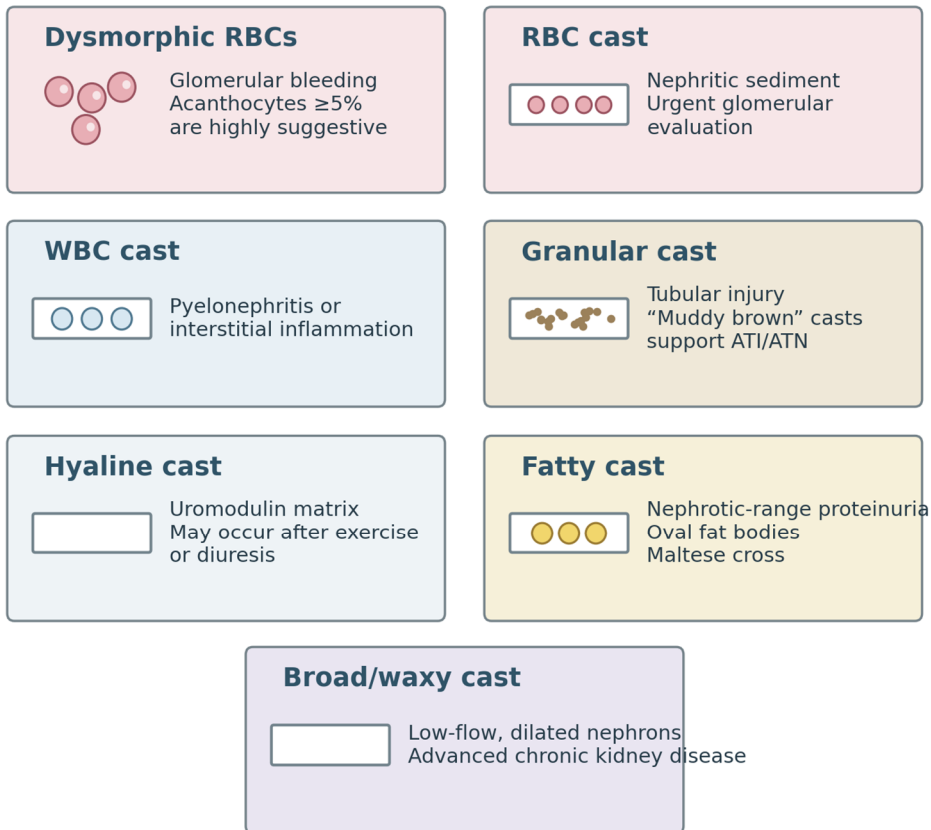


Figure 4.2. Schematic appearance and clinical associations of the urinary casts and cells most useful to medical students.

Sediment finding	Most important association	Caution
RBC casts	Glomerulonephritis or renal vasculitis	Urgent finding; absence does not exclude GN
WBC casts	Pyelonephritis or interstitial nephritis	Differentiate from contaminated free WBCs
Renal tubular epithelial cells / granular casts	Acute tubular injury	Muddy-brown casts are supportive, not perfectly sensitive
Fatty casts / oval fat bodies	Heavy proteinuria and nephrotic syndrome	Show birefringent Maltese crosses under polarized light
Hyaline casts	Low flow, exercise, fever or diuretic use	Small numbers can be normal
Broad waxy casts	Advanced CKD with dilated low-flow nephrons	Suggest chronic severe parenchymal disease

4.6 Crystals

Crystals depend on urine pH, concentration, temperature, medicines and solute load. Calcium oxalate may appear as envelopes or dumbbells; uric acid has variable rhomboid forms in acidic urine; triple-phosphate crystals are coffin-lid shaped and suggest alkaline urine, often with

urease-producing infection. Hexagonal cystine crystals are abnormal and strongly suggest cystinuria.

Crystals alone do not prove stone disease or crystal nephropathy. Clinical context matters: ethylene glycol can produce calcium oxalate crystals, tumor lysis can produce abundant uric acid, and medicines such as acyclovir, indinavir, sulfadiazine and methotrexate can crystallize under favorable conditions.

Case resolution

The combination of AKI, proteinuria, acanthocytes and RBC casts indicates glomerular inflammation. Initial assessment should include blood pressure, urine ACR/PCR, complement, IgA-related clinical context and targeted serology. The patient requires prompt nephrology assessment and may need kidney biopsy depending on trajectory and suspected diagnosis.

Take-home messages

- Correct collection and prompt analysis determine the value of urinalysis.
- Dipstick blood detects heme; microscopy determines whether RBCs are present.
- More than 3 RBCs/high-power field defines microscopic hematuria in a properly collected specimen.
- Dysmorphic RBCs and RBC casts support a glomerular source.
- Cellular casts localize pathology to the kidney and can change urgency.

Self-assessment

1. Why can dipstick blood be strongly positive when no RBCs are seen?
2. Which findings distinguish glomerular from lower urinary tract hematuria?
3. What is the diagnostic significance of an RBC cast?
4. Name four causes of sterile pyuria.
5. Which crystal morphology strongly suggests cystinuria?

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CHAPTER 5

Proteinuria and Albuminuria*Detection, quantification, mechanisms and clinical risk***LEARNING OBJECTIVES**

After studying this chapter, the student should be able to:

- Differentiate albuminuria from total proteinuria.
- Classify albuminuria using KDIGO A1–A3 categories.
- Recognize glomerular, tubular, overflow and postrenal proteinuria.
- Confirm persistent proteinuria and identify transient causes.
- Recognize nephrotic-range proteinuria and urgent referral patterns.

Opening case**CLINICAL CASE**

A 54-year-old man with type 2 diabetes has eGFR 78 mL/min/1.73 m² and a urine dipstick reported as 'trace protein.' First-morning ACR is 420 mg/g (47 mg/mmol). Why is the dipstick description inadequate?

The ACR places him in KDIGO category A3, despite preserved GFR and only trace semiquantitative dipstick protein. Albuminuria establishes kidney damage, predicts cardiovascular and renal risk, and changes treatment. A numerical ACR is clinically more informative than a dipstick label.

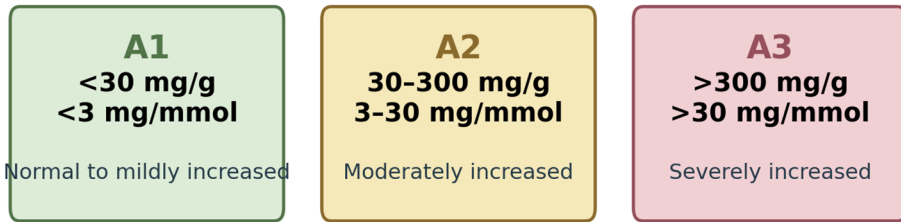
5.1 Normal protein handling

The glomerulus filters only small amounts of albumin, and proximal tubular cells reclaim much of the filtered protein. Normal total urinary protein is generally less than 150 mg/day, while albumin excretion is usually below 30 mg/day. Persistent excess may reflect increased glomerular permeability, failed tubular retrieval, excess circulating small proteins or inflammation within the urinary tract.

5.2 How to measure it

KDIGO recommends urine ACR as the preferred initial quantitative test for albuminuria. A spot first-morning sample reduces variability and corrects albumin concentration for urine creatinine. PCR measures total protein and is useful when nonalbumin protein is suspected or when total protein burden is required.

Quantifying albuminuria and proteinuria



Preferred test Spot urine ACR, preferably a first-morning specimen

Confirm Repeat an unexpected result; exclude exercise, fever, UTI, menstruation and marked hyperglycemia

Nephrotic range Protein ≥ 3.5 g/day; spot PCR $\approx 3,500$ mg/g

Important Dipsticks mainly detect albumin and may miss light chains.

Figure 5.1. KDIGO albuminuria categories and a practical framework for confirmation and recognition of nephrotic-range proteinuria.

Category	ACR	Approximate excretion	albumin	Description
A1	<30 mg/g (<3 mg/mmol)	<30 mg/day		Normal to mildly increased
A2	30–300 mg/g (3–30 mg/mmol)	30–300 mg/day		Moderately increased
A3	>300 mg/g (>30 mg/mmol)	>300 mg/day		Severely increased

Conversion between mg/g and mg/mmol is approximate: divide mg/g by about 8.84 to obtain mg/mmol. ACR is not a direct 24-hour excretion measurement and can be distorted by unusually low or high creatinine generation.

5.3 Confirming persistence

CKD requires persistence for more than 3 months. Unexpected albuminuria should be repeated, ideally using a first-morning sample. Transient increases occur after strenuous exercise, fever, urinary infection, decompensated heart failure, marked hyperglycemia, menstruation and acute illness.

When the result is urgent—such as heavy proteinuria with edema, low serum albumin, AKI or active sediment—evaluation should proceed immediately rather than waiting three months. Chronicity and urgency are different questions.

5.4 Mechanistic classification

Type	Mechanism	Typical clues
Glomerular	Increased filtration-barrier permeability	Albumin predominates; diabetes, IgA nephropathy, membranous nephropathy, FSGS
Tubular	Reduced proximal reabsorption of low-molecular-weight proteins	Usually lower-grade; Fanconi syndrome, tubulointerstitial disease
Overflow	Excess production of small filtered proteins	Light chains, myoglobin or hemoglobin; dipstick may underestimate
Postrenal	Protein added distal to the kidney	UTI, inflammation, stones or bleeding

PROTEIN DISCREPANCY

A high PCR with a relatively low ACR suggests substantial nonalbumin protein. In the appropriate clinical context, investigate monoclonal light chains with serum free light chains and serum/urine immunofixation rather than relying on dipstick protein.

5.5 Nephrotic-range proteinuria and nephrotic syndrome

Nephrotic-range proteinuria is classically at least 3.5 g/day in adults; a spot PCR of approximately 3,500 mg/g is often used as a practical estimate, although agreement with timed excretion is imperfect. Nephrotic syndrome requires heavy proteinuria plus hypoalbuminemia and usually edema; hyperlipidemia and lipiduria are common but are not required for the definition.

The term 'nephrotic-range albuminuria' is not interchangeable with total protein excretion because the proportion of albumin varies by disease. In diabetic kidney disease, severe albuminuria may be clinically important well below the classical nephrotic threshold.

5.6 Clinical consequences and referral

Albuminuria predicts CKD progression, cardiovascular events and mortality across the GFR range. Risk increases continuously; A1–A3 categories provide clinically useful bands rather than biological cliffs. Rapidly rising proteinuria, ACR above 700 mg/g, nephrotic syndrome, proteinuria with hematuria or declining GFR, and suspected systemic or monoclonal disease generally warrant nephrology assessment.

For follow-up, a doubling of ACR exceeds expected laboratory variability and should prompt evaluation. Treatment response is often tracked by proportional reduction in ACR, but the meaningful target depends on cause and therapy.

Case resolution

The patient has CKD on the basis of A3 albuminuria if persistence is confirmed, even though eGFR is above 60 mL/min/1.73 m². Management includes repeat first-morning ACR, blood-pressure assessment, retinal and systemic context, RAAS blockade when indicated, an SGLT2 inhibitor if appropriate, cardiovascular risk reduction and evaluation for atypical features suggesting nondiabetic kidney disease.

Take-home messages

- ACR is preferred for initial albuminuria assessment and should be reported numerically.
- A1 is below 30 mg/g, A2 is 30–300 mg/g and A3 is above 300 mg/g.
- Persistent albuminuria can diagnose CKD even when GFR is preserved.
- Dipsticks may miss low-level albumin and nonalbumin proteins.
- Heavy proteinuria, active sediment or declining GFR requires timely specialist evaluation.

Self-assessment

1. Why is ACR preferred to urine albumin concentration alone?
2. What are the KDIGO A1–A3 thresholds in mg/g and mg/mmol?
3. What pattern suggests overflow proteinuria?
4. How does nephrotic-range proteinuria differ from nephrotic syndrome?
5. Name five transient causes of albuminuria.

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CHAPTER 6

Renal Imaging and Kidney Biopsy*Choosing the test that answers the clinical question***LEARNING OBJECTIVES**

After studying this chapter, the student should be able to:

- Select first-line imaging for common renal presentations.
- Interpret kidney size, echogenicity and hydronephrosis cautiously.
- Recognize when CT, MRI or nuclear imaging adds value.
- Identify common indications and contraindications for kidney biopsy.
- Explain the complementary roles of light microscopy, immunofluorescence and electron microscopy.

Opening case**CLINICAL CASE**

A 39-year-old man has creatinine 2.3 mg/dL, ACR 1,100 mg/g and microscopic hematuria. Ultrasound shows two 10.8-cm kidneys without hydronephrosis. Has imaging established the diagnosis?

No. Ultrasound has excluded major obstruction and shown that the kidneys are not markedly small, but it cannot distinguish IgA nephropathy, membranous nephropathy, vasculitis or many other parenchymal diseases. The active urinary phenotype may require serology and kidney biopsy.

6.1 Renal ultrasound

Ultrasound is the first-line structural test in AKI with obstruction risk, CKD of uncertain cause, recurrent UTI, urinary retention, cystic disease and many cases of hematuria. It is portable, lacks ionizing radiation and can assess kidneys, collecting systems and bladder.

Adult renal length is commonly about 9–12 cm, but normal values depend on height, sex and age. A difference greater than approximately 1.5–2 cm between kidneys is potentially significant. Increased cortical echogenicity, cortical thinning and loss of corticomedullary differentiation support chronic parenchymal disease, but echogenicity is neither sensitive nor specific enough to determine cause.

Hydronephrosis suggests collecting-system dilatation, not necessarily clinically important obstruction. It can be absent early in obstruction or in retroperitoneal fibrosis and can occur without obstruction during pregnancy, reflux or a full bladder. Clinical probability and bladder assessment remain essential.

Imaging and biopsy: complementary roles

RENAL ULTRASOUND

Measures / detects

- Length and cortical thickness
- Echogenicity and symmetry
- Hydronephrosis
- Cysts, masses and bladder retention

Typical adult kidney length

≈9–12 cm
Interpret with body size and age

PERCUTANEOUS KIDNEY BIOPSY

Best for

- Unexplained AKI or active sediment
- Glomerular syndrome
- Systemic disease with kidney involvement
- Transplant dysfunction

Tissue examined by

- Light microscopy
- Immunofluorescence
- Electron microscopy

BIOPSY SAFETY CHECK

Control blood pressure • review antithrombotic drugs • check hemoglobin, platelets and coagulation • use real-time ultrasound guidance

Ultrasound shows structure; biopsy identifies tissue diagnosis.

Figure 6.1. *Ultrasound and kidney biopsy provide complementary structural and tissue-level information.*

6.2 CT, MRI and nuclear studies

Modality	Best uses	Main limitations
Noncontrast CT	Stones, calcification, hemorrhage	Radiation; less soft-tissue characterization
Contrast-enhanced CT	Masses, infection, vascular and traumatic pathology	Iodinated contrast risk must be considered in context
CT urography	Risk-stratified urothelial evaluation	Radiation and iodinated contrast
MRI / MR urography	Mass characterization, vessels and collecting system without CT radiation	Gadolinium considerations, time, availability and implants
Doppler ultrasound	Renal vessels, perfusion and transplant assessment	Operator and body-habitus dependent
Nuclear renography	Differential function and drainage	Limited anatomic detail

The decision to administer iodinated contrast should balance diagnostic benefit against patient-specific risk. Modern evidence does not support denying necessary contrast-enhanced imaging solely because eGFR is reduced; risk is greatest in severe CKD, AKI and concurrent hemodynamic stress. Use the lowest adequate dose, avoid dehydration and follow current local radiology protocols.

6.3 When kidney biopsy is useful

Percutaneous biopsy is the reference standard for diagnosing many intrinsic renal diseases. Common indications include unexplained AKI, nephritic syndrome, nephrotic syndrome, substantial or increasing proteinuria, suspected systemic disease affecting the kidney, unexplained transplant dysfunction and selected hereditary or tubulointerstitial disorders.

Biopsy is most valuable when the result can change diagnosis, prognosis or treatment. It is less useful when kidneys are markedly small and scarred, the diagnosis is already secure and tissue will not change management, or procedural risk exceeds expected benefit.

6.4 Contraindications and preparation

Important contraindications include uncontrolled severe hypertension, uncorrected bleeding diathesis, inability to cooperate and absence of a safe percutaneous route. A solitary kidney is no longer an absolute contraindication but requires individualized assessment. Infection at the entry site, hydronephrosis, large cysts and vascular abnormalities may require an alternative approach.

Preparation includes informed consent, blood pressure control, full blood count, platelet count and coagulation assessment, review of antiplatelet/anticoagulant medicines, blood grouping according to local protocol and ultrasound localization. Thresholds vary by institution; many centers aim for blood pressure below approximately 140/90 mmHg and platelet count above $50 \times 10^9/L$, while recognizing that risk is continuous rather than binary.

BLEEDING RISK

Macroscopic hematuria, perinephric hematoma and transfusion are the clinically important complications. Most major bleeding becomes evident within the first 24 hours, although delayed events occur. New flank pain, hypotension, falling hemoglobin or persistent visible hematuria requires urgent reassessment.

6.5 How tissue is examined

Method	What it shows	Examples
Light microscopy	Glomerular architecture, cellularity, sclerosis, crescents, interstitium and vessels	FSGS, diabetic nodules, crescents, interstitial nephritis
Immunofluorescence	Location and pattern of immunoglobulins, complement and light chains	IgA-dominant, linear IgG, granular immune complexes
Electron microscopy	Basement membranes, deposits, podocyte foot processes and fibrils	Alport pattern, minimal change disease, amyloid or fibrillary disease

Adequacy depends on the clinical question and distribution of lesions. Focal diseases can be missed in a small sample. The biopsy report must therefore be interpreted together with serology, urine findings, kidney function and treatment history.

Case resolution

Normal-sized unobstructed kidneys do not exclude important glomerular disease. Because the patient has marked albuminuria, hematuria and reduced GFR, targeted serology and nephrology assessment are required. If no noninvasive diagnosis is secure and treatment would differ by histology, biopsy is appropriate after risk assessment.

Take-home messages

- Ultrasound is first-line for kidney size, obstruction, cysts and bladder assessment.
- Normal-sized kidneys do not exclude severe intrinsic renal disease.
- CT and MRI are selected according to the clinical question, not by a single creatinine threshold.
- Biopsy should be performed when tissue can change diagnosis, prognosis or treatment.
- LM, IF and EM answer complementary pathological questions.
-

Self-assessment

1. What does increased renal echogenicity mean, and what can it not tell you?
2. Why can obstruction exist without hydronephrosis?
3. Name five common indications for native kidney biopsy.
4. What pre-biopsy factors increase bleeding risk?
5. What information is added by immunofluorescence and electron microscopy?

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PART II

A Clinical Approach to Renal Presentations

From an abnormal finding to a safe first decision

HOW TO USE PART II

Each chapter begins with a presentation rather than a diagnosis. First identify immediate danger, then define the time course, localize the process, choose targeted tests and reassess the trajectory. Numerical thresholds support—not replace—clinical judgment.

CHAPTER 7

The Patient With Increased Creatinine

Confirm the change, define the time course and search for reversible causes

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Apply KDIGO creatinine and urine-output criteria for acute kidney injury.
- Distinguish AKI, acute kidney disease, CKD and a non-GFR rise in creatinine.
- Recognize immediate complications that require urgent treatment or nephrology input.
- Use history, examination, urinalysis and imaging to separate hemodynamic, intrinsic and postrenal causes.
- Interpret creatinine changes after RAAS blockade, SGLT2 inhibition and drugs that inhibit tubular creatinine secretion.

Opening case

CLINICAL CASE

A 73-year-old man with CKD G3a, heart failure and hypertension presents after four days of diarrhea. His medicines include ramipril, spironolactone, dapagliflozin and furosemide. Creatinine is 2.4 mg/dL; the most recent value was 1.3 mg/dL six weeks earlier. Potassium is 6.1 mmol/L, bicarbonate 17 mmol/L and blood pressure 96/58 mmHg. Urine output is uncertain. What must be done before assigning a renal diagnosis?

7.1 Increased creatinine is a presentation, not a diagnosis

Serum creatinine rises when generation exceeds elimination, but the concentration does not identify the mechanism. A rise may represent reduced filtration, evolving AKI, established CKD, urinary obstruction, altered creatinine generation or inhibited tubular secretion. The first task is therefore not to label the patient 'renal failure'; it is to verify the change, establish the baseline and identify danger.

Creatinine kinetics lag behind abrupt GFR loss. After a major fall in filtration, several half-lives may be required before a new steady state is reached. During rapidly changing kidney function, a creatinine-based eGFR is mathematically calculated but physiologically unreliable. Drug dosing and clinical decisions must use the direction and rate of change, urine output and the patient's condition.

A practical response to increased creatinine

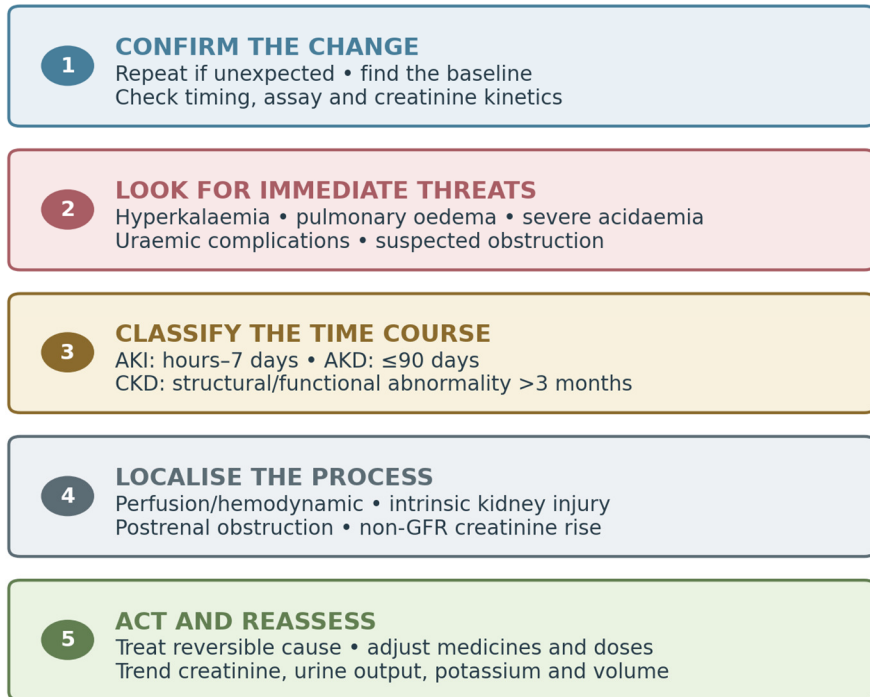


Figure 7.1. A five-step response to increased creatinine: confirm, identify threats, classify time course, localize the process and reassess.

7.2 Define AKI, AKD and CKD

KDIGO defines AKI by any of three criteria: an increase in serum creatinine of at least 0.3 mg/dL (26.5 μ mol/L) within 48 hours; an increase to at least 1.5 times baseline known or presumed to have occurred within seven days; or urine volume below 0.5 mL/kg/h for six hours. Creatinine and urine output identify partly different populations, so both should be assessed when possible.

KDIGO stage	AKI	Serum creatinine	Urine output
1		1.5–1.9 $\times$ baseline OR rise $\geq$ 0.3 mg/dL	<0.5 mL/kg/h for 6–12 h
2		2.0–2.9 $\times$ baseline	<0.5 mL/kg/h for $\geq$ 12 h
3		3.0 $\times$ baseline OR creatinine $\geq$ 4.0 mg/dL OR kidney replacement therapy	<0.3 mL/kg/h for $\geq$ 24 h OR anuria $\geq$ 12 h

Acute kidney disease (AKD) is a broader concept that includes kidney abnormalities lasting up to 90 days and bridges the interval between AKI and CKD. CKD requires abnormalities of kidney structure or function present for more than three months with implications for health. A patient can have AKI superimposed on CKD; the old creatinine, urine albumin, imaging and previous records are therefore essential.

EVIDENCE STATUS

The published KDIGO 2012 AKI guideline remains the formal international guideline at this manuscript's evidence cutoff. The March 2026 KDIGO AKI/AKD document is a public-review draft and may change; it is cited for educational awareness, not as an approved standard.

7.3 First identify immediate threats

- Potassium ≥ 6.5 mmol/L, a rapidly rising potassium or hyperkalemic ECG changes.
- Pulmonary edema, severe hypoxemia or respiratory distress from congestion.
- Severe or worsening metabolic acidaemia, particularly pH around or below 7.10 despite treatment of the cause.
- Uraemic complications: pericarditis, encephalopathy, otherwise unexplained bleeding or severe symptoms.
- Anuria, a blocked urinary catheter, bilateral obstruction or obstruction of a solitary functioning kidney.
- Shock, sepsis, major hemorrhage, rapidly progressive glomerulonephritis or a pulmonary–renal syndrome.

The need for kidney replacement therapy is based on refractory complications and the overall clinical trajectory, not a single creatinine or urea threshold. Creatinine 5 mg/dL may be tolerated in one stable patient yet coexist with life-threatening hyperkalemia or pulmonary edema in another.

7.4 Confirm the baseline and the trajectory

1. Repeat an unexpected or internally inconsistent result, especially if hemolysis, sampling error or laboratory interference is plausible.
2. Search for prior creatinine values. A remote 'normal' value does not prove that the current change is acute.
3. Plot creatinine and urine output against time. A rise of 0.3 mg/dL over 24 hours is clinically different from the same change over two years.
4. Review fluid balance, weight, blood pressure, hemodynamics, exposure to contrast, surgery, infection and medication changes.
5. Ask whether muscle mass, meat intake, creatine supplements, rhabdomyolysis or amputation alters interpretation.

CALCULATION

For unit conversion: creatinine in $\mu\text{mol/L} \div 88.4 = \text{mg/dL}$. Thus 132 $\mu\text{mol/L}$ is approximately 1.49 mg/dL. Avoid false precision when the patient is not at steady state.

7.5 Localize the process

Category	Typical clues	Examples
Reduced perfusion / hemodynamic	Hypotension, volume loss, low effective arterial volume; often bland sediment	Diarrhea, hemorrhage, sepsis, heart failure, cirrhosis; NSAID–RAASi interaction
Intrinsic renal	Proteinuria, hematuria, cellular casts, systemic features or nephrotoxic exposure	Glomerulonephritis, acute tubular injury, interstitial nephritis, vascular disease
Postrenal	Retention, hydronephrosis, pelvic/ureteric symptoms; sediment may be bland	Prostate obstruction, stones, tumors, blocked catheter
Non-GFR creatinine rise	Stable urine output and alternative pharmacologic or metabolic explanation	Trimethoprim, cobicistat, cimetidine; increased creatinine generation

The historical term 'prerenal azotemia' can be useful, but it should not end the reasoning process. Sepsis, venous congestion and drug-related changes may combine functional hemodynamic reduction with structural tubular injury. A patient may also have more than one cause—for example diarrhea, NSAID exposure and urinary retention.

7.6 Urine testing and urinary indices

Urinalysis and microscopy often provide more localization than another blood test. Dysmorphic RBCs or RBC casts support a glomerular source; WBC casts suggest interstitial inflammation or pyelonephritis; renal tubular epithelial cells and granular 'muddy brown' casts support acute tubular injury. A bland sediment does not exclude important disease.

Index	Formula	Traditional interpretation and limitations
FENa	$100 \times (\text{urine Na} \times \text{plasma creatinine}) / (\text{plasma Na} \times \text{urine creatinine})$	<1% may support sodium avidity; >2% may support tubular injury. Diuretics, CKD, contrast, sepsis and glomerular disease limit accuracy.
FEUrea	$100 \times (\text{urine urea} \times \text{plasma creatinine}) / (\text{plasma urea} \times \text{urine creatinine})$	<35% has been used when diuretics confound FENa, but performance is imperfect and context dependent.
Urine Na	Spot urine sodium concentration	Values <20–30 mmol/L may reflect sodium avidity; recent diuretics and CKD can invalidate a simple cutoff.

Urinary indices should support a clinical hypothesis, not replace examination, sediment review or imaging. They are least reliable when the physiology is mixed—which is common in hospitalized patients.

7.7 Medicines and an expected creatinine change

Medicine exposure	Mechanism	Practical interpretation
ACE inhibitor or ARB	Efferent arteriolar dilation lowers intraglomerular pressure	Check creatinine and potassium within about 2–4 weeks after starting or increasing dose. A rise >30% should prompt evaluation for volume depletion, NSAIDs, renal artery disease or another cause.
SGLT2 inhibitor	Restores tubuloglomerular feedback and lowers intraglomerular pressure	An early reversible eGFR dip—often about 3–6 mL/min/1.73 m ² —may occur. Assess a large or progressive fall rather than reflexively stopping beneficial therapy.
Trimethoprim cobicistat cimetidine	/ / Inhibits tubular creatinine secretion	Creatinine may rise without a proportional fall in measured GFR; cystatin C may help in selected cases.
NSAID	Reduces prostaglandin-dependent afferent vasodilation	Risk rises with hypovolemia, CKD, heart failure and concurrent RAAS blockade/diuretics.

7.8 Initial management

- Treat shock, sepsis, hemorrhage and obstruction promptly.
- Give fluid only when reduced effective circulating volume is plausible; reassess after each intervention.
- Stop avoidable nephrotoxins and review all doses against current, changing kidney function.
- Do not use loop diuretics to 'treat the creatinine'; use them for clinically important volume overload.
- Monitor creatinine, urine output, potassium, bicarbonate, weight and fluid balance at a frequency matched to severity.
- Seek early nephrology input for stage 2–3 AKI, uncertain cause, active sediment, nephrotic syndrome, rapidly progressive disease or kidney replacement therapy consideration.

Case resolution

The patient has KDIGO stage 1 AKI by creatinine ratio and clinically important hyperkalemia. Immediate priorities are ECG assessment and treatment of hyperkalemia, evaluation of perfusion and congestion, medication review and measurement of urine output. Examination and bedside ultrasound support hypovolemia without pulmonary congestion. Ramipril, spironolactone and dapagliflozin are temporarily withheld; cautious isotonic crystalloid is given with reassessment. Creatinine and potassium improve. The long-term medicines are reviewed for staged reintroduction after recovery because an episode of AKI should not automatically lead to permanent withdrawal of cardiorenal-protective therapy.

Take-home messages

- A creatinine rise is a signal; determine baseline, trajectory and mechanism.
- AKI is defined by creatinine and/or urine output; eGFR is unreliable during rapid change.

- Treat immediate complications before completing etiological classification.
- Urine sediment and obstruction assessment are high-value early tests.
- Interpret hemodynamic medication-related changes in context and reassess rather than reacting to a single value.

Self-assessment

1. State the three KDIGO criteria that can diagnose AKI.
2. Why can eGFR be misleading when creatinine is rising rapidly?
3. Name four immediate threats that change the urgency of an increased creatinine.
4. What findings support a glomerular rather than a hemodynamic cause?
5. How should a creatinine rise after starting an ACE inhibitor be evaluated?

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CHAPTER 8

The Patient With Oliguria or Anuria

Verify the measurement, exclude obstruction and assess perfusion and congestion

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Define oliguria and anuria using practical and KDIGO thresholds.
- Distinguish urinary retention from true low kidney output.
- Evaluate perfusion, venous congestion, intrinsic renal injury and obstruction.
- Avoid indiscriminate fluid loading and inappropriate use of diuretics.
- Recognize complications that require emergency treatment or kidney replacement therapy.

Opening case

CLINICAL CASE

A 68-year-old woman is 12 hours after abdominal surgery. The chart shows 90 mL of urine over six hours. Blood pressure is 104/66 mmHg, heart rate 96/min and oxygen saturation 92% on room air. She has bibasal crackles, a distended lower abdomen and a urethral catheter. Should she receive a rapid liter of saline?

8.1 Definitions

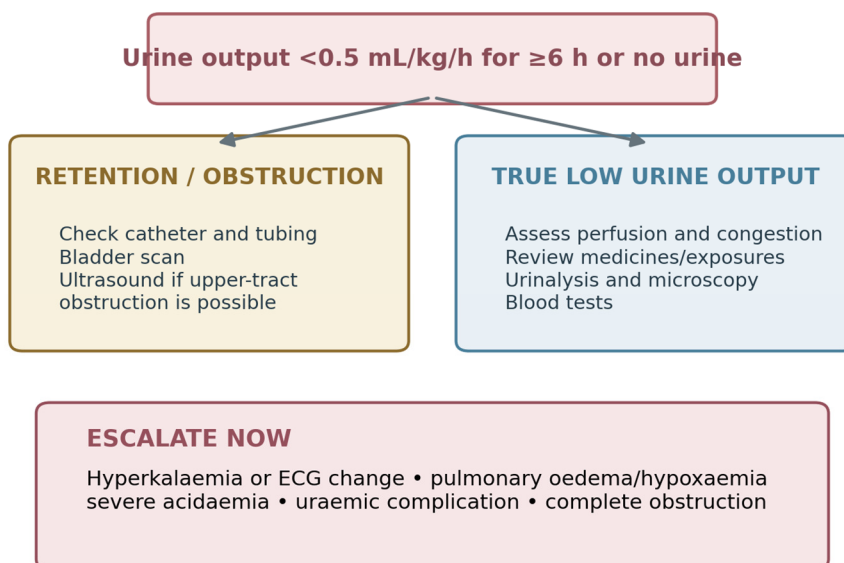
Oliguria is best defined by weight and time: urine output below 0.5 mL/kg/h for at least six hours meets a KDIGO AKI criterion. A pragmatic adult threshold of less than about 400–500 mL/day is often used, but it ignores body size and may delay recognition. Anuria commonly means less than 100 mL/day; KDIGO stage 3 urine-output criteria include anuria for at least 12 hours.

WORKED EXAMPLE

For a 70-kg adult, 0.5 mL/kg/h equals 35 mL/h. Over six hours the threshold is 210 mL. A recorded output of 120 mL over six hours therefore meets the urine-output criterion for AKI.

Oliguria may precede a rise in creatinine and can be an early marker of physiological stress. Conversely, nonoliguric AKI can be severe. Urine volume therefore adds information but does not measure GFR directly.

Oliguria or anuria: first-hour pathway



Do not give repeated fluid boluses unless hypovolaemia is plausible and response is reassessed.

Figure 8.1. First-hour assessment of oliguria or anuria: verify drainage, distinguish retention from true low output and escalate for complications.

8.2 First verify that urine can leave the patient

1. Check the time interval, patient weight and whether all urine was captured.
2. Inspect catheter tubing for kinks, dependent loops, clots or a closed clamp.
3. Flush or replace a catheter only according to local sterile protocols and the clinical indication.
4. Palpate/percuss the bladder and use a bladder scan when retention is possible.
5. Use kidney and bladder ultrasound when upper-tract obstruction, hydronephrosis or a solitary kidney is possible.

A full bladder with low bag output is retention until proved otherwise. An empty bladder does not exclude bilateral ureteric obstruction, early obstruction without hydronephrosis or obstruction in a dehydrated patient.

8.3 Assess the circulation: perfusion and congestion

Finding	Supports reduced effective perfusion	Supports congestion
History	Vomiting, diarrhea, hemorrhage, poor intake	Heart failure, kidney failure, recent positive fluid balance
Examination	Orthostatic symptoms, cool peripheries, low JVP	Raised JVP, crackles, edema, ascites, hepatomegaly
Bedside data	Falling pressure, narrow pulse pressure, collapsible venous profile in context	Weight gain, B-lines, plethoric venous system in context
Response	Improves after a cautious, indicated fluid challenge	Improves with effective decongestion

Venous congestion can lower GFR even when total body volume is high. Oliguria in a patient with raised JVP and pulmonary edema is not an indication for routine fluid loading. Clinical examination, weight trajectory, cumulative balance and focused ultrasound should be interpreted together.

8.4 Common mechanisms

Mechanism	Examples	High-yield clues
Reduced renal perfusion	Volume loss, vasodilation, shock, low cardiac output	Hemodynamic instability; often bland sediment
Venous congestion	Acute heart failure, right-sided failure, intra-abdominal hypertension	Raised JVP, edema/ascites, pulmonary or systemic congestion
Intrinsic renal injury	Acute tubular injury, glomerulonephritis, interstitial nephritis, vascular disease	Active sediment, proteinuria, systemic or exposure clues
Obstruction	Catheter blockage, prostate disease, pelvic tumor, stones	Retention, colic, hydronephrosis; may be painless
Physiological antidiuresis	Postoperative stress, pain, nausea, vasopressin release	Low output without progressive injury; diagnosis only after excluding danger

8.5 Fluids: a treatment, not a reflex

Give isotonic crystalloid when hypovolemia or fluid responsiveness is plausible and there is no prohibitive congestion. A common diagnostic-therapeutic approach is a small bolus—often 250–500 mL in an adult—followed immediately by reassessment of blood pressure, perfusion, lungs, JVP, urine output and oxygenation. The amount and speed must be individualized; smaller aliquots are appropriate in older adults and patients with cardiac or renal disease.

DO NOT

Do not prescribe repeated liters solely because urine output is low. A fluid bolus that does not improve perfusion or urine output but worsens crackles and oxygenation has supplied diagnostic information—and should not be automatically repeated.

8.6 Diuretics and the furosemide stress test

Loop diuretics increase urine flow when functioning nephrons can deliver drug to the tubular lumen. They may relieve congestion but do not reverse structural AKI or improve survival simply by converting oliguria to nonoliguria. A poor response should prompt reassessment of dose, delivery, congestion, obstruction and kidney severity—not endless escalation without a goal.

In selected monitored patients with early AKI, the furosemide stress test may help estimate progression risk: approximately 1 mg/kg IV in a loop-diuretic-naïve patient or 1.5 mg/kg IV after recent loop exposure. Urine output below about 200 mL over two hours predicts a higher risk of progression. This is a specialist risk-stratification test, not routine treatment and not appropriate in hypovolemia or obstruction.

8.7 When low output becomes an emergency

- Anuria or suspected complete obstruction.
- Potassium ≥ 6.5 mmol/L, rapidly rising potassium or ECG changes.
- Pulmonary edema, worsening hypoxemia or severe fluid overload.
- Severe acidaemia not responding to treatment of the cause.
- Uraemic pericarditis, encephalopathy or otherwise unexplained severe symptoms.
- Progressive AKI with inability to meet metabolic, electrolyte or fluid demands.

Kidney replacement therapy should be initiated for life-threatening fluid, electrolyte or acid–base complications or when metabolic demands exceed kidney capacity. Waiting for an arbitrary creatinine or urea concentration can be dangerous; starting solely because a number is high can also be unnecessary.

Case resolution

The catheter tubing is kinked and the bladder scan shows 650 mL. After correcting the drainage problem, 700 mL is released. Crackles and hypoxemia make empiric rapid fluid loading inappropriate. The team reviews cumulative fluid balance, obtains renal function and electrolytes, and continues surveillance because postoperative retention and congestion can coexist with AKI.

Take-home messages

- Calculate urine output per kilogram per hour and specify the time interval.
- Inspect the drainage system and bladder before assuming the kidneys have stopped producing urine.
- Separate hypovolemia from venous congestion; both can reduce GFR but require opposite fluid strategies.
- Use diuretics for congestion, not to normalize the urine chart.
- Anuria, obstruction and refractory complications require rapid escalation.

Self-assessment

1. What six-hour urine volume meets the oliguria threshold in an 80-kg adult?
2. Why does an empty bladder not exclude obstruction?
3. Name four findings that support venous congestion rather than hypovolemia.
4. What is the role and main limitation of the furosemide stress test?
5. List five complications that may require urgent kidney replacement therapy.

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CHAPTER 9

The Patient With Edema

Decide whether the problem is systemic congestion, low oncotic pressure or a local process

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain edema using hydrostatic pressure, oncotic pressure, permeability and lymphatic drainage.
- Recognize that total body fluid excess and effective arterial blood volume are different concepts.
- Distinguish cardiac, renal, hepatic, venous and lymphatic patterns at the bedside.
- Select high-yield laboratory and imaging tests.
- Use sodium restriction and diuretics safely while monitoring decongestion.

Opening case

CLINICAL CASE

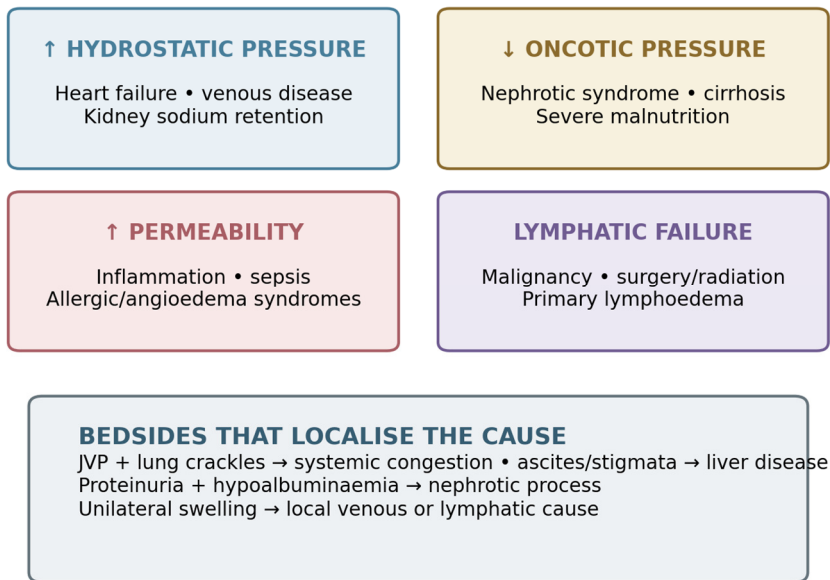
A 54-year-old woman with type 2 diabetes reports a 7-kg weight gain over two weeks. She has bilateral pitting edema to the thighs, blood pressure 158/92 mmHg and clear lungs. Urine dipstick shows 4+ protein; serum albumin is 2.1 g/dL and creatinine is 1.0 mg/dL. Is the edema explained by 'too much water,' and what should be measured next?

9.1 What edema means

Edema is clinically detectable excess fluid in the interstitial space. Generalized edema usually becomes apparent only after several liters have accumulated, although the threshold varies with tissue compliance and distribution. A change in body weight is often the most practical serial measure: in a short interval, 1 kg of weight change approximates 1 L of net fluid change, provided nutrition and measurement conditions are stable.

The classical Starling framework remains useful, but the endothelial glycocalyx and lymphatic return are central to modern interpretation. Edema develops when capillary filtration exceeds lymphatic removal because hydrostatic pressure rises, plasma oncotic pressure falls, permeability increases or lymphatic drainage fails.

Edema: identify the dominant mechanism



A patient may be edematous yet have low effective arterial blood volume.

Figure 9.1. Four dominant mechanisms of edema and bedside findings that help localize the underlying disorder.

9.2 Edema does not equal intravascular fullness

A patient can have marked edema while the effective arterial blood volume is reduced. In heart failure, low forward flow and venous congestion activate the sympathetic nervous system and RAAS. In cirrhosis, splanchnic vasodilation produces arterial underfilling despite ascites. In nephrotic syndrome, low oncotic pressure, altered capillary dynamics and primary renal sodium retention may coexist. These patients may retain sodium avidly even when total body sodium and water are increased.

CORE DISTINCTION

Total extracellular volume describes the amount of sodium-associated fluid in the body. Effective arterial blood volume describes the circulation sensed by pressure and perfusion receptors. They often move together—but not always.

9.3 Pattern recognition at the bedside

Pattern	Typical distribution and clues	Common causes
Cardiac/systemic congestion	Raised JVP, crackles or pleural effusions, hepatomegaly, ascites, cool peripheries in low output	Left/right heart failure, pulmonary hypertension, constrictive pericardial disease
Renal retention sodium	Hypertension, weight gain, reduced GFR; lung findings may be present	AKI, advanced CKD, glomerular disease
Nephrotic	Soft pitting edema, often periorbital or dependent; heavy proteinuria and low albumin	Membranous nephropathy, diabetic kidney disease, minimal change disease, FSGS
Hepatic	Ascites, stigmata of chronic liver disease, low albumin; peripheral edema later	Cirrhosis and portal hypertension
Local venous/lymphatic	Asymmetric or unilateral; venous skin changes or nonpitting thickened skin	DVT, chronic venous insufficiency, lymphatic obstruction

Dependent edema is shaped by gravity: ankles when ambulant, sacrum in a bedbound patient and eyelids after recumbency. Unilateral acute swelling should prompt evaluation for local venous obstruction rather than automatic escalation of systemic diuretics.

9.4 High-yield investigations

- Daily weight under standardized conditions; fluid balance when reliable.
- Blood pressure, orthostatic change, JVP, cardiac and lung examination.
- Creatinine/eGFR, sodium, potassium, bicarbonate, albumin and liver tests.
- Urinalysis plus ACR or PCR; quantify heavy protein loss rather than relying on dipstick alone.
- ECG, natriuretic peptide and echocardiography when heart failure is plausible.
- Ultrasound for ascites, venous thrombosis, kidney structure or focused congestion assessment when it answers a defined question.

BNP and NT-proBNP support heart-failure assessment but are affected by age, atrial fibrillation, obesity and kidney function. They should be interpreted with clinical probability and imaging, not as isolated binary tests.

9.5 Recognizing nephrotic syndrome

Nephrotic-range proteinuria in adults is conventionally at least 3.5 g/day or a spot PCR around at least 3,500 mg/g, accompanied clinically by hypoalbuminemia and often edema and hyperlipidemia. Serum albumin below 3.0 g/dL is common, but the exact phenotype depends on disease, liver synthesis, inflammation and timing.

Finding	Why it matters	Practical next step
Heavy albuminuria/proteinuria	Identifies glomerular barrier failure	Quantify ACR/PCR; consider timed collection when needed
Low serum albumin	Contributes to edema and may increase thrombosis risk	Assess liver disease, inflammation and nutrition as alternative contributors
Hematuria or reduced GFR	May indicate an inflammatory or mixed glomerular process	Microscopy, serology and timely nephrology assessment
Thrombosis, infection or severe edema	Important nephrotic complications	Urgent complication-specific management and cause-directed therapy

9.6 Treating systemic edema

Treatment targets the cause and the retained sodium. A practical sodium target is below 2 g/day (below approximately 87 mmol/day), particularly in CKD and heart failure, while avoiding malnutrition and excessive restriction that patients cannot sustain. Fluid restriction is not automatically required for every edematous patient; it is most relevant with significant hyponatremia or inability to excrete water.

Loop diuretics are the foundation of treatment for clinically important systemic congestion. Oral absorption may be unreliable in severe edema; IV therapy may be needed in hospitalized patients. Response should be judged by symptoms, urine output, weight, physical findings and spot urine sodium when used in a structured protocol—not by dose alone.

Problem	Reason	Possible response
Poor oral response	Gut edema, impaired absorption, insufficient dose	Use adequate dose; consider IV loop diuretic
Distal nephron adaptation	Increased sodium reabsorption beyond the loop	Sequential nephron blockade with a thiazide-type agent in monitored patients
Low albumin nephrotic state	Altered delivery plus strong sodium retention	Higher loop exposure may be needed; treat underlying disease
Advanced CKD	Reduced tubular delivery of diuretic	Higher doses often required; monitor electrolytes and volume closely

A common inpatient goal is net weight loss around 0.5–1.0 kg/day, but the correct rate depends on blood pressure, perfusion, degree of overload and symptoms. Faster decongestion may be

appropriate in pulmonary edema; slower removal is safer when intravascular refill is limited. A modest creatinine rise during successful decongestion does not necessarily mean structural kidney injury, but hypotension, worsening perfusion or progressive renal dysfunction requires reassessment.

9.7 Disease-specific cautions

- Heart failure: persistent congestion is harmful; do not stop decongestion solely for a small creatinine rise without assessing the whole patient.
- Nephrotic syndrome: loop diuretics are preferred; severe hypoalbuminemia may increase diuretic resistance and thrombosis risk.
- Cirrhosis with ascites: sodium restriction and aldosterone antagonism are central; dosing, paracentesis and albumin use require liver-specific protocols.
- Local venous or lymphatic edema: compression and treatment of the local cause are often more effective than systemic diuresis.
- Pulmonary edema with respiratory distress is an emergency requiring oxygen/ventilatory support as appropriate and rapid treatment of congestion and precipitating cause.

Case resolution

The patient has nephrotic syndrome: PCR is 6,200 mg/g, albumin is 2.1 g/dL and microscopy shows oval fat bodies without RBC casts. The priorities are sodium restriction, monitored loop-diuretic therapy, thrombosis and infection assessment, optimization of antiproteinuric treatment and evaluation of the cause. Normal creatinine does not make the presentation benign; heavy proteinuria can precede GFR loss.

Take-home messages

- Edema results from altered capillary filtration and/or lymphatic removal.
- Edema can coexist with low effective arterial blood volume.
- JVP, lungs, distribution of edema, urine protein and albumin localize the cause.
- Use weight and clinical decongestion—not edema appearance alone—to follow treatment.
- Diuretic resistance is a pharmacological and physiological problem that requires structured reassessment.

Self-assessment

1. Name the four dominant mechanisms that produce edema.
2. How can a patient be edematous but have low effective arterial blood volume?
3. What findings distinguish nephrotic edema from cardiac congestion?
4. What does a 3-kg weight decrease over 72 hours approximately represent?
5. Give four causes of an inadequate response to a loop diuretic.

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CHAPTER 10

The Patient With Hematuria

Confirm red cells, localize the source and stratify urgency

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Confirm microhematuria by microscopy rather than dipstick alone.
- Distinguish glomerular from urological bleeding using sediment, proteinuria and clinical features.
- Recognize visible hematuria, clot retention and pulmonary–renal syndromes as urgent presentations.
- Use risk-stratified urological evaluation without overlooking intrinsic kidney disease.
- Plan follow-up after exercise, menstruation, infection or anticoagulant-associated bleeding.

Opening case

CLINICAL CASE

A 62-year-old man taking apixaban reports painless red urine. Dipstick is 3+ blood; microscopy shows numerous isomorphic RBCs without casts. Creatinine is unchanged and ACR is 18 mg/g. He smoked 35 pack-years. Can anticoagulation be accepted as the diagnosis?

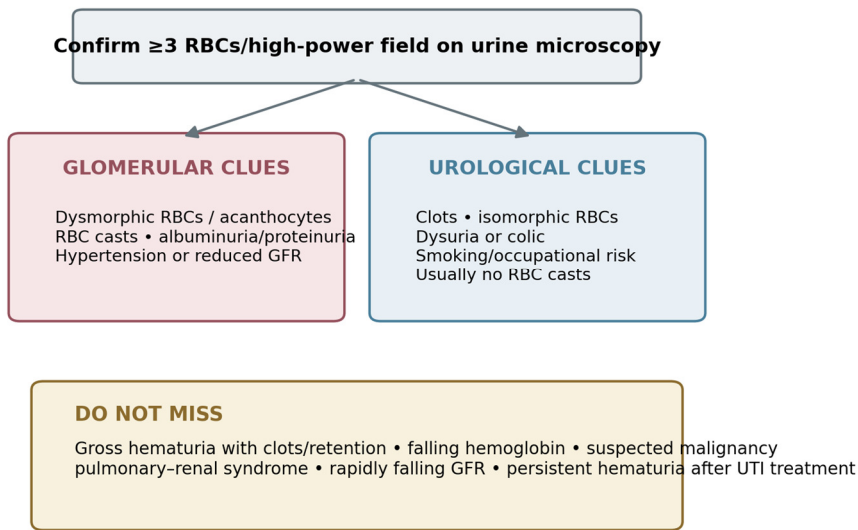
10.1 Confirm that the urine contains red cells

The 2025 AUA/SUFU guideline defines microhematuria as at least 3 RBCs per high-power field on microscopic evaluation of a properly collected urine specimen. A positive dipstick alone is not sufficient because the heme reaction also detects free hemoglobin and myoglobin. Microscopy should therefore confirm red cells and describe their morphology.

Dipstick	Microscopy	Likely interpretation
Positive blood	RBCs present	True hematuria
Positive blood	Few or no RBCs	Hemoglobinuria, myoglobinuria, lysed RBCs or interference
Red/brown urine	Dipstick negative or weak	Pigments, foods or medicines; investigate context
Negative blood	RBCs present	Consider technical issues, high urinary vitamin C or delay/error

Visible or gross hematuria is urine discoloration evident to the patient or clinician. The appearance does not quantify blood loss and cannot reliably localize the source. Clots favor a nonglomerular source and can cause painful urinary retention.

Hematuria: glomerular or urological?



Anticoagulation may reveal bleeding; it does not explain away the need for evaluation.

Figure 10.1. Localization of hematuria using microscopy, proteinuria, clinical features and urgent red flags.

10.2 Ensure a valid specimen

- Use a clean-catch midstream specimen when possible.
- Record menstruation, vaginal bleeding, recent instrumentation and vigorous exercise.
- Process a fresh specimen; delayed analysis can alter cells and casts.
- If infection is suspected, obtain culture and repeat microscopy after successful treatment.
- Do not diagnose hematuria from urine color alone.

Transient hematuria after vigorous exercise may resolve within 48–72 hours, but persistence requires evaluation. Menstrual contamination should prompt collection at another time or a carefully obtained alternative specimen when urgent clarification is needed.

10.3 Glomerular hematuria

Glomerular bleeding is supported by dysmorphic RBCs, especially acanthocytes, RBC casts and concomitant albuminuria/proteinuria. Acanthocytes around at least 5% of urinary RBCs are highly suggestive when microscopy is performed by experienced observers, but sensitivity varies. RBC casts are strongly supportive of glomerulonephritis or renal vasculitis and should trigger urgent assessment.

Finding	Interpretation
Dysmorphic RBCs / acanthocytes	Deformation during passage through the glomerular barrier and tubules supports a glomerular source
RBC casts	Red cells incorporated into tubular matrix; strongly supports nephritic glomerular inflammation
Albuminuria/proteinuria	Substantial albumin with hematuria increases the probability of glomerular disease
Reduced GFR, hypertension, edema	Suggests clinically important renal involvement rather than isolated lower-tract bleeding
Systemic features	Purpura, pulmonary hemorrhage, sinus disease, infection, autoimmune features or malignancy may identify cause

EMERGENCY PATTERN

Hematuria plus rapidly rising creatinine, RBC casts or pulmonary hemorrhage is a nephrological emergency. Send urgent serology and involve nephrology; do not delay evaluation while waiting for every result.

10.4 Urological hematuria

Isomorphic RBCs, clots, dysuria, colicky pain or urinary symptoms favor bleeding from the collecting system, ureter, bladder, prostate or urethra. Common causes include infection, stones, benign prostatic disease, tumors, trauma and instrumentation. The absence of pain does not reassure against malignancy.

The AUA/SUFU framework uses age, sex, smoking exposure, degree/persistence of microhematuria, previous gross hematuria and additional urothelial cancer risks to classify patients as low/negligible, intermediate or high risk. Evaluation is then matched to risk, commonly using repeat urinalysis in low-risk patients, cystoscopy and ultrasound in intermediate risk, and cystoscopy plus axial upper-tract imaging in high risk. Local European pathways may differ, so students should understand the principle of risk stratification rather than memorize one national pathway.

10.5 Initial clinical assessment

1. Ask about visible blood, clots, pain, dysuria, fever, exercise, trauma, instrumentation and menstruation.
2. Record smoking in pack-years and occupational exposure to aromatic amines or other urothelial carcinogens.
3. Review anticoagulants, antiplatelet drugs, cyclophosphamide and analgesic exposures.
4. Measure blood pressure and assess edema, rash, joints, lungs, abdomen, flank and bladder.
5. Order creatinine/eGFR, full blood count, urinalysis with microscopy, ACR/PCR and culture when indicated.
6. Choose ultrasound, CT urography and cystoscopy according to the suspected source, cancer risk and contraindications.

Anticoagulants and antiplatelet drugs can increase the visibility of bleeding but do not remove the possibility of cancer, stones or glomerular disease. Patients receiving these drugs should undergo the same cause-directed evaluation as comparable patients not receiving them.

10.6 Red flags and referral

Presentation	Why urgent	First actions
Gross hematuria with clots/retention	Obstruction, pain and ongoing blood loss	Bladder assessment; urgent urological management and irrigation protocol when indicated
Falling hemoglobin or hemodynamic instability	Clinically important hemorrhage	Resuscitation, blood count/coagulation, urgent source control
AKI + active sediment	Rapidly progressive intrinsic kidney disease	Urgent nephrology, serology and biopsy consideration
Pulmonary–renal syndrome	Potential life-threatening vasculitis or anti-GBM disease	Emergency respiratory and nephrology assessment
Persistent painless hematuria with cancer risk	Possible urothelial or renal malignancy	Timely risk-stratified cystoscopy and upper-tract imaging

10.7 Hematuria in CKD and after UTI

CKD does not itself explain hematuria. Persistent hematuria may indicate the cause of CKD or an independent urological disorder. Similarly, attributing hematuria to infection is reasonable only when symptoms, pyuria and culture support infection and the blood resolves after treatment. Persistent hematuria after a treated UTI requires reassessment.

Case resolution

Apixaban may have made the bleeding visible, but it is not accepted as the underlying diagnosis. The patient's painless visible hematuria, age and 35 pack-year smoking history create substantial urological risk. He requires prompt cystoscopy and appropriate upper-tract imaging while anticoagulation decisions are individualized to bleeding severity and thromboembolic risk. The absence of proteinuria, dysmorphic RBCs and casts makes an active glomerular process less likely but does not replace urological evaluation.

Take-home messages

- Microhematuria requires microscopy: ≥ 3 RBCs/high-power field.
- Dipstick blood without RBCs suggests hemoglobinuria or myoglobinuria.
- Dysmorphic RBCs, RBC casts and albuminuria support a glomerular source.
- Clots, retention, painless gross hematuria and cancer risk require urological attention.
- Anticoagulation does not explain away hematuria.

Self-assessment

1. What microscopic threshold defines microhematuria?
2. Why can dipstick be positive for blood when no RBCs are seen?
3. Name four features that support glomerular hematuria.
4. What should be done after hematuria attributed to a UTI?
5. Why does anticoagulation not remove the need for evaluation?

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CHAPTER 11

Hypertension and Kidney Disease

Measure accurately, identify secondary clues and reduce cardiovascular and renal risk

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Classify office blood pressure and distinguish routine from standardized measurement.
- Explain how hypertension causes kidney injury and kidney disease sustains hypertension.
- Recognize hypertensive emergency and common secondary renal causes.
- Select treatment targets and first-line agents for albuminuric CKD.
- Evaluate resistant hypertension and monitor treatment safety.

Opening case

CLINICAL CASE

A 46-year-old man has clinic blood pressures of 168/102 and 172/104 mmHg while taking amlodipine 10 mg/day. Creatinine is 1.4 mg/dL, potassium 3.1 mmol/L and ACR 420 mg/g. He reports loud snoring and uses ibuprofen most days. Which findings suggest more than uncomplicated essential hypertension?

11.1 Accurate measurement comes before classification

Use a validated upper-arm device and an appropriate cuff. The patient should avoid exercise, caffeine and smoking for at least 30 minutes, empty the bladder, sit quietly for about five minutes with back supported and feet flat, keep the arm supported at heart level and remain silent during measurement. Take at least two readings one minute apart and average them; repeat on separate occasions unless the pressure or clinical situation requires immediate action.

2025 AHA/ACC category	Systolic BP	Diastolic BP
Normal	<120 mmHg	and <80 mmHg
Elevated	120–129 mmHg	and <80 mmHg
Stage 1 hypertension	130–139 mmHg	or 80–89 mmHg
Stage 2 hypertension	≥140 mmHg	or ≥90 mmHg

Home blood pressure monitoring and 24-hour ambulatory monitoring identify white-coat and masked hypertension and are particularly useful when office readings and organ damage disagree. A common home protocol uses two morning and two evening readings for at least three—and preferably seven—days, discarding the first day in some protocols and averaging the rest.

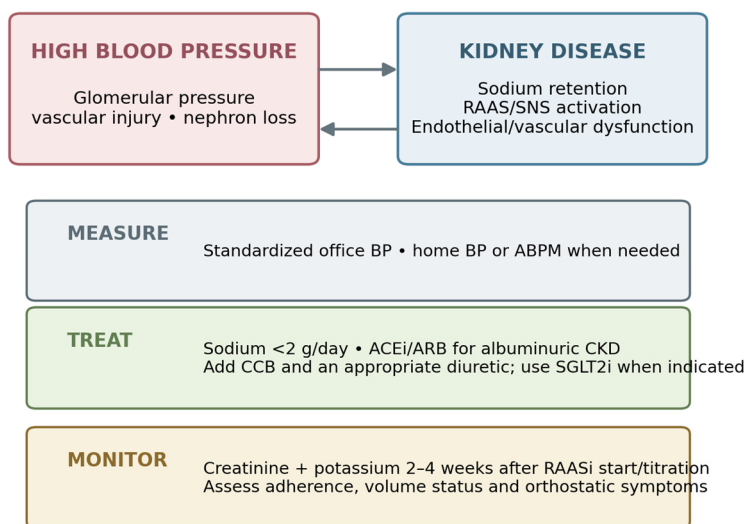
MEASUREMENT WARNING

KDIGO's suggested SBP target <120 mmHg for most adults with non-dialysis CKD is tied to standardized office measurement. Applying the same number to an unattended, rushed or routine clinic measurement may overtreat patients.

11.2 The bidirectional kidney–blood-pressure cycle

High systemic and intraglomerular pressure promotes arteriolar injury, glomerulosclerosis, albuminuria and nephron loss. In turn, kidney disease promotes sodium retention, RAAS and sympathetic activation, endothelial dysfunction, vascular stiffness and impaired pressure natriuresis. This feedback loop explains why hypertension is both a cause and a consequence of CKD.

Hypertension and kidney disease reinforce each other



KDIGO SBP <120 mmHg applies only to standardized measurement and when tolerated.

Figure 11.1. *The bidirectional relationship between hypertension and kidney disease, followed by measurement, treatment and monitoring priorities.*

11.3 Assess kidney involvement and global risk

- Creatinine/eGFR and serum potassium, sodium and bicarbonate.
- Urinalysis plus ACR; albuminuria is both kidney damage and cardiovascular risk.
- ECG for left ventricular hypertrophy or ischemia when appropriate.
- Fundoscopy in severe hypertension or visual symptoms.
- Cardiovascular risk factors: diabetes, lipids, smoking, obesity and established vascular disease.
- Medication and substance review: NSAIDs, decongestants, stimulants, glucocorticoids, oral contraceptives, calcineurin inhibitors, liquorice and excess alcohol.

A patient with G1–G2 eGFR but A3 albuminuria has clinically important CKD. Conversely, hypertension with a normal dipstick has not been fully assessed until quantitative ACR is measured.

11.4 When to suspect a secondary cause

Clue	Causes to consider	Initial direction
Abrupt onset, age <30 or rapid worsening	Renovascular, endocrine, renal parenchymal disease	History, examination, creatinine/ACR, targeted imaging and hormones
Hypokalemia or metabolic alkalosis	Primary aldosteronism; diuretics	Aldosterone–renin assessment under an appropriate protocol
Creatinine rise after ACEi/ARB, flash pulmonary edema	Bilateral renal artery stenosis or stenosis to a solitary kidney	Renal/vascular assessment in selected patients
Snoring, obesity, daytime somnolence	Obstructive sleep apnea	Sleep study pathway
Episodic headache, sweating, palpitations	Pheochromocytoma/paraganglioma	Plasma free or urinary fractionated metanephrines
Resistant hypertension, CKD or active urine sediment	Renal parenchymal disease	Urinalysis, ACR, imaging and nephrology evaluation

11.5 Treatment targets in CKD

The 2025 AHA/ACC guideline generally targets blood pressure below 130/80 mmHg for adults with hypertension. KDIGO 2021 suggests a standardized office SBP below 120 mmHg for adults with non-dialysis CKD when tolerated. These recommendations differ in measurement method and population framing, so treatment should consider orthostatic symptoms, frailty, falls, diastolic pressure, comorbidity and patient preference.

Hypertensive emergency is severe blood pressure elevation—often at or above 180/120 mmHg—with acute target-organ injury such as encephalopathy, pulmonary edema, acute coronary syndrome, aortic syndrome, AKI or retinal injury. The emergency is defined by organ damage, not the number alone. It requires monitored IV therapy tailored to the organ syndrome; rapid uncontrolled normalization can cause ischemia.

11.6 Lifestyle and sodium

- Sodium intake below 2 g/day (below 5 g sodium chloride/day) in CKD, unless a specific condition requires another plan.
- Regular physical activity—about 150 minutes/week of moderate intensity when tolerated.
- Weight reduction when overweight, smoking cessation and moderation of alcohol.
- Adequate sleep and evaluation for obstructive sleep apnea when suspected.
- Avoid NSAIDs and other pressor substances when possible.

11.7 Choosing antihypertensive medicines

Clinical setting	Preferred foundation	Important monitoring
CKD with A2–A3 albuminuria	ACE inhibitor or ARB at the highest tolerated approved dose	Creatinine and potassium about 2–4 weeks after initiation or titration
CKD without albuminuria	RAAS blocker, dihydropyridine CCB or diuretic according to indication	Volume, electrolytes, kidney function and adverse effects
Volume excess / low eGFR	Loop diuretic often required; thiazide-like agents may remain useful	Weight, sodium, potassium, magnesium, creatinine
Diabetes/CKD or indicated nondiabetic CKD	SGLT2 inhibitor for kidney/cardiovascular protection in addition to BP therapy	Expected early eGFR dip, volume status and sick-day risks
Resistant hypertension	Confirm true resistance; optimize diuretic and consider mineralocorticoid blockade	Potassium and kidney function; secondary causes

Do not combine an ACE inhibitor with an ARB for routine CKD treatment. After starting or increasing a RAAS inhibitor, a creatinine rise greater than 30% should trigger assessment of volume depletion, NSAIDs, renal artery disease and other causes. Smaller stable changes may reflect the intended reduction in intraglomerular pressure.

11.8 Resistant hypertension

Apparent treatment-resistant hypertension is blood pressure above goal despite three antihypertensive classes at maximally tolerated doses, ideally including a long-acting calcium-channel blocker, a RAAS blocker and an appropriate diuretic; controlled pressure requiring at least four classes also qualifies. Before labeling true resistance, verify standardized measurement, adherence, white-coat effect, dosing, sodium intake and interfering drugs.

1. Confirm out-of-office blood pressure.
2. Assess adherence nonjudgmentally and simplify the regimen where possible.
3. Ensure the diuretic matches kidney function and volume state.
4. Remove NSAIDs and other pressor agents.
5. Screen for primary aldosteronism, sleep apnea, renal disease and renovascular disease when clinically indicated.
6. Consider spironolactone or another targeted fourth-line strategy with close potassium and kidney-function monitoring.

Case resolution

The patient has stage 2 hypertension with A3 albuminuria, hypokalemia and several secondary clues. Ibuprofen is stopped, standardized and home BP are arranged, ACE-inhibitor therapy is introduced with creatinine and potassium monitoring, and the albuminuric CKD is evaluated. Hypokalemia prompts screening for primary aldosteronism, while snoring prompts assessment for sleep apnea. Treatment is intensified without waiting for every secondary test because his cardiovascular and renal risk is already high.

Take-home messages

- A target is meaningful only when the measurement method is defined.
- Albuminuria should be measured in every patient with hypertension and possible CKD.
- ACE inhibitors or ARBs are foundational for albuminuric CKD.
- A small hemodynamic creatinine rise can be expected; a rise >30% requires evaluation.
- Before diagnosing resistant hypertension, exclude poor measurement, nonadherence, white-coat effect, sodium excess and inadequate diuresis.

Self-assessment

1. What is the difference between routine and standardized office BP?
2. State the 2025 AHA/ACC stage 1 and stage 2 thresholds.
3. Why can kidney disease sustain hypertension?
4. Which CKD patients particularly benefit from ACEi or ARB therapy?
5. List six steps in evaluating apparent resistant hypertension.

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CHAPTER 12

Electrolyte and Acid–Base Disorders

Recognize emergencies, calculate carefully and correct at a safe rate

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Use symptoms, timing and osmolality to evaluate dysnatremia.
- Treat severe hyperkalemia with membrane stabilization, intracellular shift and potassium removal.
- Apply a stepwise method to metabolic and respiratory acid–base disorders.
- Calculate anion gap, albumin correction and expected respiratory compensation.
- Recognize correction limits that prevent osmotic demyelination or cerebral edema.

Opening case

CLINICAL CASE

A 59-year-old woman taking hydrochlorothiazide presents with confusion and a generalized seizure. Serum sodium is 112 mmol/L, potassium 2.9 mmol/L, glucose 96 mg/dL and measured serum osmolality 238 mOsm/kg. What should be treated before the complete diagnostic classification is finished?

Electrolyte and acid–base emergencies

HYPONATREMIA

Na⁺ <135 mmol/L
Seizure/coma → 3% saline bolus
Aim initial rise 4–6 mmol/L

HYPERKALAEMIA

K⁺ ≥6.5 mmol/L = severe
ECG change → IV calcium
Insulin-glucose + removal strategy

SEVERE ACIDAEMIA

pH ≤7.10: urgent evaluation
Check lactate, ketones and toxins
Assess kidney failure
Dialysis if refractory

HYPERNATREMIA

Na⁺ >145 mmol/L
Stabilize circulation first
Then replace water
Chronic: fall ≤10–12 mmol/L/day

SAFE FIRST ACTIONS

Repeat implausible results • obtain ECG for significant dyskalaemia • assess symptoms and timing
review medicines • measure osmolality/urine indices when relevant • monitor during correction

Treat the patient and the trajectory—not an isolated laboratory value.

Figure 12.1. Immediate recognition and first actions for severe dysnatremia, hyperkalemia and acidaemia.

A SIMPLE MENTAL MODEL

For every electrolyte or acid–base result, ask four questions in order: (1) Is the result real? (2) Is the patient in immediate danger? (3) Is the body gaining or losing the substance, or is it shifting between compartments? (4) What numerical correction limit will keep treatment safe?

12.1 A safe general approach

1. Confirm an implausible result and exclude sampling or hemolysis artifacts, but do not delay emergency treatment when the clinical picture is convincing.
2. Assess symptoms, ECG, hemodynamics and the speed of change. The same laboratory value has different risk when acute or chronic.
3. Review kidney function, medicines, intake, losses, glucose, osmolality and urine indices.
4. Treat immediate physiological danger while investigating the cause.
5. Set a correction goal, a maximum safe rate, a monitoring interval and a plan for overcorrection.

12.2 Hyponatremia

Hyponatremia is serum sodium below 135 mmol/L. It is a disorder of water balance relative to exchangeable sodium and potassium—not necessarily sodium depletion. First determine tonicity. Measured serum osmolality below 275 mOsm/kg confirms hypotonic hyponatremia. Hyperglycemia causes translocational hyponatremia; marked hyperlipidemia or paraproteinemia can cause pseudohyponatremia with some laboratory methods.

Plain-language explanation: serum sodium is a concentration. It falls when the amount of water in the extracellular space is too large for the amount of exchangeable sodium and potassium. A patient can therefore be hyponatremic while total body sodium is low, normal or high. This is why the physical examination and urine studies are needed after confirming hypotonicity.

Step	Key threshold	Interpretation
Serum osmolality	<275 mOsm/kg	Hypotonic hyponatremia
Urine osmolality	≤100 mOsm/kg	Appropriately suppressed vasopressin; consider excess water or low solute intake
Urine osmolality	>100 mOsm/kg	Vasopressin effect is present
Urine sodium	≤30 mmol/L	Supports low effective arterial volume, with important exceptions
Urine sodium	>30 mmol/L	Consider SIAD, adrenal insufficiency, renal salt loss or diuretics

Urine sodium is confounded by diuretics, CKD and recent fluids. SIAD is a diagnosis of hypotonic hyponatremia with inappropriately concentrated urine after excluding adrenal insufficiency, severe hypothyroidism, kidney failure and effective volume depletion.

12.3 Severe symptomatic hyponatremia

Seizure, coma, severe confusion, respiratory compromise or signs of cerebral edema require immediate hypertonic saline regardless of whether the hyponatremia is known to be acute or chronic. A European regimen gives 150 mL of 3% saline over 20 minutes, checks sodium and may repeat to obtain an initial rise of about 5 mmol/L. Other protocols use 100-mL boluses; clinicians must follow a validated local protocol.

CORRECTION LIMITS

Aim for an initial increase of about 4–6 mmol/L sufficient to improve severe symptoms. Limit total correction to no more than 10 mmol/L in the first 24 hours and 8 mmol/L in each subsequent 24 hours. In patients at high risk for osmotic demyelination—very low sodium, alcohol use disorder, malnutrition, advanced liver disease or hypokalemia—use the stricter limit of ≤8 mmol/L in 24 hours.

Check serum sodium frequently during active therapy—often every 2–4 hours—and monitor urine output. A sudden water diuresis can cause rapid overcorrection. Stop active correction and seek expert help if limits are approached; desmopressin and electrolyte-free water may be used to prevent or reverse overcorrection under a defined protocol.

WORKED EXAMPLE

A patient begins at Na 112 mmol/L. After hypertonic saline, Na is 117 mmol/L and the seizure stops. The therapeutic goal has been achieved: the rise is 5 mmol/L. Treatment now changes from rescue to control. If the patient is at high risk for osmotic demyelination, no more than about 3 additional mmol/L should be allowed during the first 24 hours.

12.4 Chronic or minimally symptomatic hyponatremia

Mechanism	Examples	Initial management principle
Hypovolemic	GI loss, thiazide, mineralocorticoid deficiency	Restore circulation with isotonic fluid and remove cause; monitor for water diuresis
Euvolemic	SIAD, low solute intake, glucocorticoid deficiency	Treat cause; fluid restriction and adequate solute are common first measures
Hypervolemic	Heart failure, cirrhosis, advanced kidney failure	Treat congestion/underlying disease; individualized fluid restriction
Water excess	Primary polydipsia	Reduce intake and address behavioral/drug cause

Vaptans produce aquaresis and can correct selected euvolemic or hypervolemic hyponatremia, but they are not emergency therapy for severe symptoms and can overcorrect sodium. Their use varies between guidelines and should be specialist-directed.

12.5 Hypernatremia

Hypernatremia is serum sodium above 145 mmol/L and usually indicates water deficit relative to sodium. First stabilize circulation with isotonic crystalloid if shock or severe hypovolemia is present; then replace free water orally, enterally or intravenously. Identify impaired access to water, altered thirst, osmotic diuresis, gastrointestinal losses and diabetes insipidus.

WATER DEFICIT ESTIMATE

Free-water deficit $\approx$ total body water $\times$ [(measured Na / 140) – 1]. Total body water is commonly estimated as 0.6 $\times$ weight in younger men, 0.5 $\times$ weight in younger women and lower fractions in older or obese adults. The formula is only a starting estimate; ongoing losses and serial sodium determine treatment.

When hypernatremia is chronic or of uncertain duration, a common maximum fall is about 0.5 mmol/L/h and 10–12 mmol/L/day. Acute sodium loading can be corrected more rapidly in a monitored setting. Measure sodium every 2–4 hours during active correction and adjust to the observed trajectory.

12.6 Potassium disorders

Hypokalemia is potassium below 3.5 mmol/L; hyperkalemia is often defined above 5.5 mmol/L. Risk depends on concentration, rate of change, ECG, comorbidity and coexisting acid–base disorders. Repeat a surprising high potassium when hemolysis or collection artifact is plausible, but obtain an ECG and begin treatment immediately when severe hyperkalemia or ECG toxicity is suspected.

Potassium	Clinical category	Immediate concern
5.5–5.9 mmol/L	Mild hyperkalemia	Confirm, identify cause and prevent progression
6.0–6.4 mmol/L	Moderate hyperkalemia	Urgent assessment, ECG and active treatment according to context
≥ 6.5 mmol/L	Severe hyperkalemia	Medical emergency even if ECG is initially normal
<3.0 mmol/L	Moderate–severe hypokalemia	Arrhythmia and weakness risk; assess magnesium and losses
<2.5 mmol/L	Severe hypokalemia	Urgent monitored replacement, especially with symptoms or ECG change

12.7 Emergency hyperkalemia treatment

Think of treatment as three separate jobs. Calcium protects the myocardium but does not remove potassium. Insulin and beta α -agonists temporarily move potassium into cells. Diuretics, binders or dialysis remove potassium from the body. A safe prescription states which job each treatment is doing.

Goal	Typical adult intervention	Important point
Stabilize myocardium	10 mL 10% calcium chloride IV over 5 min OR 30 mL 10% calcium gluconate IV over 10 min, according to access/protocol	Indicated for ECG toxicity; calcium does not lower potassium
Shift K ⁺ into cells	10 units soluble insulin IV + 25 g glucose	Check glucose repeatedly for at least 6 h; hypoglycemia risk is substantial
Adjunct shift	Nebulized salbutamol 10–20 mg	Do not use alone in severe hyperkalemia; response varies
Remove potassium	Loop diuretic if producing urine; potassium binder in selected patients; dialysis when severe/refractory	Definitive control requires potassium removal
Monitor	Repeat potassium and ECG; watch for rebound	Intracellular shift is temporary

Sodium bicarbonate is not routine acute hyperkalemia treatment but may contribute when significant metabolic acidosis is present. Stop exogenous potassium and review RAAS inhibitors, mineralocorticoid antagonists, trimethoprim, NSAIDs, heparin, calcineurin inhibitors and supplements. Long-term management should try to preserve indicated cardiorenal therapy when safe, using dietary, diuretic and binder strategies rather than automatically discontinuing RAAS blockade forever.

WORKED EXAMPLE

K⁺ is 7.1 mmol/L with a broad QRS complex. Give IV calcium first because electrical instability can cause cardiac arrest within minutes. Give insulin–glucose and an adjunct shift therapy next, then arrange potassium removal. Repeat ECG and potassium because the intracellular shift is temporary and rebound can occur.

12.8 Hypokalemia

Common causes are gastrointestinal loss, diuretics, hyperaldosteronism, renal tubular disorders, insulin/beta-agonist shifts and low intake. Check magnesium because hypomagnesemia causes renal potassium wasting and makes hypokalemia refractory. Oral potassium is preferred when the patient is stable and the gut works. IV potassium requires concentration and rate limits defined by local policy, a controlled infusion pump and ECG monitoring for faster replacement.

DIAGNOSTIC CLUE

Urine potassium excretion helps distinguish renal from extrarenal loss. In hypertension plus hypokalemia, consider primary aldosteronism; in metabolic acidosis, consider diarrhea or renal tubular acidosis; in metabolic alkalosis, urine chloride and blood pressure help localize the mechanism.

12.9 A systematic acid–base method

The easiest way to avoid confusion is to separate description from diagnosis. First describe the pH, PaCO₂ and bicarbonate mathematically. Only then use the history to explain the process. Compensation moves the pH toward normal but does not overshoot; an observed value outside the expected range signals a second primary disorder.

1. Look at pH: acidaemia <7.35 or alkalaemia >7.45.
2. Identify the primary process from PaCO₂ and bicarbonate.
3. Calculate the anion gap and correct it for albumin.
4. Check whether respiratory compensation is appropriate.
5. Use the delta relationship, urine chloride and clinical context to identify mixed disorders.

Normal teaching range	Value
Arterial pH	7.35–7.45
PaCO ₂	35–45 mmHg
Serum bicarbonate	22–26 mmol/L
Anion gap without potassium	Approximately 8–12 mmol/L; laboratory dependent

FORMULAS

Anion gap = $\text{Na} - (\text{Cl} + \text{HCO}_3^-)$. Corrected AG $\approx$ measured AG + $2.5 \times (4.0 - \text{albumin in g/dL})$. Winter's formula for metabolic acidosis: expected $\text{PaCO}_2 \approx 1.5 \times \text{HCO}_3^- + 8 \pm 2$.

WORKED ACID-BASE EXAMPLE

Na 140, Cl 108, HCO_3^- 14 mmol/L and PaCO_2 24 mmHg. Anion gap = $140 - (108 + 14) = 18$ mmol/L, so a high-gap metabolic acidosis is present. Winter's expected $\text{PaCO}_2 = 1.5 \times 14 + 8 = 29 \pm 2$ mmHg. The measured PaCO_2 of 24 mmHg is lower than expected, proving an additional respiratory alkalosis.

12.10 Metabolic acidosis

Type	Common causes	High-yield tests
High anion gap	Lactate, ketoacids, kidney failure, methanol, ethylene glycol, salicylate, pyroglutamate	Lactate, ketones, osmolar gap/toxicology in context, renal function
Normal anion gap	Diarrhea, renal tubular acidosis, saline load, early kidney failure	Urine pH, urine electrolytes/urine anion gap in selected cases
Mixed disorder	Gap rise disproportionate to bicarbonate fall; compensation outside expected range	Delta ratio plus clinical context and blood gas

Severe acidaemia—particularly pH around or below 7.10—can impair cardiovascular function and requires urgent cause-directed treatment. Bicarbonate is appropriate in selected bicarbonate-loss states and some severe metabolic acidoses, but it generates CO_2 and sodium load and does not replace treatment of shock, ketoacidosis or toxins. Kidney replacement therapy is considered when severe acidaemia is refractory or accompanies other dialysis indications.

12.11 Metabolic alkalosis and respiratory disorders

Metabolic alkalosis requires both generation and impaired renal excretion of bicarbonate. Urine chloride below about 20 mmol/L suggests a chloride-responsive process such as vomiting or remote diuretic exposure; urine chloride at least 20 mmol/L suggests ongoing diuretics, mineralocorticoid excess or a chloride-resistant process, interpreted with blood pressure and volume.

Primary disorder	Expected compensation (approximate)
Metabolic acidosis	$\text{PaCO}_2 \approx 1.5 \times \text{HCO}_3^- + 8 \pm 2$
Metabolic alkalosis	PaCO_2 rises about 0.6–0.75 mmHg per 1 mmol/L rise in HCO_3^-
Acute respiratory acidosis	HCO_3^- rises about 1 mmol/L per 10 mmHg PaCO_2 rise
Chronic respiratory acidosis	HCO_3^- rises about 3.5–4 mmol/L per 10 mmHg PaCO_2 rise
Acute respiratory alkalosis	HCO_3^- falls about 2 mmol/L per 10 mmHg PaCO_2 fall
Chronic respiratory alkalosis	HCO_3^- falls about 4–5 mmol/L per 10 mmHg PaCO_2 fall

Compensation never fully normalizes pH. A 'normal' pH with markedly abnormal PaCO_2 and bicarbonate therefore suggests a mixed or compensated disorder, not normal acid–base physiology.

12.12 Calcium and magnesium: brief clinical orientation

Total calcium is influenced by albumin, while ionized calcium is the biologically active fraction. Use ionized calcium when symptoms, critical illness, major pH disturbance or citrate exposure make corrected total calcium unreliable. Symptomatic hypocalcemia with tetany, seizure or QT prolongation requires monitored IV calcium. Severe hypercalcemia commonly causes volume depletion and AKI; treatment begins with cause assessment and restoration of appropriate volume.

Hypomagnesemia causes arrhythmia, neuromuscular excitability, hypokalemia and hypocalcemia; replacement is required when clinically important. Hypermagnesemia occurs

mainly with kidney failure plus magnesium-containing laxatives or antacids and can cause hyporeflexia, hypotension and conduction abnormalities.

Case resolution

The patient has severe symptomatic hypotonic hyponatremia. Seizure treatment and a protocolized 3% saline bolus take priority over completing the etiological work-up. The initial goal is a 4–6 mmol/L rise with symptom improvement, followed by strict correction limits and frequent sodium/urine-output monitoring. Hydrochlorothiazide is stopped; hypokalemia is corrected carefully because potassium replacement can also raise serum sodium. Subsequent urine studies and endocrine assessment classify the cause.

Take-home messages

- Symptoms and speed of change determine urgency in dysnatremia.
- Severe symptomatic hyponatremia requires hypertonic saline and a correction-limit plan.
- Severe hyperkalemia treatment has three goals: stabilize, shift and remove.
- Always correct the anion gap for albumin and test expected compensation.
- Correction formulas start a prescription; serial measurements control it.

Self-assessment

1. What serum and urine measurements classify hypotonic hyponatremia?
2. State the initial target and 24-hour limits for severe symptomatic hyponatremia.
3. What are the three physiological goals of emergency hyperkalemia treatment?
4. Calculate the anion gap for Na 140, Cl 108 and HCO_3^- 14 mmol/L.
5. What PaCO_2 is expected by Winter's formula when HCO_3^- is 12 mmol/L?

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PART III

Acute Kidney Injury

Recognize early, reverse what is reversible and support the patient while kidneys recover

HOW TO USE PART III

AKI is not one disease. It is a clinical syndrome produced by altered perfusion, parenchymal injury, obstruction or a combination of these mechanisms. Begin every case with the same sequence: confirm and stage the change, assess immediate danger, identify the dominant mechanism, act on reversible causes and follow the trajectory.

CHAPTER 13

Acute Kidney Injury and Acute Kidney Disease

Define the syndrome, stage severity and follow recovery over time

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Apply serum-creatinine and urine-output criteria to diagnose and stage AKI.
- Distinguish AKI, acute kidney disease and chronic kidney disease by time course.
- Explain why serum creatinine may lag behind a sudden fall in GFR.
- Use a structured initial assessment to identify cause and immediate complications.
- Plan follow-up according to AKI severity, recovery and pre-existing kidney risk.

Opening case

CLINICAL CASE

A 71-year-old man with diabetes is admitted with pneumonia. His outpatient creatinine was 1.0 mg/dL two months ago. It is 1.2 mg/dL on admission and 1.7 mg/dL 30 hours later. During the last 8 hours he has produced 180 mL of urine and weighs 75 kg. Does he have AKI, and what stage is it?

AKI is a trajectory, not a single creatinine value

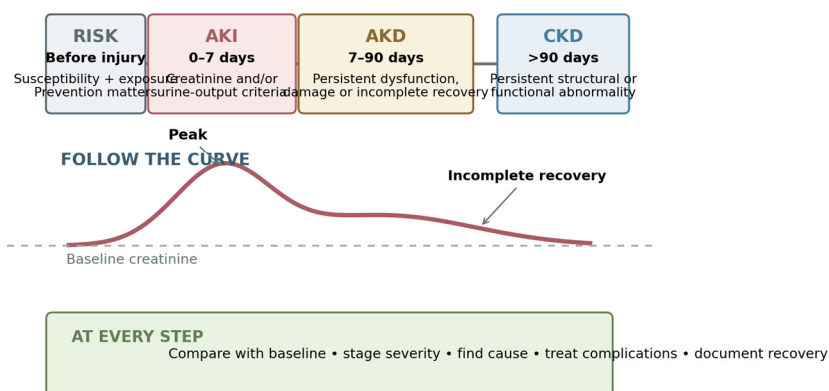


Figure 13.1. *The AKI–AKD–CKD continuum and the importance of following the trajectory rather than one laboratory value.*

13.1 What AKI means

Acute kidney injury is a rapid decrease in kidney excretory function. The word injury does not always mean that kidney tissue is structurally damaged: a reversible fall in filtration caused by altered glomerular hemodynamics can meet the same creatinine criteria. Conversely, real tubular injury may exist before serum creatinine rises. For this reason, AKI is a syndrome defined by functional changes and then explained by clinical evaluation.

KDIGO criterion	AKI is present when any one criterion is met	Student interpretation
Absolute creatinine rise	≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 h	A small absolute rise can be important
Relative creatinine rise	$\geq 1.5 \times$ baseline within the previous 7 days	Requires a credible baseline
Urine output	<0.5 mL/kg/h for ≥ 6 h	Must use patient weight and an accurate time interval

CALCULATE IT

For the case patient, urine output = $180 \text{ mL} \div 75 \text{ kg} \div 8 \text{ h} = 0.30 \text{ mL/kg/h}$. He meets AKI criteria by both creatinine and urine output. His creatinine is $1.7 \times$ baseline, which is stage 1 by creatinine; urine output $<0.5 \text{ mL/kg/h}$ for 8 hours is also stage 1.

13.2 Stage severity using the worst criterion

Stage	Serum creatinine	Urine output
1	$1.5\text{--}1.9 \times$ baseline or rise $\geq 0.3 \text{ mg/dL}$	$<0.5 \text{ mL/kg/h}$ for 6–12 h
2	$2.0\text{--}2.9 \times$ baseline	$<0.5 \text{ mL/kg/h}$ for $\geq 12 \text{ h}$
3	$\geq 3.0 \times$ baseline, or $\geq 4.0 \text{ mg/dL}$, or kidney replacement therapy	$<0.3 \text{ mL/kg/h}$ for $\geq 24 \text{ h}$, or anuria $\geq 12 \text{ h}$

Assign the highest stage reached by either creatinine or urine output. The two criteria often disagree because they measure different aspects of the syndrome. Urine output can change within hours; creatinine generally changes more slowly. A nonoliguric patient can still have severe AKI, and an oliguric patient can have a modest creatinine rise early in the course.

13.3 Why creatinine lags behind GFR

Serum creatinine is the result of production, distribution and elimination. When GFR falls abruptly, creatinine begins to accumulate, but time is required before the new concentration is visible in blood. The delay can be 24–48 hours or longer, especially in a patient with a large volume of distribution. Large-volume fluid administration can further dilute creatinine and temporarily hide the severity of AKI.

THINK IN TRENDS

A creatinine rise from 0.6 to 1.2 mg/dL is a doubling and represents stage 2 AKI even though 1.2 mg/dL may still appear inside a laboratory reference interval. Always compare with the patient's baseline, not only with the population reference range.

Creatinine also becomes an unreliable input for steady-state eGFR equations while it is changing rapidly. Drug dosing should therefore use the direction and speed of creatinine change, urine output, clinical severity and, where available, measured or kinetic estimates rather than treating the reported eGFR as exact.

13.4 Choose the best baseline

1. Prefer a stable outpatient creatinine measured before the acute illness, commonly within the previous 8–365 days.
2. If several stable values exist, use a representative recent value rather than an isolated outlier.
3. An admission value can be used for elective admissions but may already include community-acquired AKI in an emergency admission.
4. Back-calculation from an assumed normal GFR can misclassify older adults and patients with unrecognized CKD; use it cautiously and state the assumption.

13.5 AKI, AKD and CKD are a time continuum

Term	Time frame	Core idea
AKI	Hours to 7 days	Rapid functional change meeting creatinine or urine-output criteria
AKD	Abnormality lasting ≤ 90 days	AKI that has not fully resolved, or another acute/subacute kidney abnormality
CKD	>3 months	Persistent structural or functional kidney abnormality with health implications

The labels describe time, not etiology. A patient can have AKI on CKD. This combination is common and confers less renal reserve, higher risk of complications and a greater probability of incomplete recovery.

13.6 The first assessment: danger, cause and trajectory

1. Look immediately for hyperkalemia, pulmonary edema, severe acidemia, uremic complications and complete obstruction.
2. Confirm the time course using previous creatinine values, urine output, weight and fluid balance.
3. Review exposures: infection, hypotension, surgery, contrast, medicines, toxins and muscle injury.
4. Examine circulation and congestion rather than using the vague label 'dehydrated.'
5. Perform urinalysis and microscopy; quantify protein when glomerular disease is possible.
6. Use ultrasound promptly when obstruction is possible or the cause remains unclear.
7. Reassess after every intervention and document whether creatinine and urine output are improving, stable or worsening.

Pattern	Clues	Typical next step
Hemodynamic	Fluid loss, vasodilation, low output, congestion; bland sediment	Correct the specific circulatory problem and reassess
Tubular injury	Ischemic/toxic exposure; granular casts or tubular cells	Supportive care, remove insult, dose medicines safely
Glomerular	Hematuria, proteinuria, dysmorphic RBCs or RBC casts	Urgent serology and nephrology assessment; consider biopsy
Interstitial	Drug/infection exposure; pyuria or WBC casts	Stop culprit, assess need for biopsy/specific therapy
Postrenal	Retention, anuria, pelvic disease or hydronephrosis	Bladder scan/ultrasound and decompression when indicated

13.7 Recovery is an outcome that must be measured

A falling creatinine is encouraging but does not prove return to baseline. Recovery should be described explicitly: complete, partial or absent, with the comparison value and time stated. The 2026 KDIGO public-review draft proposes complete AKI resolution when creatinine or cystatin C is $<1.2 \times$ baseline within 7 days, and partial resolution when it remains ≥ 1.2 but $<1.5 \times$ baseline. These definitions are provisional until the guideline is finalized.

After discharge, review blood pressure, volume status, creatinine/eGFR, urine albumin and medicines. Higher-risk patients—stage 2–3 AKI, dialysis-treated AKI, incomplete recovery, albuminuria or pre-existing CKD—need earlier and more structured follow-up. Every discharge summary should state the AKI cause, maximum stage, dialysis requirement, recovery status, medication changes and follow-up plan.

Case resolution

The patient has stage 1 AKI by both creatinine and urine-output criteria. Pneumonia and possible sepsis create a hemodynamic and inflammatory risk, but the cause cannot be assumed from the diagnosis alone. The team evaluates perfusion and congestion, checks urinalysis, reviews medicines, treats infection, measures urine output accurately and repeats creatinine and potassium. A stable outpatient value of 1.0 mg/dL is documented as baseline, enabling later assessment of recovery.

Take-home messages

- AKI is diagnosed by change from baseline, not by whether creatinine is outside a reference interval.
- Use the worst creatinine or urine-output stage.
- Creatinine rises late and steady-state eGFR is unreliable during rapid change.
- AKI describes severity and time course; it does not identify the cause.
- Document recovery and arrange follow-up because AKI increases future CKD and cardiovascular risk.

Self-assessment

1. State the three KDIGO diagnostic criteria for AKI.
2. A 60-kg patient produces 240 mL in 12 hours. What is the urine output in mL/kg/h and the AKI urine-output stage?
3. Why can a creatinine of 1.2 mg/dL represent severe change in a patient whose baseline is 0.6 mg/dL?
4. Distinguish AKI, AKD and CKD by time.
5. What information should be included in an AKI discharge summary?

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CHAPTER 14

Prerenal and Hemodynamic Kidney Dysfunction

Understand when kidneys need fluid, pressure, cardiac support or decongestion

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain how arterial pressure, cardiac output and venous congestion affect GFR.
- Distinguish true intravascular depletion from low effective arterial volume and congestion.
- Use a fluid challenge as a monitored test rather than an automatic treatment.
- Recognize medicine-related changes in afferent and efferent arteriolar tone.
- Choose initial fluid, vasopressor or decongestive strategies according to physiology.

Opening case

CLINICAL CASE

A 76-year-old woman with heart failure has dyspnea, raised JVP, bilateral crackles, leg edema and blood pressure 102/66 mmHg. Creatinine increased from 1.3 to 1.8 mg/dL after admission. A colleague proposes repeated saline boluses because the creatinine rose. What physiological problem should be defined first?

Hemodynamic AKI: pressure, flow and congestion

1 PRELOAD

Too little effective circulating volume

Bleeding • GI loss • vasodilation

ACTION: give fluid only when a measurable response is plausible

2 PUMP / TONE

Low cardiac output or low vascular tone

Heart failure • sepsis • anesthesia

ACTION: treat the cause; add vasoactive support after initial fluid when needed

3 BACK PRESSURE

High venous or intra-abdominal pressure

Right-heart failure • fluid overload

ACTION: decongest; more fluid can worsen kidney function

BEDSIDE QUESTION: WILL THIS PATIENT BENEFIT FROM MORE FLUID?

Look for a reversible fluid-loss history and use dynamic reassessment:
blood pressure/MAP • capillary refill • JVP/lungs • passive leg raise • urine output

STOP THE AUTOMATIC BOLUS

A fluid challenge is a monitored diagnostic-therapeutic trial. Stop if there is no hemodynamic benefit or if JVP, crackles, oxygen need or edema worsens.

Figure 14.1. *The three principal hemodynamic routes to reduced kidney filtration: inadequate preload, inadequate forward pressure and excessive venous back pressure.*

14.1 'Prerenal' is a mechanism, not a synonym for dehydration

Hemodynamic kidney dysfunction means that GFR falls because the forces sustaining filtration have changed. Kidney tissue may initially remain structurally intact and filtration can improve rapidly when the circulatory problem is corrected. If ischemia is severe or prolonged, however, functional change can progress to acute tubular injury. The categories therefore overlap in time.

A useful simplification is: renal perfusion pressure depends on arterial inflow pressure minus venous and interstitial back pressure. GFR also depends on afferent and efferent arteriolar tone. This explains why low MAP, low cardiac output and high venous pressure can all reduce filtration, but require different treatments.

14.2 Autoregulation and medicine effects

Factor	Glomerular effect	When AKI risk rises
Prostaglandins	Help dilate the afferent arteriole	NSAIDs block this support during low effective circulation
Angiotensin II	Preferentially constricts the efferent arteriole	ACEi/ARB reduce efferent tone when filtration is pressure-dependent
SGLT2 inhibition	Restores tubuloglomerular feedback and lowers intraglomerular pressure	A small early eGFR dip is expected; severe illness or depletion requires reassessment
Calcineurin inhibitors	Can cause afferent vasoconstriction	High exposure, interacting drugs or volume disturbance

An early creatinine rise after a hemodynamically active medicine is not automatically tubular injury. The task is to decide whether the change is expected and stable or excessive and progressive. A rise >30% after RAAS blockade should prompt evaluation of volume status, NSAID use, renal artery disease and other causes.

14.3 Four bedside hemodynamic phenotypes

Phenotype	Common clues	Initial direction
True volume loss	Bleeding, diarrhea, vomiting, poor intake, orthostasis, low JVP	Control loss; cautious isotonic crystalloid or blood as indicated
Vasodilation	Sepsis/anesthesia, warm peripheries, low vascular tone	Initial fluid if responsive; vasopressor when hypotension persists
Low cardiac output	Cool peripheries, narrow pulse pressure, cardiac disease	Treat pump problem; avoid indiscriminate fluid
Venous congestion	Raised JVP, edema, ascites, crackles, right-heart dysfunction	Decongest and treat cardiac/hepatic cause

CORE DISTINCTION

Edema tells you that extracellular fluid is increased; it does not tell you that arterial circulation is adequate. A patient with heart failure or cirrhosis can be edematous and still have reduced effective arterial volume.

14.4 Decide whether more fluid is likely to help

Static findings are imperfect. Combine history and examination with a dynamic maneuver when possible. Passive leg raising transiently transfers venous blood toward the thorax; an increase in stroke volume or cardiac output suggests fluid responsiveness. Pulse-pressure or stroke-volume variation may help in selected ventilated patients but fails under many common conditions.

1. Define the reason for fluid: suspected volume-responsive hypoperfusion, not simply 'AKI.'
2. Choose the fluid and a finite amount; for example, a small 250–500 mL crystalloid challenge in an adult when appropriate.
3. Define the response before giving it: MAP, capillary refill, stroke volume, mentation or urine output.
4. Stop and reassess if the goal is not achieved or congestion worsens.
5. Record cumulative fluid balance and weight; repeated unrecorded boluses can create harmful overload.

The 2026 KDIGO public-review draft recommends crystalloids rather than colloids for initial intravascular expansion and buffered crystalloids rather than 0.9% saline in most patients at risk of or with AKI, except settings such as traumatic brain injury. This draft recommendation should be interpreted with the indication, serum sodium, chloride, acid–base state and local protocol.

14.5 Pressure and vasopressors

When hypotension persists after appropriate initial fluid, vasopressors restore perfusion pressure without forcing more volume into the interstitium. In critically ill adults at risk of or with AKI, the 2026 KDIGO draft suggests using MAP >65 mmHg as an initial target, then individualizing. Patients with chronic hypertension may require a higher pressure to maintain organ perfusion, whereas excessive vasopressor doses can impair peripheral and splanchnic circulation.

DO NOT USE RENAL-DOSE DOPAMINE

Low-dose dopamine does not prevent or treat AKI and can cause tachyarrhythmia and ischemic complications. It should not be used for 'kidney protection.'

14.6 Sepsis-associated AKI

Sepsis-associated AKI is not explained by simple whole-kidney ischemia. Vasodilation, altered microcirculation, inflammation, endothelial injury, tubular metabolic adaptation, nephrotoxins and venous congestion can coexist. Treat infection rapidly, obtain source control, use physiological fluid resuscitation and vasopressors when indicated, and reassess for evolving intrinsic injury.

14.7 Acute heart failure: decongestion can protect organs

In acute heart failure, elevated central venous pressure can be transmitted to the renal veins and interstitium. This reduces the pressure gradient across the kidney and promotes sodium retention. A modest creatinine rise during effective decongestion may reflect hemoconcentration and altered filtration rather than new tubular damage. If congestion is improving and perfusion remains adequate, automatically stopping diuresis because creatinine rose can leave the major pathogenic problem untreated.

Reassuring during decongestion	Concerning during decongestion
Weight, JVP, edema or oxygenation improve	Progressive hypotension or poor peripheral perfusion
Urine output and natriuretic response are adequate	Oliguria with worsening metabolic complications
Small, stabilizing creatinine rise	Large progressive rise with another injury signal
No new active urine sediment	New hematuria, casts or proteinuria suggesting intrinsic disease

14.8 Cirrhosis and hepatorenal syndrome—AKI

Advanced cirrhosis produces marked splanchnic vasodilation, reduced effective arterial volume and intense renal vasoconstriction. Before diagnosing HRS-AKI, evaluate infection, bleeding, nephrotoxins, hypovolemia, obstruction and intrinsic renal disease. Albumin is used in defined diagnostic/treatment pathways, and vasoconstrictor therapy—preferably terlipressin or norepinephrine according to setting and availability—requires specialist supervision and careful monitoring for ischemic and respiratory adverse effects.

Case resolution

The patient is clinically congested. Her low-normal blood pressure does not prove that she is fluid responsive, and repeated saline could increase renal venous pressure and pulmonary edema. The team assesses perfusion dynamically, reviews medicines and infection, and treats the dominant problem with monitored decongestion and heart-failure management. Creatinine, urine output, weight, JVP, oxygen requirement and electrolytes are followed together.

Take-home messages

- Hemodynamic AKI can result from low arterial pressure, low cardiac output or high venous pressure.
- A fluid bolus is appropriate only when fluid responsiveness and benefit are plausible.
- Use crystalloids for volume expansion and reassess after a finite dose.
- MAP >65 mmHg is a starting critical-care target, not a universal endpoint.
- In congested heart failure, effective decongestion may remain appropriate despite a small creatinine rise.

Self-assessment

1. Why is 'prerenal AKI equals dehydration' an unsafe simplification?
2. How do NSAIDs and ACE inhibitors affect glomerular arteriolar tone?
3. List four findings that would make venous congestion likely.
4. How should a fluid challenge be prescribed and reassessed?
5. Why may creatinine rise during successful decongestion?

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CHAPTER 15

Intrinsic Acute Kidney Injury

Use the clinical setting and urine sediment to identify the injured compartment

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Distinguish tubular, glomerular, interstitial and vascular causes of intrinsic AKI.
- Recognize urine-sediment patterns that support acute tubular injury or glomerulonephritis.
- Identify common causes and immediate management of acute interstitial nephritis.
- Recognize pigment nephropathy and treat rhabdomyolysis safely.
- Know when urgent serology, hematology assessment or kidney biopsy is required.

Opening case

CLINICAL CASE

A 64-year-old man develops septic shock after abdominal surgery. Creatinine rises from 0.9 to 2.4 mg/dL over 48 hours. He remains oliguric after perfusion is restored. Urine microscopy shows renal tubular epithelial cells and coarse granular casts. What kidney compartment is most likely injured?

Intrinsic AKI: let the urine sediment localize the injury

GLOMERULUS	Dysmorphic RBCs • RBC casts albuminuria/proteinuria	GN, vasculitis, anti-GBM disease
TUBULE	Granular “muddy brown” casts renal tubular epithelial cells	Ischemic or toxic acute tubular injury
INTERSTITIUM	Pyuria • WBC casts possible low-grade proteinuria	Drug-associated AIN, infection
VASCULATURE	Hematuria/proteinuria may occur sediment can be nonspecific	TMA, emboli, malignant hypertension
WHEN TO CONSIDER BIOPSY Unexplained or nonrecovering AKI • active sediment • systemic disease suspected treatable glomerular or interstitial process		

A bland sediment does not exclude serious intrinsic disease.

Figure 15.1. Localization of intrinsic AKI using urinary sediment, clinical context and the pattern of kidney involvement.

15.1 Intrinsic AKI is organized by compartment

The kidney contains glomeruli, tubules, interstitium and vessels. Disease in each compartment produces a recognizable combination of clinical context, urine findings and extrarenal features. These patterns are not perfect, but they turn a large differential diagnosis into a manageable bedside problem.

Compartment	High-yield pattern	Examples
Tubular	Ischemic/toxic exposure; granular casts; tubular epithelial cells	Sepsis, shock, aminoglycosides, pigment
Glomerular	Hematuria, proteinuria, dysmorphic RBCs, RBC casts	ANCA vasculitis, anti-GBM disease, immune-complex GN
Interstitial	Drug/infection exposure; pyuria; WBC casts possible	Antibiotics, PPIs, NSAIDs, infection-associated AIN
Vascular	Hypertension, thrombocytopenia/hemolysis, ischemic features	TMA, atheroembolism, malignant hypertension, infarction

15.2 Acute tubular injury

Acute tubular injury is the preferred pathological description for the syndrome often called acute tubular necrosis, because extensive necrosis is not always present. Tubular epithelial cells lose polarity, detach or become dysfunctional; filtrate can leak back, casts obstruct tubular flow, and intrarenal vasoconstriction and inflammation reduce GFR.

The course is often described as initiation, extension, maintenance and recovery, but real patients do not pass through neat phases. Urine output may be low or preserved. During recovery, urine output can rise before tubular concentrating and electrolyte-handling capacity normalizes, creating risks of volume depletion, hypokalemia and hypomagnesemia.

SEDIMENT CLUE

Coarse granular 'muddy brown' casts and renal tubular epithelial cells strongly support acute tubular injury in the correct clinical setting. Their absence does not exclude it, especially when microscopy is delayed or the sample is dilute.

15.3 Ischemic and septic tubular injury

Prolonged hypotension, major surgery, hemorrhage and sepsis are common triggers. The outer medulla is vulnerable because oxygen delivery is limited while active sodium transport consumes energy. In sepsis, microvascular and inflammatory mechanisms may cause tubular dysfunction even when global renal blood flow is not profoundly reduced.

Management is supportive: restore adequate perfusion without causing overload, treat infection and source, avoid additional nephrotoxins, adjust drug doses and manage complications. Neither dopamine nor diuretics reverse tubular injury. Loop diuretics are used only to manage clinically important volume overload.

15.4 Pigment nephropathy and rhabdomyolysis

Myoglobin released from injured skeletal muscle causes renal vasoconstriction, direct tubular toxicity and intratubular cast formation, especially when urine is acidic and flow is low. Rhabdomyolysis is commonly diagnosed when creatine kinase is >5 times the upper reference limit or >1,000 U/L, but AKI risk increases with the total clinical burden rather than one CK threshold.

Clue	Interpretation
Dipstick strongly positive for blood with few/no RBCs	Suggests myoglobin or free hemoglobin
CK markedly elevated	Supports muscle injury; follow the trend
Hyperkalemia, hyperphosphatemia, early hypocalcemia	Reflect release from injured muscle and AKI
Crush, seizure, ischemic limb, extreme exertion, drugs	Search for and treat the precipitating cause

Begin isotonic crystalloid early when the patient is not overloaded, then titrate to hemodynamics and urine output. A trauma consensus suggests a starting adult rate near 400 mL/h, adjusted within roughly 200–1,000 mL/h, with a urine-output goal around 1–3 mL/kg/h up to about 300

mL/h. These are guideposts, not permission for unmonitored high-volume fluid. Stop escalation if anuria or congestion develops.

DO NOT ADD RITUALS WITHOUT EVIDENCE

Routine bicarbonate alkalization, mannitol or loop diuretics have not shown consistent benefit for preventing rhabdomyolysis-associated AKI. Use bicarbonate for a separate acid–base indication and diuretics for volume management, not to force pigment clearance.

15.5 Acute interstitial nephritis

AIN is an inflammatory injury of the interstitium and tubules. Medicines are common causes, but infection, autoimmune disease and immune-checkpoint inhibitors are increasingly important. The classic triad of fever, rash and eosinophilia is uncommon; its absence must not reassure the clinician.

Feature	Teaching point
Timing	Can occur days to weeks after a new drug; latency varies by agent and re-exposure
Urine	Pyuria, WBC casts, microscopic hematuria or modest proteinuria; NSAID-AIN may have heavier proteinuria
Eosinophils	Blood or urine eosinophils are neither sensitive nor specific enough to confirm/exclude AIN
Diagnosis	Kidney biopsy is the reference test when certainty changes treatment
Treatment	Stop the suspected agent; treat infection/immune cause; consider early corticosteroids with nephrology input when appropriate

Evidence for corticosteroids is mainly observational and regimens vary. Earlier treatment after withdrawal of the culprit appears more likely to help than delayed treatment after fibrosis develops, but infection must be excluded and the benefit–risk decision individualized.

15.6 Glomerular emergencies

Rapidly progressive glomerulonephritis can destroy kidney function over days to weeks and may be accompanied by pulmonary hemorrhage. The combination of AKI, hematuria, proteinuria, dysmorphic RBCs or RBC casts should trigger urgent nephrology assessment.

1. Ask about hemoptysis, dyspnea, purpura, sinus/ear disease, arthritis, infection and systemic symptoms.
2. Obtain CBC, blood film, complements, ANCA, anti-GBM antibodies, ANA/dsDNA and infection studies as guided by context.
3. Quantify proteinuria and inspect the urine sediment promptly.
4. Coordinate kidney biopsy rapidly when it can define therapy.
5. If pulmonary–renal syndrome is strongly suspected and the patient is deteriorating, diagnostic and treatment decisions proceed in parallel.

15.7 Vascular intrinsic AKI

Syndrome	Clues	Urgency
Thrombotic microangiopathy	Thrombocytopenia, schistocytes, hemolysis, organ ischemia	Emergency hematology/nephrology pathway; treatment depends on cause
Malignant hypertension	Very high BP with retinal/neurologic injury, hematuria and AKI	Controlled BP reduction with monitored IV therapy
Cholesterol emboli	Recent vascular procedure, livedo, blue toes, eosinophilia	Supportive care and vascular risk management
Renal infarction	Sudden flank pain, hematuria, LDH rise, embolic risk	Urgent imaging and cause-specific vascular therapy

15.8 When biopsy changes the case

Consider kidney biopsy for unexplained or nonrecovering AKI, active glomerular sediment, substantial proteinuria, systemic disease, suspected AIN when treatment is uncertain, or a possible disease requiring immunosuppression. Before biopsy, control blood pressure, review antithrombotic medicines and check hemoglobin, platelets, coagulation and imaging. The question should be explicit: what diagnosis is being distinguished, and how would the result change treatment?

Case resolution

The septic and surgical exposures, persistent oliguria after restoration of perfusion, and granular casts with tubular epithelial cells support acute tubular injury. Further fluid is not given automatically. The team treats infection, maintains adequate pressure, avoids nephrotoxins, doses medicines for changing kidney function, manages volume and electrolytes, and monitors for recovery or dialysis indications.

Take-home messages

- Localize intrinsic AKI to tubules, glomeruli, interstitium or vessels.
- Granular casts and tubular epithelial cells support acute tubular injury.
- AIN often lacks the classic allergic triad; stop the culprit and consider biopsy when treatment depends on certainty.
- Rhabdomyolysis requires early cause-directed fluid when appropriate, not routine bicarbonate or mannitol.
- Active glomerular sediment, pulmonary–renal features or TMA require urgent specialist evaluation.

Self-assessment

1. Which urine findings support acute tubular injury?
2. Why can sepsis cause tubular injury without profound global renal ischemia?
3. What dipstick/microscopy discrepancy suggests myoglobinuria?
4. Why do normal eosinophils not exclude AIN?
5. List four indications to consider kidney biopsy in AKI.

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CHAPTER 16

Obstructive Nephropathy

Exclude a reversible blockage before it causes infection, electrolyte danger or permanent damage

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain how urinary obstruction reduces GFR and damages tubules.
- Localize obstruction to the bladder outlet, ureters or intrarenal collecting system.
- Recognize situations in which ultrasound can be falsely reassuring.
- Identify indications for urgent urinary decompression.
- Monitor and treat post-obstructive diuresis safely.

Opening case

CLINICAL CASE

A 79-year-old man with prostatic symptoms presents with confusion and no urine for 10 hours. Creatinine is 5.8 mg/dL and potassium 6.6 mmol/L. The lower abdomen is tender and distended. What should happen before an elaborate intrinsic-AKI work-up?

Obstructive AKI: find the level and drain when urgent

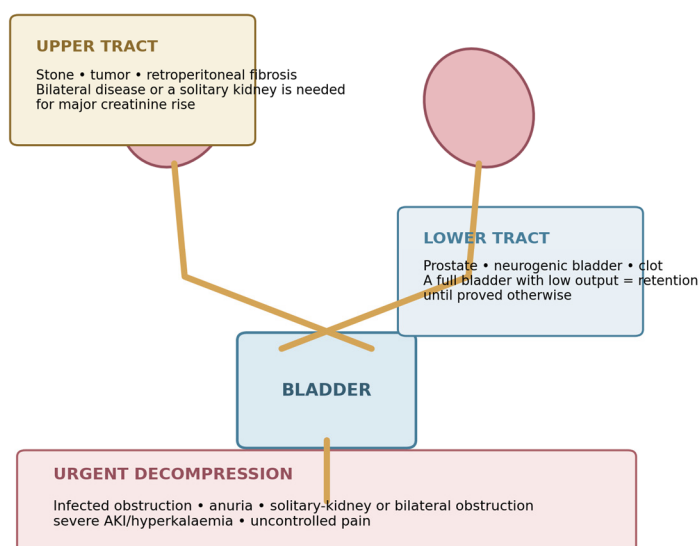


Figure 16.1. Common levels of urinary obstruction and the clinical situations requiring urgent decompression.

16.1 Why obstruction lowers filtration

Urine normally flows down a pressure gradient from tubule to bladder. Obstruction raises pressure upstream. Initially this pressure opposes glomerular filtration; later, renal blood flow falls, tubular transport fails, inflammation and interstitial fibrosis develop. Rapid relief is therefore both diagnostic and therapeutic.

A major creatinine rise usually requires bilateral upper-tract obstruction, obstruction of a solitary functioning kidney, or lower-tract obstruction affecting both kidneys. Unilateral obstruction can still cause pain, infection and permanent loss of function in the affected kidney without a large serum-creatinine change.

16.2 Localize the level

Level	Common causes	Clues
Bladder outlet/urethra	Prostatic enlargement/cancer, stricture, clot, neurogenic bladder, catheter problem	Distended bladder, weak stream, retention, low catheter output
Ureter	Stone, pelvic/retroperitoneal tumor, fibrosis, iatrogenic injury	Colic or silent obstruction; hydronephrosis; cancer/surgical history
Intrarenal	Crystals, papillary sloughing, fungal balls	Drug/metabolic exposure; may be less visible on routine imaging

16.3 First minutes in anuria

1. Confirm that urine was actually measured and inspect the catheter and tubing for kinks, clots or a closed clamp.
2. Palpate/percuss the bladder and perform a bedside bladder scan when retention is possible.
3. If the bladder is full, obtain prompt urethral drainage unless urethral injury is suspected.
4. Check potassium, bicarbonate, ECG and volume status while arranging imaging and definitive drainage.
5. Escalate immediately for infected obstruction, bilateral/solitary-kidney obstruction, anuria or severe metabolic complications.

CATHETER WARNING

Blood at the urethral meatus, pelvic trauma or suspected urethral disruption is a reason not to perform blind urethral catheterization. Obtain urgent urological assessment and appropriate imaging.

16.4 Ultrasound: powerful but not infallible

Renal and bladder ultrasound is the first structural test in most patients because it is rapid, nonionizing and can show hydronephrosis, kidney size and bladder retention. Hydronephrosis describes dilation; it is not identical to clinically significant obstruction. Pregnancy, vesicoureteral reflux and high urine flow can dilate the system without obstruction.

Conversely, important obstruction can exist without hydronephrosis early after onset, in severe dehydration, with retroperitoneal fibrosis or tumor encasement, or when the collecting system cannot dilate. If clinical suspicion remains high, discuss CT or other targeted imaging with radiology/urology rather than closing the diagnosis because one ultrasound is negative.

16.5 Drainage is selected by level and urgency

Problem	Typical decompression	Important point
Bladder outlet retention	Urethral catheter; suprapubic route if needed	Record immediate and subsequent output; do not repeatedly clamp as a routine
Ureteric obstruction	Retrograde ureteric stent or percutaneous nephrostomy	Choice depends on anatomy, infection, stability and local expertise
Infected obstructed system	Urgent drainage plus antibiotics and sepsis care	Antibiotics alone do not provide source control
Clot retention	Large-bore/three-way catheter and irrigation under protocol	Correct bleeding cause and involve urology

If severe hyperkalemia, pulmonary edema or acidemia cannot be controlled quickly, kidney replacement therapy may be required while the obstruction is being relieved. Dialysis does not replace drainage of an infected or mechanically obstructed system.

16.6 Post-obstructive diuresis

After drainage, retained salt and water are excreted and temporarily impaired tubules may be unable to concentrate urine. Post-obstructive diuresis is commonly defined as urine output >200 mL/h for at least 2 consecutive hours or >3 L in 24 hours. It is more likely after bilateral or bladder-outlet obstruction, marked azotemia and volume overload.

1. Measure urine output hourly initially and record fluid balance and weight.
2. Check blood pressure, sodium, potassium, magnesium, phosphate and creatinine frequently.
3. Allow appropriate excretion of excess volume; do not replace every milliliter automatically.
4. If the patient becomes volume depleted, a common starting approach replaces about 50–75% of recent urine losses with a fluid chosen from serum/urine composition, then adjusts to examination and laboratory trends.
5. Reduce replacement as tubular function and urine output normalize.

WHY PARTIAL REPLACEMENT?

Replacing 100% of every urine loss can perpetuate diuresis and prevent removal of previously retained fluid. Replacing too little can cause hypotension, hypernatremia, hypokalemia and recurrent kidney hypoperfusion. The prescription must follow the patient's changing volume state.

16.7 Prognosis after relief

Recovery depends on completeness and duration of obstruction, infection and baseline kidney function. Creatinine can improve rapidly but may not return to baseline after prolonged obstruction. Arrange follow-up of kidney function, electrolytes, blood pressure and the underlying urological cause; a successful catheterization is not a definitive treatment plan for prostatic, neurological or malignant obstruction.

Case resolution

The patient has probable acute urinary retention with life-threatening hyperkalemia. ECG and emergency hyperkalemia treatment occur while the catheter system and bladder are assessed. Bladder drainage is obtained promptly and renal ultrasound evaluates the upper tracts. Urine output, pressure, electrolytes and creatinine are then monitored for post-obstructive diuresis. Urology addresses the cause rather than leaving an indwelling catheter without a plan.

Take-home messages

- Anuria is obstruction until drainage failure and bilateral/solitary-kidney obstruction are actively excluded.
- A large creatinine rise usually requires obstruction affecting both functioning kidneys.
- Ultrasound may be falsely negative early or in nondilated obstruction.
- Infected obstruction requires urgent drainage plus antimicrobials.
- After relief, watch for post-obstructive diuresis and replace losses according to volume and electrolyte trends.

Self-assessment

1. Why may unilateral ureteric obstruction not raise serum creatinine substantially?
2. List four causes of bladder-outlet obstruction.
3. When can significant obstruction occur without hydronephrosis?
4. State two common numerical definitions of post-obstructive diuresis.
5. Why should urine losses not routinely be replaced milliliter for milliliter?

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CHAPTER 17

Nephrotoxins and Contrast-Associated AKI

Identify the mechanism, reduce avoidable exposure and preserve necessary treatment

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

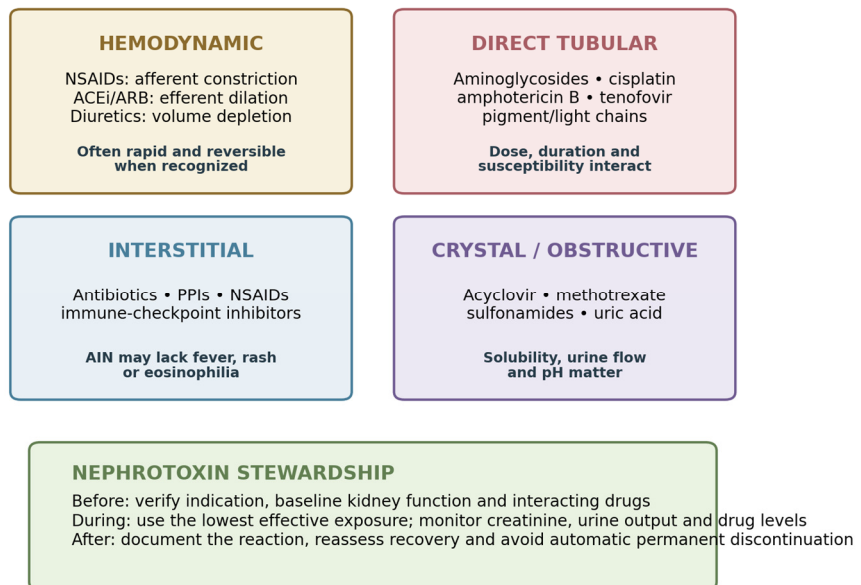
- Classify drug-associated kidney dysfunction by hemodynamic, tubular, interstitial and crystal mechanisms.
- Recognize pseudo-AKI caused by inhibited creatinine secretion.
- Apply nephrotoxin stewardship before, during and after high-risk treatment.
- Distinguish contrast-associated from contrast-induced AKI.
- Use a risk–benefit approach to iodinated contrast rather than reflexively denying useful imaging.

Opening case

CLINICAL CASE

A 68-year-old woman with eGFR 24 mL/min/1.73 m² and sepsis needs contrast-enhanced CT to identify a possible intra-abdominal abscess. The noncontrast study is unlikely to answer the question. Should the scan be cancelled solely because kidney function is reduced?

Nephrotoxins injure kidneys by different mechanisms



The label “nephrotoxic” is incomplete unless the mechanism and clinical context are specified.

Figure 17.1. Major mechanisms of nephrotoxin-associated kidney dysfunction and the stewardship actions that reduce avoidable harm.

17.1 'Nephrotoxic' is not one mechanism

A medicine can reduce GFR without destroying tubules, directly injure tubular cells, trigger immune interstitial inflammation, precipitate as crystals or obstruct urine flow. The mechanism determines the timing, urine findings, reversibility and whether the medicine can later be restarted.

Mechanism	Examples	Typical clues
Hemodynamic	NSAIDs, ACEi/ARB, calcineurin inhibitors, excessive diuresis	Rapid creatinine change; often bland sediment; context of pressure/volume dependence
Direct tubular	Aminoglycosides, cisplatin, amphotericin B, tenofovir	Exposure-related rise; tubular dysfunction or granular casts
Interstitial immune	Beta-lactams, sulfonamides, PPIs, NSAIDs, checkpoint inhibitors	AKI with pyuria/proteinuria; systemic allergy often absent
Crystal/obstructive	Acyclovir, methotrexate, sulfadiazine, uric acid	Crystals, flank pain or abrupt AKI; risk increases with low urine flow
Thrombotic/vascular	Gemcitabine, VEGF-pathway drugs, calcineurin inhibitors	Hypertension, hemolysis/thrombocytopenia or proteinuria

17.2 Pseudo-AKI: creatinine rises but GFR does not fall

Creatinine is secreted by proximal tubules as well as filtered. Trimethoprim, cobicistat, dolutegravir and several targeted anticancer agents inhibit tubular creatinine secretion. Serum creatinine rises, often within days, while true GFR may remain unchanged. Cystatin C, measured GFR, urinalysis and the clinical trajectory can help distinguish pseudo-AKI from injury.

DO NOT ASSUME

A known pseudo-AKI medicine does not protect the patient from real AKI caused by sepsis, hypoperfusion or another nephrotoxin. The diagnosis requires a stable clinical picture and absence of other injury signals.

17.3 High-yield drug patterns

Exposure	Practical prevention/monitoring
Aminoglycoside	Use only when indicated; optimize dosing interval; monitor concentrations and creatinine; avoid additive nephrotoxins
Vancomycin	Use AUC-guided dosing where feasible; review combination therapy and changing kidney function
Amphotericin B	Prefer lipid formulation when appropriate; monitor K ⁺ , Mg ²⁺ and creatinine; saline strategies follow protocol
Cisplatin	Protocolized hydration, magnesium and dose assessment; consider alternatives according to oncological efficacy
Methotrexate	Hydration, urine alkalinization and drug levels for high-dose therapy; urgent glucarpidase/extracorporeal strategy when indicated
NSAID + RAAS blocker + diuretic	The combination reduces autoregulatory reserve during illness; educate, monitor and avoid unnecessary NSAIDs

17.4 Nephrotoxin stewardship

1. Verify that the medicine is indicated and whether a less nephrotoxic option offers similar benefit.
2. Record baseline creatinine/eGFR, urine findings, electrolytes, volume status and interacting medicines.
3. Use the lowest effective dose and duration; apply therapeutic drug monitoring when available.
4. During AKI, reassess renal elimination daily because yesterday's dose may be unsafe today.
5. Stop or adjust the likely culprit, but do not discontinue every evidence-based cardiorenal medicine without a mechanism.
6. Document the suspected reaction and a plan for reassessment or cautious reintroduction when benefit remains important.

17.5 Contrast-associated is not the same as contrast-induced

Contrast-associated AKI (CA-AKI) means AKI occurring after contrast exposure, regardless of cause. Contrast-induced AKI (CI-AKI) means that contrast caused the injury. Hospitalized

patients often have infection, hypotension, surgery and medicines that can explain a creatinine rise; therefore association must not automatically be called causation.

Modern controlled studies suggest that the nephrotoxic risk of intravenous low-osmolar contrast has historically been overstated, particularly when eGFR is ≥ 30 mL/min/1.73 m² and AKI is absent. Risk is higher and uncertainty greater with active AKI, eGFR < 30 , arterial procedures, large exposure and multiple concurrent insults.

17.6 A practical contrast decision

1. Define the diagnostic question and whether contrast materially changes sensitivity, treatment or outcome.
2. Assess active AKI, stable eGFR, volume state, heart failure and concurrent nephrotoxins.
3. If benefit exceeds risk, do not delay a necessary diagnostic or life-saving procedure.
4. Use low- or iso-osmolar contrast and the lowest dose that still provides diagnostic imaging.
5. For high-risk adults without fluid overload, use protocolized periprocedural isotonic saline; individualize or avoid prophylactic volume when congestion risk is high.
6. Reassess creatinine 48–72 hours later when clinically indicated and continue to search for noncontrast causes of AKI.

Intervention	Current teaching
0.9% saline prophylaxis	Recommended for selected high-risk adults without fluid overload; regimen depends on procedure and local protocol
N-acetylcysteine	No consistent benefit; not a substitute for appropriate imaging and volume strategy
Prophylactic dialysis	Not recommended and may be harmful
Metformin	If AKI or eGFR ≤ 30 , withhold at/before iodinated contrast and reconsider after ≥ 48 h when kidney function is stable; if eGFR > 30 without AKI, routine interruption is generally unnecessary
RAAS inhibitors	The 2026 KDIGO draft suggests not routinely withholding them solely for iodinated contrast; individual clinical factors still matter

EMERGENCY PRINCIPLE

Do not withhold contrast-enhanced imaging that is likely to diagnose a life-threatening condition merely because creatinine is elevated. Reduce preventable risk, but preserve the diagnostic benefit.

17.7 Gadolinium in advanced kidney disease

The risk of nephrogenic systemic fibrosis is extremely low with contemporary group II gadolinium agents, even in advanced CKD, but the indication and agent must be selected with radiology. Do not initiate or alter dialysis solely to remove a group II agent. Gadolinium and iodinated contrast have different adverse-effect profiles and should not be discussed as if they were interchangeable.

Case resolution

The CT is likely to identify a drainable abscess and provide source control; the diagnostic benefit exceeds the renal risk. Active sepsis already places the patient at high risk of AKI. The team uses the lowest diagnostic dose of contemporary contrast, avoids unnecessary nephrotoxins, assesses whether isotonic saline is safe, monitors hemodynamics and follows creatinine. Any subsequent AKI is evaluated broadly rather than automatically attributed to contrast.

Take-home messages

- Name the nephrotoxic mechanism; it guides diagnosis and reversibility.
- Some drugs cause pseudo-AKI by inhibiting creatinine secretion.
- Nephrotoxin stewardship preserves necessary therapy while reducing avoidable exposure.
- CA-AKI is a temporal association; CI-AKI requires causal attribution.
- Necessary contrast imaging should proceed when benefit exceeds risk, with targeted prevention in high-risk patients.

Self-assessment

1. List four mechanisms of drug-associated kidney dysfunction.
2. Name three medicines that can raise creatinine by inhibiting secretion.
3. What is the difference between CA-AKI and CI-AKI?
4. Which adults are at greatest risk from iodinated contrast?
5. Why is prophylactic dialysis not used after contrast administration?

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CHAPTER 18

Management of AKI and Kidney Replacement Therapy

Support recovery, treat complications and start dialysis for clinical need—not a creatinine number

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Construct a daily supportive-care prescription for AKI.
- Treat fluid, electrolyte, acid–base and nutritional complications safely.
- Recognize urgent and refractory indications for kidney replacement therapy.
- Compare intermittent, prolonged, continuous and peritoneal modalities.
- Assess recovery and decide when a trial off kidney replacement therapy is appropriate.

Opening case

CLINICAL CASE

A 67-year-old man with septic-shock AKI has creatinine 5.6 mg/dL and urea 168 mg/dL. Potassium is 5.3 mmol/L, pH 7.31, oxygenation is stable and urine output has increased to 45 mL/h. Is the high urea or creatinine alone an indication to begin dialysis today?

AKI management: support recovery and recognize KRT need

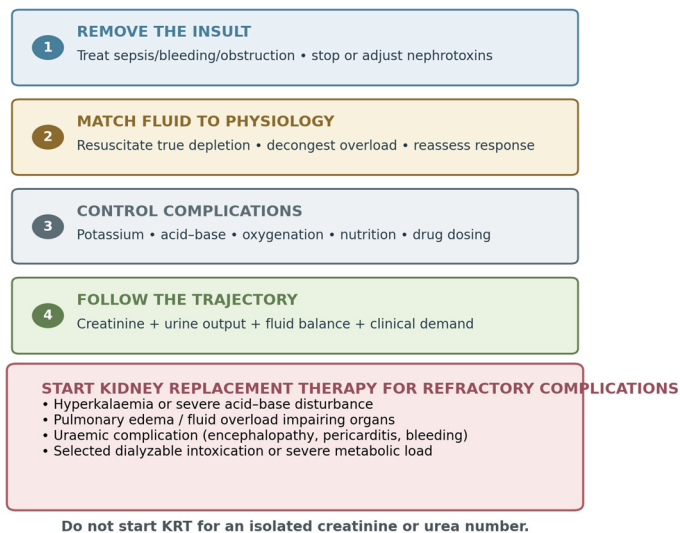


Figure 18.1. A stepwise AKI management bundle and the clinical complications that justify kidney replacement therapy.

18.1 AKI treatment is a daily prescription

1. Treat the cause: infection/source, bleeding, obstruction, hemodynamic failure, inflammation or toxin.
2. Define fluid goals: resuscitation, neutral balance or active decongestion.
3. Review every medicine for indication, nephrotoxicity, renal elimination and restart plan.
4. Monitor creatinine, urine output, fluid balance, weight, potassium, bicarbonate and other context-specific tests.
5. Provide nutrition and glycemic management; prevent infection, thrombosis, bleeding and pressure injury.
6. Ask whether kidney function meets the patient's current metabolic and fluid demand; reassess KRT need and recovery each day.

18.2 Fluid management: one patient, changing phases

Phase	Goal	Common error
Rescue	Restore life-threatening circulatory failure	Giving too little when shock is present
Optimization	Use dynamic response to refine fluid/vasopressor therapy	Repeating boluses without measurable benefit
Stabilization	Avoid unnecessary maintenance and hidden fluid	Ignoring drug/nutrition carrier volumes
De-escalation	Remove accumulated fluid when perfusion permits	Stopping decongestion solely because creatinine rises modestly

Balanced or buffered crystalloids are generally preferred for volume expansion in adults with AKI risk unless a specific indication favors saline, such as some neurological settings. Colloids are not routine initial fluid. Albumin has selected indications—for example, defined cirrhosis pathways—but is not a universal kidney-rescue fluid.

18.3 Diuretics: control volume, not the AKI stage

Loop diuretics can relieve pulmonary and systemic congestion when the patient still produces urine. They do not accelerate tubular recovery or reduce mortality simply by converting oliguric AKI to nonoliguric AKI. Prescribe a dose likely to reach the tubular lumen, define a urine-output or natriuretic response and stop escalating ineffective therapy.

FUROSEMIDE STRESS TEST

In selected stable patients with early AKI and adequate circulation, 1.0 mg/kg IV furosemide if loop-naïve or 1.5 mg/kg if recently exposed can assess tubular functional reserve. Urine output <200 mL over 2 hours predicts higher risk of progression. It is a prognostic test—not a treatment mandate—and should not be performed in hypovolemia or obstruction.

18.4 Electrolyte and acid–base complications

Problem	First principles	When KRT becomes likely
Hyperkalemia	ECG; calcium for toxicity; shift; remove potassium; repeat for rebound	Persistent/recurrent severe hyperkalemia despite medical therapy
Metabolic acidemia	Treat shock, sepsis, ketoacidosis or toxin; consider bicarbonate in selected severe acidosis	Severe acidemia that remains refractory or limits resuscitation
Pulmonary edema	Oxygen/ventilatory support; vasodilator/diuretic when appropriate	Hypoxemia or organ dysfunction despite medical decongestion
Uremia	Look for syndrome, not a urea threshold	Encephalopathy, pericarditis, bleeding or severe symptoms attributable to uremia

The 2026 KDIGO public-review draft suggests IV bicarbonate rather than KRT for severe metabolic acidosis with pH <7.20 when no other urgent KRT indication is present. This is provisional guidance and requires attention to sodium load, carbon dioxide generation, ionized calcium and volume status.

18.5 Nutrition and drug dosing

Prefer enteral nutrition when feasible. Do not restrict protein merely to delay dialysis; this worsens muscle loss and malnutrition. At the other extreme, very high protein delivery is not automatically beneficial in critically ill adults with AKI. Use a dietitian and critical-care nutrition targets appropriate to illness severity and KRT losses.

Drug dosing is difficult because GFR is changing, extracorporeal clearance may vary and critical illness changes volume of distribution. Loading doses are often determined by volume of distribution and should not automatically be reduced; maintenance dose and interval depend more on clearance. Reassess after every major creatinine, urine-output or KRT-prescription change.

18.6 When to start kidney replacement therapy

Start KRT for a clinical demand that exceeds the kidneys' and medical therapy's capacity. Do not use an isolated creatinine, urea value or AKI stage as an automatic trigger.

Indication	Examples
Refractory electrolyte disturbance	Severe hyperkalemia or other dangerous dyskalemia not controlled medically
Refractory acid–base disturbance	Severe acidemia despite cause-directed and appropriate bicarbonate therapy
Refractory fluid overload	Pulmonary edema/hypoxemia or organ dysfunction despite diuretics/medical therapy
Uremic complication	Encephalopathy, pericarditis, bleeding, severe nausea or neurological confounding
Dialyzable toxin/metabolic load	Selected intoxications, tumor lysis, severe hyperammonemia or hypercatabolism according to context

TIMING EVIDENCE

In adults with moderate-to-severe AKI but no urgent complication, large trials support a deferred/watchful strategy rather than pre-emptive KRT. Planning should begin before crisis—nephrology referral, transfer and access preparation—but some patients recover without dialysis.

18.7 Choose the modality for the patient

Modality	Strengths	Limitations / preferred context
Intermittent hemodialysis (IHD)	Rapid solute and potassium removal; treatment-free intervals	Can cause hypotension/osmotic shifts; useful when rapid clearance is needed and tolerated
Prolonged intermittent KRT (PIRRT/SLED)	Slower than IHD; flexible and resource-efficient	Requires prolonged session; useful bridge for hemodynamic instability
Continuous KRT (CKRT/CRRT)	Gentle continuous fluid/solute control	Continuous access, anticoagulation and staffing; preferred with severe instability or raised ICP risk
Acute peritoneal dialysis	No vascular access; valuable where extracorporeal resources are limited	Less predictable rapid clearance; limitations after some abdominal conditions

The 2026 KDIGO draft suggests CRRT or acute PD over conventional IHD in hemodynamically unstable critically ill adults, and prefers CRRT when acute brain injury or cerebral edema makes rapid osmotic shifts hazardous. Modality can change as physiology changes.

18.8 Essentials of an acute KRT prescription

Component	Teaching value
Access	Temporary nontunneled dialysis catheter for most acute extracorporeal KRT; select site/length to provide reliable flow and reduce complications
Dose	For adult CRRT, deliver effluent 20–25 mL/kg/h; prescribe more if needed to account for downtime
Fluid removal	Set a patient-specific net ultrafiltration goal and revise it frequently; 'zero' machine balance is not zero total balance
Anticoagulation	Regional citrate is preferred for CRRT when available and not contraindicated; follow calcium and acid–base protocol
Solution	Select potassium, bicarbonate, phosphate and calcium composition according to current laboratory goals
Monitoring	Hemodynamics, access/circuit, delivered dose, electrolytes, phosphate, magnesium, temperature and drug clearance

DELIVERED DOSE MATTERS

CRRT interruptions for procedures, clotting or access dysfunction reduce delivered clearance. A prescription of 25 mL/kg/h does not guarantee delivery of 25 mL/kg/h; review effective treatment time and effluent actually delivered.

18.9 When and how to stop KRT

Assess recovery every day. Improvement in the underlying illness, rising spontaneous urine output, stable fluid balance and falling interdialytic creatinine support a trial off KRT. The key question is whether native kidney function can meet current fluid and metabolic demand without recurrent complications.

The 2026 KDIGO draft lists urine output >450 mL/24 h without diuretics or >2,300 mL/24 h with diuretics, and a 2-hour creatinine clearance ≥ 23 mL/min, as predictors of successful discontinuation in adults. These are provisional predictors, not mandatory rules. Diuretics may manage fluid after stopping KRT but have not been proven to cause kidney recovery.

1. Pause KRT when immediate indications have resolved and recovery is plausible.
2. Track urine output, fluid balance, potassium, bicarbonate, urea/creatinine trajectory and symptoms.
3. Avoid unnecessary fluid or protein restriction that hides the kidney's ability to meet demand.
4. Restart KRT if refractory metabolic or fluid complications recur.
5. If dialysis dependence persists toward discharge, plan appropriate access, outpatient dialysis and repeated recovery assessment; do not prematurely label end-stage kidney disease.

Case resolution

The patient has high creatinine and urea but no refractory electrolyte, acid–base, fluid or uremic complication. Urine output is improving and infection is being controlled. Dialysis is not started solely for the numbers. The team continues close monitoring and prepares for KRT if demand exceeds recovery. If potassium, acidemia, pulmonary edema or uremic manifestations become refractory, treatment begins without waiting for a higher creatinine.

Take-home messages

- AKI care is a daily cause, fluid, medicine, complication and recovery prescription.
- Diuretics treat volume overload; they do not heal tubular injury.
- Start KRT for refractory clinical complications, not an isolated creatinine or urea value.
- Choose modality according to hemodynamics, neurological risk, required clearance and resources.
- Reassess delivered dose, net ultrafiltration and the possibility of KRT discontinuation every day.

Self-assessment

1. List six components of a daily AKI supportive-care prescription.
2. What does the furosemide stress test predict, and what is a poor response?
3. List five categories of KRT indication.
4. Why is CRRT often preferred in severe hemodynamic instability or raised intracranial pressure?
5. Which clinical findings support a trial off KRT?

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PART IV

Chronic Kidney Disease

Classify risk, protect remaining function, treat complications and prepare before crisis

HOW TO USE PART IV

CKD is not a creatinine value and it is not simply 'chronic renal failure.' Describe every patient with three coordinates—cause, GFR category and albuminuria category—then estimate risk, apply kidney- and cardiovascular-protective treatment, look for complications and plan ahead. The clinical aim is not only to delay dialysis, but to preserve life, function and treatment choices.

CHAPTER 19

Definition Classification and Prognosis of CKD

Name the disease correctly and use risk—not stage alone—to guide action

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Apply the CKD definition and confirm chronicity without delaying appropriate treatment.
- Classify CKD by cause, GFR category and albuminuria category.
- Explain why eGFR and albuminuria provide different prognostic information.
- Recognize clinically important changes in eGFR and albuminuria.
- Use kidney-failure risk to guide referral, multidisciplinary care and preparation.

Opening case

CLINICAL CASE

A 62-year-old man with hypertension and type 2 diabetes has eGFR 52 mL/min/1.73 m² and urine ACR 420 mg/g. Six months earlier, eGFR was 55 and ACR was 380 mg/g. He feels well. Does he have CKD? How should it be classified, and why is the urine result as important as the eGFR?

Classify CKD with three coordinates: Cause + GFR + Albuminuria

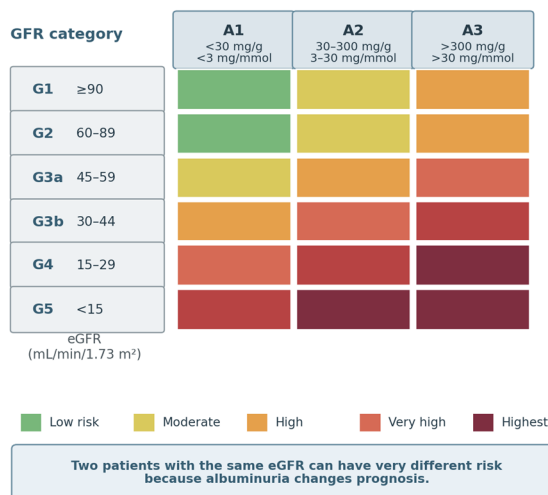


Figure 19.1. The KDIGO cause–GFR–albuminuria framework. Risk increases as eGFR falls and albuminuria rises; the colors support follow-up intensity but do not replace clinical judgment.

19.1 What CKD means

Chronic kidney disease is an abnormality of kidney structure or function that has been present for at least 3 months and has implications for health. The definition contains three questions. Is there an abnormality? Has it persisted long enough to be chronic? Does it matter clinically?

Route to the diagnosis	Examples	Important clarification
Reduced filtration	eGFR <60 mL/min/1.73 m ² for ≥3 months	This alone qualifies as CKD even if ACR is normal
Marker of kidney damage	ACR ≥30 mg/g; urine sediment abnormality; persistent hematuria of renal origin	Can diagnose CKD even when eGFR is ≥60
Structural or pathological abnormality	Polycystic kidneys, reflux scarring, biopsy abnormality, previous kidney transplant	The cause should be named whenever possible
Tubular disorder	Persistent electrolyte or acid–base abnormality caused by tubular disease	A normal creatinine does not exclude kidney disease

STUDENT MENTAL MODEL

CKD can be present because the filter is slower, because the kidney is damaged, or both. eGFR describes filtration; ACR describes glomerular barrier injury and carries independent kidney and cardiovascular risk.

19.2 Confirm chronicity

A single low eGFR or high ACR does not prove CKD. It may reflect AKI, acute kidney disease, exercise, fever, urinary infection, menstruation or laboratory variability. Chronicity can be demonstrated by results separated by at least 3 months, previous records, long-standing imaging abnormalities, or pathology showing fibrosis and atrophy.

1. Look for previous creatinine, eGFR, ACR, PCR, urinalysis and blood-pressure values.
2. Ask whether an acute illness, medication change, obstruction or volume disturbance could explain the result.
3. Repeat eGFR and ACR at an interval determined by clinical urgency; use a first-morning ACR when possible.
4. Use ultrasound, history and sometimes biopsy or genetic testing to establish cause.
5. Begin appropriate protective treatment at first presentation when CKD is already highly likely; confirmation should not become a reason for therapeutic delay.

DO NOT WAIT THREE MONTHS IN DANGER

Active urine sediment, rapidly falling eGFR, severe hypertension, nephrotic syndrome, obstruction, hyperkalemia or systemic disease requires prompt evaluation. The three-month rule distinguishes chronicity; it is not a waiting period for urgent care.

19.3 Classify with CGA

KDIGO classification uses Cause, GFR category and Albuminuria category—CGA. A useful diagnosis therefore reads: 'CKD due to diabetic kidney disease, G3a A3,' not simply 'stage 3 CKD.'

G category	eGFR mL/min/1.73 m ²	Description
G1	≥90	Normal or high; CKD requires another marker of damage
G2	60–89	Mildly decreased; CKD requires another marker of damage
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

A category	Urine ACR	Description
A1	<30 mg/g (<3 mg/mmol)	Normal to mildly increased
A2	30–300 mg/g (3–30 mg/mmol)	Moderately increased
A3	>300 mg/g (>30 mg/mmol)	Severely increased

Albuminuria is a continuous risk marker; category boundaries simplify communication. An ACR of 299 mg/g and 301 mg/g are biologically similar, so interpret the value, trend and context—not only the label.

19.4 Prognosis is two-dimensional

Lower eGFR predicts impaired excretory and endocrine capacity. Higher albuminuria signals glomerular injury and predicts faster kidney decline and cardiovascular events. A patient with G2 A3 disease may be at greater risk than a patient with G3a A1 disease. This is why every CKD assessment needs both eGFR and ACR.

MONITORING THRESHOLDS

In a person with CKD, an eGFR change >20% on a subsequent test exceeds expected variability and warrants evaluation. After a hemodynamically active treatment, a fall >30% warrants evaluation. A doubling of ACR exceeds expected laboratory variability and warrants evaluation.

19.5 Follow the slope, not two isolated dots

The eGFR slope is the rate of change over time, expressed in mL/min/1.73 m² per year. It is more informative when calculated from several stable outpatient measurements than from two values around an acute illness. A small early dip after RAAS blockade or an SGLT2 inhibitor can be functional and reversible; a sustained downward slope suggests progression.

WORKED TRAJECTORY

eGFR values are 48, 44 and 40 mL/min/1.73 m² at 0, 12 and 24 months. The approximate slope is $(40 - 48) \div 2 = -4$ mL/min/1.73 m²/year. If unchanged, this patient may reach advanced CKD within a few years, but prediction must also incorporate ACR, age, cause, competing mortality and treatment response.

19.6 Use absolute kidney-failure risk

For adults with CKD G3–G5, use an externally validated risk equation such as the four-variable Kidney Failure Risk Equation (KFRE). The four variables are age, sex, eGFR and urine ACR. The result estimates the probability of treated kidney failure over 2 or 5 years; it does not predict every important CKD outcome and is not validated for G1–G2.

KDIGO 2024 risk threshold	Possible use in care	Meaning for the student
5-year risk 3%–5%	Support nephrology referral	Adds to eGFR, ACR, cause and clinical red flags
2-year risk >10%	Time multidisciplinary CKD care	Dietitian, pharmacist, education and complication management may be needed
2-year risk >40%	Begin modality education and KRT preparation	Consider access planning and transplant referral before a crisis

Risk thresholds guide organization of care; they do not replace referral for uncertain cause, active urine sediment, hereditary disease, refractory hypertension, recurrent hyperkalemia or rapidly progressive loss.

19.7 Who should be screened

Test people at increased risk using both eGFR and urine ACR. High-yield groups include diabetes, hypertension, cardiovascular disease, previous AKI, structural urinary disease, systemic inflammatory disease, family history of kidney disease and exposure to nephrotoxins. A negative dipstick does not reliably exclude A2 albuminuria.

Case resolution

The patient has persistent abnormalities for more than 3 months. His diagnosis is CKD due to probable diabetic and hypertensive kidney disease, G3a A3. The eGFR indicates moderately reduced filtration, while A3 albuminuria identifies high kidney and cardiovascular risk and a strong indication for protective therapy. His KFRE should be calculated, the cause reviewed for atypical features, and eGFR plus ACR followed as a trajectory.

Take-home messages

- CKD requires an abnormality of kidney structure or function for at least 3 months.
- Describe CKD by cause, GFR category and albuminuria category.
- eGFR and ACR measure different dimensions of disease and prognosis.
- An eGFR change >20% or ACR doubling warrants evaluation in established CKD.
- Use validated kidney-failure risk in G3–G5 to guide referral and preparation.

Self-assessment

1. Can a patient with eGFR 95 mL/min/1.73 m² have CKD? Give two examples.
2. Classify a patient with eGFR 38 and ACR 12 mg/mmol.
3. Why does one abnormal ACR not automatically prove CKD?
4. What four variables are used in the four-variable KFRE?
5. State the KDIGO 2024 two-year risk threshold used to support KRT preparation.

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CHAPTER 20

Slowing CKD Progression

Combine kidney protection, cardiovascular prevention and complication control

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain the main mechanisms that accelerate nephron loss.
- Construct a layered treatment plan for an adult with CKD.
- Use RAAS inhibitors and SGLT2 inhibitors safely.
- Interpret the early eGFR dip after hemodynamically active treatment.
- Set practical blood-pressure, sodium, protein and activity goals.

Opening case

CLINICAL CASE

A 58-year-old woman has CKD G3b A3, blood pressure 148/84 mmHg, potassium 4.7 mmol/L and eGFR 37 mL/min/1.73 m². She takes amlodipine but no ACE inhibitor, ARB or SGLT2 inhibitor. She asks for the single best tablet to protect her kidneys. How should the answer be framed?

Slowing CKD progression: protect the nephron in layers

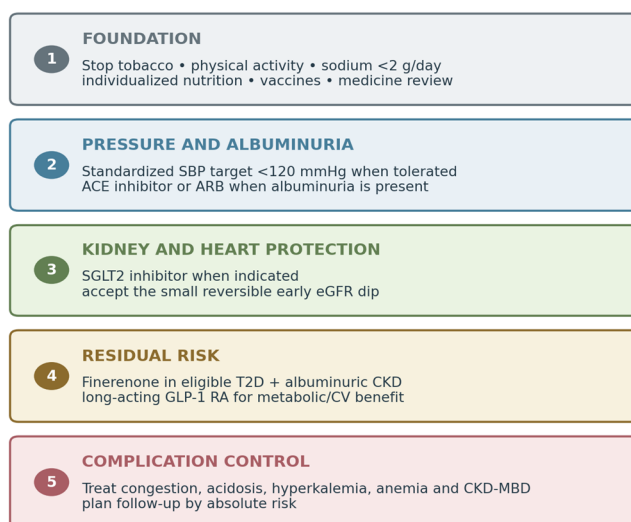


Figure 20.1. Layered CKD protection. Each layer addresses a different driver of kidney or cardiovascular risk; the treatment plan is stronger than any single drug.

20.1 Why CKD progresses

When nephrons are lost, the remaining nephrons filter more to maintain total GFR. This adaptation is useful in the short term, but increased intraglomerular pressure and flow can injure the filtration barrier. Albumin then enters the tubule, where it activates inflammatory and fibrotic pathways. Hypertension, hyperglycemia, sodium retention, obesity, smoking, repeated AKI and ongoing disease-specific injury accelerate this cycle.

PLAIN-LANGUAGE MODEL

Imagine fewer workers carrying the same total load. Each remaining nephron works harder. Treatment protects the surviving nephrons by lowering the pressure and workload inside each glomerulus, controlling the original disease and preventing new injuries.

20.2 Blood pressure: measure correctly before treating a target

KDIGO suggests a standardized office systolic blood pressure target <120 mmHg for adults with high blood pressure and CKD when tolerated. Standardized measurement means quiet rest, a validated device, correct cuff, supported posture and repeated readings. A casual clinic value is not equivalent. Less intensive treatment may be safer with symptomatic orthostasis, frailty, high fall risk or very limited life expectancy.

Clinical situation	Preferred foundation	Practical note
Albuminuria A2 or A3	ACE inhibitor or ARB	Use the highest approved tolerated dose
A1 without another indication	Dihydropyridine CCB or diuretic may be used	ACEi/ARB can still be indicated for heart failure or hypertension
Volume expansion	Dietary sodium reduction plus a diuretic	Thiazide-like agents lose natriuretic power as GFR falls; loop diuretics are often needed in advanced CKD
Resistant hypertension	Confirm adherence, standardized/out-of-office BP and diuretic adequacy	Search for secondary causes and interfering drugs

20.3 RAAS inhibition reduces glomerular pressure

ACE inhibitors and ARBs dilate the efferent arteriole. This lowers pressure inside the glomerular capillary and reduces albumin leakage. Because filtration pressure falls, creatinine may rise modestly before stabilizing. The same hemodynamic effect that produces the early change contributes to long-term protection.

1. Start an ACE inhibitor or ARB for CKD G1–G4 with A3 albuminuria without diabetes; consider it for A2 without diabetes.
2. Use an ACE inhibitor or ARB for CKD G1–G4 with diabetes and A2 or A3 albuminuria.
3. Titrate toward the highest approved tolerated dose.
4. Check blood pressure, creatinine and potassium within 2–4 weeks after initiation or dose increase; use earlier review when risk is high.
5. Continue unless creatinine rises >30% within 4 weeks, symptomatic hypotension occurs, or hyperkalemia remains uncontrolled despite treatment.

WHAT NOT TO DO

Do not combine an ACE inhibitor with an ARB or direct renin inhibitor. Do not stop RAAS blockade automatically for a potassium value that can be managed or simply because eGFR has fallen below 30 mL/min/1.73 m².

20.4 SGLT2 inhibitors protect beyond glucose lowering

SGLT2 inhibitors increase sodium delivery to the macula densa, restore tubuloglomerular feedback and reduce glomerular hyperfiltration. Their kidney and heart benefits occur in people with and without diabetes. The glucose-lowering effect weakens at low eGFR, but organ protection persists.

KDIGO 2024 indication	Strength	Student interpretation
T2D + CKD with eGFR ≥20	Recommend	Use unless contraindicated or not tolerated
Adult CKD with eGFR ≥20 and ACR ≥200 mg/g	Recommend	Applies with or without diabetes
Heart failure with CKD	Recommend	Benefit is independent of albuminuria
eGFR 20–45 with ACR <200 mg/g	Suggest	Benefit is supported but certainty is lower

Once started, continuing below eGFR 20 is reasonable until kidney replacement therapy begins, if tolerated. Withhold during prolonged fasting, major surgery or critical illness because ketosis risk rises. Counsel about genital mycotic infection and the rare possibility of euglycemic ketoacidosis.

EARLY EGFR DIP

A small, reversible fall in eGFR after an SGLT2 inhibitor reflects reduced intraglomerular pressure and is usually not a reason to stop. Evaluate a fall >30%, marked volume depletion, hypotension, obstruction, nephrotoxins or another cause of AKI.

20.5 Treat residual cardiorenal risk

In adults with type 2 diabetes, eGFR >25, normal potassium and persistent albuminuria >30 mg/g despite maximum tolerated RAAS blockade, KDIGO suggests a nonsteroidal mineralocorticoid receptor antagonist with proven benefit, currently finerenone. It can be combined with RAAS and SGLT2 therapy, but potassium must be monitored.

A long-acting GLP-1 receptor agonist with cardiovascular benefit is recommended in type 2 diabetes when individualized glycemic targets are not achieved despite metformin and an SGLT2 inhibitor, or when those drugs cannot be used. These agents can also support weight reduction and reduce cardiovascular risk.

20.6 Lifestyle is treatment, not decoration

Area	Teaching target	Why it matters
Sodium	<2 g sodium/day, equivalent to <5 g salt/day	Lowers BP, congestion and albuminuria; individualize in sodium-wasting disease
Protein	About 0.8 g/kg/day in CKD G3–G5	Avoid >1.3 g/kg/day in people at risk of progression; prevent malnutrition
Activity	≥150 min/week moderate intensity if tolerated	Improves cardiovascular health, function and weight
Tobacco	Do not use tobacco products	Reduces vascular and kidney risk
Diet pattern	More plant-based, less ultraprocessed food	May reduce sodium, acid load and cardiometabolic risk; potassium advice must be individualized

WORKED PROTEIN TARGET

For a stable 70-kg adult with CKD G4, 0.8 g/kg/day is about 56 g protein/day. This means grams of protein, not grams of food: 100 g of meat contains roughly 20–30 g protein. Do not prescribe restriction in a patient who is metabolically unstable, undernourished or losing muscle without specialist dietetic support.

20.7 Protect the plan during illness

Medication review should identify NSAIDs, herbal toxins, duplicate RAAS blockade and renally cleared drugs. If a medication is temporarily stopped during vomiting, severe dehydration, surgery or critical illness, document exactly when it should be restarted. Failure to restart beneficial therapy can produce long-term harm.

20.8 Measure response

Follow blood pressure, symptoms, weight, eGFR, potassium and ACR. The aim is not a perfectly flat creatinine every week. Successful treatment may produce an early functional dip followed by a slower long-term slope, lower albuminuria and fewer heart-failure or cardiovascular events.

EVIDENCE IN NUMBERS

In DAPA-CKD, dapagliflozin reduced the primary kidney/cardiovascular composite from 14.5% to 9.2% over a median 2.4 years (HR 0.61; NNT 19). In EMPA-KIDNEY, empagliflozin reduced kidney-disease progression or cardiovascular death by 28% (HR 0.72). Trial populations and endpoints differ, so these numbers illustrate class benefit rather than predict an individual patient's exact response.

Case resolution

No single tablet is the complete answer. She needs standardized blood-pressure assessment, an ACE inhibitor or ARB titrated with creatinine and potassium monitoring, and an SGLT2 inhibitor if no contraindication. Sodium intake, volume status, cardiovascular prevention, adherence and disease-specific causes must also be addressed. A modest early eGFR dip may be acceptable; a >30% fall requires evaluation.

Take-home messages

- Progression reflects both the original disease and maladaptive stress on surviving nephrons.
- Use standardized BP measurement; aim for SBP <120 mmHg when tolerated.
- RAAS blockade and SGLT2 inhibitors reduce intraglomerular pressure and albuminuric risk.
- An early hemodynamic eGFR dip can coexist with long-term benefit.
- Lifestyle, cardiovascular prevention, complication control and safe prescribing belong in the same plan.

Self-assessment

1. Why can ACE inhibitor treatment raise creatinine yet protect the kidney?
2. When should creatinine and potassium be checked after starting an ACE inhibitor or ARB?
3. Name three KDIGO 2024 indications for an SGLT2 inhibitor in CKD.
4. What fall in GFR after hemodynamically active therapy warrants evaluation?
5. Calculate the daily protein target at 0.8 g/kg for an 85-kg adult.

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CHAPTER 21

Diabetes and Kidney Disease

Recognize the usual pattern, search for atypical disease and sequence organ-protective therapy

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Screen for CKD in diabetes using both eGFR and urine ACR.
- Use the terms diabetes with CKD, diabetic kidney disease and diabetic nephropathy precisely.
- Explain the hemodynamic and metabolic mechanisms of diabetic kidney disease.
- Distinguish a typical diabetic kidney disease pattern from red flags for another diagnosis.
- Construct an integrated treatment sequence using RAAS blockade, SGLT2 inhibition, GLP-1 receptor agonism and finerenone.
- Adjust glycemic assessment and medication choices as GFR declines.

Opening case

CLINICAL CASE

A 49-year-old woman has had type 2 diabetes for 11 years. Her ACR rose from 85 to 260 mg/g over 18 months and eGFR fell from 78 to 62 mL/min/1.73 m². Urine sediment is bland and diabetic retinopathy is present. HbA1c is 8.1%. Does she need a kidney biopsy, and which treatments protect organs rather than only lower glucose?

Diabetes with kidney disease: expected pattern or another diagnosis?

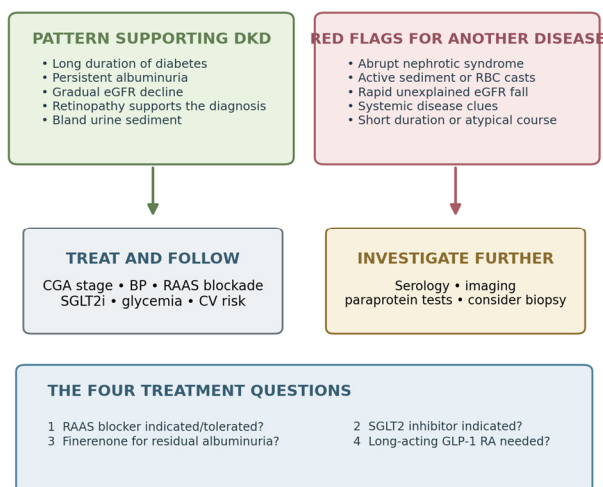


Figure 21.1. A reasoning pathway for kidney disease in diabetes. A typical pattern supports clinical diagnosis; red flags should trigger evaluation for another or additional kidney disease.

21.1 Use the correct term

The terms diabetic kidney disease and diabetic nephropathy are often used interchangeably in older articles and in everyday clinical language. That usage can hide an important distinction. Diabetic kidney disease is a clinical diagnosis; diabetic nephropathy is, when terminology is used precisely, a pathological diagnosis.

Term	When to use it	Important qualification
Diabetes with CKD	The patient has both diabetes and CKD, but the cause of CKD is uncertain	This neutral wording avoids premature attribution
Diabetic kidney disease (DKD)	CKD is clinically attributed to diabetes from the overall pattern and after considering alternatives	Kidney biopsy is not required; DKD includes albuminuric and nonalbuminuric phenotypes
Diabetic nephropathy	Kidney biopsy demonstrates the characteristic lesions caused by diabetes	Use this as the precise pathology term, although some literature still uses it as a synonym for DKD
Nondiabetic kidney disease	Another renal disease explains all or part of the kidney abnormality	It may occur alone or together with diabetic nephropathy

TERMINOLOGY RULE FOR THIS BOOK

Use diabetic kidney disease for the usual clinical diagnosis. Use diabetic nephropathy when characteristic diabetic lesions are demonstrated on kidney biopsy. If attribution is uncertain, write diabetes with CKD until the cause is clarified.

21.2 Screening and clinical diagnosis

Diabetic kidney disease is CKD attributed to diabetes after integrating diabetes duration, persistent albuminuria, eGFR trajectory, retinopathy, urine sediment and competing diagnoses. A typical pattern raises confidence, but diabetes does not make every kidney abnormality diabetic.

Who to screen	Tests	Frequency principle
Type 2 diabetes	eGFR plus urine ACR	Begin at diagnosis; repeat at least annually
Type 1 diabetes	eGFR plus urine ACR	Begin 5 years after diagnosis; repeat at least annually
Established CKD	eGFR, ACR, potassium and treatment-specific tests	More often when risk is high or results change management

Confirm ACR ≥ 30 mg/g on a subsequent first-morning sample unless the presentation is clearly chronic. Fever, strenuous exercise, marked hyperglycemia, urinary infection, menstruation and heart failure can transiently increase albuminuria.

21.3 How diabetes injures the kidney

Diabetic kidney disease is not simply glucose leaking through a damaged glomerulus. It is a whole-nephron disorder in which hemodynamic overload, metabolic stress, inflammation and fibrosis reinforce one another. Glomeruli, arterioles, tubules, interstitium and the microcirculation are all involved.

Hemodynamic pathway

Hyperglycemia increases the filtered glucose load. The proximal tubule responds by reabsorbing more glucose together with sodium, largely through SGLT2. Less sodium chloride reaches the macula densa, so tubuloglomerular feedback behaves as if filtration were too low. Local nitric oxide and prostaglandin signals favor afferent arteriolar dilation, while intrarenal RAAS activity can maintain efferent arteriolar tone. The pressure inside the glomerular capillaries and single-nephron GFR therefore rise.

Early in diabetes, total kidney size and measured GFR may increase by roughly 10%–20%. Studies often define hyperfiltration using measured GFR values around 125–140 mL/min/1.73 m² or more, but no universal cutoff exists because normal GFR varies with age, sex, body size and method. Hyperfiltration is therefore a physiological clue, not a diagnostic criterion. Persistent capillary pressure stretches the filtration barrier and promotes albumin leakage and segmental scarring.

Metabolic and inflammatory pathway

Excess intracellular glucose activates several overlapping pathways: advanced glycation end products bind RAGE; protein kinase C, the polyol and hexosamine pathways become more

active; and mitochondrial reactive oxygen species increase. These signals reduce normal nitric-oxide biology and activate NF- κ B, JAK-STAT and inflammasome pathways. Cytokines, chemokines, TGF- β , connective-tissue growth factor, VEGF and endothelin then promote inflammation, abnormal permeability and extracellular-matrix accumulation. The important student concept is that hyperglycemia leaves a biochemical signal that continues to drive injury even before serum creatinine changes.

Glomerular cellular injury

The glomerular endothelium loses part of its negatively charged glycocalyx and becomes more permeable. Podocytes cannot divide adequately to cover an expanding glomerular surface; they hypertrophy, lose slit-diaphragm proteins such as nephrin, detach and are not replaced. The glomerular basement membrane thickens and the mesangial matrix expands. When podocyte coverage becomes insufficient, exposed capillary segments adhere to Bowman capsule and glomerulosclerosis develops. Albuminuria is therefore both a marker of barrier injury and a mediator of downstream tubular inflammation.

Tubular hypoxia and fibrosis

The proximal tubule uses more oxygen to reabsorb the increased glucose and sodium load. At the same time, endothelial dysfunction and peritubular capillary rarefaction reduce oxygen delivery. This mismatch creates relative hypoxia, mitochondrial stress and tubular inflammatory signaling. Filtered albumin and other proteins further activate tubular cells. Tubular atrophy and interstitial fibrosis become the final common pathway that most closely tracks irreversible loss of GFR.

How diabetes injures the whole nephron

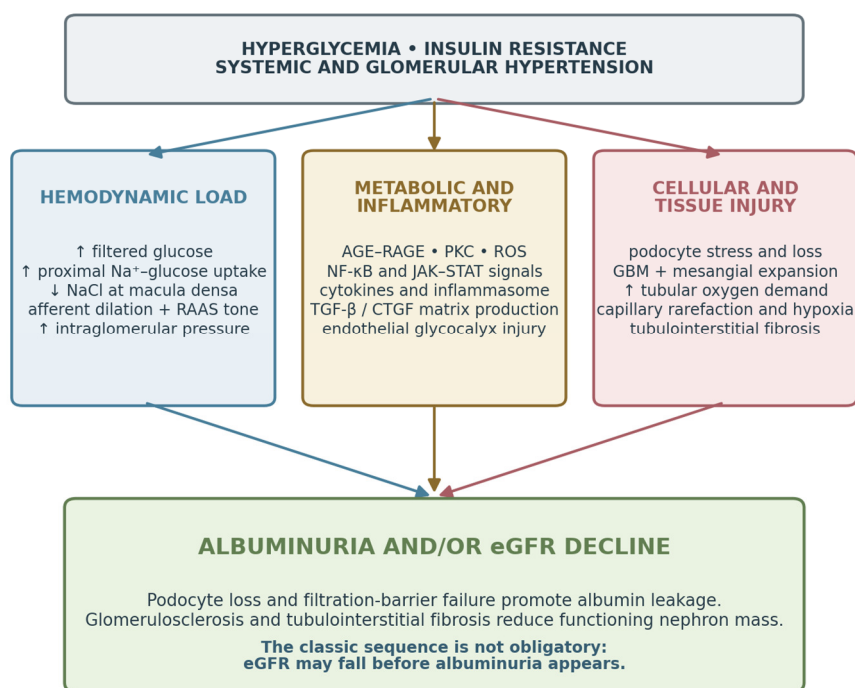


Figure 21.2. Diabetic kidney disease is a whole-nephron process. Hemodynamic, metabolic and cellular pathways converge on albuminuria, glomerulosclerosis and tubulointerstitial fibrosis.

Dominant mechanism	Tissue consequence	Clinical expression	Treatment connection
Glomerular hyperfiltration and pressure	Barrier stretch and glomerulosclerosis	High GFR early; later albuminuria	RAAS blockade and SGLT2 inhibition lower intraglomerular pressure
AGEs, oxidative stress and inflammation	Endothelial injury and matrix accumulation	Gradual ACR rise and cardiovascular risk	Glycemic control, and SGLT2 inhibition finerenone reduce selected relevant pathways
Podocyte loss	Slit-diaphragm failure and segmental sclerosis	Persistent albuminuria or nephrotic-range proteinuria	Lowering albuminuria stress pressure and reduces further
Tubular oxygen demand and capillary loss	Tubular atrophy and interstitial fibrosis	Progressive eGFR decline, sometimes without albuminuria	Avoid AKI and nephrotoxins; preserve organ-protective therapy

The clinical course is heterogeneous

The traditional sequence—hyperfiltration, moderately increased albuminuria, severely increased albuminuria, falling GFR and kidney failure—is useful but not obligatory. Albuminuria may regress, remain stable or never become prominent. Especially in older adults with type 2 diabetes, eGFR may fall with ACR persistently below 30 mg/g. Conversely, albuminuria may be present while eGFR remains preserved. This is why both ACR and eGFR must be followed.

What diabetic nephropathy looks like on biopsy

The Renal Pathology Society classification describes four glomerular classes. Class I has isolated glomerular basement-membrane thickening detectable by electron microscopy. Class II has mesangial expansion, mild in IIa and severe in IIb. Class III has at least one convincing Kimmelstiel–Wilson nodular lesion without the advanced global sclerosis of class IV. Class IV has advanced diabetic glomerulosclerosis involving more than 50% of glomeruli. Arteriolar hyalinosis, including efferent arteriolar involvement, and the degree of interstitial fibrosis and tubular atrophy are also reported because they support diagnosis and prognosis.

MECHANISM TO TREATMENT

RAAS blockade dilates the efferent arteriole. SGLT2 inhibition reduces proximal sodium-glucose reabsorption and restores macula-densa feedback. Finerenone limits mineralocorticoid-receptor-mediated inflammation and fibrosis. These mechanisms explain why a small early eGFR dip can accompany long-term organ protection.

21.4 When to suspect another kidney disease

Finding	Why it is atypical	Possible next step
RBC casts or dysmorphic hematuria	Suggests active glomerular inflammation	Urgent serology and nephrology review
Abrupt nephrotic syndrome	Typical DKD usually evolves gradually	Evaluate membranous disease, amyloid, FSGS and other causes
Rapid unexplained eGFR fall	May indicate AKI, obstruction, vascular or inflammatory disease	Medication review, ultrasound, sediment, serology
Systemic clues	Rash, arthritis, low complement, paraprotein or infection suggests another process	Targeted testing; consider biopsy
Very short diabetes duration	Insufficient exposure for usual DKD pattern, especially in type 1 diabetes	Reconsider attribution

Absence of retinopathy does not exclude diabetic kidney disease in type 2 diabetes, but it lowers confidence when other atypical features are present. Kidney biopsy is considered when the result could reveal a treatable alternative and change management.

21.5 Glycemic monitoring in CKD

HbA1c remains useful, but accuracy decreases in advanced CKD and dialysis because shortened red-cell survival, iron deficiency, ESA therapy, transfusion and acidosis alter the

relationship between glucose and hemoglobin glycation. Continuous or self-monitored glucose helps when HbA1c does not match symptoms or capillary readings.

Tool	Strength	Limitation in CKD
HbA1c	Familiar estimate of chronic glycemia	Less reliable in G4–G5, dialysis, anemia, ESA use or recent transfusion
Continuous glucose monitoring	Shows time in range and hypoglycemia	Access, cost and interpretation burden
Capillary glucose	Immediate treatment decisions	Limited picture unless measured systematically

KDIGO recommends an individualized HbA1c target ranging from <6.5% to <8.0% for people with diabetes and CKD not treated with dialysis. A lower target suits patients with long life expectancy and low hypoglycemia burden; a higher target suits frailty, severe comorbidity or high hypoglycemia risk.

21.6 Build therapy in layers

1. Foundation: nutrition, activity, weight, tobacco avoidance, standardized BP control and statin-based cardiovascular prevention.
2. RAAS blockade: ACE inhibitor or ARB for hypertension with A2–A3 albuminuria, titrated to the highest tolerated approved dose.
3. SGLT2 inhibitor: use in type 2 diabetes with CKD and eGFR ≥ 20 mL/min/1.73 m² unless contraindicated.
4. Glycemic therapy: metformin is generally usable at eGFR ≥ 30 , with dose review below 45 and temporary withholding in acute hypoxic, septic or dehydrating illness.
5. Long-acting GLP-1 receptor agonist: add for unmet individualized glycemic goals or when metformin/SGLT2 therapy cannot be used; prioritize agents with proven cardiovascular benefit.
6. Finerenone: consider when eGFR >25 , potassium is normal and albuminuria >30 mg/g persists despite maximum tolerated RAAS blockade; monitor potassium.

DO NOT SEQUENCE TOO SLOWLY

High-risk patients can lose months or years while clinicians wait for one treatment to be maximized before discussing the next. Introduce indicated therapies in a deliberate sequence over weeks, with safety monitoring, rather than one drug per annual visit.

21.7 Practical safety points

Treatment	Monitor	Pause or reassess when
ACE inhibitor / ARB	BP, creatinine, potassium in 2–4 weeks	Creatinine rises $>30\%$, symptomatic hypotension or uncontrolled hyperkalemia
SGLT2 inhibitor	Volume symptoms, genital infection, ketosis risk	Major surgery, prolonged fasting or critical illness
Finerenone	Potassium and eGFR according to product/guideline protocol	Potassium rises outside the safe treatment range
GLP-1 receptor agonist	GI tolerance, weight, glucose-lowering combination	Persistent vomiting/dehydration or severe intolerance
Metformin	eGFR and acute illness	eGFR <30 or major acute hypoxic/septic/dehydrating risk

SGLT2 inhibitors rarely cause euglycemic ketoacidosis. Suspect it with nausea, abdominal pain, tachypnea or high anion-gap acidosis even when glucose is not markedly elevated. Ketones and acid–base status—not glucose alone—make the diagnosis.

21.8 What landmark trials add

Large trials show that organ protection is not captured by HbA1c alone. DAPA-CKD and EMPA-KIDNEY demonstrated kidney benefit from SGLT2 inhibitors across broad CKD populations. The pooled FIDELITY analysis found finerenone reduced the cardiovascular composite by about 14% and the kidney composite by about 23% in type 2 diabetes with CKD. In FLOW, weekly semaglutide reduced the primary kidney/cardiovascular death composite by 24% (HR

0.76). Different entry criteria and endpoints mean the percentages should not be compared as if the trials were head-to-head.

Case resolution

Her long diabetes duration, retinopathy, gradual albuminuria rise, slow eGFR decline and bland sediment support diabetic kidney disease. Biopsy is not routinely needed unless an atypical feature emerges. Treatment should combine standardized BP control, maximally tolerated RAAS blockade, an SGLT2 inhibitor, individualized glucose management and cardiovascular prevention. A long-acting GLP-1 receptor agonist is appropriate for glycemic and cardiorenal benefit; finerenone is considered if albuminuria persists and potassium permits.

Take-home messages

- Use DKD for the clinical syndrome and reserve diabetic nephropathy for characteristic biopsy-proven lesions when precise terminology matters.
- Screen with both eGFR and ACR because the classical albuminuria-first sequence is not obligatory.
- Hemodynamic overload, metabolic signaling, podocyte loss and tubulointerstitial hypoxia act together.
- Do not attribute active sediment, abrupt nephrotic syndrome or rapid decline automatically to diabetes.
- Organ-protective therapy is layered: RAAS blockade, SGLT2 inhibition, GLP-1 receptor agonism and selected finerenone.

Self-assessment

1. Distinguish diabetes with CKD, diabetic kidney disease and diabetic nephropathy.
2. How does increased proximal sodium-glucose reabsorption cause glomerular hyperfiltration?
3. Why can eGFR decline in diabetes without preceding albuminuria?
4. List four findings that should make you consider another or additional kidney disease.
5. State the usual eGFR thresholds for starting an SGLT2 inhibitor and for metformin, and the main eligibility features for finerenone.

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CHAPTER 22

Cardiovascular Disease and CKD

Treat the heart and kidneys as one connected circulation

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

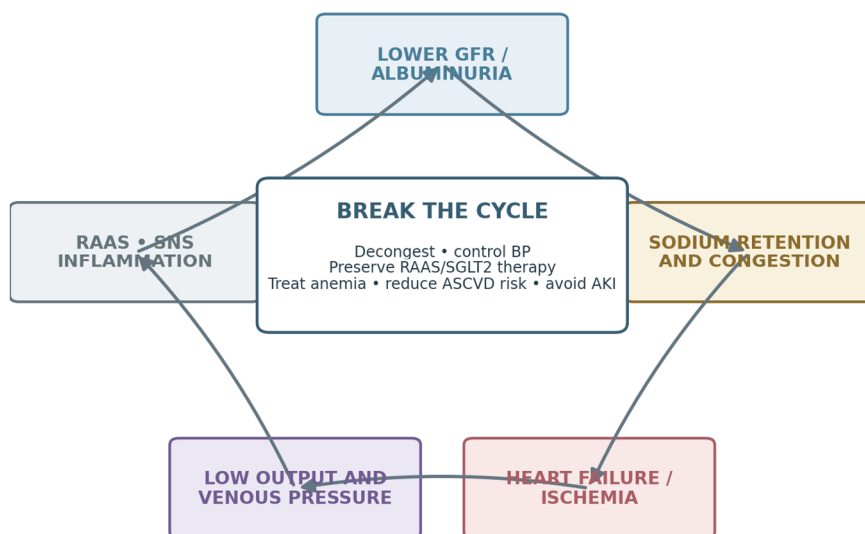
- Explain why CKD increases atherosclerotic, heart-failure and arrhythmic risk.
- Assess congestion and distinguish it from true intravascular depletion.
- Use diuretics and kidney-protective heart-failure therapy without reacting to creatinine alone.
- Interpret troponin and natriuretic peptides as clinical trajectories.
- Apply basic lipid, antiplatelet and anticoagulant principles in CKD.

Opening case

CLINICAL CASE

A 73-year-old man with CKD G4 and HFrEF is admitted with orthopnea, edema and elevated jugular venous pressure. After IV loop diuretics, he loses 3.2 kg and breathes better, but creatinine rises from 2.2 to 2.6 mg/dL. Should decongestion stop?

CKD and cardiovascular disease amplify each other



A modest creatinine rise during effective decongestion may coexist with clinical improvement.

Figure 22.1. The cardiorenal cycle. Lower GFR, neurohormonal activation, congestion and heart dysfunction reinforce one another; treatment aims to interrupt several links at once.

22.1 CKD is a cardiovascular risk state

Cardiovascular disease is a leading cause of illness and death in CKD. Risk rises with lower eGFR and higher albuminuria. Traditional factors—age, diabetes, hypertension, dyslipidemia and smoking—combine with CKD-related factors such as sodium retention, inflammation, anemia, endothelial dysfunction, vascular calcification and disordered mineral metabolism.

TWO CARDIOVASCULAR PHENOTYPES

Think of both atherosclerotic disease—myocardial infarction, stroke and peripheral arterial disease—and nonatherosclerotic disease—heart failure, left-ventricular hypertrophy, arrhythmia and sudden death. CKD promotes both.

22.2 Cardiorenal syndrome in plain language

The kidney needs forward arterial perfusion and low enough venous pressure to drain. Heart failure can lower cardiac output, but venous congestion is often equally important: high renal venous pressure reduces the filtration gradient and activates sodium-retaining pathways. The result is more congestion, which further stresses the heart and kidney.

Bedside domain	Findings supporting congestion	Findings supporting depletion
History	Orthopnea, rapid weight gain, abdominal fullness	Thirst, vomiting, diarrhea, poor intake
Examination	Raised JVP, edema, ascites, crackles, warm/cool congestion	Orthostasis, flat neck veins, dry mucosa, low filling
Trend	Weight gain, positive balance, increasing diuretic requirement	Weight loss without intent, negative balance, low intake
Ultrasound where skilled	Venous congestion, lung B-lines, plethoric IVC in context	Small collapsible IVC is supportive but not definitive

22.3 Diuresis in CKD

Loop diuretics must reach the tubular lumen, so a higher dose is often required when GFR is low. Define success by urine output, urine sodium when used, weight, symptoms and physical signs—not by whether any urine appears. If response is inadequate, confirm dose and administration, review sodium intake and adherence, and consider sequential nephron blockade under close electrolyte monitoring.

CREATININE DURING DECONGESTION

A modest creatinine rise can occur because plasma volume and intraglomerular pressure fall while total-body congestion improves. If dyspnea, JVP, edema and weight improve without hypotension or another AKI cause, do not stop effective decongestion solely because creatinine rose. Reassess the whole patient.

22.4 Guideline-directed heart-failure therapy

CKD should not automatically exclude evidence-based heart-failure therapy. RAAS inhibition or ARNI, beta-blockade, SGLT2 inhibition and mineralocorticoid receptor antagonism are considered according to ejection fraction, potassium, blood pressure and eGFR. Start carefully, monitor soon and address hyperkalemia rather than reflexively removing life-prolonging therapy.

Treatment	Kidney-related issue	Safe-practice principle
ACEi/ARB/ARNI	Early creatinine rise and hyperkalemia	Accept a modest stable change; evaluate >30% and monitor potassium
SGLT2 inhibitor	Small early eGFR dip; volume effects	Review diuretic/volume status; benefit persists at low eGFR within indications
MRA	Hyperkalemia risk rises as eGFR falls	Use eligibility criteria and scheduled potassium monitoring
Loop diuretic	Higher threshold dose in advanced CKD	Treat congestion; titrate to response rather than a familiar dose

22.5 Troponin and natriuretic peptides

Baseline troponin can be chronically elevated in CKD because structural heart disease is common and clearance/fragment handling differs. A single elevated value does not diagnose acute myocardial infarction, but neither does CKD make troponin meaningless. Use symptoms, ECG, imaging and a rise/fall pattern with the assay-specific pathway.

BNP and NT-proBNP may be higher with lower GFR, older age, atrial fibrillation and structural heart disease. Low values can still help exclude acute heart failure, while high values must be interpreted against prior values, congestion and treatment response. There is no universal 'renal correction factor.'

COMMON MISTAKE

Do not dismiss chest pain because 'troponin is always high in CKD.' Serial change and the clinical syndrome remain essential.

22.6 Atherosclerotic prevention

Statin-based therapy lowers major vascular events in nondialysis CKD, although relative benefit becomes smaller at very low eGFR and initiation in dialysis has not shown the same benefit. KDIGO 2024 emphasizes choosing a statin-based regimen that achieves substantial LDL reduction rather than chasing an unvalidated CKD-specific LDL target.

Question	Practical answer
Statin in nondialysis CKD?	Usually indicated according to age and cardiovascular risk; CKD strengthens the case
Start statin routinely after dialysis begins?	Evidence for initiating solely because of dialysis is weak; continue established therapy according to guideline context
Aspirin for secondary prevention?	Use low-dose aspirin for established ischemic cardiovascular disease unless contraindicated
Aspirin for primary prevention?	Net benefit is uncertain because bleeding risk may offset vascular benefit

22.7 Coronary disease, PAD and anticoagulation

Do not undertreat acute coronary syndromes because CKD increases procedural and bleeding risk; use the same diagnostic framework while adjusting renally cleared medicines and contrast strategy. In stable stress-test-confirmed ischemic heart disease, intensive medical therapy can be an appropriate initial alternative to an invasive strategy.

Peripheral arterial disease is often silent in CKD; examine pulses, feet and skin, ask about exertional symptoms and protect against ulceration. For atrial fibrillation, estimate stroke and bleeding risk and select an anticoagulant plus dose using the product-specific renal method. eGFR and creatinine clearance are not interchangeable for every drug.

Case resolution

The patient is clinically decongesting: weight, dyspnea and venous pressure are improving. A creatinine rise of 0.4 mg/dL should trigger reassessment of blood pressure, perfusion, medications and alternative AKI causes, but not automatic cessation of diuresis. If congestion persists and he remains hemodynamically stable, continue goal-directed decongestion with close electrolyte and kidney-function monitoring.

Take-home messages

- eGFR and albuminuria identify both kidney and cardiovascular risk.
- Venous congestion can lower GFR even when total body fluid is excessive.
- Treat the patient's congestion trajectory, not creatinine in isolation.
- Troponin and natriuretic peptides require clinical context and serial interpretation.
- Use statin-based therapy and secondary-prevention aspirin appropriately while individualizing bleeding and drug-dosing risk.

Self-assessment

1. Name four CKD-specific contributors to cardiovascular disease.
2. How can venous congestion reduce GFR?
3. Why may loop-diuretic doses need to be higher in advanced CKD?
4. How should an elevated troponin be interpreted in CKD?

5. What is the role of low-dose aspirin in secondary versus primary prevention?

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CHAPTER 23

Anemia in CKD

Correct iron and reversible causes before deciding how to stimulate erythropoiesis

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain the major mechanisms of anemia in CKD.
- Evaluate anemia without assuming that CKD is the only cause.
- Interpret ferritin and transferrin saturation together.
- Choose oral or intravenous iron using CKD stage, response and patient factors.
- Describe safe ESA and HIF-PHI principles and minimize unnecessary transfusion.

Opening case**CLINICAL CASE**

A 66-year-old woman with CKD G4 reports fatigue. Hemoglobin is 9.4 g/dL, MCV 86 fL, reticulocyte count is low, ferritin 145 ng/mL and TSAT 14%. CRP is elevated. Is iron deficiency excluded because ferritin is not low? Should an ESA be started immediately?

Anemia in CKD: production, iron access and blood loss

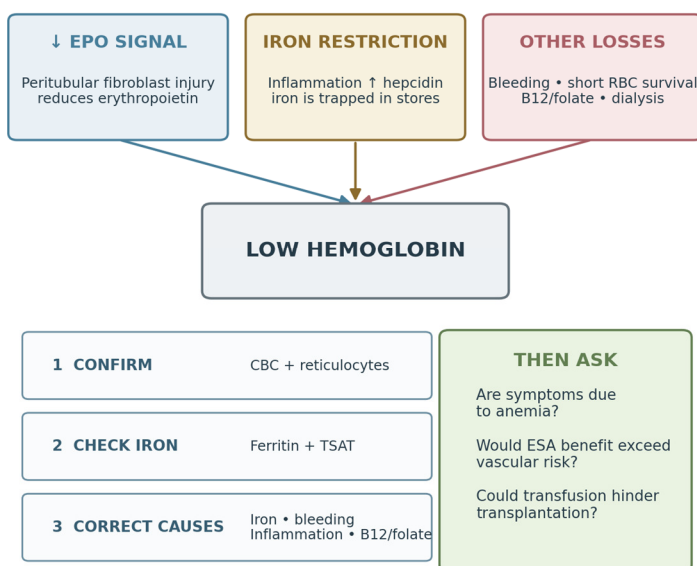


Figure 23.1. The main mechanisms and clinical sequence in CKD anemia. Low EPO signaling, restricted access to stored iron and additional blood loss frequently coexist.

23.1 Definition and pattern

KDIGO 2026 uses hemoglobin <13 g/dL in adult males and <12 g/dL in adult females to diagnose anemia. CKD anemia is usually normocytic and hypoproliferative, but morphology does not prove the cause. Microcytosis suggests iron deficiency or hemoglobinopathy; macrocytosis suggests B12/folate deficiency, alcohol, liver disease, hypothyroidism or marrow disease.

Anemia becomes more common as GFR falls, but its severity varies. A hemoglobin of 8 g/dL in CKD G3 should not be accepted as 'renal anemia' without a full search for blood loss, inflammation, deficiency, hemolysis or marrow disease.

23.2 Why CKD causes anemia

1. Reduced erythropoietin signaling: injured peritubular fibroblast-lineage cells produce an inadequate EPO response for the degree of anemia.
2. Iron restriction: inflammation raises hepcidin, which reduces intestinal absorption and traps iron in macrophages and stores.
3. Absolute iron loss: gastrointestinal bleeding, phlebotomy, dialysis-circuit loss and menstruation deplete total iron.
4. Shortened red-cell survival: uremic and inflammatory factors reduce erythrocyte lifespan.
5. Additional contributors: B12 or folate deficiency, severe hyperparathyroidism, hypothyroidism, infection, medications and bone-marrow disease.

FERRITIN IS A STORAGE AND INFLAMMATION MARKER

A normal or high ferritin does not guarantee that iron is available to marrow. In inflammation, ferritin may rise while TSAT falls. This pattern is often called iron-restricted erythropoiesis or functional iron deficiency.

23.3 Initial evaluation

Test	Question answered	High-yield interpretation
CBC and indices	Is anemia present and what is the morphology?	Look for other cytopenias that suggest marrow/systemic disease
Reticulocytes	Is marrow production appropriate?	Low/inappropriately normal count supports hypoproliferation
Ferritin + TSAT	Are stores low and is circulating iron available?	Interpret together and with inflammation
Smear, LDH, haptoglobin	Is there hemolysis or abnormal morphology?	Order when clinical or CBC clues are present
B12, folate, CRP, TSH, liver tests	Is there a reversible nonrenal cause?	Select according to presentation; broaden when anemia is unexplained
Bleeding evaluation	Is iron being lost?	GI, gynecologic or urologic evaluation according to symptoms and risk

23.4 Iron deficiency: two useful patterns

Pattern	Typical laboratory picture	Meaning
Systemic/absolute iron deficiency	Ferritin <100 ng/mL in CKD G1–G5 or <200 ng/mL in G5HD; TSAT often <20%	Total body iron stores are low
Iron-restricted erythropoiesis	Ferritin >100–200 ng/mL with TSAT <20%	Iron exists in stores but is not adequately available to marrow
Severe iron deficiency	Ferritin <45 ng/mL	Search for clinically important blood loss according to age, sex and symptoms

Ferritin and TSAT are imperfect, but remain the standard practical tests. Do not label all high-ferritin, low-TSAT states as iron overload; inflammation commonly produces this combination.

23.5 When and how to give iron

For CKD not receiving hemodialysis, KDIGO 2026 suggests starting iron when ferritin is <100 ng/mL with TSAT <40%, or ferritin is 100–300 ng/mL with TSAT <25%. Choose oral or intravenous therapy according to severity, venous access, tolerance, cost, preferences and need for rapid response. Switch from oral to IV iron if an adequate trial is ineffective or not tolerated.

For CKD G5 receiving hemodialysis, IV iron is usually preferred. KDIGO suggests initiation when ferritin ≤500 ng/mL and TSAT ≤30%, with proactive scheduled dosing supported by PIVOTAL-type evidence in appropriate patients.

WITHHOLD THRESHOLDS

Withhold routine iron if ferritin is >700 ng/mL or TSAT $\geq$ 40%, and consider temporarily suspending iron during systemic infection. These are safety boundaries, not proof that tissue iron overload begins at one exact value.

Context	Monitoring principle
Hemodialysis	Check hemoglobin, ferritin and TSAT about monthly during active management
CKD not receiving dialysis	Check iron indices about every 3 months during therapy, and sooner when clinically indicated
IV ferric carboxymaltose or similar risk	Monitor phosphate with repeated exposure or susceptibility to hypophosphatemia

23.6 ESA therapy: replace a missing signal safely

Before ESA therapy, correct iron deficiency and other reversible causes. In maintenance dialysis, hemoglobin $\leq$ 9–10 g/dL is a reasonable initiation range, individualized by symptoms, transfusion avoidance and thrombotic risk. In nondialysis CKD, initiation is individualized; for most adults it is considered around 8.5–10 g/dL rather than at a single universal number.

For adults treated with an ESA, maintain hemoglobin below 11.5 g/dL, typically 10–11.5 g/dL. Higher targets do not restore normal physiology and increase hypertension, stroke and vascular-access thrombosis. Use the lowest dose that achieves the clinical purpose.

RATE MATTERS

Aim for a gradual rise. If hemoglobin increases by more than about 1 g/dL in 2 weeks, reduce the ESA dose by approximately 25%–50%. Suspend and reassess during acute stroke, access thrombosis or another thromboembolic event.

23.7 ESA hyporesponsiveness

When hemoglobin does not rise despite increasing ESA dose, do not continue escalation blindly. Look for iron restriction, inflammation or infection, occult blood loss, inadequate dialysis, severe hyperparathyroidism, hemolysis, B12/folate deficiency, malignancy, marrow disease and nonadherence. Treating the cause is safer than pursuing a number with very high ESA doses.

23.8 HIF prolyl hydroxylase inhibitors

HIF-PHIs are oral drugs that stabilize hypoxia-inducible factors and stimulate endogenous EPO-related pathways. KDIGO 2026 suggests an ESA rather than a HIF-PHI as first-line erythropoietic therapy because ESA outcome experience is longer. A HIF-PHI may be considered when ESA is not tolerated, response is inadequate or parenteral administration is impractical.

Avoid or use extreme caution with active malignancy, recent cardiovascular or thrombotic events, proliferative retinal disease, pulmonary hypertension, pregnancy and ADPKD according to agent and guidance. Do not combine an ESA and HIF-PHI. Stop a HIF-PHI if an adequate erythropoietic response is absent after 3–4 months.

23.9 Transfusion is a clinical decision

Transfusion can rapidly correct severe or unstable anemia but carries volume, reaction, infection and alloimmunization risks. Alloimmunization can make future kidney transplantation more difficult. Do not use an arbitrary hemoglobin threshold for stable chronic CKD; use symptoms, active bleeding, ischemia, hemodynamic stability, treatment response and transplant plans.

Case resolution

Her TSAT of 14% shows poor circulating iron availability despite ferritin 145 ng/mL, which may be raised by inflammation. Investigate the inflammatory source and blood loss, and treat iron deficiency according to CKD context and route preference. An ESA is not the first automatic step; reassess symptoms and hemoglobin after correctable causes and iron have been

addressed. If ESA is later used, the goal is symptom/transfusion reduction, not normalization above 11.5 g/dL.

Take-home messages

- Anemia in CKD is usually multifactorial; never stop at the label 'renal anemia.'
- Ferritin may be raised by inflammation, so interpret it with TSAT.
- Correct iron and other reversible causes before starting or escalating an ESA.
- Individualize ESA initiation and keep adult maintenance hemoglobin below 11.5 g/dL.
- Avoid unnecessary transfusion, especially in potential transplant candidates.

Self-assessment

1. What hemoglobin values define anemia in adult men and women in KDIGO 2026?
2. Explain why ferritin may be normal while TSAT is low in CKD.
3. State the KDIGO 2026 iron initiation patterns for nondialysis CKD.
4. What adult hemoglobin ceiling should not be maintained with ESA therapy?
5. List five causes of ESA hyporesponsiveness.

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CHAPTER 24

CKD Mineral and Bone Disorder

Read calcium phosphate and PTH as one changing biological system

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

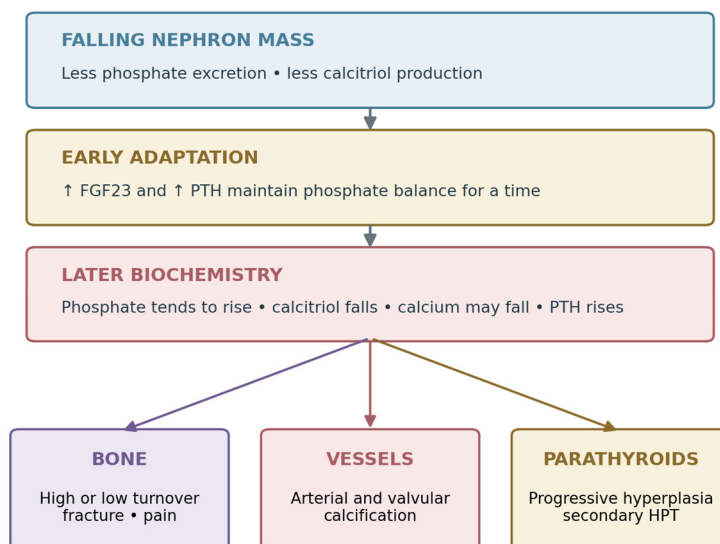
- Explain the phosphate–FGF23–vitamin D–PTH response to falling GFR.
- Distinguish CKD-MBD from renal osteodystrophy.
- Interpret calcium, phosphate, PTH and alkaline phosphatase as trends.
- Describe the basic roles and risks of diet, binders, vitamin D and calcimimetics.
- Recognize why vascular calcification is part of CKD-MBD.

Opening case

CLINICAL CASE

A 60-year-old man with CKD G4 has phosphate 4.8 mg/dL, corrected calcium 8.6 mg/dL, PTH 210 pg/mL and alkaline phosphatase at the upper limit of normal. Six months earlier PTH was 145 pg/mL. Should treatment target the PTH number alone?

CKD-MBD: one disturbed mineral system, three organs



Interpret calcium, phosphate and PTH together and over time—not as isolated targets.

Figure 24.1. *The CKD-MBD axis. Early endocrine adaptations maintain mineral balance, but progressive CKD can produce secondary hyperparathyroidism, bone disease and vascular calcification.*

24.1 Definitions

CKD-mineral and bone disorder is a systemic disorder caused by CKD. It may include biochemical abnormalities, bone abnormalities and vascular or soft-tissue calcification. Renal osteodystrophy is narrower: it describes bone morphology and turnover in CKD, ideally defined by bone biopsy.

Term	What it includes
CKD-MBD	Abnormal calcium, phosphate, PTH or vitamin D metabolism; bone turnover/mineralization/volume/growth/strength; vascular or soft-tissue calcification
Renal osteodystrophy	The bone component of CKD-MBD, classified by turnover, mineralization and volume
Osteoporosis	Low bone strength and fracture risk; can coexist with CKD-MBD

24.2 The sequence of adaptation

1. As functioning nephron mass falls, each nephron must excrete more phosphate.
2. FGF23 rises early and increases phosphate excretion per nephron while suppressing calcitriol.
3. Lower calcitriol reduces intestinal calcium absorption and removes restraint from PTH synthesis.
4. PTH rises and increases phosphaturia, calcium conservation and bone turnover.
5. In advanced CKD, the remaining nephrons cannot excrete the phosphate load; hyperphosphatemia and parathyroid hyperplasia become more likely.

WHY PHOSPHATE MAY BE NORMAL EARLY

A normal serum phosphate in CKD G3 does not mean mineral metabolism is normal. FGF23 and PTH may already be compensating to keep the serum value within range.

24.3 What to measure and when

KDIGO recommends beginning serum calcium, phosphate, PTH and alkaline-phosphatase monitoring in CKD G3a. Frequency depends on the abnormality and the rate of CKD progression.

Stage	Calcium and phosphate	PTH	Alkaline phosphatase
G3a–G3b	Every 6–12 months	According to baseline and CKD progression	As clinically indicated
G4	Every 3–6 months	Every 6–12 months	At least yearly in G4–G5D; more often if PTH is high
G5 including G5D	Every 1–3 months	Every 3–6 months	At least yearly; more often if PTH is high

Measure 25-hydroxyvitamin D when deficiency is plausible and repeat according to baseline and treatment. Use the laboratory's assay and reference range; PTH assays vary.

24.4 Trends are safer than single targets

Base treatment on serial phosphate, calcium and PTH considered together. PTH is a signal, not a toxin meter. In nondialysis CKD, the optimal PTH is unknown. A progressive or persistently high PTH should prompt evaluation of hyperphosphatemia, high phosphate intake, hypocalcemia and vitamin D deficiency before active vitamin-D therapy.

COMMON MISTAKE

Do not react to one moderately high PTH by immediately prescribing calcitriol. First check the trend and modifiable drivers; oversuppression can cause adynamic bone and hypercalcemia.

24.5 Phosphate management

Treat overt, progressive or persistent hyperphosphatemia rather than trying to 'prevent' it with binders when phosphate is normal. Start with dietary source assessment. Inorganic phosphate additives are highly absorbable; plant phosphate is less bioavailable than many animal and processed-food sources.

When binders are required, take them with meals so they meet dietary phosphate in the gut. Calcium-based binders are inexpensive but increase calcium load; restrict their dose when hypercalcemia, arterial calcification, adynamic bone or low PTH makes calcium loading undesirable. Non-calcium binders avoid calcium load but differ in pill burden, cost and adverse effects.

24.6 Calcium and vitamin D

Avoid hypercalcemia in adults with CKD G3a–G5D. Correct nutritional vitamin-D deficiency using general-population strategies adapted to the patient. Calcitriol and vitamin-D analogues

are not routinely used in adults with G3a–G5 not receiving dialysis; reserve them mainly for severe, progressive secondary hyperparathyroidism in G4–G5 under specialist care.

24.7 Dialysis secondary hyperparathyroidism

In CKD G5D, KDIGO suggests keeping PTH approximately 2–9 times the assay's upper normal limit, with marked movement within this range prompting reassessment. Calcimimetics, calcitriol or vitamin-D analogues, alone or in combination, may be used when PTH lowering is needed. Parathyroidectomy is considered for severe hyperparathyroidism that does not respond to medical treatment.

WHY THE RANGE IS BROAD

Very low PTH may indicate low-turnover adynamic bone, while very high PTH suggests high-turnover bone disease. Assay variability and imperfect correlation with bone histology make a narrow universal target unsafe.

24.8 Bone and vascular assessment

Fragility fracture or low bone density changes clinical risk. DXA can be used when the result will influence treatment, but it does not define bone turnover. PTH and bone-specific alkaline phosphatase can support a turnover estimate when values are markedly high or low; bone biopsy is considered when knowing turnover would change a major treatment decision.

Lateral abdominal radiography or echocardiography can identify vascular or valvular calcification where the result would change risk assessment. Calcification reflects active osteogenic transformation of vascular smooth-muscle cells as well as mineral load; it is not simply passive 'calcium deposition.'

Case resolution

The rising PTH is interpreted with calcium, phosphate, vitamin D, diet, CKD trajectory and alkaline phosphatase. His PTH is not treated as an isolated target. The team reviews phosphate sources, confirms serial abnormalities and vitamin-D status, avoids hypercalcemia and follows the trend. Active vitamin-D therapy is reserved for severe progressive hyperparathyroidism after modifiable factors are addressed.

Take-home messages

- CKD-MBD links laboratory abnormalities, bone disease and vascular calcification.
- FGF23 and PTH may rise before serum phosphate becomes high.
- Begin calcium, phosphate, PTH and alkaline-phosphatase monitoring in CKD G3a.
- Treat serial patterns, not one PTH or phosphate value.
- Avoid hypercalcemia and inappropriate PTH oversuppression.

Self-assessment

1. What is the difference between CKD-MBD and renal osteodystrophy?
2. Why does FGF23 rise early in CKD?
3. At what CKD category should routine biochemical monitoring begin?
4. Why is calcitriol not routinely used in nondialysis CKD G3a–G5?
5. What broad PTH range is suggested in CKD G5D?

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CHAPTER 25

Other Complications of Advanced CKD

Recognize the multisystem syndrome and treat reversible problems before they become emergencies

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Explain why advanced CKD produces hyperkalemia, acidosis and uremic symptoms.
- Recognize protein-energy wasting and assess nutrition without relying on albumin alone.
- Manage chronic hyperkalemia while preserving organ-protective therapy when possible.
- Identify common manifestations including pruritus, bleeding, infection and cognitive change.
- Know which complications require urgent nephrology or dialysis assessment.

Opening case

CLINICAL CASE

A 76-year-old man with CKD G5 not receiving dialysis has potassium 5.8 mmol/L, bicarbonate 17 mmol/L, poor appetite, pruritus and 5% unintentional weight loss over 3 months. He takes an ARB and spironolactone. Which findings are immediately dangerous, which are potentially reversible, and does eGFR alone decide dialysis?

Advanced CKD: think in systems, then prioritize reversible threats

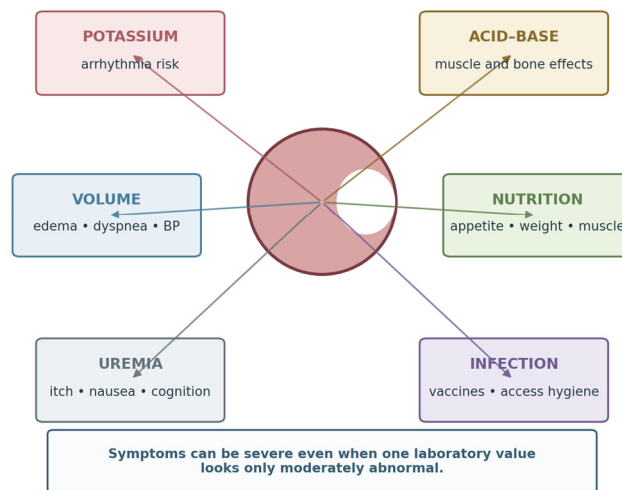


Figure 25.1. Advanced CKD affects multiple systems. Prioritize life-threatening potassium, acid–base and volume problems while also treating nutrition, symptoms and infection risk.

25.1 Why complications accumulate

GFR measures filtration, but advanced CKD also impairs potassium excretion, acid excretion, sodium balance, endocrine signaling and removal of many small and protein-bound solutes. Symptoms reflect the total physiological burden and comorbid disease, not one 'urea level.' Two patients with the same eGFR can feel very different.

25.2 Chronic hyperkalemia

Hyperkalemia results from reduced distal potassium secretion plus modifiable contributors: RAAS blockade, MRAs, NSAIDs, trimethoprim, heparin, constipation, metabolic acidosis, insulin deficiency and high intake of readily absorbable potassium. Pseudohyperkalemia from

hemolysis, fist clenching, thrombocytosis or leukocytosis must be considered when the result does not fit the patient.

1. Assess urgency: symptoms, ECG, rate of rise, absolute potassium and concurrent acidosis or tissue breakdown.
2. Repeat a possibly spurious sample without delaying treatment when danger is plausible.
3. Stop potassium supplements and remove nonessential contributors.
4. Correct constipation, insulin deficiency and metabolic acidosis; optimize diuretic therapy if volume and urine output permit.
5. Individualize dietary advice toward highly absorbable potassium additives and problematic foods rather than automatically removing all fruit and vegetables.
6. Use a chronic potassium binder when appropriate to preserve beneficial RAAS or MRA therapy.

EMERGENCY BOUNDARY

ECG toxicity, rapidly rising potassium or severe hyperkalemia requires the emergency sequence from Chapter 12: stabilize the myocardium, shift potassium into cells, remove potassium and repeat measurements for rebound. Chronic binders do not replace emergency treatment.

25.3 Metabolic acidosis

Healthy kidneys reclaim filtered bicarbonate and excrete daily nonvolatile acid as ammonium and titratable acid. With fewer nephrons, acid excretion per nephron increases but eventually becomes insufficient. Serum bicarbonate falls, contributing to muscle catabolism, bone buffering, hyperkalemia and possibly faster CKD progression.

KDIGO 2024 advises considering pharmacological treatment, with or without dietary intervention, when acidosis has potential clinical implications—for example, serum bicarbonate <18 mmol/L in adults. Monitor so treatment does not cause alkalosis, sodium-related hypertension, fluid overload or an adverse potassium change.

PRACTICAL INTERPRETATION

Confirm a low bicarbonate and calculate the anion gap. Normal-gap acidosis is common earlier; the anion gap may rise in advanced CKD as unmeasured anions accumulate. Exclude diarrhea, renal tubular acidosis, ketoacidosis, lactate and toxins when the pattern is disproportionate.

25.4 Volume and sodium balance

Advanced CKD narrows the kidney's ability to respond to sudden sodium or water loads. Edema, hypertension and pulmonary congestion are common, but aggressive diuresis can also produce depletion. Use symptoms, JVP, edema, lung findings, weight and trends. Loop diuretics usually become the main natriuretic agents; combination therapy may be needed in resistant congestion.

25.5 Protein-energy wasting

Protein-energy wasting is loss of body protein and energy stores caused by reduced intake, inflammation, acidosis, endocrine changes, catabolism and dialysis-related loss. Serum albumin is strongly influenced by inflammation and volume, so it is not a nutritional diagnosis by itself.

Domain	What to assess	Concerning clue
Intake	Appetite, nausea, taste, diet restrictions, food access	Persistently low energy or protein intake
Body mass	Serial weight after accounting for fluid	Unintentional loss >5% over about 3 months
Muscle/function	Handgrip, gait, chair rise, visible muscle loss	Declining strength or sarcopenia
Laboratory context	Albumin, bicarbonate, CRP and dialysis adequacy	Interpret together; no single value proves wasting

Do not impose multiple broad dietary restrictions that make adequate intake impossible. A renal dietitian can prioritize sodium, potassium, phosphate and protein advice according to the patient's actual abnormalities.

25.6 Uremic symptoms

System	Possible manifestations	Important alternative causes
Neurologic	Poor concentration, sleep disturbance, restless legs, neuropathy, encephalopathy	Medication toxicity, stroke, infection, CO ₂ retention
Gastrointestinal	Anorexia, nausea, vomiting, metallic taste, weight loss	Ulcer disease, malignancy, gastroparesis, drugs
Serosal	Uremic pericarditis	Acute coronary syndrome, infection, autoimmune disease
Skin	Pruritus, excoriation, xerosis	Liver disease, scabies, allergy, hematologic disease
Hematologic	Platelet dysfunction and bleeding	Antithrombotic drugs, thrombocytopenia, liver disease

Uremic encephalopathy, pericarditis, clinically important bleeding attributable to uremia, refractory nausea with malnutrition, or medically resistant fluid/electrolyte/acid–base disturbance can be indications for dialysis.

25.7 CKD-associated pruritus

Pruritus is common in advanced CKD and dialysis and can severely impair sleep and quality of life. Assess distribution, skin lesions, xerosis, medications, liver and thyroid disease, scabies and adequacy of CKD-MBD control. Use emollients and avoid irritating products. Dialysis optimization, gabapentinoids with strict renal dosing, and selected newer agents such as difelikefalin in hemodialysis may be considered under local availability and specialist supervision.

25.8 Bleeding and thrombosis

Uremic platelet dysfunction impairs adhesion and aggregation, causing mucosal bleeding despite a normal platelet count and coagulation tests. CKD simultaneously increases thrombosis risk. Review aspirin, P2Y₁₂ inhibitors, anticoagulants and drug accumulation; do not assume every bleed is 'uremic.' Urgent management may include dialysis and selected hemostatic therapy guided by the clinical situation.

25.9 Infection and vaccination

CKD impairs innate and adaptive immunity, and dialysis access adds exposure. Review influenza, COVID-19, pneumococcal, hepatitis B and other age/risk-based vaccines according to current national schedules. Hepatitis B vaccination is more likely to produce protective antibody before kidney failure, so begin early enough to complete the series and check response when indicated.

25.10 Sexual health cognition and function

Fatigue, sexual dysfunction, infertility concerns, sleep disturbance, depression and cognitive decline are frequent but under-asked. They may reflect anemia, vascular disease, medications, endocrine dysfunction, uremia or psychosocial burden. Ask directly and respectfully; symptom care is not postponed until dialysis.

Case resolution

Potassium 5.8 mmol/L requires ECG assessment, confirmation and active review of drugs, acidosis, diet and bowel function. Bicarbonate 17 mmol/L is clinically important acidosis and may worsen potassium and muscle loss. The 5% weight loss, appetite loss and pruritus require nutritional and uremic assessment. The ARB and MRA are not stopped reflexively, but their indications and safe continuation are reassessed while reversible contributors and potassium-lowering strategies are addressed. Dialysis depends on refractory complications and symptoms, not eGFR alone.

Take-home messages

- Advanced CKD is a multisystem syndrome, not an isolated rise in urea or creatinine.
- Treat hyperkalemia systematically and preserve beneficial RAAS therapy when safely possible.
- Consider alkali treatment when bicarbonate is <18 mmol/L and monitor sodium-related effects.
- Weight loss, appetite and function are more informative than albumin alone for nutrition.
- Uremic symptoms and refractory complications—not eGFR alone—can indicate dialysis.

Self-assessment

1. List six reversible contributors to chronic hyperkalemia in CKD.
2. At what bicarbonate level does KDIGO 2024 give an example of acidosis with potential clinical implications?
3. Why is serum albumin not a stand-alone nutritional marker?
4. Name four uremic manifestations that may support dialysis initiation.
5. Why should hepatitis B vaccination be considered before dialysis begins?

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CHAPTER 26

Preparing for Kidney Failure

Create time for informed choices and avoid an unplanned dialysis start

LEARNING OBJECTIVES

After studying this chapter, the student should be able to:

- Identify patients who need multidisciplinary advanced-CKD care and KRT education.
- Compare transplantation, peritoneal dialysis, hemodialysis and comprehensive conservative care.
- Use eGFR, kidney-failure risk and trajectory to time preparation.
- Recognize clinical indications to start dialysis.
- Explain shared decision-making and an individualized life-plan approach.

Opening case

CLINICAL CASE

A 69-year-old woman with CKD G5 has eGFR 9 mL/min/1.73 m², potassium 4.8 mmol/L, bicarbonate 21 mmol/L and mild stable edema controlled with diuretics. She eats well, has no nausea, pruritus, cognitive change or pericarditis, and prefers home treatment if it becomes necessary. Must dialysis start because eGFR is below 10?

Preparing for kidney failure: plan early, start treatment for need

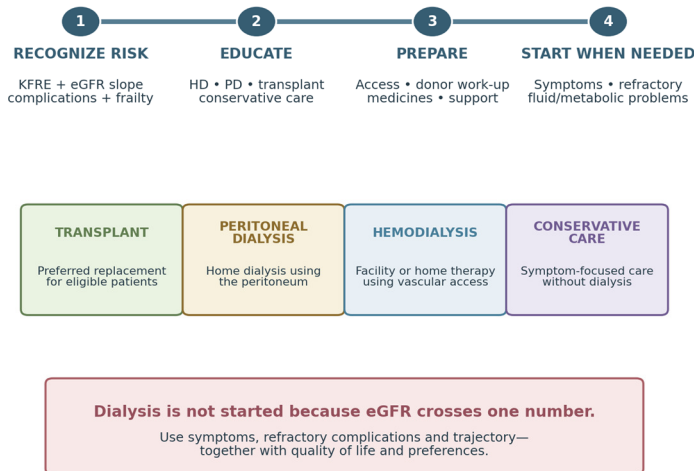


Figure 26.1. Preparation is a timeline rather than a last-minute procedure. Treatment options are discussed early, but dialysis begins for clinical need rather than an isolated eGFR.

26.1 Kidney failure is a phase of care

Kidney failure usually corresponds to CKD G5, but the need for kidney replacement therapy depends on symptoms, complications, trajectory and patient goals. Preparation should begin before treatment is needed because education, transplant evaluation and durable access take time.

LANGUAGE MATTERS

Use 'kidney failure' rather than 'end-stage renal disease' when possible. The kidney has failed to meet current needs, but the person is not at the end of care and several active treatment pathways remain.

26.2 When to intensify care

Trigger	KDIGO 2024 use	Practical action
5-year KFRE 3%–5%	Support nephrology referral	Clarify cause, optimize protection and plan follow-up
2-year KFRE >10%	Support multidisciplinary care	Add dietetic, pharmacy, education and psychosocial support
2-year KFRE >40%	Support modality education and KRT preparation	Consider transplant referral and access planning
eGFR <15–20	Alternative trigger for preparation	Do not wait for symptoms before discussing options

Risk equations add precision but can be wrong for an individual. Also consider eGFR slope, recurrent AKI, cause, proteinuria, frailty, competing mortality, hospitalizations and how long local access or transplant pathways take.

26.3 Shared decision-making

Shared decision-making combines medical evidence with the person's goals, daily life, caregiving, treatment burden and acceptable trade-offs. It is not asking the patient to choose from a brochure without guidance. The clinical team explains realistic benefits and burdens, checks understanding, involves family if desired and revisits the choice as health changes.

1. Ask what the person most wants treatment to preserve: survival, independence, travel, cognition, symptom control, home time or another goal.
2. Explain all medically appropriate options in balanced language.
3. Discuss treatment schedule, access, transport, home space, caregiver role and likely symptom burden.
4. Use teach-back: ask the person to explain the options in their own words.
5. Document the current preference and the conditions that would make the person reconsider.

26.4 Kidney transplantation

Transplantation offers the best survival and quality-of-life potential for many eligible patients and may occur before dialysis. Evaluation examines cardiovascular disease, cancer, infection, anatomy, adherence capacity and psychosocial support. Age alone is not an exclusion; suitability depends on total risk and expected benefit.

PREEMPTIVE TRANSPLANTATION

Referral should occur early enough for evaluation and possible living-donor assessment before dialysis. A transplant is kidney replacement, not a cure: immunosuppression, infection, malignancy, rejection and cardiovascular risk continue.

26.5 Peritoneal dialysis

Peritoneal dialysis uses the peritoneal membrane for solute and fluid exchange. Dialysate enters the abdomen through a catheter, dwells and drains. Continuous ambulatory PD uses manual exchanges; automated PD usually performs exchanges overnight.

Potential advantage	Potential burden or limitation
Home-based schedule and travel flexibility	Daily responsibility, training and supply storage
Preserves vascular access	Peritonitis and catheter infection risk
Gentler continuous fluid removal	Glucose exposure, weight/metabolic effects and protein loss
May preserve residual kidney function	Membrane or ultrafiltration limitations can develop

Prior abdominal surgery is not an automatic contraindication; feasibility requires individualized surgical and PD-team assessment.

26.6 Hemodialysis

Hemodialysis circulates blood through a dialyzer. It can be performed in a center or at home with different schedules. A native arteriovenous fistula is often preferred when likely to mature and be used, but the best access follows an individualized 'ESKD Life-Plan' rather than a fistula-first slogan.

Access	Strength	Major limitation
AV fistula	Low infection risk and durable when mature	Needs time to mature; primary failure and cannulation burden
AV graft	Can be used sooner and suits some anatomy	More infection and intervention than a mature fistula
Central venous catheter	Immediate use	Highest bloodstream infection and central-vein complication risk

PROTECT FUTURE ACCESS

Avoid unnecessary venipuncture and PICC lines in veins that may be needed for dialysis access. Coordinate with nephrology before central devices in advanced progressive CKD.

26.7 Comprehensive conservative kidney management

Conservative kidney management is active, planned treatment without dialysis. It includes symptom control, fluid and electrolyte management, anemia and acidosis care, psychosocial support, advance care planning and end-of-life care when appropriate. It is not abandonment.

For some patients with severe frailty, major comorbidity or limited life expectancy, dialysis may offer little survival or functional advantage and substantial treatment burden. The discussion must remain individualized and revisable.

26.8 When to start dialysis

KDIGO 2024 advises a composite assessment of symptoms, signs, quality of life, preferences, GFR and laboratory abnormalities. Indications often—but not invariably—appear at GFR 5–10 mL/min/1.73 m².

Indication category	Examples
Symptoms/signs attributable to kidney failure	Neurologic uremia, pericarditis, anorexia, intractable pruritus, medically resistant acid–base or electrolyte abnormality
Inability to control volume or blood pressure	Recurrent pulmonary edema or severe congestion despite appropriate therapy
Progressive nutritional or cognitive deterioration	Declining intake, weight or cognition attributable to uremia despite treatment
Other clinical demand	A metabolic or clearance burden that cannot be safely managed conservatively

WHAT EGFR DOES—AND DOES NOT—DO

eGFR helps time education and access planning. It does not, by itself, prove that dialysis today will improve how a stable patient feels or lives. Starting too early exposes the patient to treatment burden without demonstrated benefit.

26.9 Planned versus unplanned starts

An unplanned start commonly uses a temporary catheter during hospitalization, before adequate education. It increases infection, distress and loss of choice. A planned start allows the selected modality, appropriate access, medication reconciliation, vaccination and psychosocial preparation. Planning early does not commit the patient to starting early.

26.10 Can dialysis be time-limited

When benefit is uncertain, a time-limited trial can define specific goals—such as improved cognition, relief of dyspnea or discharge home—and a review date. The team and patient agree in advance what outcome would support continuing, changing or stopping treatment.

Case resolution

She does not need dialysis solely because eGFR is 9. Her potassium, acid–base state, volume, nutrition, cognition and symptoms are currently manageable. She does need urgent preparation: calculate short-term kidney-failure risk, provide balanced education, assess transplant eligibility, discuss home PD versus home/center HD, and arrange access at an appropriate time. Start dialysis if symptoms or refractory metabolic/volume problems develop.

Take-home messages

- Plan kidney-failure care before a crisis, using risk and trajectory as well as eGFR.
- Transplantation, PD, HD and comprehensive conservative care are distinct active pathways.
- Access choice should fit the patient's life-plan and probability of use.
- Initiate dialysis from a composite clinical assessment, not an isolated eGFR.
- Early planning preserves choice; it does not require early dialysis.

Self-assessment

1. State the KFRE thresholds used to support referral, multidisciplinary care and KRT preparation.
2. Name four domains that belong in shared decision-making.
3. Give two advantages and two burdens of peritoneal dialysis.
4. Compare AV fistula, graft and catheter in one sentence each.
5. List four clinical categories that may indicate dialysis initiation.

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Answers to self-assessment questions

The questions are intended for retrieval practice. Compact model answers for Part III are provided below. Students should attempt each question before reading the response.

Part III model answers

Chapter 13

1. AKI: creatinine rise ≥ 0.3 mg/dL within 48 hours, $\geq 1.5 \times$ baseline within 7 days, or urine output < 0.5 mL/kg/h for ≥ 6 hours.
2. $240 \div 60 \div 12 = 0.33$ mL/kg/h; because this is < 0.5 for 12 hours, urine-output stage 2.
3. The creatinine has doubled, meeting stage 2 criteria despite remaining near a population reference range.
4. AKI occurs within 7 days; AKD lasts up to 90 days; CKD persists > 3 months.
5. Cause, maximum stage, dialysis, recovery status, medication changes and follow-up plan.

Chapter 14

1. Filtration can fall from true loss, vasodilation, low cardiac output or venous congestion; only some states benefit from fluid.
2. NSAIDs reduce afferent prostaglandin-mediated dilation; ACEi/ARB reduce efferent angiotensin-II-mediated constriction.
3. Raised JVP, edema, ascites, crackles, right-heart dysfunction or worsening congestion after fluid.
4. Give a finite amount for a defined indication, measure a predefined hemodynamic response and stop if ineffective or congestive.

5. Hemoconcentration and reduced intraglomerular pressure can raise creatinine while total congestion and prognosis improve.

Chapter 15

1. Coarse granular casts and renal tubular epithelial cells in the appropriate setting.
2. Microcirculatory, endothelial, inflammatory and tubular metabolic mechanisms contribute beyond global ischemia.
3. Positive blood dipstick with few or no RBCs suggests myoglobin or hemoglobin.
4. Eosinophilia and urine eosinophils have inadequate sensitivity and specificity.
5. Unexplained/nonrecovering AKI, active sediment, substantial proteinuria, systemic disease or suspected treatable AIN/GN.

Chapter 16

1. The unobstructed contralateral kidney can maintain total GFR and creatinine.
2. Prostate disease, urethral stricture, neurogenic bladder, clot or catheter failure.
3. Early obstruction, severe dehydration, retroperitoneal fibrosis/tumor encasement or inability of the collecting system to dilate.
4. >200 mL/h for 2 hours or >3 L/24 h.
5. Complete replacement can perpetuate diuresis; insufficient replacement can cause hypovolemia and electrolyte loss.

Chapter 17

1. Hemodynamic, direct tubular, interstitial immune, crystal/obstructive and vascular injury.
2. Trimethoprim, cobicistat and dolutegravir; several targeted cancer agents also inhibit secretion.
3. CA-AKI occurs after contrast regardless of cause; CI-AKI is causally attributable to contrast.
4. Active AKI, eGFR <30 , arterial/high-dose exposure and multiple concurrent insults.
5. It has not prevented injury, may cause harm and contrast removal does not reverse the initiating exposure.

Chapter 18

1. Treat cause; set fluid goal; review medicines/doses; monitor trajectory; manage nutrition/complications; reassess KRT need and recovery.
2. It predicts progression/need for KRT; <200 mL urine in 2 hours after 1.0 or 1.5 mg/kg IV furosemide is a poor response.
3. Refractory electrolyte, acid–base or fluid disturbance; uremic complication; selected toxin/metabolic load.
4. It provides slower continuous control with less hypotension and fewer rapid osmotic shifts.
5. Improving illness, rising spontaneous urine output, stable fluid/metabolic balance and favorable interdialytic creatinine/clearance.

Part IV model answers

Chapter 19

1. Yes. Examples include persistent ACR ≥ 30 mg/g, ADPKD, a kidney transplant, renal pathology or persistent renal-origin hematuria despite eGFR ≥ 90 .
2. eGFR 38 is G3b; ACR 12 mg/mmol is A2. Add the cause: CKD due to [cause], G3b A2.
3. Albuminuria can be transient with exercise, fever, infection, menstruation, severe hyperglycemia or heart failure; confirm chronicity and context.
4. Age, sex, eGFR and urine ACR.
5. A 2-year kidney-failure risk $>40\%$ can support modality education and KRT preparation.

Chapter 20

1. Efferent arteriolar dilation reduces intraglomerular pressure, causing an early functional fall in GFR while reducing albumin leakage and long-term glomerular injury.
2. Usually within 2–4 weeks after initiation or dose increase, earlier when risk is high.
3. T2D with CKD and eGFR ≥ 20 ; adult CKD with eGFR ≥ 20 plus ACR ≥ 200 mg/g; heart failure regardless of albuminuria; also consider eGFR 20–45 with ACR <200 .
4. A fall $>30\%$ after hemodynamically active therapy exceeds expected variability and warrants evaluation.
5. $85 \times 0.8 = 68$ g protein/day.

Chapter 21

1. Diabetes with CKD states coexistence without assigning cause. DKD is CKD clinically attributed to diabetes and does not require biopsy. Diabetic nephropathy is the precise term for characteristic diabetic lesions demonstrated on biopsy.
2. More proximal sodium-glucose reabsorption lowers NaCl delivery to the macula densa, causing afferent dilation; intrarenal RAAS activity maintains efferent tone, so intraglomerular pressure and single-nephron GFR rise.
3. Tubulointerstitial hypoxia, vascular disease, aging and nephron loss can drive fibrosis and eGFR decline even when glomerular albumin leakage is minimal.
4. RBC casts/active sediment, abrupt nephrotic syndrome, rapid unexplained eGFR loss, systemic clues, or an atypically short diabetes duration.
5. Start an SGLT2 inhibitor at eGFR ≥ 20 when indicated; metformin is generally used at eGFR ≥ 30 . Finerenone is considered in T2D with eGFR >25 , normal potassium and persistent ACR >30 mg/g despite maximum tolerated RAAS blockade.

Chapter 22

1. Sodium retention, inflammation, anemia, endothelial dysfunction, vascular calcification, CKD-MBD and neurohormonal activation.
2. Raised renal venous pressure reduces the transrenal perfusion/filtration gradient and promotes interstitial pressure and sodium retention.
3. Less drug reaches the tubular lumen and sodium-retaining adaptation is stronger, so the threshold dose is higher.
4. Use symptoms, ECG, serial rise/fall and imaging; CKD can raise baseline troponin but does not make it diagnostically meaningless.
5. Low-dose aspirin is recommended for secondary prevention of established ischemic CVD; primary-prevention benefit is uncertain because bleeding may offset benefit.

Chapter 23

1. Hemoglobin <13 g/dL in adult men and <12 g/dL in adult women.
2. Inflammation raises hepcidin and ferritin while restricting circulating iron, so ferritin can be normal/high and TSAT low.
3. Ferritin <100 ng/mL with TSAT $<40\%$, or ferritin 100–300 ng/mL with TSAT $<25\%$.
4. Do not maintain adult hemoglobin ≥ 11.5 g/dL with ESA therapy.
5. Iron deficiency/restriction, inflammation/infection, occult blood loss, inadequate dialysis, severe hyperparathyroidism, hemolysis, B12/folate deficiency, marrow disease or nonadherence.

Chapter 24

1. CKD-MBD includes biochemical, bone and vascular/soft-tissue abnormalities; renal osteodystrophy is the bone morphology component.
2. It increases phosphaturia per remaining nephron and helps maintain serum phosphate while suppressing calcitriol.
3. Begin in CKD G3a.
4. The optimal PTH is unknown; routine active vitamin D can cause hypercalcemia and oversuppress bone turnover. Address modifiable drivers first.
5. Approximately 2–9 times the assay's upper normal limit, interpreted as a trend.

Chapter 25

1. RAASi/MRA, NSAIDs, trimethoprim, heparin, constipation, metabolic acidosis, insulin deficiency, supplements and highly absorbable potassium intake.
2. Serum bicarbonate <18 mmol/L is KDIGO's example of acidosis with potential clinical implications.
3. Albumin falls with inflammation and dilution and therefore does not specifically measure intake or body stores.
4. Encephalopathy, pericarditis, refractory nausea/anorexia with deterioration, severe pruritus, bleeding attributable to uremia, or refractory fluid/electrolyte/acid–base problems.
5. Vaccine response is generally better before advanced uremia, and protection is needed before dialysis-related exposure.

Chapter 26

1. Five-year KFRE 3%–5% for referral; 2-year risk >10% for multidisciplinary care; 2-year risk >40% for KRT education and preparation.
2. Goals, expected benefits, treatment burden, schedule, access, home circumstances, caregiver role, transplant suitability and the conditions for reconsideration.
3. Advantages include home flexibility and gentle continuous fluid removal; burdens include daily responsibility, storage, infection risk and metabolic/protein effects.
4. A fistula is durable with low infection risk when mature but may fail to mature; a graft can be used sooner but needs more interventions; a catheter works immediately but has the highest infection and central-vein risk.
5. Kidney-failure symptoms/signs, refractory volume/BP problems, progressive nutritional or cognitive deterioration, and a metabolic/clearance burden not safely managed conservatively.

PART V

Glomerular Diseases

Classify the syndrome, define the tempo, then identify the immune or systemic cause

HOW TO USE PART V

Use two axes at the same time. Acute versus chronic describes tempo; primary versus secondary describes cause. IgA nephropathy, lupus nephritis or infection-related GN may present acutely, chronically, or as rapidly progressive disease. The five chapters deliberately revisit these diseases from different clinical viewpoints, but the detailed pathology is placed in the most relevant disease chapter.

CHAPTER 27

Nephritic and Nephrotic Syndromes

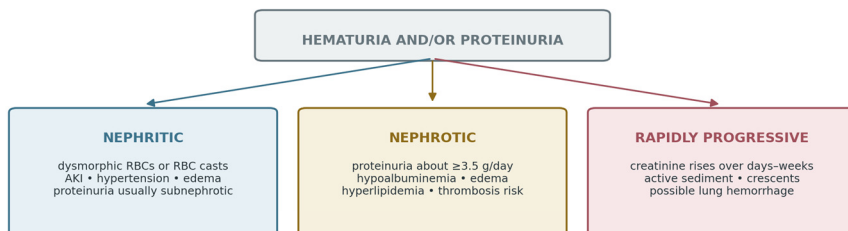
Recognize what the filtration barrier is doing before naming the disease

- Distinguish nephritic, nephrotic and mixed glomerular syndromes.
- Explain why inflammatory capillary injury causes hematuria and reduced GFR.
- Explain why podocyte or basement-membrane injury causes heavy protein loss.
- Recognize complications that require urgent action before a biopsy diagnosis is available.
- Choose a focused first investigation set and know when nephrology referral is urgent.

Opening case

A 22-year-old man develops cola-colored urine, facial edema and blood pressure 162/98 mmHg. Creatinine is 176 $\mu\text{mol/L}$ (2.0 mg/dL), urine shows dysmorphic red cells and RBC casts, and ACR is 145 mg/mmol. The task is first to identify a nephritic syndrome and its severity—not to guess the biopsy diagnosis from hematuria alone.

Recognize the glomerular syndrome before naming the disease



FIRST QUESTIONS

- 1 Is kidney function falling?
- 2 Lung hemorrhage or severe hypertension?
- 3 What does microscopy show?
- 4 Is complement low?
- 5 Urgent biopsy?

Treat life-threatening complications while the diagnostic work-up continues.

Figure 27.1. A syndrome-first approach to glomerular disease. Nephritic, nephrotic and rapidly progressive features may overlap; tempo and dangerous extrarenal involvement determine urgency.

27.1 A syndrome is a pattern, not a diagnosis

A glomerular syndrome describes the consequence of injury at the filtration barrier. It narrows the differential diagnosis but does not identify the cause. Nephritic disease is dominated by inflammation and capillary-wall disruption; nephrotic disease is dominated by loss of the barrier's selectivity for plasma proteins. Many patients have a mixed pattern.

Feature	Nephritic pattern	Nephrotic pattern	Mixed or severe disease
Urine	Hematuria; dysmorphic RBCs; RBC casts	Heavy proteinuria; lipiduria; oval fat bodies	Hematuria plus heavy proteinuria
Protein loss	Usually subnephrotic, but may be heavy	Typically ≥ 3.5 g/day or PCR $\approx \geq 3.5$ g/g	Heavy protein loss does not exclude inflammatory GN
Kidney function	May fall over days to weeks	Often preserved initially	Rapid fall suggests crescentic injury or severe inflammation
Blood pressure/volume	Hypertension and salt retention common	Edema often prominent; effective arterial filling may be reduced	Pulmonary edema can occur in either pattern
Main barrier lesion	Endothelial/mesangial inflammation and capillary rupture	Podocyte slit-diaphragm or GBM injury	Multiple barrier layers involved

27.2 Why glomerular hematuria looks different

Red cells cross a disrupted glomerular capillary wall and are deformed by mechanical stress and changing tubular osmolality. Acanthocytes—ring-shaped cells with membrane blebs—are highly suggestive of a glomerular source. RBC casts form when red cells become trapped in uromodulin within tubules; therefore an RBC cast localizes bleeding to the nephron, usually from glomerulonephritis.

COMMON MISTAKE

A negative dipstick does not exclude glomerular disease if urine is very dilute or the specimen is delayed. Conversely, a positive dipstick for blood detects heme and may reflect hemoglobin or myoglobin without intact RBCs. Always relate the dipstick to microscopy.

27.3 Why nephritic disease reduces GFR

Immune deposits, complement activation, leukocyte recruitment and endothelial swelling narrow or occlude glomerular capillary lumina. Filtration surface area and hydraulic permeability fall. Tubular sodium delivery falls, activating sodium-retaining pathways; reduced GFR further limits sodium excretion. The result is edema, hypertension and azotemia. If fibrin and plasma proteins escape into Bowman's space, parietal epithelial cells and macrophages form crescents, a marker of severe capillary-wall rupture.

27.4 Why nephrotic syndrome causes edema and thrombosis

Nephrotic-range proteinuria is usually defined in adults as total protein excretion ≥ 3.5 g/day, or an approximately equivalent PCR ≥ 3.5 g/g (about 350 mg/mmol). Nephrotic syndrome additionally requires the clinical consequences of protein loss—typically hypoalbuminemia and edema. There is no single universal serum-albumin cutoff, although concentrations <30 g/L are common in established syndrome.

Edema is produced by two interacting models. In the underfill model, low plasma oncotic pressure allows fluid to leave the vascular space; reduced effective arterial volume then activates RAAS, sympathetic tone and vasopressin. In the overfill model, the kidney retains sodium directly, partly through increased distal sodium-channel activity. Real patients often have elements of both, which is why indiscriminate albumin infusion or excessive diuresis can be harmful.

Urinary loss and altered synthesis of anticoagulant and procoagulant proteins create a hypercoagulable state. Venous thromboembolism risk is particularly high in membranous nephropathy and with severe hypoalbuminemia. Loss of immunoglobulins and complement factors contributes to infection risk; hepatic lipoprotein production and reduced lipid catabolism cause dyslipidemia.

27.5 The first investigation set

Question	Test	How it changes reasoning
Is bleeding glomerular?	Fresh urine microscopy	Acanthocytes or RBC casts strongly support glomerular bleeding.
How much protein?	ACR and/or PCR	Quantifies severity; albumin predominance favors a glomerular barrier lesion.
Is function changing?	Creatinine trend and urine output	Trajectory is more informative than one creatinine value.
Is complement consumed?	C3 and C4	Low C3, low C4, or both direct the immune-complex differential.
Is there systemic disease?	ANA, anti-dsDNA, ANCA, anti-GBM, HBV/HCV/HIV and monoclonal studies as indicated	Order according to phenotype; indiscriminate panels produce misleading weak positives.
Is biopsy needed?	Nephrology assessment	Biopsy integrates LM, IF and EM and often determines therapy.

MEDICAL EMERGENCY

Call nephrology urgently for a rapidly rising creatinine, oliguria, pulmonary hemorrhage, RBC casts with kidney dysfunction, severe hypertension, pulmonary edema, hyperkalemia, severe acidosis, or suspected anti-GBM/ANCA disease. Stabilization and diagnostic sampling proceed in parallel.

27.6 Treat dangerous physiology before the biopsy diagnosis

Initial management has two levels. First, correct problems that are dangerous regardless of the final diagnosis: pulmonary edema, severe hypertension, hyperkalemia, acidosis, infection and thrombosis. Second, treat the specific disease mechanism after the clinical phenotype, serology and biopsy have been integrated. Blood and protein in the urine are not, by themselves, an indication for immunosuppression. Infection-related glomerulonephritis can look intensely inflammatory and may deteriorate if infection is overlooked.

- For edema, restrict dietary sodium and use a loop diuretic when clinically indicated. Adjust treatment according to breathing, body weight, blood pressure, perfusion, urine output and kidney function.
- Use an ACE inhibitor or ARB to reduce blood pressure and proteinuria when potassium, perfusion and kidney function permit. Reassess a progressive creatinine rise rather than assuming that every early eGFR fall is acceptable.
- Assess venous thromboembolism risk in severe nephrotic syndrome. Serum albumin, the underlying disease, bleeding risk, immobility and previous thrombosis all contribute; one albumin value cannot decide prophylaxis alone.
- Vaccination, investigation of fever, avoidance of NSAIDs, renal dose adjustment and nutritional assessment are part of treatment.
- Seek urgent nephrology review for a rapidly rising creatinine, oliguria, RBC casts, pulmonary hemorrhage, severe proteinuria or suspected crescentic disease.

Clinical problem	Main mechanism	Initial response
Edema and congestion	Sodium retention plus altered Starling forces	Sodium restriction, loop diuretic and repeated assessment of volume, perfusion and creatinine.
Hypertension	Sodium excess, RAAS activation and reduced filtration	Control volume and use kidney-protective antihypertensives without causing abrupt hypotension.
Thrombosis	Urinary anticoagulant loss and increased procoagulant activity	Assess VTE and bleeding risks; investigate symptoms urgently; individualize prophylaxis.
Infection	Immunoglobulin loss and immunosuppressive exposure	Culture suspected infection, treat its source and update appropriate vaccination.
Rapid GFR loss	Necrosis, severe capillary inflammation or crescents	Stabilize immediately and arrange same-day serology, biopsy planning and specialist assessment.

27.7 Evolution and prognosis across glomerular syndromes

Evolution describes change over time. Complete remission usually combines very low proteinuria with stable or improved kidney function. Partial remission is a clinically important fall in proteinuria without full normalization. Relapse is renewed activity after remission. Trial definitions differ between diseases, so clinical documentation should include the actual proteinuria, eGFR and time interval rather than the word response alone.

Low or falling eGFR, persistent proteinuria, uncontrolled blood pressure and tubular atrophy with interstitial fibrosis are the most consistent adverse prognostic markers. Cellular inflammation and cellular crescents may improve with prompt treatment. Global sclerosis, fibrous crescents and interstitial fibrosis represent lost nephrons and limit recovery even when the urine sediment becomes quiet.

Case resolution

The patient has an acute nephritic syndrome. Repeat creatinine confirms progression, while normal C3 and a history of visible hematuria beginning during an upper respiratory infection raise suspicion for IgA nephropathy. Kidney biopsy is arranged because kidney function is impaired; the syndrome directs urgency, while LM, IF and EM establish the disease.

Take-home messages

- Nephritic and nephrotic are clinical patterns, not histological diagnoses.
- RBC casts localize hematuria to the nephron and usually indicate glomerular inflammation.
- Heavy proteinuria may occur in inflammatory GN; it does not automatically mean a purely nephrotic disease.
- Nephrotic edema reflects both altered Starling forces and renal sodium retention.
- Trajectory, systemic danger signs and urine microscopy determine urgency.

Self-assessment

1. Why does an RBC cast strongly support a glomerular source of bleeding?
2. What distinguishes nephrotic-range proteinuria from nephrotic syndrome?
3. Name two mechanisms that contribute to edema in nephrotic syndrome.
4. Which bedside and laboratory features suggest rapidly progressive glomerular disease?
5. Why should serologic tests be selected according to the clinical phenotype?

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CHAPTER 28

Acute Glomerulonephritis

Acute post-infectious glomerulonephritis from mechanism to recovery

- Recognize acute post-infectious glomerulonephritis as a cause of acute nephritic syndrome.
- Explain how infection, immune complexes and complement activation injure the glomerulus.
- Correlate the clinical syndrome with light microscopy, immunofluorescence and electron microscopy.
- Choose the initial investigations and identify when kidney biopsy is required.
- Treat the infection and kidney complications, then assess recovery and prognosis.

Opening case

A 12-year-old boy develops cola-colored urine, periorbital edema and a blood pressure of 145/92 mmHg. Two weeks earlier he had fever and a sore throat. Serum creatinine is 1.2 mg/dL, increased from an expected baseline near 0.6 mg/dL; C3 is low and C4 is normal. Urinalysis shows dysmorphic erythrocytes, red-cell casts and proteinuria of 1.1 g/day. The key question is whether a recent infection has triggered a self-limited immune-complex nephritis or whether the course suggests another disease.

28.1 Definition and terminology

Acute glomerulonephritis is a pathological process that usually presents clinically as acute nephritic syndrome: hematuria, a fall in GFR, sodium retention, edema and hypertension. In this chapter, the term refers specifically to acute post-infectious glomerulonephritis. Other causes of acute nephritic syndrome are discussed in their disease-specific chapters.

Classic post-infectious glomerulonephritis begins after the responsible infection has improved, as in acute post-streptococcal glomerulonephritis. The broader modern term infection-related glomerulonephritis also includes cases in which the infection is still active when nephritis appears. This is especially important in older adults, people with diabetes, patients with endocarditis and those with infected vascular devices or deep staphylococcal infection.

28.2 Infectious settings

Clinical form	Typical infection and timing	Important clue
Classic post-streptococcal GN	Usually 1-3 weeks after streptococcal pharyngitis or approximately 2-6 weeks after impetigo	Low C3, evidence of recent streptococcal infection and a typical nephritic syndrome
Other post-infectious GN	After selected bacterial, viral, fungal or parasitic infections	The pathogen and latency vary; diagnosis requires clinical-pathological correlation
Active bacterial infection-related GN	Often concurrent with staphylococcal skin, soft-tissue, bone, joint or visceral infection	Older age, diabetes or immunocompromise; IgA-dominant staining may occur
Endocarditis-associated GN	During subacute or acute infective endocarditis	Fever, murmur, embolic or immunologic signs, positive blood cultures and low complement
Shunt or device-associated nephritis	Persistent infection of an intravascular shunt, graft or device	Prolonged systemic inflammation; cure requires infection control and often device removal

The latency is a useful clue, not a diagnostic rule. Hematuria that begins at the same time as a minor respiratory infection is less typical of classic post-streptococcal GN. Conversely, nephritis during fever or bacteremia should prompt an immediate search for an ongoing infection rather than an assumption that the infection has already resolved.

28.3 Pathophysiology

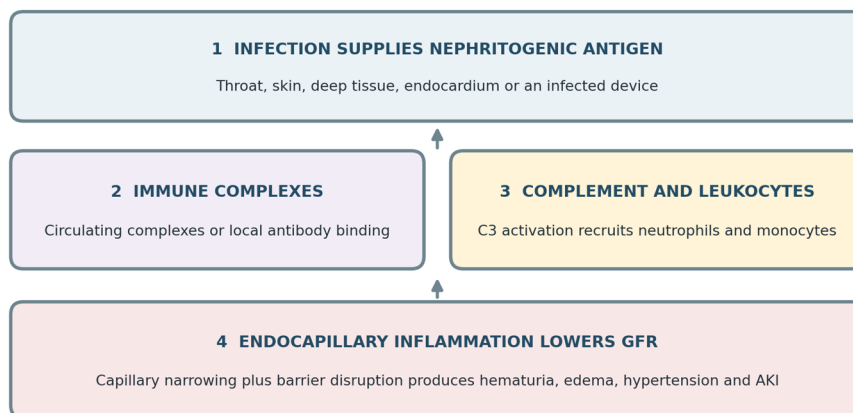
The initiating event is exposure to a nephritogenic microbial antigen. Antigen may circulate within immune complexes or become planted in the glomerulus and bind antibody locally. Only a small fraction of infections cause GN because the risk depends on microbial antigen properties, the host immune response, antigen clearance and complement regulation.

Immune deposits activate complement, commonly with strong participation of the alternative pathway. C3 fragments accumulate in the mesangium and capillary walls and generate chemotactic signals. Neutrophils and monocytes enter glomerular capillaries, endothelial and mesangial cells proliferate, and the swollen capillary tuft becomes crowded. This produces the exudative endocapillary pattern seen on light microscopy.

Inflammation disrupts the filtration barrier, allowing erythrocytes and protein to enter Bowman's space. Erythrocytes become dysmorphic while passing through the damaged barrier and may form red-cell casts in distal tubules. At the same time, narrowed capillary lumina reduce the ultrafiltration coefficient and GFR. The tubules retain sodium and water, so edema and hypertension can be prominent even when total urine protein is below the nephrotic range.

When antigen is eliminated, immune stimulation declines, complement is replenished and glomerular inflammation resolves. Persistent antigenemia, incomplete source control or an underlying abnormality of alternative-pathway regulation can sustain C3 activation. A course that does not resolve should therefore trigger a search for ongoing infection and reconsideration of the pathological diagnosis.

How infection produces acute post-infectious GN



Biopsy findings are three views of the same process

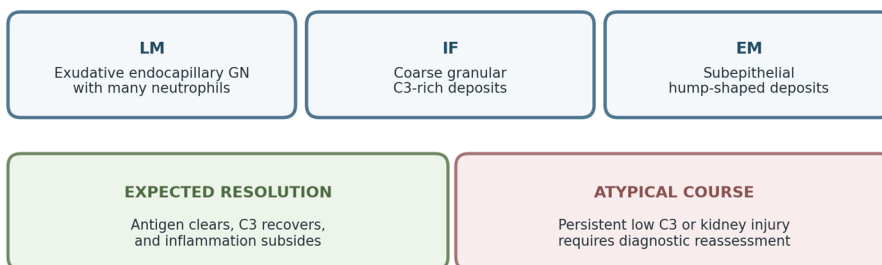


Figure 28.1. Infection supplies antigen, immune complexes activate complement, and leukocyte-rich endocapillary inflammation produces acute nephritic syndrome. LM, IF and EM show different parts of the same process.

28.4 Clinical presentation and laboratory findings

The typical presentation is abrupt visible or microscopic hematuria, periorbital or dependent edema, hypertension and reduced urine output. Headache, nausea or dyspnea may result from hypertension and fluid overload. Severe disease can cause pulmonary edema, hyperkalemia, metabolic acidosis, hypertensive encephalopathy or dialysis-requiring AKI.

Urine microscopy shows dysmorphic erythrocytes and red-cell casts. Proteinuria is usually subnephrotic, although nephrotic-range proteinuria can occur, particularly in adults and IgA-dominant infection-related GN. Serum creatinine reflects severity but may lag behind the fall in GFR. C3 is commonly reduced; C4 is often normal or less markedly reduced. In classic post-streptococcal disease, C3 usually returns toward normal within approximately 6-8 weeks.

Evidence of recent group A streptococcal infection may include an elevated antistreptolysin O titre after pharyngitis and anti-DNase B after either pharyngeal or skin infection. A single antibody titre must be interpreted with the clinical timing and local laboratory reference range. If active infection is possible, obtain appropriate cultures before antibiotics when this can be done without delaying treatment.

28.5 Diagnostic approach and indications for biopsy

1. Confirm a glomerular syndrome with urinalysis, urine microscopy and quantitative protein measurement.
2. Assess severity using creatinine trend, urine output, potassium, bicarbonate, blood pressure, oxygenation and volume status.
3. Search for the infection: examine the skin and soft tissues, teeth, heart, bones, joints and intravascular devices; obtain cultures and echocardiography when clinically indicated.
4. Measure C3 and C4 and select infection serology according to the suspected pathogen and timing.
5. Review the trajectory. Improvement in kidney function, urine findings and complement supports resolving post-infectious disease.

Kidney biopsy is often unnecessary in a child with a typical post-streptococcal presentation and prompt recovery. Biopsy should be considered when the diagnosis is uncertain, kidney dysfunction is severe or progressive, nephrotic syndrome is prominent, complement remains low beyond the expected recovery period, systemic findings suggest another disease, or renal abnormalities fail to improve. Biopsy is urgent when rapidly progressive kidney failure or pulmonary hemorrhage raises concern for crescentic GN.

28.6 Pathology

Light microscopy usually shows diffuse endocapillary proliferative and exudative GN. Glomeruli are enlarged and hypercellular because of endothelial and mesangial proliferation together with numerous neutrophils and monocytes. Capillary lumina are narrowed or occluded. Crescents and necrosis may appear in severe cases. During healing, hypercellularity declines; persistent segmental or global sclerosis and interstitial fibrosis indicate irreversible injury.

Immunofluorescence shows coarse granular C3 staining in capillary walls and mesangium, often with IgG. Patterns have been described as starry sky, garland or mesangial, but these names are descriptive rather than separate diseases. In staphylococcal infection-related GN, IgA may be dominant or co-dominant. C1q-dominant full-house staining is not typical and should prompt reconsideration of the diagnosis.

Electron microscopy classically shows large subepithelial hump-shaped electron-dense deposits. Mesangial and subendothelial deposits may coexist, especially early in the process. Humps strongly support infection-related GN in the correct clinical setting, but they are not absolutely specific. Deposit distribution and density change during resolution, so a late biopsy may show fewer humps and more mesangial deposits.

Method	Typical finding	What it means clinically
LM	Diffuse endocapillary hypercellularity with neutrophil-rich exudation; crescents may occur	Active inflammatory injury narrows capillaries and lowers GFR
IF	Coarse granular C3-dominant or C3 plus immunoglobulin staining in capillary walls and mesangium	Supports immune-complex and complement-mediated injury; IgA dominance suggests a staphylococcal setting but is not sufficient alone
EM	Subepithelial humps with variable mesangial and subendothelial electron-dense deposits	Confirms deposit location and phase; humps support but do not prove infection-related GN
Chronicity markers	Global glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis	Predict incomplete recovery more strongly than active hypercellularity alone

28.7 Treatment

Treat active infection promptly with culture-directed antimicrobial therapy and source control. Drain an abscess, remove an infected device when necessary and treat endocarditis for the recommended organism-specific duration. In classic post-streptococcal GN, antibiotics eradicate residual streptococci and reduce transmission, but they do not reliably reverse glomerular inflammation once the immune process is established.

Supportive kidney care is central. Restrict dietary sodium, and restrict fluid when edema, oliguria or hyponatremia is present. Use a loop diuretic for clinically important volume overload and treat severe hypertension without causing abrupt renal hypoperfusion. Stop NSAIDs and other avoidable nephrotoxins, adjust drug doses to kidney function, and treat hyperkalemia, acidosis or pulmonary edema urgently. Kidney replacement therapy is indicated for refractory life-threatening complications, not for a creatinine value alone.

Routine immunosuppression is not recommended because it can impair infection control and most classic cases recover with supportive care. Glucocorticoids or other immunosuppression may be considered only in exceptional biopsy-proven severe crescentic disease after active infection has been adequately treated or controlled and competing diagnoses have been excluded. This decision requires nephrology and infectious-disease input.

Clinical problem	First management step	Important caution
Active infection	Cultures when feasible, prompt targeted antibiotics and source control	Do not delay treatment in sepsis while waiting for kidney biopsy
Edema or pulmonary congestion	Sodium restriction and loop diuretic; oxygen and ventilatory support if required	Repeated fluid boluses worsen congestion unless true hypovolemia is present
Severe hypertension	Controlled blood-pressure reduction using agents appropriate to severity and setting	Avoid an abrupt fall that compromises kidney or cerebral perfusion
Hyperkalemia, acidosis or pulmonary edema refractory to medical therapy	Urgent nephrology assessment for kidney replacement therapy	Dialysis decisions depend on the whole clinical picture
Crescentic progressive GN	Confirm pathology, control infection and discuss individualized specialist therapy	Do not begin routine high-dose immunosuppression during uncontrolled infection

28.8 Evolution and prognosis

Children with classic post-streptococcal GN usually recover kidney function completely. Edema and hypertension often improve within days as GFR and natriuresis recover. Gross hematuria usually resolves within weeks, while microscopic hematuria and low-grade proteinuria can persist for months. C3 should recover within approximately 6-8 weeks; persistent hypocomplementemia at 8-12 weeks is a reason to reassess the diagnosis and ongoing infection rather than simply wait.

Adults have a less predictable course. Older age, diabetes, persistent staphylococcal infection, endocarditis, low baseline GFR and extensive chronic injury on biopsy increase the risk of incomplete recovery, CKD, kidney failure and death. Dialysis-requiring AKI, extensive

crescents, persistent proteinuria and tubular atrophy or interstitial fibrosis are adverse renal prognostic markers.

Follow serum creatinine, blood pressure, urinalysis, urine protein and C3 until recovery is established. A normal creatinine alone does not prove complete recovery if hypertension, albuminuria or hematuria persists. After severe AKI, reassess for CKD at approximately three months and continue longer follow-up when abnormalities remain.

28.9 When the course is atypical

Atypical finding	What to reconsider
C3 remains low beyond approximately 8-12 weeks	Ongoing infection, complement dysregulation or another immune-complex disease
Creatinine continues to rise or pulmonary hemorrhage appears	Rapidly progressive GN requiring urgent serology and biopsy
Nephrotic syndrome persists after inflammatory features settle	A second glomerular process or irreversible structural injury
Blood cultures remain positive or systemic inflammation continues	Uncontrolled endocarditis, abscess or infected device
Biopsy lacks the expected infection-related pattern	Re-examine the clinical diagnosis, IF pattern and EM findings

Case resolution

The boy's antistreptolysin O titre is elevated and throat culture is negative, consistent with a recently cleared pharyngeal infection. He receives salt restriction, a short course of loop diuretic therapy and blood-pressure treatment. Kidney function improves over one week, C3 normalizes by eight weeks and proteinuria falls progressively. Because the presentation and recovery are typical, kidney biopsy is not required.

Take-home messages

- Acute post-infectious GN is an immune-complex and complement-mediated cause of acute nephritic syndrome.
- Classic post-streptococcal GN follows infection, whereas modern infection-related GN may occur while infection is still active.
- The pathology triad is exudative endocapillary GN on LM, granular C3-rich deposits on IF and subepithelial humps on EM.
- Treatment combines infection eradication with careful control of volume, blood pressure and AKI complications; routine immunosuppression is inappropriate.
- Failure of C3, kidney function or urine abnormalities to improve should trigger reassessment and often kidney biopsy.

Self-assessment

1. Why can acute post-infectious GN cause marked edema even when proteinuria is below the nephrotic range?
2. How does the timing of classic post-streptococcal GN differ from infection-related GN during active staphylococcal infection?
3. State the characteristic LM, IF and EM findings of acute post-infectious GN.
4. Why are antibiotics necessary when infection is active but insufficient to treat pulmonary edema or severe hyperkalemia?
5. Which clinical or laboratory findings should prompt biopsy or reconsideration of the diagnosis?

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CHAPTER 29

Primary Chronic Glomerulopathies

Connect the target within the glomerulus to the long-term clinical pattern

- Explain the major mechanisms of IgA nephropathy, minimal change disease, FSGS, membranous nephropathy and complement-mediated disease.
- Recognize typical nephritic, nephrotic and mixed presentations.
- Describe the defining LM, IF and EM findings for each major disease.
- Distinguish a histological lesion such as FSGS or MPGN from an etiologic diagnosis.
- Identify clinical features that should prompt a search for a secondary or genetic cause.

Opening case

A 39-year-old woman has edema, serum albumin 22 g/L and proteinuria 7.2 g/day. Creatinine is normal, urine has few red cells, PLA2R antibody is positive and secondary screening is unrevealing. The nephrotic phenotype and subepithelial immune mechanism point toward primary membranous nephropathy, but clinical risk and biopsy context still guide management.

Primary glomerular diseases: connect presentation to biopsy pattern

ENTITY OR PATTERN	COMMON PRESENTATION	KEY BIOPSY CLUE
IgA NEPHROPATHY	hematuria ± proteinuria	mesangial IgA-dominant deposits
MINIMAL CHANGE	abrupt nephrotic syndrome	normal LM diffuse foot-process effacement
FSGS PATTERN	nephrotic or subnephrotic proteinuria	segmental scar in some glomeruli
MEMBRANOUS	nephrotic syndrome thrombosis risk	subepithelial deposits granular IgG/C3
MPGN PATTERN	mixed nephritic-nephrotic picture	mesangial/endocapillary growth double contours

FSGS and MPGN are patterns of injury: always search for the cause.

Figure 29.1. Mechanism-based map of the major primary glomerular diseases.

29.1 Read every biopsy in three layers

Light microscopy (LM) shows the distribution and pattern of injury: focal or diffuse, segmental or global, proliferative, necrotizing, crescentic, sclerosing or membranous. Immunofluorescence (IF) identifies the deposited proteins and their pattern—granular, linear, mesangial, capillary-wall or pauci-immune. Electron microscopy (EM) localizes deposits and demonstrates podocyte foot-process effacement, basement-membrane remodeling or organized fibrils. No layer is sufficient alone.

Where the lesion sits predicts the clinical syndrome

A simplified glomerular capillary loop

Deposit location is a strong clue, not an absolute rule; mixed patterns are common.

NEPHRITIC TENDENCY

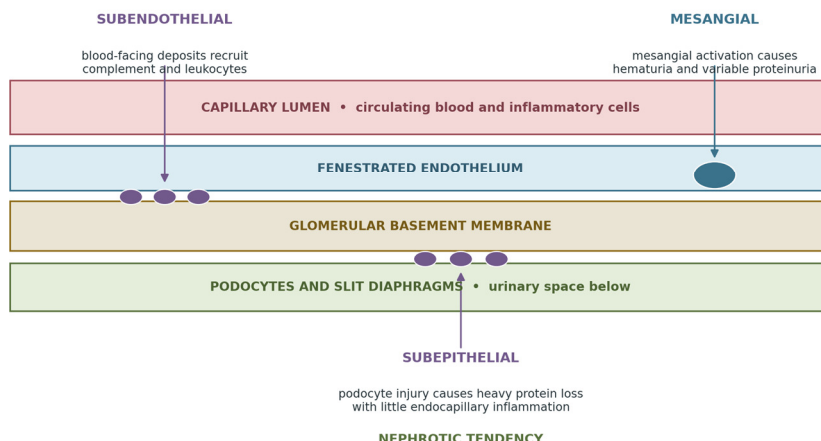


Figure 29.2. Deposit location predicts clinical behavior: subendothelial deposits are accessible to circulating inflammatory cells, whereas subepithelial deposits mainly disturb the podocyte–GBM barrier and produce proteinuria.

29.2 IgA nephropathy

IgA nephropathy is an immune-complex disease, not simply excess IgA. A useful four-hit model is: increased galactose-deficient IgA1; formation of antibodies against this altered IgA1; circulating immune-complex formation; and mesangial deposition with complement-mediated inflammation. Repeated injury produces segmental sclerosis and tubulointerstitial fibrosis, which are major drivers of long-term GFR loss.

The presentation ranges from microscopic hematuria to recurrent visible hematuria, proteinuria, hypertension and progressive CKD. Diagnosis generally requires biopsy. LM varies; IF shows dominant/codominant mesangial IgA; EM shows mesangial deposits. The Oxford MEST-C score describes lesions, but prognosis also depends strongly on eGFR, blood pressure and time-averaged proteinuria.

29.3 Minimal change disease

Minimal change disease is a podocytopathy. Circulating and immune-cell signals alter the podocyte actin cytoskeleton and slit diaphragm, causing abrupt loss of albumin selectivity without immune deposits. LM appears normal or nearly normal; IF is negative or nonspecific; EM shows diffuse foot-process effacement. Adults may have AKI, especially with severe edema, intravascular underfilling or NSAID-associated interstitial injury.

29.4 Focal segmental glomerulosclerosis

FSGS is a pattern of scar, not one disease. 'Focal' means only some glomeruli are involved; 'segmental' means only part of an affected tuft is scarred. Primary FSGS is thought to involve a circulating podocyte-toxic factor and commonly causes abrupt nephrotic syndrome with diffuse foot-process effacement. Genetic FSGS results from variants affecting podocyte or basement-membrane proteins. Secondary/adaptive FSGS follows glomerular hyperfiltration or reduced nephron number and often has less complete foot-process effacement and subnephrotic proteinuria.

LM shows segmental sclerosis and hyalinosis; early disease can be missed because only a few glomeruli are affected. IF may trap IgM and C3 nonspecifically in sclerotic segments. EM shows foot-process effacement whose extent helps, but does not perfectly distinguish primary from secondary disease. The cause matters because immunosuppression is appropriate for selected primary disease, not for adaptive or most genetic forms.

29.5 Membranous nephropathy

Antibodies bind podocyte antigens—most commonly PLA2R in primary disease—forming subepithelial immune deposits. Complement-mediated podocyte injury increases protein permeability but produces little endocapillary inflammation because deposits are separated from the circulation by the GBM. LM shows diffuse capillary-wall thickening and, with silver stains, spikes between deposits. IF shows granular capillary-wall IgG and C3. EM shows subepithelial deposits with foot-process effacement and later incorporation into remodeled GBM.

A positive PLA2R antibody strongly supports PLA2R-associated disease, but patients still require evaluation for clinically indicated secondary causes. Membranous nephropathy carries a notable venous thromboembolism risk, particularly when albumin is very low.

29.6 MPGN is a pattern; C3 glomerulopathy is a mechanism-defined group

The membranoproliferative pattern consists of mesangial/endocapillary hypercellularity and capillary-wall duplication. It is a response to chronic subendothelial or intramembranous deposits rather than a single disease. IF then separates immunoglobulin-positive immune-complex MPGN—prompting a search for infection, autoimmunity or monoclonal proteins—from C3-dominant disease, which suggests alternative complement dysregulation. EM distinguishes C3 glomerulonephritis from dense deposit disease by deposit character and location.

29.7 Pathology matrix for primary chronic glomerulopathies

Disease	LM	IF	EM	Mechanistic meaning
IgA nephropathy	Mesangial proliferation ± segmental sclerosis/crescents	Mesangial dominant/codominant with C3	Mesangial deposits	IgA complexes activate mesangial/complement injury
Minimal change disease	Normal or near-normal	Negative/nonspecific	Diffuse foot-process effacement	Functional podocyte/slit-diaphragm injury without deposits
FSGS	Focal segmental scar ± hyalinosis	IgM/C3 trapping in scars	Variable foot-process effacement	Final common scar from primary, genetic or adaptive podocyte stress
Membranous nephropathy	Capillary-wall thickening; spikes	Granular capillary IgG/C3; antigen typing	Subepithelial deposits; foot-process effacement	Antibody-mediated podocyte injury
C3 glomerulopathy	MPGN/mesangial/crescentic patterns	C3 dominant	Intramembranous dense deposits or mesangial/subendothelial deposits	Alternative complement dysregulation

CLINICAL REASONING

If a biopsy report says FSGS or MPGN, ask a second question: what caused this pattern? The pathology name is not yet the complete etiologic diagnosis.

29.8 Management evolution and prognosis by disease

IgA nephropathy

Pathophysiology. The four-hit model explains immune-complex formation, while progression reflects repeated injury plus maladaptive nephron responses. Mesangial cytokines injure podocytes and tubules. Segmental scars transfer filtration pressure to surviving nephrons, and

filtered protein activates tubular inflammation and fibrosis. Treatment therefore addresses both continuing IgA-mediated injury and nonspecific CKD progression.

Pathology. LM may be nearly normal, mesangioproliferative, endocapillary proliferative, segmentally sclerosing or crescentic. IF shows dominant or codominant mesangial IgA with C3. EM shows mesangial deposits. Oxford MEST-C records mesangial and endocapillary hypercellularity, segmental sclerosis, tubular atrophy/interstitial fibrosis and crescents. The T score reflects established tubulointerstitial damage and must be interpreted with eGFR and longitudinal proteinuria.

Treatment. Use sodium restriction, blood-pressure control and maximally tolerated ACE inhibitor or ARB when indicated. Add an SGLT2 inhibitor in eligible proteinuric CKD. Patients with continuing progression risk may be considered for targeted-release budesonide or sparsentan according to current guidance and local approval; sparsentan replaces rather than accompanies ACE inhibitor or ARB therapy. Reserve systemic glucocorticoids for carefully selected higher-risk patients after toxicity assessment. Treat rapidly progressive disease urgently.

Evolution. The disease may alternate between quiet periods and recurrent hematuria. Proteinuria can fall within months after hemodynamic therapy, whereas the eGFR slope requires longer observation. Remission lowers risk but does not eliminate the need for follow-up. Recurrence after transplantation is common but does not always threaten the graft.

Prognosis. Time-averaged proteinuria, eGFR, blood pressure and the Oxford T lesion are major predictors. Sustained proteinuria reduction is a meaningful treatment goal. The International IgAN Prediction Tool supports counseling but cannot predict one patient's outcome with certainty.

Minimal change disease

Pathophysiology. Immune and circulating signals disrupt the podocyte actin cytoskeleton and slit diaphragm without forming immune deposits. The lesion is mainly functional rather than destructive, so albumin permeability can change abruptly and can reverse with treatment. This explains sudden edema and very heavy, often selective proteinuria.

Pathology. LM is normal or nearly normal, IF is negative or nonspecific, and EM shows diffuse foot-process effacement with microvillous transformation. The biopsy must contain enough glomeruli because early FSGS can be missed. Mesangial immune deposits, extensive chronic scarring or only patchy effacement should prompt diagnostic reconsideration.

Treatment. Adults usually receive high-dose oral glucocorticoids with toxicity prevention and monitoring. Treat edema cautiously with sodium restriction and diuretics. Frequently relapsing, steroid-dependent or steroid-intolerant disease may receive rituximab, cyclophosphamide, a calcineurin inhibitor or mycophenolate. Withdraw an associated drug or treat an associated malignancy when present.

Evolution. More than 80 percent of adults eventually achieve remission with glucocorticoids, although response is slower than in children and relapse is common. AKI usually improves when nephrosis and hemodynamics recover, but tubular injury can delay recovery.

Prognosis. Kidney survival is excellent after remission. Steroid resistance should trigger review of biopsy sampling, adherence and possible FSGS or genetic/secondary podocytopathy. Thrombosis, infection and cumulative treatment toxicity often cause more morbidity than progressive scarring in classic steroid-sensitive disease.

Focal segmental glomerulosclerosis

Pathophysiology. FSGS begins with podocyte stress or loss, but the cause varies. Primary FSGS probably involves a circulating permeability factor and usually causes full nephrotic syndrome with diffuse podocyte dysfunction. Adaptive FSGS develops when reduced nephron number or obesity raises single-nephron filtration pressure. Genetic FSGS results from defects

in podocyte, cytoskeletal, mitochondrial or GBM proteins. Podocyte detachment exposes GBM, which adheres to Bowman's capsule and develops a segmental scar.

Pathology. LM shows sclerosis involving part of some glomeruli, with tip, perihilar, cellular, collapsing and not-otherwise-specified variants. IF often shows nonspecific IgM and C3 trapping in scars. EM assesses the distribution of foot-process effacement: diffuse effacement supports primary podocytopathy in the correct phenotype, while patchy effacement favors adaptive disease, but overlap is substantial. Collapsing lesions require evaluation for viral, drug, ischemic and APOL1-associated settings.

Treatment. Treat the cause, not the biopsy word alone. Primary FSGS with nephrotic syndrome usually receives high-dose glucocorticoids; use a calcineurin inhibitor for steroid-resistant or selected steroid-intolerant disease. Treat adaptive FSGS by lowering intraglomerular pressure and correcting the driver with RAAS blockade, SGLT2 inhibition when eligible, weight reduction or treatment of reflux and sleep apnea. Routine immunosuppression is inappropriate for adaptive and most genetic forms.

Evolution. Complete or partial proteinuria remission is the important turning point. Primary disease may remit, relapse or become treatment-resistant. Adaptive FSGS progresses if hyperfiltration persists. Primary FSGS can recur rapidly after transplantation, whereas many monogenic forms have a lower recurrence risk because the defect resides in the kidney.

Prognosis. Failure to achieve proteinuria remission, low baseline eGFR, collapsing morphology and advanced interstitial fibrosis predict poor kidney survival. Histologic variant contributes information but does not replace etiology and treatment response.

Membranous nephropathy

Pathophysiology. Autoantibodies bind antigens on or near the podocyte surface, most commonly PLA2R, and form subepithelial immune complexes. Complement injures podocytes and disrupts slit-diaphragm function. Because deposits lie outside the GBM and away from circulating inflammatory cells, proteinuria is marked while glomerular proliferation is limited. Continuing antigen-antibody activity creates new deposits while older deposits become incorporated into remodeled GBM.

Pathology. LM shows diffuse capillary-wall thickening; silver stain reveals spikes and later a chain-link pattern. IF shows granular capillary-wall IgG and C3, often with IgG4 dominance in PLA2R-associated disease. EM demonstrates subepithelial deposits and foot-process effacement followed by GBM reaction around deposits. Mesangial deposits, proliferation or an unusual IgG subclass pattern should prompt evaluation for lupus, infection, drug exposure, malignancy or another secondary cause.

Treatment. Begin supportive care immediately: edema and blood-pressure treatment, RAAS blockade when tolerated, lipid management, vaccination and individualized thrombosis prevention. Choose immunosuppression according to progression risk and complications. Specialist regimens include rituximab, cyclophosphamide plus glucocorticoids, or a calcineurin inhibitor strategy. Treat secondary causes. Serial PLA2R antibodies help assess immunologic response.

Evolution. Immunologic remission usually precedes proteinuria reduction because deposits and podocyte structure clear slowly. Proteinuria soon after antibody disappearance does not necessarily mean treatment failure. Lower-risk patients may enter spontaneous remission. Relapse can follow reappearance of PLA2R antibodies. Recurrence after transplantation is recognized.

Prognosis. Declining eGFR, persistent heavy proteinuria, high or rising PLA2R antibody levels, severe complications and chronic scarring are adverse. Sustained antibody reduction is favorable, but long-term prognosis is judged by proteinuria and eGFR. Severe hypoalbuminemia increases venous-thromboembolism risk.

Immune complex MPGN and C3 glomerulopathy

Pathophysiology. MPGN is the architectural response to chronic mesangial and subendothelial injury. Immune-complex MPGN is driven by persistent antigen-antibody complexes from infection, autoimmunity or monoclonal immunoglobulin. C3 glomerulopathy is driven mainly by alternative complement dysregulation. Mesangial interposition and new basement-membrane material produce double contours as glomeruli attempt to repair repeated endothelial-side injury.

Pathology. LM shows mesangial and endocapillary hypercellularity with double contours, sometimes with crescents. IF determines the etiologic branch: immunoglobulin plus complement supports immune-complex MPGN, while C3 staining at least two intensity grades stronger than immunoglobulin supports C3 glomerulopathy. EM localizes deposits and distinguishes dense deposit disease from C3 GN. Adults require a monoclonal-protein evaluation because a small clone can drive either pattern.

Treatment. Treat the cause. Eradicate infection, control autoimmune disease or use clone-directed therapy for monoclonal disease. Add optimal antiproteinuric and blood-pressure therapy. Selected idiopathic immune-complex disease or C3G with continuing active inflammation may receive mycophenolate plus glucocorticoids. Complement inhibitors are considered in specialist centers as evidence, approval and access evolve. Extensive chronic scar limits likely benefit.

Evolution. Infection-associated lesions may remit after antigen removal, whereas complement- or clone-driven disease often relapses or progresses. Proteinuria and hematuria can fluctuate while capillary remodeling and interstitial fibrosis accumulate. Immune-complex MPGN and C3G may recur after transplantation.

Prognosis. Historical cohorts suggest roughly one-third to one-half of patients with persistent MPGN-pattern disease reach kidney failure within about 10 years, but prognosis varies greatly by cause and treatment. Low eGFR, persistent proteinuria, crescents and interstitial fibrosis are adverse. Identifying a treatable infection or clone is more useful than assigning an old MPGN type number.

Disease	Disease modifying treatment	Best response or prognostic signal
IgA nephropathy	Supportive care, SGLT2 inhibitor and selected targeted therapy	Time-averaged proteinuria, eGFR slope and Oxford T lesion
Minimal change	Glucocorticoid; steroid-sparing therapy for relapse or dependence	Remission predicts excellent kidney survival
Primary FSGS	Glucocorticoid; calcineurin inhibitor when resistant or intolerant	Complete or partial proteinuria remission
Adaptive or genetic FSGS	Treat hyperfiltration or cause; avoid routine immunosuppression	Persistent proteinuria, eGFR and fibrosis
Membranous	Risk-based rituximab, cyclophosphamide-steroid or CNI strategy	PLA2R response usually precedes proteinuria response
MPGN or C3G	Treat infection, autoimmunity, clone or complement mechanism	Cause control, eGFR, proteinuria and chronicity

Case resolution

Biopsy confirms membranous nephropathy with subepithelial deposits and PLA2R staining. Her disease is risk-stratified using proteinuria, albumin, eGFR trend, antibody level and complications. Supportive therapy begins immediately; immunologic treatment is chosen according to risk rather than proteinuria alone.

Take-home messages

- Primary glomerular diseases are best understood by the injured target: immune complex, podocyte, GBM antigen or complement pathway.

- LM gives the injury pattern, IF identifies deposited proteins, and EM localizes deposits and podocyte injury.
- FSGS and MPGN are patterns that demand an etiologic search.
- Subendothelial deposits tend to provoke inflammation; subepithelial deposits tend to produce proteinuria.
- Chronic prognosis depends heavily on eGFR, proteinuria, blood pressure and tubulointerstitial scarring.

Self-assessment

1. Describe the four-hit model of IgA nephropathy.
2. What are the LM, IF and EM findings in minimal change disease?
3. Why is FSGS not a complete etiologic diagnosis?
4. How does deposit location explain the nephrotic presentation of membranous nephropathy?
5. How does IF distinguish immune-complex MPGN from C3 glomerulopathy?

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CHAPTER 30

Rapidly Progressive Glomerulopathies

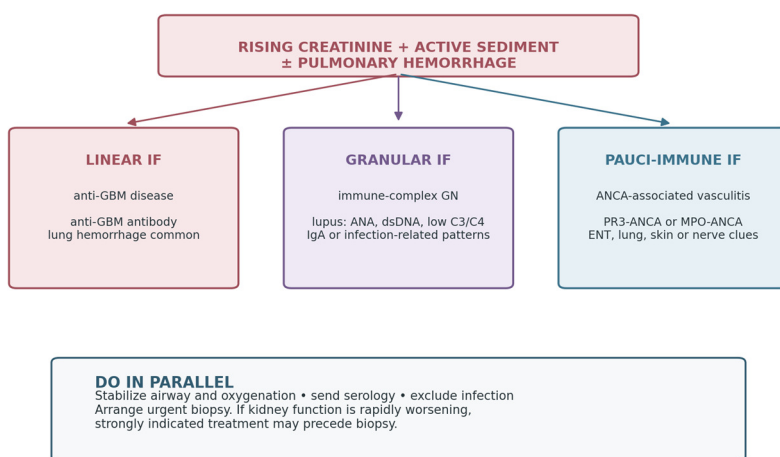
Recognize crescentic injury as a kidney-threatening emergency

- Define rapidly progressive glomerulonephritis clinically and crescents pathologically.
- Compare anti-GBM, immune-complex and pauci-immune crescentic GN.
- Recognize pulmonary–renal syndrome and initiate an emergency diagnostic pathway.
- Interpret ANCA and anti-GBM tests in clinical context.
- Explain why treatment may need to begin before the final biopsy report.

Opening case

A 58-year-old woman develops fatigue, hemoptysis and oliguria over 10 days. Creatinine has risen from 88 to 486 $\mu\text{mol/L}$ (1.0 to 5.5 mg/dL), urine contains RBC casts, and hemoglobin has fallen. This is pulmonary–renal syndrome until proved otherwise; diagnostic sampling and specialist treatment planning must occur immediately.

Rapid glomerulonephritis: use immunopathology to organize the emergency



Pulmonary hemorrhage may occur without hemoptysis; falling hemoglobin and new infiltrates matter.

Figure 30.1. The three immunopathological categories of rapidly progressive crescentic glomerulonephritis.

30.1 RPGN is a clinical trajectory

Rapidly progressive glomerulonephritis (RPGN) is a syndrome in which GFR falls substantially over days to weeks, usually with active glomerular urine sediment. Crescentic GN is the corresponding pathological pattern. They overlap strongly but are not synonyms: a biopsy may show crescents without a dramatic creatinine rise, and early RPGN may have only a limited sampled crescent burden.

A crescent forms when severe capillary-wall rupture allows fibrin, plasma proteins and inflammatory mediators to enter Bowman's space. Parietal epithelial cells proliferate and macrophages accumulate. Cellular crescents represent active injury and may respond to prompt treatment; fibrocellular and fibrous crescents increasingly represent irreversible scar.

30.2 The three immunopathological categories

Category	Mechanism	IF pattern	Common causes	Key clue
Anti-GBM	Antibody against $\alpha 3$ chain of type IV collagen	Strong linear IgG $\pm$ C3 along GBM	Anti-GBM disease; kidney-limited or pulmonary–renal	Anti-GBM antibody; alveolar hemorrhage
Immune-complex	Deposited complexes activate complement and leukocytes	Granular immunoglobulin/complement	Lupus, IgA/IgAV, infection-related GN, cryoglobulinemia	Complement pattern and disease-specific serology
Pauci-immune	ANCA-activated neutrophils injure small vessels	Little or no immune staining	MPO-ANCA or PR3-ANCA vasculitis; some ANCA-negative	Systemic vasculitis; pulmonary, ENT, skin or nerve disease

30.3 ANCA-associated vasculitis

Inflammatory priming exposes proteinase 3 (PR3) or myeloperoxidase (MPO) on neutrophils. ANCA binding activates neutrophils, which adhere to endothelium, release proteases and reactive oxygen species, and amplify the alternative complement pathway. The result is necrotizing small-vessel inflammation with few immune deposits. Kidney biopsy typically shows focal necrosis and crescents on LM, pauci-immune IF, and capillary-wall breaks without substantial deposits on EM.

PR3-ANCA is more often associated with granulomatosis with polyangiitis and relapse; MPO-ANCA is more common in microscopic polyangiitis, but antibody specificity and clinical syndrome do not map perfectly. A positive ANCA is not diagnostic by itself—drugs, infections and inflammatory disease can cause positivity. Conversely, a minority of pauci-immune GN is ANCA negative.

30.4 Anti-GBM disease

Autoantibodies target the noncollagenous domain of the $\alpha 3$ chain of type IV collagen in glomerular and alveolar basement membranes. This explains the kidney–lung phenotype. LM shows necrosis and crescents, often at a similar stage because the insult is temporally focused. IF shows the defining smooth linear IgG pattern; EM shows basement-membrane rupture but no immune-complex deposits. Anti-GBM serology should be drawn urgently, but a negative result does not completely exclude tissue-bound or atypical disease.

30.5 Immune-complex crescentic GN

Severe lupus nephritis, IgA nephropathy/vasculitis, infection-related GN and cryoglobulinemic GN can all rupture capillary loops and form crescents. IF remains granular and disease-specific rather than pauci-immune or linear. The distinction is clinically decisive: infection-related disease prioritizes antimicrobial source control, while severe autoimmune disease generally requires immunosuppression.

30.6 The first-hour pathway

Action	Purpose
Assess airway, oxygenation, hemoptysis and chest imaging	Identify diffuse alveolar hemorrhage; oxygen saturation can initially be misleading.
Repeat creatinine, potassium, bicarbonate, blood count and urine microscopy	Measure trajectory and immediate dialysis-threatening complications.
Send ANCA, anti-GBM, ANA, anti-dsDNA, C3/C4 and infection tests as indicated	Differentiate categories before therapy alters results.
Obtain blood cultures when infection is plausible	Endocarditis and other infections can mimic vasculitis and ANCA may be positive.
Contact nephrology and plan urgent biopsy	Histology establishes category, activity and chronicity.
Discuss immediate immunosuppression/plasma exchange with specialists	In life-threatening disease, treatment may precede final histology; regimen depends on cause and severity.

MEDICAL EMERGENCY

Do not wait for creatinine to reach a particular value. The combination of a rapid rise, active urine sediment and pulmonary hemorrhage or oliguria is sufficient for emergency nephrology involvement.

30.7 Activity versus chronicity on biopsy

Active lesions—fibrinoid necrosis, cellular crescents and interstitial inflammation—suggest potentially recoverable tissue but also urgent ongoing injury. Chronic lesions—global sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis—predict limited recovery. Treatment decisions balance both: severe active disease can justify urgent therapy, while extensive irreversible scar changes the expected benefit and toxicity tradeoff.

30.8 Treatment evolution and prognosis for each RPGN mechanism**Pauci immune ANCA associated glomerulonephritis**

Pathophysiology. ANCA-activated neutrophils damage endothelium and amplify C5a-dependent inflammation. Capillary walls rupture, but little immunoglobulin is deposited, explaining how an intensely inflammatory lesion can be pauci-immune. Successive glomeruli may be injured over days, producing necrosis and crescents of different ages.

Pathology. LM shows focal segmental fibrinoid necrosis and crescents with a mixture of normal, active and sclerosed glomeruli. IF shows little or no immunoglobulin. EM confirms capillary breaks without substantial electron-dense deposits. The percentage of normal glomeruli and tubular atrophy/interstitial fibrosis provide major prognostic information.

Treatment. Induce remission promptly with glucocorticoids plus rituximab or cyclophosphamide. Reduced-dose glucocorticoid regimens limit infection risk for many patients. Consider plasma exchange selectively in severe kidney disease or hypoxemic diffuse alveolar hemorrhage after weighing benefit and risk. Use rituximab- or azathioprine-based maintenance after remission. Include Pneumocystis prophylaxis, vaccination, infection surveillance and fertility counseling. The pivotal ADVOCATE avacopan report was retracted in June 2026; avacopan should therefore not be presented as settled evidence pending authoritative reassessment, even where regulatory status has not yet changed.

Evolution. Creatinine may continue to rise briefly because injured nephrons recover slowly. Hematuria often improves before eGFR. Dialysis at presentation does not prove irreversibility; recovery can occur over weeks when active lesions predominate. Relapse is more frequent with PR3-ANCA, previous relapse and upper-airway disease.

Prognosis. Baseline eGFR, dialysis requirement, percentage of normal glomeruli and interstitial fibrosis strongly predict renal outcome. Early mortality and morbidity are also influenced by age, infection and treatment toxicity. ANCA titers support follow-up but should not alone trigger treatment escalation in an asymptomatic patient.

Anti GBM disease

Pathophysiology. IgG autoantibodies bind the alpha-3 chain noncollagenous domain of type IV collagen in glomerular and alveolar basement membranes. Antibody binding activates complement and inflammatory cells along the capillary wall. The intrinsic, continuously distributed antigen produces a temporally focused and often severe injury.

Pathology. LM shows widespread necrosis and crescents, often at a similar stage; chronic cases develop fibrous crescents. IF demonstrates bright, smooth linear IgG along the GBM, commonly with C3. EM shows GBM rupture without immune-complex deposits. Double-positive patients have anti-GBM antibodies plus ANCA and retain the relapse tendency of ANCA vasculitis.

Treatment. When organ salvage is plausible, start plasma exchange to remove antibody, high-dose glucocorticoids to suppress inflammation and cyclophosphamide to stop antibody

production. Do not wait for biopsy when clinical probability is high and pulmonary hemorrhage is present. Benefit is limited when a patient is dialysis-dependent, has no pulmonary hemorrhage and biopsy shows near-total irreversible crescents; this decision requires individualized specialist assessment. Defer transplantation until antibodies have remained undetectable for at least 6 months.

Evolution. Antibody levels can fall rapidly with plasma exchange, but kidney recovery depends on remaining salvageable glomeruli. Classic isolated anti-GBM disease rarely relapses after antibodies remain absent. Double-positive disease requires longer surveillance and often ANCA-style maintenance planning.

Prognosis. Presentation before dialysis dependence, lower creatinine, fewer crescents and more normal glomeruli favor recovery. Patient survival is often good with prompt treatment, but kidney survival remains poor when dialysis is required at presentation and crescents are extensive. Pulmonary hemorrhage may recover and remains a reason to treat even when renal recovery seems unlikely.

Immune complex crescentic glomerulonephritis

Pathophysiology. Crescents are a response to severe capillary injury, not a separate etiology. In lupus, IgA disease, infection-related GN and cryoglobulinemia, immune deposits activate complement and leukocytes until capillary loops rupture. IF retains disease-specific granular deposits, unlike pauci-immune and anti-GBM disease.

Pathology. LM shows necrosis and cellular or fibrocellular crescents superimposed on the parent pattern: endocapillary lupus, mesangial IgA, exudative infection-related GN or MPGN-pattern cryoglobulinemia. IF and EM identify the parent disease through full-house deposits, IgA-dominant mesangial deposits, C3-rich humps or organized cryoglobulin deposits.

Treatment. Treat the parent mechanism. Proliferative lupus requires immunosuppressive induction; infection-related GN requires antimicrobial source control; severe rapidly progressive IgA or IgAV may require specialist immunosuppression; cryoglobulinemia requires treatment of infection, autoimmunity or the clone. Glucocorticoids given before exclusion of infection can worsen sepsis.

Evolution. Cellular crescents can regress after prompt control of injury. Fibrocellular and fibrous crescents increasingly leave permanent nephron loss. Relapse follows the biology of the underlying disease rather than the generic presence of crescents.

Prognosis. More normal glomeruli, prompt cause control and little interstitial fibrosis favor recovery. Extensive crescents, oliguria, dialysis requirement and delayed therapy are adverse, but crescent percentage must be interpreted with chronicity, cause and response.

RPGN category	Immediate disease directed strategy	Key prognostic discriminator
Pauci-immune or ANCA	Rituximab or cyclophosphamide plus glucocorticoids; selective plasma exchange	Normal glomeruli, baseline eGFR and interstitial fibrosis
Anti-GBM	Plasma exchange plus glucocorticoids and cyclophosphamide when salvage is plausible	Dialysis at presentation and proportions of crescents and normal glomeruli
Immune-complex	Treat the parent cause with immune suppression or infection/clone control	Cause control plus the activity-chronicity balance

Case resolution

MPO-ANCA is strongly positive and biopsy shows pauci-immune necrotizing crescentic GN with predominantly cellular crescents. The patient receives specialist-directed remission-induction therapy and kidney-replacement support for severe complications. The early recognition of pulmonary–renal syndrome prevents a dangerous delay.

Take-home messages

- RPGN is defined by rapid functional decline; crescents are the pathological response to severe capillary rupture.
- IF separates linear anti-GBM, granular immune-complex and pauci-immune disease.
- Pulmonary–renal syndrome is a medical emergency.
- ANCA and anti-GBM results must be interpreted with the phenotype and biopsy.
- Biopsy activity and chronicity together inform both urgency and reversibility.

Self-assessment

1. How does a cellular crescent form?
2. What IF pattern distinguishes the three major categories of crescentic GN?
3. Why does anti-GBM disease affect both glomerular and alveolar capillaries?
4. Give two reasons why a positive ANCA alone does not establish ANCA vasculitis.
5. Which biopsy findings suggest active potentially reversible injury and which suggest chronic scar?

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CHAPTER 31

Secondary Chronic Glomerulopathies

When the glomerulus is injured by systemic autoimmunity, deposits, infection, metabolism or a clone

- Recognize major categories of chronic secondary glomerular disease.
- Explain the pathophysiology and pathology of lupus nephritis, renal amyloidosis and monoclonal gammopathy of renal significance.
- Use LM, IF, EM and protein typing to distinguish organized and nonorganized deposits.
- Understand why a small B-cell or plasma-cell clone can cause severe kidney disease.
- Use a structured causes table to guide targeted secondary investigation.

Opening case

A 67-year-old man has progressive edema, proteinuria 6.8 g/day, albumin 24 g/L and eGFR 42 mL/min/1.73 m². Serum electrophoresis shows only a small monoclonal band. The kidney lesion may nevertheless be severe: clone size predicts hematologic tumor burden, not the nephrotoxicity of the secreted immunoglobulin.

31.1 A practical map of chronic glomerular causes

Chronic glomerulopathy means persistent glomerular injury that causes albuminuria/proteinuria, hematuria, reduced GFR or structural scarring over more than three months. The list below is intentionally broad and organized by mechanism. It contains the major recognized causes rather than every case report. Some entities—especially IgA disease, infection-related GN and vasculitis—may present acutely or rapidly progressively but become chronic when injury persists or scars.

Etiologic group	Major causes	Typical glomerular pattern	High-yield clue or test
Primary immune/podocyte	IgA nephropathy; minimal change disease; primary FSGS; primary membranous nephropathy; C3 glomerulopathy	Mesangial GN; podocytopathy; segmental scar; membranous; MPGN	Biopsy LM/IF/EM; PLA2R; complement studies; IgA dominant IF
Metabolic/hemodynamic	Diabetic kidney disease; obesity-related glomerulopathy; adaptive FSGS from reduced nephron mass, reflux or hyperfiltration; sickle-cell glomerulopathy	Mesangial expansion/nodules; glomerulomegaly; secondary FSGS	Diabetes duration/retinopathy; obesity; nephron loss; hemoglobinopathy
Autoimmune/systemic	Lupus nephritis; IgA vasculitis; ANCA-associated GN with chronic scars; anti-GBM sequelae; rheumatoid/inflammatory disease causing AA amyloid	Immune-complex GN; crescentic/sclerosing GN; amyloid	ANA/anti-dsDNA/complement; ANCA/anti-GBM; systemic inflammatory activity
Chronic infection	HBV; HCV/cryoglobulinemia; HIV; endocarditis or infected devices/shunts; selected parasitic infections	Membranous, MPGN, collapsing FSGS, immune-complex GN	Viral tests; cryoglobulins and low C4; cultures; exposure/geography
Monoclonal/deposition	AL amyloid; monoclonal immunoglobulin deposition disease; PGNMID; cryoglobulinemic GN; immunotactoid GN; light-chain proximal tubulopathy; cast nephropathy	Amyloid, nodular sclerosis, MPGN/proliferative GN, organized deposits, casts	Serum/urine immunofixation; free light chains; biopsy typing; marrow/clone assessment
Other amyloid	AA amyloid; hereditary transthyretin and other hereditary amyloidoses; ALECT2; dialysis-related β 2-microglobulin amyloid	Amyloid deposits; kidney involvement varies by protein	Mass-spectrometry typing; chronic inflammation; family history; dialysis vintage
Genetic/hereditary	COL4A3/A4/A5-related disease (Alport spectrum); podocyte-gene disorders; APOL1-associated nephropathy; Fabry disease; LMX1B/nail–patella syndrome; complement-gene variants	GBM disorder, FSGS, storage disease, C3 glomerulopathy	Family history; hearing/ocular or systemic features; genetic testing; EM
Drug/toxin-associated	NSAIDs (MCD or membranous); lithium (chronic tubulointerstitial disease/FSGS); interferons, bisphosphonates or heroin (FSGS); hydralazine/propylthiouracil (ANCA); immune-checkpoint therapies	Podocytopathy, membranous, FSGS, pauci-immune or mixed lesions	Medication timeline; stop culprit; biopsy if phenotype is severe or atypical
Malignancy-associated	Solid tumors associated with membranous nephropathy; Hodgkin lymphoma with MCD; lymphoid/plasma-cell neoplasms with monoclonal lesions	Membranous, MCD or monoclonal-deposit disease	Age-appropriate cancer evaluation; hematologic work-up directed by biopsy

SCOPE NOTE

Hypertensive nephrosclerosis is primarily a vascular and tubulointerstitial process, although chronic glomerular ischemia and secondary focal scars occur. It should not be used as an automatic explanation for proteinuria without considering diabetic, primary glomerular, genetic and monoclonal causes.

31.2 Lupus nephritis: pathophysiology

Loss of immune tolerance permits autoantibodies to bind nuclear antigens. Circulating or in-situ immune complexes deposit in mesangial, subendothelial and subepithelial locations. Complement activation, Fc-receptor signaling, neutrophils, monocytes, T cells and local kidney cells amplify inflammation. Deposit location explains phenotype: subendothelial deposits are exposed to the circulation and provoke proliferative nephritis; subepithelial deposits chiefly injure podocytes and cause nephrotic proteinuria.

Persistent inflammation activates fibroblasts and drives tubular atrophy, interstitial fibrosis and glomerulosclerosis. These chronic lesions may progress even when serologic activity improves. Clinical activity, anti-dsDNA and complement trends are useful, but none can reliably replace biopsy when the result will change treatment.

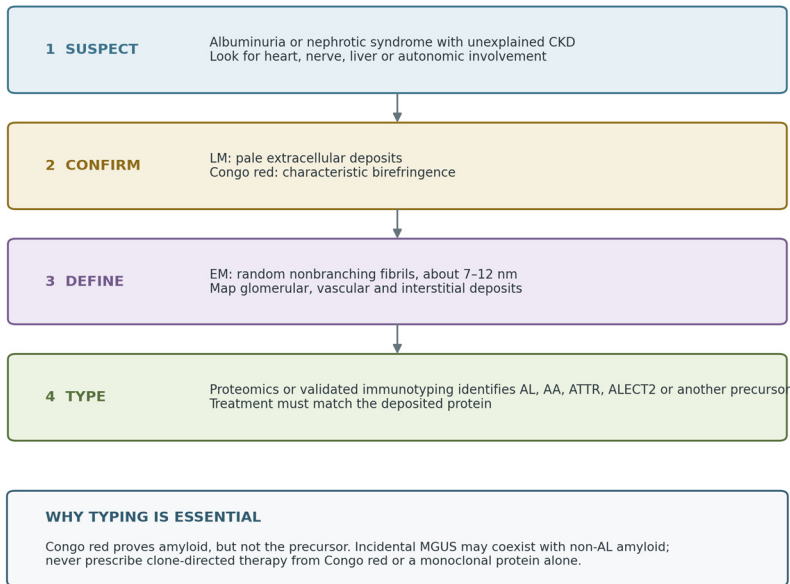
31.3 Lupus nephritis: pathology classes

ISN/RPS class	Main pathology	Typical clinical expression	Student interpretation
I Minimal mesangial	Normal LM; mesangial immune deposits on IF/EM	Often clinically silent	Deposits exist without LM proliferation
II Mesangial proliferative	Mesangial hypercellularity and deposits	Hematuria/proteinuria; GFR often preserved	Inflammation remains mainly mesangial
III Focal	Active/chronic lesions in <50% of glomeruli	Nephritic or mixed; variable GFR	Focal proliferative immune-complex GN
IV Diffuse	Active/chronic lesions in ≥50% of glomeruli; wire loops, necrosis or crescents may occur	Often severe nephritic/mixed syndrome and reduced GFR	Most extensive proliferative class
V Membranous	Subepithelial deposits and capillary-wall thickening; may coexist with III/IV	Nephrotic proteinuria common	Podocyte-facing deposits dominate phenotype
VI Advanced sclerosing	≥90% globally sclerosed glomeruli without residual activity	Advanced irreversible CKD	Chronic scar dominates; aggressive immunosuppression is unlikely to restore lost tissue

IF commonly shows the 'full-house' combination of IgG, IgA, IgM, C3 and C1q. EM localizes deposits and may show tubuloreticular inclusions related to interferon signaling. The pathology report should also state activity and chronicity features; class alone does not capture reversibility.

31.4 Renal amyloidosis: how misfolded proteins damage the glomerulus

Renal amyloidosis: confirm the material, then type the precursor



Morphology → Congo red → ultrastructure → protein typing

Figure 31.1. Amyloid pathology: extracellular Congo-red-positive deposits contain randomly arranged fibrils and must be typed to identify the precursor protein.

Amyloid proteins misfold into β -pleated-sheet-rich fibrils that resist degradation and accumulate extracellularly. In the glomerulus, mesangial and capillary-wall deposits disrupt filtration architecture and cause heavy proteinuria; vascular and interstitial deposits contribute to ischemia and reduced GFR. AL amyloid derives from a monoclonal immunoglobulin light chain; AA amyloid derives from serum amyloid A during sustained inflammation. Hereditary proteins, ALECT2 and other types have different organ distributions and treatments.

LM shows amorphous, acellular eosinophilic deposits that expand the mesangium and capillary walls. Congo red staining produces apple-green birefringence under appropriately aligned polarized light. IF may demonstrate light-chain restriction in AL but can be misleading because of nonspecific trapping. EM shows randomly arranged nonbranching fibrils, usually about 7–12 nm. Laser microdissection followed by mass spectrometry is the preferred typing method when available; typing is mandatory because treatment targets the precursor protein, not the fibril itself.

31.5 Monoclonal gammopathy of renal significance

How a small clone can cause major kidney injury

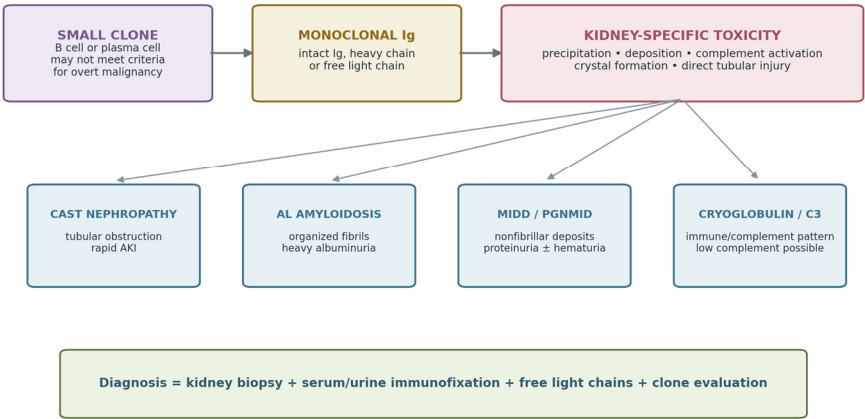


Figure 31.2. A small clone can produce a highly nephrotoxic monoclonal immunoglobulin and cause MGRS even without myeloma-defining tumor burden.

MGRS describes kidney lesions caused by a monoclonal immunoglobulin from a B-cell or plasma-cell clone that does not meet conventional criteria for treatment of a hematologic malignancy. The kidney is the reason the clone becomes clinically significant. Injury depends on the physicochemical properties of the protein—its tendency to aggregate, activate complement, bind basement membranes or crystallize—not simply its serum concentration.

Lesion	Mechanism and LM	IF	EM / key distinction
AL amyloidosis	Fibrillar extracellular deposition; amorphous deposits	Usually one light-chain type	Random 7–12 nm fibrils; Congo red positive
Monoclonal immunoglobulin deposition disease	Nonfibrillar deposits; nodular sclerosis and thickened basement membranes	Linear monotypic light/heavy-chain staining	Powdery electron-dense deposits; Congo red negative
PGNMID	Proliferative or MPGN pattern	Single heavy-chain subclass and single light chain	Granular nonorganized deposits
Immunotactoid GN	Often MPGN pattern	Frequently monotypic immunoglobulin	Parallel microtubules, usually >30 nm
Fibrillary GN	Mesangial proliferative/MPGN/sclerosing patterns	Usually IgG; DNAJB9 positive	Random fibrils commonly 10–30 nm; Congo red usually negative
Cryoglobulinemic GN	MPGN with intracapillary pseudothrombi	Immunoglobulin and complement; may be monoclonal	Curved/organized deposits; correlate with cryoglobulin testing

31.6 The monoclonal work-up

Screen with serum and urine immunofixation plus serum free light chains. Both κ and λ rise as GFR falls, so interpret the ratio using a kidney-adjusted reference range and the assay used locally. A negative serum electrophoresis alone does not exclude a small clone. Kidney biopsy defines the lesion; immunofluorescence, EM and often proteomic typing establish whether deposits are truly monoclonal. Hematology then searches for the responsible clone.

COMMON MISTAKE

Do not diagnose AL amyloidosis from a monoclonal blood result plus Congo-red-positive tissue without typing the amyloid. Monoclonal gammopathy of undetermined significance is common in older adults and may coexist incidentally with AA, ATTR or another amyloid type.

31.7 Principles of management

All patients need kidney-protective supportive care tailored to blood pressure, volume, proteinuria, thrombosis risk and GFR. Disease-specific treatment differs: lupus therapy suppresses immune-complex generation and inflammation; AA amyloid treatment suppresses the inflammatory source; AL amyloid and MGRS require clone-directed therapy; infection-related secondary disease requires eradication of the infection. These decisions are multidisciplinary and biopsy-led.

31.8 Lupus nephritis treatment evolution and prognosis

Class I and II disease generally requires systemic lupus treatment rather than kidney-specific induction unless another lesion is present. Active class III or IV disease, with or without class V, requires glucocorticoids plus mycophenolate or low-dose intravenous cyclophosphamide. Selected patients may receive add-on belimumab or a calcineurin inhibitor such as voclosporin. A calcineurin inhibitor may reduce heavy proteinuria through immune and podocyte effects but can lower GFR hemodynamically and requires monitoring. Treat pure class V according to proteinuria, nephrotic complications and extrarenal activity. Class VI represents advanced sclerosis, so care focuses on CKD and kidney-replacement planning.

A useful early response is a substantial fall in proteinuria with stable or improving GFR during the first 6 to 12 months; complete response may take longer. Persistent proteinuria may reflect active immune disease, chronic scar or a membranous/podocyte component. Repeat biopsy is considered when distinguishing these mechanisms would change treatment. Complement and anti-dsDNA trends support assessment but cannot establish histologic activity or remission alone.

Low baseline eGFR, delayed response, recurrent flares, persistent proteinuria, hypertension, high chronicity index, thrombotic microangiopathy and poor treatment adherence or access worsen prognosis. Early proteinuria reduction is favorable. Maintenance treatment prevents flare and protects remaining nephrons. Pregnancy should be planned during stable quiescent disease using pregnancy-compatible medication.

Class	Dominant pathology and phenotype	Treatment logic and expected course
I	Minimal mesangial deposits with normal LM	Treat systemic lupus; renal course is usually excellent.
II	Mesangial deposits and hypercellularity	Treat systemic activity; worsening urine or GFR may indicate transformation.
III	Focal proliferative lesions in less than 50 percent of glomeruli	Induction plus maintenance; activity can reverse, chronic scar cannot.
IV	Diffuse proliferative lesions in at least 50 percent of glomeruli	Urgent induction; major inflammatory burden and CKD risk.
V	Subepithelial membranous deposits	Treat nephrotic risk and immune activity; proteinuria may improve slowly.
VI	At least 90 percent globally sclerosed glomeruli	Immunologic rescue is unlikely; focus on CKD and kidney-failure care.

31.9 Renal amyloidosis treatment evolution and prognosis

Amyloidosis is a precursor-production disease. Existing fibrils clear slowly, so treatment first stops production of the amyloid-forming protein. In AL amyloidosis, a plasma-cell clone produces an unstable and directly toxic light chain. In AA amyloidosis, continuing inflammation maintains high serum amyloid A. Hereditary transthyretin, fibrinogen A alpha-chain and apolipoprotein amyloidoses, as well as ALECT2, require different evaluation and treatment. A monoclonal protein does not prove AL amyloid in an older adult; mass-spectrometric typing prevents treatment of the wrong precursor.

Treat AL amyloidosis rapidly with plasma-cell-directed therapy. A common modern first-line regimen combines daratumumab with bortezomib, cyclophosphamide and dexamethasone;

selected fit patients undergo autologous stem-cell transplantation. Treat AA amyloidosis by sustained control of the inflammatory disease or infection so serum amyloid A falls. Supportive care includes cautious diuresis, blood-pressure management and thrombosis assessment. ACE inhibitor or ARB therapy may be poorly tolerated with autonomic hypotension or cardiac amyloid. Dialysis and transplantation remain options in selected patients with controlled systemic disease.

In AL disease, hematologic response precedes renal response. Proteinuria may require 6 to 12 months or longer to fall because deposits and glomerular injury resolve slowly. In AA disease, sustained suppression of serum amyloid A can stabilize or improve kidney manifestations. Continued precursor production drives new deposits and can cause recurrence after transplantation.

Cardiac involvement and cardiac biomarkers are the main determinants of early survival in AL amyloidosis. Baseline eGFR and proteinuria influence renal survival, while a deep and rapid hematologic response improves both. In AA disease, outcome depends on durable inflammatory control and accumulated organ damage. Extensive vascular or interstitial deposition, low eGFR and continuing precursor production are adverse.

31.10 Monoclonal gammopathy of renal significance lesions

Monoclonal immunoglobulin injures the glomerulus through several structures. AL or AH amyloidosis forms Congo-red-positive fibrils. Monoclonal immunoglobulin deposition disease produces nonfibrillar deposits along glomerular and tubular basement membranes. Proliferative GN with monoclonal immunoglobulin deposits produces a granular immune-complex pattern restricted to one heavy-chain subclass and one light chain. Immunotactoid GN contains organized microtubules, while type I cryoglobulinemic GN can form pseudothrombi. A monoclonal gammopathy may also dysregulate complement and present as C3G without visible monoclonal deposits.

LM defines the pattern of injury. IF on frozen or paraffin tissue identifies heavy and light chains, while EM defines fibrillar, microtubular, powdery or granular organization. Congo red and mass spectrometry type amyloid. Pathology must establish monotypy convincingly. Some patients with PGNMID have no detectable circulating clone, so negative marrow and immunofixation studies do not invalidate a well-characterized renal lesion.

Treatment is clone-directed even when the clone is too small to meet malignancy criteria. Plasma-cell clones receive plasma-cell regimens, often proteasome-inhibitor or anti-CD38 based. B-cell or lymphoplasmacytic clones commonly receive rituximab-based therapy. The regimen depends on lesion, clone, GFR, frailty and toxicity. Supportive antiproteinuric therapy is added but cannot stop continuing monoclonal protein production.

Hematologic response usually precedes renal response. Proteinuria may improve slowly, while persistent production drives new deposits and CKD. Recurrence after kidney transplantation is common if the clone is not in a deep and durable response. Baseline eGFR, proteinuria, chronic scarring and depth of clone response determine renal prognosis; small clone size is not reassuring.

31.11 Other secondary chronic glomerulopathies

Cause and typical lesion	Pathophysiology and pathology clue	Treatment evolution and prognosis
Diabetes / diabetic nephropathy	Hyperfiltration, metabolic injury and podocyte loss; GBM thickening, mesangial expansion, nodules and arteriolar hyalinosis	Use multifactorial cardiorenal therapy. Albuminuria may regress; eGFR decline, fibrosis and vascular disease determine prognosis.
Obesity or reduced nephron mass / adaptive FSGS	Single-nephron hyperfiltration; glomerulomegaly, perihilar scars and partial foot-process effacement	Treat weight or cause and use RAAS/SGLT2 therapy when eligible. Progression slows when hyperfiltration falls.
Hepatitis B / membranous or MPGN	Viral antigen immune complexes	Antiviral therapy is central; immunosuppression may reactivate infection. Outcome follows viral control and chronicity.
Hepatitis C / Mixed cryoglobulinemic MPGN	Mixed cryoglobulin complexes, low C4 and an MPGN pattern	Use direct-acting antivirals and selected rituximab for severe vasculitis. Relapse suggests persistent antigen or clone.
HIV / collapsing or immune-complex disease	Viral and APOL1-associated podocyte injury or immune deposits	Start antiretroviral therapy and supportive care. Baseline GFR and fibrosis predict recovery.
Endocarditis, shunt or chronic infection	Persistent microbial antigen with C3-rich proliferative GN	Use source control and antibiotics. Chronic infection and crescents worsen prognosis.
Drugs / membranous, MCD, FSGS or immune-complex GN	Drug-specific podocyte or immune injury	Withdraw the culprit. Recovery varies; checkpoint-inhibitor lesions may need specialist immune treatment.
Malignancy / membranous, MCD or monoclonal lesions	Tumor antigen, cytokine or paraprotein-mediated injury	Treat malignancy and renal complications. Kidney response often tracks tumor response.
Systemic autoimmunity	Immune complexes and complement activation	Control systemic disease. Relapses, response and chronicity determine outcome.
Genetic glomerulopathy	Inherited COL4A, podocyte or complement defect	Use supportive or mechanism-specific care; immunosuppression is often ineffective. Offer family counseling.

Case resolution

Biopsy shows Congo-red-positive glomerular and vascular deposits. Mass spectrometry identifies AL- λ amyloid, and marrow assessment finds a small plasma-cell clone. Despite the small clone, the patient has organ-threatening disease and begins hematology–nephrology coordinated clone-directed therapy plus careful edema management.

Take-home messages

- Secondary chronic glomerulopathy is a mechanism-based category that includes metabolic, autoimmune, infectious, clonal, genetic, drug and malignancy-associated disease.
- In lupus, deposit location explains whether proliferative nephritis or nephrotic proteinuria dominates.
- Amyloid must be demonstrated and typed; Congo red alone does not identify the precursor.
- MGRS severity depends on protein nephrotoxicity, not clone size.
- Kidney biopsy links the glomerular pattern to the systemic cause and directs multidisciplinary treatment.

Self-assessment

1. Why do subendothelial lupus deposits usually cause more inflammation than subepithelial deposits?
2. Which lupus nephritis classes are proliferative, and what does the 50% threshold describe?
3. What are the defining LM, Congo red and EM findings of amyloid?

4. Why must amyloid deposits be typed even when a monoclonal protein is present?
5. Define MGRS and explain why a small clone may require treatment.

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Part V model answers

Chapter 27

1. RBCs are trapped within tubular uromodulin, so the bleeding occurred upstream within the nephron, usually the glomerulus.
2. Nephrotic-range proteinuria is a quantity of protein loss; nephrotic syndrome adds hypoalbuminemia and clinical consequences such as edema.
3. Reduced plasma oncotic pressure with effective underfilling and primary renal sodium retention are the two major, overlapping mechanisms.
4. Rapid creatinine rise, oliguria, RBC casts, severe hypertension and pulmonary hemorrhage or edema are key danger features.
5. Pretest probability matters: broad panels produce weak or incidental positives that can misdirect diagnosis and treatment.

Chapter 28

1. Reduced GFR activates tubular sodium and water retention, expanding extracellular volume; nephrotic hypoalbuminemia is not required for edema.
2. Classic post-streptococcal GN begins after a latent interval, whereas staphylococcal infection-related GN often develops while infection is still active.
3. LM shows neutrophil-rich endocapillary proliferation; IF shows coarse granular C3-dominant or C3 plus immunoglobulin deposits; EM shows subepithelial humps with variable mesangial or subendothelial deposits.
4. Antibiotics remove the antigen source, but established volume overload, hyperkalemia and acidosis require direct supportive or emergency treatment.
5. Progressive kidney failure, pulmonary hemorrhage, prominent nephrotic syndrome, persistent low C3 beyond 8-12 weeks, ongoing infection or failure of urine and kidney abnormalities to improve should prompt reassessment and often biopsy.

Chapter 29

1. Galactose-deficient IgA1, autoantibody formation, circulating immune complexes, then mesangial deposition and complement injury.
2. LM near-normal, IF negative/nonspecific, EM diffuse podocyte foot-process effacement.
3. FSGS is a scar pattern produced by primary, genetic or adaptive mechanisms; treatment depends on the cause.
4. Subepithelial deposits injure podocytes without direct access to circulating inflammatory cells, producing heavy proteinuria with limited proliferation.
5. Immune-complex MPGN has immunoglobulin plus complement; C3 glomerulopathy has C3-dominant staining.

Chapter 30

1. Capillary rupture releases fibrin and mediators into Bowman's space, causing parietal epithelial proliferation and macrophage accumulation.
2. Anti-GBM is linear, immune-complex is granular, and pauci-immune disease has little or no staining.
3. The target $\alpha 3$ type IV collagen domain is shared by glomerular and alveolar basement membranes.
4. ANCA can occur with infection, drugs or other inflammation, and phenotype/biopsy may not support vasculitis.
5. Necrosis and cellular crescents indicate activity; global sclerosis, fibrous crescents and interstitial fibrosis indicate chronic scar.

Chapter 31

- 1.** Subendothelial deposits face the circulation and readily activate complement and leukocytes; subepithelial deposits are separated by the GBM.
- 2.** Classes III and IV are proliferative; the threshold is the proportion of glomeruli affected—below versus at least 50%.
- 3.** Amorphous extracellular deposits on LM, Congo-red positivity with apple-green birefringence, and random 7–12 nm fibrils on EM.
- 4.** An incidental monoclonal gammopathy may coexist with another amyloid type; therapy differs completely by precursor protein.
- 5.** MGRS is kidney injury from a nephrotoxic monoclonal immunoglobulin made by a clone below usual malignancy-treatment thresholds; organ injury makes treatment necessary.

PART VI

Tubulointerstitial Cystic and Hereditary Kidney Diseases

Three focused disorders approached through localization, mechanism, morphology and longitudinal care

How to use Part VI

First locate the dominant compartment. Tubulointerstitial disease produces tubular dysfunction and a relatively bland urine sediment; ADPKD is recognized primarily by its structural and familial phenotype; Alport syndrome is a glomerular-basement-membrane disorder signaled by persistent hematuria. Each chapter follows the same sequence: diagnosis, pathophysiology, pathology, treatment, clinical evolution and prognosis.

CHAPTER 32

Tubulointerstitial Diseases

Acute inflammation and chronic scarring of the tubules and interstitium

- Recognize findings that localize kidney injury to the tubules and interstitium.
- Diagnose acute tubulointerstitial nephritis without relying on the insensitive fever-rash-eosinophilia triad.
- Relate tubular transport defects to light-microscopy findings and to the patient's laboratory results.
- Separate potentially reversible active inflammation from irreversible tubular atrophy and interstitial fibrosis.
- Plan cause-directed treatment, follow recovery and explain the major prognostic factors.

Opening case

A 71-year-old woman has taken omeprazole for several months and received amoxicillin-clavulanate three weeks ago. Creatinine has risen from 0.9 to 2.7 mg/dL (80 to 239 micromol/L). Urinalysis shows 1+ protein, 20–30 leukocytes per high-power field and no bacteriuria. Urine ACR is 120 mg/g, whereas urine PCR is 760 mg/g. Ultrasound shows unobstructed, normal-sized kidneys. She has no fever, rash or eosinophilia.

Clinical	reasoning
The urine contains much more total protein than albumin, suggesting low-molecular-weight proteins that damaged proximal tubules failed to reabsorb. Sterile pyuria supports interstitial inflammation. Absence of the classic hypersensitivity triad does not exclude acute tubulointerstitial nephritis.	

32.1 Diagnosis: first localize the lesion

The interstitium is the tissue between tubules and peritubular capillaries. Because tubules perform segment-specific transport, tubulointerstitial injury often causes electrolyte, acid-base or concentrating defects before heavy proteinuria appears. Glomerular filtration may decline when edema compresses peritubular capillaries, inflammatory mediators alter local blood flow, and injured tubules activate tubuloglomerular feedback.

Finding	Why it occurs	How to interpret it
Sterile pyuria or leukocyte casts	Leukocytes migrate from inflamed interstitium through tubular epithelium.	Supports interstitial inflammation after excluding UTI, stones and contamination; leukocyte casts are helpful but insensitive.
Tubular proteinuria	Proximal tubules fail to reclaim filtered low-molecular-weight proteins.	PCR may be much higher than ACR; beta-2-microglobulin or alpha-1-microglobulin can support proximal injury.
Normoglycemic glycosuria	Proximal sodium-glucose transport is impaired.	Suggests proximal tubular injury if the patient is not taking an SGLT2 inhibitor.
Non-anion-gap metabolic acidosis	Proximal bicarbonate loss or distal acidification failure.	Confirm renal rather than gastrointestinal bicarbonate loss and interpret urine pH in clinical context.
Hypokalemia, hypophosphatemia or hypomagnesemia	Damaged segments fail to reclaim specific solutes.	Urinary excretion helps distinguish renal wasting from low intake or extrarenal loss.
Polyuria and low urine osmolality	Medullary concentration response and are impaired.	Exclude high fluid intake, hyperglycemia and other osmotic diuresis.
Mild or moderate proteinuria	Tubular proteins and secondary glomerular leakage contribute.	Nephrotic-range proteinuria is unusual; if present, consider NSAID-associated minimal change disease or a second glomerular lesion.

A medication timeline is essential. Record every prescription, over-the-counter drug, supplement and exposure, together with start and stop dates. Antibiotics and NSAIDs may cause symptoms within days; proton-pump inhibitors may produce an indolent presentation after

weeks or months; immune-checkpoint-inhibitor nephritis often appears several weeks to months after exposure. Previous tolerance does not guarantee safety on re-exposure.

Etiologic group	Representative causes	High-yield clue
Drugs	Beta-lactams, sulfonamides, rifampicin, fluoroquinolones, PPIs, NSAIDs, anticonvulsants, diuretics	Temporal relationship; NSAID-associated disease may have little fever/rash and can coexist with nephrotic proteinuria.
Cancer immunotherapy	PD-1, PD-L1 and CTLA-4 inhibitors	Other immune adverse events, concurrent PPI exposure or combination therapy may increase suspicion.
Infection	Pyelonephritis; bacterial, viral, fungal or parasitic interstitial nephritis	Organism, immune status and imaging determine therapy; do not assume that every interstitial infiltrate is drug allergic.
Systemic disease	Sjögren syndrome, sarcoidosis, IgG4-related disease, lupus, TINU syndrome	Dry eyes/mouth, uveitis, hypercalcemia, organ enlargement or disease-specific serology.

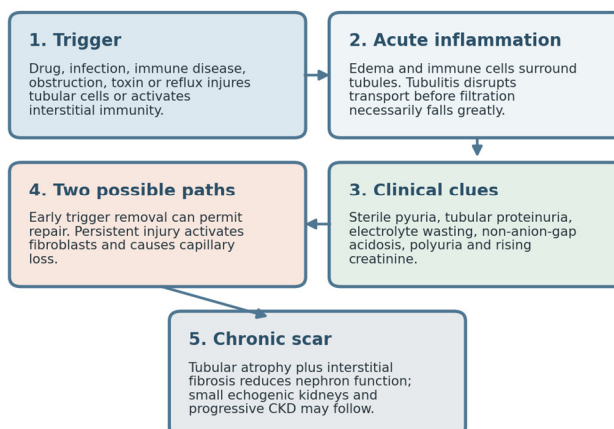
32.2 Pathophysiology of acute tubulointerstitial nephritis

Most drug-induced acute interstitial nephritis is an idiosyncratic, cell-mediated immune reaction rather than dose-dependent toxicity. A drug or metabolite may behave as a hapten, bind to tubular structures, mimic an endogenous antigen or become trapped in the interstitium. Tubular epithelial cells and antigen-presenting cells activate drug-specific T lymphocytes. Cytokines recruit monocytes, lymphocytes and sometimes eosinophils. Interstitial edema separates tubules from capillaries and tubulitis directly injures epithelial cells.

This explains three bedside observations. First, a very small drug dose can trigger severe disease. Second, recurrence after re-exposure can be faster and more severe because immune memory persists. Third, creatinine may keep rising briefly after the drug is stopped because the inflammatory response does not cease immediately.

Tubular epithelial cells can recover if basement-membrane scaffolding and peritubular blood supply remain intact. If inflammation persists, maladaptive repair activates fibroblasts and extracellular-matrix deposition. Peritubular capillary rarefaction causes chronic hypoxia, while arrested tubular cells secrete profibrotic mediators. The endpoint is tubular atrophy and interstitial fibrosis, the strongest morphologic predictors of incomplete recovery.

Tubulointerstitial injury: why time matters



Student mental model: active inflammation may be reversible; established tubular atrophy and interstitial fibrosis are not.

Figure 32.1. Acute tubulointerstitial inflammation can resolve after early trigger removal or progress through maladaptive repair to chronic tubular atrophy and interstitial fibrosis.

32.3 Pathology: what LM, IF and EM show

Kidney biopsy is not required in every patient. It is most useful when the diagnosis remains uncertain, kidney dysfunction is severe or progressive, a competing glomerular disease is possible, or glucocorticoids are being considered after the suspected trigger has been removed. A biopsy samples a small part of the kidney, so focal disease may be missed; morphology must be interpreted with the clinical timeline.

Modality	Acute tubulointerstitial nephritis	Chronic tubulointerstitial nephritis	Meaning
LM	Interstitial edema with lymphocytes and monocytes; variable plasma cells/eosinophils; tubulitis; acute tubular injury. Granulomas in selected causes.	Tubular atrophy, thick or wrinkled tubular basement membranes, interstitial fibrosis, chronic mononuclear inflammation and peritubular capillary loss.	The amount of fibrosis and tubular atrophy estimates chronic irreversible damage better than the density of eosinophils.
IF	Usually negative or nonspecific; occasional linear tubular-basement-membrane staining in rare antibody-mediated forms.	Usually nonspecific. Immune deposits suggest another disease or a systemic process.	A negative IF study is expected and does not exclude AIN.
EM	Tubular epithelial injury, widened interstitium and inflammatory cells; glomerular ultrastructure is usually preserved.	Tubular-basement-membrane multilayering/thickening, epithelial simplification and interstitial collagen.	EM is mainly used to exclude a subtle glomerular lesion when proteinuria is disproportionate.

Pathology translation

Tubulitis means inflammatory cells have crossed the tubular basement membrane and entered the tubular epithelium. Tubular atrophy means the tubule has become small and simplified. Interstitial fibrosis means normal tissue has been replaced by collagen. Active tubulitis may respond to therapy; established atrophy and fibrosis generally do not.

32.4 Treatment of acute disease

1. Stop the most likely offending drug promptly and document it as a probable adverse reaction. Avoid rechallenge unless a specialist judges the drug indispensable and no alternative exists.
2. Correct volume depletion, obstruction, sepsis and electrolyte abnormalities. Adjust medication doses to current kidney function and avoid additional nephrotoxins.
3. Treat a proven infection and the relevant systemic disease. Infection-associated interstitial nephritis is not treated as drug allergy.
4. Discuss kidney biopsy when kidney function fails to improve, diagnosis is uncertain, or immunosuppression carries meaningful risk.
5. Consider glucocorticoids for biopsy-supported or strongly suspected drug-induced AIN with persistent kidney dysfunction after trigger removal. Evidence is observational; regimens vary, but prednisone approximately 0.5–1 mg/kg/day followed by taper is commonly used under nephrology supervision.
6. Monitor creatinine, electrolytes, urine protein and adverse treatment effects. Dialysis is used for standard urgent indications, not for a creatinine threshold alone.

Common mistake

Do not wait for fever, rash and eosinophilia. The full triad occurs in a minority of patients. Urine eosinophils have inadequate sensitivity and specificity and should not be used to confirm or exclude acute interstitial nephritis.

32.5 Clinical evolution and prognosis of acute disease

Creatinine may begin to improve over days after the trigger is removed, but recovery often continues for weeks to months. Outcomes range from complete return to baseline, through partial recovery with new CKD, to persistent kidney failure. Worse recovery is associated with delayed culprit withdrawal, longer duration of AKI, older age, severe peak dysfunction and a

larger burden of tubular atrophy/interstitial fibrosis. Early treatment of a reversible cause is therefore more important than the presence or absence of eosinophils.

Recheck kidney function and proteinuria after discharge—commonly within 1–2 weeks when recovery is incomplete or medication changes are active, and again by approximately 3 months to identify AKD/CKD. The interval should be shorter if creatinine is still rising, electrolyte losses persist or the patient is taking glucocorticoids.

32.6 Chronic tubulointerstitial nephritis

Chronic tubulointerstitial nephritis is not simply “old AIN.” It is a final common pathway caused by sustained toxic, metabolic, obstructive, infectious, ischemic, reflux-related or immune injury. Tubular dysfunction is often prominent, urine sediment is bland, proteinuria is usually below nephrotic range and hypertension may appear as nephron mass falls. Ultrasound may show small echogenic kidneys, irregular scars or papillary calcification, but normal kidney size does not exclude chronic disease.

Pathophysiologically, repeated tubular injury causes failed epithelial repair, macrophage activation, fibroblast proliferation, matrix deposition and loss of peritubular capillaries. Surviving nephrons hyperfilter, which can add secondary glomerulosclerosis. At biopsy, tubular atrophy and interstitial fibrosis dominate; chronic inflammation may be sparse even when injury is continuing.

Cause	Mechanism and diagnosis	Pathology	Treatment, evolution and prognosis
Analgesic nephropathy	Long cumulative exposure, historically combination analgesics, causes medullary ischemia and oxidant injury. CT may show papillary calcification or sloughed papillae.	Papillary necrosis, chronic interstitial fibrosis and irregular cortical scarring.	Stop exposure and manage CKD. Established scar is irreversible; progression may stabilize. Urothelial carcinoma risk is increased in classic phenacetin-associated disease.
Lithium nephropathy	Lithium enters principal cells through ENaC, reduces AQP2 expression and causes concentrating failure; long exposure can produce chronic distal-nephron injury.	Chronic TIN with distal/collecting-duct microcysts; secondary FSGS may coexist.	Use the lowest effective level; monitor eGFR, calcium and concentrating function. Coordinate withdrawal with psychiatry. Amiloride may reduce nephrogenic diabetes insipidus. CKD may progress after long exposure.
Reflux/obstructive nephropathy	Intrarenal reflux, recurrent infection or sustained high pressure causes focal parenchymal injury. Imaging may show calyceal distortion, hydronephrosis or asymmetric scars.	Patchy corticomedullary scars, tubular atrophy and “thyroidization”; secondary FSGS in remnant nephrons.	Relieve obstruction, treat infection and manage bladder dysfunction/BP/proteinuria. Earlier correction preserves function; advanced bilateral scars confer CKD risk.
Aristolochic-acid nephropathy	Herbal or contaminated products produce DNA adducts and dose-related proximal tubular toxicity. Exposure history is critical.	Paucicellular, severe interstitial fibrosis with tubular atrophy, often corticomedullary; urothelial atypia may coexist.	Eliminate exposure, manage CKD and provide specialist-guided urothelial cancer surveillance. Progression may be rapid; fibrosis is irreversible.
Immune/metabolic chronic TIN	Sjögren syndrome, sarcoidosis, IgG4-related disease, hypercalcemia, hypokalemia and other systemic disorders injure tubules and interstitium.	Cause-dependent chronic inflammation or granulomas superimposed on tubular atrophy and fibrosis.	Treat the systemic cause and complications. Prognosis depends on reversibility, treatment timing and chronic scar burden.

The treatment of chronic TIN has four goals: remove ongoing injury; correct tubular losses and acid-base disturbances; reduce cardiovascular and CKD progression risk; and prepare early for kidney replacement therapy if disease advances. Immunosuppression is useful only when active immune disease remains; it cannot reverse a scarred small kidney.

Prescribing safely

A bland urine does not make CKD benign. Review NSAIDs, PPIs, lithium, herbal products and cumulative chemotherapy exposure; measure ACR as well as total protein; correct metabolic acidosis and potassium disorders; and dose drugs to current kidney function.

Case resolution

Omeprazole and amoxicillin-clavulanate are stopped. Because creatinine continues to rise to 3.2 mg/dL and no alternative cause is found, biopsy is performed. LM shows edema, lymphocyte-rich interstitial inflammation and tubulitis with limited fibrosis; IF is negative and glomeruli are preserved. After infection is excluded, nephrology initiates a glucocorticoid course. Creatinine falls to 1.3 mg/dL over eight weeks. The patient is told to avoid the suspected drugs and has repeat eGFR and ACR at three months.

Take-home messages

- Tubulointerstitial disease causes transport defects, sterile pyuria and tubular proteinuria more often than a nephritic sediment.
- The classic hypersensitivity triad is insensitive; diagnosis depends on exposure chronology and exclusion of competing causes.
- AIN is usually T-cell-mediated; edema and tubulitis can become chronic fibrosis if the trigger persists.
- LM defines activity and chronicity; IF is usually negative and EM mainly excludes a second glomerular lesion.
- Rapid cause removal offers the best chance of recovery; fibrosis and tubular atrophy predict incomplete recovery.
- Chronic TIN treatment is cause-directed plus full CKD and tubular-complication care.

Self-assessment

1. Why may urine PCR be much higher than ACR in proximal tubular injury?
2. Which three common clinical findings are too insensitive to exclude acute interstitial nephritis?
3. What do tubulitis and interstitial fibrosis mean pathologically?
4. When should kidney biopsy be considered in suspected acute interstitial nephritis?
5. Name three factors associated with incomplete kidney recovery after AIN.

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CHAPTER 33

Autosomal Dominant Polycystic Kidney Disease

Diagnose the structural phenotype, estimate progression risk and intervene before eGFR falls

- Explain how PKD1 or PKD2 dysfunction produces focal but progressively expanding kidney cysts.
- Use family history, ultrasound, MRI and genetic testing appropriately for diagnosis.
- Describe gross, light-microscopy, immunofluorescence and electron-microscopy findings.
- Estimate rapid progression using age-adjusted total kidney volume and eGFR trajectory.
- Apply blood-pressure treatment, tolvaptan selection and complication management.
- Counsel patients about clinical evolution, extrarenal disease, family screening and prognosis.

Opening case

A 38-year-old woman with hypertension has bilaterally enlarged kidneys containing innumerable cortical and medullary cysts and several liver cysts. Her father reached kidney failure at 54 years. eGFR is 82 mL/min/1.73 m², ACR is 65 mg/g and MRI height-adjusted total kidney volume places her in Mayo Imaging Class 1D.

Clinical reasoning

A normal eGFR does not mean early disease. In ADPKD, cyst burden and total kidney volume often increase for years before the remaining nephrons can no longer compensate. Mayo Class 1D and early-onset hypertension make rapid progression likely.

33.1 Diagnosis

ADPKD is usually caused by a heterozygous pathogenic variant in PKD1 or PKD2; rarer genes can produce an ADPKD-like phenotype. Begin with a three-generation pedigree, including kidney failure age, intracranial aneurysm or subarachnoid hemorrhage, unexplained early death and relatives with mild disease. Ask about hypertension, episodic gross hematuria, cyst infection, stones, chronic pain and liver symptoms.

In a person with a 50% pretest risk because a parent is affected, age-specific ultrasound criteria are highly useful. These criteria were developed for typical PKD1/PKD2 families and should not be applied mechanically to people without a known family history or with an atypical imaging pattern.

Age in a person at 50% risk	Unified ultrasound supporting ADPKD criterion	Student caution
15–39 years	At least 3 cysts in total, unilateral or bilateral	A negative ultrasound may not exclude disease, especially with PKD2 or a milder genotype.
40–59 years	At least 2 cysts in each kidney	MRI or genetic testing may be needed when living donation depends on confident exclusion.
60 years or older	At least 4 cysts in each kidney	Simple cysts are common with aging, so stricter criteria are required.

When family history is absent, diagnosis requires a typical bilateral diffuse cystic phenotype and exclusion of mimics. MRI detects smaller cysts and measures total kidney volume more reproducibly than ultrasound. Genetic testing is especially valuable when imaging is equivocal, disease is unusually mild or severe, the pedigree is unclear, syndromic features are present, or a potential related living donor is being evaluated. A negative panel does not completely exclude ADPKD because some variants remain technically difficult to detect or interpret.

Do not biopsy typical ADPKD

The diagnosis is usually made by imaging plus family/genetic information. Biopsy adds risk and seldom changes management. Consider tissue only when a superimposed disease is suspected—for example, rapidly progressive AKI or unexplained nephrotic syndrome.

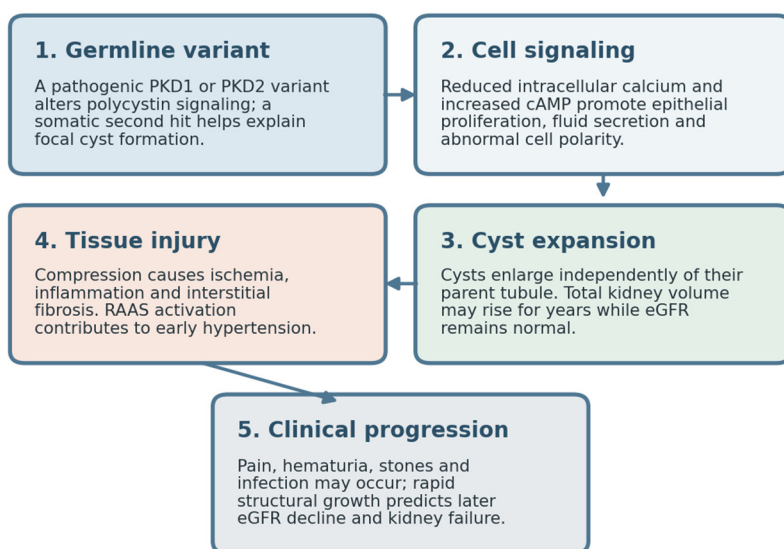
33.2 Pathophysiology

Polycystin-1 and polycystin-2 form a signaling complex involved in tubular cell calcium signaling, mechanosensation and maintenance of differentiated epithelial architecture. The patient inherits one altered allele, but cysts arise only from a small fraction of tubules. A somatic “second hit,” reduced dosage or other cellular stress allows individual tubular clones to lose enough polycystin function to initiate a cyst. This focal model explains why every cell carries the germline variant but not every tubule becomes cystic.

Reduced intracellular calcium favors increased cyclic AMP. cAMP stimulates chloride and fluid secretion into the cyst lumen and promotes epithelial proliferation through growth pathways. Cells lose normal planar orientation, so tubules dilate. Once a cyst separates from its parent tubule, transepithelial secretion sustains growth. Cyst expansion compresses vessels and neighboring nephrons, activates inflammation and fibrosis, and increases kidney size.

RAAS activation contributes to hypertension, which often appears before eGFR falls. Glomerular hyperfiltration in remaining nephrons temporarily maintains overall GFR. Eventually nephron loss and interstitial fibrosis exceed compensatory capacity, and eGFR declines. Liver cysts arise from biliary epithelium through related signaling abnormalities; intracranial aneurysms reflect systemic vascular effects rather than kidney cysts spreading outside the kidney.

ADPKD: from a focal cyst to progressive kidney disease



Key idea: in ADPKD, structural progression usually precedes measurable loss of filtration.

Figure 33.1. ADPKD structural progression begins with altered polycystin signaling and focal cyst initiation; kidney enlargement and fibrosis usually precede a sustained decline in eGFR.

33.3 Pathology

Level	Typical finding	Clinical interpretation
Gross examination	Both kidneys are enlarged and distorted by numerous cysts of variable size in cortex and medulla. Cysts may contain clear, hemorrhagic or infected fluid.	The structural burden can be very large while eGFR remains preserved. Hemorrhage explains sudden pain and gross hematuria.
LM	Cysts arise from multiple nephron segments and have flattened or cuboidal epithelium. Intervening parenchyma shows tubular atrophy, interstitial inflammation/fibrosis, vascular compression and later glomerulosclerosis.	The amount of preserved tissue and fibrosis—not simply cyst count—determines filtration. Secondary lesions may coexist.
IF	No disease-specific immune-deposit pattern.	Positive immune staining suggests a superimposed glomerular disorder rather than ADPKD itself.
EM	Attenuated or simplified cyst-lining epithelium, altered cell junctions and basement-membrane remodeling; findings are not diagnostic.	EM is a research or problem-solving tool, not a routine diagnostic test for typical ADPKD.

33.4 Predicting clinical evolution

The most useful question is not only “Does this patient have ADPKD?” but also “Is progression likely to be rapid?” For patients with typical bilateral diffuse disease, the Mayo Imaging Classification uses age and height-adjusted total kidney volume. Classes 1A–1E represent progressively faster predicted growth; classes 1C–1E may indicate rapid progression, but 1C is a mixed group and should be interpreted with eGFR slope, genotype, family history and clinical events.

A historical eGFR decline of at least about 3 mL/min/1.73 m² per year, when attributable to ADPKD and observed over an adequate interval, supports rapid progression. Avoid calculating a slope from only two measurements during illness, dehydration or medication initiation. PKD1 truncating variants, male sex, early hypertension or urologic events and relatives reaching kidney failure young can add prognostic information. The PROPKD score may help selected adults when genetic data are available.

Progression marker	What it measures	Important limitation
Height-adjusted total kidney volume	Structural disease burden before GFR falls	Mayo classification is validated mainly for typical Class 1 morphology; asymmetric/segmental Class 2 disease needs individualized assessment.
Serial eGFR slope	Observed functional decline	Acute illness, hemodynamic drug effects and too few values can create a misleading slope.
Genotype and family history	Biological severity and familial trajectory	Substantial variation exists within families; a relative's kidney-failure age is informative, not deterministic.
Early hypertension/urologic events	Clinical expression at a young age	Supports higher risk but does not replace quantitative imaging and eGFR assessment.

33.5 Treatment

Blood-pressure control is foundational. An ACE inhibitor or ARB is generally preferred because RAAS activation is central to early hypertension. For selected adults aged 18–49 years with CKD G1–G2 and hypertension, KDIGO 2025 suggests a standardized home blood-pressure target at or below 110/75 mmHg if tolerated. Older patients, more advanced CKD and patients with orthostatic symptoms require individualized targets; avoid combining an ACE inhibitor with an ARB.

Tolvaptan, a vasopressin V2-receptor antagonist, lowers cAMP signaling and slows kidney-volume growth and eGFR decline. KDIGO recommends considering it in adults with eGFR at least 25 mL/min/1.73 m² who are at risk of rapid progression—for example Mayo Class 1C–1E or a compatible historical eGFR decline of at least 3 mL/min/1.73 m²/year. Shared decision-making must cover polyuria, thirst, nocturia, cost, pregnancy considerations and rare serious hepatotoxicity. Liver tests are obtained before treatment, monthly for the first 18 months and every 3 months thereafter according to the guideline and local regulatory requirements.

Problem	Practical management
Hypertension and cardiovascular risk	Standardized BP measurement; ACE inhibitor or ARB; dietary sodium reduction; exercise, weight and smoking care; treat dyslipidemia according to CKD/CV guidance.
Acute cyst hemorrhage	Analgesia avoiding NSAID overuse, rest and hydration as appropriate; image persistent/severe bleeding, falling hemoglobin or uncertainty. Exclude stones, infection and malignancy when indicated.
Cyst infection	Look for sustained fever, focal tenderness and inflammatory markers; obtain cultures and use an antibiotic with suitable cyst penetration, guided by microbiology and specialist advice. Drain selected refractory large infected cysts.
Nephrolithiasis	CT when needed, analgesia and obstruction/infection assessment; perform metabolic prevention as in other stone disease, recognizing distorted anatomy.
Chronic pain	Identify a treatable cause first; use multidisciplinary non-opioid strategies. Selected patients need cyst intervention or surgical expertise.
Intracranial aneurysm	Screen people with a personal history of subarachnoid hemorrhage or a strong family history of aneurysm/hemorrhage; also consider screening in selected high-risk occupations, before major surgery/transplant, or after informed preference. Use noncontrast MRA when appropriate.
Kidney failure	Plan hemodialysis, peritoneal dialysis or transplantation early. Transplant outcomes are generally excellent; massively enlarged kidneys may require surgical planning but routine pretransplant nephrectomy is unnecessary.

Explain it to the patient

“The kidneys enlarge because many fluid-filled cysts grow slowly over years. Kidney function can remain normal while this is happening, so MRI kidney volume and your trend over time help us decide whether disease-modifying treatment is worthwhile. Treatment aims to protect the working tissue between cysts.”

33.6 Prognosis

ADPKD has highly variable severity. Some patients reach kidney failure in mid-adulthood; others retain useful function into old age. PKD1—especially truncating variants—tends to be more severe than PKD2, but genotype does not predict an individual outcome perfectly. Rapidly increasing total kidney volume, sustained eGFR decline, early hypertension and early urologic events indicate higher risk. Cardiovascular disease remains a major source of morbidity, and liver cyst burden can dominate symptoms even when kidney function is stable.

Follow-up should include BP, eGFR, ACR, complications, treatment tolerance and periodic reassessment of progression risk. A sudden fall in eGFR is not automatically “ADPKD progression”: evaluate dehydration, infection, obstruction, stones, hemorrhage and nephrotoxic medications as in any patient.

Case resolution

Her phenotype is typical ADPKD and Mayo Class 1D indicates rapid structural progression. Home BP averages 132/84 mmHg; an ARB is titrated with creatinine and potassium monitoring. After counseling about aquaresis, liver monitoring and reproductive issues, she elects to start tolvaptan. Baseline liver tests are normal. She receives a written hydration and sick-day plan and is assessed for family-history-based intracranial aneurysm screening.

Take-home messages

- ADPKD is a focal cystic process caused mainly by PKD1 or PKD2 dysfunction and amplified by cAMP-dependent secretion and proliferation.
- Use age-dependent imaging criteria in at-risk relatives; use MRI and genetic testing when ultrasound or pedigree is insufficient.
- Kidney size can increase long before eGFR declines, so structural risk assessment matters.
- Mayo Imaging Class and a reliable eGFR slope identify patients likely to progress rapidly.
- RAAS-based BP control protects kidney and cardiovascular health; tolvaptan is reserved for eligible rapid progressors with structured liver monitoring.
- Acute pain or eGFR loss requires evaluation for hemorrhage, infection, stones, obstruction and other reversible causes.

Self-assessment

1. Why can eGFR remain normal while total kidney volume is increasing?
2. What ultrasound finding supports ADPKD in a 35-year-old first-degree relative of an affected patient?
3. Which two commonly used findings support rapid progression when considering tolvaptan?
4. What liver-test schedule is used after starting tolvaptan?
5. Name three situations in which intracranial aneurysm screening should be discussed.

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CHAPTER 34

Alport Syndrome

A COL4A-related glomerular basement membrane disorder with kidney, hearing and ocular manifestations

- Recognize the phenotype of persistent glomerular hematuria, progressive albuminuria and characteristic family history.
- Explain how loss of the mature type IV collagen network produces GBM injury and secondary scarring.
- Interpret light microscopy, collagen immunostaining and electron microscopy by disease stage.
- Use genetic testing to establish inheritance, guide family screening and assess prognosis.
- Start kidney-protective treatment early and coordinate hearing, eye, reproductive and transplant care.
- Explain genotype-dependent clinical evolution without falsely reassuring women or heterozygous relatives.

Opening case

A 19-year-old man has microscopic hematuria documented since childhood. ACR is now 420 mg/g, eGFR is 108 mL/min/1.73 m² and BP is 128/76 mmHg. His maternal uncle reached kidney failure at 36 years and uses hearing aids. Audiometry reveals mild bilateral high-frequency sensorineural hearing loss. Genetic testing identifies a pathogenic COL4A5 variant.

Clinical reasoning

Persistent glomerular hematuria from childhood, maternal-family transmission, hearing loss and a COL4A5 variant establish X-linked Alport syndrome. Albuminuria signals progression even though eGFR is normal, so kidney-protective therapy should not wait for filtration to decline.

34.1 Diagnosis

Suspect Alport syndrome in persistent glomerular hematuria, especially when accompanied by albuminuria, CKD, sensorineural hearing loss, ocular abnormalities or a family history of hematuria/kidney failure. Dysmorphic erythrocytes support a glomerular source, but red-cell casts are uncommon in stable hereditary disease. Ask specifically about relatives of both sexes, hearing aids, early kidney failure, “thin basement membrane” diagnoses and transplant complications.

Genetic testing for COL4A3, COL4A4 and COL4A5 is the preferred confirmatory test because it identifies inheritance, enables cascade testing and often avoids biopsy. X-linked disease results from COL4A5; biallelic COL4A3 or COL4A4 variants cause autosomal recessive disease; heterozygous COL4A3 or COL4A4 variants produce a variable autosomal-dominant/monoallelic COL4A phenotype. Digenic combinations occur. Variant interpretation must follow formal pathogenicity criteria and be linked to genetic counseling.

Diagnostic component	What to look for	Why it matters
Urine and kidney function	Persistent glomerular hematuria; increasing ACR; eGFR and BP trend	Albuminuria usually marks transition from isolated hematuria toward progressive glomerular injury.
Pedigree	Maternal transmission in XLAS; affected siblings with unaffected parents in ARAS; variable vertical transmission in heterozygous COL4A3/4 disease	Directs testing but small families, de novo variants and variable expression can obscure inheritance.
Audiology	Bilateral high-frequency sensorineural hearing loss	Supports diagnosis and may correlate with a more severe genotype; normal childhood hearing does not exclude disease.
Ophthalmology	Anterior lenticonus, dot-and-fleck retinopathy, temporal retinal thinning or recurrent corneal erosion	Anterior lenticonus is highly suggestive; ocular disease helps phenotype but is not required.
Genetic testing	Pathogenic/likely pathogenic COL4A3, COL4A4 or COL4A5 variant	Confirms molecular diagnosis, inheritance, family risk and transplant-donor implications.
Kidney biopsy	GBM thinning/lamellation with secondary chronic lesions	Useful when genetics is unavailable, negative/uncertain or a second kidney disease is suspected.

Terminology for students

"Alport syndrome" is appropriate when a pathogenic COL4A variant produces the characteristic progressive kidney phenotype, with or without hearing/eye features. Do not assume that "thin basement membrane nephropathy" is always benign: a heterozygous COL4A3 or COL4A4 variant can carry lifelong albuminuria and CKD risk.

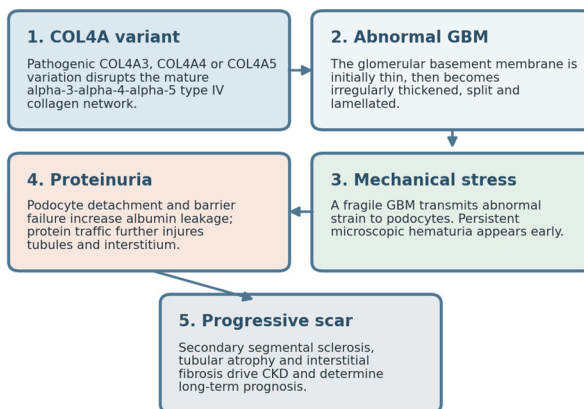
34.2 Pathophysiology

The normal mature GBM contains a cross-linked alpha-3-alpha-4-alpha-5 type IV collagen network. It replaces the fetal alpha-1-alpha-1-alpha-2 network during development and provides both elasticity and resistance to mechanical stress. Pathogenic COL4A3, COL4A4 or COL4A5 variants reduce or alter this mature network. The exact chain affected and whether functional collagen remains determine inheritance and much of severity.

The abnormal GBM is initially diffusely thin in many patients. Repeated capillary-wall stress then causes irregular thickening, splitting and lamellation. Podocytes sense abnormal matrix stiffness and strain, alter their cytoskeleton and lose attachment. Albumin begins to cross the filtration barrier; secondary focal segmental glomerulosclerosis develops as podocyte number falls. Filtered proteins and nephron loss activate tubular inflammation, interstitial fibrosis and further CKD progression.

The same alpha-3-alpha-4-alpha-5 network is important in cochlear basement membranes and ocular structures. This explains high-frequency sensorineural hearing loss and characteristic eye findings. Hearing loss is not caused by uremia and may occur while eGFR is normal.

Alport syndrome: collagen defect to chronic glomerular scarring



The biopsy evolves with age: a thin GBM early does not exclude Alport syndrome, and genetic testing defines inheritance and family risk.

Figure 34.1. In Alport syndrome, defective type IV collagen changes GBM mechanics; hematuria precedes albuminuria, podocyte loss, secondary segmental sclerosis and tubulointerstitial fibrosis.

34.3 Pathology: LM, IF and EM across time

Morphology evolves with age and disease severity. A young patient may have normal light microscopy and only a diffusely thin GBM on EM. Later biopsies can resemble primary FSGS if the pathologist is not given the hematuria and family history. Always integrate the three modalities with genetic findings.

Modality	Early disease	Established disease	Interpretive caution
LM	Glomeruli may appear normal; mild mesangial prominence can occur.	Segmental sclerosis, global glomerulosclerosis, tubular atrophy, interstitial fibrosis and interstitial foam cells.	FSGS is usually a secondary scar in this setting, not a separate primary podocytopathy.
IF for immune deposits	Usually negative or nonspecific.	Usually negative; trapped IgM/C3 may occur in scarred segments.	Immune-complex staining suggests a superimposed disease.
Collagen-chain IF/IHC	Loss or altered distribution of alpha-3/alpha-4/alpha-5 chains in some genotypes.	The same genotype-dependent pattern persists.	Normal staining does not exclude Alport syndrome, especially with missense variants or heterozygous COL4A3/4 disease.
EM	Diffuse or segmental GBM thinning; measurements require age-appropriate laboratory standards.	Alternating thinning and thickening, splitting and multilamination of the lamina densa—the “basket-weave” pattern—with podocyte foot-process effacement when proteinuria develops.	A thin GBM alone is not specific; integrate phenotype and genetics. Sampling and age affect sensitivity.

Pathology translation
 The basket-weave appearance is created when the lamina densa splits into multiple irregular layers. It is highly suggestive in the right clinical setting, but its absence in a young patient does not rule out Alport syndrome.

34.4 Treatment

There is no approved treatment that repairs the collagen network. Management reduces intraglomerular pressure and secondary scarring. An ACE inhibitor or ARB should be started early according to genotype, sex and disease marker—certainly when albuminuria is present, and in high-risk X-linked or autosomal-recessive disease often before overt proteinuria under specialist guidance. Titrate to the maximally tolerated dose while monitoring BP, creatinine and potassium. Do not combine ACE inhibitor and ARB therapy.

Treat hypertension, avoid smoking and nephrotoxins, maintain healthy weight and apply general CKD cardiovascular care. SGLT2 inhibitors are biologically attractive when albuminuric CKD criteria are met, but Alport-specific evidence remains limited; use current CKD guidance and specialist judgment rather than presenting them as collagen-directed therapy. Immunosuppression does not treat genetic Alport disease and should not be used merely because LM shows FSGS.

Care domain	Practical action
Kidney protection	ACE inhibitor or ARB early; standardized BP and ACR/eGFR monitoring; avoid nephrotoxins; manage CKD complications and cardiovascular risk.
Hearing	Baseline and periodic audiometry from an age appropriate to genotype/risk; provide hearing aids or other rehabilitation promptly.
Eyes	Ophthalmology assessment when symptomatic and according to genotype/risk; manage lenticonus, corneal disease and visual impairment.
Family reproduction and	Cascade genetic testing, counseling about inheritance and reproductive options; test at-risk relatives rather than relying on urinalysis alone.
Living donation	A relative carrying the familial pathogenic variant is generally unsuitable because nephrectomy may increase lifelong CKD risk; assessment requires genetic and transplant expertise.
Kidney failure/transplant	Plan transplantation early. Outcomes are generally excellent and Alport disease does not recur in the graft. Rare post-transplant anti-GBM nephritis requires urgent specialist assessment.

34.5 Clinical evolution

Microscopic hematuria is usually the earliest sign and may be present from childhood. Albuminuria then emerges, followed by hypertension, declining eGFR and kidney failure in

higher-risk genotypes. Hearing loss often becomes evident in later childhood or early adulthood in severely affected males with XLAS and in ARAS, but timing varies. Eye findings are less frequent and are not required for diagnosis.

In males with XLAS, truncating, deletion or severe splice variants generally predict earlier kidney failure than many missense variants. Females with XLAS have a broad spectrum because X-chromosome inactivation differs among cells; some remain mildly affected, whereas others develop substantial albuminuria and kidney failure. ARAS is often severe in both sexes. Heterozygous COL4A3 or COL4A4 disease is usually milder but not uniformly benign; risk rises with albuminuria, hypertension, reduced eGFR and additional kidney insults.

34.6 Prognosis

The strongest practical prognostic markers are genotype/inheritance, sex in XLAS, onset and magnitude of albuminuria, eGFR trajectory, hypertension and hearing loss. Early RAAS blockade is associated with delayed kidney failure, with greater benefit when started before substantial scarring. Prognosis should be described as a range rather than a fixed kidney-failure age, because even relatives with the same variant can differ.

Transplant prognosis is generally excellent because the genetic collagen defect is intrinsic to the native kidneys and does not recur in the allograft. A small minority—classically males with severe COL4A5 variants—develop antibodies to normal alpha-5-containing GBM after transplant, causing anti-GBM nephritis. This is uncommon but can threaten the graft rapidly.

Explain	it	to	the	patient
"The kidney filter is built with an abnormal collagen network. Blood in the urine is often the first sign; protein in the urine tells us that scarring risk is increasing. Blood-pressure medicines reduce stress on the filter and work best when started before much scar has formed. Testing relatives can protect them and also prevents an affected relative from donating a kidney."				

Case resolution

He begins an ACE inhibitor because albuminuria indicates progressive glomerular injury despite normal eGFR. Creatinine and potassium are checked after initiation and dose increases. He receives audiology follow-up, ophthalmology assessment and genetic counseling. His mother and siblings are offered targeted testing for the familial COL4A5 variant; potential kidney donation is deferred until genetic status is known.

Take-home messages

- Alport syndrome is caused by pathogenic COL4A3, COL4A4 or COL4A5 variation affecting the mature type IV collagen GBM network.
- Persistent glomerular hematuria is early; albuminuria, hypertension and falling eGFR indicate progression.
- Genetic testing is preferred because it confirms diagnosis, inheritance, family risk and donor implications.
- EM evolves from a thin GBM to irregular splitting and lamellation; LM later shows secondary FSGS and tubulointerstitial scar.
- ACE inhibitor or ARB therapy should begin early according to genotype and albuminuria risk; immunosuppression does not treat genetic disease.
- Women with XLAS and heterozygous COL4A3/4 relatives require long-term follow-up because disease is variable, not automatically benign.

Self-assessment

1. Which type IV collagen chains form the mature GBM network affected in Alport syndrome?
2. Why can Alport syndrome be misdiagnosed as primary FSGS on a late biopsy?
3. What are the typical early and late EM findings?
4. Why is genetic testing important when a relative is being considered as a living kidney donor?

5. Which clinical features indicate a worse renal prognosis?

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Part VI model answers

Chapter 32

1. Damaged proximal tubules fail to reclaim filtered low-molecular-weight proteins, so total protein rises more than albumin.
2. Fever, rash and peripheral eosinophilia are all insensitive; their absence does not exclude acute interstitial nephritis.
3. Tubulitis is invasion of tubular epithelium by inflammatory cells and may represent active treatable injury; interstitial fibrosis is collagenous scar and is largely irreversible.
4. Biopsy is considered when diagnosis is uncertain, kidney dysfunction is severe or progressive, a glomerular lesion is possible, or immunosuppression is being contemplated.
5. Delayed withdrawal, prolonged/severe AKI, older age and extensive tubular atrophy/interstitial fibrosis predict incomplete recovery.

Chapter 33

1. Expanding cysts are initially offset by hyperfiltration in remaining nephrons, so total kidney volume can increase before global GFR falls.
2. At least three cysts in total across one or both kidneys support ADPKD in an at-risk person aged 15–39 years.
3. Typical Mayo Imaging Class 1C–1E and an ADPKD-attributable historical eGFR decline of at least about 3 mL/min/1.73 m²/year support rapid progression.
4. Obtain liver tests before treatment, monthly for the first 18 months, then every three months thereafter, alongside local regulatory requirements.
5. Discuss screening with a personal history of subarachnoid hemorrhage, a strong family history of aneurysm/hemorrhage, selected high-risk occupation or surgery/transplant context, or an informed patient preference.

Chapter 34

1. The mature GBM network contains alpha-3, alpha-4 and alpha-5 type IV collagen chains.
2. Later Alport disease causes podocyte loss and secondary segmental sclerosis; without the hematuria, pedigree, EM and genetics, that scar may be mistaken for primary FSGS.
3. EM often shows diffuse thinning early and irregular thickening, splitting and lamellation—the basket-weave pattern—later.
4. Testing identifies relatives who carry the pathogenic variant and should generally not donate because nephrectomy may increase their lifetime CKD risk.
5. A severe genotype, male sex in XLAS, early/increasing albuminuria, hypertension, hearing loss and a falling eGFR indicate higher risk.

PART VII

Hypertension and the Kidneys

Renal arterial disease, pressure-mediated parenchymal injury and pregnancy-specific hypertension

Part VII asks three different questions. Is the kidney driving systemic hypertension because its arterial perfusion is reduced? Has sustained or accelerated pressure injured the renal microvasculature? Or has pregnancy created a placenta-mediated endothelial disorder? The answer determines imaging, pathology, urgent treatment and prognosis.

CHAPTER 35

Renovascular Hypertension

Identify a hemodynamically important renal-artery lesion and select the few patients likely to benefit from revascularization

- Distinguish renal-artery stenosis, renovascular hypertension and ischemic nephropathy.
- Explain how reduced renal perfusion activates renin, sodium retention and systemic vasoconstriction.
- Recognize the clinical syndromes that justify vascular imaging.
- Choose duplex ultrasound, CT angiography, MR angiography or catheter angiography appropriately.
- Interpret renal parenchymal pathology and markers of irreversible ischemic damage.
- Apply medical therapy first and identify high-risk presentations for revascularization.

Opening case

A 72-year-old man with diffuse atherosclerosis has office blood pressure of 176/94 mmHg despite an ARB, amlodipine and a loop diuretic. During the previous six months he was admitted twice with sudden pulmonary edema. eGFR fell from 48 to 29 mL/min/1.73 m², and creatinine rose by 38% after the ARB dose was increased. Duplex ultrasound shows a high velocity at the right renal-artery origin and a small left kidney.

Clinical reasoning. Resistant hypertension alone is common and does not prove renovascular disease. Recurrent flash pulmonary edema, a substantial hemodynamic creatinine rise and asymmetric kidneys form a high-risk syndrome in which a flow-limiting lesion may be clinically causal and revascularization deserves specialist evaluation.

35.1 Definitions and causes

Renal-artery stenosis is an anatomical narrowing. Renovascular hypertension means that reduced perfusion from the lesion is driving systemic blood pressure. Ischemic nephropathy means that chronic vascular insufficiency has reduced kidney function or renal mass. These states overlap, but an incidental stenosis may cause neither hypertension nor loss of function.

Cause	Typical location and patient	Morphology	Clinical pattern
Atherosclerotic renovascular disease	Ostium and proximal renal artery; older patient with smoking, diabetes, coronary or peripheral arterial disease	Eccentric plaque, calcification and possible aortic disease; bilateral involvement is common	Resistant hypertension, CKD, asymmetric kidneys, pulmonary edema or an acute fall in GFR with RAAS blockade
Fibromuscular dysplasia	Middle to distal artery; more often a younger or middle-aged woman	Multifocal medial fibroplasia produces alternating stenosis and dilatation, the "string-of-beads" pattern	Earlier-onset or abrupt hypertension; bruit; renal or cervicocephalic arterial involvement
Other uncommon causes	Dissection, vasculitis, radiation injury, external compression, neurofibromatosis, transplant-artery stenosis	Cause-specific arterial wall injury	Age, systemic phenotype, procedure history or transplant timing directs the diagnosis

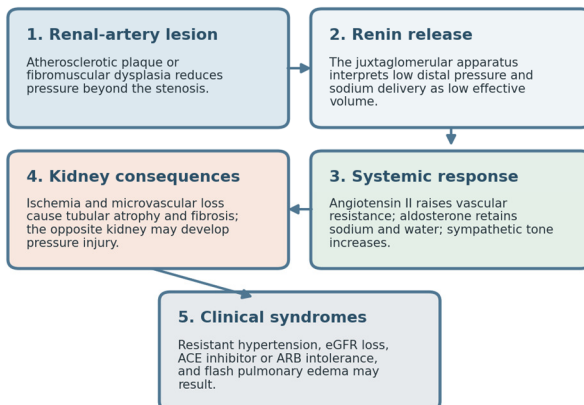
35.2 Pathophysiology

When pressure beyond a stenosis falls enough, the juxtaglomerular apparatus releases renin. Angiotensin II constricts systemic arterioles and the efferent arteriole; aldosterone retains sodium; vasopressin and sympathetic activity reinforce volume and vascular responses. In unilateral disease, the opposite kidney is exposed to the resulting hypertension and excretes sodium through pressure natriuresis. In bilateral severe disease, or stenosis of a solitary functioning kidney, both kidneys retain sodium and pulmonary edema becomes more likely.

The same physiology explains the creatinine response to ACE inhibitors or ARBs. A post-stenotic kidney may depend on angiotensin-II-mediated efferent constriction to maintain glomerular pressure. Blocking that response can lower GFR. A creatinine increase is not itself proof of stenosis because volume depletion, NSAIDs and heart failure can produce the same effect; the clinical context and reversibility matter.

Chronic hypoperfusion causes peritubular capillary loss, tubular atrophy and interstitial fibrosis. Glomeruli become ischemically wrinkled and globally sclerotic. Once the parenchyma is small and extensively scarred, restoring arterial patency may not restore filtration because the tissue capable of using the blood flow has been lost.

Renovascular hypertension: reduced perfusion becomes systemic hypertension



The lesion is anatomically visible; it becomes clinically important when it produces a hemodynamic and organ-level syndrome.

Figure 35.1. A hemodynamically important renal-artery lesion activates renin-dependent vasoconstriction and sodium retention, then may progress to parenchymal ischemic scarring.

35.3 When to suspect renovascular disease

Clinical clue	Why it raises suspicion	Important alternative
Hypertension beginning before 30 years or abrupt worsening after 55 years	Suggests FMD in younger patients or atherosclerotic disease in older patients	Primary hypertension, endocrine causes and medication-related elevation remain more common
True resistant hypertension	Persistent BP despite three appropriate drugs including a diuretic may reflect renin-driven disease	Confirm adherence, standardized measurement, sodium excess and sleep apnea first
Recurrent flash pulmonary edema or otherwise unexplained heart failure admissions	Bilateral or solitary-kidney ischemia promotes abrupt sodium retention and afterload	Acute coronary syndrome, arrhythmia and valvular disease
Creatinine rise above approximately 30% after ACE inhibitor or ARB	Loss of efferent support may expose bilateral severe stenosis or solitary-kidney disease	Hypovolemia, NSAIDs, sepsis and decompensated heart failure
Rapid unexplained eGFR decline or asymmetric kidney size	May indicate ischemic nephropathy	Obstruction, reflux scarring and embolic disease
Abdominal bruit plus systemic atherosclerosis	Increases pretest probability	A bruit is neither sensitive nor specific

35.4 Diagnostic imaging

Order vascular imaging when the result could change management. Screening every patient with hypertension detects many incidental lesions and exposes patients to contrast, radiation and downstream procedures without benefit.

Test	Strengths	Limitations and interpretation
Duplex ultrasound	No radiation or contrast; measures anatomy and velocity; can estimate kidney size and intrarenal resistance	Operator and body-habitus dependent. Peak systolic velocity around 180–200 cm/s or renal-aortic ratio above about 3.5 suggests significant stenosis, but laboratories must use validated local criteria.
CT angiography	Excellent spatial resolution; shows ostial plaque, calcification, accessory arteries and aorta	Iodinated contrast and radiation; heavy calcification can overestimate stenosis. Balance contrast-associated risk against diagnostic value.
MR angiography	Good vascular map without ionizing radiation; useful when CTA is undesirable	Gadolinium considerations in advanced CKD, motion/metal artifacts and possible overestimation. Noncontrast techniques are available in selected centers.
Catheter angiography	Best anatomical and pressure assessment; permits treatment during the same procedure	Invasive, with risks of atheroembolism, bleeding, dissection and contrast exposure. Reserve for strong indications or planned intervention.

A diameter stenosis of 70% or more is more likely to be hemodynamically important. Intermediate lesions require functional assessment, such as a translesional pressure gradient, and correlation with the clinical syndrome. Captopril renography and plasma renin measurements are not reliable general screening tests and are rarely decisive in modern practice.

35.5 Pathology

Modality	Typical findings	Meaning
Gross vascular and	Small post-stenotic kidney; ostial/proximal atherosclerotic plaque or mid-distal FMD; cortical thinning in advanced disease	Kidney asymmetry and loss of parenchymal volume suggest chronicity but do not by themselves prove active renovascular hypertension.
LM	Ischemic glomeruli with capillary tuft shrinkage, wrinkled GBM and periglomerular fibrosis; tubular atrophy, interstitial fibrosis and arterial intimal thickening. The contralateral kidney may show hypertensive arteriolosclerosis.	Extensive global sclerosis and interstitial scar predict limited functional recovery after revascularization.
IF	Usually negative or nonspecific; segmental trapping of IgM/C3 can occur in scars	A specific immune-deposit pattern suggests a superimposed glomerular disease.
EM	GBM wrinkling and capillary collapse in ischemic glomeruli; endothelial injury may occur	EM supports ischemic injury but is not required to diagnose a renal-artery lesion.

35.6 Treatment

Medical therapy is first-line for most atherosclerotic disease. Control BP with a RAAS blocker when tolerated, a calcium-channel blocker and an appropriate diuretic; treat lipids, diabetes and smoking; use antiplatelet therapy when indicated for systemic atherosclerotic disease. Check creatinine and potassium after starting or increasing ACE inhibitor or ARB therapy. A stable modest eGFR dip can be acceptable, but progressive or greater than approximately 30% decline requires reassessment of volume, drugs and bilateral/solitary-kidney disease.

ASTRAL and CORAL found no cardiovascular or kidney benefit from routine stenting added to contemporary medical therapy in broadly selected atherosclerotic renal-artery stenosis. These trials do not prove that every high-risk patient is unsuitable, because patients with recurrent pulmonary edema or rapidly progressive syndromes were underrepresented.

Management path	Best candidates or rationale	Student caution
Continue optimized medical therapy	Stable kidney function, controllable BP and no high-risk cardiac destabilization syndrome	An anatomical stenosis alone is not an indication for a stent.
Multidisciplinary revascularization evaluation	Recurrent flash pulmonary edema; rapidly declining eGFR with bilateral severe disease or a solitary functioning kidney; true resistant hypertension with a high-grade hemodynamically significant lesion	Confirm that the syndrome and lesion match and that viable kidney tissue remains.
FMD angioplasty	Clinically important FMD with hypertension, especially when cure or major BP improvement is plausible	Balloon angioplasty without routine stenting is preferred; stents are reserved for complications or failed angioplasty.
Surgery	Complex anatomy, failed endovascular therapy or concomitant aortic reconstruction in selected patients	Higher procedural burden; requires experienced vascular and renal teams.

35.7 Clinical evolution and prognosis

Atherosclerotic renovascular disease reflects systemic vascular risk. Cardiovascular events and death are often more likely than kidney failure. eGFR may remain stable with medical therapy, decline slowly as atherosclerosis and parenchymal scar progress, or fall rapidly during bilateral ischemia, cholesterol embolization, dehydration or medication changes. After successful intervention, BP often improves more reliably than eGFR. A small kidney, high intrarenal resistance, heavy proteinuria and extensive fibrosis predict less renal recovery.

FMD has a more favorable BP response, especially in younger patients with shorter hypertension duration. Cure is not guaranteed because primary hypertension and irreversible vascular remodeling may coexist. Surveillance after intervention is guided by BP, kidney function and vascular imaging rather than a fixed universal schedule.

Case resolution

CTA confirms severe right ostial stenosis supplying the dominant kidney and an atrophic left kidney. After volume status and adherence are reviewed, the team judges that recurrent pulmonary edema and progressive kidney dysfunction form a high-risk syndrome. He receives intensive atherosclerotic medical therapy and undergoes specialist renal-artery stenting. Pulmonary edema does not recur, BP falls to 142/78 mmHg on fewer drugs and eGFR stabilizes at 32 mL/min/1.73 m²; established left-kidney atrophy does not recover.

Take-home messages

- Renal-artery stenosis is anatomical; renovascular hypertension and ischemic nephropathy require clinical consequences.
- Reduced perfusion activates renin, vasoconstriction and sodium retention; bilateral disease favors volume-dependent pulmonary edema.
- Image patients with a meaningful pretest probability and a result that could change management.
- Duplex ultrasound is a useful first test; CTA and MRA define anatomy; angiography is reserved for selected or interventional cases.
- Routine stenting of stable atherosclerotic disease does not improve outcomes beyond medical therapy.
- Recurrent flash pulmonary edema, rapidly declining function in bilateral/solitary-kidney disease and selected resistant hypertension merit revascularization assessment.

Self-assessment

1. How do renal-artery stenosis, renovascular hypertension and ischemic nephropathy differ?
2. Why can bilateral renal-artery stenosis produce flash pulmonary edema?
3. Name four clinical clues that justify renal vascular imaging.
4. What did ASTRAL and CORAL show about routine atherosclerotic renal-artery stenting?

5. Which pathological findings predict limited recovery after revascularization?

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CHAPTER 36

Nephroangiosclerosis (Benign and Malignant)

Benign chronic vascular remodeling and malignant pressure-mediated renal microangiopathy

- Explain why hypertensive nephrosclerosis is a clinicopathologic diagnosis and often a diagnosis of exclusion.
- Describe the vascular, glomerular and tubulointerstitial mechanisms of chronic pressure injury.
- Compare benign nephrosclerosis with malignant nephrosclerosis using LM, IF and EM.
- Recognize hypertensive emergency and distinguish its renal TMA from primary TMA syndromes.
- Treat chronic disease according to CKD risk and lower BP safely during an emergency.
- Estimate kidney recovery and long-term cardiovascular prognosis.

Opening case

A 66-year-old man has had hypertension for 18 years. BP is 154/88 mmHg, eGFR is 44 mL/min/1.73 m² and ACR is 180 mg/g. Ultrasound shows symmetric 9.4-cm echogenic kidneys. Urine sediment is bland. There is no diabetes, systemic disease or family history. Three years of records show a gradual eGFR decline of 2 mL/min/1.73 m²/year.

Clinical reasoning. Long-standing hypertension, modest albuminuria, bland sediment, symmetric chronic change and slow decline fit nephroangiosclerosis. The label remains probabilistic: heavy proteinuria, active sediment, rapid loss, systemic features or a strong family history should trigger investigation for another kidney disease.

36.1 Terminology and diagnosis

Arterionephrosclerosis describes renal small-artery and arteriolar sclerosis with secondary ischemic parenchymal injury. “Hypertensive nephrosclerosis” is often used clinically when long-standing hypertension, mild-to-moderate proteinuria, bland urine and slowly progressive CKD occur without a better cause. Hypertension is both cause and consequence: nephron loss raises BP, and higher BP accelerates further vascular and glomerular injury.

Benign does not mean harmless. It describes the slower vascular pattern associated with chronic hypertension and aging. Malignant nephrosclerosis describes acute severe microvascular injury, traditionally associated with grade III/IV hypertensive retinopathy. Modern practice uses hypertensive emergency for severe BP accompanied by acute target-organ injury; the absolute BP is less important than the organ damage and the rate of rise.

Feature	Supports chronic nephroangiosclerosis	Suggests another or additional disease
History	Years of hypertension preceding or accompanying CKD	Kidney disease clearly predates hypertension; hereditary, immune or toxic clues
Urine	Bland sediment; A1–A2 or modest A3 albuminuria	Dysmorphic RBCs, RBC casts, persistent leukocyte casts or nephrotic syndrome
Course	Slow eGFR decline	Abrupt or rapidly progressive decline without hypertensive emergency
Imaging	Symmetric small or normal-sized echogenic kidneys	Marked asymmetry, obstruction, cystic disease or large kidneys
Biopsy need	Often unnecessary when phenotype is typical and stable	Consider when proteinuria is heavy, sediment active, course atypical or diagnosis would change treatment

36.2 Pathophysiology of benign nephrosclerosis

Chronic pressure stimulates medial hypertrophy and intimal matrix deposition in small arteries. In arterioles, endothelial leakage and smooth-muscle injury allow plasma proteins to accumulate as hyaline. The lumen narrows, downstream perfusion becomes heterogeneous and glomeruli

undergo ischemic collapse and global sclerosis. Tubules supplied by those glomeruli atrophy, peritubular capillaries disappear and interstitial fibrosis expands.

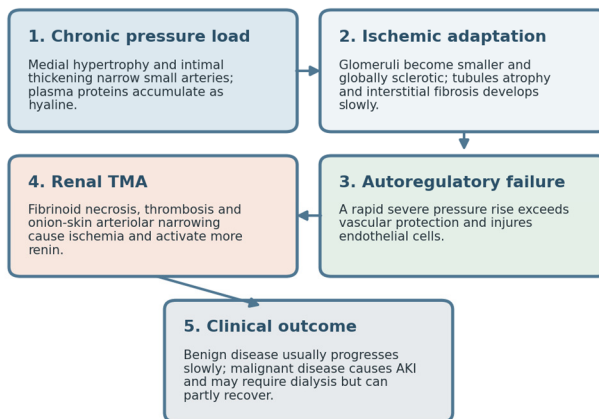
Not all glomeruli respond in the same way. Some are ischemic and small; surviving nephrons may hyperfilter and become enlarged, causing secondary segmental sclerosis and more albuminuria. Aging, diabetes, smoking and pre-existing CKD amplify the same vascular lesions. In people with high-risk APOL1 genotypes, progressive CKD previously attributed only to hypertension may represent genetically mediated podocyte disease; ancestry must not be used as a substitute for diagnosis.

36.3 Pathophysiology of malignant nephrosclerosis

When a rapid pressure rise exceeds autoregulatory capacity, endothelial cells are damaged. Plasma and fibrin enter vessel walls, platelets are activated and arteriolar lumens narrow. Fibrinoid necrosis reflects acute wall destruction; concentric smooth-muscle and intimal proliferation produces hyperplastic “onion-skin” arteriolosclerosis. Renal ischemia releases more renin, creating a cycle of vasoconstriction, pressure elevation and further injury.

The renal lesion is a thrombotic microangiopathy. Patients may have thrombocytopenia, schistocytes and elevated LDH, but hematologic abnormalities are often less severe than in immune TTP. Severe ADAMTS13 deficiency, Shiga-toxin disease, pregnancy-associated TMA and complement-mediated TMA must still be considered when the presentation is atypical or organ injury persists despite BP control.

Pressure injury in the kidney: slow remodeling or acute microvascular failure



The terms benign and malignant describe tempo and morphology; hypertensive emergency is defined by acute target-organ injury.

Figure 36.1. Chronic pressure causes hyaline and intimal vascular remodeling, whereas abrupt autoregulatory failure produces endothelial injury, renal TMA and malignant nephrosclerosis.

36.4 Pathology

Modality	Benign nephrosclerosis	Malignant nephrosclerosis
Gross	Finely granular, symmetrically contracted kidneys in advanced disease	Petechial cortical hemorrhages may produce a “flea-bitten” surface; kidneys can be normal-sized early
LM vessels	Hyaline arteriolosclerosis; fibroelastic intimal thickening and medial hypertrophy in small arteries	Fibrinoid necrosis, intraluminal thrombi and concentric hyperplastic onion-skin arteriolosclerosis
LM glomeruli and interstitium	Ischemic tuft retraction, GBM wrinkling, global sclerosis; tubular atrophy and patchy interstitial fibrosis; possible secondary FSGS	Capillary collapse, ischemic wrinkling, mesangiolysis or thrombi; acute tubular injury and cortical infarction; chronic lesions may coexist
IF	Usually negative or nonspecific; IgM/C3 may be trapped in sclerotic areas	Fibrin/fibrinogen in necrotic vessel walls and thrombi; no disease-specific immune-complex pattern
EM	Endothelial injury, GBM wrinkling and chronic capillary collapse; podocyte effacement if secondary FSGS is present	Endothelial swelling, subendothelial widening, loss of fenestrations, GBM duplication and platelet-fibrin thrombi

Pathology interpretation. Hyaline arteriolosclerosis is common with aging and diabetes and is not specific for hypertension. Malignant-type lesions establish severe microvascular injury but do not identify its cause. Biopsy can reveal IgA nephropathy, FSGS, complement-mediated TMA or another disease that presented with severe hypertension.

36.5 Treatment of chronic nephroangiosclerosis

Treatment follows CKD and cardiovascular-risk principles. Confirm BP with standardized office and home or ambulatory measurements. Restrict dietary sodium, support exercise and weight management, stop smoking and treat sleep apnea. An ACE inhibitor or ARB is preferred when albuminuria is present; monitor potassium and creatinine. Add a dihydropyridine calcium-channel blocker and a thiazide-like or loop diuretic according to eGFR and volume status. Use SGLT2 inhibitors when current CKD indications are met, regardless of whether the historical label is “hypertensive nephrosclerosis.”

The BP target should follow the current CKD/hypertension guideline and individual tolerance. KDIGO suggests a standardized office systolic target below 120 mmHg for many adults with CKD when tolerated, whereas ESC guidance frames an on-treatment target around 120–129/70–79 mmHg for suitable adults. Frailty, orthostatic symptoms, limited life expectancy and measurement method require individualization.

36.6 Hypertensive emergency

A hypertensive emergency is severe BP elevation with acute injury such as encephalopathy, intracranial hemorrhage, acute coronary syndrome, pulmonary edema, aortic dissection, AKI or pregnancy-related severe hypertension. Admit for continuous monitoring and intravenous therapy. For most emergencies, lower mean arterial pressure by no more than about 20–25% during the first hour, then toward approximately 160/100–110 mmHg over the next 2–6 hours, followed by cautious normalization over 24–48 hours. Aortic dissection, acute ischemic stroke, intracranial hemorrhage and pregnancy have specific targets and timelines.

Clinical situation	Common IV approach	Renal consideration
General hypertensive emergency with AKI or neurologic injury	Nicardipine or clevidipine infusion; IV labetalol is an alternative	Titrate smoothly and avoid overshoot that worsens renal/cerebral ischemia
Acute pulmonary edema	IV nitrate plus loop diuretic when congested; noninvasive ventilation as needed	Do not treat every creatinine rise with fluid; assess congestion and perfusion
Aortic dissection	Rapid beta-blockade followed by vasodilator as needed under aortic protocol	This is an exception requiring faster pressure and heart-rate control
Pregnancy with severe hypertension	IV labetalol, IV hydralazine or immediate-release oral nifedipine	Treat urgently using obstetric protocol; magnesium prevents seizures but is not the primary antihypertensive

Draw a blood film, platelet count, LDH, haptoglobin, bilirubin, creatinine, urinalysis and ACR/PCR when renal TMA is possible. Send ADAMTS13 before plasma therapy if TTP is a serious possibility, but do not delay life-saving treatment. Plasma exchange is not routine therapy for pressure-mediated TMA; persistent hemolysis or kidney injury after BP control should prompt reassessment for primary TMA.

36.7 Clinical evolution and prognosis

Benign nephrosclerosis often progresses slowly, but risk rises with uncontrolled ambulatory BP, albuminuria, lower baseline eGFR, smoking and cardiovascular disease. A faster course or heavy proteinuria should reopen the diagnosis. Cardiovascular events are a major competing risk, so kidney treatment and vascular prevention are inseparable.

Malignant nephrosclerosis can require acute dialysis. Kidney recovery may continue for weeks or months after BP is controlled, so dialysis dependence at presentation does not always mean permanent kidney failure. Extensive cortical necrosis, global sclerosis, tubular atrophy/interstitial fibrosis, very low baseline eGFR and persistent proteinuria predict poorer recovery. Survivors need close BP, kidney and cardiovascular follow-up because recurrent severe hypertension is dangerous.

Case resolution

Home BP confirms persistent hypertension. An ARB is titrated, chlorthalidone is added with electrolyte monitoring and an SGLT2 inhibitor is started because albuminuric CKD criteria are met. BP falls to 126/76 mmHg, ACR declines to 82 mg/g and eGFR slope slows. Biopsy is not performed because the phenotype remains typical and no result would change management.

Take-home messages

- Hypertensive nephrosclerosis is a clinicopathologic diagnosis; a typical clinical phenotype does not make the label certain.
- Benign nephrosclerosis combines hyaline arteriolosclerosis, arterial intimal thickening, ischemic glomerulosclerosis and tubulointerstitial scar.
- Malignant nephrosclerosis is pressure-mediated renal TMA with fibrinoid necrosis and hyperplastic onion-skin arteriolosclerosis.
- Hypertensive emergency is defined by acute target-organ injury, not by a BP number alone.
- Lower BP in a controlled sequence to avoid worsening ischemia, except when a condition-specific protocol requires faster treatment.
- Kidney recovery after malignant hypertension can continue for months; chronic scar burden and persistent proteinuria worsen prognosis.

Self-assessment

1. Why is hypertensive nephrosclerosis usually a diagnosis of exclusion?
2. Compare the arteriolar LM findings of benign and malignant nephrosclerosis.
3. Why does malignant hypertension create a renin-driven vicious cycle?
4. How quickly should BP usually be lowered in a hypertensive emergency?
5. Which findings should prompt evaluation for a primary TMA rather than pressure injury alone?

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CHAPTER 37

Hypertension in Pregnancy

Recognize chronic and gestational hypertension, diagnose preeclampsia and protect both mother and fetus

- Classify chronic hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia.
- Explain how impaired spiral-artery remodeling and antiangiogenic factors cause systemic endothelial injury.
- Interpret proteinuria, kidney function, platelets, liver tests, symptoms and fetal findings.
- Describe glomerular endotheliosis and the LM, IF and EM pathology of preeclampsia.
- Use pregnancy-compatible antihypertensives and treat severe hypertension as an emergency.
- Plan prevention, delivery, postpartum monitoring and long-term kidney/cardiovascular follow-up.

Opening case

A 32-year-old primigravida at 31 weeks has BP 166/112 mmHg, severe headache and visual scotomata. Two weeks earlier BP was 138/86 mmHg. Platelets are $88 \times 10^9/L$, AST is 96 U/L, creatinine is 1.1 mg/dL compared with 0.55 mg/dL early in pregnancy, and urine PCR is 0.52 mg/mg. Ultrasound shows a growth-restricted fetus.

Clinical reasoning. This is preeclampsia with severe features and a hypertensive emergency. The creatinine looks “normal” by nonpregnant standards but has doubled from a pregnancy baseline in which GFR should be increased. Severe BP requires treatment within minutes, while maternal stabilization, magnesium, fetal assessment and delivery planning proceed together.

37.1 Normal renal adaptation to pregnancy

Systemic vasodilatation and increased plasma volume raise renal plasma flow and GFR by approximately 40–50% early in pregnancy. Serum creatinine therefore falls, often to about 0.4–0.7 mg/dL. A creatinine of 1.0 mg/dL can represent important kidney dysfunction in pregnancy. BP commonly falls in mid-pregnancy and returns toward prepregnancy values near term. Mild increases in urinary protein occur, but protein excretion of 300 mg/day or more is abnormal.

37.2 Classification and diagnosis

Disorder	Diagnostic framework	Key distinction
Chronic hypertension	Hypertension predating pregnancy, present before 20 weeks, or persisting beyond the postpartum period	May coexist with CKD and raises the risk of superimposed preeclampsia.
Gestational hypertension	New BP at least 140/90 mmHg after 20 weeks without proteinuria or maternal organ dysfunction	Can progress to preeclampsia; requires repeated maternal and fetal assessment.
Preeclampsia	New hypertension after 20 weeks plus proteinuria or maternal organ dysfunction, uteroplacental dysfunction, or both	Proteinuria is not required when thrombocytopenia, kidney/liver injury, pulmonary edema, neurologic features or placental dysfunction is present.
Superimposed preeclampsia	Preeclampsia develops in chronic hypertension	A rise in BP alone is insufficient; look for new proteinuria, organ dysfunction or uteroplacental disease.
Eclampsia	New generalized seizures in a patient with preeclampsia when another cause is not more likely	Treat seizure and prevent recurrence with magnesium sulfate; stabilize and plan delivery.
HELLP syndrome	Hemolysis, elevated liver enzymes and low platelets, usually within the preeclampsia spectrum	Hypertension or proteinuria may be absent initially; this remains an obstetric emergency.

Confirm non-severe hypertension with repeated standardized measurements. Severe hypertension is systolic BP at least 160 mmHg or diastolic BP at least 110 mmHg; confirm promptly, usually within 15 minutes, and treat urgently rather than waiting four hours. Use a validated pregnancy device and an appropriate cuff.

Proteinuria can be confirmed by 24-hour protein of at least 300 mg, urine protein-to-creatinine ratio at least 0.3 mg/mg (approximately 30 mg/mmol), or ACR according to local guidance. Dipstick testing is less accurate. Increasing protein quantity after diagnosis does not by itself define severe disease or determine delivery timing.

Assessment	What to obtain	Why it matters
Maternal symptoms and examination	Headache, visual symptoms, epigastric/right-upper-quadrant pain, dyspnea, reflexes, edema, oxygen saturation	Detects cerebral, hepatic and pulmonary complications; edema alone is nonspecific.
Laboratory tests	CBC/platelets, creatinine, AST/ALT, LDH/hemolysis tests, urine PCR or ACR	Identifies thrombocytopenia, kidney injury, liver injury and HELLP/TMA.
Fetal/placental assessment	Growth ultrasound, amniotic fluid, Doppler and cardiotocography according to gestation	Uteroplacental dysfunction can establish disease and determines urgency.
Angiogenic biomarkers	PIGF or sFlt-1/PIGF ratio where validated and recommended locally	Useful mainly to help rule out or risk-stratify suspected preterm preeclampsia; not a substitute for clinical assessment.

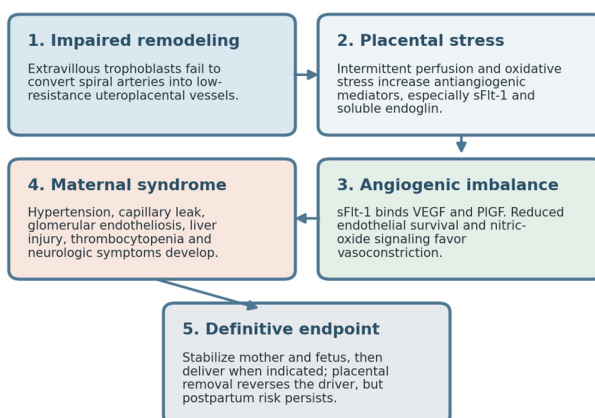
37.3 Pathophysiology

In normal placentation, extravillous trophoblasts transform spiral arteries from narrow muscular vessels into wide, low-resistance channels. In preeclampsia this remodeling is incomplete. Placental perfusion becomes intermittent, producing oxidative and inflammatory stress. The placenta releases excess soluble fms-like tyrosine kinase-1 (sFlt-1), soluble endoglin and other mediators.

sFlt-1 acts as a circulating decoy receptor for VEGF and placental growth factor. Loss of VEGF/PIGF signaling impairs endothelial maintenance and nitric-oxide-dependent vasodilatation. Vasoconstriction raises BP; endothelial permeability causes edema and pulmonary leak; platelet activation and microangiopathy lower the platelet count; hepatic sinusoidal injury causes pain and enzyme elevation; cerebral endothelial dysfunction produces headache, visual symptoms, seizures and stroke.

The glomerulus is particularly sensitive to VEGF disruption because podocytes supply VEGF to adjacent fenestrated endothelial cells. Endothelial swelling narrows capillary lumens and reduces GFR. Protein crosses the injured barrier, causing proteinuria. The lesion usually improves after placental delivery, which removes the major source of antiangiogenic factors.

Preeclampsia: placental malperfusion produces systemic endothelial disease



Preeclampsia is a multisystem placental disorder. Proteinuria supports the diagnosis but is not required when organ dysfunction is present.

Figure 37.1. Inadequate spiral-artery remodeling causes placental stress and antiangiogenic signaling, leading to systemic endothelial dysfunction and the maternal-fetal syndrome of preeclampsia.

37.4 Kidney pathology

Modality	Typical preeclampsia finding	Interpretation
LM	Glomerular endotheliosis: enlarged relatively bloodless glomeruli with swollen endothelial cells and narrowed/occluded capillary lumens; mesangial interposition may occur	Explains reduced GFR and proteinuria. Fibrin thrombi or cortical necrosis indicate severe TMA/ischemia.
IF	Usually nonspecific; fibrin/fibrinogen, IgM or C3 may be seen in capillary walls or mesangium	A strong disease-specific immune pattern suggests lupus nephritis or another superimposed glomerulopathy.
EM	Endothelial swelling, loss of fenestrations, subendothelial widening and electron-lucent material; GBM duplication in severe/prolonged injury; variable foot-process effacement	The lesion is endothelial rather than a primary podocytopathy. Marked deposits suggest another disease.
Placenta	Maternal vascular malperfusion, decidual arteriopathy, infarction and accelerated villous maturation	Supports placental disease but is generally assessed after delivery and does not guide immediate renal treatment.

Kidney biopsy is rarely needed during acute preeclampsia because clinical diagnosis and delivery decisions do not depend on tissue and pregnancy increases procedural complexity. Consider biopsy when disease begins unusually early, nephrotic syndrome or active sediment suggests another glomerulopathy, kidney function fails to recover postpartum, or diagnosis will change immunosuppressive treatment.

37.5 Prevention and treatment of non-severe hypertension

Women at high risk of preeclampsia, including those with prior preeclampsia, chronic hypertension, CKD, diabetes or multifetal pregnancy, should receive low-dose aspirin according to the local obstetric protocol, commonly 75–150 mg daily beginning at 12 weeks and preferably before 16 weeks. Calcium supplementation is recommended where dietary calcium intake is low. Optimize BP, diabetes and medications before conception whenever possible.

The CHAP trial showed that treating mild chronic hypertension to a strategy below 140/90 mmHg improved pregnancy outcomes without increasing small-for-gestational-age births. ACOG therefore uses 140/90 mmHg as a threshold to initiate or titrate treatment in chronic hypertension; NICE targets approximately 135/85 mmHg. Use the protocol adopted locally and avoid maternal hypotension that could compromise placental perfusion.

Medication	Role in pregnancy	Kidney and safety note
Labetalol	Common first-line oral drug; also used IV for severe hypertension	Avoid or use cautiously with asthma, bradycardia or heart block.
Nifedipine extended-release	Common first-line maintenance drug; immediate-release oral nifedipine is an emergency option	Do not use sublingual dosing. Headache and edema can mimic disease symptoms.
Methyldopa	Long safety experience; useful when other agents are unsuitable	Slower and less potent; sedation and depression limit use. Stop postpartum if mood risk is important.
Hydralazine	IV option for acute severe hypertension	Can cause tachycardia, headache and unpredictable hypotension; requires close monitoring.
ACE inhibitor, ARB or direct renin inhibitor	Contraindicated during pregnancy	Fetotoxic, especially after the first trimester; review immediately when pregnancy is recognized. Selected ACE inhibitors can be used postpartum during breastfeeding.

37.6 Severe hypertension and preeclampsia with severe features

1. Activate the obstetric emergency pathway. Treat persistent BP at least 160/110 mmHg as soon as possible, generally within 30–60 minutes.
2. Use IV labetalol, IV hydralazine or immediate-release oral nifedipine according to contraindications and protocol. Recheck BP frequently and avoid an abrupt fall.
3. Give magnesium sulfate for eclampsia treatment and seizure prophylaxis in preeclampsia with severe features. Reduce maintenance dosing and monitor reflexes, respiration and serum magnesium when kidney function is impaired.
4. Assess pulmonary edema, neurologic symptoms, HELLP, TMA, kidney injury and fetal status. Restrict unnecessary fluid because endothelial leak and reduced oncotic pressure increase pulmonary-edema risk.
5. Administer antenatal corticosteroids for fetal lung maturation when preterm delivery is expected and time allows, but do not delay indicated maternal delivery.
6. Stabilize the mother, then determine delivery timing with obstetrics and neonatology. Delivery is definitive treatment; gestational age modifies timing but does not override uncontrolled severe disease.

Delivery is generally recommended at 37 weeks for gestational hypertension or preeclampsia without severe features, and at or beyond 34 weeks for preeclampsia with severe features after stabilization. Before 34 weeks, carefully selected stable patients may undergo expectant management in a tertiary center. Uncontrolled severe BP, eclampsia, pulmonary edema, progressive kidney/liver/hematologic injury, placental abruption or nonreassuring fetal status requires delivery regardless of gestational age. Exact thresholds must follow the current obstetric protocol.

37.7 Chronic kidney disease and superimposed preeclampsia

Baseline creatinine, platelets, liver tests and quantified proteinuria should be documented early in pregnancy for women with CKD or chronic hypertension. Later diagnosis is difficult because BP and proteinuria may already be abnormal. A sudden BP escalation, thrombocytopenia, liver injury, neurologic symptoms, pulmonary edema, fetal growth restriction or a major change in proteinuria supports superimposed preeclampsia. Angiogenic biomarkers can be helpful where validated, but no single test replaces serial clinical assessment.

37.8 Clinical evolution and prognosis

BP and laboratory abnormalities often improve after delivery, but disease can first present or worsen postpartum. BP commonly peaks between 3 and 7 days after birth. Provide an early BP check, symptom education and a clear route for urgent assessment. Persistent headache, visual symptoms, dyspnea, epigastric pain, seizure or severe BP is an emergency. NSAIDs can worsen BP or kidney function in selected patients with AKI, CKD or difficult hypertension and should be individualized.

Kidney function and proteinuria should be reassessed postpartum, commonly at 6–12 weeks and earlier when abnormalities are severe. Persistent proteinuria, hematuria or reduced eGFR may reveal previously unrecognized CKD and can justify nephrology evaluation or delayed biopsy. ACE inhibitors such as enalapril can be appropriate postpartum and during breastfeeding under local guidance; ARBs have less lactation evidence.

A history of preeclampsia increases long-term risk of chronic hypertension, CKD, heart failure, ischemic heart disease and stroke. Early-onset or recurrent disease and preterm delivery confer greater risk. The postpartum visit should therefore create a long-term primary-care and nephrology/cardiovascular prevention plan rather than closing the episode after six weeks.

Case resolution

An obstetric emergency team gives IV labetalol and magnesium sulfate while monitoring respiration, reflexes and urine output. BP falls to 150/98 mmHg without hypotension. HELLP syndrome and fetal growth restriction are confirmed. After maternal stabilization and antenatal corticosteroid assessment, delivery is performed because disease is severe and progressive. Creatinine falls to 0.72 mg/dL and platelets recover postpartum. At 10 weeks, BP remains 136/84 mmHg and ACR is 48 mg/g, so cardiovascular and kidney follow-up continues.

Take-home messages

- Pregnancy increases GFR, so a creatinine that appears normal outside pregnancy can represent important kidney dysfunction.
- Preeclampsia requires new hypertension plus proteinuria or maternal/uteroplacental dysfunction; proteinuria is not mandatory.
- Placental malperfusion raises sFlt-1 and reduces VEGF/PlGF signaling, producing systemic endothelial injury.
- Glomerular endotheliosis is the characteristic renal lesion; IF is usually nonspecific and EM shows endothelial swelling and subendothelial widening.
- Persistent BP at least 160/110 mmHg requires urgent treatment; magnesium prevents seizures but is not the main antihypertensive.
- Delivery removes the placental driver, but postpartum hypertension and long-term CKD/cardiovascular risk require follow-up.

Self-assessment

1. How are chronic hypertension, gestational hypertension and preeclampsia distinguished?
2. Why can serum creatinine of 1.0 mg/dL be abnormal during pregnancy?
3. How does excess sFlt-1 produce hypertension and proteinuria?
4. What are the LM and EM features of glomerular endotheliosis?
5. Which three drugs are first-line options for acute severe hypertension in pregnancy?

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PART VIII

Urinary Tract Infections and Pyelonephritis

From localized bladder infection to systemic infection, sepsis and special populations

Part VIII separates lower from upper urinary tract infection, then revisits both syndromes during pregnancy. The central clinical task is to decide whether infection is localized to the bladder or has become systemic, whether urine flow is obstructed, and whether host factors change drug choice, route or duration. Antibiotic examples are teaching regimens; local resistance data, renal dosing, allergy history and national protocols determine the final prescription.

CHAPTER 38

Lower Urinary Tract Infections

Recognize localized infection, avoid treating colonization and prescribe the narrowest effective therapy

- Distinguish acute cystitis from asymptomatic bacteriuria, urethritis, vaginitis and bladder pain syndrome.
- Explain how bowel organisms ascend, adhere to urothelium and provoke the symptoms of cystitis.
- Use symptoms, urinalysis and urine culture according to pretest probability and clinical risk.
- Choose an appropriate first-line drug and duration for localized cystitis while protecting antimicrobial effectiveness.
- Recognize recurrence, treatment failure and signs that indicate upper or systemic infection.

Opening case

A 24-year-old nonpregnant woman reports 24 hours of dysuria, frequency and urgency. She has no vaginal discharge, fever, rigors, flank pain or vomiting. Temperature is 36.8°C and there is mild suprapubic tenderness. Dipstick is positive for leukocyte esterase and nitrite.

Clinical reasoning. The symptom cluster has a high probability of acute localized cystitis. The absence of vaginal symptoms makes vaginitis less likely, and the absence of systemic features argues against pyelonephritis. In an otherwise healthy woman with a typical first episode, treatment can begin without imaging; culture is useful when the presentation is atypical, recurrent, resistant or occurs in a higher-risk host.

38.1 Definitions and clinical classification

A lower urinary tract infection is infection confined mainly to the urethra and bladder. In everyday practice, acute cystitis is the main bacterial syndrome. Dysuria, frequency, urgency and suprapubic discomfort are localized symptoms. Fever, rigors, hypotension, delirium or costovertebral-angle pain suggest systemic spread and should move the patient out of the “simple cystitis” pathway.

Modern EAU terminology classifies UTI as localized or systemic rather than assuming that every infection outside a healthy nonpregnant woman is “complicated.” Risk factors are then added separately because obstruction, stones, catheterization, recent antibiotics, resistant organisms, immunosuppression and renal impairment predict a more difficult course. IDSA 2025 uses a related clinical approach, emphasizing symptoms beyond the bladder when defining complicated infection for treatment decisions.

Term	Meaning	Practical implication
Acute cystitis	New dysuria, frequency or urgency without systemic features	Usually outpatient therapy; culture selectively in healthy nonpregnant women.
Asymptomatic bacteriuria	Significant bacterial growth without urinary symptoms	Do not treat routinely; major exceptions are pregnancy and selected urological procedures that breach mucosa.
Urethritis	Dysuria with urethral discharge or sexual exposure, often due to an STI	Use first-void urine or swab NAAT; ordinary cystitis therapy may miss the cause.
Recurrent cystitis	At least 2 episodes in 6 months or at least 3 in 12 months	Confirm at least one typical recurrence by culture and look for modifiable risk factors.
Relapse	Recurrence with the same organism soon after therapy	Consider persistence, stone, obstruction, abscess or inadequate drug exposure.
Reinfection	A new episode after clearance, often with a different strain	Common in otherwise healthy women and does not itself prove structural disease.

38.2 Etiology

Most community cystitis begins with the patient's own bowel flora. Uropathogenic *Escherichia coli* causes approximately 70–95% of typical community episodes. *Staphylococcus saprophyticus* is important in younger sexually active women. *Klebsiella*, *Proteus*, *Enterococcus* and other *Enterobacterales* become more likely with prior antibiotics, healthcare exposure or urinary abnormalities. *Pseudomonas aeruginosa*, *Candida* and highly resistant Gram-negative organisms usually signal instrumentation, catheters, obstruction, immunosuppression or repeated antimicrobial exposure.

Organism or group	Typical context	Mechanistic or clinical clue
Uropathogenic <i>E. coli</i>	Most community-acquired cystitis	Type 1 pili and FimH promote attachment to urothelium; recurrence may reflect a new strain or a persistent reservoir.
<i>S. saprophyticus</i>	Young sexually active women	Nitrite may be negative; symptoms resemble <i>E. coli</i> cystitis.
<i>Proteus</i> spp.	Stones, obstruction, catheter or recurrent infection	Urease raises urine pH and promotes struvite stones; persistent isolation should prompt stone assessment.
<i>Klebsiella</i> and <i>Enterobacterales</i>	Diabetes, healthcare exposure, prior antibiotics	Resistance patterns are more variable; previous cultures are clinically valuable.
<i>Enterococcus</i> spp.	Older age, instrumentation or recent broad-spectrum therapy	Cephalosporins lack enterococcal activity.
<i>Pseudomonas</i> or <i>Candida</i>	Catheter, structural disease, ICU or immunosuppression	Distinguish true symptoms from colonization before treating.

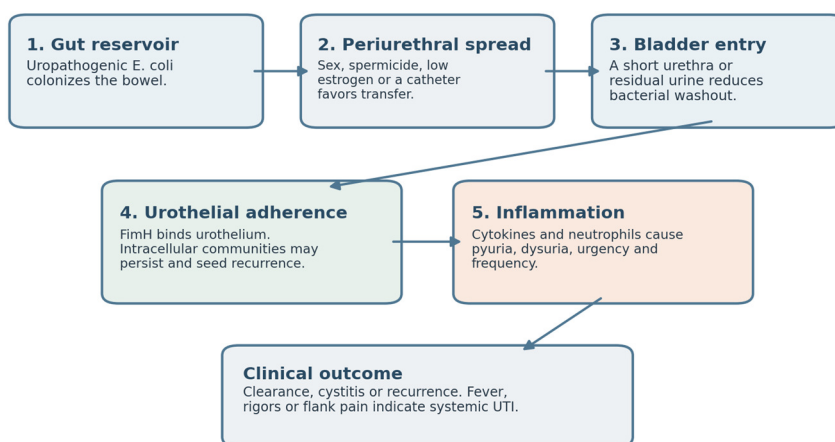
38.3 Pathophysiology

The usual route is ascending. Bacteria move from the intestinal reservoir to the periurethral area, enter the urethra and reach the bladder. A short urethra explains much of the higher incidence in women. Sexual intercourse can mechanically facilitate ascent, spermicides alter protective vaginal flora, and postmenopausal estrogen loss reduces lactobacilli and raises vaginal pH. Residual urine, obstruction and catheters reduce the washout effect of normal voiding.

Uropathogenic *E. coli* is adapted to the urinary tract. Type 1 pili with the FimH adhesin bind receptors on superficial urothelial cells, preventing bacteria from being washed away. Some bacteria invade urothelial cells and form intracellular bacterial communities. Quiescent intracellular reservoirs help explain why genetically related strains can recur after apparently successful treatment.

The bladder is not a passive container. Urothelial Toll-like receptors recognize bacterial structures and trigger cytokines, neutrophil recruitment and exfoliation of infected cells. These defenses clear many exposures but also produce pyuria, mucosal edema, dysuria, frequency and urgency. Therefore, symptoms arise largely from the host inflammatory response; bacterial counts alone cannot distinguish colonization from disease.

How a lower urinary tract infection develops



Urine flow, regular bladder emptying and an intact uroepithelium are major defenses; bacteriuria alone does not equal infection.

Figure 38.1. Lower UTI usually develops through ascending colonization, urothelial adherence and a neutrophil-rich inflammatory response.

38.4 Diagnosis

In a nonpregnant woman with new dysuria and frequency or urgency and no vaginal discharge or irritation, the clinical probability of cystitis is high. A dipstick supports but does not replace clinical reasoning. Leukocyte esterase reflects pyuria; nitrite is specific when positive but can be negative with frequent voiding, low dietary nitrate or organisms that do not reduce nitrate. Pyuria without urinary symptoms is not an indication for antibiotics.

Culture thresholds depend on context. The traditional threshold of 10^4 CFU/mL was designed for specificity in asymptomatic people. In a symptomatic woman, a pure uropathogen at 10^2 – 10^3 CFU/mL can be clinically meaningful. Mixed growth, several organisms and abundant squamous cells suggest contamination. The result must be interpreted with symptoms and collection quality.

Clinical situation	Culture?	Reason
Typical first cystitis in a healthy nonpregnant woman	Often optional	Symptoms may be sufficiently diagnostic; follow local policy.
Pregnancy or male patient	Yes	Drug choice and follow-up depend on organism and susceptibility.
Fever, flank pain, sepsis or kidney dysfunction	Yes before antibiotics if this does not delay treatment	This is no longer a simple lower UTI.
Recurrent, atypical or treatment failure	Yes	Distinguishes resistance, relapse and a noninfectious mimic.
Catheter, obstruction, stone, immunosuppression or recent resistant isolate	Yes	The pathogen spectrum and resistance risk are broader.
Vaginal discharge, genital ulcer or urethral discharge	Urine culture alone is insufficient	Assess vaginitis and use STI testing when indicated.

38.5 Treatment

The treatment goal is rapid symptom relief with the narrowest effective drug. Ask about pregnancy, allergies, eGFR, previous urine cultures, recent antibiotics and local resistance. Encourage normal hydration and regular voiding, but forced large-volume drinking does not sterilize the bladder. Short-term analgesia may help; analgesia must not delay reassessment when systemic features appear.

Teaching regimen for localized cystitis in women	Typical duration	Important limitation
Nitrofurantoin 100 mg twice daily	5 days	Avoid for pyelonephritis; do not use when eGFR is below the locally accepted threshold, commonly <30 mL/min/1.73 m ² .
Fosfomycin trometamol 3 g orally	Single dose	Lower-tract drug; not suitable for renal parenchymal infection.
Pivmecillinam 400 mg three times daily	3–5 days	Availability varies by country.
Trimethoprim-sulfamethoxazole 160/800 mg twice daily	3 days	Use when the isolate is susceptible or local E. coli resistance is <20%; check interactions, potassium and kidney function.
Selected oral cephalosporin	Usually 3–5 days according to protocol	Generally an alternative; ecological effect and local susceptibility matter.

Fluoroquinolones should be preserved for infections that require their tissue penetration or when safer narrow-spectrum options are unsuitable. Aminopenicillins should not be used empirically for ordinary cystitis because E. coli resistance is often high. Once culture is available, narrow or stop therapy when the result and clinical picture do not support bacterial infection.

38.6 Recurrent cystitis

Confirm that episodes are true bacterial cystitis. Persistent urgency or pelvic pain with repeatedly negative cultures suggests another diagnosis. Routine cystoscopy or imaging has low yield in a young woman with typical recurrent cystitis, but hematuria after infection resolves, stones, obstruction, unusual organisms, childhood abnormalities or rapid relapse justify further assessment.

Begin with behavioral measures that match the patient's risk: avoid spermicides, do not delay voiding, and consider postcoital timing. Vaginal estrogen reduces recurrence in postmenopausal women without contraindications. When infections remain frequent and culture-proven, shared decisions may include patient-initiated short-course therapy, postcoital prophylaxis or continuous low-dose prophylaxis. Select the agent from previous susceptibilities and reassess the ongoing need.

38.7 Evolution and prognosis

Symptoms usually begin to improve within 24–48 hours of effective therapy. Persistent symptoms at the end of treatment or recurrence within two weeks require culture and review of adherence, resistance and diagnosis. Ordinary cystitis in an otherwise healthy adult does not usually damage the kidney or cause CKD. Prognosis changes when infection ascends, urine is obstructed, the patient is pregnant or immunocompromised, or recurrent episodes reflect stones, reflux or incomplete emptying.

Case resolution

The patient receives a first-line lower-tract regimen selected from the local formulary. She is advised to seek urgent review for fever, rigors, flank pain, vomiting or failure to improve within 48 hours. Her symptoms resolve by the second day, supporting the diagnosis of localized cystitis.

Take-home messages

- New dysuria plus frequency or urgency without vaginal or systemic symptoms strongly suggests acute cystitis.
- Bacteriuria and pyuria are laboratory findings; symptoms determine whether infection is present.
- Most cystitis is caused by ascending uropathogenic E. coli that adheres to and inflames the urothelium.
- Nitrofurantoin, fosfomycin and pivmecillinam are lower-tract drugs and must not be used for pyelonephritis.

- Culture is especially important in pregnancy, men, recurrent disease, treatment failure and systemic infection.

Self-assessment

1. Which findings distinguish localized cystitis from systemic UTI?
2. Why can a symptomatic patient have a clinically important culture below 10³ CFU/mL?
3. How do type 1 pili and FimH help uropathogenic E. coli cause cystitis?
4. When is urine culture necessary in a patient with lower urinary symptoms?
5. Why should nitrofurantoin not be used when pyelonephritis is suspected?

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CHAPTER 39

Upper Urinary Tract Infections and Acute Pyelonephritis

Identify systemic infection, detect obstruction and protect the kidney through early source control

- Recognize the clinical syndrome of acute pyelonephritis and systemic UTI.
- Explain ascending infection, intrarenal inflammation and the special danger of an obstructed collecting system.
- Use urine culture, laboratory tests and imaging according to severity and risk.
- Select oral or intravenous treatment, narrow therapy and determine an evidence-based duration.
- Predict complications, recovery and situations requiring urgent urology, intensive care or infectious-disease input.

Opening case

A 46-year-old woman with diabetes presents with fever 39.2°C, rigors, vomiting and right flank pain. Heart rate is 118/min, BP 96/60 mmHg and there is right costovertebral-angle tenderness. Creatinine is 1.8 mg/dL compared with 0.8 mg/dL previously. Urinalysis shows pyuria and nitrite. Ultrasound shows right hydronephrosis.

Clinical reasoning. This is a systemic UTI with AKI and possible sepsis. Hydronephrosis raises concern for an infected obstruction. Antibiotics are essential but insufficient: the collecting system may require urgent decompression. Delay allows rising intrarenal pressure, bacteremia and septic shock.

39.1 Definition and etiology

Acute pyelonephritis is bacterial infection of the renal pelvis and parenchyma. It is suggested by fever above 38°C, chills, flank pain, nausea, vomiting or costovertebral-angle tenderness, with or without cystitis symptoms. A patient with hypotension, delirium, tachycardia or organ dysfunction has a systemic infection that must be assessed for sepsis.

Ascending infection is the usual route. *E. coli* remains the most frequent organism. *Klebsiella*, *Proteus*, *Enterobacter*, *Enterococcus* and *Pseudomonas* are more common with healthcare exposure, catheters, obstruction and prior antibiotics. Hematogenous renal infection is much less common; *Staphylococcus aureus* or *Candida* in blood may seed the kidney and should prompt a search for a bloodstream source.

Risk factor	Why it matters	Action
Stone or obstruction	Prevents drainage and creates a pressurized infected system	Urgent imaging and urological decompression when infection and obstruction coexist.
Diabetes	Raises risk of severe infection, papillary necrosis and emphysematous infection	Lower threshold for imaging, admission and close metabolic monitoring.
Pregnancy	Urinary stasis and reflux promote ascent; maternal and fetal complications occur	Use pregnancy-specific pathway and initially manage pyelonephritis in hospital.
Catheter instrumentation or	Biofilm and resistant organisms broaden the pathogen spectrum	Obtain culture correctly; remove or replace the device when appropriate.
Recent antibiotics resistant isolate or	Predicts inadequate empiric coverage	Review cultures from the previous 3–6 months and recent drug exposure.
Immunosuppression or severe CKD	Presentation can be subtle and complications more frequent	Individualize drug, dose, duration and admission decision.

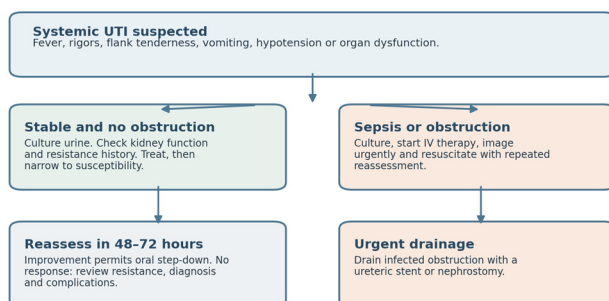
39.2 Pathophysiology and pathology

Bacteria ascend from the bladder through the ureter. Vesicoureteral reflux and high bladder pressure facilitate ascent; intrarenal reflux can carry infected urine from the papilla into collecting ducts. Bacterial products activate tubular epithelial cells and resident immune cells. Neutrophils enter the interstitium and tubular lumen, producing pyuria and white-cell casts.

Edema and neutrophilic inflammation impair tubular function and reduce local perfusion. Patchy suppurative foci can merge into a renal or perinephric abscess. In diabetes or severe ischemia, papillary necrosis may obstruct the ureter. Gas-forming organisms can cause emphysematous pyelonephritis. When a stone blocks the ureter, pressure and infection reinforce each other; drainage becomes the decisive treatment.

Pathology level	Typical acute finding	Clinical meaning
Gross and imaging correlation	Patchy cortical pale or suppurative areas; striated nephrogram; renal swelling; possible abscess	Explains focal pain and why imaging may be normal early but essential when complications are suspected.
Light microscopy	Neutrophils in interstitium and tubules, tubular necrosis and microabscesses; glomeruli relatively spared	White-cell casts localize inflammation above the bladder but are not always present.
Immunofluorescence and electron microscopy	No disease-specific immune-deposit pattern	IF and EM are not routinely required; biopsy is reserved for an alternative diagnosis.
Healing	Resolution or focal tubulointerstitial scar	Repeated childhood infection with reflux causes more scarring than a single treated adult episode.

Acute pyelonephritis: decide severity and source control first



Nitrofurantoin, oral fosfomycin and pivmecillinam do not reach adequate renal parenchymal concentrations and must not be used for pyelonephritis.

Figure 39.1. Acute pyelonephritis management begins by identifying sepsis and obstruction, because an infected obstructed kidney requires drainage as well as antibiotics.

39.3 Diagnosis

Obtain urinalysis and a urine culture with susceptibility testing in every suspected case. Collect the culture before antibiotics when possible, but never delay treatment in a septic patient. Check CBC, creatinine, electrolytes and inflammatory markers; obtain lactate and blood cultures when sepsis, shock or severe illness is present. Blood cultures are most useful when bacteremia will change management or urine culture may be unreliable.

Ultrasound detects hydronephrosis, retention and some stones but a normal scan does not exclude pyelonephritis or early obstruction. CT is more sensitive for stones, abscess, gas and parenchymal complications. Image urgently when obstruction is suspected, the patient is septic, kidney function is deteriorating, pain is severe or anatomy is abnormal. Obtain cross-sectional imaging when fever or clinical instability persists after 48–72 hours of effective therapy.

Finding	Interpretation	Pitfall
Pyuria and bacteriuria	Support UTI in a compatible syndrome	Pyuria can occur without bacterial infection; bacteriuria can represent colonization.
White-cell casts	Suggest inflammation within kidney tubules	Insensitive and not specific for infection; interstitial nephritis can also cause them.
Hematuria	Can accompany infection or stone	Persistent hematuria after recovery requires separate evaluation.
No growth after antibiotics	Does not exclude pyelonephritis	Timing, fastidious organisms and prior drugs matter; reconsider alternative diagnoses.
S. aureus in urine	May reflect catheter infection or hematogenous seeding	In an uninstrumented ill patient, evaluate for bacteremia and another source.

39.4 Initial treatment and source control

1. Assess sepsis immediately. Stabilize airway and circulation, measure urine output and give fluids in reassessed aliquots rather than assuming every patient needs a fixed volume.
2. Collect urine and, when indicated, blood cultures. Start effective empiric therapy promptly in sepsis or shock.
3. Look for obstruction. Infection plus an obstructed collecting system requires urgent ureteric stent or percutaneous nephrostomy; nephrectomy is rarely needed for uncontrolled destructive infection.
4. Choose empiric therapy from severity, previous cultures, antibiotic exposure, allergy, kidney function, drug interactions and a recent local antibiogram.
5. Narrow therapy when susceptibility is known. Switch from IV to an active oral drug once the patient is clinically improving, hemodynamically stable and able to absorb medication.

Clinical setting	Teaching approach	Important qualification
Stable outpatient without sepsis	Oral fluoroquinolone when local susceptibility permits; alternatives require culture guidance and sometimes an initial long-acting IV dose	Fluoroquinolone resistance and adverse effects limit empiric use; follow national restrictions.
Hospitalized or unable to take oral therapy	Start IV ceftriaxone or another appropriate cephalosporin; cefepime or piperacillin-tazobactam when broader coverage is justified	Dose for kidney function and de-escalate promptly.
Sepsis or shock with ESBL risk	Use a regimen likely to be active from prior cultures and local epidemiology; a carbapenem may be needed	Newer broad agents should be reserved for documented or strongly suspected resistance.
Gram-negative bacteremia with source control	Oral step-down is reasonable after clinical stability when the drug is active in blood, kidney and urine	The oral agent must have adequate bioavailability and susceptibility.
Infected obstruction	IV antibiotics plus urgent drainage	Do not wait for antibiotics to "work" before decompressing a septic obstructed kidney.

Nitrofurantoin, oral fosfomycin and pivmecillinam do not achieve reliable renal parenchymal concentrations and must not be used for pyelonephritis. Aminoglycosides can be effective but require cautious dosing and toxicity monitoring, particularly in AKI or CKD.

39.5 Duration of therapy

Count duration from the first day of effective therapy. IDSA 2025 suggests 5–7 days of a fluoroquinolone or 7 days of an effective non-fluoroquinolone for improving complicated UTI, including pyelonephritis. The trials often excluded obstruction, abscess, severe sepsis, immunocompromise, severe renal insufficiency and bacterial prostatitis. EAU tables retain longer courses for some oral beta-lactams and trimethoprim-sulfamethoxazole. Therefore, use the shortest regimen supported for the drug and patient, but individualize when source control is delayed or a poorly studied high-risk condition is present.

Situation	Typical total duration	Interpretation
Improving uncomplicated adult pyelonephritis treated with fluoroquinolone	5–7 days	Use only when active and locally acceptable.
Improving cUTI treated with effective non-fluoroquinolone	About 7 days in IDSA 2025	Evidence for short-course oral beta-lactams is less robust; local protocols may use 7–10 days.
Gram-negative bacteremia with clinical response and source control	7 days	Supported by IDSA 2025 for selected stable patients.
Abscess, persistent obstruction, severe immunosuppression or slow response	Individualized, often longer	Correct the nidus and seek specialist advice rather than extending antibiotics automatically.
Pregnancy or suspected bacterial prostatitis	Use condition-specific course	Pregnancy and prostate involvement are discussed in Chapter 40.

39.6 Evolution and prognosis

Most appropriately treated patients become afebrile and feel better within 48–72 hours. Failure to improve should trigger four questions: Is the organism resistant? Is the urinary tract obstructed? Is there an abscess or emphysematous infection? Is the diagnosis wrong? Repeating the same antibiotic without answering these questions delays source control.

Possible complications include bacteremia, septic shock, AKI, renal or perinephric abscess, papillary necrosis and emphysematous pyelonephritis. A single promptly treated adult episode usually heals without clinically important loss of GFR. Repeated infection with reflux or obstruction can produce focal scars, hypertension and CKD. Prognosis depends more on shock, obstruction, comorbidity, resistant organisms and timing of drainage than on the urine bacterial count.

Case resolution

Blood and urine cultures are collected and IV antibiotics are started immediately. Urology inserts a ureteric stent and drains purulent urine above an obstructing stone. BP and creatinine improve over 24 hours. Culture grows susceptible *E. coli*, therapy is narrowed, and she changes to an active oral agent after she is afebrile and able to eat.

Take-home messages

- Fever, rigors, flank pain or organ dysfunction moves a patient from localized cystitis to systemic UTI assessment.
- Every suspected pyelonephritis requires urine culture and susceptibility testing.
- An infected obstructed kidney is a source-control emergency requiring drainage.
- Nitrofurantoin and oral fosfomycin are bladder drugs, not pyelonephritis drugs.
- Lack of improvement by 48–72 hours requires reassessment for resistance, obstruction, abscess or an alternative diagnosis.

Self-assessment

1. Which clinical findings suggest that a UTI has become systemic?
2. Why can antibiotics alone fail in obstructive pyelonephritis?
3. What are the characteristic light-microscopy findings of acute pyelonephritis?
4. When should imaging be obtained urgently or repeated after treatment begins?
5. How does IDSA 2025 define an appropriate short duration for an improving complicated UTI?

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CHAPTER 40

Urinary Tract Infections in Pregnancy

Adapt screening, diagnosis, treatment and follow-up to the physiological changes of pregnancy

- Explain why pregnancy promotes urinary stasis and ascending infection.
- Screen, diagnose and treat asymptomatic bacteriuria, cystitis and pyelonephritis during pregnancy.
- Recognize maternal, fetal and obstetric complications of pyelonephritis.
- Choose pregnancy-compatible antibiotics according to culture, gestational age, allergy and kidney function.
- Recognize when pyelonephritis requires inpatient treatment, imaging or urgent source control.

Opening case

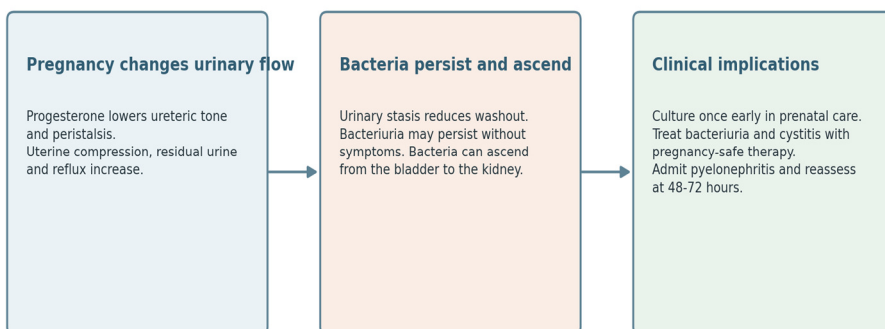
Pregnancy case. A woman at 12 weeks' gestation has no urinary symptoms, but a screening culture grows 10^4 CFU/mL *E. coli* in a single-organism culture. This is asymptomatic bacteriuria in pregnancy and requires targeted treatment because pregnancy increases the risk of ascending infection.

40.1 Etiology and pathophysiology

Pregnancy does not create a unique pathogen spectrum; *E. coli* remains dominant. It changes the urinary tract so that colonization is more likely to ascend. Progesterone relaxes ureteral smooth muscle, the enlarging uterus compresses the ureters, bladder capacity and residual urine increase, and physiologic glycosuria can support bacterial growth. Hydroureter and vesicoureteral reflux become more prominent as pregnancy progresses.

Asymptomatic bacteriuria occurs in approximately 2–10% of pregnancies. It matters because bacteria can persist without dysuria, then ascend through a dilated, slowly draining system. Screening and treatment reduce pyelonephritis, although much of the evidence is old and modern baseline risk may be lower. Pyelonephritis can provoke a systemic inflammatory response, uterine contractions, placental dysfunction and preterm birth.

Why pregnancy increases the risk of ascending urinary infection



Symptoms determine the syndrome; culture identifies the organism; severity and obstruction determine urgency.

Figure 40.1. Pregnancy promotes urinary stasis, bacterial persistence and ascending infection; these mechanisms explain the need for screening and early treatment.

40.2 Diagnosis

Syndrome	Diagnostic approach	Key threshold or clue
Asymptomatic bacteriuria	Screen once with urine culture early in prenatal care	Treat a single uropathogen at $\geq 10^5$ CFU/mL; lower counts often reflect contamination, except organism-specific obstetric implications such as group B streptococcus.
Acute cystitis	Symptoms plus urinalysis; obtain culture before therapy	Culture confirms and guides a 5–7-day targeted course.
Acute pyelonephritis	Fever $\geq 38^\circ\text{C}$ plus urine evidence, usually with flank pain or costovertebral-angle tenderness	Assess CBC, creatinine, sepsis and obstetric status; culture before therapy without delaying treatment.
Failure to improve	Review susceptibility and image the urinary tract	No improvement by 48–72 hours suggests resistance, stone, obstruction or abscess.

40.3 Treatment

Treat asymptomatic bacteriuria and acute cystitis with a 5–7-day targeted course; single-dose fosfomycin is an accepted exception in selected lower-tract infection. Avoid empiric ampicillin or amoxicillin because *E. coli* resistance is often high. Common lower-tract options include nitrofurantoin, selected beta-lactams and fosfomycin, but selection depends on trimester, allergy, G6PD status, kidney function and susceptibility. Nitrofurantoin and fosfomycin must not be used for pyelonephritis.

Drug or class	Use in pregnancy	Important caution
Nitrofurantoin	Effective for lower UTI when susceptible	Avoid for pyelonephritis; avoid in G6PD deficiency and near delivery when neonatal hemolysis is a concern; follow local trimester guidance.
Fosfomycin	Single-dose option for lower UTI or bacteriuria	No adequate renal tissue penetration for pyelonephritis.
Cephalexin or other selected beta-lactam	Common culture-directed lower-tract option	Choose from susceptibility and local obstetric formulary; dose for kidney function.
Trimethoprim-sulfamethoxazole	Sometimes used when benefit outweighs risk and susceptibility supports it	Trimethoprim antagonizes folate early; sulfonamide near term raises neonatal concerns. Use trimester-specific specialist guidance.
Fluoroquinolone	Generally avoided	Alternative only in exceptional situations with specialist assessment.

ACOG recommends initial inpatient management of pyelonephritis in pregnancy. Start an IV regimen with renal tissue penetration, such as an appropriate cephalosporin, and tailor it to culture. Continue parenteral therapy until clinical improvement, then change to an active oral drug to complete 14 days. EAU guidance permits shorter total therapy in selected mild cases with close follow-up, but the obstetric protocol used locally should govern practice.

40.4 Evolution and prognosis

Most patients improve within 48–72 hours. Pyelonephritis can cause sepsis, septic shock, AKI, anemia, disseminated intravascular coagulation and acute respiratory distress syndrome. Obstetric risks include uterine contractions, preterm delivery and low birth weight. Consider a test-of-cure culture after cystitis according to local practice; after pyelonephritis, confirm microbiological clearance and consider suppressive therapy when recurrent infection risk is high. Recurrent pyelonephritis can occur before delivery, so follow-up must include rapid access to care for new fever or flank pain.

Case resolution

The patient receives culture-directed lower-tract therapy that is appropriate for pregnancy and a follow-up plan. She remains asymptomatic and does not develop pyelonephritis. The result illustrates why asymptomatic bacteriuria in pregnancy is treated even when the patient feels well.

Take-home messages

- Pregnancy causes ureteral dilation, residual urine and reflux, increasing the risk that bacteriuria will ascend.
- Screen once early in pregnancy with urine culture and treat asymptomatic bacteriuria at $\geq 10^5$ CFU/mL.
- Pyelonephritis in pregnancy is initially an inpatient condition and carries maternal, fetal and obstetric risks.
- Treat asymptomatic bacteriuria and acute cystitis with a culture-directed regimen that is appropriate for gestational age and kidney function.
- Nitrofurantoin and oral fosfomycin are lower-tract drugs and must not be used for pyelonephritis.

Self-assessment

1. Which physiological changes in pregnancy promote ascending UTI?
2. How and when should asymptomatic bacteriuria be screened for and treated during pregnancy?
3. Why are nitrofurantoin and fosfomycin inappropriate for pyelonephritis in pregnancy?
4. Why is untreated asymptomatic bacteriuria clinically important during pregnancy despite the absence of urinary symptoms?
5. What should be reconsidered when pyelonephritis in pregnancy does not improve within 48-72 hours?

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PART IX

Kidney Transplantation

From candidate selection to long-term graft care

Kidney transplantation replaces renal function but introduces a new clinical state: a functioning foreign organ that must be protected from immune attack while the patient is protected from infection, toxicity, cardiovascular disease and malignancy. This part gives the medical student a practical framework for understanding that balance.

CHAPTER 41

Kidney Transplantation

Understand compatibility, rejection, immunosuppression and the approach to a dysfunctional graft

- Describe the principal milestones that made clinical kidney transplantation possible.
- Explain how candidates and donors are evaluated and how ABO, HLA, donor-specific antibodies and crossmatch results affect risk.
- Recognize the surgical anatomy and important early vascular and urological complications.
- Distinguish T-cell-mediated from antibody-mediated rejection and relate each process to LM, IF/IHC and EM findings.
- Describe induction and maintenance immunosuppression, major adverse effects and clinically important interactions.
- Use a systematic approach to rising creatinine, infection surveillance and long-term graft protection.

Opening case

A 42-year-old man received a deceased-donor kidney transplant 18 days ago. His creatinine fell from 8.1 to 1.6 mg/dL, but is now 2.4 mg/dL. Urine output has decreased. He has no graft pain and no fever. Tacrolimus, mycophenolate and prednisone were prescribed. Three days ago, clarithromycin was started for cough. Examination shows BP 152/92 mmHg, mild tremor and no edema.

Clinical reasoning. The graft is denervated, so absence of pain does not reassure us. A macrolide can inhibit CYP3A metabolism and raise tacrolimus exposure, causing vasoconstriction and tubular toxicity. Rejection, obstruction, infection and reduced perfusion remain possible. The correct first step is a structured assessment—not empirical antirejection therapy.

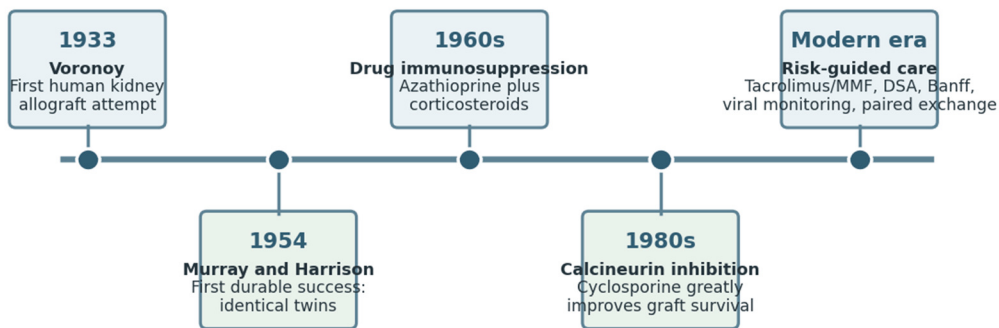
41.1 A short history of kidney transplantation

Kidney transplantation developed through several discoveries rather than one operation. Vascular surgeons first learned how to connect arteries and veins reliably. In 1933, Ukrainian surgeon Yuri Voronoy performed the first human kidney allograft attempt using a deceased-donor kidney. The graft did not provide lasting function, but the procedure demonstrated that a human kidney could be implanted and reperfused.

The decisive milestone came in Boston in 1954, when Joseph Murray, John Merrill and J. Hartwell Harrison transplanted a kidney between the identical Herrick twins. Because identical twins share essentially the same transplantation antigens, immune rejection was avoided. The operation proved that a transplanted kidney could sustain long-term life; Murray later shared the 1990 Nobel Prize in Physiology or Medicine for discoveries concerning organ transplantation.

Transplantation then became available to genetically different people. Azathioprine and corticosteroids enabled clinical programs in the 1960s. Cyclosporine transformed results in the 1980s by suppressing T-cell activation more selectively. Tacrolimus and mycophenolate later became central components of maintenance therapy. Modern practice adds sensitive HLA-antibody testing, standardized Banff biopsy classification, better preservation, living-donor and paired-exchange programs, and systematic viral surveillance.

Kidney transplantation: milestones that changed clinical practice



The operation became reproducible only after immunology, organ preservation and immunosuppression advanced together.

Figure 41.1. Kidney transplantation became successful when surgical technique, immunology, preservation and pharmacology advanced together.

41.2 Why transplant, and who should be evaluated?

For a suitable patient with kidney failure, transplantation is usually the preferred kidney replacement therapy because it can restore endocrine and excretory kidney functions more continuously than dialysis, improve quality of life and provide a survival advantage. It is treatment, not cure: the recipient requires lifelong follow-up and usually lifelong immunosuppression.

Evaluation should begin before dialysis when progressive kidney failure is expected. A pre-emptive transplant occurs before maintenance dialysis begins. It avoids dialysis exposure, but it must never bypass the same medical, immunological, psychosocial and ethical assessment required for every recipient. Age alone is not an absolute exclusion. The question is whether the expected benefits outweigh perioperative, infectious, cardiovascular, cancer and adherence-related risks.

Domain	What the team is trying to establish
Kidney disease	Confirm irreversible kidney failure, recurrence risk and whether native nephrectomy is needed.
Cardiovascular	Assess symptoms, functional status and risk; optimize heart failure, ischemia and peripheral vascular disease.
Infection	Treat active infection; define tuberculosis, hepatitis B/C, HIV, CMV and EBV status; update non-live vaccines.
Cancer	Exclude active malignancy and apply cancer-specific waiting or surveillance plans rather than one universal interval.
Urological/surgical	Assess bladder function, urinary obstruction, iliac vessels, body habitus and previous operations.
Psychosocial	Assess understanding, adherence barriers, substance use, cognition, support and ability to manage complex medication.
Immunological	ABO type, HLA typing, sensitization history, antibody screen, donor-specific antibodies and crossmatch.

Usually temporary contraindications include active serious infection, untreated active cancer, unstable cardiovascular disease and uncontrolled conditions that make surgery or immunosuppression immediately unsafe. The purpose of evaluation is often to correct risk—not simply to accept or reject the patient. Living-donor assessment is independent and must protect the donor's autonomy and long-term health.

41.3 Donors, sensitization and immunological compatibility

A kidney may come from a living or deceased donor. Living donation permits planned surgery, short cold-ischemia time and often immediate graft function. Deceased donation increases availability but introduces variable ischemia and donor factors. Donation after brain death and donation after circulatory death are both established pathways. Allocation rules differ by country and balance urgency, waiting time, compatibility, expected benefit and fairness.

ABO compatibility is checked first. HLA molecules present peptides to T cells and are major targets of alloimmunity. Traditional matching focuses on HLA-A, HLA-B and HLA-DR, although modern risk assessment considers more detailed molecular mismatch. A recipient may become sensitized after pregnancy, transfusion or previous transplantation and develop anti-HLA antibodies. Calculated panel-reactive antibody (cPRA) estimates the proportion of donors against whom the recipient is likely to react; a high cPRA means access is more difficult, not that transplantation is impossible.

Donor-specific antibodies (DSA) are recipient antibodies directed against the actual donor's HLA. Crossmatching asks whether recipient serum reacts with donor lymphocytes. Complement-dependent cytotoxicity crossmatch detects strong complement-fixing antibodies; flow-cytometric crossmatch is more sensitive. A virtual crossmatch compares the recipient's defined antibody profile with the donor's HLA type. A positive crossmatch usually indicates high hyperacute or early antibody-mediated rejection risk and demands specialist interpretation or a desensitization strategy.

Compatibility assessment: four questions before transplantation

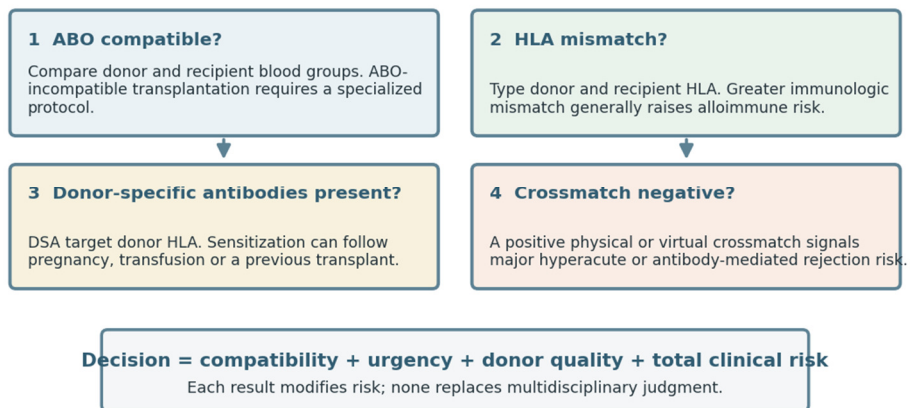


Figure 41.2. Compatibility assessment combines ABO, HLA mismatch, donor-specific antibodies and crossmatch results with total clinical risk.

41.4 Surgical anatomy and early graft function

The graft is usually placed extraperitoneally in the right or left iliac fossa. The donor renal artery and vein are connected to the recipient iliac vessels, and the donor ureter is implanted into the bladder. Native kidneys usually remain because removing them adds risk without benefit. Their removal may be considered for recurrent infection, uncontrolled bleeding, suspected cancer, extreme polycystic enlargement or severe refractory symptoms.

The transplanted kidney is superficial and denervated. It can be examined and biopsied easily, but ischemia, obstruction and rejection may be painless. Immediately after reperfusion, living-donor grafts often produce urine; deceased-donor grafts may recover more slowly. Delayed graft function is commonly defined for research and clinical audit as a need for dialysis during

the first postoperative week, although that operational definition is influenced by the clinician’s dialysis threshold.

Where the transplanted kidney is placed

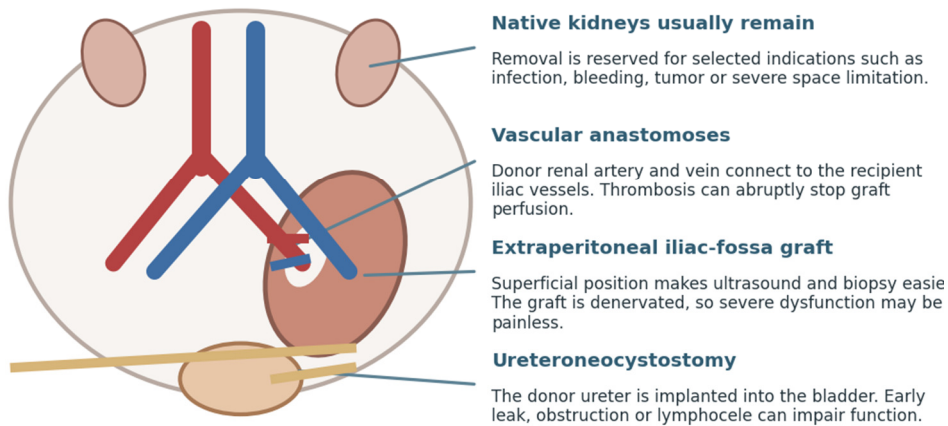


Figure 41.3. The graft lies extraperitoneally in the iliac fossa, with vascular connections to the iliac vessels and ureteric implantation into the bladder.

Timing	Important causes	Clinical implication
Minutes–hours	Renal artery/vein thrombosis, major bleeding, hyperacute rejection	Abrupt anuria or poor function; Doppler ultrasound is urgent.
Days	Ischemia-reperfusion acute tubular injury, volume or pressure problems, calcineurin-inhibitor vasoconstriction	Trend urine output, creatinine, electrolytes and drug exposure.
Days–weeks	Urinary leak, ureteric obstruction, lymphocele, infection, acute rejection	Ultrasound defines anatomy; biopsy defines unexplained parenchymal dysfunction.

Ischemia-reperfusion injury causes endothelial activation, tubular ATP depletion, loss of epithelial polarity and inflammatory recruitment. On light microscopy, acute tubular injury shows tubular epithelial flattening, loss of brush border, luminal debris and regenerative mitoses. Immunofluorescence is usually nonspecific, and electron microscopy may show epithelial simplification and organelle injury. Delayed function increases the need for diagnostic biopsy because rejection can coexist with ischemic injury.

41.5 Why rejection occurs

The immune system is designed to recognize non-self. Donor dendritic cells can directly present donor HLA to recipient T cells, while recipient antigen-presenting cells process donor proteins and present donor peptides indirectly. Activated CD4 and CD8 T cells produce cytokines, recruit macrophages and injure tubules, interstitium and arteries. B cells can differentiate into plasma cells and make DSA. Antibodies bind graft endothelium, activate complement and Fc-receptor pathways, and produce microvascular inflammation.

Rejection is not diagnosed by creatinine alone. Creatinine rises only after function has fallen and cannot identify the mechanism. The biopsy is interpreted with the clinical timeline, DSA and molecular or serological information using the evolving Banff classification. “Borderline,” T-cell-mediated rejection (TCMR), antibody-mediated rejection (ABMR) and chronic injury are clinicopathological categories, not interchangeable synonyms.

How rejection appears on biopsy

Pattern	Mechanism and usual timing	LM, IF/IHC and EM
Hyperacute	Minutes–hours; preformed antibody	LM: fibrin thrombi, congestion, cortical necrosis. IF/IHC: strong vascular C4d may be present. EM: severe endothelial injury.
Acute TCMR	Usually days–months, but possible later with under-immunosuppression	LM: interstitial inflammation and tubulitis; intimal arteritis in vascular grades. IF: no disease-defining immune deposits. EM: not usually required.
Active ABMR	Early with pre-existing DSA or later with de novo DSA	LM: glomerulitis, peritubular capillaritis, arteritis or acute TMA. IHC/IF: C4d may support antibody–endothelium interaction but can be negative. EM: endothelial swelling/subendothelial widening.
Chronic active ABMR	Months–years	LM: transplant glomerulopathy with double contours and chronic microvascular inflammation. IF/IHC: C4d may be positive or negative. EM: glomerular basement-membrane duplication and peritubular-capillary basement-membrane multilayering.
Chronic nonspecific injury	Months–years; multiple insults	Interstitial fibrosis and tubular atrophy (IFTA), glomerulosclerosis and vascular disease. Arteriolar hyalinosis and striped fibrosis may suggest CNI effect but are not fully specific.

Treatment and expected course

Pattern	Treatment principle	Evolution and prognosis
Hyperacute	Often irreversible; stop antibody exposure and usually remove a nonviable graft.	Rare with modern crossmatching; graft loss likely.
Acute TCMR	IV corticosteroids; T-cell–depleting therapy for severe or steroid-resistant disease; correct adherence/exposure.	Often reversible when recognized early; vascular or recurrent episodes worsen prognosis.
Active ABMR	Optimize baseline therapy; many centers use plasma exchange plus IVIG, with selected additional agents. Evidence and protocols vary.	Response is variable; persistent DSA and microvascular inflammation predict chronic injury.
Chronic active ABMR	Address adherence and immunosuppression; control BP/proteinuria. No treatment reliably reverses established remodeling.	Common pathway to progressive proteinuria and graft failure.
Chronic nonspecific injury	Identify reversible causes; minimize toxicity without provoking rejection; treat CKD complications.	Depends on active inflammation, fibrosis burden, eGFR slope, proteinuria and cause.

Pathology shorthand. Tubulitis means lymphocytes crossing tubular basement membrane into tubular epithelium. Intimal arteritis means inflammatory cells beneath the arterial endothelium. Glomerulitis and peritubular capillaritis together form microvascular inflammation. C4d is a complement split product deposited in peritubular capillaries; it supports ABMR but is neither required in every case nor sufficient by itself. Transplant glomerulopathy describes chronic capillary-wall remodeling, not recurrence of one specific native-kidney glomerulopathy.

41.6 Immunosuppression: suppress rejection without disabling host defense

Induction therapy is intense treatment around the operation. Basiliximab blocks the interleukin-2 receptor and is often used in lower immunological risk. Rabbit antithymocyte globulin depletes T cells and is often chosen when rejection risk is higher, but it causes more leukopenia and infection risk. Choice varies with immunological risk, donor factors and center protocol.

A common maintenance regimen is tacrolimus, mycophenolate and a corticosteroid. Tacrolimus inhibits calcineurin, reducing T-cell cytokine transcription; mycophenolate inhibits inosine monophosphate dehydrogenase and lymphocyte purine synthesis; corticosteroids broadly suppress inflammatory gene transcription. Drug-level targets are center-, time- and risk-specific, so a single universal tacrolimus trough target should not be memorized.

Drug/class	Mechanism	Major adverse effects	Practical safety point
Tacrolimus cyclosporine	Calcineurin inhibition → less IL-2 and T-cell activation	Acute vasoconstriction, chronic nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, tremor; tacrolimus more diabetogenic	CYP3A inhibitors (azoles, clarithromycin, some calcium-channel blockers, grapefruit) raise levels; rifampin and some anticonvulsants lower levels.
Mycophenolate	Blocks de novo guanosine synthesis in lymphocytes	Diarrhea, leukopenia, infection; teratogenic	Antacids/binders may reduce absorption; pregnancy requires specialist substitution before conception.
Corticosteroids	Broad genomic suppression of inflammation	Diabetes, infection, osteoporosis, cataract, weight gain	Never stop abruptly after long exposure; use bone and metabolic prevention.
mTOR inhibitors	Sirolimus/everolimus inhibit mTOR signaling and proliferation	Proteinuria, dyslipidemia, cytopenia, mouth ulcers, impaired wound healing	Avoid or delay when wound healing is important; levels and interactions require monitoring.
Belatacept	Blocks CD80/86–CD28 costimulation	Rejection risk early; post-transplant lymphoproliferative disorder	Use only in EBV-seropositive recipients because PTLN risk is excessive in EBV-seronegative patients.

Prescribing safely. Never start a macrolide, azole antifungal, rifamycin, anticonvulsant, herbal preparation or interacting anticoagulant without checking transplant medications. Diarrhea can unpredictably raise tacrolimus exposure. A “therapeutic” trough does not exclude calcineurin-inhibitor toxicity, and a low level may indicate nonadherence, impaired absorption or induction of metabolism.

41.7 A practical approach to rising creatinine

First confirm that the change is real and clinically important. Compare with the patient’s best post-transplant baseline, repeat the measurement when appropriate, and assess urine output, potassium, bicarbonate and volume status. Review blood pressure, fever, sepsis, diarrhea, vomiting and every new prescription or over-the-counter drug. A urinary catheter may be blocked; a patient may be hypovolemic; a tacrolimus level may be toxic.

Urinalysis and culture look for infection; proteinuria or hematuria may suggest recurrent glomerular disease, ABMR or another parenchymal lesion. Ultrasound with Doppler is the first anatomical study because it can show hydronephrosis, perinephric collection and major perfusion abnormalities. Resistive indices are nonspecific and cannot diagnose rejection. Test for BK polyomavirus, CMV or DSA according to timing and risk. If dysfunction remains unexplained, graft biopsy is usually the decisive test.

A rising creatinine after kidney transplantation

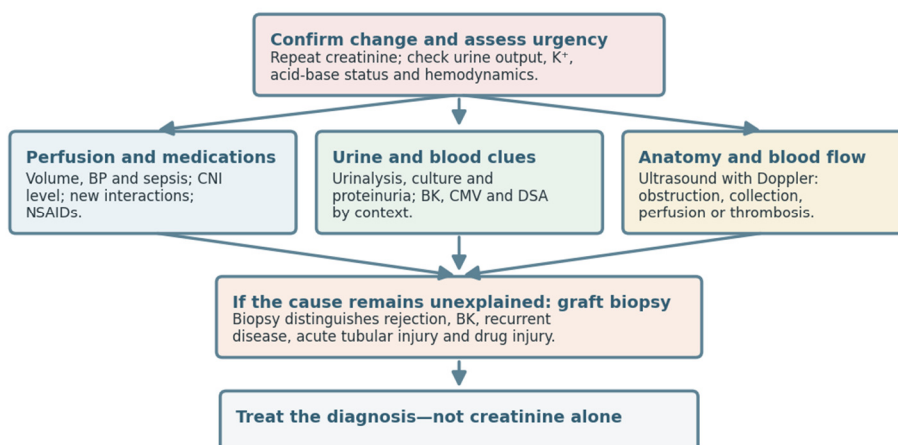


Figure 41.4. A rising creatinine requires simultaneous assessment of perfusion, medications, infection, anatomy and alloimmunity; biopsy is used when the cause remains unexplained.

41.8 Infection after transplantation

Immunosuppression changes both the probability and the appearance of infection. Fever and inflammatory responses may be muted. In the first month, surgical-site, catheter-related, urinary, donor-derived and hospital-acquired infections dominate. From approximately 1–6 months, opportunistic infections become more important, including CMV, BK polyomavirus and *Pneumocystis jirovecii*. After six months, community infections predominate in a stable recipient, while persistent heavy immunosuppression continues to permit opportunistic disease.

Pathogen/problem	Risk pattern	Clinical effect	Prevention/management principle
CMV	Highest classic risk: donor seropositive/recipient seronegative (D+/R–)	Fever, cytopenia, hepatitis, gastrointestinal or tissue-invasive disease; can amplify alloimmunity	Prophylaxis or pre-emptive viral-load monitoring according to risk and protocol; valganciclovir/ganciclovir treatment with dose and CBC monitoring.
BK polyomavirus	High immunosuppressive exposure; often asymptomatic DNAemia	Tubulointerstitial nephritis and graft dysfunction; biopsy may mimic TCMR	Screen plasma monthly to month 9, then every 3 months to 2 years in adults. Sustained >1,000 copies/mL or >10,000 copies/mL prompts immunosuppression reduction; assay trends matter.
Pneumocystis	Highest risk early or after augmented immunosuppression	Hypoxemic interstitial pneumonia	Trimethoprim-sulfamethoxazole prophylaxis is standard; duration is protocol- and risk-dependent.
EBV / PTLD	Greatest risk in EBV-seronegative recipient exposed to EBV-positive graft, especially with T-cell depletion	Fever, lymphadenopathy, extranodal masses, graft or CNS disease	Reduce immunosuppression and obtain tissue diagnosis; treatment is multidisciplinary and often includes anti-CD20 therapy.

Vaccinate before transplantation whenever possible. Inactivated vaccines are generally safe after transplantation, although responses may be weaker. Live attenuated vaccines are generally contraindicated after transplantation because vaccine organisms may replicate in an immunosuppressed host. Exposure prophylaxis, food and water safety, travel advice and local epidemiology belong to routine care.

BK nephropathy deserves special attention because treatment is counterintuitive: the principal therapy is a careful reduction of immunosuppression, not an antiviral drug. Histology shows viral cytopathic enlargement and intranuclear inclusions in tubular epithelial cells with tubulointerstitial inflammation. SV40 large T-antigen immunohistochemistry supports polyomavirus infection. Focal disease can be missed, and excessive immunosuppression reduction can provoke rejection; plasma viral-load trends and biopsy context must be integrated.

41.9 Long-term complications and recurrent kidney disease

A functioning graft does not remove cardiovascular risk. Hypertension, diabetes, dyslipidemia, obesity and smoking should be treated actively. New-onset diabetes may be promoted by tacrolimus and corticosteroids. Proteinuria is both a diagnostic clue and a prognostic marker. CKD complications can recur as graft function declines, and drug doses must be adjusted to current kidney function.

Cancer risk increases because tumor immune surveillance is suppressed. Skin cancer and post-transplant lymphoproliferative disorder are particularly important, but age-appropriate cancer screening and organ-specific surveillance remain necessary. Prevention includes sun protection, smoking cessation, oncogenic-virus vaccination before transplantation where appropriate, and prompt assessment of unexplained weight loss, lymphadenopathy, cytopenia or graft mass.

Native kidney disease may recur. FSGS can recur rapidly with nephrotic proteinuria; membranous nephropathy, IgA nephropathy, complement-mediated disease, lupus nephritis and atypical hemolytic uremic syndrome have different recurrence patterns. Diabetes and hypertension can injure the graft again. A transplant biopsy should therefore ask not only “Is this

rejection?” but also “Has the original disease returned, is there a new disease, infection or drug injury?”

41.10 Evolution and prognosis

Early outcome depends on donor quality, ischemia time, surgical complications, delayed graft function and rejection. Long-term outcome depends on the cumulative burden of alloimmune injury, infection, cardiovascular disease, malignancy, recurrent disease, medication toxicity and adherence. Living-donor kidneys generally have shorter ischemia and better average outcomes, but prognosis for an individual recipient must be based on donor and recipient risk rather than donor category alone.

Useful prognostic observations are the best achieved baseline creatinine/eGFR, eGFR slope, proteinuria, DSA development, rejection phenotype and chronic damage on biopsy. Active inflammation may respond to treatment; established interstitial fibrosis, tubular atrophy and transplant glomerulopathy are much less reversible. If graft failure becomes progressive, preparation for dialysis or re-transplantation should begin early. Immunosuppression after graft failure is individualized because continuing it preserves residual function and sensitization options but increases infection and cancer risk.

Medical emergency

Contact the transplant team urgently for anuria or abrupt oliguria, a rapid creatinine rise, severe hyperkalemia, hypotension or shock, fever with organ dysfunction, suspected vascular thrombosis, urinary leak or obstruction, inability to take immunosuppression, markedly abnormal calcineurin-inhibitor exposure, or a new interacting drug. Do not stop immunosuppression casually and do not give empirical high-dose corticosteroids before excluding dangerous infection unless the transplant team directs it.

Case resolution

Clarithromycin is stopped after immediate discussion with the transplant team. The tacrolimus trough is markedly elevated; ultrasound shows preserved perfusion and no hydronephrosis, and urine culture is negative. Tacrolimus is temporarily withheld and then restarted at an adjusted dose with close monitoring. Creatinine returns toward baseline. The case demonstrates that drug interaction can imitate rejection and that systematic assessment prevents unnecessary immunosuppression.

Take-home messages

- Transplantation is the preferred kidney replacement therapy for suitable patients, but it creates lifelong immunological and medication-related risks.
- ABO, HLA mismatch, sensitization, DSA and crossmatch results estimate different parts of immunological risk.
- The graft is superficial and denervated; serious dysfunction may be painless, and ultrasound identifies anatomy rather than rejection.
- TCMR mainly produces interstitial inflammation, tubulitis and sometimes arteritis; ABMR targets microvascular endothelium and requires integrated pathology, DSA and clinical evidence.
- A rising creatinine is a signal, not a diagnosis: assess perfusion, medications, obstruction, infection, recurrent disease and rejection.
- Immunosuppression is a balance—too little permits rejection, while too much causes infection, malignancy and drug toxicity.

Self-assessment

1. Why was the 1954 identical-twin transplant successful without modern immunosuppression, and what did it prove?
2. How do cPRA, donor-specific antibodies and crossmatch results differ?

3. Compare acute T-cell-mediated rejection with active antibody-mediated rejection by mechanism and biopsy findings.
4. List the first investigations in a transplant recipient with an unexplained rise in creatinine.
5. Why is reducing immunosuppression the main treatment for BK polyomavirus nephropathy, and what risk does that strategy create?

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Part VII model answers

Chapter 35

1. Stenosis is an anatomical lesion; renovascular hypertension is BP driven by reduced renal perfusion; ischemic nephropathy is loss of kidney function or mass from chronic vascular insufficiency.
2. When both kidneys, or a solitary functioning kidney, perceive low perfusion, sodium excretion cannot compensate; abrupt volume expansion and afterload can produce pulmonary edema.
3. Clues include early or abrupt hypertension, true resistance, recurrent flash pulmonary edema, a greater than approximately 30% creatinine rise with RAAS blockade, rapid eGFR decline and asymmetric kidneys.
4. In broadly selected atherosclerotic disease, routine stenting added no cardiovascular or kidney benefit beyond medical therapy.
5. A small kidney, extensive global sclerosis, tubular atrophy/interstitial fibrosis, high intrarenal resistance and heavy proteinuria predict limited recovery.

Chapter 36

1. The phenotype is nonspecific and common; diabetes, aging, APOL1-related disease and occult glomerulopathy can produce similar findings.
2. Benign disease shows hyaline arteriosclerosis and fibroelastic intimal thickening; malignant disease shows fibrinoid necrosis, thrombi and hyperplastic onion-skin narrowing.
3. Ischemia stimulates renin, which raises pressure through angiotensin II and sodium retention, causing further endothelial and vascular injury.
4. For most emergencies, reduce mean arterial pressure by no more than about 20–25% in the first hour, then toward 160/100–110 mmHg over the next 2–6 hours.
5. Severe persistent thrombocytopenia/hemolysis, neurologic predominance, severe ADAMTS13 deficiency, Shiga-toxin context, pregnancy-associated disease or injury that persists despite BP control suggests another TMA.

Chapter 37

1. Chronic hypertension predates 20 weeks; gestational hypertension begins after 20 weeks without organ dysfunction; preeclampsia adds proteinuria or maternal/uteroplacental dysfunction.
2. Normal pregnancy raises GFR and lowers creatinine, so 1.0 mg/dL may represent a substantial decline from the pregnancy baseline.
3. sFlt-1 sequesters VEGF and PlGF, impairing endothelial maintenance and nitric-oxide signaling; systemic vasoconstriction and glomerular endothelial injury cause hypertension and proteinuria.
4. LM shows enlarged bloodless glomeruli with endothelial swelling and narrowed capillaries; EM shows loss of fenestrations, subendothelial widening and endothelial swelling.
5. IV labetalol, IV hydralazine and immediate-release oral nifedipine are standard first-line emergency options.

Part VIII model answers

Chapter 38

1. Cystitis causes dysuria, frequency, urgency and suprapubic discomfort without fever, rigors, hypotension or flank pain; systemic features require pyelonephritis assessment.
2. In a symptomatic woman, 10^2 – 10^3 CFU/mL of a pure uropathogen can represent true infection; the 10^4 CFU/mL threshold was designed mainly for specificity in asymptomatic populations.
3. Type 1 pili and FimH bind urothelial receptors, resist urinary washout and permit invasion and intracellular bacterial communities.
4. Culture is especially indicated in pregnancy, men, recurrent or atypical infection, treatment failure, systemic illness and hosts with urinary risk factors.
5. Nitrofurantoin concentrates in urine but does not achieve reliable renal parenchymal levels, so it cannot treat pyelonephritis.

Chapter 39

1. Fever, rigors, flank pain, costovertebral-angle tenderness, vomiting, hypotension, delirium or organ dysfunction suggest systemic UTI.
2. Obstruction prevents drainage and creates a pressurized infected collecting system; decompression is required because antibiotics alone cannot provide source control.
3. LM shows patchy neutrophilic tubulointerstitial inflammation, neutrophils within tubular lumens and sometimes microabscesses; glomeruli are relatively spared.
4. Image urgently with sepsis, AKI, stone or obstruction risk, severe pain or abnormal anatomy; obtain cross-sectional imaging when improvement is absent after 48–72 hours.
5. IDSA 2025 supports 5–7 days of an effective fluoroquinolone or 7 days of an effective non-fluoroquinolone in clinically improving cUTI, while excluded high-risk conditions require individualization.

Chapter 40

1. Progesterone relaxes ureters, the gravid uterus compresses them, and bladder residual volume and reflux increase, promoting bacterial persistence and ascent.
2. Obtain one urine culture early in prenatal care; treat a single uropathogen at $\geq 10^4$ CFU/mL with a targeted 5–7-day course, with single-dose fosfomycin as an accepted selected exception.
3. Both drugs act mainly in the lower urinary tract and do not reach adequate renal tissue levels for pyelonephritis.
4. Pregnancy-related stasis allows bacteria to persist and ascend. Untreated asymptomatic bacteriuria therefore increases the risk of pyelonephritis and its maternal and obstetric complications.
5. Reassess culture susceptibility, adherence and absorption, then investigate obstruction, stone, renal or perinephric abscess, or an alternative diagnosis. Imaging is indicated when the clinical course is atypical or improvement is absent after 48–72 hours.

Part IX model answers

Chapter 41

1. Identical twins share essentially the same HLA antigens, so the recipient did not mount the usual allogeneic immune response. The operation proved that a transplanted human kidney could provide durable life-sustaining function when rejection was avoided.
2. cPRA estimates the percentage of donors against whom the recipient is likely to have antibodies. DSA are antibodies directed against the actual donor. Crossmatch tests whether recipient serum reacts with donor lymphocytes, physically or by a validated virtual comparison.
3. TCMR is driven mainly by activated T cells and shows interstitial inflammation, tubulitis and sometimes intimal arteritis. ABMR is driven by antibody–endothelial interaction and shows glomerulitis, peritubular capillaritis, arteritis or TMA, integrated with DSA, C4d or validated molecular evidence.
4. Confirm the creatinine change; assess urine output, potassium, acid-base status, BP and volume; review infection and all drugs/interactions; obtain urinalysis, culture and proteinuria; check calcineurin-inhibitor exposure; perform ultrasound with Doppler; add BK/CMV and DSA testing by context; biopsy unexplained dysfunction.
5. BK replicates when antiviral immune control is excessively suppressed, and no antiviral drug has consistently replaced immune recovery. Reducing immunosuppression permits viral control but may provoke acute rejection or DSA formation, so viral load, graft function and sometimes biopsy must be followed closely.