# Structure of Renal Disease: A Systematic Framework for Clinical Organization

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## Structure of Renal Disease: A Systematic Framework for Clinical Organization

### Learning Objectives

By the end of this handout, you will: - Understand the systematic organization of renal disease by anatomic location - Apply a structured approach to differential diagnosis of kidney disease - Recognize how pathophysiologic mechanisms determine clinical presentation - Use this framework to organize clinical thinking during case discussions - Integrate assessment of both structure (anatomy) and function (physiology)

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### Introduction: Why Organization Matters

Nephrology can seem overwhelming with hundreds of disease entities. This handout provides a **structured framework** that organizes all renal disease by: 1. **Anatomic location** — Where in the kidney is the disease? 2. **Pathophysiologic mechanism** — What is the disease doing? 3. **Clinical presentation** — How does the patient present? 4. **Diagnostic approach** — How do we confirm the diagnosis?

This systematic approach transforms memorization into logical clinical reasoning.

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### PART 1: STRUCTURAL ANATOMY AND ASSESSMENT

#### I. GROSS (MACROSCOPIC) KIDNEY ANATOMY

**Definition:** Large-scale kidney architecture visible on imaging (ultrasound, CT, MRI)

#### A. Size Assessment

- **Normal:** 11-12 cm length; 120-170 g weight per kidney
- **Enlarged kidneys:**
  - Polycystic kidney disease (ADPKD, ARPKD)
  - Early diabetic nephropathy

  - Lymphoma, leukemia
  - Amyloidosis
- **Shrunken kidneys:**
  - Chronic kidney disease (end-stage fibrosis)
  - Chronic glomerulonephritis
  - Chronic pyelonephritis
  - Renal infarction (old)

**B. Cystic Lesions**

- **Single cysts:** Benign; common in older adults
- **Multiple cysts:**
  - Autosomal dominant polycystic kidney disease (ADPKD) ☐ progressive to ESRD
  - Autosomal recessive polycystic kidney disease (ARPKD) ☐ neonatal presentation
  - Simple cysts (benign variant)
- **Cystic complications:** Infection, hemorrhage, rupture ☐ pain, hematuria

**C. Masses**

- **Solid tumors:**
  - Renal cell carcinoma (most common)
  - Oncocytoma, angiomyolipoma (benign variants)
  - Lymphoma (can be primary or secondary)
- **Assessment:** Size >3 cm concerning; vascular invasion indicates aggressive disease

**D. Drainage Assessment**

- **Hydronephrosis:** Dilation of renal pelvis/calyces from obstruction
  - Causes: Stones, strictures, malignancy, fibrosis
  - Risk: Progressive kidney damage if unrelieved
- **Atrophic kidneys with normal drainage:** Chronic disease (fibrosis, atrophy)

**E. Assessment Methods**

- **Ultrasound:** First-line (no radiation); assesses size, echogenicity, hydronephrosis, doppler flow
- **CT (non-contrast):** Gold standard for stones; excellent for masses
- **MRI:** Best for patients avoiding radiation; limited use in severe CKD (gadolinium risk)
- **Doppler ultrasound:** Assesses renal artery flow; screens for renal artery stenosis

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**II. MICROANATOMY (HISTOLOGIC STRUCTURE)**

**Definition:** Tissue-level kidney architecture requiring kidney biopsy

**A. The Nephron and Glomerular Changes  Normal Structure:** - Glomerulus: Fenestrated endothelium + basement membrane + podocytes - Capillaries: 50 $m^2$ filtration surface area - Mesangium: Structural support, immune clearance

**Pathologic Changes Seen on Biopsy:** - **Proliferative lesions:** Cell multiplication (mesangial, endothelial) - Examples: IgA nephropathy, MPGN, post-infectious GN - Significance: Active inflammation; often responsive to treatment

- **Membranous changes:** Basement membrane thickening
  - Examples: Membranous nephropathy, diabetic disease
  - Significance: Structural damage; may indicate chronic process
- **Sclerosis:** Fibrosis/scarring of glomeruli
  - Examples: FSGS, late diabetic disease, chronic hypertension
  - Significance: Irreversible damage; worse prognosis
- **Crescent formation:** Extracapillary proliferation (ominous sign)
  - Examples: RPGN, ANCA vasculitis, anti-GBM disease
  - Significance: Rapidly progressive; requires urgent treatment

### B. Tubular Changes

- **Acute tubular injury:** Cell swelling, necrosis (acute tubular necrosis)
- **Chronic changes:** Atrophy, fibrosis (tubular atrophy and interstitial fibrosis—TAIF)
- **Cast formation:** Proteinous or cellular casts within tubules

### C. Interstitial Changes

- **Interstitial inflammation:** Acute interstitial nephritis (AIN)
- **Interstitial fibrosis:** Progressive scarring (TAIF—most common final pathway of all CKD)
- **Immune infiltrates:** Cell type indicates cause (eosinophils in drug AIN, lymphocytes in infection)

### D. Vascular Changes

- **Intimal fibrosis:** Narrowed arterioles (hypertensive/diabetic injury)
- **Arterial stenosis:** Renal artery narrowing (atherosclerotic or fibromuscular dysplasia)
- **Thrombosis:** Vessel occlusion (thrombotic microangiopathy)

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## PART 2: PHYSIOLOGIC FUNCTION AND DYSFUNCTION

### I. GLOMERULAR FILTRATION (GFR = Kidney's Primary Job)

**Normal Function:** - GFR ~100-120 mL/min/1.73m² (young adult) - Filters 180 L/day while retaining proteins and cells - Determined by: Hydrostatic pressure, oncotic pressure, filtration coefficient

**Mechanisms of GFR Reduction:**

| Mechanism | Pathophysiology | Examples |
|---|---|---|
| **Decreased filtration pressure** | Low perfusion pressure | Hypovolemia, cardiorenal syndrome, renal artery stenosis |

| Mechanism | Pathophysiology | Examples |
|---|---|---|
| **Increased downstream pressure** | Obstruction of tubular flow | Stones, strictures, malignancy |
| **Loss of filtration barrier** | Structural damage to glomerulus | Glomerulonephritis, diabetic disease |
| **Loss of nephrons** | Permanent nephron loss | End-stage disease, surgical loss |

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## II. TUBULAR FUNCTION DISORDERS

### Tubular Reabsorption Defects:

### A. Sodium Handling

- **Normal:** Proximal tubule reabsorbs 65% of filtered Na+
- **Pathology:** Loop diuretics block ascending limb; thiazides block DCT
- **Clinical result:** Salt wasting or salt retention depending on location/medication

### B. Water Balance

- **Normal:** ADH allows water reabsorption in collecting duct
- **Pathology:**
  - Central diabetes insipidus: Inadequate ADH production
  - Nephrogenic diabetes insipidus: Kidney unresponsive to ADH
  - SIADH: Excess ADH ☐ water retention
- **Clinical result:** Polyuria (DI) or hyponatremia (SIADH)

### C. Electrolyte Handling ($K^+$, $Mg^{2+}$, $Ca^{2+}$, $PO_4^{3-}$)

- **Potassium:** DCT and collecting duct excrete; aldosterone increases excretion
- **Magnesium:** Thick ascending limb reabsorbs; PPI use causes wasting
- **Calcium:** PTH increases DCT reabsorption; varies inversely with sodium
- **Phosphate:** Normally filtered; PTH decreases proximal reabsorption
- **Clinical result:** Hyperkalemia in ESRD, hypomagnesemia from PPIs, secondary hyperparathyroidism in CKD

### D. Acid-Base Regulation

- **Proximal tubule:** Reabsorbs filtered $HCO_3^-$ (99% normally)
- **Distal tubule/collecting duct:** Secretes $H^+$ via intercalated cells
- **Pathology:** Renal tubular acidosis (RTA) from impaired $H^+$ or $HCO_3^-$ handling
- **Clinical result:** Non-anion-gap metabolic acidosis despite normal anion gap

### E. Protein/Albumin Reabsorption

- **Normal:** Proximal tubule reabsorbs virtually all filtered proteins (<150 mg/day urine)
- **Pathology:** Proteinuria occurs when filtered protein exceeds reabsorptive capacity
- **Significance:** Proteinuria is both sign of kidney damage AND risk factor for progression

### F. Glucose Handling

- **Normal:** All filtered glucose reabsorbed; urine glucose = 0
- **Pathology:** Glucosuria indicates either hyperglycemia or proximal dysfunction
- **Clinical result:** Diabetes mellitus or Fanconi syndrome

### G. Organic Acid Handling

- **Normal:** Uric acid secreted in proximal tubule
- **Pathology:** Impaired secretion ☐ hyperuricemia; increased reabsorption possible
- **Clinical result:** Gout risk increases in CKD; hyperuricemia promotes stone formation

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## III. ENDOCRINE FUNCTIONS

### A. Blood Pressure Regulation

- **Mechanism:** RAAS activation by decreased renal perfusion
- **Pathophysiology:** Renin ☐ Angiotensin II ☐ Vasoconstriction & aldosterone ☐ sodium retention
- **Failure in CKD:** Inability to control extracellular volume ☐ hypertension

### B. Erythropoietin Production

- **Normal:** Peritubular fibroblasts produce EPO in response to hypoxia
- **Pathophysiology:** EPO deficiency in CKD ☐ anemia (normocytic, hypoproliferative)
- **Clinical result:** Hematocrit drops ~10 points in ESRD without treatment

### C. Vitamin D Synthesis

- **Normal:** Proximal tubule converts 25-OH vitamin D ☐ active 1,25-dihydroxy vitamin D
- **Pathophysiology:** Impaired conversion in CKD despite normal 25-OH levels
- **Clinical result:** Secondary hyperparathyroidism from low calcitriol

### D. Metabolic Functions

- **Gluconeogenesis:** During fasting; impaired in CKD
- **Ammonia production:** Critical for acid excretion; reduced in CKD
- **Drug metabolism:** Renally cleared drugs accumulate in CKD

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## PART 3: PATHOPHYSIOLOGY — DISEASE MECHANISMS

### I. CHRONIC KIDNEY DISEASE (CKD)

**Definition:** Progressive, irreversible loss of kidney function staged by eGFR

**Two Main Categories:**

**A. Glomerular Diseases** **Mechanism:** Primary immune-mediated damage to glomerulus - **Examples:** - IgA nephropathy (hematuria, progressive) - Membranous nephropathy (nephrotic proteinuria) - FSGS (progressive proteinuria) - Lupus nephritis (systemic disease) - ANCA vasculitis (rapidly progressive)

**Presentation:** Often presents with proteinuria ± hematuria

**B. Interstitial/Tubular Disease** **Mechanism:** Primary damage to tubules and interstitium, glomeruli secondary - **Examples:** - Diabetic nephropathy (progressive, but mixed glomerotubular) - Hypertensive nephrosclerosis (chronic hypertension damage) - Chronic pyelonephritis (recurrent infections) - Drug-induced CKD (NSAIDs, lithium, amphotericin) - Reflux nephropathy (vesicoureteral reflux)

**Presentation:** May present without proteinuria initially; later develops as glomerulosclerosis occurs

**C. Final Common Pathway: TAIF** **TAIF = Tubular Atrophy and Interstitial Fibrosis** - **Significance:** ALL chronic diseases progress to TAIF if untreated - **Mechanism:** Fibroblast proliferation, myofibroblast transformation, collagen deposition - **Implication:** Irreversible once established; can't regain function once TAIF prominent

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### II. ACUTE KIDNEY INJURY (AKI)

**Definition:** Acute loss of kidney function, potentially reversible

**Three Main Categories:**

**A. Prerenal AKI (55-60% of cases)** **Mechanism:** Decreased renal perfusion without direct kidney damage - **Causes:** - Hypovolemia: Hemorrhage, dehydration, GI losses, burns - Decreased effective circulating volume: CHF, cirrhosis, nephrotic syndrome - Systemic vasodilation: Sepsis, medications - Renal vasoconstriction: ACEi/ARB in specific patients, NSAIDs - Aortic dissection, renal artery stenosis

**Key Finding:** FENa <1% (kidney conserves sodium appropriately)

**Prognosis:** Reversible with treatment of underlying cause; responds to fluid resuscitation

**B. Intrinsic (Parenchymal) AKI (35-40% of cases)** **B1. Acute Tubular Necrosis (ATN)** - **Mechanism:** Direct injury to tubular epithelium - **Causes:** - **Ischemic:** Prolonged renal hypoperfusion (shock, severe dehydration) - **Nephrotoxic:** Medications (aminoglycosides, amphotericin B, cisplatin), contrast dye, myoglobin (rhabdo), hemoglobin (massive hemolysis),

uric acid (tumor lysis) - **Key Finding:** FENa >2%, muddy brown granular casts - **Prognosis:** Reversible with appropriate supportive care; typically recovers in 1-3 weeks

**B2. Acute Interstitial Nephritis (AIN)** - **Mechanism:** Immune-mediated inflammation of interstitium and tubules - **Causes:** Medications (NSAIDs, antibiotics—especially beta-lactams, PPIs), infections, autoimmune - **Key Finding:** Eosinophiluria, pyuria without bacteria - **Prognosis:** Often reversible if offending agent removed promptly; permanent damage if delayed

**B3. Acute Glomerulonephritis** - **Mechanism:** Immune complex deposition or vasculitis affecting glomeruli - **Causes:** Post-infectious GN, ANCA vasculitis, anti-GBM disease, lupus, IgA nephropathy (acute exacerbation) - **Key Finding:** RBC casts, dysmorphic RBCs, hematuria + proteinuria - **Prognosis:** Varies by type; RPGN requires urgent plasma exchange; others may recover with immunosuppression

**B4. Other Intrinsic Causes** - **Vascular:** Renal infarction, thrombosis, dissection, thrombotic microangiopathy (HUS, TTP, scleroderma)

**Key Finding:** Elevated LDH, low platelets, schistocytes on smear in microangiopathy

**C. Postrenal AKI (5% of cases)** **Mechanism:** Urinary obstruction preventing urine flow - **Causes:** - Upper urinary tract: Stones, strictures, malignancy, fibrosis - Lower urinary tract: BPH, urethral stricture, functional (severe constipation) - **Key Finding:** Hydronephrosis on ultrasound - **Prognosis:** Excellent if decompressed promptly; permanent damage if prolonged obstruction

**Clinical Pearl:** Always ask "Did the AKI develop suddenly in previously well kidneys (AKI) or is there a history of progressive kidney disease (CKD)?" Baseline creatinine is essential for interpretation.

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### III. HYPERTENSION IN KIDNEY DISEASE

**Two-Way Relationship:** 1. **Hypertension causes kidney disease** ☐ chronic hypertensive injury ☐ nephrosclerosis 2. **Kidney disease causes hypertension** ☐ inability to excrete sodium ☐ volume expansion and RAAS activation

**Mechanisms:** - **Renin-angiotensin-aldosterone system:** Renal hypoperfusion ☐ renin release ☐ vasoconstriction and sodium retention - **Volume expansion:** Impaired sodium excretion in CKD ☐ fluid retention ☐ hypertension - **Endothelial dysfunction:** Vascular injury from proteinuria and hemodynamic changes

**Clinical Implications:** - Tight BP control slows CKD progression - ACEi/ARB first-line (reduce intraglomerular pressure, reduce proteinuria) - Salt restriction critical for volume-dependent hypertension

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## PART 4: CLINICAL INTEGRATION — USING THE FRAMEWORK

### How to Organize Your Thinking About Any Renal Disease

**Step 1: Assess STRUCTURE (What does it look like?)** - Is the kidney enlarged, normal, or shrunken? - Are there cysts, masses, or obstruction? - Biopsy findings? (If available)

**Step 2: Assess PHYSIOLOGY (What is broken?)** - Is GFR decreased? (By how much? How fast?) - Is there proteinuria? (Glomerular disease likely) - Are there electrolyte abnormalities? (Tubular dysfunction likely) - Is there acid-base disturbance? (Tubular secretion problem likely)

**Step 3: Determine PATHOPHYSIOLOGY (Why is it broken?)** - Is this a glomerular disease? (RBC casts, proteinuria, hematuria) - Is this tubular/interstitial disease? (Electrolyte wasting, minimal proteinuria initially) - Is this acute or chronic? (Rapidly rising Cr = acute; slow decline = chronic) - Is this reversible (AKI) or permanent (CKD)?

**Step 4: Apply CLINICAL KNOWLEDGE (What do we do about it?)** - What is the cause? (Needs specific treatment) - Is it progressive? (Needs prevention of progression) - Are there complications? (Hypertension, proteinuria, anemia, bone disease)

### Example Case Integration

**Case:** 65-year-old with 10-year history of hypertension, now eGFR 35 mL/min, creatinine 2.0 (baseline 1.0 three years ago).

**Structure:** Kidney ultrasound shows normal-sized kidneys with normal echogenicity, no hydronephrosis **Physiology:** eGFR 35 (Stage 3b CKD); spot protein/creatinine 2.5 g/g (heavy proteinuria) **Pathophysiology:** Chronic disease (slow creatinine rise over 3 years); glomerular disease component (heavy proteinuria) overlaying hypertensive/diabetic injury **Clinical:** Likely hypertensive nephrosclerosis with diabetic overlap (if diabetic), or primary glomerular disease. Needs: tight BP control, ACEi/ARB, low sodium diet, monitoring for complications.

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## Quick Reference Tables

### Anatomic Patterns in Kidney Disease

| Location | Disease Type | Example | Presentation |
|---|---|---|---|
| **Glomerulus** | Glomerulonephritis | IgA nephropathy, FSGS, membranous | Hematuria, proteinuria, RBC casts |
| **Tubule** | Tubular dysfunction | Renal tubular acidosis, Bartter syndrome | Electrolyte abnormalities, minimal proteinuria |

| Location | Disease Type | Example | Presentation |
|---|---|---|---|
| **Interstitium** | Interstitial nephritis | Drug-induced AIN, chronic pyelonephritis | Pyuria, eosinophiluria, sometimes fever/rash |
| **Vasculature** | Vascular disease | Renal artery stenosis, renal infarction | Hypertension, AKI, flank pain |
| **Collecting System** | Obstruction | Kidney stone, malignancy | Hydronephrosis, obstruction on imaging |

**Progression Patterns**

| Pattern | Reversibility | Examples | Prognosis |
|---|---|---|---|
| **Acute (days-weeks)** | Reversible if treated | ATN, AIN, prerenal | Can return to baseline |
| **Progressive chronic (months-years)** | Partially reversible | Early CKD, nephrotic syndrome | Slowing possible with treatment |
| **End-stage (years)** | Irreversible | ESRD with TAIF | Requires RRT |

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## Summary: The "Big Picture" Framework

**All kidney disease fits into this structure:**

1. **Where:** Glomerulus, tubule, interstitium, vessels, or collecting system?
2. **How bad:** Normal ☐ CKD 1 ☐ CKD 2 ☐ CKD 3a ☐ CKD 3b ☐ CKD 4 ☐ CKD 5/ESRD?
3. **How fast:** Acute (reversible) or chronic (progressive)?
4. **Why:** Specific diagnosis determines specific treatment
5. **What next:** Prevent progression, manage complications, prepare for RRT if needed

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## Clinical Pearl Summary

- **All CKD ultimately progresses to TAIF** (tubular atrophy and interstitial fibrosis) — the final common pathway

- **Proteinuria is both a marker and driver of progression** — reduce it aggressively
- **Tight BP control is universal therapy** — all CKD patients benefit
- **Early intervention is key** — once ESRD develops, only RRT or transplant available
- **Know the baseline creatinine** — it's the most important number you're missing

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## Practice Integration Questions

1. **Distinguish:** Glomerular disease typically presents with _____ and _____; tubular disease may have _____ but preserve _____.
2. **Classify:** A patient with hypertension, hypokalemia, metabolic alkalosis, and elevated renin likely has _____ dysfunction at the _____ level.
3. **Predict:** Progressive CKD with rising proteinuria will eventually develop complications: _____, _____, _____, and _____.

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## Related Handouts

- nephrology quick start guide — Foundational concepts
- nephrology glossary student handout — 100 terms explained
- nephrology study topics guide — Reading recommendations

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*This framework transforms nephrology from memorization of hundreds of diseases into systematic, logical clinical reasoning*.