Acute Tubular Necrosis (ATN): Ischemic & Nephrotoxic Patterns

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> [!info] **Updated March 2026 to reflect KDIGO 2026 AKI/AKD guideline recommendations.**

Definition & Epidemiology

ATN is acute injury to the proximal and distal tubular epithelium from either: 1. **Ischemia** (shock, sepsis, major surgery) → 45–50% of ATN 2. **Nephrotoxins** (drugs, pigments, contrast) → 35–40% of ATN 3. **Combined** (sepsis + aminoglycosides) → 15–20%

ATN is the **#1 cause of intrinsic AKI in ICU** (50% of ICU AKI cases). Unlike AIN, damage is necrotic (tubular epithelial death), not inflammatory.

> [!important] **Key feature of ATN:** Tubular epithelial cells DIE and slough into urine. Diagnosis confirmed by muddy brown casts (hemoglobin- or myoglobin-laden cellular debris).

Pathophysiology: The Three Phases

Phase 1: Initiation (0–24 hours)

Ischemic ATN: - Reduced renal perfusion → hypoxia in proximal tubule (S3 segment = most vulnerable) - ATP depletion → loss of Na-K-ATPase function - Cellular swelling, brush border loss, cell death

Nephrotoxic ATN: - Direct tubular epithelial toxicity (aminoglycoside, myoglobin, hemoglobin) - ROS generation, mitochondrial dysfunction - Tubular obstruction (pigment casts in pigmenturia) - Na reabsorption blocked → FeNa elevation

Phase 2: Maintenance (1–3 weeks)

- **Continued GFR decline** despite removal of offending agent
- Persistent tubular dysfunction
- Tubular obstruction from casts
- Back-leak of glomerular filtrate across damaged epithelium

- **Urine output variable:** Oliguric (40%) vs non-oliguric (60%)
  - **Oliguric = worse prognosis** (higher mortality, longer recovery)

Phase 3: Recovery (1–4 weeks)

- **Tubular epithelial regeneration** (cells redifferentiate)
- Restoration of tight junctions, brush border, transporter function
- GFR gradually improves
- **Timeline:** Non-oliguric recovers in 1–3 weeks; oliguric in 3–8 weeks

[!tip] **Clinical pearl:** If patient enters oliguric ATN phase, mortality risk ↑ 2–3× despite same initial AKI severity. Early RRT, tight fluid balance, and avoidance of secondary insults critical.

Ischemic ATN: Hypoperfusion Patterns

Classic Scenarios

1. **Cardiogenic shock** — MI, acute decompensated HF, severe bradycardia
2. **Septic shock** — vasodilation + hypovolemia
3. **Major surgery** — especially bypass, vascular surgery
4. **Massive hemorrhage** — inadequate fluid resuscitation
5. **Aortic dissection/cross-clamp** — renal artery occlusion

Tubular Vulnerability: The S3 Segment

Proximal tubule has 3 segments: - **S1 & S2:** Glucose, amino acid reabsorption; better oxygenation - **S3** (**thick ascending limb**): High Na reabsorption, low oxygen supply → **FIRST to die** in hypoxia

Result: S3 injury → natriuresis (tubular reabsorption loss) → FeNa >2% early

Laboratory & Urinalysis Signature

- **Urine microscopy is the gold standard for ATN diagnosis** — prioritize over FeNa/FeUrea
- **Muddy brown granular casts are DIAGNOSTIC of ATN** — high specificity, underused in practice
- **Granular casts** (coarse or fine — tubular protein + cells)
- **Urine osmolality: <400 mOsm/L** (tubular concentration failure)
- **No hematuria or proteinuria >3 g/day** (unless rhabdo)

[!warning] **FeNa is overrated.** FeNa only reliably answers ONE question: Is this oliguric patient prerenal or ATN? Even then, it is confounded by **diuretics** (use FeUrea instead — but FeUrea has its own limitations), **CKD** (baseline tubular Na wasting), and **sepsis** (FeNa can be <1% in septic ATN). FeNa >2% supports ATN, but **urine microscopy with muddy brown granular casts is more specific and should be your first-line diagnostic tool.**

Nephrotoxic ATN: Drug & Pigment Mechanisms

Aminoglycoside-Induced ATN

Mechanism: - Uptake by proximal tubule via megalin/cubilin (high specificity) - Accumulation in lysosomes → generation of free radicals - Dose-dependent (correlates with cumulative dose) - **Onset:** 2–5 days (sometimes up to 2 weeks)

Risk factors: - Age >70, female - CKD or DM baseline - Volume depletion, sepsis - Concurrent nephrotoxins (vancomycin, amphotericin, NSAIDs)

Prevention: - Extended-interval dosing (15 mg/kg Q24-48h) safer than conventional divided dosing - Monitor aminoglycoside levels (peak, trough) - Check baseline renal function, adjust dose - Avoid polypharmacy with other nephrotoxins

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Contrast-Induced Nephropathy (CIN) / Contrast-Associated AKI (CA-AKI)

Mechanism: - Osmotic load → tubular obstruction, hypoxia, ROS - Direct tubular epithelial toxicity (rare with modern iso-osmolar agents)

Risk stratification (KDIGO): - **High risk:** eGFR <30, DM + CKD, elderly, dehydration, CHF - **Moderate risk:** eGFR 30–60 - **Low risk:** eGFR >60, no DM, young

Prevention (evidence-based): 1. **Hydration:** IV isotonic saline 1–1.5 L before/after (best prevention) 2. **Hold metformin** 48h post-contrast if Cr↑ 3. **Avoid NSAIDs** × 48h post-contrast 4. **Use iso-osmolar or low-osmolar agents** if possible 5. **Minimize contrast volume** (not >5 mL/kg body weight)

> [!warning] **Bicarbonate, N-acetylcysteine, theophylline:** NOT proven effective in recent RCTs. Hydration + careful dosing sufficient.

Rhabdomyolysis & Myoglobinuria-Induced ATN

Mechanism: - Muscle breakdown → myoglobin release (molecular weight 17 kDa, filtered freely) - Myoglobin precipitation in acidic tubular fluid (forms casts) - Tubular obstruction + direct cytotoxicity - **Dark urine** (cola-colored); dipstick+ for blood BUT no RBCs on microscopy

Severity spectrum: - **Mild:** CK 1,000–5,000, no AKI - **Moderate:** CK 5,000–50,000, risk of AKI - **Severe:** CK >50,000, very high AKI risk (~50% develop AKI)

Common causes: - Trauma, crush injuries, prolonged immobilization - Statin-induced (especially with gemfibrozil or other CYP3A4 inhibitor) - Statins + NSAIDs + AKI precipitant - Exertional (extreme exercise, heat stroke, malignant hyperthermia) - Infections (influenza, HIV, EBV), seizures

Management: 1. **Aggressive hydration:** IV NS 1–1.5 L/h until myoglobin clears (dark urine → clear) - Goal: Urine output >200 mL/h (maintain tubular flow to prevent precipitation) 2. **Urine**

alkalinization: NaHCO3 to keep urine pH >6.5 (myoglobin soluble above pH 6.5) - Sodium bicarb 50–100 mEq in D5W until pH target met 3. **Monitor:** CK, K, Ca, PO4, Cr, urine myoglobin 4. **RRT if AKI severe:** Hyperkalemia, severe acidosis, uremia

> [!tip] **Clinical pearl:** Rhabdo-induced AKI is **preventable with aggressive early hydration**. Don't delay — start IV NS immediately if CK >1,000 and dark urine.

Cisplatin & Other Chemotherapy-Induced ATN

Mechanism: - **Cisplatin:** Nephrotoxicity in S3 proximal tubule; cumulative dose-dependent; up to 35% patients develop AKI - **Amphotericin B:** Lipid formulations safer; conventional more toxic - **Ifosfamide, methotrexate, gemcitabine:** Variable toxicity

Prevention: - Pre-chemotherapy hydration - Cisplatin: mannitol diuresis + saline hydration - Monitor baseline Cr, electrolytes, Mg - Avoid NSAIDs, ACE-I during chemo

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Hemoglobinuria-Induced ATN (Intravascular Hemolysis)

Mechanism: Hemoglobin precipitates in acidic tubular fluid; same mechanism as myoglobin

Causes: - Massive transfusion reaction - Prosthetic valve hemolysis - Microangiopathic hemolytic anemia (MAHA) - Snake bite envenomation

Diagnostic clue: - Dipstick+ for blood, but RBC count <3 on microscopy - Serum LDH ↑, haptoglobin ↓, indirect bilirubin ↑

Management: Similar to rhabdo — hydration + urine alkalinization

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Clinical Decision Tree: Ischemic vs Nephrotoxic ATN

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ATN Suspected (muddy brown granular casts on microscopy — diagnostic; FeNa supportive but not requ
    │
    ├─ ISCHEMIC ATN?
    │  History: shock, sepsis, major surgery, cardiogenic event
    │  Timing: AKI coincides with hypotensive episode
    │  Exam: Hypotension (current or recent), cool extremities
    │  Labs: Lactate ↑, base deficit, CK normal, urine myoglobin−
   │  Prognosis: 60–80% recover; ICU patients have 20–60% mortality (multiorgan failure)
    │
    └─ NEPHROTOXIC ATN?
       History: aminoglycoside, contrast, rhabdo, hemolysis, cisplatin
       Timing: AKI 2–7 days post-drug
       Exam: Normal BP if volume replete
       Labs:
         └─ If myoglobin/hemoglobin: Dark urine, dipstick+/RBC−, CK ↑↑, LDH ↑
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    Prognosis: Better if toxic agent removed early; rhabdo/hemolysis: mortality 10–
30%
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Management Principles (Both Types) — Updated per KDIGO 2026

Acute Phase

1. **Remove trigger:** Stop drug, restore perfusion, treat shock
2. **Fluid resuscitation:** Buffered crystalloids preferred over 0.9% NaCl (KDIGO 2026 Rec 3.1.2, **1B**) — except in traumatic brain injury where NS remains appropriate
3. **Hemodynamic targets:**
   - **MAP ≥65 mmHg** (KDIGO 2026 Rec 3.2.1, **2C**) — individualize; higher targets not proven beneficial
   - **No low-dose dopamine** for renal protection (KDIGO 2026 Rec 3.2.2, **1A**) — unchanged from prior guidelines but frequently violated in practice. Low-dose dopamine does not prevent, treat, or improve outcomes in AKI.
4. **Avoid secondary hits:** No NSAIDs, ACE-I, nephrotoxins, contrast

Volume Management & Diuretics (KDIGO 2026)

> [!important] **KDIGO 2026 formally endorses diuretics in AKI** — a shift from prior guideline ambiguity.

- **Diuretics for volume overload in AKI** (Rec 3.3.1, **2B**) — use to treat fluid overload, not to "prevent" AKI or convert oliguric to non-oliguric
- **Try diuretics BEFORE extracorporeal fluid removal** (Rec 3.3.2, **1C**) — give the patient a chance to respond to diuretics before initiating ultrafiltration or RRT for volume alone
- **Intermittent IV boluses as initial strategy** (PP 3.3.1) — start with bolus dosing before continuous infusion

Furosemide Stress Test (FST) — now guideline-recommended (KDIGO 2026 Rec 2.3.1, **2B–2C**): - 1.0 mg/kg IV furosemide (1.5 mg/kg if prior loop diuretic use) - Urine output <200 mL in 2 hours = **high risk for severe AKI / need for RRT** - Useful for prognostication and triage in AKI Stage 2–3

Diuretic Escalation Pathway (KDIGO 2026 Table 22):

Step	Strategy	Details
1. **Assessment**	Evaluate volume status	Clinical exam, urine output trend, lung ultrasound
2. **Escalation**	Increase loop diuretic dose	Double furosemide dose if inadequate response; switch to bumetanide if gut edema
3. **Synergism**	Add thiazide (sequential nephron blockade)	Metolazone 5–10 mg PO or chlorothiazide 500 mg IV 30 min before loop diuretic
4. **Intensify**	Continuous infusion	Furosemide 10–40 mg/h after bolus loading dose

Step	Strategy	Details
5. **Failure → RRT**	Diuretic resistance	If escalation pathway fails, proceed to extracorporeal fluid removal

Maintenance Phase

- Monitor K, Ca, PO4, Mg daily
- Renal dosing medications
- Nutrition: 30 kcal/kg/day, 1–1.2 g/kg/day protein (catabolic state)

RRT Timing (KDIGO 2026)

- **Deferred (watchful waiting) RRT preferred over early/preemptive initiation** (Rec 5.1.1, **1C**) — unless life-threatening indications exist (refractory hyperkalemia, severe acidosis, uremic symptoms, refractory volume overload after diuretic escalation)
- Initiate RRT for **emergent indications** regardless of timing strategy

Recovery Phase

- Watch for **postobstructive diuresis** if oliguric phase (may occur during recovery)
- Continue supportive care even as Cr improves
- Follow-up: ~50% develop CKD long-term; monitor at 3–6 months

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Related Resources

- Comprehensive ATN Review
- AKI Staging & Differential
- AIN vs ATN Differential
- AKI Workup Protocol
- Prerenal AKI Assessment

Board-Style Questions

1. **35M post-MVA with crush injury to leg; CK 120,000; dark urine; Cr 0.8 → 2.6 in 8h**
   - Diagnosis: Rhabdomyolysis-induced ATN
   - Immediate management: IV NS 1–1.5 L/h until urine clear, NaHCO3 for alkalinization
2. **72F post-cardiac angiography; baseline Cr 1.2; now Cr 1.8; muddy brown casts; FeNa 3%**
   - Diagnosis: Contrast-induced ATN (CA-AKI)
   - Prevention for future: Hydration, minimize contrast, hold metformin
3. **Pt on gentamicin × 10 days for sepsis; AKI onset day 5; FeNa 2.5%; granular casts**

- Diagnosis: Aminoglycoside-induced ATN
- Action: Switch to alternative AB, aggressive hydration, consider RRT

Version 2.0 | PA/Medical student level | Updated 2026-03-29 per KDIGO 2026 AKI/AKD Guidelines

References: [1] Schrier RW, Wang W. Acute tubular necrosis. Kidney Int. 2004;66(12). [2] Bellomo R, Ronco C. Acute tubular necrosis: ischemic and nephrotoxic. Crit Care Clin. 2015;31(4). [3] KDIGO 2026 Clinical Practice Guideline for Acute Kidney Injury and Acute Kidney Diseases. Kidney Int Suppl. 2026. [4] Koyner JL, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. JASN. 2015;26(8):2023-2031.