Student Handout: Immune Checkpoint Inhibitor Nephrotoxicity

Andrew Bland, MD, FACP, FAAP

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> **Learning objective:** Understand the epidemiology, pathophysiology, clinical presentation, and management approach to immunotherapy-related kidney injury

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What Are ICIs?

Immune checkpoint inhibitors are a revolutionary class of immunotherapy drugs used across many cancer types:

Drug	Target	Examples
Anti-PD-1	Programmed death receptor 1	Nivolumab, pembrolizumab
Anti-PD-L1	PD-1 ligand	Atezolizumab, durvalumab
Anti-CTLA-4	Cytotoxic T-lymphocyte antigen 4	Ipilimumab

Key concept: These drugs release immune brakes, activating T cells to attack cancer—but sometimes attack the kidneys too.

Epidemiology

- **Frequency:** 1–3% of ICI-treated patients develop clinical nephrotoxicity
- **Severity:** Most Grade 1–2 (mild), but Grade 3–4 (severe) requires discontinuation
- **Timing:** Usually occurs within 3–6 months, but can appear later
- **Risk factors:** Baseline CKD, diabetes, prior nephrotoxic drugs, combination therapy (ICI + CTLA-4 higher risk)

Pathophysiology: How ICIs Injure the Kidney

The mechanism (simplified for PA level):

1. **Checkpoint release** — Anti-PD-1/PD-L1 or anti-CTLA-4 blocks inhibitory signals
2. **T-cell activation** — T cells hyperactivate against cancer antigens
3. **Cross-reactivity** — T cells recognize epitopes in kidney tubules and glomeruli
4. **Inflammation** — Predominantly **acute interstitial nephritis (AIN)**, less commonly glomerular disease
5. **Result:** Tubular damage → ↑ creatinine, proteinuria, microscopic hematuria

Why AIN? Mechanism mirrors classic drug-induced AIN, but driven by immune activation rather than direct toxin.

Clinical Presentation & Diagnosis

Typical Picture

- **Asymptomatic ↑ creatinine** (40–90% of cases)
- **Baseline:** Usually occurs 3–6 months post-initiation
- **Labs:**
  - ↑ Serum creatinine (often 1.5–3× baseline)
  - ↑ BUN
  - Proteinuria (usually <2 g/day unless glomerular)
  - Microscopic or gross hematuria possible
  - **Sterile pyuria** (hallmark)
  - ↓ Complement (usually normal)

Diagnostic Approach

Step	Action	Finding
1. Suspect ICI nephrotoxicity	Timeline (Cr ↑ during/after ICI)	Clinical probability high
2. Check urine	Urinalysis, urine Pt-Cr ratio	AIN: sterile pyuria, granular casts, muddy casts
3. Check labs	BMP, LDH, phosphate, uric acid	Normal complement distinguishes from GN
4. Assess volume	Physical exam, I/Os	Usually euvolemic or hypervolemic
5. Consider biopsy	If uncertain OR grade 3–4 AKI	Confirms AIN vs glomerular; guides further management

When to Biopsy

Strongly consider if: - Persistent Grade 3–4 AKI after 3–5 days of corticosteroids - Rapidly worsening renal function despite treatment - Need to rule out alternative pathology (GN, thrombotic, infection) - Considering rechallenge with ICI

Pathology (Brief)

If a biopsy is done:

Finding	Interpretation
Tubuloint. nephritis	Lymphocytic infiltration of tubules and interstitium (dominant)
Tubular damage	Acute tubular injury, flattened epithelium
Glomeruli	Usually spared (unlike classic drug allergy); some cases show RPGN or membranous
IF microscopy	Usually negative (no immune complex deposition)

Management Algorithm

Mild (Grade 1–2) AKI

Creatinine $\leq$1.5$\times$ baseline or <50% $\uparrow$ from pretreatment baseline

1. **Hold ICI** — Pause immunotherapy during kidney injury recovery
2. **Supportive care** — Ensure euvolemia, avoid nephrotoxins, monitor labs (Cr, BUN q2–3 days)
3. **Monitor & reassess** — 60–70% recover spontaneously within 2–3 weeks
4. **Restart** — If Cr recovers toward baseline AND clinical improvement, may cautiously resume ICI (risk of recurrence ~10–15%)

Moderate (Grade 2–3) AKI

Creatinine 1.5–3$\times$ baseline

1. **Hold ICI immediately**
2. **Empiric corticosteroids:**
   - **Methylprednisolone 0.5–1 g IV daily $\times$ 1–3 days**, then taper
   - OR **Prednisone 0.5–1 mg/kg PO daily, taper over 4–6 weeks**
3. **Supportive care** — Hydration, avoid NSAIDs/ACEi if severely reduced GFR
4. **Monitor** — Cr, BUN, electrolytes q2–3 days
5. **Response:**
   - **Good response (Cr $\downarrow$ 25%+ within 3–5 days)** $\rightarrow$ Continue corticosteroid taper, consider resumption of ICI at completion of steroid course
   - **Poor response (no improvement in 3–5 days)** $\rightarrow$ Escalate to Grade 3–4 protocol

Severe (Grade 3–4) AKI

Creatinine >3$\times$ baseline OR need for dialysis

1. **Discontinue ICI** — Permanent discontinuation typically recommended
2. **Aggressive corticosteroids:**
   - **Methylprednisolone 1 g IV daily $\times$ 3 days**, then switch to PO prednisone 1 mg/kg daily with taper over 6–12 weeks

3. **Consider immunosuppression:**
    - If **no response within 3–7 days**, add **infliximab 5 mg/kg IV** (TNF-α inhibitor)
    - Or **mycophenolate mofetil (MMF) 1–1.5 g BID** for RPGN-pattern disease
4. **Supportive:**
    - Renal replacement therapy if oliguria, hyperkalemia, severe fluid overload, metabolic acidosis
    - Monitor closely; some patients require long-term dialysis (10–15%)
5. **Prognosis:** 30–40% recover renal function; others have chronic kidney disease

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Special Considerations

Combination Therapy (ICI + ICI)

- Anti-CTLA-4 + anti-PD-1 (e.g., ipilimumab + nivolumab) = higher nephrotoxicity risk (~5–10%)
- If AKI develops, usually higher grade $\rightarrow$ More likely to require aggressive immunosuppression

Atypical Presentations

- **Glomerular disease:** Some patients develop RPGN, membranous nephropathy, or crescentic GN (10–20% of ICI-AKI)
    - Clue: RBC casts, hypertension, nephritic sediment $\rightarrow$ Biopsy
- **Hyperkalemia without severe AKI:** Type 4 RTA-like picture (aldosterone suppression)

Monitoring After Recovery

- Serial creatinine even after recovery (relapse possible)
- If rechallenge ICI: More frequent Cr monitoring (weekly $\times$ 4, then biweekly)
- Consider baseline and periodic kidney biopsy if considering re-initiation after Grade 3–4 AKI

Key Clinical Pearls

☐ **Diagnosis:** AIN on biopsy; sterile pyuria is a clue ☐ **Timing:** Usually 3–6 months post-ICI initiation ☐ **Mild cases:** Often resolve with ICI hold + supportive care ☐ **Moderate–Severe:** Require corticosteroids $\pm$ immunosuppression ☐ **Escalate:** If no improvement in 3–5 days $\rightarrow$ infliximab/MMF ☐ **Prognosis:** Mild/Mod often recover; Severe may require long-term dialysis

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Related Clinical Content

For more detailed information, see the Onconephrology Hub:

- ICI Fundamentals & Mechanisms — Deeper mechanistic review
- ICI Kidney Injury: Diagnosis & Pathology — Comprehensive diagnostic algorithms
- ICI Nephrotoxicity Treatment — Extended management protocols

- ICI Glomerular Diseases — Atypical presentations (RPGN, MN, ANCA)

Cross-reference: - Acute Kidney Injury Hub — General AKI workup framework - Student Handout: AIN — Detailed acute interstitial nephritis overview

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References

- **Kidney Disease: Improving Global Outcomes (KDIGO).** Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. 2021.
- **Cortazar FB, et al.** Clinicopathological Features of Immune Checkpoint Inhibitor-Associated AKI. J Am Soc Nephrol. 2020;31(12):2861–2873.
- **Perazella MA, Sprangers B.** Drug-Induced Acute Interstitial Nephritis. UpToDate. 2024.
- **Chowdhury TA, et al.** Immunotherapy-Induced Nephropathy. Nephrology Self-Assessment Program. 2022.

Study Tips: - Use the management algorithm table when seeing ICI patients - Memorize the 3 grades and corresponding corticosteroid dosing - Remember: AIN is the dominant pathology; think of it like an immune drug allergy - Infliximab is your “rescue” drug for failures

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