Acute Interstitial Nephritis: Diagnosis and Management

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Acute Interstitial Nephritis (AIN): Student Handout

Learning Objectives

By the end of this handout, you should be able to: - Recognize AIN as a major cause of AKI (accounting for 15-27% of cases) - Identify drug and non-drug causes of AIN - Understand the pathophysiology of drug-induced immune-mediated AIN - Recognize diagnostic limitations and pitfalls - Interpret urinalysis and novel biomarkers - Distinguish AIN from acute tubular necrosis - Recognize TINU syndrome (tubulointerstitial nephritis + uveitis) - Implement appropriate diagnostic and therapeutic approaches

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Definition and Epidemiology

Acute Interstitial Nephritis: Immune-mediated inflammatory response affecting the kidney tubulointerstitium (interstitial space and tubules), sparing glomeruli (in primary AIN).

Incidence: - Accounts for **15-27% of kidney biopsies** performed for unexplained AKI - Represents **1-3% of all AKI** in general population - **70-75% are drug-induced** (medication-related)

Mortality & Morbidity: - In-hospital mortality: ~20% of severe cases requiring dialysis - Many patients progress to chronic kidney disease if untreated - Early recognition and intervention critical for outcomes

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Pathophysiology: The Immune Mechanism

The Pathogenic Process

Step 1: Initial Injury - Medication acts as hapten (chemical conjugates with protein) - Creates neo-antigen complex recognized as “foreign”

Step 2: Sensitization - Antigen-presenting cells process the hapten-protein complex - Helper T cells become activated - T cell–mediated hypersensitivity reaction develops

Step 3: Inflammatory Infiltrate - Lymphocytes (predominantly T cells) infiltrate interstitium - Eosinophils may be present (but inconsistently) - Inflammatory cytokines cause cellular injury

Step 4: Tubulointerstitial Damage - Tubule epithelial cells injured first - Interstitial edema and inflammation develop - Progressive fibrosis if untreated

Key Feature: Primary damage is **immune-mediated**, not dose-dependent. This explains why AIN can occur at therapeutic doses and after brief exposure.

Causes: Drug and Non-Drug Etiologies

Drug-Induced AIN (Most Common Cause)

Most Common Drug Causes (In Descending Frequency):

Drug Class	Examples	Frequency
Antibiotics	Amoxicillin, ciprofloxacin, TMP-SMX, cephalosporins	49% of drug-induced AIN
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole	14% of drug-induced AIN
NSAIDs	Ibuprofen, naproxen, indomethacin	11% of drug-induced AIN
Diuretics	Thiazides, furosemide	~5%
Anticonvulsants	Phenytoin, carbamazepine, allopurinol	Rare
Biologics	TNF-alpha inhibitors, monoclonal antibodies	Emerging cause

Timing Patterns: - **Antibiotics:** Early onset (typically first 1-2 weeks) - **NSAIDs:** Intermediate timing (weeks 2-4) - **PPIs:** Delayed onset (weeks 3-8 or even months of exposure)

Clinical Presentation: The Classic Triad Is Uncommon

Classic Triad (Absent in ~2/3 of Cases)

1. **Fever** (~20-30% of patients)
2. **Rash** (~25% of patients)
3. **Eosinophilia** (~20% of patients)

Critical Point: The **absence** of the classic triad does NOT exclude AIN. Many patients have AIN without any of these findings.

More Common Presentation

Most Typical Scenario: - **Nonoliguric AKI** (preserved or only mildly reduced urine output despite rising creatinine) - **AKI developing days to weeks after new medication initiation** - **Bland or nonspecific symptoms** (fatigue, anorexia, nausea) - **Physical exam unremarkable** (no fever, no rash visible)

Clinical Pearl: The key clue is **nonoliguric AKI temporally related to new medication**—this should raise high suspicion for AIN.

Diagnostic Approach: Urinalysis Findings

Urinalysis Pattern in AIN

Finding	Typical Pattern	Significance
Proteinuria	Mild (usually <1-2 g/day)	Heavy proteinuria suggests glomerular disease
Hematuria	Mild to moderate	RBCs and WBCs present
Leukocyte esterase	2+ (positive)	Indicates WBCs in urine
WBC count	Elevated (>5/hpf, often 13-138/μL)	Strong finding in AIN
WBC casts	May be present	Support diagnosis but not required
RBC casts	Absent (or rare)	Suggests GN instead; if present, consider dual pathology

Urine Microscopy Interpretation

Characteristic Pattern: - Numerous WBCs without bacteria (sterile pyuria) - Occasional RBCs - White cell casts when present - Mild proteinuria - **ABSENCE of RBC casts** (helps differentiate from glomerulonephritis)

Important Distinction: - **RBC casts = GN/RPGN** (glomerular disease) - **WBC casts = AIN** (interstitial disease) - **Muddy brown casts = ATN** (tubular disease)

Tests That DON'T Help (Important Limitations)

Urine Eosinophils: - Historically considered diagnostic for AIN - **Recent evidence: NO diagnostic utility** - Poor sensitivity (<50%) and specificity (<50%) - Should NOT be ordered as diagnostic test for AIN - **Not recommended in current practice guidelines**

Peripheral Eosinophilia: - Occurs in only minority of drug-induced AIN cases - Absence doesn't exclude diagnosis - No diagnostic value as screening test

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Novel Diagnostic Biomarkers

Beta-2 Microglobulin (B2M)

What It Is: Low-molecular-weight protein freely filtered and reabsorbed by proximal tubule. Elevation indicates tubular dysfunction.

Why It's Mentioned: Historically discussed as AIN marker, but limited utility for general AIN diagnosis.

Current Role: - **Moderate utility for TINU syndrome** (tubulointerstitial nephritis + uveitis) - Limited for differentiation of AIN from ATN (both cause elevated B2M) - Pre-analytical instability (degrades at pH <6.0) limits reliability

Bottom Line: B2M is outdated for general AIN diagnosis; newer biomarkers superior.

CXCL9: The Emerging Gold Standard

What It Is: C-X-C motif chemokine ligand 9—a T cell–recruiting chemokine directly involved in immune response.

Why It's Revolutionary: - **Directly mechanistically linked** to T cell–mediated inflammation (the actual AIN pathophysiology) - Not elevated in ATN (unlike B2M, NGAL) - Excellent stability (remains stable >24 hours at room temperature) - Fewer pre-analytical issues

Diagnostic Performance: | Metric | Value | |———|——-| | AUC for AIN vs ATN | 0.84-0.95 (excellent) | | Sensitivity | 85-92% | | Specificity | 80-92% | | Outperforms all traditional biomarkers | YES |

Cutoff Interpretation: - High CXCL9 supports AIN diagnosis - Can distinguish AIN from other AKI causes - Increasingly available in specialized centers

Clinical Pearl: CXCL9 is the future of non-invasive AIN diagnosis; traditional markers (urinary eosinophils) are outdated.

Kidney Biopsy: Definitive Diagnosis

Indication: When clinical diagnosis uncertain and diagnosis would change management.

Histologic Findings: - Dense lymphoplasmacytic infiltration of interstitium - Sparing of glomeruli (primary AIN) - Eosinophils may or may not be present - Tubular epithelial cell injury - Possible interstitial edema

Timing: Biopsy within 2-3 weeks of symptom onset optimal for diagnosis and prognosis assessment.

Not Always Necessary: In obvious cases (classic timeline + medication history + urinalysis pattern + clinical context), biopsy may be deferred if patient improving with drug discontinuation.

TINU Syndrome: A Special Entity

Definition and Epidemiology

TINU = Tubulointerstitial Nephritis + Uveitis Syndrome

Key Statistics: - Represents ~1-2% of uveitis cases in specialized centers - **NOT just a pediatric disease:** Affects patients aged 9-76 years - Female predominance (3:1 ratio) - Often misdiagnosed as isolated uveitis or drug-induced AIN alone

Important Note: Historical literature emphasized adolescent presentation; modern recognition shows substantial adult involvement (30-40% of cases are adults).

Clinical Presentation

Dual System Involvement: 1. **Renal:** Acute interstitial nephritis (elevated creatinine, pyuria, RBC+WBC casts possible) 2. **Ocular:** Bilateral anterior uveitis (eye pain, photophobia, visual symptoms) 3. **Systemic:** Often nonspecific (fever, malaise, arthralgia)

Timeline: - Simultaneous presentation common - Ocular findings may precede renal manifestations (diagnosed as isolated uveitis first) - Renal manifestations may occur months after ocular symptoms

Diagnostic Criteria

Definite TINU: 1. Kidney biopsy confirming AIN 2. Bilateral anterior uveitis on ophthalmology exam 3. No other systemic disease explaining both

Probable TINU: 1. Clinical AIN (elevated Cr + compatible urinalysis; biopsy not required if clinical picture clear) 2. Bilateral anterior uveitis confirmed 3. No alternative diagnosis

Role of B2M in TINU

This is where B2M has established utility: In TINU syndrome specifically, urinary B2M has superior sensitivity/specificity compared to general AIN.

Performance in TINU: - Sensitivity: 88-100% - Specificity: 70-80% - Elevated B2M + bilateral uveitis = high probability TINU

Practical Application: - Screen for bilateral anterior uveitis in any patient with AKI (ophthalmology exam) - If uveitis present + elevated B2M, TINU diagnosis highly likely - Refer to rheumatology/immunology for systemic workup

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Management Principles

Immediate Steps

1. Discontinue Offending Medication - **Most critical intervention** - Discontinue as soon as AIN suspected - Many cases improve significantly with drug withdrawal alone

2. Supportive Care - Fluid and electrolyte management - Renal function monitoring - RRT if necessary (same indications as ATN)

Corticosteroid Therapy

Evidence & Recommendation: - Corticosteroids may improve outcomes if started early (within 2-3 weeks) - Typical regimen: Prednisone 0.5-1 mg/kg/day (or IV methylprednisolone in severe cases) - Duration: Usually 2-4 weeks with taper

Outcome Data: - 49% complete recovery (creatinine returns to baseline) - 39% partial recovery (improved but not to baseline) - 12% no recovery (permanent renal impairment)

Factors Associated with Better Outcomes: - Earlier steroid initiation (within 1-2 weeks) - Shorter duration of drug exposure before diagnosis - Lower peak creatinine at presentation

Clinical Pearl: If biopsied early and treated with steroids early, outcomes improve; delayed diagnosis/treatment associated with permanent renal damage.

When to Escalate to Immunosuppression

Some cases with severe AIN or inadequate response to steroids may require: - Mycophenolate mofetil (MMF) - Tacrolimus - Other immunosuppressive agents - Typically reserved for severe/refractory cases

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Differential Diagnosis: AIN vs. ATN vs. RPGN

Feature	AIN	ATN	RPGN
Mechanism	Immune-mediated inflammation	Tubular necrosis	Glomerular crescents
Urine output	Nonoliguric (preserved)	Oliguric or nonoliguric	Often oliguric
Proteinuria	Mild (<1-2 g/day)	Mild	Heavy (often >3 g/day)
RBC casts	Absent	Absent	PRESENT (diagnostic)
WBC casts	May be present	Absent	May be present
Muddy brown casts	Absent	PRESENT	Absent
WBC in urine	Elevated (13-138/μL)	Low	Low
Timeline	Days-weeks post-medication	Hours-days post-injury	Days-weeks
Classic triad	Rare	N/A	Hemoptysis possible

Practice Questions

Question 1: A 54-year-old on omeprazole (3 months) for GERD develops AKI (Cr 1.1 to 2.8 in 1 week). Urinalysis: WBC 45/hpf, RBCs 8/hpf, protein 1+, no casts. Most likely diagnosis? A) Acute tubular necrosis B) Acute interstitial nephritis C) Rapidly progressive glomerulonephritis D) Prerenal AKI

Answer: B) Acute interstitial nephritis. The timeline (3-month PPI use with recent AKI), nonoliguric pattern (Cr rise despite presumably preserved urine output), elevated WBCs in urine without casts, and mild proteinuria are classic for drug-induced AIN. PPIs are 2nd-most common drug

cause of AIN. Absence of RBC casts excludes RPGN. The absence of muddy brown casts argues against ATN.

Question 2: A 32-year-old woman presents with red eyes (bilateral anterior uveitis, confirmed by ophthalmology) and AKI (Cr 2.1). Urinalysis: WBCs, mild proteinuria, no RBC casts. Urine B2M elevated. Most likely diagnosis? A) Goodpasture syndrome B) Systemic lupus erythematosus C) TINU syndrome D) Medication-induced AIN only

Answer: C) TINU syndrome. The combination of bilateral anterior uveitis (ocular finding) + AIN (renal finding) + elevated B2M = TINU syndrome diagnosis. This is the specific scenario where B2M has excellent diagnostic utility. Goodpasture would present with hemoptysis and RBC casts. SLE possible but bilateral uveitis less typical.

Question 3: A 68-year-old on amoxicillin (day 7) develops AKI. Biopsy confirms AIN. Current Cr is 3.2 (baseline 1.0). Which statement represents best management? A) Discontinue amoxicillin and observe; most cases self-limited B) Discontinue amoxicillin + start prednisone immediately (within first 2-3 weeks) C) Discontinue amoxicillin + start dialysis; steroids contraindicated in infections D) Continue amoxicillin (needed for infection); add corticosteroids for kidney protection

Answer: B) Discontinue amoxicillin + start prednisone immediately (within first 2-3 weeks). Antibiotic-induced AIN requires both: (1) drug discontinuation AND (2) corticosteroids if started early. Early steroid therapy (within 1-3 weeks) improves outcomes (49% complete recovery vs lower rates if delayed). Continuing the offending drug defeats the purpose. Dialysis may be needed for complications, but shouldn't delay appropriate therapy.

Key Takeaways

1. **AIN accounts for 15-27% of biopsy-proven AKI** — must maintain high suspicion
2. **Classic triad absent in 2/3 of cases** — don't rely on fever/rash/eosinophilia
3. **Nonoliguric AKI + new medication = suspect AIN** until proven otherwise
4. **Urine eosinophils unreliable** (outdated test; don't order)
5. **CXCL9 emerging biomarker** for non-invasive AIN diagnosis
6. **Discontinue offending agent immediately** — most critical intervention
7. **Early corticosteroids improve outcomes** if started within 2-3 weeks
8. **TINU is not just pediatric** — affects adults; requires ophthalmology screening

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See Also

Related Student Handouts

- AKI Workup and Diagnostic Approach
- Drug-Induced AKI
- AKI Biomarkers and Early Detection
- Magnesium Disorders

Clinical Content (01-Clinical-Medicine/Nephrology)

- AKI Hub - Full Clinical Reference
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

Related Resources

- AKI Workup and Diagnostic Framework
- Detailed B2M and TINU Discussion
- Drug-Induced AKI Overview
- PPI-Associated Kidney Disease

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