

Acute drug-induced interstitial nephritis

Etiology • immune mechanisms • morphology • clinical correlation

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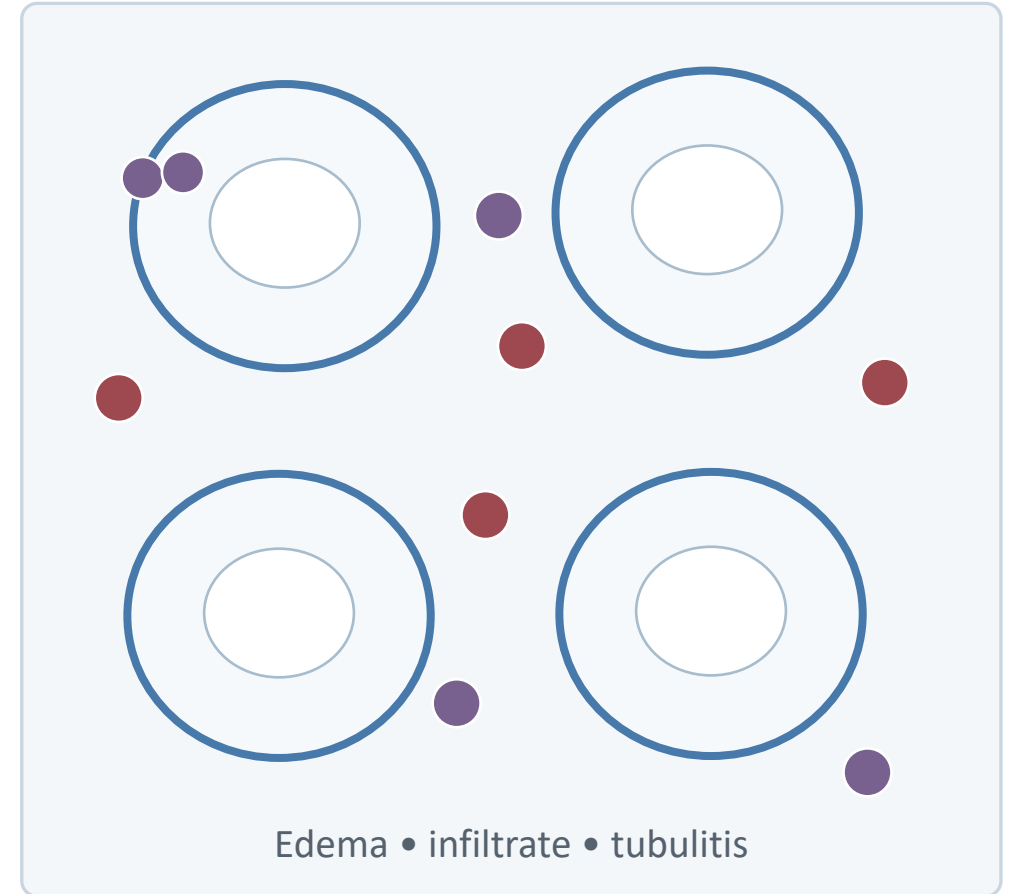
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Learning outcomes

- Recognize the drug-exposure and hypersensitivity pattern
- Explain the immune mechanisms and defining biopsy changes
- Integrate urinary findings, renal impairment, differential diagnosis, and recovery

An acute inflammatory injury of tubules and interstitium

- The disease is a drug-associated form of tubulointerstitial nephritis.
- Inflammation is centered on the renal interstitium and commonly invades tubules.
- Tubular dysfunction and acute kidney injury may accompany the lesion.



Schematic — not a histologic specimen

Why this diagnosis deserves recognition

- Withdrawal of the offending agent is often followed by recovery.
- Improvement can require months rather than days.
- Irreversible renal damage remains possible if the injury is not resolved.

Suspect a drug trigger



Identify the exposure



Withdraw the offending drug



Follow renal recovery

Schematic — conceptual sequence

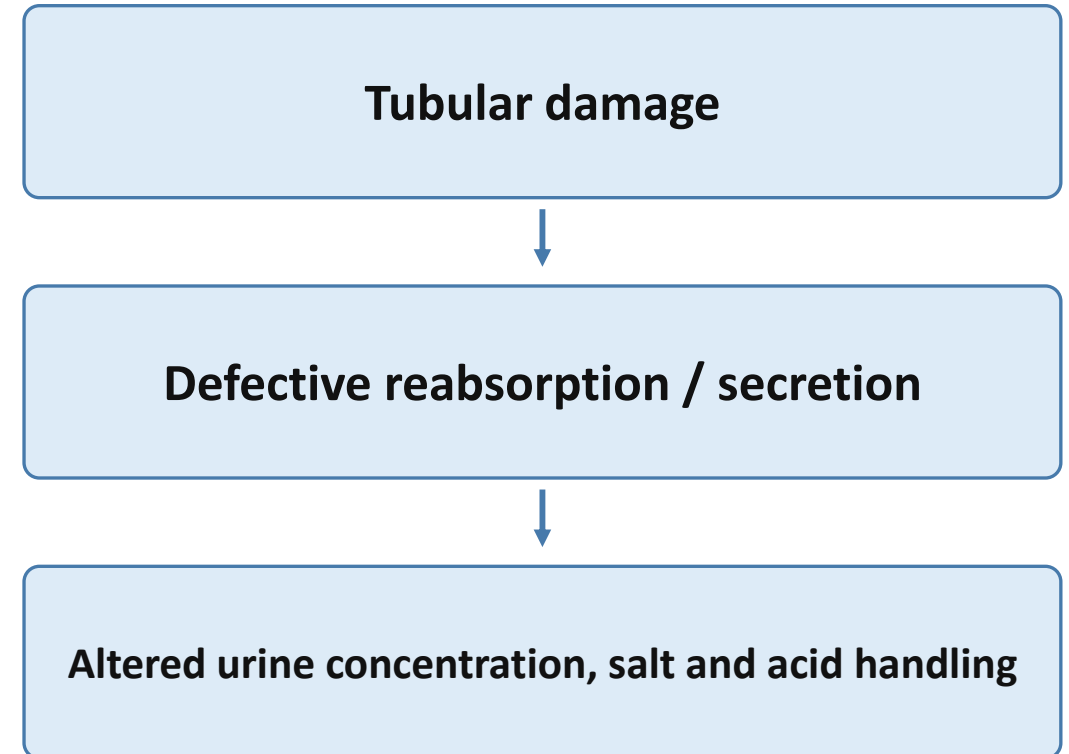
Tubulointerstitial disease: A different clinical emphasis

The renal tubular and interstitial compartments are the principal sites of injury. Classic nephritic or nephrotic syndromes are generally absent in isolated tubulointerstitial disease.

Tubulointerstitial emphasis	Glomerular emphasis
Tubular dysfunction and azotemia	Nephritic or nephrotic syndrome
Polyuria/nocturia can occur	More conspicuous glomerular urinary syndrome
Interstitial/tubular lesion	Primary glomerular lesion

Tubular dysfunction explains characteristic symptoms

- Reduced urine-concentrating ability can produce polyuria or nocturia.
- Tubular transport defects may cause salt wasting.
- Impaired acid excretion may cause metabolic acidosis.



Schematic — conceptual sequence

Drugs can injure kidneys through three routes

- Hypersensitivity reactions cause interstitial inflammation.
- Direct or indirect toxic effects can cause acute tubular injury.
- Cumulative, often subclinical injury may produce chronic renal disease.

Immune response

Acute interstitial nephritis

Acute tubular injury

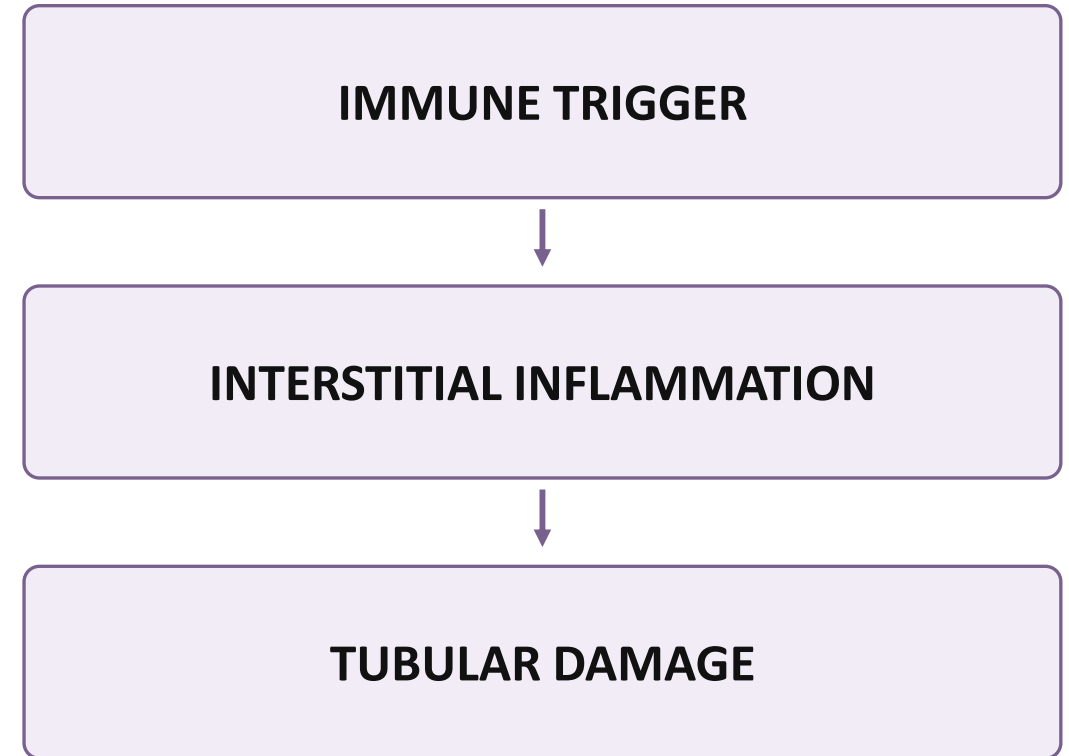
Tubular epithelial injury

Cumulative injury

Delayed chronic kidney disease

What makes drug-induced AIN distinct?

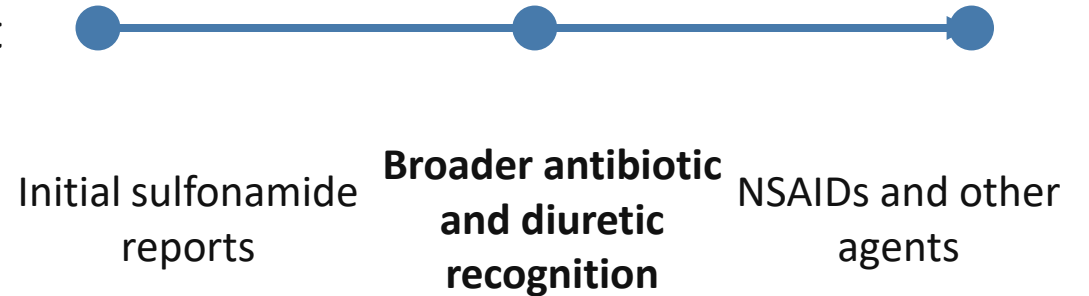
- The central feature is an immune inflammatory lesion rather than isolated tubular toxicity.
- Eosinophils, tubulitis and edema may coexist in the biopsy.
- The same medication class can also cause other forms of kidney injury.



Schematic — conceptual sequence

Historical clue: Sulfonamides

- Drug-associated acute interstitial nephritis was first reported after sulfonamide use.
- Later reports implicated multiple unrelated medication classes.
- The broad drug spectrum favors an idiosyncratic immune response rather than a single chemical toxicity.



Principal medication groups

Synthetic penicillins and other antibiotics are classic causes. Diuretics and NSAIDs are prominent non-antibiotic examples.

Class / group	Examples named in Robbins
Synthetic penicillins	Methicillin; ampicillin
Other antibiotic	Rifampin
Diuretic	Thiazides
Anti-inflammatory agents	NSAIDs
Other medications	Allopurinol; cimetidine; immune checkpoint inhibitors

Synthetic penicillins: Classic examples

- Methicillin and ampicillin are specifically named as frequent triggers.
- These agents illustrate the acute drug-hypersensitivity phenotype.
- The medication history must include the interval after initiation.

METHICILLIN / AMPICILLIN

Synthetic penicillins

Rifampin: A non-penicillin antibiotic trigger

- Rifampin is specifically included among implicated synthetic antibiotics.
- The diagnosis should not be restricted to beta-lactam exposure.
- Causality rests on the compatible clinical course and pathologic pattern.

RIFAMPIN

Other implicated antibiotic

Thiazide diuretics and interstitial inflammation

- Thiazides appear in the list of acute drug-induced AIN triggers.
- Some thiazide-associated cases may show interstitial nonnecrotizing granulomas.
- Granulomas are a possible pattern—not a required finding.

THIAZIDES

Diuretic-associated AIN

NSAIDs: More than one renal lesion

- NSAIDs can produce immune-mediated acute interstitial nephritis.
- They can also reduce renal prostaglandin-dependent perfusion.
- Minimal change disease or membranous nephropathy may occur as distinct glomerular injuries.

Hemodynamic AKI

Acute AIN

Minimal change disease

**Membranous
nephropathy**

Allopurinol and cimetidine

- Both drugs are specifically identified among miscellaneous triggers.
- Their inclusion illustrates the varied pharmacologic classes involved.
- A recent exposure is more informative than assuming that only antibiotics are implicated.

ALLOPURINOL / CIMETIDINE

Miscellaneous drug triggers

Immune checkpoint inhibitors

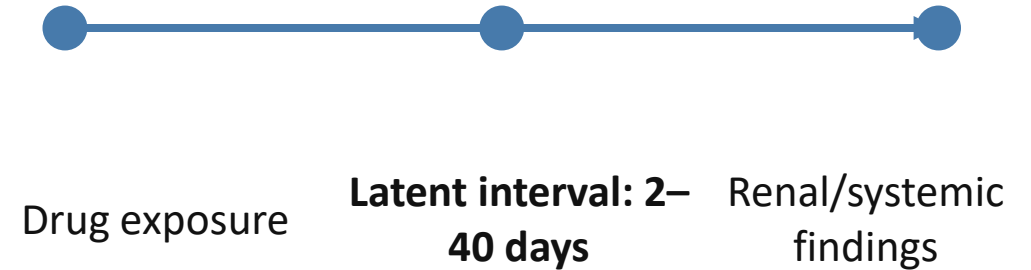
- Immune checkpoint inhibitors are explicitly included in the Robbins list.
- Their association extends the etiologic spectrum to anticancer immunotherapy.
- A new cancer treatment should be part of the renal exposure history.

IMMUNE CHECKPOINT INHIBITORS

Immunotherapy exposure

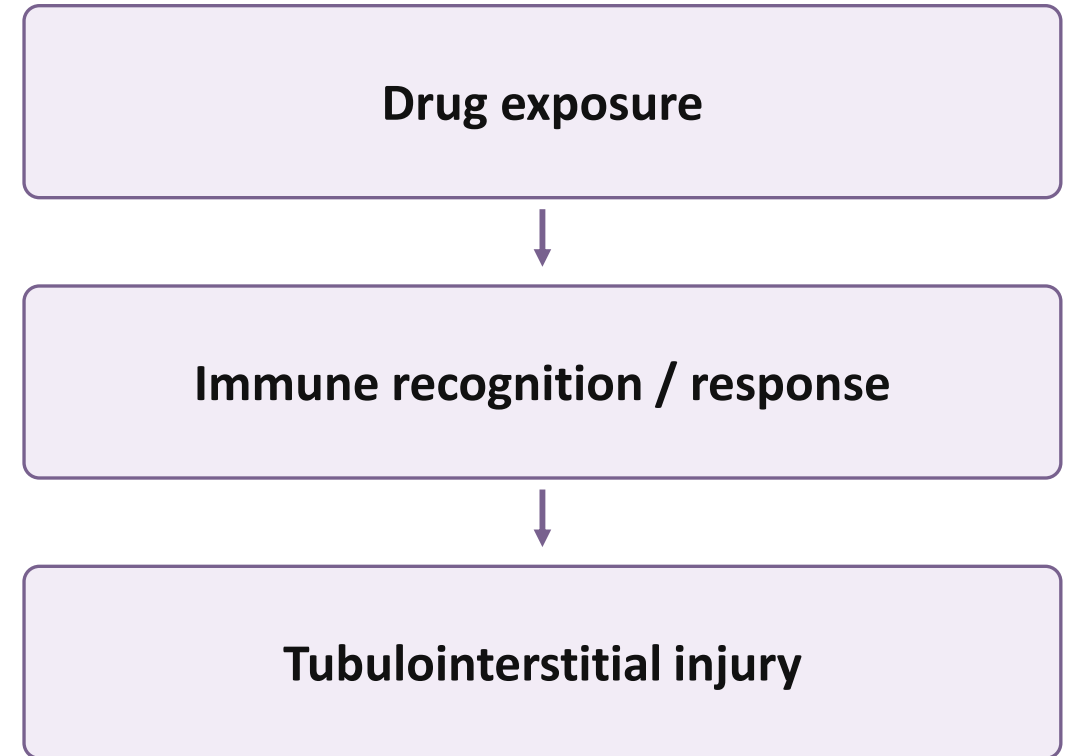
Drug causality begins with the timeline

- The typical reported onset is 2–40 days following exposure.
- A compatible interval strengthens suspicion but does not, alone, prove causation.
- The same history must be interpreted alongside urinary and renal findings.



Immune latency explains delayed onset

- The latent interval is one of the observations supporting hypersensitivity.
- A delay separates drug contact from clinically recognizable renal inflammation.
- This is a mechanistic distinction from immediate concentration-dependent toxicity.



Schematic — conceptual sequence

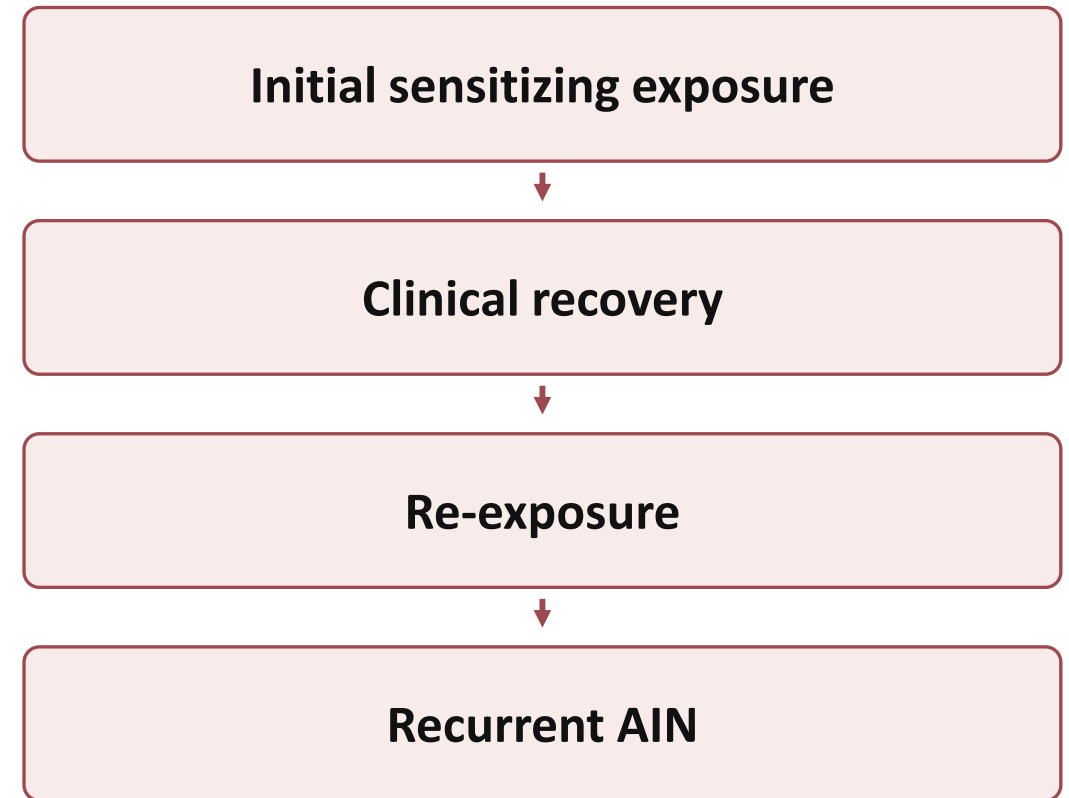
The injury is not dose-dependent

A lack of relation between drug dose and onset of nephropathy. This supports an idiosyncratic immune process.

Immune hypersensitivity	Simple dose toxicity
Not necessarily dose related	Risk often follows exposure burden
Latent inflammatory response	Direct tubular injury mechanism
Re-exposure can recur	Toxicity depends on toxic conditions

Recurrence after re-exposure is strong evidence

- Clinical and pathologic manifestations can recur after re-exposure.
- The same drug or a chemically related drug may trigger recurrence.
- This is an etiologic observation—not a recommendation for diagnostic rechallenge.



Schematic — conceptual sequence

The hypersensitivity phenotype is variable

- Fever, rash and eosinophilia are recognized manifestations.
- Urinalysis and kidney function may show more direct evidence of renal involvement.
- Not every finding must be present simultaneously.

Systemic

Fever, rash, eosinophilia

Urinary

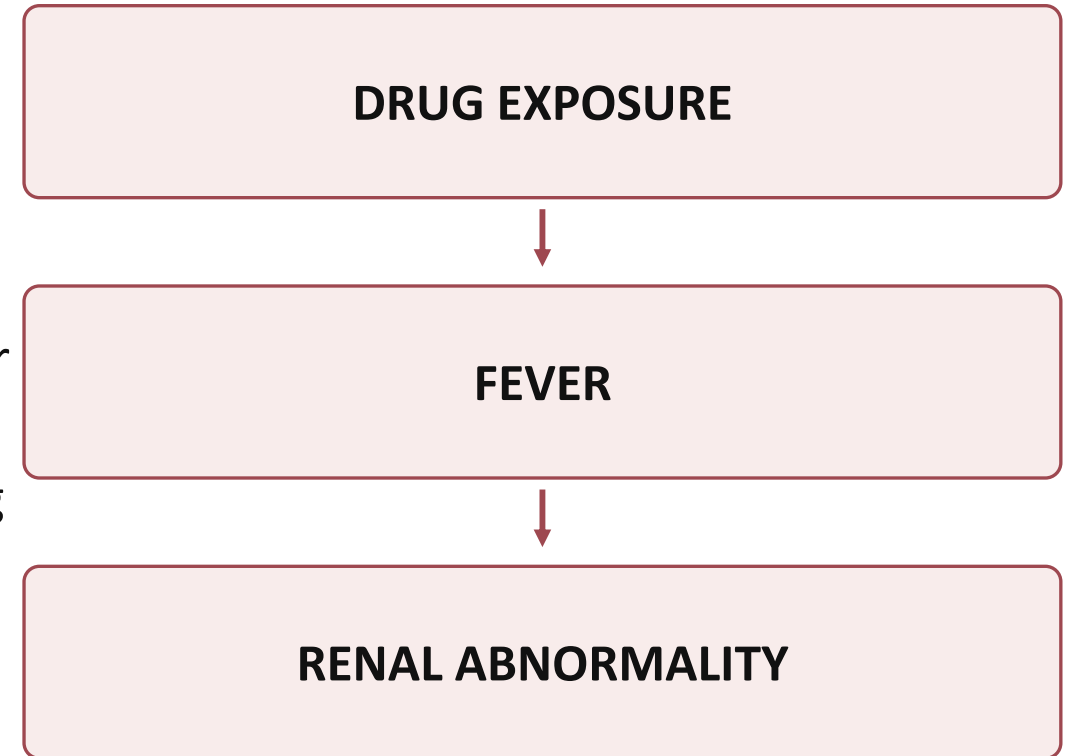
Hematuria, mild proteinuria,
leukocyturia

Renal function

Creatinine rise; AKI; Sometimes
oliguria

Fever can signal a systemic drug reaction

- Fever is one of the characteristic systemic features.
- In a patient exposed to a relevant medication, fever plus urinary changes raises concern.
- Fever is not specific: Infection remains a competing clinical explanation.



Schematic — conceptual sequence

Rash is supportive, not universal

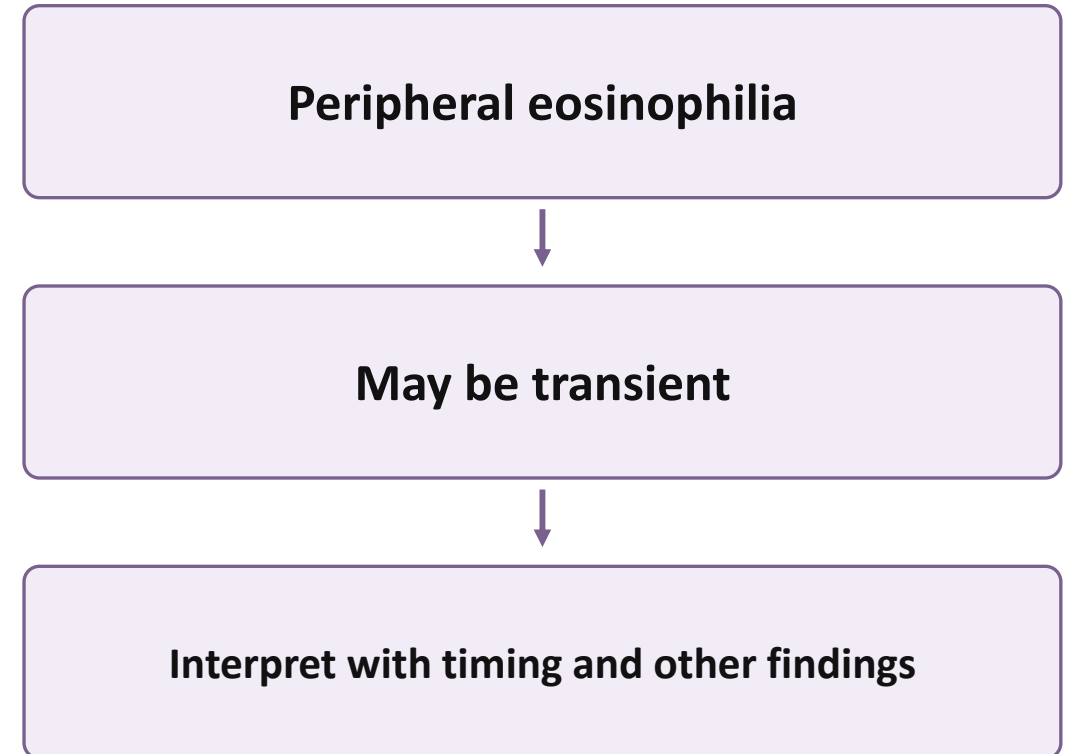
- Rash occurs in about 25% of cases description.
- Therefore, most affected patients in that description did not have rash.
- Absence of rash cannot exclude acute drug-induced AIN.

~25%

Reported with rash

Peripheral eosinophilia may be transient

- Eosinophilia is among the classic hypersensitivity features.
- The text specifically notes that it may be transient.
- A normal count at a single time point does not negate the overall clinical pattern.



Schematic — conceptual sequence

Do not require the complete clinical triad

- Fever, eosinophilia and rash vary across patients.
- Rash is absent in many patients, and eosinophilia may be transient.
- The clinical assessment must integrate exposure, urine and renal function.

Timing

Compatible medication exposure

Clinical signs

Signs may be incomplete

Kidney findings

Urine and creatinine changes matter

Hematuria reflects renal involvement

- Hematuria is a reported urinary abnormality in acute drug-induced AIN.
- It accompanies rather than defines the drug hypersensitivity syndrome.
- Interpret it together with proteinuria and leukocyturia.

HEMATURIA

Urinary finding

Proteinuria is usually mild pattern

The usual urinalysis description specifies mild proteinuria. Marked nephrotic protein loss suggests an additional or alternative lesion.

Typical acute AIN	NSAID + minimal change disease
Mild proteinuria	Nephrotic syndrome may appear
Predominant interstitial lesion	Podocyte-associated glomerular lesion
Glomeruli usually normal	Coexistent glomerular involvement

Leukocyturia often accompanies AIN

- Urinary white blood cells are a typical feature.
- The urinary leukocyte population can include eosinophils.
- Leukocyturia must be interpreted alongside possible urinary infection.

Interstitial/tubular inflammation



Leukocytes in urinary space



Leukocyturia ± eosinophils

Schematic — conceptual sequence

Rising creatinine and acute kidney injury

- A rising serum creatinine or acute kidney injury with oliguria in about 50% of cases.
- Kidney functional impairment may therefore be clinically prominent.
- The estimated percentage is source-specific, not a universal diagnostic sensitivity.

~50%

Reported with creatinine rise or AKI with
oliguria

Oliguria marks more severe functional disturbance

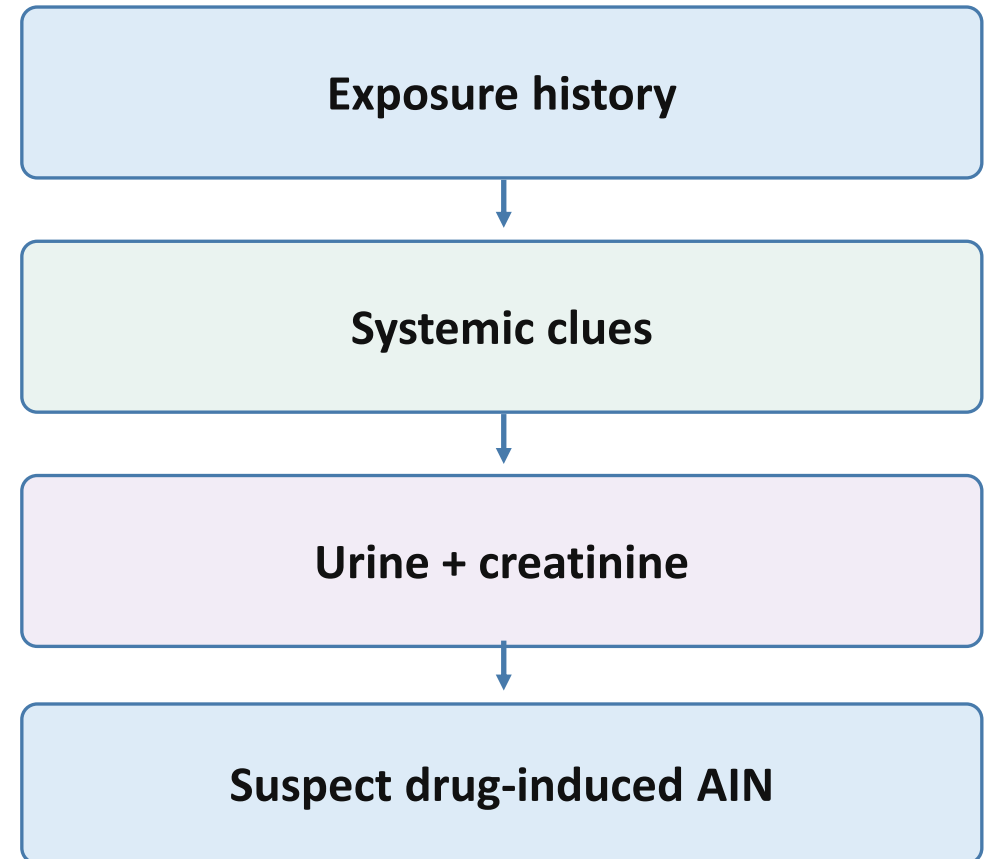
- Oliguria can accompany acute kidney injury in the reported syndrome.
- It signals clinically important reduction in urine output.
- Not all patients develop oliguria, even when histologic inflammation is present.

OLIGURIA

Possible AKI manifestation

Integrating the clinical manifestations

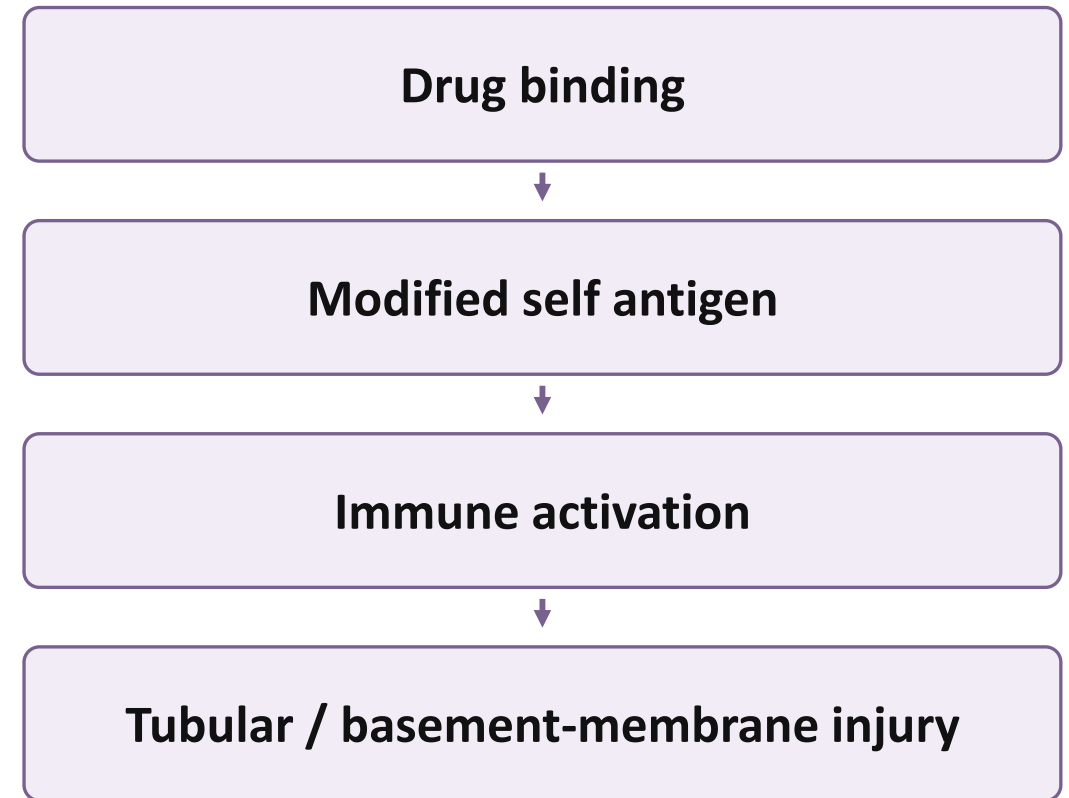
- The drug exposure is the starting etiologic clue.
- Systemic hypersensitivity findings support—but do not establish—the cause.
- Urinary abnormalities and rising creatinine indicate renal injury.



Schematic integration, not a validated score

Hypothesis: Drugs generate modified self antigens

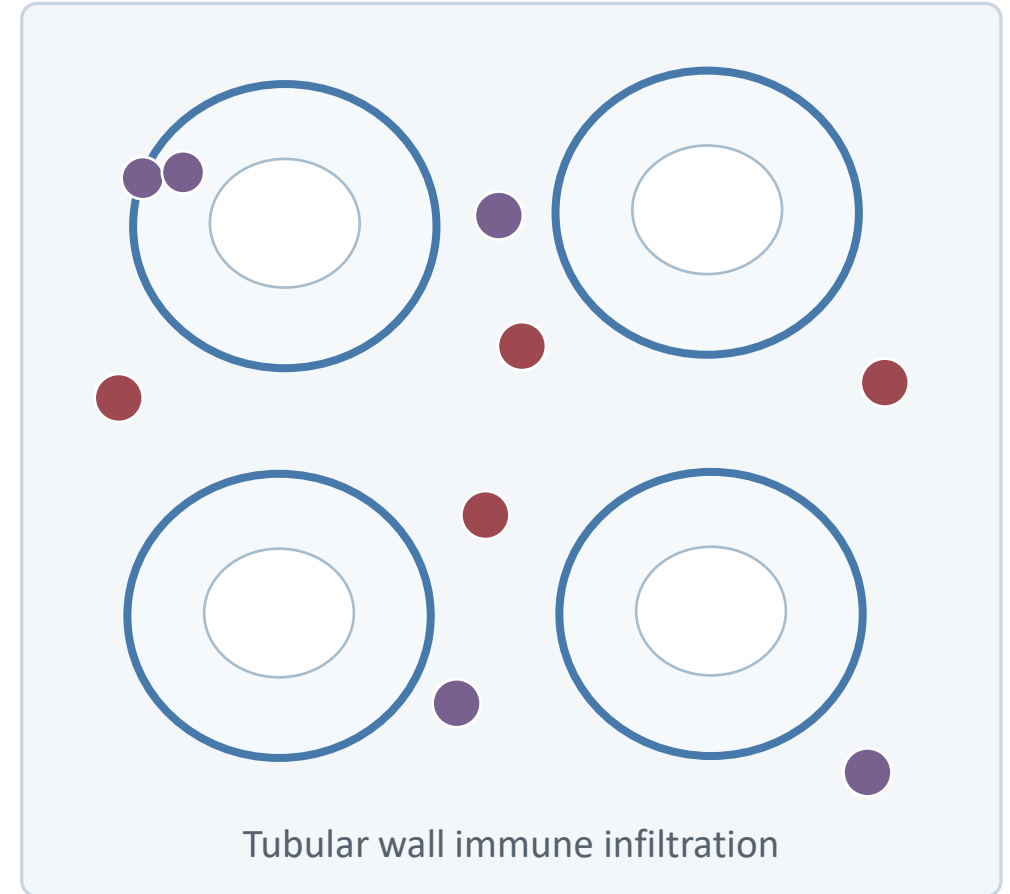
- Binding of drug to a tubular plasma-membrane or extracellular component.
- The modified component is recognized as an altered self antigen.
- An immune response then damages tubular structures.



Schematic — conceptual sequence

Targets include tubular cells and basement membranes

- The elicited immune reaction is directed against tubular cells or tubular basement membranes.
- The location of antigenic targets explains why tubular and interstitial compartments dominate.
- This connects the proposed mechanism to the characteristic microscopic distribution.



Schematic — not a histologic specimen

Type I hypersensitivity: Supporting evidence

- Some patients show increased serum IgE.
- IgE-containing plasma cells and basophils can occur in lesions.
- These observations suggest involvement of the late phase of an IgE-mediated reaction.

IgE-associated immune response



Basophils / IgE+ plasma cells



Interstitial inflammatory injury

Schematic — conceptual sequence

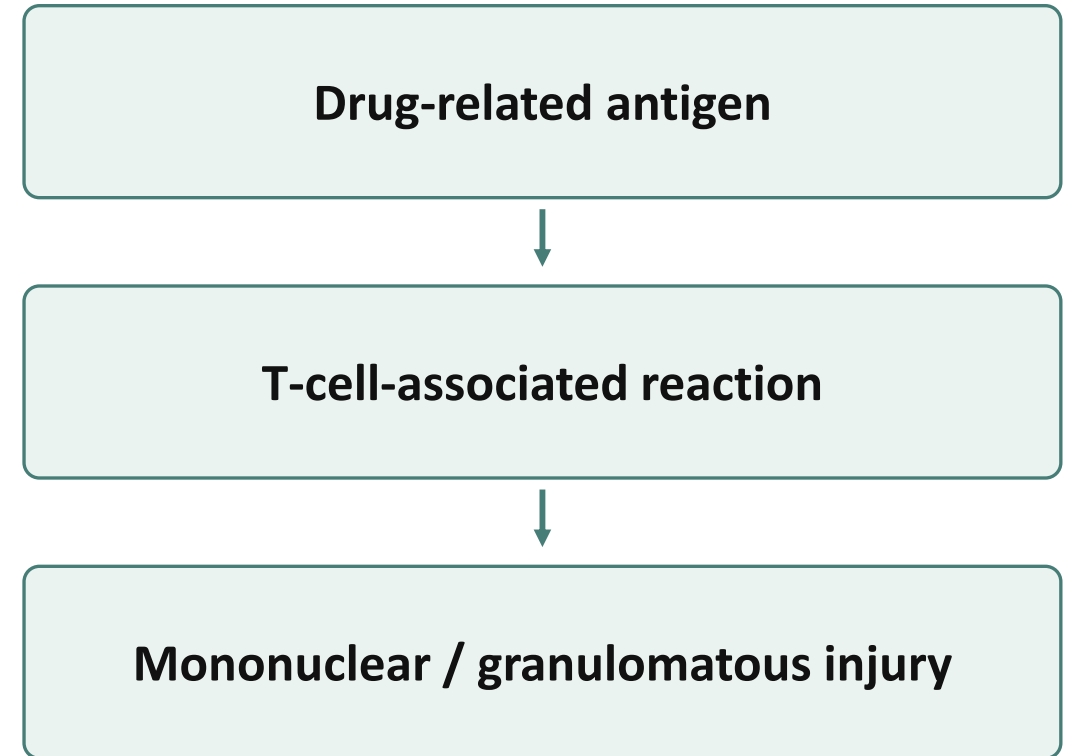
IgE-associated findings are not universal

The described IgE and basophil findings occur in some patients. They support one plausible immunologic route but do not characterize every case.

Observed in some cases	Not required in every biopsy
Increased serum IgE	No universal IgE finding stated
IgE-containing plasma cells	Mononuclear infiltrate may dominate
Basophils	Granulomas may accompany T-cell pattern

Type IV hypersensitivity: Supporting evidence

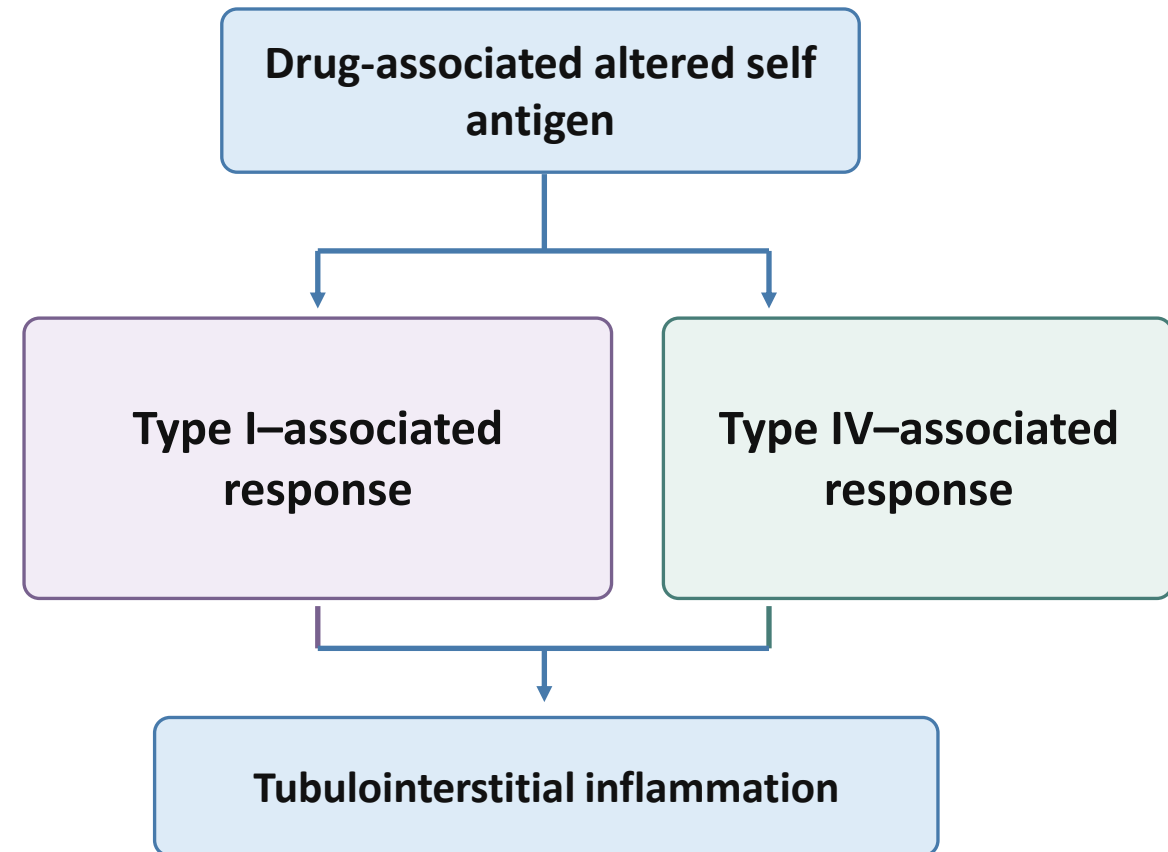
- Mononuclear inflammatory infiltrates suggest cellular immune participation.
- Granulomatous reactions occur in some cases.
- Positive drug skin tests in some patients support delayed T-cell-mediated hypersensitivity.



Schematic — conceptual sequence

Two immune pathways converge on the same lesion

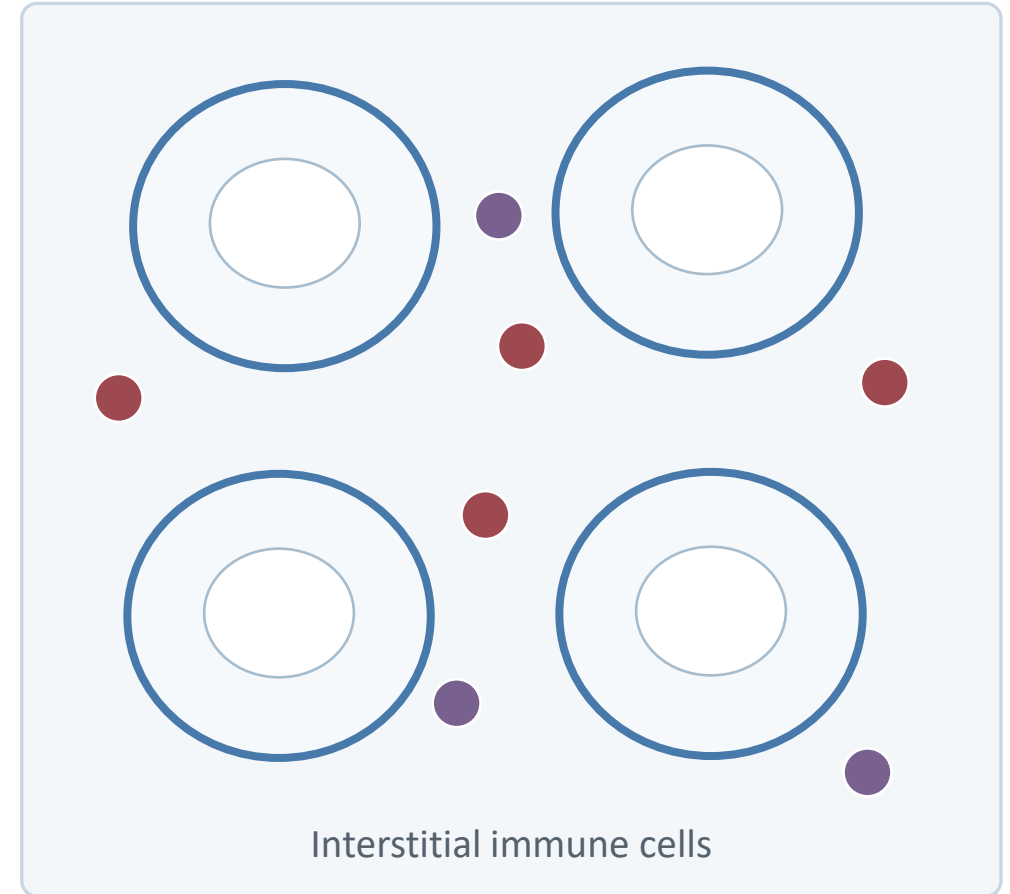
- Type I–associated and type IV–associated features are described in different cases.
- Both may culminate in tubulointerstitial inflammation and tubular injury.
- The tissue pattern is therefore more consistent than a single immune signature.



Schematic — alternative injury pathways

The interstitium is the center of the lesion

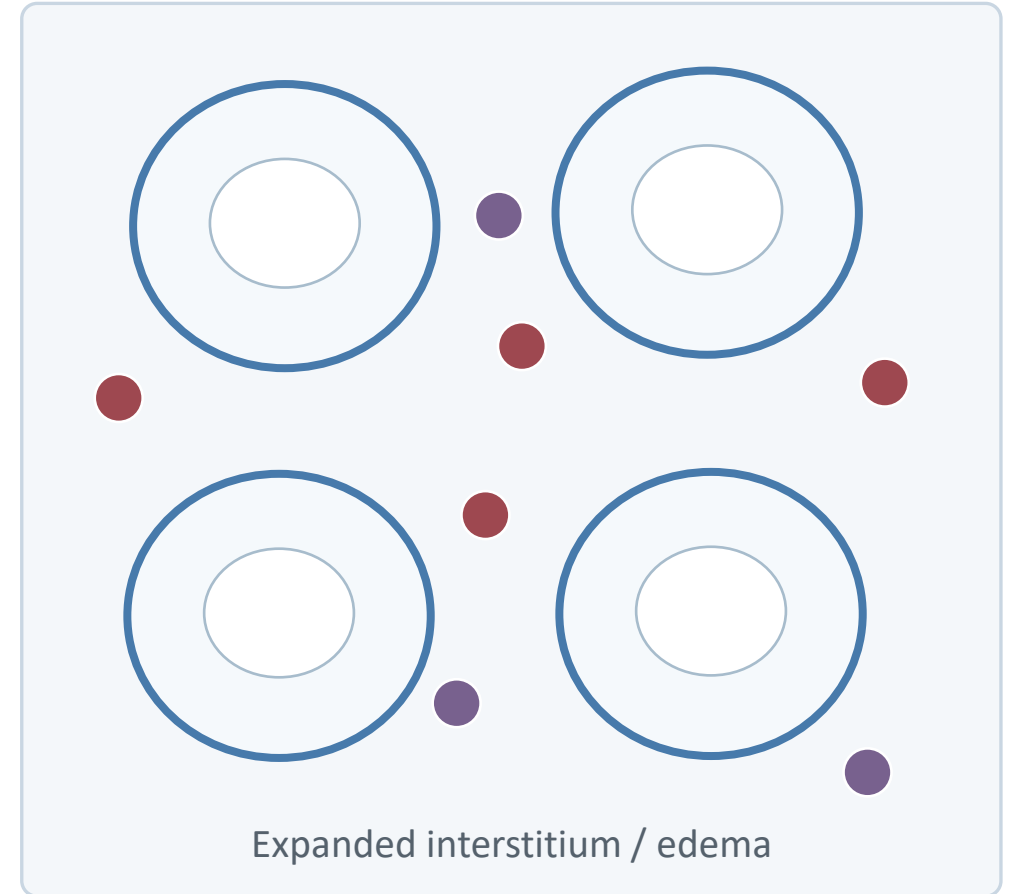
- Histology often shows marked expansion of the interstitium.
- Edema and inflammatory cells separate injured tubular profiles.
- The appearance is distinct from a purely glomerular lesion.



Schematic — not a histologic specimen

Interstitial edema expands tissue spaces

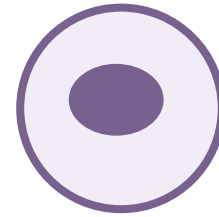
- Interstitial edema can be pronounced.
- The widened interstitial compartment accommodates and accompanies inflammatory infiltrates.
- Tubules may appear spatially separated in an educational tissue schematic.



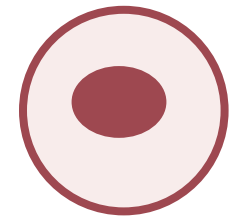
Schematic — not a histologic specimen

Lymphocytes and macrophages predominate

- The typical mononuclear infiltrate principally comprises lymphocytes and macrophages.
- This is the dominant inflammatory-cell description in the pathology text.
- Eosinophils are possible but not obligatory.



Lymphocytes

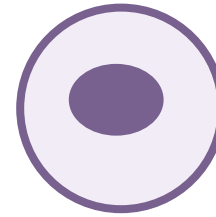


Macrophages

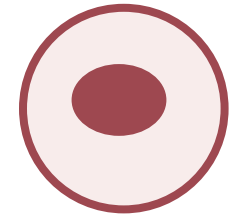
Cell icons are conceptual, not photomicrographs

Eosinophils and neutrophils are variable

- Both eosinophils and neutrophils may be present.
- They can form clusters and may occur in large numbers.
- A diagnostic description should not imply that eosinophils are invariably present.



Eosinophils

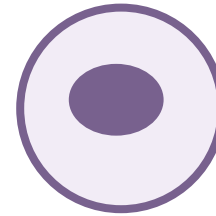


Neutrophils

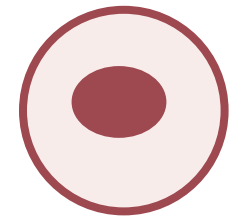
Cell icons are conceptual, not photomicrographs

Plasma cells and mast cells may contribute

- Smaller numbers of plasma cells and mast cells can occur in the infiltrate.
- Their presence broadens the inflammatory-cell spectrum.
- An infiltrate is best described by its overall composition and distribution.



Plasma cells

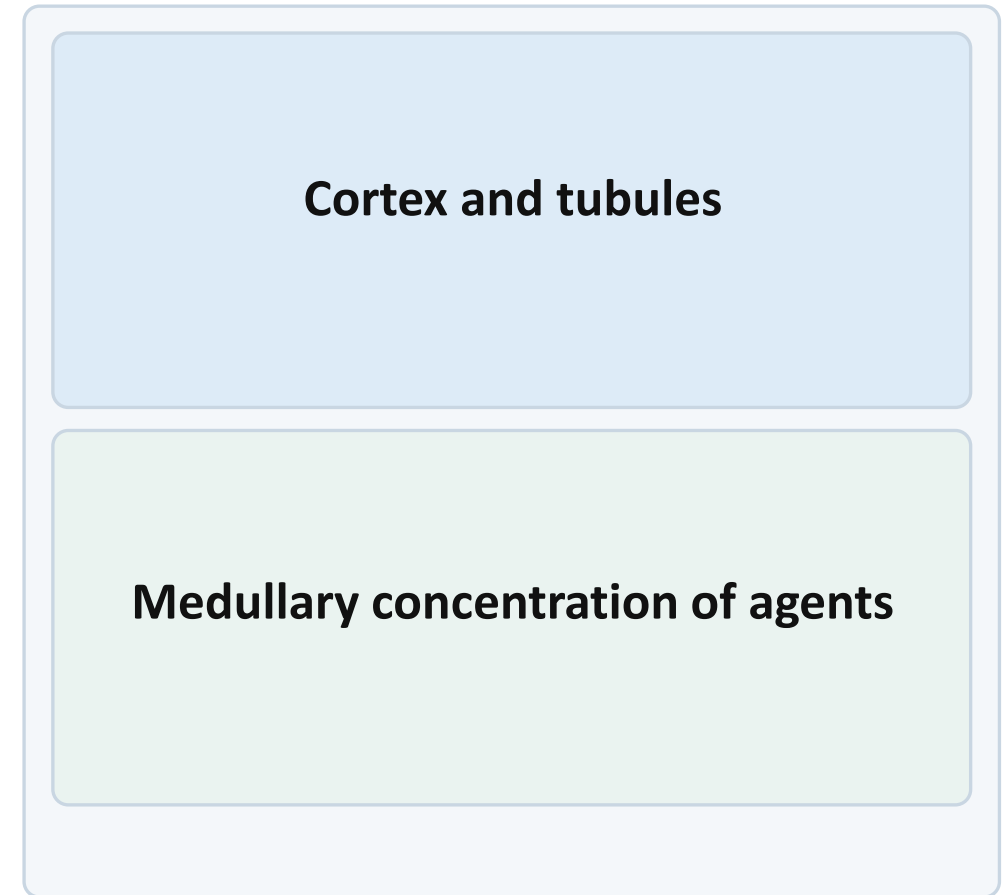


Mast cells

Cell icons are conceptual, not photomicrographs

The medulla may have conspicuous inflammation

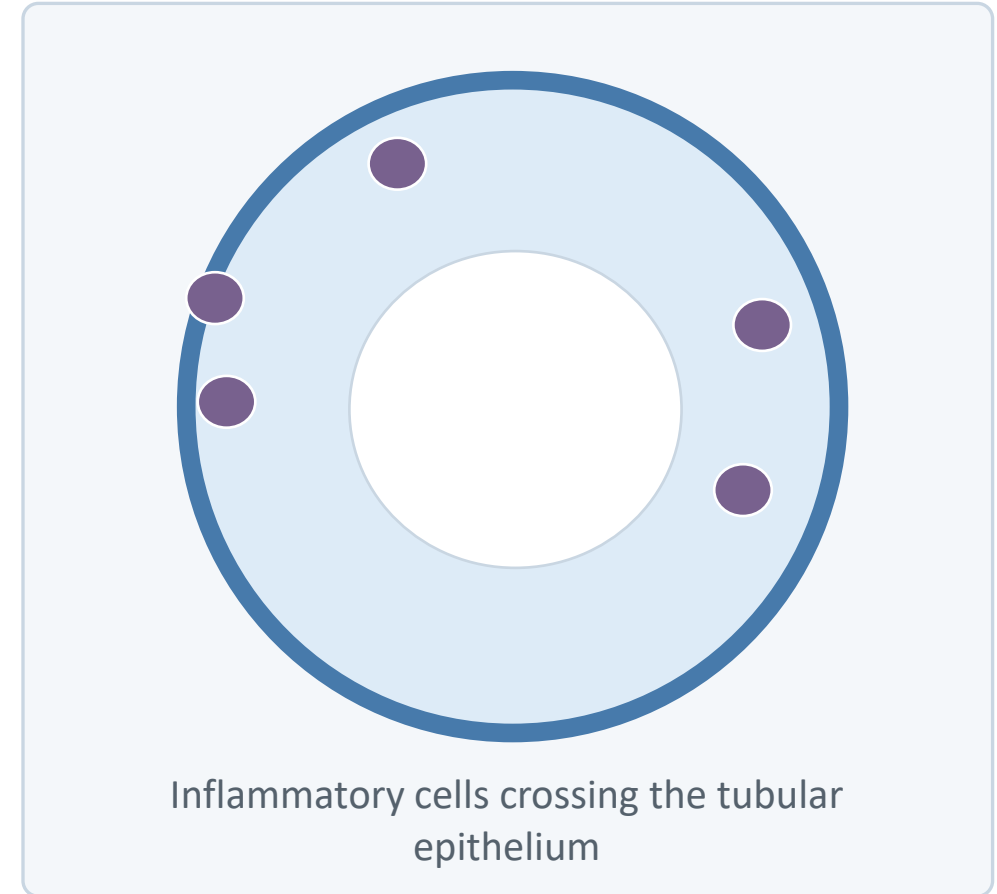
- Inflammation can be more prominent in the medulla.
- The source relates this to concentration of the inciting agent.
- Sampling location can therefore influence the pattern seen on a section.



Schematic — regional concept, not specimen

Tubulitis means inflammatory cells within tubules

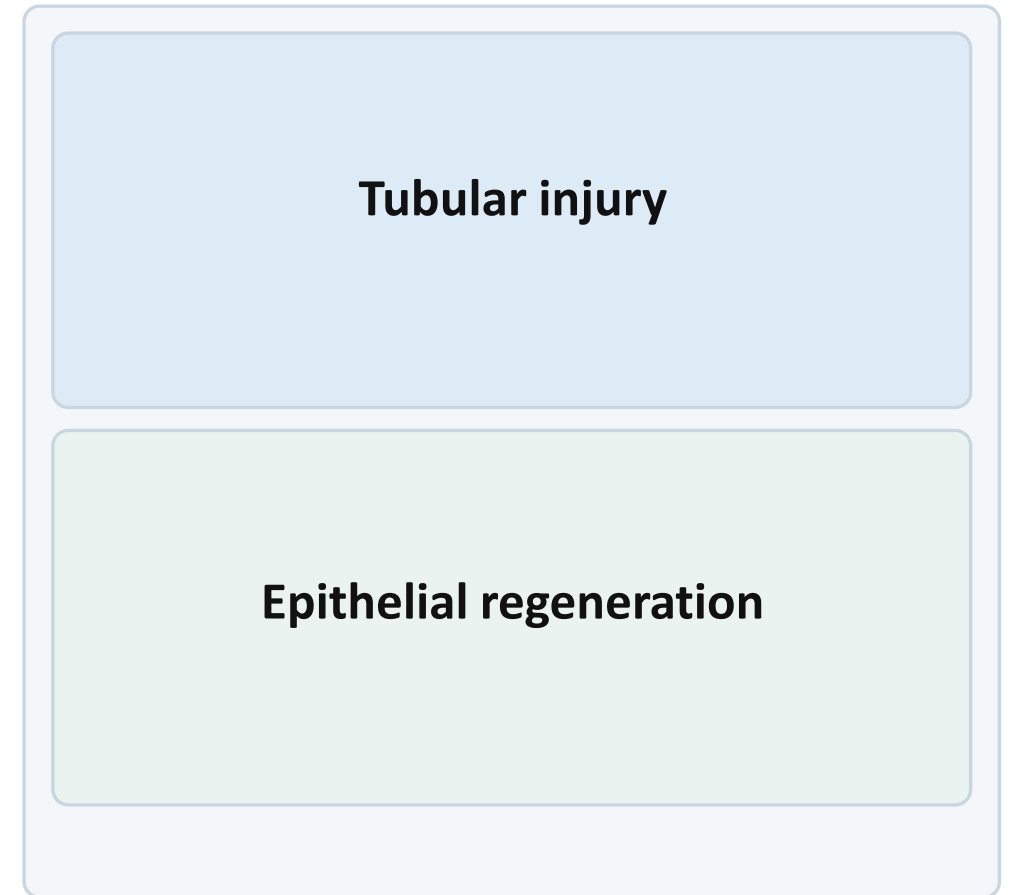
- Lymphocytes infiltrate tubular structures, a finding termed tubulitis.
- Tubulitis is common in drug-associated acute interstitial nephritis.
- It links interstitial inflammation directly to epithelial injury.



Schematic tubulitis — not a biopsy image

Tubular injury is accompanied by regeneration

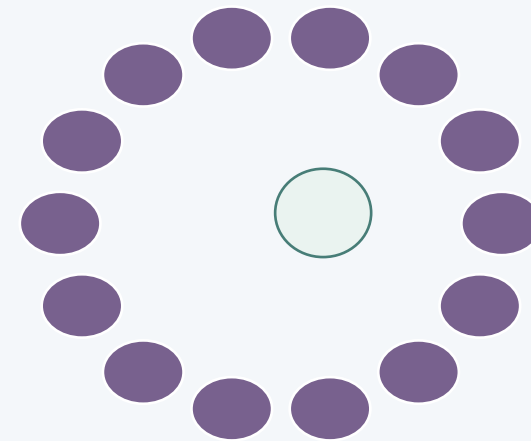
- Biopsies may show variable degrees of tubular epithelial damage.
- Regenerative change can accompany that injury.
- The severity of epithelial change need not be identical in every affected tubule.



Schematic — regional concept, not specimen

Granulomas: A selected morphological variant

- Interstitial nonnecrotizing granulomas can occur with some drugs.
- Methicillin and thiazides are named examples.
- The text associates this pattern with tubular rupture; Granulomas are not required for AIN.



Nonnecrotizing granulomatous pattern

Conceptual cell aggregate — not histology

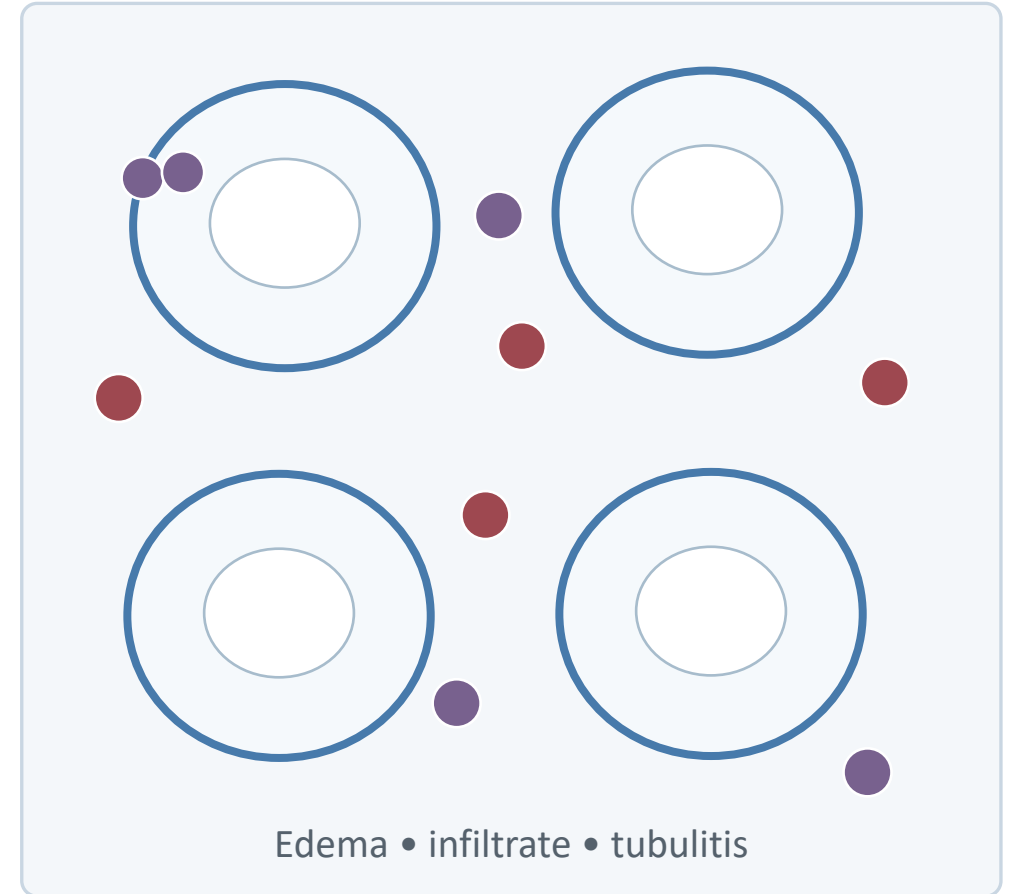
Glomeruli are usually spared

Glomeruli typically appear normal in the routine drug-induced AIN lesion. This reflects the tubulointerstitial rather than primarily glomerular target.

Most drug-induced AIN	Some NSAID-associated cases
Glomeruli morphologically normal	Coexistent minimal change disease
Tubular and interstitial changes dominate	Nephrotic syndrome can develop
Mild proteinuria typical	Podocyte lesion affects presentation

Reading a biopsy: Integrate four compartments

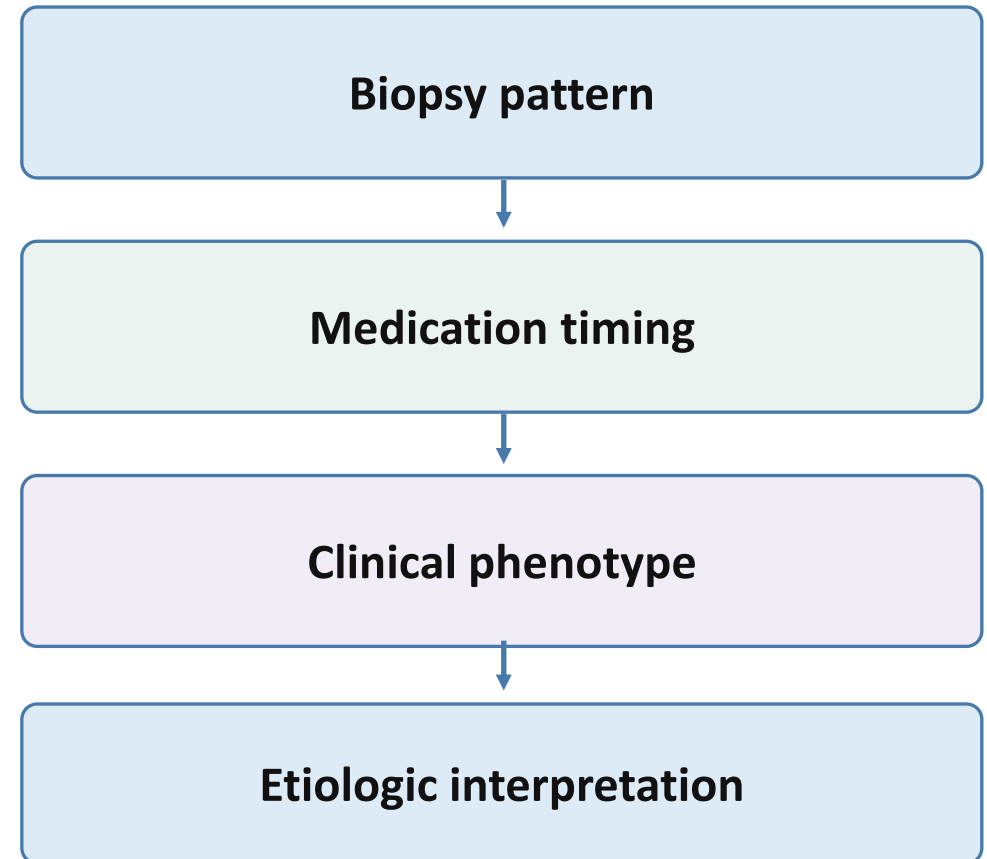
- Interstitial edema and mononuclear cells form the principal inflammatory pattern.
- Tubulitis and variable epithelial injury support tubular participation.
- Review eosinophils, granulomas, and glomerular appearance as modifiers.



Schematic — not a histologic specimen

Histology identifies a pattern, not always a culprit

- Prominent interstitial inflammation is compatible with drug-induced AIN.
- Eosinophils or granulomas may strengthen a hypersensitivity impression.
- An exposure history is still required to attribute the lesion to a particular drug.



Schematic integration, not a validated score

NSAIDs cause several distinct renal syndromes

- COX-dependent prostaglandin inhibition is a mechanism of hemodynamic injury.
- NSAIDs can also cause acute hypersensitivity interstitial nephritis.
- Glomerular injuries may coexist or occur as separate syndromes.

Perfusion-related AKI

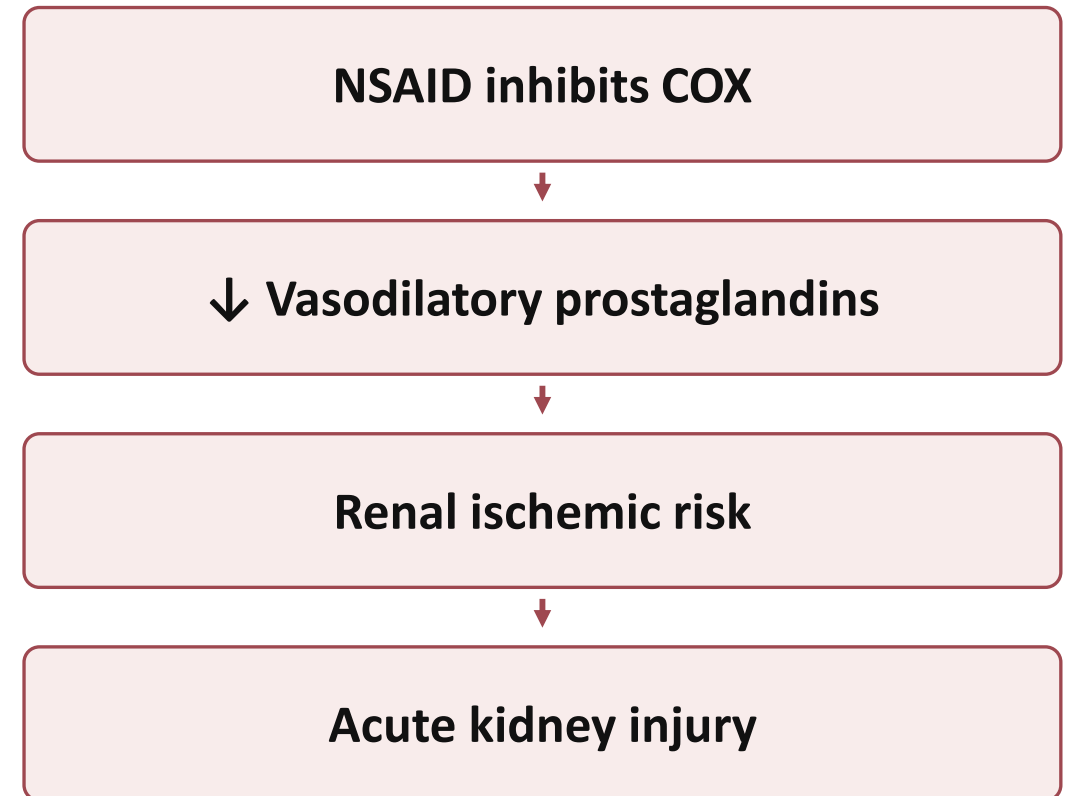
Acute AIN

Minimal change disease

**Membranous
nephropathy**

NSAID hemodynamic AKI: A different mechanism

- Cyclooxygenase inhibition reduces vasodilatory renal prostaglandin synthesis.
- A resulting ischemic decrease in renal perfusion can cause acute kidney injury.
- Other kidney disease or volume depletion increases vulnerability.



Schematic — conceptual sequence

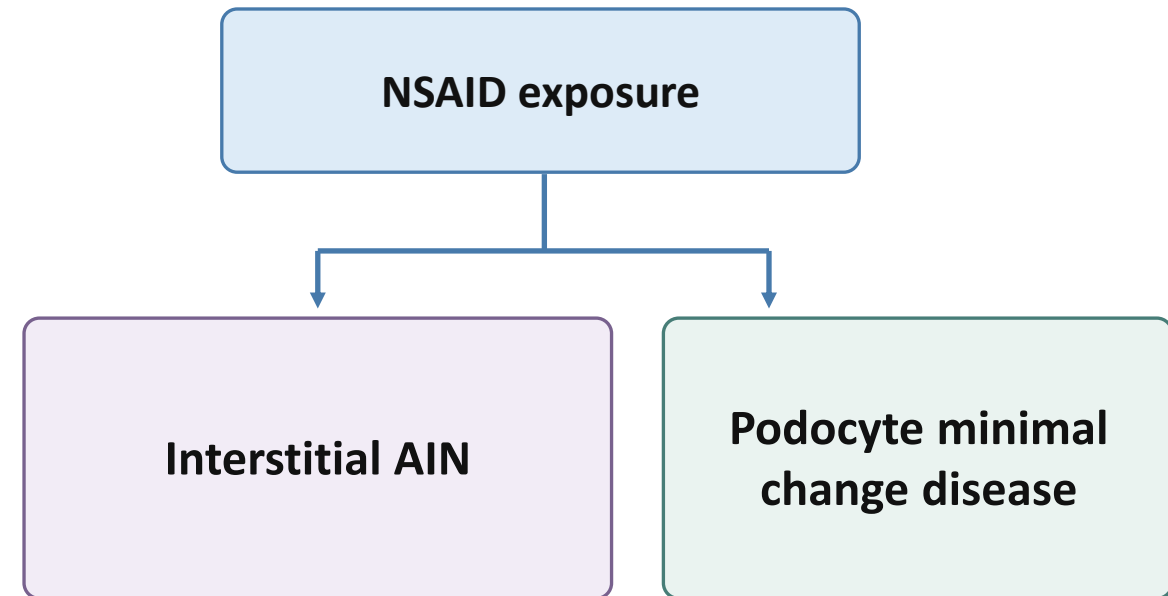
NSAID-associated AIN is immune-inflammatory

NSAIDs can trigger acute hypersensitivity interstitial nephritis. This pathway differs from prostaglandin-related renal vasoconstriction.

Hemodynamic NSAID injury	NSAID-associated AIN
Prostaglandin suppression	Immune interstitial reaction
Reduced renal vasodilatation	Interstitial infiltrate and tubulitis
Ischemic mechanism	Inflammatory renal lesion

Minimal change disease can coexist with NSAID AIN

- NSAID-related podocyte injury may occur with or without interstitial nephritis.
- Concomitant minimal change disease can generate nephrotic syndrome.
- This modifies the usual expectation of mild proteinuria in AIN.



Schematic — alternative injury pathways

Membranous nephropathy is another NSAID pattern

- Membranous nephropathy with nephrotic syndrome is listed as a rare NSAID complication.
- Its pathogenesis is described as uncertain.
- It must be distinguished from the more typical isolated tubulointerstitial injury.

MEMBRANOUS NEPHROPATHY

Rare NSAID-associated glomerular lesion

Four NSAID patterns: Tissue and mechanism

A single agent class can affect hemodynamics, tubules, interstitium or podocytes. Use the phenotype and tissue compartment to distinguish them.

Renal syndrome	Pathogenic / morphologic emphasis
Hemodynamic AKI	COX inhibition; reduced vasodilatory prostaglandins
Acute AIN	Interstitial immune inflammation
Minimal change disease	Podocyte injury; sometimes concurrent AIN
Membranous nephropathy	Rare glomerular injury; mechanism uncertain

AIN versus acute tubular injury

AIN is defined by prominent interstitial inflammation and tubulitis. Acute tubular injury emphasizes epithelial damage, often with ischemic or toxic mechanisms.

Acute interstitial nephritis	Acute tubular injury
Immune-inflammatory insult	Ischemic / toxic insult
Edema + interstitial cells	Predominant tubular epithelial injury
Tubulitis often present	Tubular epithelial changes central
Drug latency / hypersensitivity clues	Perfusion or toxin exposure context

AIN versus pyelonephritis: Etiologic contrast

Both can involve the renal interstitium and tubules. Pyelonephritis belongs to the infection category in the source classification.

Drug AIN	Pyelonephritis
Drug-associated immune response	Infectious tubulointerstitial process
Latency, rash or eosinophilia may occur	Infection-oriented clinical context
Variable eosinophils and mononuclear cells	Neutrophilic inflammatory pattern may be prominent

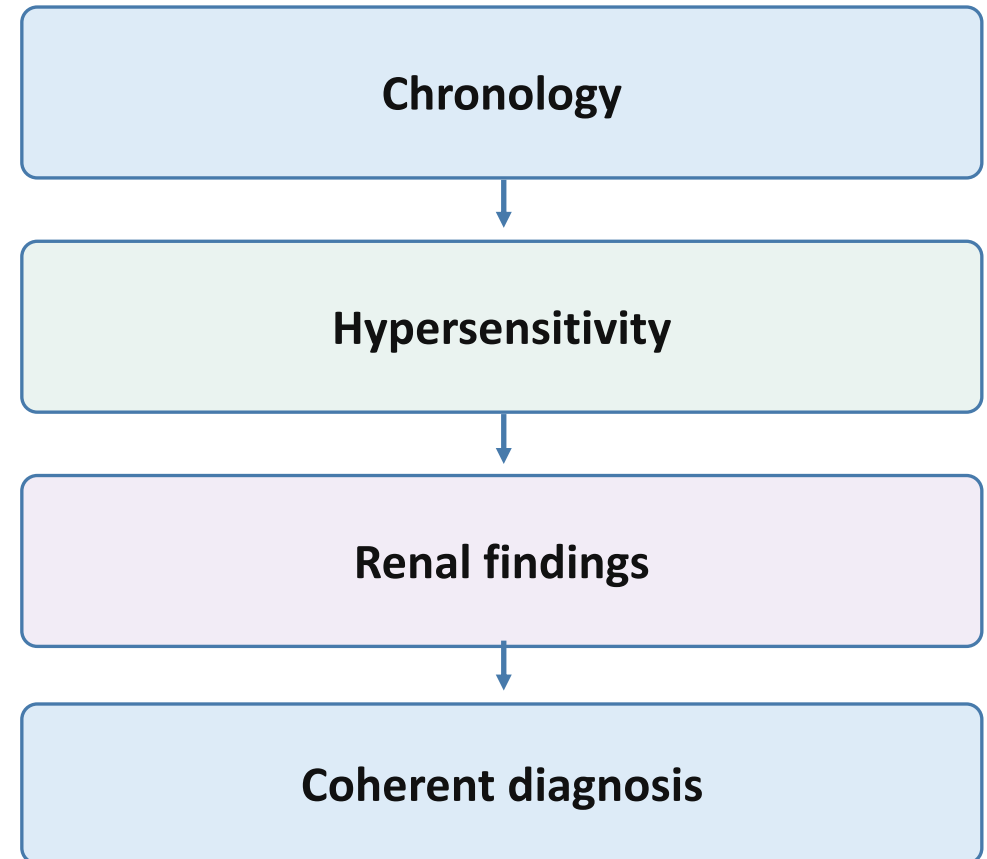
Other causes of tubulointerstitial nephritis

Infections, toxins, metabolic causes and immunologic disorders can involve the compartment. Obstruction, inherited disease and plasma-cell disorders also enter the broader differential.

Category in Robbins Table 20.8	Illustrative examples
Infections	Pyelonephritis; other infections
Metabolic / toxic	Urate; hypercalcemia; heavy metals
Immunologic	Transplant rejection; Sjögren syndrome; sarcoidosis
Other	Obstruction; light-chain cast nephropathy

Clinical reasoning: Combine three independent clues

- Document the sequence of drug exposure and onset of renal abnormalities.
- Assess systemic hypersensitivity manifestations without demanding all three.
- Correlate urinary, creatinine, and biopsy findings where available.



Schematic integration, not a validated score

Not every interstitial nephritis has an identified drug

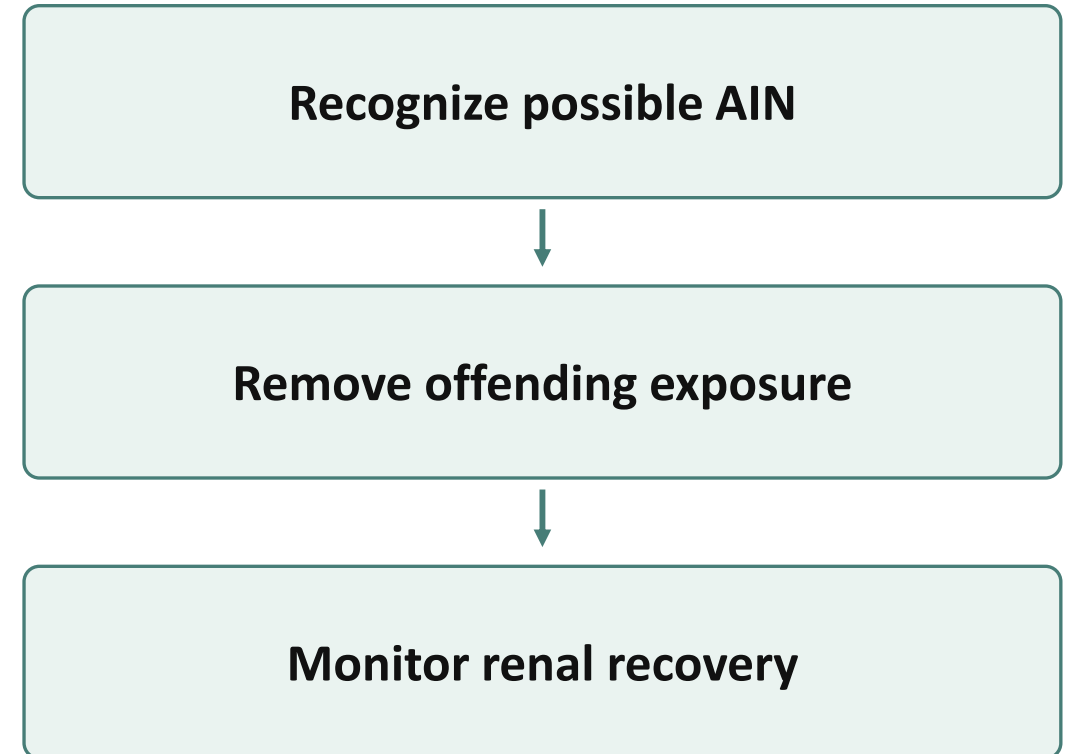
- In approximately 30–40% of affected patients, no offending drug or mechanism is identified.
- A drug history is essential but cannot resolve all cases.
- Avoid forcing a medication attribution without plausible evidence.

30–40%

No identified drug or mechanism
description

The first corrective step is removing the trigger

- Withdrawal of the offending medication is the key clinical implication emphasized by Robbins.
- Subsequent improvement supports the etiologic assessment.
- The time course may be gradual and requires follow-up.



Schematic — conceptual sequence

Recovery can be delayed or incomplete

- Renal recovery after withdrawal may take several months.
- Some patients sustain irreversible damage.
- A falling creatinine is encouraging but does not erase the need to assess residual dysfunction.



Case 1: The antibiotic-associated pattern

- An adult begins a synthetic penicillin and later develops fever, rash, hematuria and rising creatinine.
- The exposure interval is compatible with the Robbins 2–40-day description.
- Which pathologic compartment and mechanism should the learner predict?

Discussion prompt: Predict mechanism and biopsy compartment

Case 1: Expected pathologic interpretation

- The drug chronology and systemic findings support hypersensitivity.
- Expected morphology includes interstitial edema, mononuclear cells and frequent tubulitis.
- Eosinophils may be conspicuous but are not mandatory.

History

Compatible penicillin interval

Biopsy

Interstitial edema + tubulitis

Qualifier

Eosinophils variable

Case 2: NSAID exposure with heavy proteinuria

- A patient receiving an NSAID develops kidney dysfunction and nephrotic syndrome.
- Does nephrotic protein loss fit the typical isolated interstitial nephritis pattern?
- What additional glomerular lesion is listed in the text?

Discussion prompt: Predict mechanism and biopsy compartment

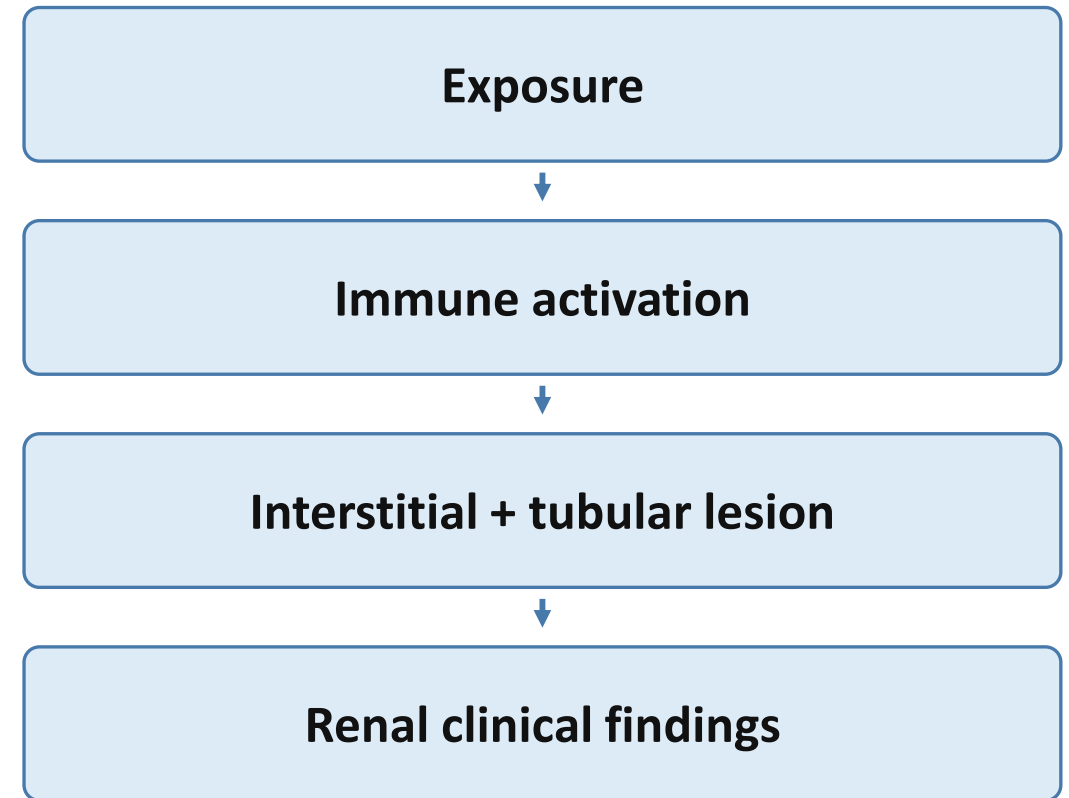
Case 2: Why NSAIDs require a broader differential

Minimal change disease can accompany NSAID-related AIN and cause nephrotic syndrome. Membranous nephropathy is another, rarer NSAID-related possibility.

Interstitial phenotype	Glomerular phenotype
Interstitial infiltrate / tubulitis	Minimal change or membranous lesion
Usually mild proteinuria	Nephrotic-range presentation possible
Drug hypersensitivity context	Podocyte / glomerular involvement

Clinicopathologic pattern recognition

- The most informative sequence is exposure → immune response → interstitial inflammation → functional consequence.
- The histologic core is edema, mononuclear infiltrates and tubulitis.
- The clinical phenotype is variable; The absence of rash or eosinophils does not remove AIN from consideration.



Schematic — conceptual sequence

Five points to retain

- Drug-induced AIN is an immune inflammatory tubulointerstitial disorder.
- Latent onset, dose independence and recurrence after re-exposure support hypersensitivity.
- Edema, mononuclear cells and tubulitis are central; Eosinophils/granulomas vary.
- NSAIDs can also cause distinct hemodynamic and glomerular syndromes.
- Drug withdrawal is important; Recovery may be slow or incomplete.

References

- Primary teaching source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 20: The Kidney, p. 846.
- Parent section used for context: Tubulointerstitial Nephritis Induced by Drugs and Toxins, pp. 845–846.
- For an authentic morphology example, consult Robbins Fig. 20.27 (figure not reproduced here).