Toxic Nephropathies: Drug-Induced and Environmental Kidney Disease

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Toxic Nephropathies: Drug-Induced and Environmental Kidney Disease

Level: PA/Medical Student **Duration:** 60–90 minutes **Version:** 2026-02-12

Learning Objectives

By the end of this module, students will be able to:

1. **Recognize** common drugs and toxins causing acute and chronic kidney disease
2. **Distinguish** acute drug-induced nephropathy from chronic tubulointerstitial nephritis (TIN)
3. **Explain mechanisms** of nephrotoxicity (oxidative stress, crystal-induced, immune-mediated, hemodynamic)
4. **Manage** contrast-associated AKI and nephropathy prevention
5. **Identify** drug-induced acute interstitial nephritis (AIN) and its clinical presentation
6. **Manage** heavy metal and environmental toxin exposures
7. **Assess** histology findings in drug-induced kidney disease

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Classification and Overview

Acute Drug-Induced Nephropathy

Mechanism	Drug/Toxin	Clinical Presentation	Urinalysis
Acute tubular necrosis (ATN)	Aminoglycosides, amphotericin B, myoglobin, hemoglobin, cisplatin	AKI (Cr ☐ 2–3× in days); ☐ UO	Muddy brown casts, epithelial cells

Mechanism	Drug/Toxin	Clinical Presentation	Urinalysis
Acute interstitial nephritis (AIN)	NSAIDs, antibiotics (β-lactams, TMP-SMX, fluoroquinolones), PPIs, diuretics	Fever, rash, arthralgias; AKI (often >50% ☐ Cr); eosinophiluria	Sterile pyuria, WBCs, RBCs, eosinophils
Crystalline nephropathy	Acyclovir, methotrexate, TMP-SMX, ethylene glycol, uric acid	Rapid AKI; oliguria; flank pain (rare)	Crystals (acyclovir, uric acid, oxalate)
Hemodynamic (prerenal-like)	NSAIDs, ACEi/ARB (in certain settings), COX-2 inhibitors	AKI; orthostatic hypotension	Usually bland (FeNa >2%)

Chronic Tubulointerstitial Nephritis (TIN)

Etiology	Timeline	Clinical Features	Biopsy Findings
Analgesic nephropathy	Years–decades	Slowly ☐ Cr; non-obstructive renal failure; recurrent UTI	TIN, papillary necrosis, chronic papillitis
Lithium nephropathy	Months–years	NDI (polyuria, polydipsia); CKD progression	Chronic TIN, cystic changes, glomerulosclerosis
NSAIDs (chronic)	Months–years	Slowly ☐ Cr; salt wasting; hyperkalemia	Chronic TIN; glomerulosclerosis (rare)
Heavy metal (lead, cadmium)	Years–decades	Slowly ☐ Cr; gout (lead); Fanconi syndrome (cadmium)	Chronic TIN; possible glomerulosclerosis
Herbal nephropathy (aristolochic acid)	Months–years	Rapid CKD progression; ESRD common	TIN, urothelial malignancy, papillary necrosis
Environmental (silica, asbestos)	Years–decades	Occupational history; slowly ☐ Cr	TIN, glomerulosclerosis (possible)

ACUTE DRUG-INDUCED NEPHROPATHY

Acute Tubular Necrosis (ATN) — Aminoglycosides

Mechanism Aminoglycosides (gentamicin, tobramycin, amikacin) are **polar cations** that bind to brush border proteins in proximal tubule ☐ accumulate intracellularly ☐ generate reactive oxygen species (ROS) ☐ mitochondrial dysfunction ☐ cell necrosis.

Pharmacokinetics and Toxicity Risk **Factors predicting aminoglycoside nephrotoxicity:** - **Dose and duration:** Single daily dosing (<3% ATN risk) vs. q8h dosing (5–10% risk) - **Duration >7 days:** Cumulative toxicity - **eGFR <60:** Increased drug accumulation - **Age >60:** Risk ☐ (reduced renal reserve) - **Volume depletion:** ☐ Renal perfusion ☐ ☐ drug concentration - **Concurrent nephrotoxins:** NSAIDs, radiocontrast, vancomycin (synergistic)

Clinical Presentation **Timeline:** Days 3–7 of therapy

Presentation: - **AKI:** Cr ☐ 2–3× from baseline (non-oliguric in 50%) - **Urine output:** Usually maintained (non-oliguric ATN favorable prognosis) - **Urinalysis:** Muddy brown granular casts, epithelial cells (classic but non-specific) - **Monitoring:** Cr rise gradual; may continue for 1–3 days post-cessation (drug still in cells)

Management

1. **Discontinue aminoglycoside** immediately if possible
2. **Hydration:** Normal saline to optimize renal perfusion (if not volume-overloaded)
3. **Avoid nephrotoxins:** NSAIDs, contrast agents, other aminoglycosides
4. **Nephrology referral** if Cr rise >0.5 mg/dL/day or eGFR <15
5. **Renal replacement therapy** if oliguria, hyperkalemia, or fluid overload
6. **Monitoring:** Daily Cr, K☐, phosphate; manage complications (hyperkalemia, metabolic acidosis)

Recovery

- **Most recover Cr within 7–14 days** post-cessation
- **Permanent renal loss** if late recognition; 5–10% may have ☐ eGFR baseline

Prevention

- **Single daily dosing** preferred (once daily gentamicin 5–7 mg/kg ideal; ☐ ATN risk vs. q8h)
- **Therapeutic drug monitoring:** Trough levels <1 μg/mL (gentamicin) for efficacy/safety
- **Hydration:** Pre-infusion hydration; maintain urine output
- **Limit duration:** <7 days if possible; reserve for severe infections
- **Monitor Cr baseline, day 3, day 7** of therapy

Acute Interstitial Nephritis (AIN)

Overview **AIN:** Acute inflammation of renal tubules and interstitium with minimal/no glomerular involvement. **Drug-induced AIN represents 10–15% of AKI in hospitalized patients.**

Pathophysiology **Mechanism varies by drug:** 1. **Immune-mediated (most common):** - Drug acts as hapten (binds tubular protein) - Generates T-cell and B-cell response - Infiltration of CD8+ T cells, macrophages into interstitium - Example: β-lactam antibiotics, NSAIDs, PPIs

2. **Toxic metabolite:**
    - Direct tubular toxicity from drug metabolite

- Example: Acyclovir (crystalline AIN), TMP-SMX (crystal-induced)

Clinical Presentation **Classic Triad (50% have all three):** 1. **Fever** (20–30%; non-specific) 2. **Rash** (5–20%; maculopapular; often urticarial) 3. **Arthralgias/arthritis** (less common than fever/rash)

Renal manifestations: - **AKI:** Often abrupt Cr rise (50–100% ☐ in days); non-oliguric in 70% - **Urinalysis:** Sterile pyuria (pyuria without bacteria), hematuria, WBC casts, eosinophils - **Absence of eosinophiluria does NOT exclude AIN** (only present in 50%)

Common Causative Drugs

Drug Class	Specific Agents	Typical Onset	% AIN Risk
Antibiotics	β-lactams (penicillin, cephalosporin), aminoglycosides, TMP-SMX, fluoroquinolones	3–14 days (or immediate if prior exposure)	1–5%
NSAIDs	Ibuprofen, naproxen, indomethacin, meloxicam	Days–weeks	1–2%
PPIs	Omeprazole, pantoprazole, lansoprazole	Weeks–months (later than other drugs)	1–2% (☐ with chronic use)
Diuretics	Thiazides, loop diuretics	Days–weeks	<1%
Anticonvulsants	Phenytoin, carbamazepine, phenobarbital	Weeks–months	Rare (<0.5%)
Immunosuppressants	Interferon-α, immunoglobulin	Weeks	Rare
Antifungals	Amphotericin B (ATN or AIN mixed)	Days–weeks	5–10%
ACEi/ARB	Less common than NSAIDs, but reported	Weeks	<0.5% (if at all)

Diagnosis **Clinical suspicion key:** Recent medication change + fever, rash, AKI + sterile pyuria

Confirmation: - **Kidney biopsy:** Gold standard (rarely needed if clinical presentation classic) - **Histology:** Interstitial infiltration of lymphocytes, plasma cells, eosinophils; tubulitis (lymphocyte invasion of tubular epithelium); glomeruli typically spared - **Immunofluorescence:** Negative (distinguishes from anti-GBM, lupus, ANCA)

Biomarkers (research only): - **Urine eosinophils:** >5 eosinophils per high-power field suggests AIN but low sensitivity/specificity - **Urinary β2-microglobulin:** Marker of tubular injury; not diagnostic

Management

1. **Discontinue offending drug immediately** (foundation of therapy)
2. **Supportive care:** Hydration if prerenal component; avoid nephrotoxins
3. **Corticosteroids:** Controversial; consider if:
    - Delayed recovery (Cr not trending down after 3–5 days off drug)
    - Severe renal dysfunction (eGFR <30)
    - Systemic symptoms (fever, rash)
    - **Dosing:** Prednisolone 1 mg/kg/day (max 60 mg) × 1–2 weeks, then taper over 2–4 weeks
    - **Evidence:** Limited; some observational studies suggest faster recovery if corticosteroids given early
    - **Randomized data sparse:** iPIKACY trial (ongoing) evaluating corticosteroids in AIN
4. **Renal replacement therapy** if oliguric, hyperkalemic, volume-overloaded

Recovery

- **Most recover within 7–14 days** of drug cessation
- **Complete renal recovery:** 80–90% achieve baseline Cr
- **Residual renal dysfunction:** 10–20% have ☐ baseline eGFR (suggests chronic TIN component)

Prevention

- **Drug allergy documentation:** If AIN suspected, document allergy to drug class
- **Caution with re-exposure:** Even after years, re-exposure may trigger AIN quickly
- **Alternative agents:** Use unrelated drug if future infection requires antibiotics

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Crystalline Nephropathy

Acyclovir-Induced Crystalline Nephropathy **Mechanism:** Acyclovir (especially IV, high-dose) crystallizes in tubular lumen ☐ obstructive AKI + AIN.

Incidence: 1–5% IV acyclovir; rare with oral

Risk factors: - **High-dose IV:** >500 mg/m² q8h (HSV encephalitis, VZV) - **Rapid infusion:** <1 hour (☐ renal concentration) - **Volume depletion:** ☐ Urine flow ☐ crystal precipitation - **eGFR <60:** ☐ clearance - **Age >60:** Reduced renal reserve

Clinical presentation: - **AKI:** Rapid onset (hours–days); oliguric possible - **Urine:** Needle-shaped crystals (acyclovir monohydrate) on microscopy

Management: 1. **Discontinue acyclovir** or reduce dose 2. **Aggressive hydration:** Normal saline IV to ☐ urine flow (☐ crystal concentration) 3. **Maintain urine pH >6:** Alkaline urine ☐ acyclovir solubility 4. **Monitor Cr, K☐:** Daily during acute phase 5. **Renal replacement therapy** if severe AKI with complications 6. **Recovery:** 7–10 days post-cessation in most; permanent loss if delayed recognition

Methotrexate-Induced Crystalline Nephropathy Mechanism: Methotrexate and metabolites (7-OH-methotrexate) precipitate in tubules ☐ crystal-induced AKI.

Incidence: 2–5% high-dose MTX (cancer treatment); rare with low-dose (rheumatologic)

Risk factors: - **High-dose MTX:** >1 g/m² (cancer therapy) - **Volume depletion** - **Acidic urine:** pH <5.5 (☐ MTX solubility) - **eGFR <60**

Prevention (crucial for high-dose MTX): 1. **Aggressive hydration:** 3–4 L/day with alkaline saline pre- and post-MTX 2. **Alkaline urine:** Sodium bicarbonate to maintain urine pH >6.5 (☐ solubility) 3. **Leucovorin (folinic acid) rescue:** Reduces MTX toxicity 4. **Monitoring:** Baseline Cr; recheck at day 1–2 post-MTX

NSAIDs and Contrast: Hemodynamic Acute Kidney Injury

NSAIDs: Renal Hemodynamic Effects Mechanism: NSAIDs inhibit prostaglandin synthesis (COX-1, COX-2) ☐ loss of afferent arteriolar vasodilation ☐ ☐ GFR

Particularly risky in: - **Chronic kidney disease** (eGFR <45) - **Congestive heart failure** (dehydration risk) - **Hepatic cirrhosis** (altered renal autoregulation) - **Acute volume depletion** (dehydration, diarrhea, diuretic use)

Clinical presentation: - **Acute Cr rise:** Often 1–3 days post-NSAID - **Oliguria possible** but often non-oliguric - **FeNa typically <1%** (prerenal pattern) but ☐ tubular dysfunction possible - **Urinalysis:** Usually bland (no casts, cells, or protein)

Management: 1. **Discontinue NSAID** immediately 2. **Hydration:** IV saline if dehydrated 3. **Monitor Cr:** Usually recovers in 3–7 days post-discontinuation 4. **Renal replacement therapy** if severe AKI with complications

Contrast-Associated Acute Kidney Injury (CA-AKI) Modern understanding: Risk lower than previously believed; contrast osmolality, hydration status more important than contrast agent choice.

Mechanism: 1. **Direct tubular toxicity:** Contrast renal accumulation; ROS generation 2. **Renal hemodynamic:** Transient vasoconstriction ☐ ☐ renal perfusion 3. **Viscosity:** High osmolality ☐ blood viscosity ☐ ☐ renal perfusion

Incidence: - **Baseline eGFR >60:** <1% risk - **Baseline eGFR 30–60:** 5–10% risk - **Baseline eGFR <30:** 15–25% risk (especially if diabetes) - **ESRD (not on dialysis):** 25–50% risk

Risk factors for CA-AKI: - **eGFR <30** (strongest predictor) - **Diabetes mellitus** (☐ risk 3–5×) - **Dehydration** (major preventable factor) - **Proteinuria** (marker of worse outcomes) - **Acute illness** (sepsis, heart failure) - **Age >70 years** - **Heart failure** (ejection fraction <40%) - **High contrast volume** (>5 mL/kg iodine load)

Prevention of Contrast-Associated AKI (Updated 2023)

Pre-contrast: 1. **Assess renal function:** Baseline Cr, eGFR (ideally <2 weeks before contrast) 2. **Hydration:** IV isotonic saline 500 mL over 4 hours pre-contrast, then 4 hours post-contrast (if eGFR <60) - **Timing:** Begin 4 hours before procedure - **Optimal IV fluid:** 0.9% NaCl (or sodium

bicarbonate 150 mEq/L if available, though superiority debated) 3. **Hold ACEi/ARB:** Consider holding 24 hours pre-contrast (if eGFR <30 or acute illness; controversial) 4. **Hold metformin:** Discontinue day of contrast; restart after 48 hours if Cr unchanged 5. **Hold NSAIDs:** Discontinue 48 hours before through 48 hours after contrast 6. **Contrast volume:** Minimize; limit to <5 mL/kg iodine content

Contrast choice: - **Low-osmolar (LOCM):** 600–850 mOsm/kg (iopamidol, iohexol) - **Iso-osmolar (IOCM):** 290 mOsm/kg (osmolality = plasma) - **Meta-analysis finding:** NO significant difference in CA-AKI between LOCM and IOCM - **Recommendation:** Any LOCM acceptable; cost/availability-driven choice reasonable

Post-contrast: 1. **Hydration:** Continue IV fluids (500 mL over 4 hours post-procedure if eGFR <60) 2. **Renal function monitoring:** Recheck Cr at 48–72 hours; peak AKI often at day 2–3 3. **Resume ACEi/ARB:** 24 hours post-contrast if stable Cr

Special populations: - **ESRD on hemodialysis:** Dialysis within 36 hours post-contrast (removes contrast iodine) - **Peritoneal dialysis:** Less urgent; monitor closely - **Severe renal failure (eGFR <15):** Consider alternative imaging (MRI without gadolinium if possible)

When NOT to use contrast: - Acute kidney injury of uncertain etiology - Hemodynamic instability - Sepsis (defer if non-emergent) - Severe dehydration (rehydrate first)

CHRONIC TUBULOINTERSTITIAL NEPHRITIS (TIN)

Analgesic Nephropathy

Epidemiology and Historical Context **Incidence:** Rare in modern era (☐ chronic NSAID use) but still significant cause of ESRD globally (2–3% of dialysis patients in some regions).

Classic patient: Women age 50–70 with history of decades-long daily analgesic use (paracetamol, aspirin, ibuprofen combinations); more common historically before NSAID restrictions.

Mechanism **Proposed pathway:** 1. **NSAID/aspirin accumulation** in renal papilla (high local concentration) 2. **Conversion** to reactive metabolites (e.g., N-acetylbenzoquinone imine from acetaminophen) 3. **Direct papillary toxicity:** Mitochondrial oxidative stress ☐ papillary necrosis 4. **Chronic inflammation** ☐ TIN, fibrosis, atrophy

Critical distinction: Acute NSAID-induced AKI is usually reversible; chronic analgesic nephropathy = cumulative, progressive, often irreversible.

Clinical Presentation **Features:** - **Slowly progressive renal insufficiency:** ☐ Cr over years (often subtle initial decline) - **Non-obstructive renal failure:** Normal renal ultrasound; creatinine progressive despite normal urinalysis initially - **Recurrent UTIs:** Often lower UTI symptoms (dysuria, frequency) with negative cultures - **Hematuria:** Microscopic or gross (from papillary sloughing) - **Anemia:** ☐ Hgb proportional to renal dysfunction - **Hypertension:** Common, often mild - **Urinary findings:** Minimal proteinuria, mild pyuria/hematuria

Diagnosis **Imaging (CT with contrast—caution if eGFR <30):** - **Classic finding:** "Bumpy contour" of renal outline (papillary degeneration) - **"Ring sign":** Contrast-enhanced

ring sign (calcification in areas of papillary necrosis) - **Papillary blunting/flattening** - **Generalized cortical thinning** (chronic atrophy) - **Renal papilla sloughing** (may be seen as filling defect in pelvis on IVP—seldom done now)

Biopsy (rarely needed): - **Histology:** Chronic TIN, tubular atrophy, interstitial fibrosis; papillary necrosis (if sampled) - **No glomerular disease** (distinguishes from glomerulonephritis)

Diagnostic algorithm: 1. **History of chronic analgesic use** (often understated by patients—ask directly) 2. **Imaging findings** (CT "bumpy kidney," ring sign) 3. **Urinalysis: minimal proteinuria** (usually <1 g/day; heavy proteinuria suggests glomerular disease) 4. **Exclusion of other causes:** Normal immunology, no glomerular IgA/IgM deposits on biopsy

Management

1. **Discontinue all NSAIDs and aspirin** immediately
2. **Treat hypertension:** ACEi/ARB preferred (renal protection)
3. **Monitor renal function:** Slow Cr decline expected but may stabilize off NSAIDs
4. **Manage UTIs:** Culture-directed antibiotics; prophylaxis if recurrent (though culture-negative dysuria often unresponsive to antibiotics)
5. **Screen for urothelial malignancy:** Analgesic nephropathy ☐ risk of renal cell carcinoma and urothelial cancer (TCC)
    - **Annual urine cytology** if feasible
    - **Annual renal ultrasound** or CT
    - **Low threshold for hematuria evaluation**
6. **Renal replacement therapy:** As needed when ESRD reached

Prognosis

- **CKD progression:** Variable; some stabilize, others progress to ESRD
- **Malignancy:** 1–5% develop renal cell carcinoma or urothelial malignancy (cumulative risk over decades)
- **Outcomes post-discontinuation:** Renal function rarely improves dramatically; primary goal = halt progression

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Lithium Nephropathy

Epidemiology Use: Lithium carbonate for bipolar disorder maintenance (decades of use in stable patients)

Prevalence: 20–40% of long-term lithium users have eGFR <60; ~7% progress to ESRD

Mechanisms of Lithium Nephrotoxicity 1. Nephrogenic Diabetes Insipidus (NDI)—Early/Reversible: - **Mechanism:** Lithium accumulation in collecting duct principal cells ☐ inhibits vasopressin (V2) receptor signaling ☐ ☐ aquaporin-2 water channel expression - **Result:** Polyuric state (6–12 L/day); polydipsia compensation - **Timeline:** Develops within weeks–months of initiation - **Reversibility:** 50% improve with lithium discontinuation; partial improvement common

2. Chronic Kidney Disease—Late/Progressive: - **Mechanism:** Chronic lithium exposure ☐ interstitial fibrosis, tubular atrophy, glomerulosclerosis - **Histology:** TIN with cystic dilation of distal tubules; possible glomerular changes - **Timeline:** Develops over years of chronic therapy - **Reversibility:** Often irreversible (progressive even after discontinuation)

Clinical Presentation **Early phase (months):** - **Polyuria:** 6–10 L/day (vs. normal 1–2 L/day) - **Polydipsia:** Compensatory increased fluid intake - **Urine specific gravity:** Low (<1.010; normally 1.010–1.030) - **Renal function:** Usually normal Cr initially

Late phase (years): - **CKD progression:** ☐ Cr over years despite normal urine output (drinking enough to maintain urine output) - **Hypertension:** Often develops - **Hyperparathyroidism:** Lithium ☐ PTH secretion; additive to CKD mineral bone disease - **Hematuria:** Possible (from cyst hemorrhage)

Diagnosis **Clinical context key:** - **History:** Years of lithium use for bipolar disorder - **NDI:** Polyuria + low urine SG + normal Cr = early lithium effect - **CKD:** ☐ Cr + polyuria (or inability to concentrate urine) = chronic lithium nephropathy

Imaging: - **Ultrasound:** Microcysts in medulla/papilla (classic but not pathognomonic) - **CT:** Cystic changes in renal medulla

Biopsy (rarely needed): - **Histology:** TIN, tubular atrophy, cysts in medulla

Laboratory: - **Serum lithium level:** Therapeutic 0.6–1.2 mmol/L; levels >1.5 ☐ ☐ toxicity risk - **Urine osmolality:** Low (osmotic diuresis pattern; unable to concentrate) - **Serum sodium:** May be high (dehydration from polyuria)

Management **1. Lithium dose optimization:** - **Maintain lowest effective therapeutic level** (0.6–0.8 mmol/L vs. 1.0–1.2) - **Once-daily dosing:** More stable levels; ☐ peak toxicity than BID dosing - **Therapeutic drug monitoring:** Baseline, then every 3–6 months

2. Nephrology referral: - **eGFR <60 or Cr rise:** Consider alternative mood stabilizer (valproic acid, lamotrigine, atypical antipsychotics) - **NDI without renal dysfunction:** Continue lithium (renal function usually preserved) - **Progressive CKD:** Strongly consider discontinuation if alternatives available

3. Renal protective measures: - **ACEi/ARB:** If hypertensive or CKD (standard CKD management) - **Hydration:** Encourage adequate fluid intake (prevent dehydration-induced Cr rise) - **NSAIDs:** Absolutely avoid (synergistic nephrotoxicity) - **Thiazide diuretics:** Avoid (☐ lithium reabsorption ☐ toxicity) - **Monitor renal function:** Baseline Cr, then annually if stable; more frequently if CKD present

4. Management of NDI: - **Thiazide diuretics:** Paradoxically ☐ polyuria (mechanism: mild volume depletion ☐ ☐ proximal reabsorption) - **NSAIDs:** ☐ Polyuria (block prostaglandin; ☐ solute-free water clearance) but caution with renal dysfunction - **Low sodium diet:** ☐ Urine output (decrease solute load) - **Amiloride:** Specific K☐-sparing diuretic blocking lithium entry into collecting duct cells; potent NDI treatment (5 mg BID; monitor K☐)

5. Phosphate binders and PTH management: - **Hyperparathyroidism:** Lithium directly stimulates PTH secretion - **Monitor:** Baseline PTH, Ca^{2}☐; then annually - **Treat:** Aggressive

CKD mineral bone disease management (phosphate binders, active vitamin D, calcimimetic if indicated)

Prognosis

- **NDI:** 50% reversible on discontinuation; degree of reversal variable
- **Progressive CKD:** Often continues despite lithium discontinuation (cumulative injury)
- **ESRD:** 5–10% of chronic lithium users progress to dialysis-dependent ESRD

HEAVY METAL NEPHROPATHY

Lead Nephropathy

Exposure Sources

- **Occupational:** Battery manufacturing, smelting, welding, lead-based paint (now restricted in US)
- **Environmental:** Contaminated water supplies (Flint, MI example); soil in older urban areas
- **Recreational:** Ammunition, lead-containing glassware (occasional exposures)

Mechanism **Lead bioaccumulation in kidneys:** 1. **Tubular reabsorption:** Lead binds tubular protein ☐ intracellular accumulation 2. **Proximal tubule effects:** ☐ Na☐-glucose cotransport ☐ Fanconi syndrome (rare) 3. **Chronic effect:** TIN, fibrosis, glomerulosclerosis (unclear mechanism)

Clinical Presentation **Acute lead poisoning (rare in chronic exposure):** - **Abdominal colic:** Severe pain (classic "saturnine colic") - **Neuropathy:** Wrist drop (motor nerve affected); sensory less common - **Encephalopathy:** Confusion, headache (severe poisoning)

Chronic lead nephropathy (more common in modern era): - **Slowly progressive CKD:** ☐ Cr over years from occupational/environmental exposure - **Hypertension:** Common; often ☐ BP before renal dysfunction evident - **Gout:** Lead impairs uric acid excretion ☐ hyperuricemia ☐ gout (classic finding in lead exposure) - **Urinalysis:** Usually normal (minimal proteinuria, no hematuria) - **Absence of systemic signs** (differs from acute poisoning)

Diagnosis **Blood lead level (BLL):** - **Normal:** <10 μg/dL (CDC 2021 recommendation for safety threshold) - **Occupational exposure:** 10–50+ μg/dL (OSHA permissible 50 μg/dL but toxicity occurs <50) - **Historical context:** Many with CKD + lead exposure have BLL measured decades ago (not current) - **Note:** BLL reflects recent exposure; bone lead (x-ray fluorescence) reflects cumulative burden (not routinely available)

Diagnosis approach: 1. **Occupational/environmental history:** Direct question about lead exposure 2. **Clinical clue:** Hypertension + gout + slowly progressive CKD + normal urinalysis 3. **BLL measurement:** If history suggestive 4. **Urine lead:** Less useful; not standardized 5. **Biopsy (rarely performed):** Shows TIN; no specific lead-induced pattern

Management

1. **Lead exposure elimination:** Occupational exposure abatement; home water lead testing/remediation
2. **Renal protective therapy:** ACEi/ARB (standard CKD management); especially important if hypertensive
3. **Gout management:** Allopurinol or febuxostat for uric acid control
4. **Renal function monitoring:** Baseline Cr, then annually; more frequent if CKD present
5. **Chelation therapy:** Controversial in chronic low-level exposure
    - **Not recommended** for asymptomatic chronic exposure (limited evidence for benefit; toxicity risk of chelating agents)
    - **Reserved for:** Acute poisoning or severe symptomatic toxicity (neuropathy, encephalopathy)
    - **Agent:** Dimercaprol (BAL), EDTA, or DMSA (succimer)

Cadmium Nephropathy

Exposure

- **Occupational:** Nickel-cadmium batteries, plating, soldering, welding
- **Environmental:** Tobacco smoke, contaminated foods
- **Consumer products:** Some paints, pigments

Mechanism **Cadmium accumulation:** - **Absorption:** GI (dietary) > pulmonary (occupational) - **Renal handling:** Glomerular filtration followed by **tubular reabsorption** - **Intracellular binding:** Metallothionein-cadmium complex - **Chronic toxicity:** Tubular damage, proteinuria (low molecular weight), TIN

Clinical Presentation **Acute exposure (rare):** - **GI symptoms:** Nausea, vomiting, diarrhea - **Respiratory:** Dyspnea, wheezing (if inhaled)

Chronic exposure: - **Early:** Low molecular weight proteinuria (β_2-microglobulin, lysozyme) without ☐ Cr - **Late:** Progressive proteinuria, ☐ Cr, CKD - **Associated findings:** Bone disease (Cd also affects calcium metabolism; osteomalacia, osteoporosis); renal stones possible - **"Itai-itai disease":** Historical endemic poisoning in Japan (Cd-contaminated rice); severe bone disease + renal dysfunction

Diagnosis **Urine cadmium:** - **24-hr urine Cd** or spot urine Cd/Cr ratio - **Threshold for concern:** >5 μg/L or >5 μg/g Cr - **Interpretation:** Reflects recent exposure (days–weeks)

Chelation challenge test (research only): - Not recommended for clinical diagnosis

Management

1. **Exposure elimination:** Occupational abatement
2. **Renal protection:** ACEi/ARB (standard CKD therapy)
3. **Calcium/vitamin D supplementation:** If bone disease present
4. **Monitoring:** Cr, Alb/protein, bone health annually

5. **Chelation:** Not recommended for chronic asymptomatic exposure

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HERBAL AND ENVIRONMENTAL NEPHROPATHY

Aristolochic Acid Nephropathy (AAN)

Epidemiology and Exposure **Source:** Traditional Chinese medicines (TCM) containing Aristolochia species

History: - **Discovered:** 1990s (Belgium) — 100+ patients with rapidly progressive CKD; retrospective link to Aristolochia-containing weight-loss herbs - **Mechanism revealed:** Aristolochic acid (AA) — direct DNA carcinogen - **Global prevalence:** Taiwan, Balkans (historically); now rare in regions with product restrictions

Mechanism **Aristolochic acid (AA) toxicity:** 1. **Metabolic activation:** Hepatic N-acetylation of AA ☐ reactive intermediate 2. **DNA binding:** Covalent AA-DNA adducts ☐ mutations 3. **Tubular toxicity:** Proximal tubule apoptosis ☐ necrosis 4. **Uroepithelial mutagenesis:** ☐ Risk urothelial carcinoma (urothelial cancer, upper urinary tract) 5. **Inflammation:** TIN development

Clinical Presentation **Typically rapid, severe progression:** - **CKD development:** Months to a few years of exposure (faster than most toxic nephropathies) - **Proteinuria:** Usually <1 g/day (tubular pattern) - **Anemia:** Often severe; disproportionate to renal dysfunction - **Risk of ESRD:** ~50% progress to ESRD within 3–5 years of diagnosis - **Urothelial cancer:** 10–20% develop TCC (ureter, bladder, rarely renal pelvis)

Diagnosis **Clinical clues:** - **History of TCM use** (specifically weight-loss supplements or unexplained TCM exposure) - **Rapidly progressive CKD** out of proportion to UA findings - **Severe anemia** relative to GFR decline - **Normal immunology, UA bland** (excludes glomerulonephritis)

Imaging: - **CT/ultrasound:** Renal atrophy, normal size to slightly small kidneys - **Upper tract imaging (IVP, CT urography):** Screen for urothelial malignancy

Biopsy (if performed): - **Histology:** TIN, tubular atrophy, interstitial fibrosis - **No glomerular disease**

AA-DNA adduct testing: Research only; not clinically available in most centers

Management

1. **Discontinue TCM containing Aristolochia** immediately
2. **Monitor renal function closely:** Monthly Cr initially; progression may continue despite cessation (cumulative injury)
3. **ACEi/ARB therapy:** Renal protection (standard CKD management)
4. **Urothelial surveillance:** Critical
    - **Baseline imaging:** CT/ultrasound + CT urography or IVP (evaluate upper urinary tract)

- **Annual follow-up:** Imaging + urine cytology for malignancy screening
- **Low threshold for hematuria investigation:** Any hematuria ☐ imaging
- **Note:** Upper urothelial cancers (ureter, renal pelvis) more common than bladder; require aggressive surveillance

5. **Renal replacement therapy:** As needed

Prognosis

- **Progressive:** Most progress to ESRD within 3–5 years
- **Malignancy:** Annual risk ~1–2% TCC; cumulative 10–20% lifetime
- **Monitoring:** Long-term surveillance even on dialysis (malignancy risk persists)

Environmental and Occupational Nephropathy

Silica-Associated Nephropathy **Exposure:** Mining, sandblasting, foundry work, stonemasonery

Mechanism: Chronic inhalation ☐ silica accumulation ☐ immune complex deposition (mimics glomerulonephritis); TIN also reported

Clinical: Slowly progressive CKD; proteinuria variable

Diagnosis: Occupational history + imaging/biopsy findings; serology often positive (ANA, ANCA) mimicking autoimmune disease

Management: Occupational cessation; standard CKD therapy

Asbestos-Associated Nephropathy **Exposure:** Insulation, construction trades

Mechanism: Chronic inflammation; uncertain exact pathway

Clinical: Slowly progressive CKD; asbestos typically affects lungs (more clinically significant than kidney)

Management: Occupational cessation; lung health monitoring

CONTRAST-INDUCED ACUTE KIDNEY INJURY: Detailed Prevention and Management

Updated Evidence (2023)

Key shift in understanding: CA-AKI less common/severe than previously believed when proper hydration given. Osmolality < 2023 recommendations suggest low-osmolar contrast adequate for nearly all patients.

Pre-Procedure Considerations

Step 1: Risk Stratification

Risk Category	eGFR	Other Factors	Risk CA-AKI
Low	>60	None	<1%
Moderate	45–60	± Diabetes, ± HTN	2–5%
High	30–45	± Diabetes, ± CHF, ± proteinuria	10–20%
Very high	<30	Diabetes, CHF, or proteinuria	25–50%

Step 2: Pre-contrast Labs - **eGFR calculated:** Contrast volume should not exceed 5 mL/kg of lean body weight (iodine content) - **Baseline Cr:** To assess post-procedure AKI (rise >0.3 mg/dL or >25% significant)

Step 3: Medication Adjustments - **Metformin:** Discontinue day of contrast; restart 48 hours if Cr unchanged (risk of lactic acidosis if AKI develops) - **NSAIDs:** Hold 48 hours before through 48 hours after - **ACEi/ARB:** Controversial; traditionally held but recent data suggest okay to continue (especially in euvolemic patients); consider holding if eGFR <30 + acute illness - **Diuretics:** Hold day before through day after (maintain intravascular volume)

Hydration Protocol

Isotonic crystalloid (0.9% NaCl or sodium bicarbonate 150 mEq/L): - **Pre-procedure:** 500 mL IV bolus over 4 hours (if eGFR <60) beginning 4 hours pre-contrast - **Post-procedure:** 500 mL IV over 4 hours post-contrast (if eGFR <60) - **Goal:** Maintain urine output 150–300 mL/hr - **Alternative for outpatients:** Oral hydration 500 mL PO fluids (water, juice) 4 hours pre and 4 hours post acceptable if euvolemic and able to drink

Special situations: - **Acute decompensated HF or severe pulmonary edema:** IV hydration risky; assess volume status carefully; consider renography/CT without contrast if possible - **ESRD on dialysis:** Not urgent; consider dialysis within 36 hours post-contrast (removes iodine)

Contrast Agent Selection

Bottom line: LOCM (low-osmolar) acceptable for all; IOCM (iso-osmolar) NOT superior

- **Low-osmolar contrast media (LOCM):** Osmolality 600–850 mOsm/kg
  - Examples: Iopamidol, iohexol, ioversol
  - Cost: Moderate
- **Iso-osmolar contrast media (IOCM):** Osmolality 290 mOsm/kg (same as plasma)
  - Example: Visipaque (osmolar contrast agent)
  - Cost: Higher
  - Superiority: NOT demonstrated in RCTs (PRESERVE trial 2018; IOCM no better than LOCM)
- **High-osmolar contrast media (HOCM):** Osmolality >1500 mOsm/kg
  - Avoid (☐ CA-AKI risk) except rare cases where already iodine-allergic and need osmolar alternative

Contrast volume limit: <5 mL/kg iodine content - **Example:** 70 kg patient ☐ max 350 mL contrast (if 100 mg I/mL concentration)

Post-Procedure Monitoring

1. **Renal function:** Recheck Cr at 48–72 hours
2. **Peak AKI:** Usually day 2–3 post-contrast; may see delayed rise
3. **Definition of CA-AKI:** ☐ Cr >0.3 mg/dL or >25% from baseline within 48–72 hours
4. **Expected outcome:** Most CA-AKI non-oliguric, self-limited (recover within 1 week)

Clinical Scenarios

Scenario 1: NSAIDs + ACEi + Diuretic (Triple Whammy) in CKD

Clinical: 68-year-old male with CKD Stage 3b (eGFR 35), hypertension (on lisinopril 10 mg daily), osteoarthritis (taking ibuprofen 600 mg TID × 3 weeks for knee pain), on furosemide 20 mg daily for hypertension. Presents with Cr 1.8 (baseline 1.5), K☐ 5.8 mmol/L, mild oliguria.

Diagnosis: Triple whammy AKI

Plan: 1. **STOP ibuprofen immediately** 2. **Hold furosemide** (assess volume status; likely volume-depleted) 3. **Hold lisinopril** temporarily (24–48 hours; reassess if Cr continues rising) 4. **Hydration:** IV normal saline 500 mL over 2–4 hours if not volume-overloaded 5. **Monitor:** Daily Cr, K☐, UO 6. **Expected recovery:** Cr should trend down in 3–7 days post-cessation 7. **Alternative for pain:** Acetaminophen 650 mg q6h; topical NSAIDs (minimal systemic absorption) 8. **Prevention:** Counsel on NSAID danger in CKD; restart lisinopril once Cr stable

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Scenario 2: Contrast Study in High-Risk Patient

Clinical: 62-year-old diabetic female with CKD Stage 4 (eGFR 22), hypertension, referred for coronary angiography (ACS concern).

Pre-procedure assessment: - **Cr:** 2.6 mg/dL (eGFR 22) - **Weight:** 80 kg ☐ max contrast volume 400 mL (5 mL/kg) - **Expected procedure:** Likely 100–150 mL contrast (high but may be necessary for angiography)

Protocol: 1. **Hold metformin** day of procedure; restart 48 hours if Cr unchanged 2. **Hold NSAIDs** 48 hours before and 48 hours after 3. **Continue ACEi/ARB** (in euvolemic patient; some still recommend holding if eGFR <30, but emerging data support continuation) 4. **IV hydration:** 500 mL 0.9% NaCl or sodium bicarbonate 150 mEq/L starting 4 hours pre-procedure, continuing 4 hours post-procedure 5. **Contrast choice:** Low-osmolar (iopamidol or iohexol); IOCM not superior but acceptable if available 6. **Post-procedure:** Recheck Cr 48–72 hours (peak AKI timing) 7. **Expectation:** 10–20% risk CA-AKI; most non-oliguric if develops; usually recovers

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Scenario 3: Lithium Nephropathy with Progression

Clinical: 55-year-old female with bipolar disorder on lithium 900 mg daily × 25 years. Recent labs: Cr 1.6 (baseline 0.9 two years ago), eGFR 42 (was 55 two years ago), K☐ 4.2, polyuria (8 L/day documented), serum lithium level 0.9 mmol/L (therapeutic).

Assessment: Chronic lithium nephropathy with progressive CKD + NDI

Plan: 1. **Discuss lithium discontinuation** with psychiatrist and patient - **Options:** Valproic acid, lamotrigine, quetiapine (alternative mood stabilizers) - **Rationale:** eGFR 42 with active decline; further Cr rise expected with continued lithium 2. **If continue lithium (patient resistant to D/C):** - **Reduce dose:** Target lower therapeutic level (0.6–0.8 mmol/L vs. current 0.9) - **Monitor:** Cr every 3 months; more frequent if further decline - **ACEi/ARB:** Optimize dose for renal protection - **NSAIDs:** Absolutely contraindicated - **Amiloride:** 5 mg BID for NDI management (□ polyuria; monitor K□) 3. **Monitor bone health:** Screen PTH, Ca^{2}□; treat if hyperparathyroidism present (lithium-induced) 4. **Expect:** Continued slow CKD progression; goal is to slow rather than reverse

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Practice Questions

Question 1

A 54-year-old male with CKD Stage 3a (eGFR 52) presents with acute kidney injury (Cr 2.2, baseline 1.2 from 5 days ago). History includes recent urinary tract infection treated with trimethoprim-sulfamethoxazole (TMP-SMX); he also developed fever (101.5°F), maculopapular rash on trunk, and joint pain during treatment. Urinalysis shows sterile pyuria, WBC casts, 2+ proteinuria, and eosinophils. Which diagnosis is MOST likely?

A) Acute tubular necrosis (ATN) from TMP-SMX
B) Acute interstitial nephritis (AIN) from TMP-SMX
C) ANCA-associated vasculitis
D) Lupus nephritis
E) Contrast-associated AKI

Answer: B (AIN from TMP-SMX)

Rationale: - **Classic AIN presentation:** Fever, rash, arthralgias ("allergic triad"; though all three only in 50%) - **Rapid AKI:** Cr rise 50–100% over days - **Urinalysis findings:** Sterile pyuria (KEY finding in AIN; no bacteria), WBC casts, eosinophils (present in 50% AIN) - **TMP-SMX:** Common AIN culprit (β-lactams, NSAIDs, PPIs, fluoroquinolones also common) - **Timing:** 3–14 days after drug initiation typical for immune-mediated AIN - **Management:** STOP TMP-SMX; consider corticosteroids if delayed recovery - ATN would have muddy brown casts, not eosinophils; no systemic symptoms (fever/rash) - Vasculitis would have active urinary sediment (RBCs, RBC casts), proteinuria often >1 g/day - Lupus would have ANA positive, complement low

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Question 2

A 71-year-old female with CKD Stage 4 (eGFR 26), diabetes, and history of decades-long daily analgesic use (aspirin + ibuprofen combination) presents with slowly progressive Cr rise (0.8 to 2.4 over 5 years), recurrent dysuria with negative urine cultures, and microscopic hematuria. Renal ultrasound shows "bumpy kidney outline" and possible ring sign. Which is the MOST likely diagnosis?

A) Diabetic nephropathy

B) IgA nephropathy
C) Analgesic nephropathy
D) Lithium nephropathy
E) Renovascular disease

Answer: C (analgesic nephropathy)

Rationale: - **Key history:** Decades of chronic NSAID/analgesic use - **Clinical triad:** Progressive CKD + recurrent UTI symptoms (dysuria) with sterile cultures + hematuria = classic analgesic nephropathy - **Imaging findings:** "Bumpy kidney" (papillary degeneration) + ring sign (calcification in papillary necrosis areas) = pathognomonic for analgesic nephropathy - **Urinalysis pattern:** Minimal proteinuria (usually <1 g/day; rules out diabetic or IgA nephropathy as primary cause) - **Biopsy would show:** Chronic TIN, papillary necrosis (if sampled), no glomerular disease - **Management:** STOP NSAIDs; screen for urothelial malignancy (10–20% develop TCC) - Diabetic nephropathy would have heavy proteinuria and retinopathy - IgA nephropathy would have active urinary sediment and biopsy-proven IgA deposits - Lithium would have polyuria and NDI findings - Renovascular disease would have renal artery stenosis on imaging

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Question 3

A 65-year-old male with eGFR 38 and diabetes is scheduled for elective coronary angiography for stable angina. His medications include metformin 500 mg BID, lisinopril 20 mg daily, ibuprofen 400 mg daily for osteoarthritis pain, and furosemide 20 mg daily. Which of the following represents the MOST appropriate pre-procedure management?

A) Continue all medications; hydrate with normal saline IV pre- and post-procedure
B) Hold metformin and NSAIDs; continue others; hydrate with normal saline IV
C) Hold all medications except lisinopril; hydrate with sodium bicarbonate IV
D) Hold NSAIDs and furosemide; continue others; moderate PO hydration acceptable
E) Continue all medications with aggressive IV hydration; use iso-osmolar contrast

Answer: B (hold metformin + NSAIDs; continue ACEi; IV saline hydration)

Rationale: - **Metformin**: Must hold (risk of lactic acidosis if CA-AKI develops); restart 48 hrs if Cr stable - **NSAIDs**: Hold 48 hrs before through 48 hrs after (synergistic nephrotoxicity risk with contrast) - **Lisinopril (ACEi)**: Controversially recommended to hold, but emerging data support continuation in euvolemic patients; conservative approach = hold 24 hrs if eGFR <30 + diabetes, but continuing acceptable - **Furosemide**: Can continue if volume replete; withholding not necessary with adequate IV hydration - **Hydration**: 500 mL 0.9% NaCl IV over 4 hours pre, then 4 hours post (LOCM adequate; IOCM not superior) - **Contrast choice**: LOCM preferred; IOCM no proven advantage (PRESERVE trial) - **Volume limit**: Max 5 mL/kg iodine content (patient 70 kg□ ~350 mL max contrast) - **Post-procedure**: Cr check 48–72 hours

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Clinical Pearl Summary

1. **Drug-induced AKI mechanisms:** ATN (aminoglycosides), AIN (NSAIDs, antibiotics), crystalline (acyclovir, MTX), hemodynamic (NSAIDs, contrast).

2. **Acute interstitial nephritis:** Immune-mediated inflammation; classic triad fever/rash/arthralgias in 50%; sterile pyuria pathognomonic finding; eosinophiluria present in 50%; discontinue drug first-line; corticosteroids if delayed recovery.
3. **Contrast-associated AKI:** Risk 1% if eGFR >60; ☐ 25–50% if eGFR <30. Hydration (500 mL pre/post), low-osmolar contrast, and volume limit (<5 mL/kg) ☐ risk. No proven superiority of iso-osmolar contrast.
4. **Analgesic nephropathy:** Decades NSAID use ☐ papillary necrosis ☐ bumpy kidney on imaging; rare now but still cause of ESRD; screen for urothelial malignancy (10–20%).
5. **Lithium nephropathy:** Early NDI (polyuria, reversible) vs. late CKD (TIN, irreversible). Consider discontinuation if eGFR declining; NDI managed with amiloride, thiazide paradox, low sodium diet.
6. **Aristolochic acid nephropathy:** Rapid progressive CKD from TCM exposure; ~50% ☐ ESRD in 3–5 years; HIGH malignancy risk (10–20% develop urothelial cancer); requires annual surveillance.
7. **Heavy metals (lead, cadmium):** Chronic occupational exposure ☐ slowly progressive TIN. Lead + gout classic combination; diagnosis via occupational history + BLL. Chelation not recommended for asymptomatic chronic exposure.
8. **Triple whammy (NSAID + ACEi + diuretic):** Synergistic nephrotoxicity; relative contraindication; if used together, close Cr monitoring essential; hold NSAIDs if AKI suspected.
9. **Ototoxicity risk (aminoglycosides):** Parallel to nephrotoxicity; single daily dosing ☐ both risks vs. q8h dosing.
10. **Prevention focus:** Drug selection based on renal function; hydration for contrast-exposed patients; dose adjustment in renal insufficiency; TDM (therapeutic drug monitoring) for aminoglycosides; avoid nephrotoxin combinations.

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