Toxic Nephropathies of the Tubulointerstitium: Core Curriculum 2024

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Toxic nephropathies are a clinically common group of disorders characterized by toxin-induced renal injury that can affect the glomerulus, vasculature, or tubulointerstitium. Various endogenous (eg, myoglobin, hemoglobin, monoclonal light chains, and lysozymes) and exogenous toxins (eg, therapeutic drugs, herbal medications, heavy metals, radiocontrast, intoxicants, and environmental exposures) have been implicated. The kidney's primary role of metabolism and excretion of substances via glomerular filtration and tubular secretion increases its susceptibility to their adverse effects. The structure, dose, metabolic handling, and excretory pathway of the drug/toxin through the kidney determines its nephrotoxic risk. Patient characteristics that impact risk include genetic determinants of drug metabolism, transport and excretion, immune response genes, and comorbid conditions. Clinical manifestations depend on site and severity of renal injury. Toxin-induced tubulointerstitial injury often presents as a decline in renal function and/or solute transport defects and renal solute wasting. Injury is often reversible with limited toxin exposure; however, irreversible renal injury can occur with prolonged exposure. In this Core Curriculum, we will focus on discussing mechanisms of common toxin-induced tubulointerstitial renal injury and review their causes, clinical presentations, diagnosis, and management.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Toxic nephropathies represent an important and relatively common category of kidney damage; the tubulointerstitium is the most common target of various nephrotoxins (both endogenous and exogenous) and will be the focus of this installment of *AJKD*'s Core Curriculum in Nephrology. Examples of endogenously produced nephrotoxins include monoclonal lights chains, heme proteins (myoglobin/hemoglobin), and lysozyme (when produced excessively), and exogenously administered nephrotoxic substances include numerous therapeutic agents, contrast media, intoxicants, and environmental exposures. The resultant tubulointerstitial injury is reversible when detected early, but kidney damage may be permanent and lead to subsequent chronic kidney disease (CKD).

Kidney injury that develops after nephrotoxin exposure involves a combination of factors including the inherent nephrotoxic potential of the substance, underlying characteristics of patients that enhance their risk for kidney injury, and the renal metabolism and excretion of the potential offending agent. Nephrotoxic risk is determined by toxin characteristics such as structure, dose, metabolic handling, and excretory pathway of the drug through the kidney and patient characteristics including genetic determinants of drug metabolism, transport and excretion, immune response genes, and comorbid conditions. The kidney is significantly exposed to potential nephrotoxins based on its role in excretion and metabolism. Renal excretion, which includes both filtration and tubular secretion of nephrotoxins, exposes cells to injury, while metabolism can lead to the production of reactive oxygen species and toxic metabolites, which can be concentrated within the renal parenchyma. The risk of kidney injury with nephrotoxins often requires some combination of the 3 risk factors previously described. The variability and heterogeneity observed in the development of nephrotoxicity results from differences in these risk factors.

Additional Readings

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Crystalline-induced Kidney Injury

Case 1: *A 44-year-old woman with fibromyalgia, hypertension, and bipolar disorder was found to be confused in her garage. In the emergency department, she was intubated and ventilated for altered mental status and respiratory compromise. The patient was taking*

naproxen, losartan, acetaminophen, and lithium. Examination revealed blood pressure of 90/60 mm Hg, altered sensorium, diminished breath sounds, normal heart sounds, and benign abdomen. Laboratory data revealed sodium, 143 mEq/L; chloride, 104 mEq/L; total CO_2, 8 mEq/L; anion gap, 31; serum urea nitrogen (SUN), 25 mg/dL; and serum creatinine, 2.3 mg/dL. Serum osmolality was 395 mOsm/kg. Her arterial blood gas was pH 7.04, and partial pressure of carbon dioxide (P_{CO_2}) was 30. Urinalysis revealed trace protein and blood, and 1+ leukocyte esterase. Her urine sediment revealed many calcium oxalate crystals (Fig 1), which were birefringent with polarization.

Question 1: What is the most likely cause of acute kidney injury in this patient?

(a) Acute tubular injury from hypotension, losartan, and naproxen
(b) Acute oxalate nephropathy from ethylene glycol intoxication
(c) Acute interstitial nephritis from naproxen
(d) Acute tubular injury from lithium

For the answers to these questions, see the following text.

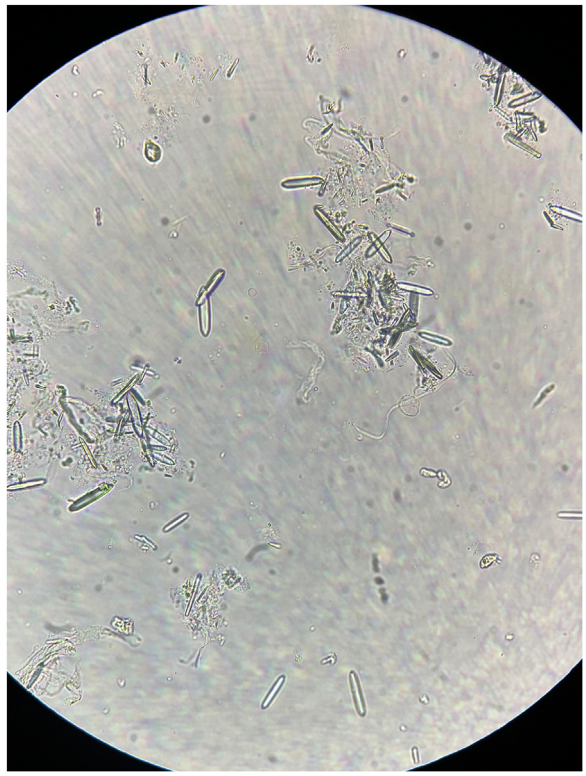

Figure 1. Calcium oxalate monohydrate crystals from ethylene glycol intoxication. Urine sediment demonstrates calcium oxalate monohydrate crystals under bright-field microscopy (original magnification, ×200).

Urine sediment demonstrating calcium oxalate crystals in this clinical setting raised concern for ethylene glycol poisoning (EG). Subsequently, her EG level returned at 298 mg/dL (toxic: >50 mg/dL), confirming the diagnosis of EG intoxication. Her lithium level was modestly elevated (2.1 mg/dL). Urinary calcium oxalate crystals provided the diagnosis of EG intoxication before the confirmation by a blood test. Thus, the correct answer is (b) acute oxalate nephropathy from EG intoxication.

Various medications and intoxicants such as EG (Table 1) can cause acute kidney injury (AKI) from crystal deposition within the tubulointerstitium. Intrarenal deposition of crystals occurs due to the drug's renal excretion and enhanced supersaturation in urine. The solubility characteristics of crystals, the patient's volume status (volume depletion with reduced urine flow rates), and increased urinary drug concentrations (excessive drug dosing) contribute to intratubular crystal precipitation and subsequent deposition. Urine pH can enhance the crystal supersaturation depending on the pharmacokinetics of the drug, while AKI and CKD may also increase the crystalline nephropathy risk. Intratubular crystal deposition causes activation of innate immunity via the NLRP3 inflammasome pathway, cytokine release, and subsequent inflammatory tubular injury.

Diagnosis of crystalline-induced AKI from drugs requires recognition of both the causative medications and the clinical and laboratory findings such as an increase in serum creatinine concentration and/or abnormal urine findings. Although urinary drug crystals and crystalline casts can be diagnostic, a kidney biopsy may be required for confirmation. The general principles of prevention and treatment for most of the drug-induced crystalline nephropathies include dose reduction/discontinuation, restoration of euvolemia, and modification of urine pH when appropriate. However, specific therapeutic approaches are appropriate for certain medications causing crystalline nephropathy. Some of those that are commonly implicated will be reviewed here, and others are noted in Table 1 along with their urine and kidney crystal morphology.

Ethylene Glycol Intoxication

Increased osmolar gap, elevated anion gap metabolic acidosis, and AKI from toxic metabolites such as glycolic acid and oxalic acid are known complications of EG intoxication. Intrarenal calcium oxalate crystal deposition causes AKI by obstructing tubular urine flow and promoting interstitial inflammation. As in case 1, rapid diagnosis of EG as the culprit toxin can be facilitated by identifying urinary calcium oxalate crystals and/or casts at the time of presentation. In addition to blocking further toxic metabolite formation with fomepizole (or ethanol) and hemodialysis to remove both EG and its toxic metabolites, intravenous fluids to enhance tubular flow rates may reduce crystal-induced kidney injury. However, severe AKI may be complicated by CKD, sometimes requiring maintenance dialysis.

Table 1. Medication-induced Crystalline Nephropathy

Medication or Intoxicant	Clinical and Laboratory Data	Crystal Morphology in Urine Sediment[a]	Findings on Kidney Biopsy	Preventive Measures[b]
Indinavir, atazanavir, darunavir	Crystalluria, nephrolithiasis, AKI, and CKD	Crystals appear as needle, rectangle, fan-shape, or starburst aggregates; positively birefringent on polarization	Needle-shaped (translucent) drug crystals within tubules with monocytic infiltrate and giant-cell reaction	No role for urine acidification
Sulfadiazine, sulfamethoxazole	Crystalluria, nephrolithiasis, AKI, and CKD	Crystals appear as shocks or sheaves of wheat, shells, or dumbbells; positively birefringent on polarization	Mononuclear inflammation and interstitial fibrosis observed without sulfa crystals within tubules or interstitium	Alkalinize urine, adjust dose for kidney function
Methotrexate	Crystalluria, AKI, and CKD	Crystals have annular shapes, which are yellow, golden, or brown; positively birefringent on polarization	Annular structures consisting of small needle-shaped crystals that stain yellow, golden, or brown on H&E stain, weak rim staining on PAS, black staining on JS; positively birefringent on polarization	IVFs before/during drug, alkalinize urine, adjust drug dose for kidney function; folinic acid; glucarpidase if toxic level (<60 hours after methotrexate exposure)
Acyclovir	Crystalluria, leukocyturia, AKI, and CKD	Crystals appear as thin needles with sharp or blunt ends; positively birefringent on polarization	Needle-shaped crystals within tubules +/− peritubular inflammation; positively birefringent on polarization	Avoid rapid IV bolus, adjust dose for kidney function
Triamterene	Crystalluria, nephrolithiasis, AKI, and CKD	Crystals are brown, green, orange, and red spheres; positive birefringence and Maltese cross	Crystals stain yellow/brown on H&E and PAS, silver positive on JS; strongly birefringent on polarization	Alkalinize urine
Ciprofloxacin, levofloxacin	Crystalluria and AKI	Crystals appear as needles, stars, fans, or sheaves; positively birefringent on polarization	Needle-shaped crystals within tubules; strongly birefringent on polarization	Avoid alkaline urine (if possible)
Amoxicillin	Crystalluria and AKI	Crystals appear as thin needles, broom/brushes; positively birefringent on polarization	No histologic evidence of intrarenal deposits of amoxicillin crystals have been described on kidney biopsy	Adjust drug dose for kidney function
IV and oral megadose ascorbic acid, orlistat (by causing enteric hyperoxaluria), EG	Crystalluria, AKI, and CKD	Calcium oxalate crystals • Monohydrated: ovoid, dumbbells, or rods • Bihydrated: bipyramidal shapes Positively birefringent on polarization	Crystals with pale blue fanlike or sunburst shapes within the tubules and interstitium with interstitial inflammation; positively birefringent on polarization	Fomepizole +/− HD for EG
Foscarnet	Hematuria, proteinuria, AKI, and CKD	Crystals appear as plates and geometric shapes; positively birefringent on polarization	Crystals like plates and geometric shapes in dilated capillary loops and tubular lumens; positively birefringent on polarization	Adjust drug dose for kidney function
Sodium phosphate purgative (oral rather than enema)	AKI and CKD	Calcium phosphate; crystals with white, amorphous, granular structures	Granular bluish-purplish crystal deposits with positive von Kossa staining; negative birefringence on polarization	Avoid concomitant NSAIDs, diuretics, and RAS inhibitors

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; EG, ethylene glycol; HD, hemodialysis; H&E, hematoxylin and eosin; IV, intravenous; IVF, intravenous fluid; JS, Jones methenamine silver; NSAIDs, nonsteroidal anti-inflammatory drugs; PAS, periodic acid-Schiff; RAS, renin-angiotensin system.

[a]For crystal images, see also Cavanaugh C, Perazella MA. Urine sediment examination in the diagnosis and management of kidney disease: core curriculum 2019. *Am J Kidney Dis*. 2019;73(2): 258-272. doi:10.1053/j.ajkd.2018.07.012

[b]Prevention includes appropriate dosing, drug discontinuation, IVFs to achieve euvolemia, and supportive care including HD.

Sulfa-based Medications

Sulfadiazine and sulfamethoxazole are sulfa-based drugs that can cause crystalline nephropathy. Low urinary solubility of these sulfa-based drugs and their metabolites, especially in acidic urine, promotes intratubular crystal precipitation, sometimes with frank stone formation. Because these drugs can also cause acute interstitial nephritis (AIN), the differential diagnosis for AKI should include AIN, urinary obstruction from ureteral stones, and sulfa-induced crystalline nephropathy. Examination of the urine sediment often reveals sulfa crystals (sometimes within casts). Kidney biopsy may be required to differentiate AIN from crystalline nephropathy. In general, AKI is reversible upon drug discontinuation, reversal of volume depletion, and urinary alkalinization.

Protease Inhibitors (Indinavir, Atazanavir, and Darunavir)

Several protease inhibitors (indinavir, atazanavir, and darunavir) have been associated with crystalline nephropathy. They are partly renally excreted and are poorly soluble in urine, which results in intratubular crystal precipitation. Indinavir was the first protease inhibitor associated with crystalline nephropathy. Atazanavir and darunavir also cause this renal lesion, albeit less frequently. Protease inhibitor-induced crystalline nephropathy is more likely to occur with volume depletion, alkaline urine, excessive drug dosing, and underlying liver disease. Drug discontinuation and achieving euvolemia are recommended to facilitate kidney recovery and avoid irreversible kidney fibrosis. However, urinary acidification is not recommended.

Methotrexate

High-dose methotrexate can cause AKI from crystalline nephropathy. The poor urinary solubility of methotrexate and its metabolites enhances distal tubular crystal precipitation. Crystal deposition is further increased with low urinary flow rates from volume depletion, acidic urine, and high urinary drug concentrations. Urine sediment sometimes demonstrates methotrexate crystals and crystal-containing casts. Prevention of intratubular crystal deposition requires a urine pH > 7.10 and high urinary flow rates. Treatment with folinic acid after methotrexate administration provides salvage metabolic therapy. When AKI develops, hemodialysis lowers methotrexate levels by ~70% but is associated with postdialysis rebound and dialysis catheter-related complications. Glucarpidase administration within 48-60 hours of methotrexate dosing metabolizes the drug to nontoxic metabolites and more effectively lowers plasma levels. In general, kidney function often recovers.

Acyclovir

Acyclovir administered as rapid intravenous infusions and/or in high doses was associated with crystalline nephropathy with associated flank pain and hematuria. By contrast, slow infusions and oral dosing rarely result in crystalline-induced AKI, except when volume depletion or excessive dosing is present. Avoiding rapid intravenous infusion and high doses of acyclovir are critical to prevent AKI, and hemodialysis effectively removes acyclovir when neurotoxicity supervenes. Recovery of kidney function is typical.

Additional Readings

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Osmotic Nephropathy

Case 2: *A 63-year-old man with stage 3a CKD, hypertension, coronary artery disease, and heart failure was admitted to the hospital with severe headache, vomiting, and new lethargy. Computed tomography (CT) scan with intravenous contrast revealed a large frontotemporal lobe mass with cerebral edema and midline shift. The patient's medications included lisinopril, amlodipine, torsemide, and isosorbide mononitrate. The patient was administered intravenous hypertonic mannitol every 6 hours for 3 days for cerebral edema. Five days later, the patient developed an increasing serum creatinine level (baseline 1.5 mg/dL to 3.1 mg/dL). Examination revealed altered sensorium, normal breath sounds, S4 cardiac gallop, benign abdomen, and 1+ lower extremity edema. Laboratory data revealed normal electrolytes with SUN of 35 mg/dL and serum creatinine of 3.1 mg/dL. Urinalysis was 1+ protein but otherwise negative. The urine sediment showed swollen renal tubular epithelial cells (RTECs) with cytoplasmic vacuoles and hyaline casts.*

Question 2: Based on the clinical data and laboratory findings, what is the most likely cause of AKI in this patient?

(a) Acute tubular injury due to naproxen and lisinopril
(b) Contrast-associated AKI in a CKD patient
(c) Mannitol-induced osmotic nephropathy
(d) Prerenal azotemia from torsemide and vomiting

For the answers to these questions, see the following text.

The urine sediment examination demonstrating swollen, vacuolated RTECs in this clinical setting suggests AKI due to "osmotic nephropathy" after 3 days of intravenous therapy with hypertonic mannitol in a patient with

underlying risk factors. The correct answer is (c) mannitol-induced osmotic nephropathy. Mannitol has been associated with osmotic nephropathy in patients with underlying risk factors such as CKD, but it is possible that contrast medium also contributed to this kidney injury.

Osmotic nephropathy was recognized when sucrose infusions were used to treat cerebral and generalized edema. It is characterized by swollen RTECs (primarily proximal tubule S2/S3 segments) filled with cytoplasmic vacuoles without apical blebbing or nuclear dropout on renal biopsy (Fig 2). These cytoplasmic vacuoles are lysosomes of varying sizes that can appear empty or contain amorphous electron-dense material. Osmotic nephropathy occurs in the setting of intravenous administration of a culprit substance that is filtered and then undergoes pinocytosis by proximal tubular (PT) epithelial cells. Drug-containing pinocytotic vacuoles fuse with each other and with cytoplasmic lysosomes, becoming engorged and distended. Cell swelling is not due to an "osmotic effect" of vacuoles containing these hyperosmotic substances; rather, the vacuoles and cellular swelling are due to the accumulation of engorged lysosomes and distension of the cell cytoplasm. The severity of cytoplasmic vacuolization and cell swelling is dose dependent, with limited exposure associated with focal lesions and minimal swelling; significant exposure is capable of producing a diffuse clear cell appearance with marked swelling and basal displacement of nuclei.

Osmotic nephropathy has been described with infusion of several different agents (Box 1). The most common culprit in the past was intravenous immunoglobulin (IVIg) preparations, especially when sucrose was the excipient employed to prevent immunoglobulin aggregation; however, rare cases have also been reported with IVIg formulations containing other stabilizers. Contrast-associated AKI likely represents another form of osmotic nephropathy that may contribute to tubular injury along with direct toxicity, oxidative stress, and ischemia. In fact, classic osmotic nephropathy is frequently observed on renal histology after contrast exposure. Intravenous mannitol, as in case 2, has also been associated with osmotic nephropathy. Infusion of this substance into animal models and humans produces a dose-related osmotic nephropathy lesion. Low-molecular-weight dextran and hydroxyethyl starch are 2 volume expanders that have been associated with dose-related osmotic nephropathy in both animals and humans. As described in a few cases, sodium/glucose cotransporter 2 (SGLT2) inhibitors may cause osmotic nephropathy by delivering excessive amounts of glucose to the S2/S3 segment of the PT.

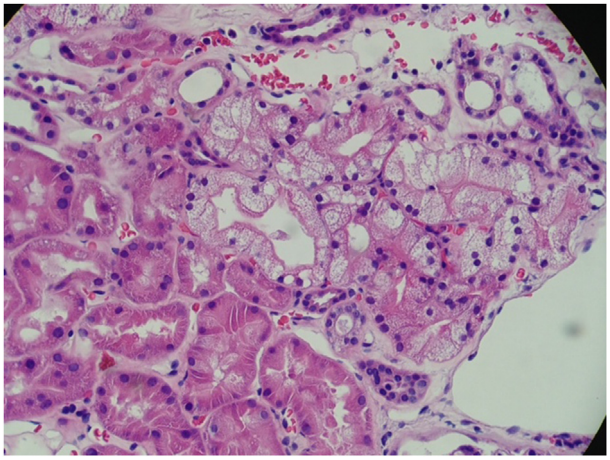

Figure 2. Osmotic nephropathy. Light microscopy of renal histology demonstrates swollen proximal tubular cells with prominent vacuolization due to an osmotic agent (mannitol, sucrose, hydroxyl-ethyl starch, dextran, etc) (hematoxylin and eosin; original magnification, ×200).

Box 1. Drug-induced Osmotic Nephropathy

- Mannitol infusion
- Sucrose (IVIg) infusion
- Contrast medium infusion
- Hydroxyethyl starch infusion
- Dextran infusion
- Maltose infusion
- Sorbitol infusion
- Glucose infusion
- SGLT2 inhibitors (glucose)?

Abbreviations: IVIg, intravenous immunoglobulin; SGLT2, sodium/glucose cotransporter 2.

Several drugs and toxins can cause tubular cell cytoplasmic vacuolization from acute injury that mimics osmotic nephropathy. However, this type of vacuolization is different from the lysosomal vacuoles seen with the drugs classically associated with osmotic nephropathy.

Certain risk factors increase the likelihood of developing osmotic nephropathy. These include the dose and duration of offending drug exposure, digestibility of the drug within lysosomes, underlying acute tubular injury (ATI) and CKD, older age, and presence of diabetes mellitus.

To diagnose osmotic nephropathy, clinicians must remember the drugs associated with this lesion and be aware of urinary findings, including tubular proteinuria and swollen tubular cells with numerous vacuoles alone and within casts. The mechanism underlying oliguric AKI is tubular cell dysfunction and tubular obstruction from massively swollen cells. Prevention of this lesion hinges on using alternative agents such as non-sucrose-containing IVIg, limiting the dose and duration of the offending agent, correcting volume depletion, and avoiding exposure to other nephrotoxins. Drug discontinuation and traditional supportive care measures are employed including renal replacement for severe AKI. Fortunately, most patients recover kidney function.

Additional Readings

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Light Chain Nephrotoxicity

Case 3: *A 59-year-old man with hypertension and osteoarthritis was evaluated for excruciating thoracic back pain, AKI, anemia, and hypercalcemia, prompting hospital admission. The patient had been taking ibuprofen 3-4 times/day along with losartan, chlorthalidone, and aspirin. Physical examination revealed normal vital signs with thoracic spine tenderness. Laboratory data revealed serum sodium, 134 mEq/L; potassium, 5.5 mEq/L; total CO_2, 18 mEq/L; SUN, 65 mg/dL; serum creatinine, 6.1 mg/dL; calcium, 14.6 mg/dL; and phosphate, 9.7 mg/dL. Thoracic spine lytic lesions were demonstrated. Urinalysis showed trace protein but was otherwise negative. Urine sediment showed RTECs and waxy casts. The spot urine protein-creatinine ratio was 4.8 mg/mg. Serum-free λ light chains (LCs) were 726 mg/dL, the κ/λ ratio was 0.3, and urine λ LCs were 539 mg/dL. Bone marrow aspiration and biopsy with flow cytometry was diagnostic of IgG λ multiple myeloma. Despite intravenous fluids and correction of hypercalcemia, his kidney function worsened, and hemodialysis was initiated. A kidney biopsy sample was obtained.*

Question 3: What kidney biopsy finding will most likely be observed in this patient?

(a) Light chain deposition disease
(b) Ibuprofen-induced acute interstitial nephritis
(c) Intratubular calcium-phosphate deposition (nephrocalcinosis)
(d) Light-chain cast nephropathy
(e) Renal amyloid light-chain (AL) amyloidosis

For the answers to these questions, see the following text.

The kidney biopsy demonstrated numerous tubular profiles with fractured casts and an associated giant cell reaction (Fig 3), which was consistent with (d) LC cast nephropathy due to myeloma. Immunofluorescence staining revealed isolated clonal λ LC staining. Electron microscopy revealed electron-dense cast material in tubular lumens. The patient was administered clone-directed chemotherapy for myeloma, and plasma exchange was not performed. After 2 months of chemotherapy, the patient's kidney function improved (serum creatinine, 2.1 mg/dL), and dialysis was discontinued.

Hematological malignancies such as multiple myeloma secrete paraproteins as monoclonal immunoglobulins and

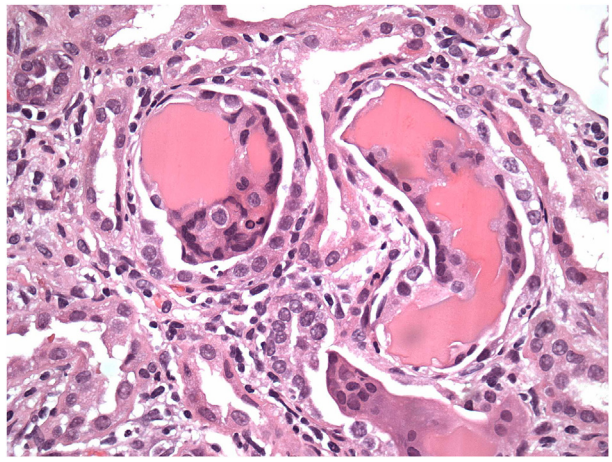

Figure 3. Myeloma light chain cast nephropathy. Light microscopy of renal histology demonstrates a monoclonal-type light chain cast with accompanying giant cell reaction within a renal tubule (hematoxylin and eosin; original magnification, ×400). Image © 2023 Glen S Markowitz and is reproduced with permission of the copyright holder.

LCs. Paraproteins may involve the preglomerular capillaries, glomeruli, and tubular system ranging from the PTs to the cortical collecting ducts. Monoclonal LCs are an example of an endogenous protein that is toxic to tubular cells. LCs injure the tubulointerstitium by causing either LC proximal tubulopathy (LCPT) or LC cast nephropathy. LC deposition disease can also cause tubulointerstitial injury but will not be discussed.

Light Chain Proximal Tubulopathy

LCPT results from the accumulation of toxic monoclonal LCs within PT cells as either crystalline structures or lysosomal inclusions/phagolysosomes. Myeloma, monoclonal gammopathy of renal significance, and lymphoproliferative cancers are associated with LCPT. The crystals in LCPT are composed primarily of monoclonal κ-LCs derived from the Vκ1 variability subgroup. LCPT presents clinically as a proximal tubulopathy characterized by features of Fanconi syndrome or an isolated proximal tubular disorder (phosphate wasting, normoglycemic glycosuria, or type 2 renal tubular acidosis). Additionally, patients may have concomitant AKI or CKD.

In crystalline LCPT, PTs contain crystals along with mild ATI/atrophy and variable degrees of interstitial fibrosis. Intracytoplasmic needle-shaped and or geometric crystals are observed within swollen PT cells. Standard immunofluorescence staining for LCs may be negative because antibody-binding sites are shielded by the crystalline structure and are resistant to antibody binding. Immunofluorescence performed on formalin-fixed, paraffin-embedded sections after antigen retrieval with pronase, which helps to expose the sequestered antibody-binding sites on the crystals, provides a solution. Electron microscopy may demonstrate dense geometric and/or needle-

shaped crystals or distended lysosomes/phagolysosomes within PT cell cytoplasm.

Treatment of LCPT requires clone-directed chemotherapy for the underlying dysproteinemia. Plasma exchange is not recommended because it has not been shown to be an effective adjuvant therapy. Prognosis for recovery from LCPT is highly variable depending on the severity of the tubulointerstitial disease and the response to therapy.

Light Chain Cast Nephropathy

In contrast to the relatively rare LCPT, LC cast nephropathy is a more common kidney lesion in myeloma patients. LC cast nephropathy develops from the high burden of LCs filtered by the glomerulus and their subsequent binding to uromodulin secreted by loop of Henle cells. Cast aggregation with uromodulin occurs as a result of binding of the LC CDR3 site with the D8C domain on uromodulin. After this binding, gel formation that transitions to intratubular cast formation is facilitated by increased osmolarity, higher sodium chloride and calcium concentrations, and acidic pH of the urine. Concomitant exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) and volume depletion enhances cast formation. The toxic casts then elicit an inflammatory response in the surrounding tubulointerstitium. This dual pathway of tubulointerstitial injury ultimately causes AKI, which may transition to CKD in the absence of an early diagnosis and rapid reduction in LC production. On biopsy, cast nephropathy appears as fractured, glassy eosinophilic casts with an accompanying giant cell reaction engulfing the cast, tubular injury (sometimes with tubular rupture), and a monocytic cell dominant interstitial infiltrate (Fig 3). Less commonly, casts composed of crystals may also be seen.

Clinically, patients present with rapidly worsening kidney function, rising serum free LCs, low-grade proteinuria, and waxy casts on urine microscopy. Diagnosis is facilitated by measurement of serum free LCs, serum protein electrophoresis (SPEP), and urine protein electrophoresis (UPEP), which demonstrate monoclonal paraproteinemia, and bone marrow studies that identify the B-cell clone.

Management includes volume repletion, correction of hypercalcemia, and effective clone-directed chemotherapy to rapidly reduce LC production. The large volume of distribution of LCs with the rapid posttherapy rebound limits the efficacy of extracorporeal techniques to lower LCs. Plasma exchange and high-cutoff hemodialysis (not available in the United States) were beneficial for some patients in uncontrolled studies, but randomized controlled trials demonstrated little or no benefit. As such, these modalities have limited application in patients with LC cast nephropathy.

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Drug-induced Acute Interstitial Nephritis

Case 4: *A 65-year-old-man presents for evaluation of a rise in serum creatinine. His node-positive melanoma was diagnosed 2 months ago, and he has been treated with adjuvant pembrolizumab every 3 weeks after surgical resection. His other medications include pantoprazole and amlodipine. When he presented for his third cycle, the serum creatinine rise was noted. He denies any nausea, vomiting, diarrhea, skin rash, new medications, or over-the-counter medication use. His vital signs are at baseline. The blood tests are notable for a rise in serum creatinine from baseline of 1.0 mg/dL to 1.6 mg/dL. Urinalysis shows 1+ protein and 1+ leucocytes; urine microscopy shows 1-5 white blood cells/high-power field (WBC/HPF) without any casts; urine culture shows no growth; and urine protein-creatinine ratio is 0.4 mg/mg. Pembrolizumab therapy is held, and 2,000 mL of lactated ringer's solution is administered. The ultrasound examination shows echogenic kidneys without hydronephrosis. Repeat serum creatinine measured 3 days later is 1.8 mg/dL.*

Question 4: What is the most likely diagnosis?

(a) Acute tubular injury
(b) Prerenal azotemia
(c) Urinary tract obstruction
(d) Acute interstitial nephritis
(e) Glomerulonephritis

For the answers to these questions, see the following text.

Persistent AKI in a patient on immune checkpoint inhibitor (ICPI) therapy that is unresponsive to volume administration, with bland urine sediment and without evidence of urinary tract obstruction, is most likely due to (d) AIN.

AIN is a histological diagnosis characterized by infiltration of lymphocytes and other immune cells in the kidney tubulointerstitium. Over 70% of cases are triggered by medication use. Patients often come to clinical attention due to acute or subacute loss of kidney function. Among

patients with AKI who undergo a biopsy, AIN is observed in up to 15% of cases. Establishing the AIN diagnosis is challenging due to an absence of typical clinical features or laboratory abnormalities; it often requires a kidney biopsy for diagnosis. Although urine biomarker tests have shown an ability to accurately diagnose AIN, they are not available for clinical use. Treatment is focused on identifying and discontinuing the culprit drug and employing immunosuppressive therapy in selected cases.

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Medication Classes Associated With AIN

Antibiotics

AIN can be triggered by many commonly used antibiotics including β-lactam antibiotics, sulfonamides including sulfamethoxazole, rifampin, and fluoroquinolones. Antibiotic-associated AIN often leads to rapid onset of kidney dysfunction (within 7-14 days of exposure) and is sometimes associated with typical allergic features. This can prompt early diagnosis and therapy resulting in significant kidney function recovery in a large majority of cases.

Proton Pump Inhibitors. The incidence rate of AIN with proton pump inhibitors (PPIs) is low and estimated to be between 0.8-3.2 per 10,000 person-years of exposure; however, given the high prevalence of PPI use, they are still one of the most common causes of AIN. In older adults, PPI use is associated with a 3-fold higher rate of AIN. Because PPI-related AIN does not have typical clinical features, the period between the start of PPI therapy and AIN diagnosis is often months, and many cases are not suspected before biopsy. Many well-controlled studies have noted the higher risk of CKD and end-stage kidney disease with PPI exposure.

Immune Checkpoint Inhibitors. ICPI medications include inhibitors of cytotoxic T-cell antigen-4 (CTLA-4; ipilimumab), programmed death 1 (PD-1; nivolumab, pembrolizumab, cemiplimab), and PD ligand 1 (PDL-1; atezolizumab, avelumab, durvalumab). These drugs restore T-cell activity against tumor cells and have revolutionized cancer treatment. However, they have been associated with various immune-related adverse events due to increased T-cell activity, including AIN. Although the overall incidence of AIN with ICPIs is unknown, AKI estimates range from 2% in clinical trials to 29% in real-world observational studies, of which an unknown subset may be due to AIN. In a recent multicenter case series of patients with ICPI-associated AKI, AIN was the histological diagnosis in 80% of patients who underwent a biopsy. AIN risk is higher in patients who take PPIs along with ICPI therapy. As with other immune-related adverse events, there is a risk of recurrence of AIN with reintroduction of ICPI therapy, but this risk (about 20%) should be weighed against the potentially lifesaving ICPI therapy by a multidisciplinary team.

Nonsteroidal Anti-inflammatory Drugs. NSAIDs account for 10%-15% of all cases of drug-induced AIN. Patients with NSAID-related AIN often present weeks or months after drug initiation and do not show typical allergic manifestations. NSAID-related AIN may be accompanied by glomerulopathies such as minimal change disease and membranous nephropathy, which manifest as nephrotic syndrome.

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Clinical Diagnosis of Drug-induced AIN

Most patients with AIN do not have typical clinical features (Box 2). A minority of patients with antibiotic-induced AIN may show classic allergic features such as fever, rash, and eosinophilia, and rapid onset after introduction of a new drug. AIN is often suspected when a patient prescribed a culprit medication presents with an acute or subacute increase in serum creatinine. About half of the cases with biopsy-diagnosed AIN meet the KDIGO AKI definition, while others develop acute kidney disease (AKD) defined as subacute loss of glomerular filtration rate (GFR) over 3 months. Therefore, in patients experiencing loss of kidney function, it is important to obtain a detailed history focused on recent prescription and over-the-counter medication exposures. The median time from drug initiation to identification ranges from <14 days with antibiotics, to weeks or months with NSAIDs and ICPIs, to several months for PPIs.

Abnormalities in urinalysis and urine sediment in patients with kidney dysfunction prompt additional investigation for AIN. For example, pyuria is seen in

Box 2. Clinical and Laboratory Manifestations of Drug-induced Acute Interstitial Nephritis

Clinical Features
- Manifestations of allergic reaction including fever, rash, and eosinophilia ("triad" <10%).
- History of exposure to a culprit medication before AIN, with appropriate latent period.
- Latent period from exposure to AIN varying by drug-class: 7-14 days for antibiotics, weeks to months for NSAIDs, weeks to many months for PPIs and immune checkpoint inhibitors.

Serum Tests
- Acute or subacute rise in serum creatinine (diagnostic of AKI or AKD).

Urine Findings
- Leukocyturia, leukocyte casts.
- Low-grade proteinuria ("tubular range"; <1 g/day), except with NSAID-associated AIN, which may have nephrotic range proteinuria (minimal change disease). Proteinuria may also reflect an underlying/accompanying glomerular disease (eg, diabetic kidney disease, membranous nephropathy, IgA nephropathy, etc).
- Urine sediment may demonstrate leukocytes and very rarely leukocyte casts (poor sensitivity).
- Urine sediment may also show renal tubular epithelial cells, renal tubular epithelial casts, and granular casts (neither sensitive nor specific).
- Normal urinalysis can be observed in ∼20% of patients.
- Urine eosinophil testing is neither sensitive nor specific.

Diagnostic Imaging
- Ultrasonography and CT scan may be obtained to rule out other causes of kidney disease. Ultrasound scan may show increased kidney size and echogenicity, but this finding is nonspecific.

Kidney Biopsy
- Gold standard. Typical findings include interstitial inflammatory cell infiltrate consisting of lymphocytes and often eosinophils, "tubulitis," and eosinophilic granulomas may also be seen.

Investigational Tests
- Urine IL-9, TNF-α, CXCL9, CXCL10, M1:M2 macrophage ratio.

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; AKD, acute kidney disease; CT, computed tomography; CXCL, chemokine (C-X-C motif) ligand; IL-9, interleukin-9; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; TNF-α, tumor necrosis factor α.

about half of the cases and low-grade proteinuria in the majority. Although leukocyte casts are often thought to be a typical feature for AIN, they are noted in <15% of carefully examined urine sediments from patients with AIN. Imaging studies (kidney ultrasound and CT scan) provide kidney size and rule out obstructive nephropathy but are not diagnostic of AIN. Urine eosinophil testing is no longer recommended for routine diagnosis of AIN after a large series showed its poor diagnostic accuracy. A recent study created and externally validated a diagnostic model (https://ainriskprediction.shinyapps.io/ain_calc/) for biopsy-proven AIN consisting of serum creatinine, serum urea nitrogen to serum creatinine ratio, dipstick proteinuria, and specific gravity. Variations in the human leukocyte antigen (HLA) region, specifically the HLA-DRB1*14 variant, have been linked to a higher predisposition to occurrence and severity of AIN.

Histological Diagnosis of AIN

Confirmation of AIN often requires a kidney biopsy for histological diagnosis, which remains the gold standard for diagnosis of AIN. AIN is characterized by presence of a mixed inflammatory infiltrate in the renal interstitial space (Fig 4) with accompanying infiltration into the tubular compartment, which is termed "tubulitis," and interstitial edema. This infiltrate consists of mixed inflammatory cells, including of $CD4^+$ and $CD8^+$ T lymphocytes, while eosinophils, macrophages, B cells, plasma cells, neutrophils, and mast cells have also been observed. Granulomas with non-necrotizing features may be seen in AIN but are not specific to this diagnosis. Notably, eosinophils are frequently absent from NSAID-induced AIN, which may have accompanying glomerular findings.

Novel Biomarkers for AIN Diagnosis

Given the lack of a reliable noninvasive biomarker and need to obtain a kidney biopsy, several studies have attempted to identify diagnostic biomarkers for AIN. Two urine cytokines, urine interleukin 9 (IL-9) and tumor necrosis factor α (TNF-α), were independently associated with AIN diagnosis, and their addition to clinicians' prebiopsy diagnosis increased the area under receiver operating characteristic curve for AIN by 0.22

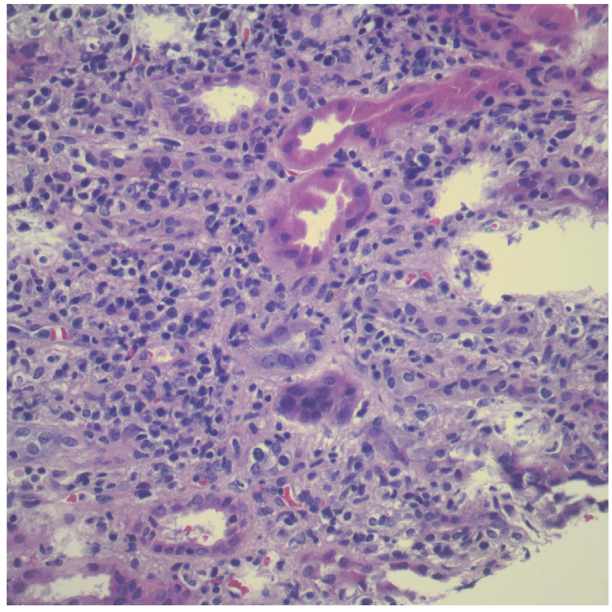

Figure 4. Acute interstitial nephritis. Light microscopy of renal histology shows a diffuse inflammatory infiltrate in the interstitium consistent with acute interstitial nephritis.

to 0.84 (95% CI, 0.78-0.91). Other recent studies have identified urine chemokines CXCL9 and CXCL10, and urine macrophage M1:M2 ratio as diagnostic biomarkers of AIN. However, none of these biomarkers are available for routine clinical use.

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Case 4, continued: *Pembrolizumab therapy continues to be held, and the patient is prescribed 1 mg/kg prednisone. One week later, his creatinine remains elevated at 2.0 mg/dL, and a kidney biopsy is performed. Histology shows mononuclear interstitial infiltrate occupying 50% of kidney tissue, tubulitis, and interstitial fibrosis/tubular atrophy occupying 50% of tissue. There is presence of scattered eosinophils, mild ATI, and edema.*

Question 5: Which of the following factors portends poor recovery of kidney function after AIN?

(a) High degree of interstitial infiltrate
(b) High degree of interstitial fibrosis
(c) Presence of tubulitis
(d) Presence of eosinophils
(e) Baseline serum creatinine of 1.0 mg/dL

For the answers to these questions, see the following text.

Several studies have identified (b) severity of interstitial fibrosis as a key predictor of poor renal function recovery in AIN. On the other hand, presence of a high degree of active inflammatory infiltrate and tubulitis has been shown to be associated with better recovery of kidney function, presumably because these tend to be treatable with immunosuppressive therapy. Lower baseline creatinine was also shown to be associated with greater recovery of kidney function.

Treatment and Prognosis

The first step in management of patients with suspected or confirmed AIN is to discontinue the culprit drug. Given the immune-mediated nature of kidney damage, corticosteroid therapy is often prescribed despite the lack of randomized controlled trials. Oral prednisone at 1 mg/kg is equally efficacious as higher dose or intravenous therapy. A shorter duration between AIN diagnosis and corticosteroid therapy initiation is associated with better kidney function outcomes. Corticosteroids tend to have a beneficial effect on kidney function in those with greater interstitial infiltrate, lower interstitial fibrosis, and higher estimated GFR (eGFR) before biopsy. Because much of the kidney function recovery occurs within the first month after diagnosis, it is reasonable to prescribe corticosteroids for approximately 4-6 weeks after diagnosis with rapid taper if no response is seen. One recent case series demonstrated at least partial recovery in 8 of 10 patients with ICPI-induced AIN treated with the TNF-α inhibitor infliximab after failing corticosteroids.

Many patients are left with some degree of permanent kidney function loss after an episode of AIN. Studies estimate that eGFR declines low enough to categorize ∼50% of patients as CKD after AIN. Greater interstitial fibrosis is associated with lower kidney function recovery, whereas greater interstitial infiltrate is associated with improved kidney function recovery, including greater rates of dialysis discontinuation. A longer duration of drug exposure and a delay in immunosuppressive medication initiation are associated with incomplete kidney function recovery.

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Toxin-induced Proximal Tubulopathy

The PT is particularly sensitive to toxin-induced injury due to its unique characteristics. First, PT cells absorb >60% of the glomerular filtrate and rely greatly on robust, oxygen-dependent mitochondrial adenosine triphosphate (ATP) production to meet their energy needs. Mitochondrial toxins can result in massive ATP depletion, oxidative stress, cell injury and death. Second, PT cells can secrete and metabolize substances that cannot be excreted by glomerular filtration. High expression of proteins such as basolateral organic anion transporters (OAT) and organic cation transporters (OCT) can mediate drug/toxin uptake from the interstitium; and apical efflux proteins such as P-glycoprotein, multidrug-resistance protein (MRP), and human multidrug and toxin extrusion (MATE) protein can facilitate drug secretion into the tubular lumen (Fig 5). Processes that increase drug uptake but limit luminal efflux can result in high intracellular drug concentration and risk of toxicity (via damage to lysosomes, mitochondria, phospholipid membranes, and other intracellular organelles). Additionally, filtered drugs (eg, aminoglycosides) and toxins (cadmium) can gain luminal entry into the PT cells via receptor-mediated endocytosis and cause injury.

Clinical manifestations of toxin-induced tubulopathy depend on the site and degree of injury and may result in solute/water transport defects alone (eg, Fanconi syndrome) (Box 3), or may have concomitant reduction in GFR (AKI). Renal solute wasting is clinically more apparent in those with preserved GFR compared to those with severe AKI or CKD. Chronic exposure to the toxin can eventually result in CKD.

Additional Readings

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Case 5: *A 72-year-old woman with hypertension, diabetes mellitus, and dyspepsia receives a diagnosis of advanced ovarian carcinoma and is started on a cisplatin-based chemotherapy regimen. After 3 months of therapy, she is noted to have an increase in her serum creatinine from 0.7 mg/dL to 1.2 mg/dL. Cisplatin is held, and she receives intravenous fluids, resulting in improvement in her serum creatinine to 0.9 mg/dL; afterward, cisplatin is resumed. The following month, her serum creatinine is 1.4 mg/dL. Her other daily medications include lisinopril, hydrochlorothiazide, oxycodone, omeprazole, and metformin. Physical examination reveals her blood pressure to be 134/60 mm Hg, with normal lung and heart sounds. She had mild abdominal*

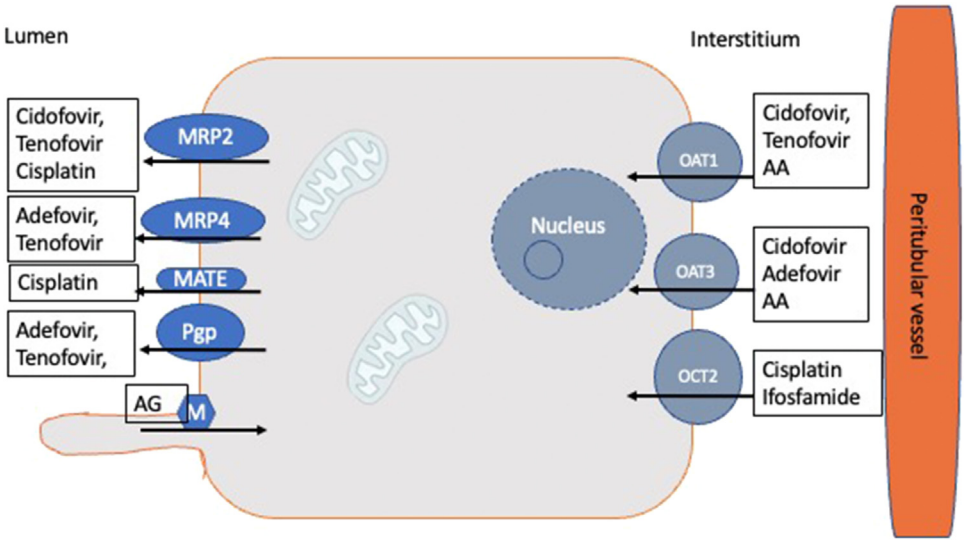

Figure 5. Mechanism of proximal tubular cell drug uptake. Drugs gain entry from the peritubular vessels and interstitium into the proximal tubular cells via organic anion and cation transporters at the basolateral membrane. They are secreted into the lumen via efflux proteins such as MRP2, MRP4, and Pgp. Aminoglycosides enter via megalin receptor (present at the base of the brush border of the luminal membrane) mediated endocytosis. Abbreviations: AA, aristolochic acid; AG, aminoglycoside; M, megalin; MATE, multidrug and toxic compound extrusion; MRP, multidrug-resistance transporter; OCT, organic cation transporter; OAT, organic anion transporter; Pgp, P-glycoprotein.

Box 3. Select Renal Tubular Toxins and Their Associated Tubulopathies

- Fanconi syndrome (due to defective proximal tubular transport mechanisms, which can lead to loss of multiple solutes: hyperaminoaciduria, glucosuria [in the face of normoglycemia], phosphate wasting, hypokalemia, hypouricemia, bicarbonate wasting/proximal renal tubular acidosis)
  - o Anticancer drugs: cisplatin, ifosfamide, imatinib, mithramycin
  - o Antivirals: tenofovir, cidofovir, adefovir, foscarnet, didanosine
  - o Antibiotics: aminoglycosides, outdated tetracyclines
  - o Heavy metals (cadmium), aristolochic acid
  - o Anticonvulsants: valproic acid
- Salt wasting and acquired Bartter syndrome (due to dysfunction of loop of Henle)
  - o Cisplatin
  - o Aminoglycosides, amphotericin, colistin
- Nephrogenic diabetes insipidus (due to dysfunction of distal nephron water-handling or severe hypokalemia)
  - o Cisplatin, foscarnet
  - o Cidofovir, tenofovir, didanosine
  - o Lithium
- Hypomagnesemia (due to effect on loop of Henle and distal nephron)
  - o Cisplatin, foscarnet
  - o Aminoglycosides
  - o Heavy metals

distension with good bowel sounds. Laboratory data reveals serum sodium, 142 mEq/L; chloride, 102 mEq/L; potassium, 3.6 mEq/L; total CO_2, 28 mEq/L; SUN, 25 mg/dL; serum creatinine, 1.4 mg/dL; lactate, normal; and magnesium, 1.2 mg/dL with urinary fractional excretion of magnesium (FEMg) 8%. Urinalysis reveals trace protein, 1+ leukocyte esterase, and no blood. Urine sediment reveals 1-3 renal tubular epithelial (RTE) cell casts/HPF and 1-2 fine granular casts/HPF.

Question 6: What is the most likely cause of AKI in this patient?

(a) Thrombotic microangiopathy
(b) Acute interstitial nephritis from omeprazole
(c) Acute tubular injury from cisplatin
(d) Metformin toxicity

For the answers to these questions, see the following text.

Urine sediment demonstrating evidence of renal tubular injury and hypomagnesemia with a high FEMg (indicative of renal magnesium wasting) raise concern for (c) ATI from cisplatin. Cisplatin-induced glomerular injury—thrombotic microangiopathy (TMA)—can be ruled out due to the absence of dysmorphic red blood cells (RBCs)/RBC casts on urine microscopy. Metformin toxicity can be seen in patients on metformin with GFR < 30 mL/min, and it results in lactic acidosis, which this patient does not have. Omeprazole can cause AIN; however, the patient has been taking omeprazole for over 10 years, making it a less likely culprit.

Cisplatin Nephrotoxicity

Cisplatin is a platinum-based chemotherapeutic agent widely used for the treatment of various solid tumors such as testicular, bladder, advanced ovarian, lung, and head and neck cancers. In cancer cells, cisplatin causes cell cycle arrest by inducing DNA cross links and adducts, resulting in DNA damage and cell death. Cisplatin is primarily cleared by glomerular filtration and tubular secretion, exposing the kidneys to high drug concentrations and the risk of nephrotoxicity.

Cisplatin nephrotoxicity is common (one-third of the patients receiving the drug) with AKI reported in ~30% after a single dose. A rise in serum creatinine is typically seen 7-10 days after cisplatin exposure but can occur earlier in those with multiple risk factors. Toxicity is dose dependent (single dose of >50 mg/m^2; peak plasma level > 400 ng/mL) and cumulative and can result in acute or chronic kidney injury. Other risk factors include duration of exposure, older age, female sex, hypoalbuminemia, and baseline CKD. CKD impacts the renal clearance of cisplatin, resulting in higher peak serum levels and toxicity risk. Hypomagnesemia is a frequently associated manifestation whereas hypokalemia, renal salt wasting, and hypocalcemia are less common. Thrombotic microangiopathy (rare) has also been described.

Tubular cell injury (apoptosis and necrosis) is the hallmark histological finding in cisplatin nephrotoxicity and results from activation of an intrinsic "mitochondrial—endoplasmic reticulum (ER)—stress" pathway. Mitochondrial dysfunction–induced oxidative stress response favors degradation of antiapoptotic proteins, dysregulated expression of antioxidative enzymes, activation of proapoptotic and inflammatory proteins (TNF-α, IL-6, interferon-γ), and accumulation of reactive oxygen species, resulting in cell injury/death. Cellular uptake of cisplatin is mediated via the basolateral OCTs (especially OCT2 isoform), and copper transporters. Notably, the cisplatin analogues carboplatin and oxaliplatin do not interact with OCT2 and have demonstrably less nephrotoxicity. Apically localized efflux transporters (MRP, MATE, and ATPases) are responsible for extrusion of cisplatin into the luminal fluid. Aberrant expression of these transporters can influence the risk of cisplatin nephrotoxicity. In addition to mitochondrial toxicity, cisplatin-induced afferent arteriolar vasoconstriction can result in direct ischemic renal injury. Hypomagnesemia (from injury to the loop of Henle and the distal tubule), often an early sign of cisplatin toxicity, can be severe and persist for months even after the drug has been discontinued.

Given the frequent occurrence of cisplatin nephrotoxicity, renoprotective measures with volume expansion and saline diuresis are routinely employed. Forced diuresis

with mannitol is controversial; however, a recent randomized controlled trial demonstrated its benefit (along with volume expansion) in preventing toxicity, especially in patients receiving > 80 mg/m^2 of cisplatin. Using the lowest effective cisplatin dose, avoiding use of concomitant nephrotoxins, and close monitoring of renal function and serum electrolytes are recommended. In animal and human observational studies, magnesium supplementation has been shown to protect against cisplatin nephrotoxicity by competing with cisplatin for the basolateral OCT2 transporter and lowering the intracellular accumulation of cisplatin. Avoiding cisplatin in patients with established CKD and considering less nephrotoxic regimens with carboplatin/oxaliplatin is reasonable. There is no clear GFR cutoff for use, and the risk of injury versus potential benefit should be individually assessed. Several drugs have been evaluated for prevention of cisplatin nephrotoxicity with proposed effects on cellular transport of cisplatin or reducing oxidative damage (eg, N-acetylcysteine, sodium thiosulfate, free oxygen radical scavengers, etc), but their benefit remains unproven. Management of cisplatin-induced AKI includes minimizing drug exposure and treatment of volume depletion and electrolyte abnormalities. Although most patients recover from cisplatin-induced AKI, progression to CKD can occur.

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Case 6: *A 42-year-old man with HIV infection on tenofovir-based antiretroviral therapy for the past 3 years and with diabetes (diagnosed a year ago) presents for a routine outpatient follow-up visit. He reports worsening fatigue and muscle cramps over the past few months and a self-limiting upper respiratory infection 3 weeks ago. His medications include HAART therapy (tenofovir disoproxil fumarate-emtricitabine-efavirenz), baby aspirin, and metformin. Physical examination reveals his blood pressure is 146/86 mm Hg, with normal lung and heart sounds. He has a soft abdomen with good bowel sounds. Laboratory data reveal serum sodium, 136 mEq/L; chloride, 109 mEq/L; potassium, 3.0 mEq/L; total CO_2, 20 mEq/L; SUN, 35 mg/dL; serum creatinine, 1.4 mg/dL; serum glucose, 95 mg/dL; and serum phosphate, 1.8 mg/dL. His CD4 count is >500 cells/mm^3, and circulating HIV RNA is undetectable. His creatinine has increased over time: 0.7 mg/dL (3 years ago), 1.1 mg/dL (a year ago), and now 1.4 mg/dL. The urinalysis reveals 1+ protein, 2+ leukocyte esterase, negative nitrites, and 1+ glucose. Urine sediment reveals 3-5 WBCs/HPF, 0-2 monomorphic RBCs/HPF, and no casts.*

Question 7: What is the most likely cause of decline in kidney function in this patient?

(a) Tenofovir-associated nephrotoxicity.
(b) Acute postinfectious glomerulonephritis
(c) HIV-induced collapsing glomerulopathy
(d) Diabetic nephropathy

For the answers to these questions, see the following text.

The clinical course is indolent with a chronic rise in serum creatinine over 2 years, notable hypokalemia, hypophosphatemia, and a bland urine sediment with low-grade proteinuria and glycosuria (without hyperglycemia), suggestive of chronic renal injury and Fanconi syndrome. This is likely from (a) tenofovir-associated nephrotoxicity. Although patient has had a recent upper respiratory infection, his chronic loss of GFR and bland urine (lack of hematuria) makes acute postinfectious glomerulonephritis unlikely. HIV-associated collapsing glomerulopathy typically presents with a rapid, severe decline in GFR over months with high-grade proteinuria, which this patient does not have. The patient's relatively recent onset of diabetes makes diabetic nephropathy an unlikely cause of his CKD.

Tenofovir-associated Nephrotoxicity

Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor widely used to treat HIV and hepatitis B infections. It has structural similarity to the well-established nephrotoxins cidofovir and adefovir. TFV is marketed as TDF (tenofovir disoproxil fumarate), and a newer prodrug approved in 2015 is known as TAF (tenofovir alafenamide). Although both formulations are renally excreted, the typical clinical dose of TAF is 25 mg daily versus 300 mg for TDF. TAF rapidly enters circulating monocytes (its target cell), resulting in lower peak serum concentration and lowered burden of drug traversing the kidneys, making it less nephrotoxic than TDF.

Dose-dependent AKI has been reported in 12%-24% of patients on TDF-based regimens. However, most patients present with a slow and modest decline in GFR, with concomitant Fanconi syndrome in ~20%. Each year of exposure to TDF is associated with a 34% increased risk of proteinuria, 11% increased risk of rapid decline in GFR, and a 33% increased risk of developing CKD. Risk factors include increasing age, concurrent use of nephrotoxins (NSAIDS, ritonavir), and baseline CKD. This rise in creatinine may be masked by the declining muscle mass that often affects those with chronic viral infections, underscoring the need for close monitoring. In randomized trials, TAF-containing regimens have shown similar efficacy as TDF-based regimens with a much smaller decline

in GFR over 96 weeks. However, AKI has also been reported with TAF use.

The mechanism of TFV toxicity appears to be PT mitochondrial injury (Fig 6). Until recently, it was thought that TFV causes inhibition of mitochondrial DNA polymerase-γ resulting in mitochondrial DNA depletion and structural injury. However, recent data suggest that TDF results in a dose-dependent decrease in mitochondrial ATP synthase or complex V, resulting in lack of ATP generation and mitochondrial dysfunction. TFV is excreted unchanged in the urine by a combination of glomerular filtration (70%-80%) and proximal tubular secretion (20%-30%). PT cell uptake is mediated by basolateral OATs (OAT1 > OAT3) and luminal excretion is via apical MRP2 and MRP4. OAT inhibition via probenecid has been a proposed strategy to mitigate TFV nephrotoxicity, but studies have been equivocal. On the contrary, MRP inhibition via drugs such as NSAIDS can increase the intracellular accumulation of TFV and increase the risk of toxicity.

HIV management guidelines recommend avoiding use of TFV in patients with an eGFR of <60 mL/min. If TFV use is unavoidable, using renal dose adjustment, close monitoring of GFR, and discontinuing the drug if the patient's GFR falls below 25% from baseline levels is recommended. The cost of TAF is significantly higher than TDF, which has limited its use as a first-line treatment in patients with normal renal function. Treatment of TFV nephrotoxicity is early drug discontinuation, which may allow significant renal recovery in ∼50% of patients with AKI. Those with TFV-induced CKD may only experience partial or no recovery.

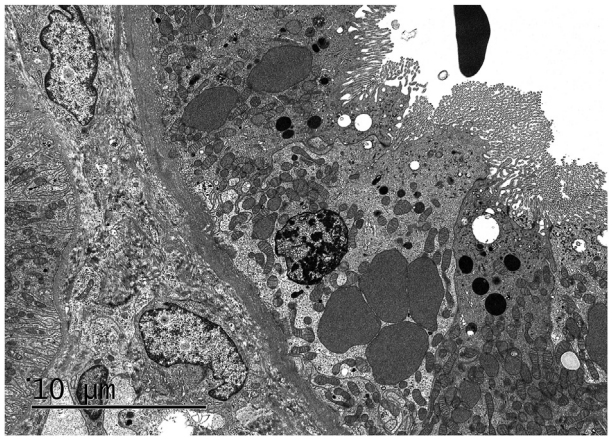

Figure 6. Tenofovir toxicity. Ultrastructural evaluation of the proximal renal tubular cells demonstrates markedly enlarged mitochondria without discernable cristae due to tenofovir toxicity (original magnification, ×6,000). Image © 2023 Glen S Markowitz and is reproduced with permission of the copyright holder.

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Aminoglycoside Nephrotoxicity

Aminoglycosides cause dose/duration-dependent ATI that primarily affects S1 and S2 segments of the PT but can also affect the thick ascending limb of the loop of Henle and the collecting duct, resulting in AKI (in 10%-20%) and less commonly Fanconi syndrome and "pseudo Bartter" syndrome (Table 2). Aminoglycosides are freely filtered across the glomerulus and excreted, but ∼10% is taken up by the PT cells via negatively charged membrane phospholipid binding and megalin/cubilin-mediated endocytosis. Cationic aminoglycosides have greater interaction with membrane phospholipids and higher nephrotoxicity (neomycin > gentamicin > tobramycin ∼ amikacin ∼ netilmicin > streptomycin).

The drug is trafficked through the intracellular organelles (lysosomes, Golgi apparatus, endoplasmic reticulum, and mitochondria) resulting in organelle injury and cell death. Aminoglycoside nephrotoxicity is noted 5-7 days after drug initiation and can occur even with closely monitored therapeutic drug levels. Concomitant use of nephrotoxins, sepsis, volume depletion, advanced age, aminoglycoside type, and multiple daily divided doses increase the risk. AKI is primarily nonoliguric, and injury is often reversible upon drug discontinuation.

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Table 2. Select Drugs Causing Direct Renal Tubular Injury

Drug/Toxin	Mechanism of Tubular Injury	Clinical Manifestations	Prevention/Management
Chemotherapeutics			
Cisplatin	• PT uptake via basolateral OCT2. • Activation of "mitochondrial–ER–stress" pathway leading to mitochondrial dysfunction, oxidative injury, and apoptosis. • Can cause vasoconstriction and ischemic tubular injury. • Affects PT, loop of Henle and DT, CD	• Common: AKI (one-third of patients), FS, and hypomagnesemia (frequently associated). • Less common: hypokalemia, renal salt wasting, and hypocalcemia. • Also described: NDI (due to CD toxicity), anemia (due to cisplatin-induced erythropoietin deficiency), and thrombotic microangiopathy (rare).	• Preventive strategies are IV isotonic crystalloid +/− mannitol-induced diuresis, using the lowest effective cisplatin dose, avoiding use of concomitant nephrotoxins, and providing close monitoring of renal function and serum electrolytes. Less nephrotoxic alternatives such as carboplatin and oxaliplatin may be used. • Treatment requires dose reduction and often drug discontinuation as well as electrolyte repletion.
Ifosfamide (alkylating chemotherapeutic agent used to treat sarcomas, testicular cancer, and refractory lymphoma in adults and children)	• Basolateral OCT2-mediated PT cell uptake. • Its intracellular metabolism results in production of an active nitrogen mustard that alkylates and damages DNA, and CAA, which results in oxidative stress and mitochondrial injury.	• Common: dose-dependent AKI and proximal tubulopathy (FS) (prevalence 15%-60%). • Rare: Cases of NDI and distal renal tubular acidosis. • Risk factors include coadministration with cisplatin and baseline CKD.	• Mesna and N-acetylcysteine have no proven efficacy in prevention of toxicity, and no definitive preventive strategies exist. • Adjust dose for underlying eGFR. • Treatment is conservative. Renal recovery is often seen with drug discontinuation, but CKD can develop.
Antivirals			
Cidofovir	OAT1-mediated uptake and PT injury via apoptosis.	• Most common: AKI • Common: CKD, proteinuria, FS • Rare: NDI	• Probenecid (inhibitor of OAT1) lowers cidofovir entry into PT cells and is used (with IV volume expansion) to limit cidofovir-induced PT injury. • Use contraindicated if GFR < 55 mL/min, Scr > 1.5 mg/dL, or proteinuria > 100 mg/dL. • Treatment of suspected kidney injury is dose reduction/drug discontinuation.
Tenofovir	• OAT1>OAT3-mediated uptake. • Dose-dependent decrease in mitochondrial ATP synthase, or complex V resulting in lack of ATP generation and mitochondrial dysfunction" and PT cell injury. Also affects DT.	AKI, CKD, FS, NDI (polyuria)	• Avoid use of TFV in patients with an eGFR < 60 mL/min (recommended). If unavoidable, use renal dose adjustment, closely monitor GFR, and discontinue drug if GFR falls below 25% from baseline levels. • Most effective treatment of TFV nephrotoxicity is early drug discontinuation
Antibiotics			
Aminoglycosides	• PT (primarily S1 and S2 segments) loop of Henle and CD • 10% of the filtered drug is taken up into PT cells via membrane phospholipid binding and megalin-mediated endocytosis resulting in organelle injury, disrupted function, and cell death.	AKI, FS, pseudo-Bartter syndrome (polyuria, salt wasting, hypokalemia, hypomagnesemia)	Toxicity can be seen even with therapeutic drug levels and is often reversible with drug discontinuation.

(Continued)

Table 2 (Cont'd). Select Drugs Causing Direct Renal Tubular Injury

Drug/Toxin	Mechanism of Tubular Injury	Clinical Manifestations	Prevention/Management
Vancomycin	• Drug enters PT cells via basolateral OAT1 and OAT3. • Dose-related PT mitochondrial injury is mediated via reactive oxygen species, activation of complement and mitochondrial stress pathways (cytochrome-c and caspase mediated). • Idiosyncratic AIN is less common. Obstruction and tubular inflammation are the proposed mechanism of vancomycin cast nephropathy.	AKI (controversy exists whether association between high serum vancomycin levels and AKI is cause and effect vs circumstantial)	• Dose should be adjusted for GFR. • Trough levels should be closely monitored; toxicity has been observed with trough levels > 30 mg/L.

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; ATP, adenosine triphosphate; CAA, chloroacetaldehyde; CD, collecting duct; CKD, chronic kidney disease; DT, distal tubule; eGFR, estimated glomerular filtration rate; ER, endoplasmic reticulum; FS, Fanconi syndrome; GFR, glomerular filtration rate; NDI, nephrogenic diabetes insipidus; OAT, organic anion transporter; OCT, organic cation transporter; PT, proximal tubule; Scr, serum creatinine; TFV, tenofovir.

Case 7: *A 25-year-old woman with a history of intravenous drug abuse is admitted with fever, shortness of breath, and hypotension. Evaluation reveals cardiac valvular vegetations, and a diagnosis of infective endocarditis is made. Blood cultures grow methicillin-resistant Staphylococcus aureus, and she is started on intravenous vancomycin at 1 g twice daily. Her creatinine level on admission is 0.6 mg/dL and remains stable during her 1-week hospitalization. She is discharged with a plan to complete 6 weeks of intravenous vancomycin. Routine laboratory tests done 2 weeks later note a creatinine of 2.0 mg/dL. Her only other medication is omeprazole, 20 mg daily (stable dose for 2 years). On examination, the patient is afebrile, and her blood pressure 120/60 mm Hg, with normal lung sounds. A 3/6 cardiac ejection systolic murmur is noted. Her abdomen is soft with good bowel sounds. Laboratory data reveals WBC 6000/μL, hemoglobin, 12.5 g/dL (stable); serum sodium, 136 mEq/L; chloride, 102 mEq/L; potassium, 4.6 mEq/L; total CO_2, 22 mEq/L; SUN, 28 mg/dL; and serum creatinine, 2.2 mg/dL. The serum vancomycin trough is 31 mg/L. Her serum complements are normal, and blood cultures are negative. Urinalysis reveals trace protein, 1+ leukocyte esterase, and no blood. Urine sediment reveals 3-5 renal tubular epithelial (RTE) cell casts/HPF and numerous muddy brown casts/HPF.*

Question 8: What is the most likely cause of AKI in this patient?

(a) Vancomycin-associated nephrotoxicity
(b) Omeprazole-induced AIN
(c) Postinfectious glomerulonephritis
(d) Sepsis-induced ATI.

For the answers to these questions, see the following text.

The case describes AKI in the setting of a supratherapeutic vancomycin trough level and evidence of tubular injury on urine sediment examination, raising concern for (a) vancomycin-associated nephrotoxicity (VANT). Although PPIs can cause AIN, this patient has been on a stable dose for several years, which makes PPI-induced AIN less likely. There is no evidence of sepsis (normal WBC, serum complements, negative blood cultures) and no hematuria, making choices (c) and (d) unlikely.

Vancomycin is a glycopeptide antibiotic used to treat serious Gram-positive infections. It undergoes glomerular filtration and enters PT cells via basolateral OATs 1 and 3. Experimental models have described dose-related vancomycin-induced renal tubular oxidative injury via reactive oxygen species and activation of complement and mitochondrial stress pathways (cytochrome-c and caspase mediated). Histopathologically, 3 distinct lesions of VANT have been observed. Dose-dependent ATI is the most common, and idiosyncratic AIN is less frequently reported. A third lesion known as vancomycin-induced cast nephropathy (first described in 2017) notes ATI along with obstructive distal tubular casts composed of noncrystalline

spherical vancomycin aggregates entangled with uromodulin (Fig 7). Tubular obstruction and inflammation are proposed mechanisms of injury; however, there is debate that these casts may simply represent decreased "washout" in VANT, and their pathogenicity remains to be proven.

Despite well-described experimental pathways of injury, the reported incidence of VANT in clinical practice is highly variable (0-40%). Studies have been limited by clinical heterogeneity, various AKI definitions, lack of randomized data, and confounders such as presence of multiple nephrotoxins. The risk factors include higher therapeutic vancomycin troughs (15-20 mg/L vs 10-15 mg/L), supratherapeutic levels (5% AKI is reported with levels of < 10 mg/L vs 85% with levels of >35 mg/L), >7 days of therapy, concomitant use of aminoglycosides and piperacillin-tazobactam (likely due to altered drug pharmacokinetics), and preexisting CKD. However, it is unclear whether the observed association between high vancomycin level and AKI reflects cause and effect or is purely circumstantial; that is, it is unclear whether the high vancomycin level results in nephrotoxicity or whether AKI from other causes results in decreased renal vancomycin clearance and a higher drug level. A recent meta-analysis (7 randomized controlled trials and 6 cohort studies) has provided moderate-quality evidence for VANT: the relative risk of developing AKI with vancomycin was 2.45 (95% CI, 1.69-3.55) when compared with other known non-nephrotoxins.

Despite the debate, it is reasonable to suspect VANT if AKI develops in the setting of elevated vancomycin levels (>30 mg/L), and discontinuation of the drug is recommended, which often results in renal recovery.

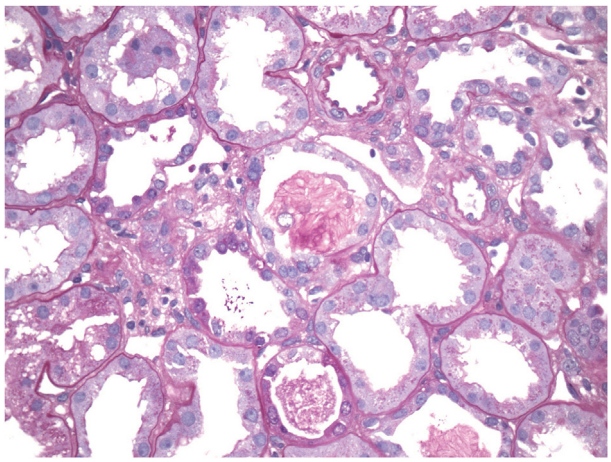

Figure 7. Vancomycin-associated cast nephropathy. Light microscopy of renal histology shows acute tubular injury (loss of apical brush border, cytoplasmic attenuation, nuclear enlargement, and prominent nucleoli) and a cast displaying pale pink material (uromodulin) that is consistent with a vancomycin-uromodulin cast (periodic acid–Schiff; original magnification, ×400). Image © 2023 M Barry Stokes and is reproduced with permission of the copyright holder.

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Herbal Nephropathies

With the rise in use of herbal medications, which are often unregulated, herbal nephropathies have become an important cause of kidney injury. The herbal substance itself or the additives/contaminants used in its manufacturing can have direct nephrotoxicity or result in serious drug interactions. Various renal syndromes have been reported, including ATI (*Securidaca longipedunculata*, *Euphorbia matabelensis*), AIN, crystalluria (*ma huang*), Fanconi's syndrome (*Aristolochia* species, cadmium), chronic interstitial nephritis (*Aristolochia, Akebia* species), and so on.

A detailed discussion on herbal nephropathies is beyond the scope of this article, and the reader is directed to several comprehensive reviews on this topic.

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In summary, toxic nephropathies are a relatively common cause of AKI and CKD and can affect various intrarenal structures utilizing a range of molecular mechanisms to result in renal injury. The kidney's primary role in metabolism and excretion of endogenous and exogenous substances via glomerular filtration and tubular secretion increases its susceptibility to their toxic effects. Drug/toxin and patient characteristics ultimately determine the impact and severity of renal injury.

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