



Drug-Induced Acute Kidney Injury

9

Randy L. Luciano and Mark A. Perazella

9.1 Introduction

Therapeutic and diagnostic agents have long been noted to alter kidney function. The kidney is a common site of drug toxicity since many drugs are filtered, secreted, reabsorbed, biotransformed, and excreted by the kidney. The resulting enhanced and prolonged renal exposure to various drugs and drug metabolites can lead to injury within all compartments of the kidney: the interstitium, tubules, glomeruli, and renal blood vessels. Recognizing acute kidney injury (AKI) syndromes that are associated with various agents can lead to early identification in the treatment course of potentially harmful drugs and therapeutic agents. Once identified, the medication or agent can be withheld or dose-reduced, thereby significantly impacting and potentially reducing the duration and severity of kidney injury. This chapter focuses on diagnosis and recognition of pat-

terns of AKI associated with certain drugs. While not all encompassing, it highlights major drugs.

9.2 Epidemiology of Drug-Induced Kidney Injury

The incidence and prevalence of drug-induced acute kidney injury (DI-AKI) are problematic and difficult to determine for several reasons. While therapeutic agents have been implicated in up to 60% of all hospital-acquired acute kidney injury (AKI) [1], the incidence is actually quite variable. In-hospital administration of medications has contributed to approximately 17–27% of all AKI, based on various studies [2–6]. The wide variability of estimating AKI prevalence in these studies is multifactorial. First, the prevalence variability of AKI may be related to the definition of AKI employed in certain studies. Second, most studies capture data on ICU patients yet miss the data on non-ICU patients, and very few studies examine AKI in non-hospitalized patients. Third, the inclusion of diagnostic agents, such as radiocontrast, can significantly alter the percentages of drug-induced versus other causes of AKI in hospitalized patients. Fourth, the effect of therapeutic agents on patients with chronic kidney disease (CKD) is often overlooked or actively excluded. Despite the variability, drug-induced AKI does have a high incidence and

R. L. Luciano
Section of Nephrology, Department of Internal
Medicine, Yale University School of Medicine,
New Haven, CT, USA
e-mail: randy.luciano@yale.edu

M. A. Perazella (✉)
Section of Nephrology, Yale University School of
Medicine, New Haven, CT, USA
Department of Medicine, Yale University,
New Haven, CT, USA
e-mail: mark.perazella@yale.edu

prevalence and is associated with an increased morbidity and mortality.

9.3 Risk Factors for Drug-Induced Kidney Injury

Risk factors for drug-induced AKI can be divided into risks specific to the drug or diagnostic agent, factors specific to the kidney's drug handling, or characteristics specific to the patient (Table 9.1) Distinguishing these various risks is critical to assess whether any modifiable factors exist that can facilitate the use of measures that prevent or alleviate injury. While medications or therapeutic agents themselves are directly toxic or injurious to the kidney,

Table 9.1 Risk factors for drug-induced acute kidney injury

Kidney-specific factors
High blood flow rate (up to 25% if cardiac output)
Differential sensitivity based on metabolic activity with kidney (cells in loop of Henle are more sensitive)
Increased accumulation and concentration of drugs or metabolites
Transport properties of renal tubular epithelial cells
Enzymes specific for biotransformation that can lead to generation of reactive oxygen species
Patient-specific factors
Older age (>65 years)
Female gender
Acute kidney injury
Chronic kidney disease
Nephrotic syndrome
Acute and chronic heart failure
Cirrhosis
True or effective volume depletion
Metabolic derangements
Hypercalcemia, hypokalemia, hypomagnesemia
Alkaline or acidic urine pH
Host genetic factors
Gene mutations in hepatic or renal CYP450 enzymes
Gene mutations in renal transport channels
Drug-specific factors
Prolonged exposure
Direct nephrotoxic effects of a compound
Combinations of medications leading to or enhancing nephrotoxicity
Insolubility leading to crystal precipitation

development of AKI is significantly influenced by the presence of concurrent patient risk factors for nephrotoxicity.

9.3.1 Renal Risk Factors

The kidney itself is more prone to injury based on several factors. First, the kidney has significant exposure to potentially nephrotoxic medications and therapeutic agents by virtue of its high blood flow rate, which averages approximately 20–25% of cardiac output. As a result, therapeutic and diagnostic agents are delivered at a high rate to the kidney, allowing for greater exposure of potentially toxic substance to the kidney, thereby contributing to the burden of kidney injury [7].

On a cellular level, certain areas of the kidney are more prone to injury. Renal tubular epithelial cells (RTECs) that exist deep in the renal medullary regions are highly metabolically active, resulting in increased oxygen consumption. This demand creates a relatively hypoxic environment that makes cells exquisitely sensitive to toxic injury. As a result, these RTECs, through localized hypoxia, have a decreased ability to adequately respond to nephrotoxic substances that are encountered. In addition to this inherent hypoxic property of the cellular environment, the medullary region also has a significant concentrating ability, which can lead to the accumulation of drugs or drug metabolites at high concentrations. Ultimately, this concentrating effect on drug levels may promote toxic renal injury [7].

The unique transport properties of proximal RTECs make this region more prone to injury. These cells have extensive apical and basolateral cellular uptake mechanisms. Apical uptake of compounds occurs through endocytosis and other uptake mechanisms [8–10]. Upon uptake via the megalin/cubilin receptor, compounds enter lysosomes, accumulate and form myeloid bodies and/or rupture, and spill toxic substances into the cytoplasm. This results in the accumulation and concentration of potentially nephrotoxic substances within cells that can result in signaling pathways and cascades that ultimately

lead to cell injury and death. Basolateral delivery also leads to proximal tubular exposure of compounds. Delivery occurs via peritubular capillaries, with uptake occurring through transporters called human organic anion/cation transporters (HOAT/HOCT) [9, 11]. This movement of potentially toxic substances into the intracellular space, and subsequent shuttling and apical excretion, increases the exposure of the proximal tubular cells to these substances, thereby contributing to AKI.

On a biochemical level, the kidney has several enzymes responsible for the biotransformation of drugs. These include CYP450 and flavin-containing monooxygenases. The breakdown of compounds in the kidney results in the generation of potentially nephrotoxic metabolites and reactive oxygen species that can promote injury (apoptosis and/or necrosis). Reactive oxygen species generation leads to oxidative stress and the generation of free radicals. Through nucleic acid oxidation and alkylation causing DNA breaks, direct protein damage, and lipid peroxidation, kidney injury can occur [7].

9.3.2 Patient Risk Factors

Various patient-specific factors also contribute to drug-induced kidney injury. Certain factors are not modifiable including age and sex. Both older age (>65 years old) and female sex increase the risk of drug-induced AKI. This effect is generally multifactorial. First, reductions in total body water are common in the elderly due to decreased lean body mass, leading to a decrease in total body water that affects drug distribution and plasma concentrations of water-soluble drugs. Second, lower muscle mass may impair the ability to detect abnormal GFRs masked by apparently normal serum creatinine concentrations. GFR estimating equations that are based on age attempt to ameliorate this concern, but oftentimes serum creatinine concentration, and not estimated GFR is assessed when clinicians are dosing drugs. Lastly, the elderly also tend to be more prone to increased renal arteriolar vasoconstriction sec-

ondary to angiotensin II or endothelin excess. This renal effect may expose the patient to increased drug concentrations [12–14].

Additional risk factors for drug-related injury unique to patients include the presence of acute or chronic kidney disease. Underlying kidney injury, either current AKI or CKD, makes a patient more susceptible to drug nephrotoxicity. Acutely injured kidneys may have ischemia preconditioned tubules that generate a more pronounced renal oxidative injury response to toxins. In both AKI and CKD, there may be an increased exposure of a decreased number of functioning nephrons to toxins, which will exacerbate pre-existing kidney dysfunction. Employing GFR estimating equations during AKI may also result in an overestimation of the GFR, especially with rapidly declining renal function. This can potentially lead to mis-dosing of medications leading to the accumulation of toxic doses of medications or metabolites [7]. More severe and prolonged AKI often develops, which risks development of CKD.

Apart from underlying kidney disease, other systemic diseases that are known to impair renal perfusion can increase susceptibility to drug injury. These include edematous states such as acute and chronic heart failure, nephrotic syndrome, and cirrhosis, which create a state of effective circulating volume depletion and renal underperfusion. This effectively volume-depleted state will lead to the activation of neurohormonal cascades that reduce renal perfusion. Patients with nephrotic syndrome and cirrhosis, and to a minor degree in malnourished heart failure patients, will develop hypoalbuminemia. As a result of reduced protein binding of drugs, low serum albumin can lead to increased free drug concentrations, thereby increasing exposure of certain potentially toxic drugs to the kidney [13, 14].

Certain host genetic differences can explain the heterogenous response that patients have to drug-induced kidney injury. For example, differences in innate host immune response genes can predispose certain patients to allergic drug reactions with acute interstitial nephritis (AIN) developing. In addition, the kidney has CYP450

enzymes, and polymorphisms in these genes may lead to altered metabolism with the potential for increased nephrotoxicity [15, 16]. Also, specific polymorphisms in transport channels may lead to altered metabolism with associated drug nephrotoxicity.

9.4 Diagnosis of Drug-Induced Acute Kidney Injury

Diagnosis of DI-AKI is similar to that of other forms of AKI and utilizes a combination of clinical, laboratory, and imaging findings (Table 9.2).

Table 9.2 Tests use to diagnose drug-induced acute kidney injury

Test	Findings	Advantages	Disadvantages
<i>Physical exam</i>			
Volume assessment	Peripheral or pulmonary edema	Relatively easy to assess	May not be an accurate representation of intravascular volume status
Rash	Multiple rashes	Superficial and easy to assess or biopsy	Non-specific and non-sensitive
Fever	Elevated temperature vs. hyperpyrexia	Objective	Non-specific and non-sensitive
Flank pain	Associated flank swelling or tenderness	Easy to obtain history	Non-specific and non-sensitive
<i>Serum laboratories</i>			
BUN or creatinine	Elevated BUN or creatinine	Easy to measure	Need to know baseline creatinine
Electrolytes	Decreased phosphorous or potassium in tubular disorders	Easy to measure	May be due to non-kidney causes
CBC	Elevated eosinophils could suggest allergic reaction	Easy to assess	Non-specific and non-sensitive
<i>Urine evaluations</i>			
FeNa, FeUrea	Alterations around a predetermined value	Easy to obtain and calculate	Non-specific and non-sensitive
Urinalysis	Evaluate for specific gravity, protein, glucose, heme, leukocyte esterase, red and white blood cells, bacteria, yeast, and casts	Easy to obtain	False negatives exist, inaccuracy with cast and crystal interpretation
Urine eosinophils	Presence of eosinophils in urine with Hansel stain	Should not be used	Low sensitivity and specificity
Urine sediment analysis	Identify abnormal cells, casts, crystals	Direct correlation with kidney injury that can be localized to the site of injury	Requires a trained nephrologist and the presence of a microscope and centrifuge
<i>Imaging</i>			
Ultrasound	Kidney size, echogenicity, hydronephrosis	Evaluation of obstruction in noninvasive safe way	Technologist dependent, limited in diagnostic capabilities
Computed tomography	Kidney size, echogenicity, hydronephrosis	Noninvasive	Requires radiation exposure, contrast not often used, but is a nephrotoxin
Gallium scintigraphy	Enhancement of kidneys with active inflammatory cells	Noninvasive	Low sensitivity and specificity, may be difficult to order
FDG-PET scan	Enhancement of kidneys with active inflammatory cells	Noninvasive	Only small studies have looked at this
Biopsy	Identifies kidney injury based on light, immunofluorescence, and electron microscopy	Direct look at site of kidney injury	Invasive with risks of bleeding and infection

Kidney injury may lead to various physical exam abnormalities. If allergic in nature, drug-induced injury may lead to a fever or rash; however these findings are relatively uncommon. The rash can present as a morbilliform, maculopapular, toxic epidermal necrolysis or a purpuric rash depending on the underlying renal lesion [17]. In addition to these findings, the patient may experience flank pain if there is swelling in the renal parenchyma and stretching of the renal capsule.

Laboratory evaluations can provide insight into the type of kidney injury. Elevations in blood urea nitrogen (BUN) and serum creatinine concentrations are often the first clinical manifestation of drug-induced kidney injury. As shown in animal (and some human) studies, novel serum and urinary biomarkers of kidney injury may provide an earlier diagnosis of acute kidney injury but are currently not available in the USA. Serum potassium and phosphorous are usually elevated in AKI; however hypophosphatemia and hypokalemia can also be important findings in the setting of certain forms of drug-induced tubular injury. Low serum phosphorus and potassium, in the correct context, can indicate adequate or modestly reduced GFR, yet impaired tubular reabsorption, suggesting proximal RTEC dysfunction. This injury pattern is often seen in a Fanconi syndrome, which occurs with several drugs.

A complete blood count can also provide clues into the type of kidney injury. Increased serum eosinophils may be seen with allergic or hypersensitivity-related renal disorders, both of which are common forms of drug-induced kidney injury. The combination of anemia and thrombocytopenia is very suggestive of a microangiopathic hemolytic anemic disease, such as drug-induced thrombotic microangiopathy, which is associated with AKI.

When evaluating drug-induced kidney injury, a thorough examination of the urine, through both automated laboratory analysis and direct sediment analysis, is critical in classifying the various types of renal injury and predicting the severity of injury. Automated urinalysis provides information that is complimentary to clinical labs and the urine sediment findings. Normoglycemic glucosuria suggests decreased proximal tubular

glucose reabsorption, indicative of tubular dysfunction. Positive leukocyte esterase indicates the presence of leukocytes in the urine suggesting infection when accompanied by bacteria or yeast in the urine or, in the absence of microorganisms, inflammation along the genitourinary tract. Urinary eosinophils have been used in the past to suggest the possibility of AIN. However, the sensitivity and specificity of this test are quite low, and therefore, it is not recommended in the diagnostic workup [18].

Protein present on automated urinalysis indicates urinary albumin and not other proteins. Protein positive on a urinalysis is qualitative and should prompt protein quantification by the direct measurement of urinary albumin and total protein. Kidney injury that is predominantly glomerular in nature will generally have a large amount of albuminuria relative to total urinary protein. In contrast, low urinary albumin levels relative to total protein suggest either the presence of excess filtered non-albumin serum proteins or tubular dysfunction with tubular proteinuria [19, 20].

Urine sediment examination is an extremely useful diagnostic tool. The presence of RTECs, white blood cells (WBCs), or red blood cells (RBCs) can be suggestive of kidney injury. While RTECs may exist in low numbers in a patient without kidney injury, an abundance of RTECs often indicates underlying tubular injury. The presence of isomorphic RBCs can suggest an injury anywhere along the genitourinary tract, from the kidney to the urethra. However, dysmorphic RBCs is highly specific for glomerular injury, although they can be seen with certain inflammatory tubular disorders. The presence of urinary WBCs suggests inflammation anywhere along the genitourinary tract. The presence of bacteria or yeast alongside WBCs should raise the suspicion for an infection, whereas sterile pyuria raises suspicion for a renal inflammatory process [21].

Apart from cells, the urinary sediment is also useful in the identification of casts (cellular and noncellular) and crystals. Casts are composed of Tamm Horsfall protein, or uromodulin, a protein secreted by loop of Henle renal tubular cells. Hyaline casts are made of this protein and

form in the setting of sluggish urinary flow rates. Cellular casts, whether RBC, WBC, RTEC, or a mix of these cells, is indicative of intrinsic kidney injury [22]. Muddy brown granular casts are also indicative of kidney injury and generally reflect ischemic or nephrotoxic acute tubular injury. Crystals may also be present in the urinary sediment [23]. Crystal-induced kidney disease will be discussed in detail in subsequent sections.

Imaging may be a useful tool in the diagnosis of acute and chronic kidney disease. Ultrasound demonstrates kidney size and echogenicity, which may indicate the possibility of chronic kidney disease or congenital or acquired unilateral kidney. Ultrasound is also helpful in evaluating for obstruction, manifested by hydronephrosis and/or hydroureter. Gallium scintigraphy and FDG-PET scans have also been used to diagnose AKI due to kidney inflammation such as AIN but are insensitive and non-specific findings [17].

Kidney biopsy is the gold standard in the diagnosis of drug-induced kidney injury. With examination of renal histology, the vasculature, glomeruli, tubules, and interstitium should be evaluated for injury patterns that can differentiate between the different etiologies of drug-induced kidney injury. Examples include drug-induced thrombotic microangiopathy and vasculitis as indicative of drug-associated vascular injury and immune-complex deposition and podocytopathies from a large number of drugs causing glomerular injury. Numerous medications promote acute tubular injury and necrosis through direct toxic effects, ischemic injury, osmotic effects, and crystal deposition within tubular lumens. An inflammatory infiltrate within the renal interstitium along with tubulitis and sometimes granulomas are histologic manifestations of drug-induced acute interstitial nephritis observed on kidney biopsy.

9.5 Drug-Induced Acute Kidney Injury

Many drugs can affect kidney function. The following sections describe drug-induced kidney injury patterns based on the underlying location

in the kidney. Common drugs or drug classes are included, with more in-depth listings of drugs included in associated tables.

9.5.1 Prerenal (Hemodynamic) Acute Kidney Injury

Glomerular filtration is modulated by a number of local and systemic hormones which include the prostaglandins (PG), angiotensin, endothelin, catecholamines, and atrial natriuretic peptide, to name a few. Afferent vasodilation and efferent vasoconstriction allow maintenance of glomerular filtration, especially when renal perfusion is compromised by hypotension and true or effective volume depletion. Perturbations of these vascular forces can lead to prerenal physiology or hemodynamic reductions in GFR. Several drugs may reduce GFR by altering afferent or efferent vascular tone (Fig. 9.1).

9.5.1.1 Afferent Vasoconstriction

Nonsteroidal anti-inflammatory drugs Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed as analgesics, antipyretics, and anti-inflammatory medications. NSAIDs are implicated in many forms of drug-related injury including hemodynamic AKI from dysregulation of glomerular blood flow [24, 25]. NSAIDs inhibit cyclooxygenase (COX) enzymes, which convert arachidonic acid (AA) to various PGs. Inhibition of the COX enzymes leads to a decrease in prostaglandin synthesis, thereby severely curtailing prostaglandin function to modulate afferent arteriolar tone. As PGs potentiate afferent arteriolar dilatation, inhibition of their synthesis through NSAID use can lead afferent vasoconstriction, thereby impairing renal blood flow leading to a decreased GFR and hemodynamic AKI. Normally the effects of prostaglandins on arteriolar tone are minimal; however in severe acute volume depletion, in effective volume depletion (cirrhosis, heart failure, nephrotic syndrome), or in CKD, patients are prostaglandin dependent for maintenance of GFR. In these settings, PG inhibition can tip the afferent arteriole to vasoconstriction, thus leading to decreased GFR. COX

9.5.2 Intrinsic Kidney Disease

9.5.2.1 Vascular Disease

Several medications have been implicated in drug-induced AKI as a result of vascular injury. As the kidney is extremely vascular organ, local and systemic disease causing renal vascular injury is often associated with AKI. Below are three forms of vascular injury that have been associated with drug-induced AKI.

Cholesterol embolization is a syndrome that can be induced by anticoagulant and thrombolytic therapy. While this complication more often occurs following arteriography and certain vascular procedures, the diagnosis is sometimes difficult to differentiate from radiocontrast-induced AKI. Upon administration of the thrombolytic agents, which dissolve thrombus covering atherosclerotic plaques, cholesterol fragments embolize to vessels in various end organs including the kidneys. Most often the skin, as manifested by acute distal cyanosis in the form of infarcted digits or livedo reticularis, or the kidney, as manifested by AKI and acute hypertension, is involved. Recognition of the syndrome can be tricky as AKI usually manifests upward to 1–2 weeks, and it mimics other syndromes including vasculitis [33, 34]. Therapy is supportive although cases of steroid therapy responsiveness have been reported. Outcomes are quite poor, with one study showing greater than 25% of patients requiring chronic hemodialysis and a large percentage of patients developing nondialysis-dependent CKD.

Drug-induced thrombotic microangiopathy (TMA) has also been reported with numerous medications (Fig. 9.2). TMA following drug administration can either be caused by drug-related induction of antibody production (targeting ADAMTS-13, inhibitory complement factors, or platelets) or direct toxicity of the drug leading to vascular injury and platelet-rich thrombus formation in small blood vessels. A list of drugs implicated in both forms of TMA is listed in Table 9.3. Anticancer agents such as the anti-angiogenesis drugs, gemcitabine, and mitomycin C are associated with TMA. Proteinuria and hypertension are the most common renal effects of the ADs; however AKI often signal

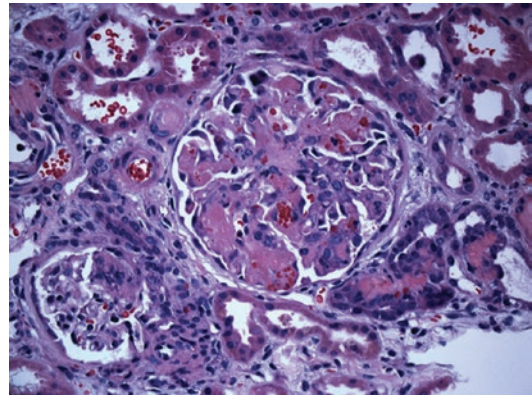


Fig. 9.2 Thrombotic microangiopathy (TMA) is seen in the glomerulus of a patient treated with gemcitabine. As seen in this image, the glomeruli containing multiple intracapillary fibrin thrombi, mesangiolysis, and numerous red blood cell fragments within the injured subendothelial and mesangial areas of the glomerular tuft. These findings characterize TMA

severe TMA. This class of drugs is now the most common cause of drug-induced TMA. Systemic evidence of TMA is absent in 50% of patients, and a renal limited form of TMA must be entertained in patients with AKI. Although relatively rare, a cumulative TMA incidence of 0.31% has been noted in patients exposed to gemcitabine. Gemcitabine use has been noted to have both immune-mediated and direct toxicity leading to its nephrotoxicity profile [35, 36]. Interferon when used in high dose and for prolonged periods is associated with TMA, especially in patients with chronic myelogenous leukemia. The antiplatelet agents (ticlopidine, clopidogrel, and prasugrel) are all associated with TMA, while quinine exposure through prescription, beverages, and health food stores is associated with TMA via formation of quinine-dependent IgG antibodies to platelets.

Kidney-specific ANCA-associated vasculitis (AAV) has been associated with certain drugs, including hydralazine, minocycline, phenytoin, penicillamine, allopurinol, sulfasalazine, antitumor necrosis factor agents, and propylthiouracil (PTU) (Table 9.4). Cocaine cut with levamisole is another cause of AAV. ANCA-associated vasculitides refer to a disease that results in the production of anti-neutrophil cytoplasmic antibodies (ANCA) that can either have a cytoplasmic

Table 9.3 Drugs associated with thrombotic microangiopathy

Antiplatelet agents
Ticlopidine, clopidogrel, prasugrel
Dipyridamole
Defibrotide
Antineoplastic agents
Anti-angiogenesis drugs
Mitomycin C
Gemcitabine
Cisplatin/carboplatin
Estramustine/Iomustine
Cytarabine
Tamoxifen
Bleomycin
Daunorubicin
Hydroxyurea
Interferon
IFN- α
IFN- β
Immunosuppressive agents
Calcineurin inhibitors
Anti-CD33
Antimicrobial agents
Valacyclovir
Penicillins
Rifampin
Metronidazole
Tetracycline
Sulfisoxazole
Albendazole
Nonsteroidal anti-inflammatory agents
Diclofenac
Piroxicam
Ketorolac
Hormones
Conjugated estrogens \pm progestins
Others
Quinine
Simvastatin
Iodine
Cocaine

(C-ANCA) or perinuclear (P-ANCA) pattern. The C-ANCA pattern is almost exclusively caused by antibodies directed against proteinase 3 (PR3), while P-ANCA is usually due to antibodies directed against myeloperoxidase (MPO) but also can be seen with antibodies against lactoferrin and human leukocyte esterase (HLE) [37, 38]. Presence of these antibodies leads to small

Table 9.4 Drugs associated with immune-mediated glomerular injury

ANCA-associated vasculitis
Hydralazine
Antithyroid medications
Propylthiouracil, methimazole
Minocycline
Allopurinol
Penicillamine
Sulfasalazine
Cocaine (levamisole)
Drug-induced lupus
<i>Anti-arrhythmics</i>
Procainamide, quinidine, amiodarone
<i>Antihypertensives</i>
Hydralazine, methyldopa, captopril
<i>Antipsychotics</i>
Chlorpromazine, lithium
<i>Antibiotics</i>
Isoniazid, minocycline, sulfamethoxazole
<i>Anticonvulsants</i>
Carbamazepine, phenytoin, valproic acid
<i>Antithyroids</i>
Propylthiouracil
<i>Diuretics</i>
Chlorthalidone, hydrochlorothiazide
<i>Biologics</i>
TNF- α inhibitors, IFN- α
<i>Miscellaneous</i>
Statins, levodopa

vessel injury and when present in the kidney is manifested as a necrotizing glomerulonephritis (Fig. 9.3). Induction of vasculitis is quite rare in these medications. PTU is the drug that is most commonly associated with an AAV. PTU-associated ANCA conversion has been reported in 20–64% of patients, with only a very small fraction of patients (4–6%) having clinical evidence of vasculitis. Although vasculitis is not common, it should be recognized early, as consequences can be fatal if the medication is not withheld and immunosuppressive therapy not administered.

9.5.2.2 Glomerular Disease

Several forms of drug-induced glomerular disease (Table 9.5) have been reported, and these agents target all glomerular cell types (podocyte, endothelial cell, and mesangial cell). Classic

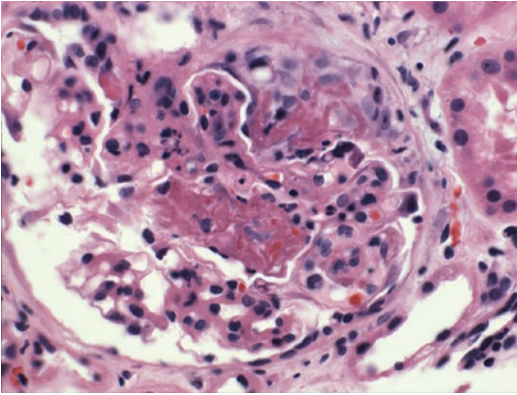


Fig. 9.3 The glomerulus reveals fibrinoid necrosis and early crescent formation in a patient with an ANCA-associated vasculitis (AAV) due to cocaine contaminated with levamisole

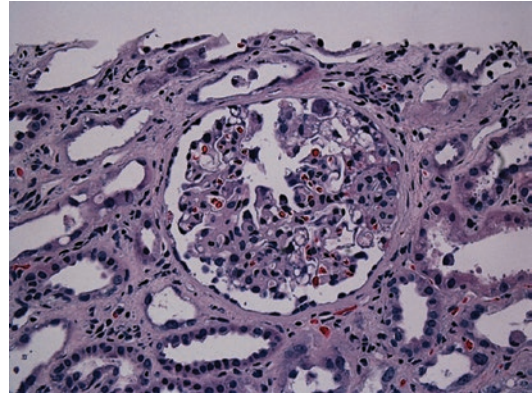


Fig. 9.4 Focal segmental glomerulosclerosis (FSGS) is a glomerular lesion due to a number of drugs including pamidronate, anabolic androgenic steroids, and interferon. There is sclerosis in a segment of the glomerular tuft (arrow), which is diagnostic for the FSGS lesion

Table 9.5 Drugs associated with glomerular injury

Minimal change disease
IFN- α , IFN- β
Pamidronate
Lithium
Nonsteroidal anti-inflammatory drugs
FSGS
IFN- α , IFN- γ
Pamidronate
Lithium
Sirolimus
Anabolic steroids

lesions include minimal change disease (MCD), membranous nephropathy (MGN), and focal and segmental glomerulosclerosis (FSGS). These are secondary forms of glomerulopathy which, while relatively uncommon, must be recognized to facilitate drug discontinuation and therapy to limit kidney injury. In these cases, drug-induced glomerular disease presents similarly to idiopathic or primary forms of glomerular diseases, although the effects, often proteinuria, may not be as severe. In general, one can demonstrate a temporal association between offending agent exposure and development of the glomerulopathy.

Drug-induced podocyte (glomerular epithelial cell) injury leading to either MCD or FSGS is well described. As with the idiopathic or primary counterparts, patients will usually have nephrotic-range proteinuria and peripheral

edema; however, it can be less severe. Drugs that have been implicated in MCD include interferon, pamidronate, lithium, and NSAIDs. Another podocytopathy associated with glomerular scarring is FSGS. Drugs implicated in causing FSGS (Fig. 9.4) include interferon, pamidronate, sirolimus, lithium, and anabolic steroids. These patients tend to have more severe AKI and may not fully recover kidney function following discontinuation. As with other forms of drug-induced injury, care is largely supportive with removal of the offending agent and sometimes a course of steroids [39].

Membranous nephropathy (Fig. 9.5) is a form of glomerular disease characterized by nephrotic syndrome and varying severities of AKI. Biopsy, unlike the two previously mentioned nephropathies, will demonstrate with thick capillary loops on light microscopy, granular immunofluorescence (IF) pattern, and glomerular subepithelial membrane immune complexes on electron microscopy. In contrast to primary MGN, immunofluorescence is often negative for anti-PLA2 antibodies with absent IgG4 subtype staining on IF [40]. MGN is described with penicillamine/bucillamine and gold salts, three antiquated agents that were used to treat rheumatoid arthritis. Now, however, MGN is reported, albeit rarely, with NSAIDs and selective COX inhibitors, the antitumor necrosis factor agent adalimumab,

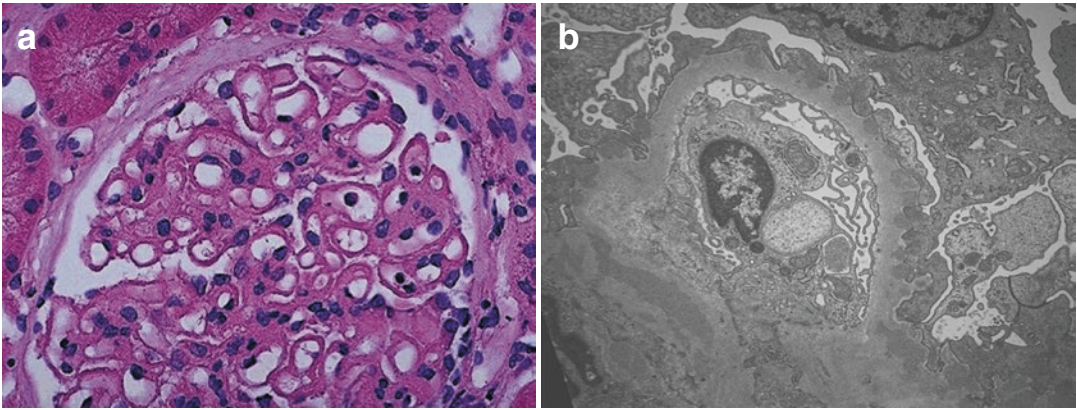


Fig. 9.5 (a) Membranous glomerulonephritis is seen on light microscopy in a patient treated with a nonsteroidal anti-inflammatory drug. The capillary loops are thickened and appear rigid. (b) On electron microscopy,

electron dense deposits are seen in the subepithelial space. These findings are diagnostic for membranous glomerulonephritis

captopril, and certain organic mercurials contained in skin-lightening creams. As NSAIDs are widely used, recognition that MGN can occur is important for clinicians, although it is less common than MCD. Drug discontinuation may reverse the lesion, but immunosuppressive therapy may also be employed.

Drug-induced lupus (DIL) is relatively uncommon, occurring more commonly in older patients (Table 9.4). Major organ involvement is rare but has been reported with glomerular involvement associated with hydralazine, sulfasalazine, penicillamine, and anti-TNF- α therapy [41]. Serologies in drug-induced lupus nephritis are slightly different than idiopathic lupus, with antihistone antibodies more prevalent, yet anti-dsDNA antibodies still present in hydralazine-induced lupus nephritis. Complement levels are variably reduced, and other abnormalities may be reported, such as the presence of p-ANCA antibodies. Treatment of drug-induced lupus nephritis includes removing the offending agent, with manifestations of disease resolving within days to weeks of this intervention. Major organ involvement including AKI can require the use of immunosuppressive agents.

9.5.2.3 Acute Interstitial Nephritis

Drugs are the most predominant cause of acute interstitial nephritis (AIN), ahead of autoim-

mune disorders and infections. In developed countries, studies have shown upward of 70% of AIN attributed to medications, especially hospital-acquired AIN. AIN typically presents as a steady, not abrupt, rise in serum creatinine approximately 2 weeks after introduction of a medications. This is not always the case, as repeat exposure may lead to a more abrupt rise in serum creatinine. Along this line, drugs such as the NSAIDs and proton-pump inhibitors may present with a gradual and prolonged rise in serum creatinine. Except for methicillin, AIN rarely presents with a systemic hypersensitivity reaction, with triad of fever, skin rash, and eosinophilia <5–10% and clearly much less common than kidney involvement. In contrast, AKI, as evidenced by a rise in serum creatinine, sterile pyuria with the presence of leukocyturia and white blood cell casts, and low-grade proteinuria are more commonly present [17].

AIN is an allergic response that is mediated predominantly by T cells in concert with plasma cells, eosinophils, neutrophils, and mast cells. The end result is an inflammatory cell-rich interstitial infiltrate accompanied by tubulitis and sometimes granuloma (Fig. 9.6). Certain factors can play a role in the development of AIN, including drugs acting as haptens, molecular mimicry, and an individual's underlying immune response genes. However at times, although rarely, a humoral

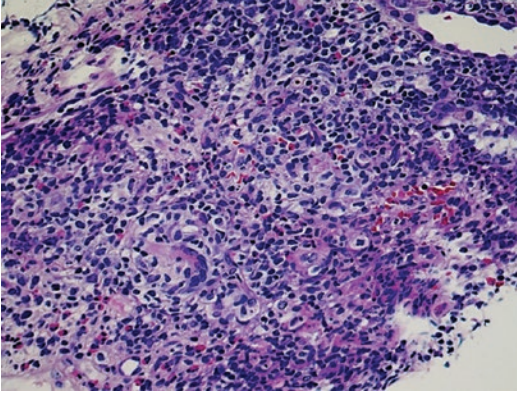


Fig. 9.6 An inflammatory infiltrate within the renal interstitium along with separation and injury to the tubules is seen. This is diagnostic of acute interstitial nephritis, which can be due to any number of medications

response may lead to the inflammatory response, whereby portion of the drug, which acts as a hapten, binds to the tubular basement membrane and evokes an antibody response with formation of tubulointerstitial immune complexes [17].

All drugs are suspect when AIN has been diagnosed, but certain medications, perhaps based on usage patterns, are more common. When discovered, the first and foremost therapy is to remove the offending agent. If AKI is severe enough, time of recognition is recent, minimal interstitial fibrosis is present on histology, and the resulting AIN is from a more acute rather than chronic exposure, a course of steroids may be warranted with the hopes of preserving kidney function. Table 9.6 lists drugs that are commonly associated with AIN. Three classes of medications that have been commonly implicated in acute interstitial nephritis are discussed.

Antimicrobials have a high potential to cause AIN [42]. Beta-lactams (penicillin derivatives and cephalosporins) are more common inducers of AIN than other antibiotics. Methicillin frequently caused AIN with an associated hypersensitivity syndrome and for this reason is no longer routinely used. Other beta-lactams remain a common cause of AIN along with the sulfonamides. As with methicillin, these drugs more tend to cause more hypersensitivity reactions, with fever, rash, and eosinophilia than other drugs. Fluoroquinolones have also been implicated in AIN, with ciprofloxacin being more common than the others. Several

Table 9.6 Drugs associated with interstitial nephritis

Antibiotics
β-lactams
Fluoroquinolones
Rifampin
Sulfa-based drugs
Vancomycin
Minocycline
Ethambutol
Antivirals
Acyclovir
Abacavir
Indinavir
Atazanavir
GI medications
Proton-pump inhibitors
Histamine-2 receptor blockers
Analgesics
Nonsteroidal anti-inflammatory drugs (including COX-2 inhibitors)
Anticonvulsants
Phenytoin
Carbamazepine
Phenobarbital
Miscellaneous
Allopurinol
Captopril
Tyrosine kinase inhibitors
Thiazide diuretics
Loop diuretics
Immune Checkpoint Inhibitors

antiviral agents can also cause AIN and must be considered when AKI develops. Discontinuation of the culprit drug is the mainstay of therapy. However, it may be difficult identifying the causative agent when several are employed. In addition, it may also be difficult to discontinue the antibiotic that is being used for a documented infection unless other good options are available. Avoidance of the particular antibiotic and possibly similar antibiotics of the same class is advised. Steroid therapy may also be warranted in cases of severe AKI, especially when AIN is documented within 2–3 weeks of drug initiation and histology has limited interstitial fibrosis. This can be tricky when patient has severe underlying infection although steroids have been employed in sepsis and septic shock. Discussion with the infectious disease consultant is often warranted.

NSAIDs are another important cause of AIN [43]. Clinical presentation tends to be more subacute or chronic and usually falls well outside the classical range of the medication initiation within 1–2 weeks. Hypersensitivity symptoms and signs are extremely rare with these drugs. Unlike other forms of AIN, NSAIDs may be accompanied by nephrotic-range proteinuria due to associated MCD. The interstitial infiltrate typically shows a mononuclear infiltrate with few or no eosinophils. NSAID-induced AIN may develop due to inhibition of COX enzyme, which leads to leukotriene overproduction through the activity of lipoxygenases on arachidonic acid. These pro-inflammatory cytokines can be responsible for the interstitial inflammatory lesion observed with NSAID therapy. All NSAIDs, including topical preparations and the selective COX-2 inhibitor celecoxib, can cause AIN [44].

Proton-pump inhibitors (PPIs), which are a mainstay of therapy for acid-related gastrointestinal (GI) disease, are a well-described cause of AIN [45–47]. AIN was first described with omeprazole and subsequently with several other PPIs. Unlike other forms of drug-induced AIN, PPIs develop the lesion at a mean time of approximately 11 weeks. Like NSAIDs, patients often do not develop a typical hypersensitivity reaction. Early recognition of PPI-induced AIN and drug discontinuation is generally associated with a good prognosis. Importantly, AIN with the PPIs is a class affect, and switching to H2 antagonists is required for further treatment of acid-related GI disorders. While kidney function usually recovers, many patients may develop CKD.

9.5.2.4 Acute Tubular Injury/Necrosis

One of the most common renal lesions associated with drug therapy is acute tubular injury/necrosis (ATI/ATN), which often develops from direct tubular toxicity [48]. As mentioned, most patients have underlying risk factors for drug-induced tubular injury (Fig. 9.7). Tubular injury usually occurs in a dose-dependent fashion with increased exposure producing progressively worse injury moving from subclinical damage to advanced stage 3 AKI from severe ATN. The proximal tubule is particularly prone to injury as it is the

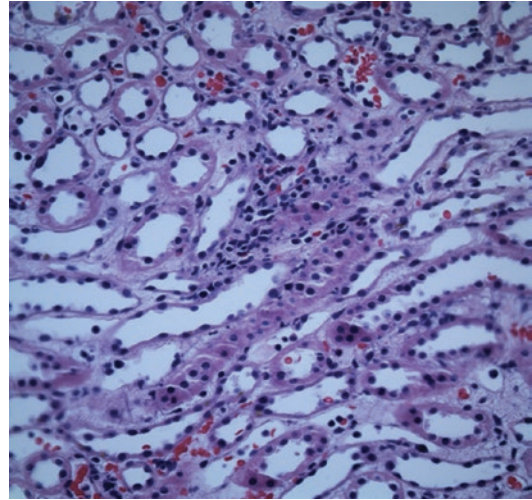


Fig. 9.7 Acute tubular injury/acute tubular necrosis (ATI/ATN) is seen with a number of medications. This lesion is characterized by tubular dilatation, tubular cell flattening with simplification, and dropout of cells into the tubular space

site of drug reabsorption through multiple pathways. Medications may injure cells through promoting mitochondrial dysfunction, disrupting lysosomal or cell membranes, enhancing cellular entry of calcium and other ions, and directly promoting the formation of free radicals. Indirect tubular injury by drugs can occur through induction of rhabdomyolysis with associated myoglobinuria and direct tubular pigment toxicity, as seen with the statin drugs. Table 9.7 lists various drugs associated with acute tubular injury/necrosis. Selected drugs or drug classes that have been commonly associated with acute tubular injury/necrosis are reviewed.

Aminoglycosides are bactericidal agents that have been employed for many years to treat gram-negative infections. Kidney injury with select aminoglycosides has been reported as high as 25% [49]. Aminoglycosides are freely filtered and due to cationic charge are attracted by apical phospholipids and reabsorbed in proximal tubules via megalin/cubilin receptor binding. Toxicity is associated with cationic charge with neomycin (most cationic) demonstrating a high degree of nephrotoxicity, followed by gentamicin, tobramycin, amikacin, and streptomycin. Tubular injury usually occurs 5–7 days

Table 9.7 Drugs associated with acute tubular necrosis

Antibiotics
Aminoglycosides
Gentamicin > amikacin > tobramycin
Cephalosporins
Cefazolin > cephalixin > ceftazidime
Vancomycin
Amphotericin B
Osmotically active agents
Contrast
Hydroxyethyl starch
Intravenous sucrose
Intravenous cyclodextrin
Mannitol
Antineoplastic agents
Platin-based chemotherapy agents
Cisplatin > carboplatin
Ifosfamide
Nucleotide analogues
Tenofovir
Cidofovir
Adefovir

after administration, with nephrotoxicity being dose dependent. Risks for AKI include volume depletion, underlying AKI or CKD, and patient age. AKI is generally nonoliguric and may be associated with electrolyte and acid-base disturbances due to aminoglycoside-related Fanconi or Bartter-like syndromes. Prevention or reductions in AKI are based on volume repletion and careful calculation of loading and maintenance doses based on eGFR. While monitoring peak and trough serum aminoglycoside levels can reduce risk of nephrotoxicity, single daily versus multiple doses per day reduced tubular injury and maintains drug efficacy. Dialysis is sometimes required for severe ATI/ATN. Dialysis does effectively remove aminoglycosides.

Several osmotically active agents that are excreted by the kidney can cause AKI from tubular injury [50]. These agents, which include intravenous sucrose (a carrier in some forms of intravenous immunoglobulin), radiocontrast dye, hydroxyethylstarch, mannitol, and intravenous cyclodextrin, are filtered macromolecules that are not metabolized by the kidney due to a lack of enzymes. These substances undergo proximal tubular uptake via pinocytosis, are internal-

ized, and taken up by lysosomes. Lysosomes are packed with these substances and due to inefficient removal cause severe cell swelling. Cellular swelling leads to disturbed cell function and tubular luminal occlusion, a process termed osmotic nephrosis or nephropathy. Risks for AKI include volume depletion, excessive drug concentrations, and underlying AKI or CKD. Patients may develop oliguric AKI and may require dialysis until renal recovery occurs within 5–7 days. Several large trials demonstrate increased AKI and dialysis requirement in critical care patients treated with hydroxyethyl starch [51, 52]. Treatment is largely supportive with avoidance of further nephrotoxin exposure and dialysis when indicated, which may also reduce drug levels and facilitate renal recovery.

Cisplatin is a member of the platinum-based chemotherapeutic agents utilized to effectively treat various malignancies. Tumor killing results from the ability of cisplatin to bind to and crosslink DNA, thereby leading to tumor cell apoptosis. AKI has long been recognized as a complication of cisplatin and is due primarily to direct tubular toxicity with some contribution from glomerular and vascular injury [11, 53]. Drug uptake into proximal tubular cells occurs primarily via OCT2. Once inside of cells, it can cause injury and apoptosis via inflammation, oxidative stress, and activation of cell death pathways (caspase, cyclin-dependent kinases, etc.). Chloride at the cis position of the molecule is thought to promote much of the injury. Risks for toxicity include volume depletion and underlying CKD. Forced diuresis with normal saline and 3% saline may reduce tubular injury. Intravenous magnesium, amifostine, and other agents may also reduce AKI. Other platin agents such as carboplatin and oxaliplatin are less nephrotoxic in part due to absent OCT2 transport and replacement of chloride at the cis position with carboxylate and cyclobutane. Therapy is mainly supportive and dialysis initiated for the usual indication, but it will not remove the drug. Other anticancer agents associated with various degrees of tubular injury include ifosfamide, pemetrexed, zoledronate, pentostatin, imatinib, and the BRAF inhibitors among others.

Tenofovir is a reverse transcriptase inhibitor that is used as part of combination anti-retroviral therapy (cART) in patients with HIV infection. The drug is structurally similar to naturally occurring oligonucleotides and the known nephrotoxins adefovir and cidofovir. This structure, along with its pathway of excretion through proximal tubular cells via OAT1, promotes cellular injury. While initial clinical trials suggested renal safety, subsequent case reports/series, systematic reviews, VHA database study, and more recent phase 3 trials have shown clear-cut AKI and proximal tubulopathy (Fanconi syndrome) associated with tenofovir [54, 55]. Animal studies and patient biopsies demonstrate ATI/ATN with associated mitochondrial disturbance/disruption [55]. Risks for tenofovir-associated kidney injury include underlying CKD, coadministration of medications that increase tenofovir levels, and endogenous apical efflux transport mutations (MRP2 gene) [56]. AKI typically resolves with drug discontinuation, and patients may rarely require dialysis. Up to 50% of patient may be left with some level of CKD [55].

9.5.2.5 Crystalline Nephropathy

Certain drugs and/or their metabolites can precipitate within tubular lumens to form crystals

(Fig. 9.8). This process usually occurs in distal tubular lumens leading to both a tubular obstruction and an interstitial cellular activation and inflammation [57]. Crystals generally form due to inherent insoluble properties, sluggish urine flow rates, urine pH effects on drug solubility, and underlying kidney disease. Risks that can therefore lead to intratubular crystal formation include true or effective volume depletion as seen in cirrhosis, CHF, renal salt wasting or chronic diarrhea, underlying AKI or CKD, and excessive drug dosing. Table 9.8 lists drugs that have been reported to cause crystalline nephropathy. A couple of illustrative examples are discussed.

Acyclovir is an antiviral agent that is used to treat herpes simplex virus infection and when employed intravenously can cause crystalluria and AKI. Rapid high-dose acyclovir bolus employed for viral meningoencephalitis leads to high concentrations of drug within tubular lumens. In fact, upward of 90% of the drug is eliminated through the kidney. Due to high urinary concentrations and the relative insolubility of acyclovir, drug crystals precipitate within the tubular lumens. As a result, AKI has been described in between 12 and 48% of patients receiving high-dose intravenous acyclovir, a number that increases with concomitant volume depletion and underlying CKD

Fig. 9.8 Crystalline nephropathy is seen with a number of medications that are insoluble in the urine and precipitate within the tubular lumens. Classic medications include acyclovir, sulfadiazine, methotrexate, and certain protease inhibitors (like indinavir seen in this biopsy specimen)

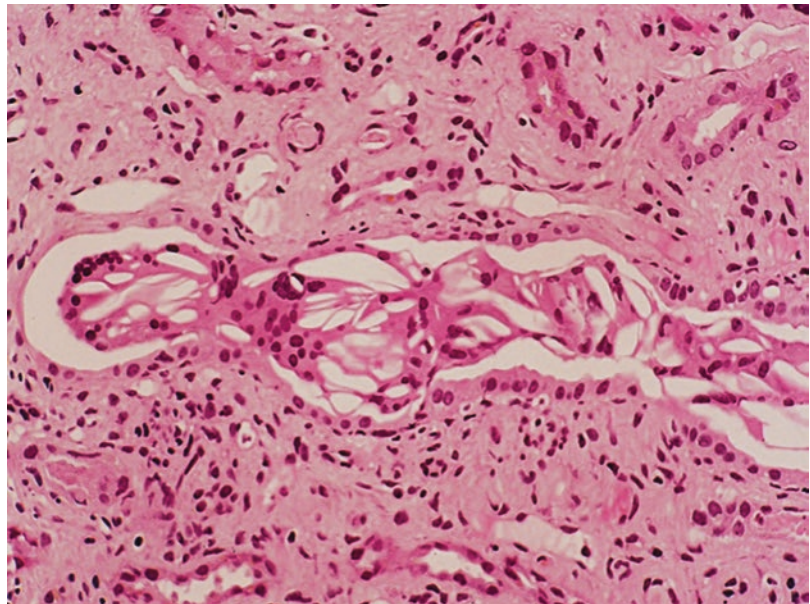


Table 9.8 Drugs associated with crystal nephropathy

Sulfadiazine
Acyclovir
Indinavir
Atazanavir
Triamterene
Methotrexate
Orlistat
Ciprofloxacin

[58, 59]. Acyclovir crystals can be identified on urine sediment exam where they are usually needle shaped and positively birefringent with polarization. Prevention or reduction of AKI can be achieved with appropriate drug dosing adjusted to GFR, volume repletion prior to drug administration, and slower infusion of drug (versus bolus). When AKI occurs and is associated with neurotoxicity, dialysis can effectively remove the drug. Most patients recover kidney function with supportive therapy.

Orlistat, an inhibitor of gastric and pancreatic lipase, is approved as a prescription and an over-the-counter medication for weight loss. It functions by promoting fat malabsorption, which can promote enteric hyperoxaluria. Fat within the bowel lumen saponifies calcium, which allows unbound oxalate to be absorbed and increase serum oxalate levels. The resulting hyperoxaluria promotes calcium oxalate precipitation with tubular lumens. This results in acute/subacute oxalate nephropathy and AKI, which stems from both tubulointerstitial inflammation and luminal obstruction. Several case reports of AKI in the setting of orlistat therapy have demonstrated biopsy-proven calcium oxalate nephropathy [60, 61]. All patients in these cases had underlying diabetes mellitus and CKD. A population-based study of 953 patients also documented increased AKI in patient-administered orlistat. CKD, hypertension, and CHF were AKI risks for those taking orlistat. Drug avoidance in patients with known CKD and careful monitoring in high-risk patients prone to volume depletion can help reduce the risk. Using lower doses may also decrease AKI risk as well. In general, AKI recovers with drug discontinuation and supportive care.

Methotrexate is dihydrofolate reductase inhibitor that is used in high intravenous doses to treat certain malignancies. The drug and its metabolite (7-OH methotrexate) are filtered and secreted by the tubules into the urine. Nephrotoxicity develops predominantly in patients treated with doses ranging from 1 to 12 grams/m², and AKI incidence ranges from 1.8 to 12% depending on the population studied [58, 62]. Methotrexate crystal precipitation within tubular lumens is associated with kidney injury (plus interstitial inflammation), although direct tubular injury from oxidative stress associated with reduced adenosine deaminase activity may contribute. The poor solubility of methotrexate/7-OH methotrexate in acidic urine as well as reduced urine flow rates enhances crystal precipitation. Prevention or reduction in AKI involves urinary alkalinization (pH > 7.1) and induction of high urinary flow rates. Treatment of AKI revolves around leucovorin rescue and in some instances the use of high-flux hemodialysis or carboxypeptidase G2 administration (to convert the drug to a harmless metabolite) [63].

Atazanavir is a protease inhibitor that is used as a once daily medication to treat HIV. IT has a rather favorable side effect profile. However, case reports of atazanavir crystal nephropathy have been reported. Early reports have shown stones with birefringent atazanavir crystals [64, 65]. About 7% of the medication is excreted non-metabolized in the urine [66]. It is poorly soluble and more likely to precipitate in alkaline urine. A large retrospective study has demonstrated nephrolithiasis in approximately 1% of patients on atazanavir with a median time of onset of 23 months [67].

9.5.3 Postrenal AKI

AKI can also present as the result of post-kidney obstruction promoted by a medication [48]. Obstruction occurring downstream of the kidney can be the result of injury or obstruction to the ureters, bladder, prostate, or urethra. This can either be the result of direct injury to these organs, luminal or outflow obstruction, or

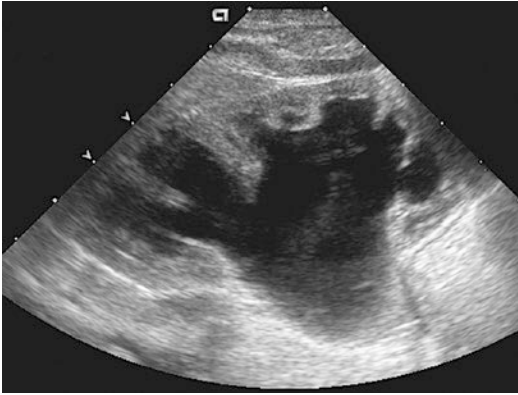


Fig. 9.9 Hydronephrosis is seen in this ultrasound image. Severe dilatation of the pelvis and calyces is demonstrated. Obstruction anywhere along the renal collecting system can cause acute kidney injury if both kidneys are involved (or a single functioning kidney is obstructed)

extrinsic compression of these organs impeding urinary flow. Ultrasonography reveals dilatation of the pelvis and calyces of the kidneys (Fig. 9.9).

Medications that increase the risk of nephrolithiasis should be suspected in patients who present with stone-related obstruction. Approximately 1–2% of kidney stones are caused by drugs with lithogenic potential [48]. Either the drug or its metabolite may form all or part of the stone, or the drug or metabolite may impair calcium oxalate or purine metabolism, thereby leading to the formation of these stones [68]. Coadministration of medications that alter drug metabolism can also enhance stone formation. Lastly, chronic drug use or high medication dose can increase the risk of stone formation. Patient-specific factors increase the risk of nephrolithiasis including either a personal or family history of lithogenesis, abnormal urine pH, current or frequent genitourinary tract infections, low urine volume, acute or chronic states of volume depletion, and underlying AKI or CKD. Table 9.9 lists drugs commonly associated with nephrolithiasis.

Aside from the formation of kidney stones, medications that cause retroperitoneal fibrosis (RPF) can also lead to ureteral encasement thereby creating a significant urinary obstruction and AKI. Ergot derivatives, beta-blockers, and dopaminergic agents have all been reported

Table 9.9 Drugs associated with postrenal kidney injury

Nephrolithiasis
Antibacterials
Sulfonamides
Aminopenicillins
Quinolones
Nitrofurantoin
Protease inhibitors
Indinavir
Nelfinavir
Atazanavir
Diuretics
Acetazolamide
Triamterene
Miscellaneous
Guaifenesin
Aluminum derivatives
Silicium derivatives
Calcium-vitamin D supplements
Retroperitoneal fibrosis
β -blockers
Ergot derivatives
Dopaminergic agonists
Urinary retention
Anticholinergic agents
Antihistamines
Anesthetic agents
Opiates

as causing RPF. Finally agents that promote urinary retention, including anticholinergics, antihistamines, anesthetic agents, opiates, ecstasy, and alcohol, can also lead to AKI from impaired bladder emptying.

9.5.4 Summary

All parts of the kidney are vulnerable to effects of medication. Certain patient- and kidney-specific factors are not modifiable and may make some patients more susceptible to injury. Medications themselves or metabolites can have varied nephrotoxic potential. Injury can take the form of hemodynamic, tubular, interstitial, or glomerular injury. Recognizing signs of kidney injury early and identifying potential medications that can cause injury can help to decrease the burden and impact of medication-induced acute kidney injury.

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