Chapter 65: Drug-Induced Kidney Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 8, Drug-Induced Kidney Disease.

KEY CONCEPTS

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1. The initial diagnosis of drug-induced kidney disease (DIKD) typically involves detection of elevated serum creatinine (S_{cr}) and blood urea nitrogen, for which there is a temporal relationship between the toxicity and use of a potentially nephrotoxic drug.
2. DIKD is best prevented by avoiding the use of potentially nephrotoxic agents for patients at increased risk for toxicity. However, when exposure to these drugs cannot be avoided, recognition of risk factors and specific techniques, such as hydration, may be used to reduce potential nephrotoxicity.
3. Acute tubular injury/necrosis (ATN) is the most common presentation of DIKD in hospitalized patients. The primary agents implicated are aminoglycosides, radiocontrast media, cisplatin, amphotericin B, and osmotically active agents.
4. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with hemodynamically mediated kidney injury, the pathogenesis of which is a decrease in glomerular capillary hydrostatic pressure.
5. Acute allergic interstitial nephritis (AIN) is observed in up to 27% of kidney biopsies performed for hospitalized patients with unexplained acute kidney injury (AKI). Clinical manifestations of AIN typically (but not always) present approximately 14 days after initiation of therapy and may include fever, maculopapular rash, eosinophilia, arthralgia, as well as pyuria, hematuria, proteinuria, and oliguria.

BEYOND THE BOOK

BEYOND THE BOOK

Visit the National Institute of Diabetes and Digestive and Kidney Diseases Website: https://tinyurl.com/y2pnoj26. This Website is useful to enhance student understanding of risk factors for and commonly used drugs that are associated with nephrotoxicity. Watch the video titled, "Keeping Kidneys Safe: Know How Medicines Affect the Kidneys,'' https://tinyurl.com/ybjao5qg. The video provides a brief overview of glomerular physiology and hemodynamically mediated nephrotoxic effects of nonsteroidal anti-inflammatory drugs and renin-angiotensin system blockers.

INTRODUCTION

Numerous diagnostic and therapeutic agents have been associated with the development of drug-induced kidney disease (DIKD) or nephrotoxicity. It is

a relatively common complication with variable presentations depending on the drug and clinical setting, inpatient or outpatient. Manifestations of DIKD may include acid–base abnormalities, electrolyte imbalances, urine sediment abnormalities, proteinuria, pyuria, and/or hematuria.[1] However, the most common manifestation of nephrotoxicity is a decline in the glomerular filtration rate (GFR) and a corresponding rise in serum creatinine (S_{cr}) concentrations. Initial diagnosis of nephrotoxicity is often delayed because it typically is based on the detection of elevated S_{cr}, for which there is a temporal relationship between the kidney injury (evidenced by the rise in S_{cr}) and exposure to the potentially nephrotoxic drug. This is consistent with contemporary definitions of acute kidney injury (AKI), which rely on either an abrupt increase in S_{cr} or an abrupt decline in urine output (see Chapter e60, "Evaluation of Kidney Function" and Chapter 61, "Acute Kidney Injury").[2]

Nephrotoxicity is often reversible if one discontinues the use of the offending agent, but in some cases it may evolve into AKI and may even progress to stage 5 chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Many different mechanisms are responsible for the pathogenesis of DIKD, and the introduction of new drugs with novel mechanisms of action provides the potential for the identification of new presentations of AKI and CKD. This chapter reviews the epidemiology, pathophysiology, risk factors, and basic principles of prevention of DIKD. Detailed discussions of these issues plus management strategies are presented for the most commonly used agents that have been associated with a moderate-to-high likelihood of DIKD.

EPIDEMIOLOGY

The incidence and characteristics of outpatient or community-acquired DIKD are not well understood since mild toxicity is often unrecognized in this setting. The incidence of community-based AKI requiring dialysis is as high as 29.5 per 100,000 person years and 522.4 per 100,000 person years for patients not requiring dialysis.[3] Although the incidence of drug-induced AKI was not specifically reported, up to 20% of hospital admissions due to AKI have been attributed to nephrotoxicity acquired in the community setting.[4] The incidence of AKI is even higher in hospitalized patients and increases over time.[3,5] As many as 22% of adults and 34% of children worldwide experience AKI during a hospital admission.[6] While up to 30% of critically ill patients experience AKI during their hospitalization, one in four cases is associated with nephrotoxic medication exposure.[7] Indeed, drugs have been implicated in 26% of all cases of in-hospital AKI and as such are a recognized source of significant morbidity and mortality.[1]

1 Because the most common manifestation of DIKD is a decline in GFR leading to a rise in S_{cr} and blood urea nitrogen (BUN), the onset of toxicity in hospitalized, acutely ill patients is most often recognized by routine laboratory monitoring. Decreased urine output may also be an early sign of toxicity, particularly with radiographic contrast media, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors (ACEIs). Other laboratory abnormalities such as electrolyte and acid-base disturbances often follow an increase in S_{cr}. In the outpatient setting, nephrotoxicity is often recognized by the development of symptoms such as malaise, anorexia, vomiting, volume overload (shortness of breath or edema), and hypertension. S_{cr} or BUN concentrations and urine collection for creatinine clearance may subsequently be measured to quantify the degree of decline in GFR. Marked intrasubject between-day variability of S_{cr} values has been noted (±20% for values within the normal range; see Chapter e60). Furthermore, they may be altered as the result of dietary changes and initiation of drug therapy, which may interfere with the assay procedure. Nevertheless, changes in S_{cr} or urine output consistent with the diagnostic criteria for AKI (see Chapter e60), when correlated temporally with the initiation of drug therapy, are a common threshold for the identification of DIKD.[1]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Drug-Induced Kidney Disease

General

- The most common manifestation is a decline in GFR leading to a rise in S_{cr} and BUN.
- Alterations in renal tubular function without loss of glomerular filtration may be evident.

Symptoms

- Patients may complain of malaise, anorexia, nausea, vomiting, shortness of breath, or edema, particularly in the outpatient setting.

Signs

- Decreased urine output may be an early sign of toxicity, particularly with radiographic contrast media, NSAIDs, and ACEIs, with progression to volume overload and hypertension.
- Proximal tubular injury: Metabolic acidosis with bicarbonaturia; glycosuria in the absence of hyperglycemia; and reductions in serum phosphate, uric acid, potassium, and magnesium due to increased urinary losses.
- Distal tubular injury: Polyuria from failure to maximally concentrate urine, metabolic acidosis from impaired urinary acidification, and hyperkalemia from impaired potassium excretion.

Laboratory Tests

- An abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in S_{cr} of greater than or equal to 0.3 mg/dL (27 μmol/L), a percentage increase in S_{cr} of greater than or equal to 50% (1.5-fold from baseline) within 7 days, or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/hr for more than 6 hours), when correlated temporally with the initiation of drug therapy may indicate drug-induced AKI.[1]
- Electrolyte (hyponatremia, hyperkalemia, hypo/hyperphosphatemia) and acid-base disturbances (metabolic acidosis) may also develop.

Other Diagnostic Tests

- Urinary excretion of *N*-acetyl-β-glucosaminidase, *γ*-glutamyl transpeptidase, glutathione *S*-transferase, and interleukin-18 are markers of proximal tubular injury and have been used for the early detection of AKI in critically ill patients.
- Kidney injury molecule-1 (KIM-1) is expressed in the proximal tubule and is upregulated for patients with ischemic acute tubular necrosis (ATN), appearing in the urine within 12 hours after the ischemic insult.
- Neutrophil gelatinase–associated lipocalin (NGAL) protein may be detected in the urine within 3 hours of ischemic injury.
- The urinary cell-cycle arrest biomarkers insulin-like growth factor–binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) can predict AKI in high-risk surgical patients, and clinical outcomes (death and the need for dialysis) in critically ill adults. These biomarkers may have an emerging role in detecting and/or minimizing DIKD.

Nephrotoxicity may also be evidenced by primary alterations in renal tubular function without a corresponding loss of glomerular filtration. In this setting, urinary enzymes and low-molecular-weight proteins may be used as earlier and more specific biomarkers of nephrotoxicity compared with S_{cr} and BUN, which are relatively insensitive markers of kidney injury.[8,9] S_{cr} and BUN are used as surrogates of kidney function, not injury per se, and typically significant kidney injury must have occurred days before a rise in either is evident. The emergence of novel biomarkers of kidney injury represents an important opportunity for earlier detection of DIKD. Urinary excretion of KIM-1, *N*-acetyl-β-glucosaminidase, γ-glutamyl transpeptidase, glutathione *S*-transferase, NGAL, and interleukin-18 (markers of proximal tubular injury) have been used for the early detection of acute kidney

damage in several patient populations.[8-10] For example, the transmembrane protein KIM-1 is upregulated for patients with ischemic ATN, appearing in the urine within 12 hours after the ischemic insult. Urinary *N*-acetylglucosamine concentrations are a highly sensitive indicator of AKI and can detect AKI in critically ill patients up to 4 days prior to a rise in S_{cr}. Similarly, urinary NGAL is an early marker of AKI, preceding a rise observed in S_{cr} by up to 3 days.[11]

The urinary cell-cycle arrest biomarkers IGFBP7 and TIMP-2 predict AKI in high-risk surgical patients,[12] and clinical outcomes (death and the need for dialysis) in critically ill adults.[13] The clinical utility of IGFBP7 and TIMP-2 in detecting and/or minimizing DIKD remain unclear, but several preclinical studies suggest a potential clinical role and utility of monitoring TIMP or IGFBP for this purpose. For example, TIMP-1 is an effective biomarker of cisplatin-induced nephrotoxicity in human kidney cells,[14] and is useful in predicting aristolochic acid–induced kidney injury in rats.[15] The urinary biomarkers may facilitate the earlier detection of kidney injury and diagnosis of nephrotoxicity and minimize the long-term consequences of this common drug-induced disorder.

PRINCIPLES FOR PREVENTION OF DRUG-INDUCED NEPHROPATHY

2 The primary principle for prevention of DIKD is to avoid the use of nephrotoxic agents for patients at increased risk for toxicity. Therefore, an awareness of potentially nephrotoxic drugs and knowledge of risk factors that increase kidney vulnerability are essential.[16] Exposure to these drugs often cannot be avoided; so, several interventions have been proposed to reduce the potential for the development of nephrotoxicity, for example, adjustment of medication dosage regimens based on accurate estimates of kidney function, and careful and adequate hydration to establish high urine flow rates.[17] Other preventative strategies are still theoretical and/or investigational and relate directly to the specific nephrotoxic mechanisms of a given drug.

The several specific drug-induced kidney structural-functional alterations that are responsible for the vast majority of cases of DIKD are listed in Table 65-1. This chapter discusses the pathophysiologic mechanisms responsible for the development of DIKD with these agents in detail, along with clinical presentation, prevention strategies, therapeutic management approaches, and relevant monitoring plans.

TABLE 65-1

Drug-Induced Kidney Structural-Functional Alterations

Tubular epithelial cell damage	
Acute tubular injury/necrosis • Aminoglycoside antibiotics • Radiographic contrast media • Cisplatin, carboplatin • Ifosfamide • Amphotericin B • Cyclosporine, tacrolimus • Adefovir, cidofovir, tenofovir • Pentamidine • Foscarnet • Zoledronate • Chimeric antigen receptor T-cells	Osmotic nephropathy • Mannitol • Dextran • IV immunoglobulin (sucrose) • Hydroxyethyl starch • SGLT-2 inhibitors
Hemodynamically mediated kidney injury	
• Angiotensin-converting enzyme inhibitors • Angiotensin II receptor blockers • SGLT-2 inhibitors	• NSAIDs • Cyclosporine, tacrolimus • OKT3

• Chimeric antigen receptor T-cells	• High dose interleukin-2
Obstructive nephropathy	
Crystal nephropathy • Acyclovir • Sulfonamides • Indinavir, atazanavir • Foscarnet • Methotrexate • Ascorbic acid, ethylene glycol, orlistat • Ciprofloxacin	Nephrolithiasis • Sulfonamides • Triamterene • Indinavir, atazanavir Nephrocalcinosis • Oral sodium phosphate solution
Glomerular disease	
Minimal change disease • NSAIDs, COX-2 inhibitors • Lithium • Pamidronate • Interferon-α and β Membranous disease • NSAIDs • Penicillamine • Captopril	Focal segmental glomerulosclerosis • Pamidronate • Interferon-α and β • Lithium • Sirolimus • Anabolic steroids • Tyrosine kinase inhibitors
Tubulointerstitial disease	
Acute allergic interstitial nephritis • β-Lactams • Ciprofloxacin • NSAIDs, cyclooxygenase-2 inhibitors • Proton pump inhibitors • Loop diuretics • Immune checkpoint inhibitors	Chronic interstitial nephritis • Cyclosporine • Lithium • Aristolochic acid • Combination analgesics Papillary necrosis • NSAIDs, combined phenacetin, aspirin, and caffeine analgesics
Renal vasculitis, thrombotic microangiopathy, and cholesterol emboli	
Vasculitis • Hydralazine • Propylthiouracil • Allopurinol • Penicillamine • Adalimumab • Minocycline • Sulfasalazine	Thrombotic microangiopathy • Cyclosporine, tacrolimus • Gemcitabine • Bevacizumab • Mitomycin C • Quinine Cholesterol emboli • Warfarin • Thrombolytic agents

COX-2, cyclooxygenase-2; SGLT-2, sodium-glucose co-transporter 2

TUBULAR EPITHELIAL CELL DAMAGE

Drugs that lead to renal tubular epithelial cell (RTEC) damage typically do so via direct cellular toxicity or ischemia. Damage is most often localized in the proximal and distal tubular epithelia and is termed "ATN" when cellular degeneration and sloughing from proximal and distal tubular basement membranes are observed. This classically manifests as cellular debris-filled, RTECs and RTEC casts and/or muddy brown granular casts in the urinary sediment.[18] Specific indicators of proximal tubular injury include metabolic acidosis with bicarbonaturia; glycosuria in the absence of hyperglycemia; and reductions in serum phosphate, uric acid, potassium, and magnesium as a result of increased urinary losses.[19] Indicators of distal tubular injury include polyuria from failure to maximally concentrate urine (ie, nephrogenic diabetes insipidus), metabolic acidosis from impaired urinary acidification, and hyperkalemia from impaired potassium excretion.[20]

Acute Tubular Injury/Necrosis

Acute tubular injury/necrosis (ATN) is the most common presentation of DIKD in the inpatient setting. The primary agents associated with this type of injury are aminoglycosides, radiocontrast media, cisplatin, amphotericin B, foscarnet, and osmotically active agents such as immunoglobulins, dextrans, hydroxyethyl starch, and mannitol.[21]

Aminoglycoside Nephrotoxicity

Incidence

Aminoglycoside antibiotic–associated nephrotoxicity may occur in between 10% and 25% of patients receiving a therapeutic course.[22,23] Critically ill patients appear to have a higher risk for nephrotoxicity with rates as high as 58%.[24] The large variance is in part a result of the use of different definitions of toxicity, variability between agents in the class, and the risk factors present in the study population.

Clinical Presentation

Clinical evidence of aminoglycoside-associated nephrotoxicity is typically seen within 5 to 7 days after initiation of therapy and manifests as a gradual progressive rise in S_{cr} and BUN and decrease in creatinine clearance.[23] Patients usually present with non-oliguria, that is, they maintain urine volumes greater than 500 mL/day and sometimes have microscopic hematuria and proteinuria.[21] Although renal magnesium wasting can occur (ie, daily excretion of more than 10-30 mg), the risk of symptomatic hypomagnesemia is generally low. Full recovery of kidney function is common if aminoglycoside therapy is discontinued immediately upon discovering signs of toxicity. However, severe AKI may develop occasionally, and for these individuals renal replacement therapy may be required (see Chapter 61). The diagnosis of aminoglycoside-associated nephrotoxicity is often difficult, particularly in critically ill patients with multiple comorbidities and is confounded by other factors that are independently associated with the development of AKI.[24] For instance, concurrent dehydration, sepsis, hypotension, ischemia, and use of other nephrotoxic drugs frequently contribute to AKI in patients who are receiving aminoglycosides.

Pathogenesis

Aminoglycoside-associated ATN is primarily due to accumulation of high drug concentrations within proximal tubular epithelial cells, and subsequent generation of reactive oxygen species that produce mitochondrial injury, which leads to cellular apoptosis and necrosis.[22] This results in cell sloughing from proximal tubular basement membranes into the tubular lumen, which can result in tubular obstruction and back leakage of the glomerular filtrate across the damaged tubular epithelium. Toxicity is related to cationic charge of the drugs in this class, which facilitates their binding to negatively charged renal tubular epithelial membrane phospholipids in the proximal tubules, followed by intracellular transport and concentration in lysosomes. The number of cationic groups on the drug molecule correlates with the degree of nephrotoxicity, which is consistent with the observation

of higher rates of toxicity with neomycin versus gentamicin, followed by tobramycin, then amikacin.[23]

Risk Factors

Multiple risk factors for aminoglycoside-associated nephrotoxicity have been identified: the aggressiveness of aminoglycoside dosing, synergistic toxicity as the result of combination drug therapy, and preexisting clinical conditions of the patient (Table 65-2).[22,24]

TABLE 65-2

Potential Risk Factors for Aminoglycoside-Associated Nephrotoxicity

(A) Related to aminoglycoside dosing:
Large total cumulative dose
Prolonged therapy
Trough concentration exceeding 2 mg/L[a]
Recent previous aminoglycoside therapy
(B) Related to synergistic nephrotoxicity—Aminoglycosides in combination with:
Cyclosporine
Amphotericin B
Vancomycin
Diuretics
Iodinated radiographic contrast agents
Cisplatin
NSAIDs
(C) Related to predisposing conditions in the patient:
Preexisting kidney disease
Diabetes mellitus
Increased age
Poor nutrition
Shock
Gram-negative bacteremia
Liver disease
Hypoalbuminemia
Obstructive jaundice
Dehydration
Hypotension
Potassium or magnesium deficiencies

[a]The equivalent concentration in SI molar units is 4.3 µmol/L for tobramycin and 4.2 µmol/L for gentamicin.

Prevention

Aminoglycoside-associated ATN may be prevented by careful and cautious selection of patients and the use of alternative antibiotics whenever possible and as soon as microbial sensitivities are known. Commonly used alternatives include fluoroquinolones (eg, ciprofloxacin or levofloxacin) and third- or fourth-generation cephalosporins (eg, ceftazidime or cefepime). When aminoglycosides are necessary, gentamicin, tobramycin, and amikacin are most commonly used, but therapy should be selected to optimize antimicrobial efficacy. Furthermore, it is imperative to avoid volume depletion, limit the total aminoglycoside dose administered, and avoid concomitant therapy with other nephrotoxic drugs.[22] Future therapeutic

alternatives may include new aminoglycoside congeners that retain the desired bactericidal activity and yet are devoid of nephrotoxicity, and may also include concurrent use of antioxidant compounds such as alpha-lipoic acid, vitamin E, and *N*-acetylcysteine.[25,26]

Prospective, individualized pharmacokinetic monitoring has been associated with a decrease in the incidence of aminoglycoside-associated nephrotoxicity.[27] High-dose intermittent administration of aminoglycosides, termed once daily dosing, used in combination with other antibiotics, has been intensively investigated as a practical cost-effective method to maintain antimicrobial efficacy while reducing the risk of AKI.[27,28] The reduction in incidence may be the result of limited proximal tubular aminoglycoside uptake during the transient, high-peak serum concentrations, and because of the presence of low aminoglycoside concentrations for a greater proportion of the dosing interval, which facilitates excretion of the aminoglycoside.[22] Although greater clinical efficacy and reduced nephrotoxicity may be realized with once daily compared with standard dosing, seriously ill, immunocompromised, and elderly patients, as well as those with preexisting kidney disease, are not ideal candidates for this approach.

Management

Aminoglycoside use should be discontinued or the dosage regimen revised if AKI is evident (ie, there is an S_{cr} increase of 0.5 mg/dL [44 µmol/L] or more that is not attributable to another cause). Other nephrotoxic drugs should be discontinued if possible, and the patient should be maintained adequately hydrated and hemodynamically stable.[28] Short-term renal replacement therapy may be necessary, but ESKD is rarely the result of aminoglycoside toxicity alone.

Radiographic Contrast Media Nephrotoxicity

Incidence

Radiographic contrast media–induced AKI (CI-AKI) is the third leading cause of hospital-acquired AKI, accounting for 10% to 13% of cases.[29] Estimates of the incidence varies widely depending on the population studied and presence of risk factors; rising from less than 2% for patients with normal kidney function, to 17% in patients with impaired kidney function, and 23% to 50% of critically ill patients.[21,30,31] However, the incidence of AKI in patients receiving radiocontrast is commonly overestimated, with the true incidence approximately 5.5%.[32] CI-AKI is extremely rare with intravenous contrast administration in patients with an eGFR >30 mL/min/1.73 m^2.[33] As the number of risk factors associated with CI-AKI increases, there is a corresponding increase in the incidence of nephrotoxicity and mortality rates. Approximately fivefold increased risk of death is seen in patients who develop CI-AKI compared with those who do not, with the highest mortality rates observed for patients who developed AKI and required renal replacement therapy. Specifically, in-hospital mortality for patients who developed CI-AKI was 34% versus only 7% of patients who received contrast but did not develop AKI.[29] Moreover, a two-year mortality rate of 81% has been observed for patients who developed CI-AKI and required dialysis.[29]

Clinical Presentation

CI-AKI is usually transient in nature, presenting most commonly as nonoliguria with kidney injury apparent within the first 24 to 48 hours after the administration of contrast. The S_{cr} concentration usually peaks between 3 and 4 days after exposure, with recovery after 7 to 10 days.[23] However, irreversible oliguric (urine volume less than 500 mL/day) AKI requiring dialysis is seenin high-risk patients.[34] Urinalysis typically reveals tubular enzymuria with hyaline and granular casts but may also be completely void of casts. The urine sodium concentration and fractional excretion of sodium are frequently low, with the latter typically less than 1% (0.01).

Pathogenesis

The primary mechanisms by which contrast media induces nephrotoxicity are renal ischemia and direct cellular toxicity.[35] Renal ischemia likely results from systemic hypotension and simultaneous acute vasoconstriction caused by disruption of normal prostaglandin synthesis and the release of adenosine, endothelin, and other renal vasoconstrictors. Subsequently, a sustained reduction in renal blood flow of up to 25% that lasts for several hours immediately following contrast administration may be evident.[35] This reduced renal blood flow leads to a 50% reduction in oxygen partial pressure and renal ischemia, along with increased concentrations of contrast in the renal tubules, which exacerbates the direct cytotoxicity.[35,36] The extent of cellular toxicity is directly related to the duration of tubular cell exposure to contrast. Thus, preservation of high urinary flow rates with

adequate hydration before, during, and after contrast administration is vital to keep renal blood flow as high as reasonably possible to minimize tubular cell exposure to the contrast agent.[36] In humans, plasma osmolality is normally between 275 and 290 mOsm/kg (mmol/kg). Since low- and high-osmolar contrast agents are hyperosmolar to plasma (ie, 600-800 mOsm/kg [mmol/kg] and ~2,000 mOsm/kg [mmol/kg], respectively), their use may result in osmotic diuresis, dehydration, renal ischemia, and increased blood viscosity caused by red blood cell aggregation.[37] Oxidative stress has also been implicated in the development of ATN after contrast administration, which may explain the possible benefit of the antioxidants *N*-acetylcysteine and ascorbic acid.[38]

Risk Factors

Decreased renal blood flow exacerbates the ischemic and direct cytotoxic effects of contrast media on the renal tubules. Therefore, preexisting kidney disease, particularly in those with estimated GFR less than 60 mL/min/1.73 m^2, is the most important risk factor, since lower GFR is associated with increasing levels of risk.[31] Other patient-specific risk factors include conditions associated with decreased renal blood flow (ie, congestive heart failure, dehydration/volume depletion, and hypotension), and patients with atherosclerosis and reduced effective circulating arterial blood volume appear to also have an elevated risk.[39,40] Diabetes is also a significant risk factor, likely due to coexisting kidney disease (diabetic nephropathy). The presence of multiple myeloma has traditionally been considered a relative contraindication for contrast use, but the risk is associated with concomitant dehydration, kidney disease, or hypercalcemia rather than the diagnosis itself. Larger volumes or doses of contrast and the use of low- as well as high-osmolar contrast agents are also independent predictors of CI-AKI.[39,40] Intra-arterial administration of contrast confers greater risk than IV administration.[31] Lastly, concurrent use of nephrotoxins and drugs that alter renal hemodynamics such as NSAIDs and ACEIs also increases risk. Risk factors are additive, and there is a proportional increase in the incidence of CI-AKI and associated mortality as the number of risk factors increases.[40]

Prevention

CI-AKI can be anticipated in the majority of patients who are at risk; so the use of preventative procedures is justified for virtually all patients. Table 65-3 lists the recommended interventions for prevention of contrast nephrotoxicity. All patients scheduled to receive contrast media should be assessed for risk factors, and the risk-to-benefit ratio should be considered.[29,39,40] High-risk patients can be identified by evaluating medical history and indication for the contrast procedure, along with their most recent S_{cr} concentrations. Nephrotoxicity is best prevented in high-risk patients by using alternative imaging procedures (eg, ultrasound, noncontrast magnetic resonance imaging, and nuclear medicine scans). However, if contrast media must be used, the smallest adequate volume should be administered.[29] If the ratio of the volume of contrast to be infused relative to the patient's creatinine clearance is greater than or equal to 3.7 (222 if creatinine clearance is expressed in units of mL/s), the likelihood of nephrotoxicity is markedly increased.[40] Therefore, in general, the volume of contrast administered should not be greater than twice the baseline estimated creatinine clearance.

TABLE 65-3

Recommended Interventions for Prevention of Contrast Media-Induced AKI[38-41]

Intervention	Recommendation	Recommendation Grade[a]
Contrast	• Minimize contrast volume/dose • Use noniodinated contrast • Use low- or iso-osmolar contrast agents	A-1 A-2 A-2
Medications	• Avoid concurrent use of potentially nephrotoxic drugs (eg, NSAIDs, aminoglycosides)	A-2
Isotonic sodium chloride (0.9%)	• Initiate infusion 3-12 hours prior to contrast exposure and continue 6-24 hours postexposure • Infuse at 1-1.5 mL/kg/hr adjusting postexposure as needed to maintain a urine flow rate of 150 mL/hr • Alternatively, in urgent cases, initiate infusion at 3 mL/kg/hr, beginning 1 hour prior to contrast exposure, then continue at 1 mL/kg/hr for 6 hours postexposure	A-1

[a] *Strength of recommendations*: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. *Quality of evidence*: (1) evidence from more than one properly randomized, controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Low-osmolar (600-800 mOsm/kg [mmol/kg]) nonionic (iohexol and iopamidol) and ionic (ioxaglate) contrast agents may be used to minimize the incidence of nephrotoxicity. Standard hyperosmolar contrast media (eg, low- and high-osmolar agent) are not reabsorbed in the kidney and cause osmotic diuresis, which contributes to the renal toxicity observed with these agents. Low-osmolar contrast agents have less than half the osmolality of high-osmolar (~2,000 mOsm/kg [mmol/kg]) agents and are associated with less toxicity, especially when used for patients with preexisting kidney disease.[37] However, use of low-osmolar agents does not preclude the development of nephrotoxicity. Even low-osmolar agents are hyperosmolar relative to plasma, which is likely the reason they have been associated with greater nephrotoxicity than the iso-osmolar nonionic contrast agent iodixanol. The relative differences in nephrotoxicity between the class of low-osmolar agents and iodixanol are unclear.[40,41]

Volume expansion and correction of dehydration prior to contrast administration is a mainstay of preventive therapy.[36] Parenteral hydration with isotonic saline before and after contrast administration reduces the incidence of toxicity, particularly in high-risk patients, and is the most widely accepted preventative intervention.[40] Volume expansion may exert its beneficial effects through dilution of contrast media, prevention of renal vasoconstriction, preservation of high urine flow rates, decreased tubular cell exposure to contrast, and avoidance of tubular obstruction. There is no benefit in using sodium bicarbonate or the thiol-containing antioxidant *N*-acetylcysteine over saline.[42] The guidelines recommend hydration with isotonic saline for CI-AKI prevention.[40,41] The use of oral hydration is also not recommended in lieu of parenteral hydration.[40,41]

Renal replacement therapy, including intermittent hemodialysis and continuous modalities, for example, continuous venovenous hemofiltration, effectively removes iodinated contrast, and was considered by some to be a therapeutic option for the prevention of CI-AKI. However, because of the logistical issues (eg, technical difficulty), potential infectious and noninfectious risks, high cost of renal replacement therapy, and lack of consistent clinical efficacy, renal replacement therapy is not recommended.[31,41]

Management

There is no specific therapy available for managing established CI-AKI. Other nephrotoxic drugs should be discontinued if possible, and subsequent contrast studies must be appropriately timed to minimize cumulative toxicity. Care is supportive as described in Chapter 61. Kidney function (eg, S_{cr}

and urine output), electrolytes (eg, sodium and potassium), and volume status should be closely monitored.

Cisplatin Nephrotoxicity

Incidence

Cisplatin is one of the most important and widely used antineoplastic drugs for the treatment of solid tumors, often demonstrating exceptional efficacy (ie, cure rates over 90% in testicular cancers).[43] The primary dose-limiting toxicity of platin-containing compounds is nephrotoxicity. Cisplatin nephrotoxicity occurs in up to one-third of patients receiving the drug and is a significant cause of morbidity.[43,44] Carboplatin, a second-generation platinum analog, is associated with a lower incidence of nephrotoxicity than cisplatin and thus is the preferred agent in high-risk patients.[45]

Clinical Presentation

Cisplatin administration results in impaired tubular reabsorption and decreased urinary concentration ability, leading to increased excretion of salt and water (ie, polyuria) within 24 hours of treatment. Polyuria persists and a decrease in GFR evidenced by a rise in S_{cr} concentration may be seen within 72 to 96 hours after cisplatin administration.[46] S_{cr} peaks approximately 10 to 14 days after initiation of therapy, with recovery by 21 days.[47] As many as 25% of patients may have reversible elevations in S_{cr} and BUN for 2 weeks after cisplatin treatment. However, kidney damage is dose related and cumulative with subsequent cycles of therapy, so the S_{cr} concentration may continue to rise, and irreversible kidney injury may result.[45]

Hypomagnesemia is a hallmark finding of cisplatin nephrotoxicity, due to impaired magnesium reabsorption and thus increased urinary losses.[48] Hypomagnesemia is often accompanied by hypocalcemia and hypokalemia and may be severe, leading to seizures, neuromuscular irritability, or personality changes. Urinalysis typically reveals leukocytes, RTECs, and granular casts.

Pathogenesis

The pathogenesis of cisplatin nephrotoxicity is multifactorial in nature and likely begins with cellular uptake and accumulation of the drug in proximal tubular epithelial cells to concentrations that may reach five times the serum concentration.[49] Tubular cell exposure to cisplatin then activates a series of cell signaling pathways, including the mitogen-activated protein kinase pathway, p53, caspase, and the generation of reactive oxygen species, that collectively promote tubular cell injury and death via necrosis and/or apoptosis.[43,44] Simultaneous production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) within tubular cells activates an inflammatory response, which may worsen the renal insult. Although tubular damage is evident in both the proximal and distal segments, the majority occurs in the proximal tubules and is followed by a progressive loss of glomerular filtration capacity and impaired distal tubular function. Kidney biopsies generally reveal necrosis-apoptosis of proximal and distal tubules and collecting ducts, with no obvious morphological changes to the glomeruli.[47]

Risk Factors

Risk factors include age more than 65 years, dehydration, preexisting kidney disease, renal irradiation, concurrent use of nephrotoxic drugs, large cumulative doses, and alcohol abuse.[50]

Prevention

The best renoprotective strategy is a combination of interventions, including prospective dose reduction and decreased frequency of administration, which usually requires using the platin compounds in combination with other chemotherapeutic agents, avoiding concurrent use of other nephrotoxic drugs, and ensuring patients are euvolemic or somewhat hypervolemic prior to initiating treatment.[50,51] Vigorous hydration with isotonic saline should be used for all patients with a goal of maintaining at least 100 to 150 mL/hr of urine output during and after cisplatin treatment. Hydration should be initiated 12 to 24 hours prior to and continued for 2 to 3 days after cisplatin administration at rates of 100 to 250 mL/hr, as tolerated, to maintain a urine flow of 3 to 4 L/day.[46]

Amifostine, an organic thiophosphate that is converted to an active metabolite, chelates cisplatin in normal cells and reduces the nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression associated with cisplatin and carboplatin therapy. It is also thought to serve as a thiol donor, thereby

reducing intracellular reactive oxygen species and corresponding oxidative stress that plays a critical role in the development of cellular injury.[44] Amifostine is Food and Drug Administration (FDA)-approved to reduce nephrotoxicity associated with repeated cisplatin treatment in patients with advanced ovarian cancer. Pretreatment with amifostine should be considered for patients who are at high risk for kidney injury, particularly patients who are elderly, volume depleted, have CKD, or are receiving other nephrotoxic drugs concurrently. The recommended dose of amifostine is 910 mg/m^2 administered IV over 15 minutes, beginning 30 minutes prior to cisplatin administration. Common toxicities include acute hypotension, nausea, and fatigue.

Other renoprotective strategies include the use of hypertonic saline (eg, administration of each dose in 250 mL of 3% saline) to reduce tubular cisplatin uptake. Classic antioxidants such as ascorbic acid, thiol-based antioxidants such as α-lipoic acid and *N*-acetylcysteine, which reduce oxidative damage by acting as a sulfhydryl donor, and the disulfiram metabolite diethyldithiocarbamate to reduce cytochrome P450 2E1–mediated generation of hydroxyl radicals have also been evaluated.[49,52] Intravenous magnesium infusion has also been administered to prevent cisplatin-related AKI with mixed effects. Finally, reduced renal exposure can be achieved with the use of localized intraperitoneal administration in conjunction with systemic administration of sodium thiosulfate for those with peritoneal tumors.[46]

Management

AKI caused by cisplatin therapy is usually partially reversible with time and supportive care, including dialysis. Kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily. Serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.[45] Hypocalcemia and hypokalemia may be difficult to reverse until hypomagnesemia is corrected. There is no role for dialysis to remove cisplatin. Progressive kidney disease caused by cumulative nephrotoxicity may be irreversible and in some cases may lead to ESKD and require chronic dialysis support.[45]

Amphotericin B Nephrotoxicity

Incidence

Variable rates of amphotericin B nephrotoxicity are seen that correspond in large part to the cumulative dose administered. Nephrotoxicity may be seen in nearly 30% of patients receiving median cumulative doses as low as 240 mg and reaches an incidence of greater than 80% when cumulative doses approach 5 g.[53-55] Although numerous studies demonstrate lower rates of nephrotoxicity with liposomal formulations compared with conventional amphotericin B, it is difficult to compare rates of toxicity between products and studies because of the variability in the study populations, doses administered, and inconsistent definitions of nephrotoxicity and methods of assessment.[53,54,56]

Clinical Presentation

Dose-dependent nephrotoxicity is often evident after administration of cumulative doses of 2 to 3 g as nonoliguria, renal tubular potassium, sodium, and magnesium wasting, impaired urinary concentrating ability, and distal renal tubular acidosis.[23,56] Although the cumulative dose is a significant risk factor, the time to onset of kidney injury varies considerably, ranging from a few days to weeks. Tubular dysfunction usually manifests 1 to 2 weeks after treatment is begun, and potassium and magnesium replacement may be necessary.[53] This is typically followed by a decrease in GFR and a rise in S_{cr} and BUN concentrations. Consequently, kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily, and serum magnesium, potassium, and calcium concentrations monitored every other day and corrected as needed.

Pathogenesis

Amphotericin B nephrotoxicity occurs predominantly via two mechanisms. The first is direct tubular epithelial cell toxicity resulting from interaction of amphotericin B with ergosterol in the cell membrane, leading to increased tubular cell membrane permeability, lipid peroxidation, and eventual necrosis of proximal tubular cells.[56] The second mechanism is afferent arteriolar vasoconstriction leading to a reduction in renal blood flow and GFR, and ischemic tubular injury.[23,56]

Risk Factors

Risk factors that impact the likelihood of developing amphotericin B nephrotoxicity include preexisting kidney disease, large individual and cumulative doses, short infusion times, volume depletion, hypokalemia, increased age, and concomitant administration of diuretics and other nephrotoxins, including vancomycin and cyclosporine.[53,56]

Prevention

Permanent decrements in GFR are best prevented by incorporating a low threshold (ie, if S_{cr} reaches 2 mg/dL [177 µmol/L] on 2 consecutive days) for stopping amphotericin B or switching to a liposomal formulation. Several lipid formulations of amphotericin B (eg, amphotericin B lipid complex, liposomal amphotericin B) are available and should be used in most high-risk patients as they reduce nephrotoxicity by enhancing drug delivery to sites of infection and reducing interaction with tubular epithelial cell membranes.[54,56] Nephrotoxicity can also be minimized by limiting the cumulative dose, increasing the infusion time, ensuring the patient is well hydrated, and avoiding concomitant administration of other nephrotoxins.[56] Administration of 1 L IV 0.9% sodium chloride daily during the course of therapy reduces toxicity and a single infusion of saline 10 to 15 mL/kg prior to administration of each dose of amphotericin B is generally recommended.[56] A number of other antifungal agents such as itraconazole, voriconazole, and caspofungin are viable alternatives and are now routinely used in lieu of amphotericin B for patients at high risk of developing nephrotoxicity. Administration of the antioxidant *N*-acetylcysteine (600 mg orally twice daily in adults) during amphotericin treatment may be nephroprotective.[57]

Management

Amphotericin B nephrotoxicity is best treated by discontinuation of therapy and substitution of alternative antifungal therapy, if possible. Renal tubular dysfunction and glomerular filtration will improve gradually to some degree in most patients, but damage may be irreversible. Kidney function indices should be closely followed, with S_{cr} and BUN concentrations checked daily, and serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.

Osmotic Nephropathy

Several drugs, including mannitol, low-molecular-weight dextran, hydroxyethyl starch, and radiographic contrast media, or drug vehicles, such as sucrose, maltose, and propylene glycol, are associated with osmotic nephropathy, which may rarely lead to ATN and AKI.[58] Since osmotic nephropathy does not necessarily negatively affect proximal tubular function, its presence may often go undetected in patients without overt signs of ATN. This likely contributes to the extremely low incidence of osmotic nephropathy reported for causative agents. IV immunoglobulin solutions containing hyperosmolar sucrose may cause osmotic nephropathy and AKI in 1% to 10% of cases, which is usually reversible shortly after discontinuing therapy.[59,60] Maltose-based IV immunoglobulin solutions have also been implicated in the development of osmotic nephropathy. Although IV immunoglobulin-induced AKI is the modern prototype for osmotic nephropathy, the vehicle (ie, sucrose or maltose) is the culprit and not the immunoglobulins themselves.[60] The SGLT-2 inhibitors have been associated with a kidney lesion reminiscent of osmotic nephropathy. Presumably, the proximal tubule encounters massive glucose loads that are reabsorbed (SGLT-1 transporter) and overwhelm cellular metabolism, though this is rare.[61]

Clinical Presentation

The clinical presentation of osmotic nephropathy is often subtle. While tubular proteinuria or vacuolated tubular cells may be observed on urinalysis for patients with AKI, the definitive diagnosis of osmotic nephropathy is only made via a kidney biopsy.[59] IV immunoglobulin-induced AKI typically presents as oliguria after 2 to 4 days of treatment and may persist for up to 2 weeks. Kidney injury occurs via uptake of the offending agent through pinocytosis into proximal tubular epithelial cells, subsequent formation of vacuoles, and accumulation of lysosomes, which collectively results in an oncotic gradient and thus cellular swelling, tubular luminal occlusion, and compromised cellular integrity.[62] Renal replacement therapy may be necessary for up to 40% of patients developing osmotic nephropathy-associated AKI.[59] However, it is usually reversible, with nearly all patients recovering normal kidney function following withdrawal of the offending drug.

Risk Factors

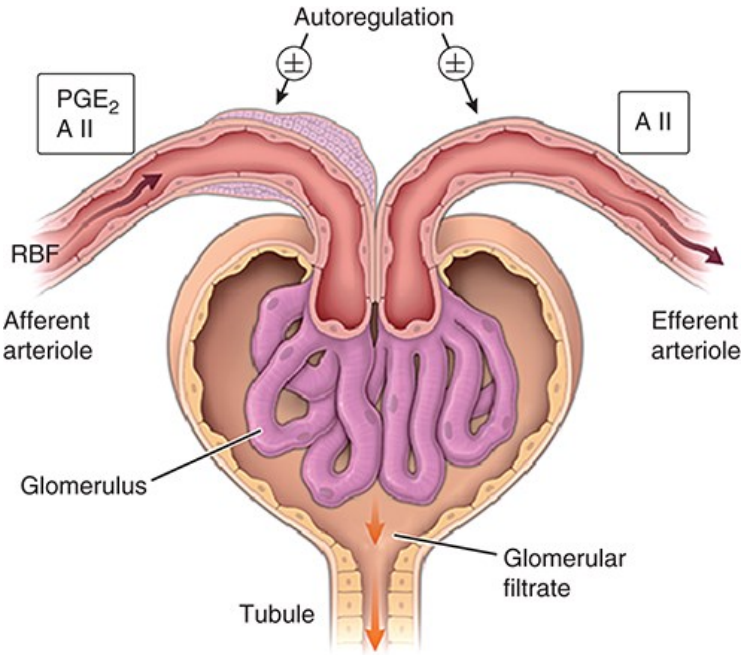
Risk factors for osmotic nephropathy include excessive doses of offending agents, preexisting kidney disease, ischemia, older age (greater than 65 years), and concomitant use of other nephrotoxins. Nephrotoxicity may be prevented by limiting the dose, reducing the rate of infusion, and avoiding dehydration and concomitant nephrotoxins.[60,62]

HEMODYNAMICALLY MEDIATED KIDNEY INJURY

Hemodynamically mediated kidney injury generally refers to any cause of AKI resulting from an acute decrease in intraglomerular pressure, including "prerenal" states leading to reduced effective renal blood flow (eg, hypovolemia and congestive heart failure) and medications that affect the renin–angiotensin system (RAS).[23,63] The kidneys receive approximately 25% of resting cardiac output, which renders them particularly susceptible to alterations in renal blood flow and enhances their exposure to circulating drugs.[16,64] Within each nephron, blood flow and pressure are regulated by glomerular afferent and efferent arterioles to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration, and urine output. Afferent and efferent arteriolar vasoconstrictions are primarily mediated by angiotensin II, whereas afferent vasodilation is primarily mediated by prostaglandins (Fig. 65-1). This specialized blood flow is precisely regulated by interrelations between arachidonic acid metabolites, natriuretic factors, nitric oxide, the sympathetic nervous system, the RAS, and the macula densa response to distal tubular solute delivery.[64] Drug-induced causes of hemodynamic kidney injury typically stem from constriction of glomerular afferent arterioles and/or dilation of glomerular efferent arterioles. ACEIs, angiotensin II receptor blockers (ARBs), and NSAIDs are the agents that have been most commonly implicated.[23,65] Capillary leak syndrome due to a severe cytokine release syndrome (CRS) is associated with hemodynamically mediated AKI with high-dose interleukin-2 and the chimeric antigen receptor (CAR) T-cells.[66]

FIGURE 65-1

Normal glomerular autoregulation serves to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration rate, and, ultimately, urine output. (A II, angiotensin II; PGE_2, prostaglandin E_2; RBF, renal blood flow.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

ACEIs and ARBs are extensively utilized for the management of hypertension and prevention of the progression of CKD even though they have been

associated with the development of AKI.

Incidence

Patients with renal artery stenosis, volume depletion, and congestive heart failure and those with preexisting kidney disease, including diabetic nephropathy, are most likely to experience a significant decline in kidney function when therapy with one of these agents is initiated.[23] For example, up to 25% of hospitalized patients with congestive heart failure develop AKI within weeks after beginning treatment with ACEIs.[67] Moreover, ACEIs and ARBs are among the most commonly implicated medications in emergency hospitalizations, contributing to nearly 3% of emergency room visits for adverse drug events.[68]

Clinical Presentation

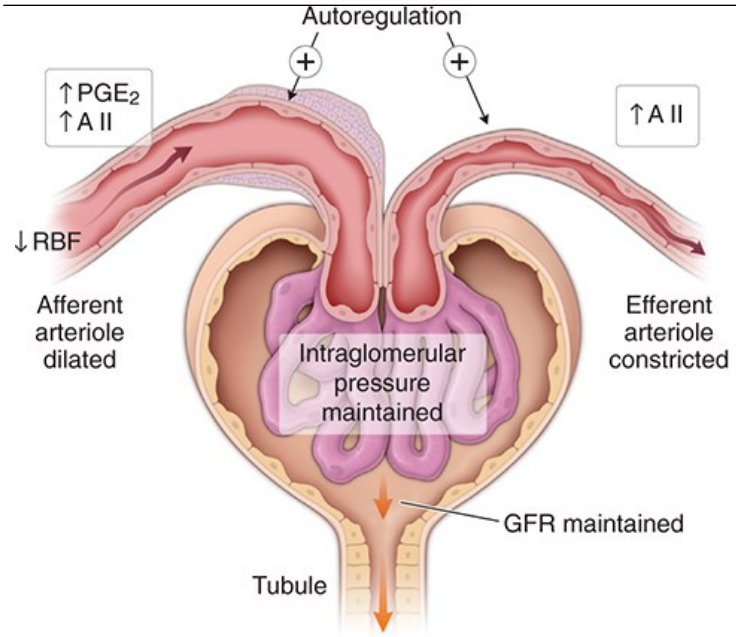
Therapy with ACEIs and ARBs will acutely reduce GFR; so a moderate rise in S_{cr} after initiation of therapy should be anticipated.[69] Importantly, a distinction must be made between a potentially detrimental reduction in GFR and a normal, predictable rise in S_{cr}. An increase in S_{cr} of up to 30% is commonly observed within 3 to 5 days of initiating therapy and is an indication that the drug has begun to exert its desired pharmacologic effect.[69] The increase in S_{cr} typically stabilizes within 1 to 2 weeks and is usually reversible upon stopping the drug. Furthermore, an association exists between acute increases in S_{cr} of less than or equal to 30% from baseline that stabilize within the first 2 months of initiating therapy and preservation of kidney function. The S_{cr} threshold for discontinuation of ACEI or ARB therapy is unclear. However, an increase in S_{cr} of more than 30% above baseline in the course of 1 to 2 weeks may necessitate discontinuation of the offending drug.[69]

Pathogenesis

ACEIs—or ARB-mediated kidney injury—is primarily the result of disruption of normal autoregulation of intraglomerular capillary hydrostatic pressure.[23] Normally, the kidney attempts to maintain GFR by dilating the afferent arteriole and constricting the efferent arteriole in response to a decrease in renal blood flow. During states of reduced blood flow, the juxtaglomerular apparatus increases renin secretion. Plasma renin converts angiotensinogen to angiotensin I, and ultimately angiotensin II by angiotensin-converting enzyme. Angiotensin II constricts the afferent and efferent arterioles, but has a greater effect on the efferent arterioles, resulting in a net increase in intraglomerular pressure.[64] Additionally, renal prostaglandins, prostaglandin E_2 in particular, are released and induce a net dilation of the afferent arteriole, thereby improving blood flow into the glomerulus. Together these processes maintain GFR and urine output (Fig. 65-2).

FIGURE 65-2

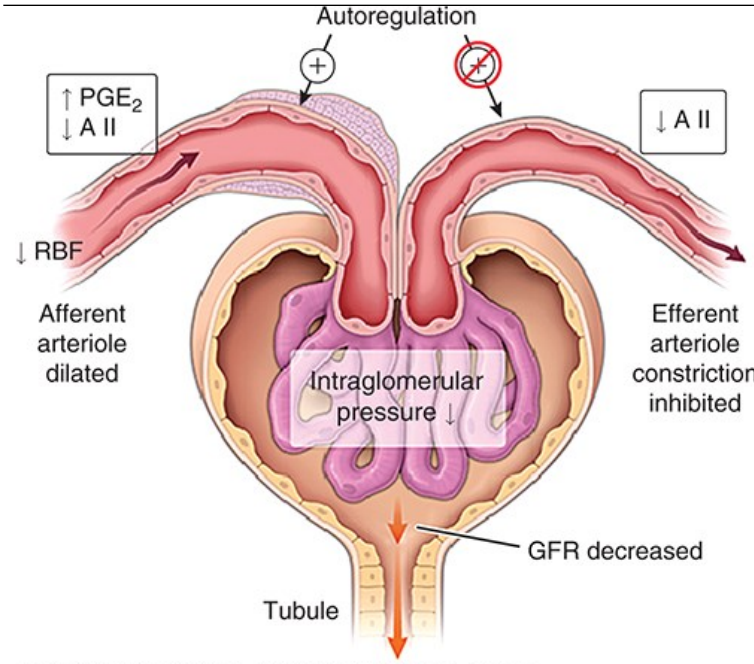
Glomerular autoregulation during “prerenal” states (ie, reduced blood flow).



When ACEI therapy (eg, enalapril or ramipril) is initiated, the synthesis of angiotensin II is decreased, thereby preferentially dilating the efferent arteriole. This reduces outflow resistance from the glomerulus and decreases hydrostatic pressure in the glomerular capillaries, which alters Starling forces across the glomerular capillaries to decrease intraglomerular pressure and GFR. This in turn often leads to nephrotoxicity, particularly in the setting of reduced renal blood flow or effective arterial blood volume (Fig. 65-3), that is, prerenal settings (eg, congestive heart failure) in which glomerular afferent arteriolar blood flow is reduced and the efferent arteriole is vasoconstricted to maintain sufficient glomerular capillary hydrostatic pressure for ultrafiltration.[23]

FIGURE 65-3

Pathogenesis of angiotensin-converting enzyme inhibitor (ACEI) nephropathy.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Risk Factors

Patients at greatest risk are those dependent on angiotensin II and renal efferent arteriolar constriction to maintain blood pressure and GFR. These include patients with bilateral renal artery stenosis or stenosis in a single kidney (ie, renal transplant); patients with decreased effective arterial blood volume (ie, prerenal states), especially those with decompensated congestive heart failure, volume depletion from excess diuresis or GI fluid loss, hepatic cirrhosis with ascites, and nephrotic syndrome; patients with preexisting kidney disease; and patients receiving concurrent nephrotoxic drugs, particularly other drugs that affect intraglomerular autoregulation such as NSAIDs.[23,65,70]

Prevention

Hemodynamically mediated AKI caused by ACEIs or ARBs is frequently preventable by recognizing the presence of preexisting kidney disease or decreased effective renal blood flow as a result of volume depletion, heart failure, or liver disease. A common strategy for at-risk patients is to initiate therapy with low doses of a short-acting ACEI (eg, captopril 6.25-12.5 mg), then gradually titrate the dose upward, and convert to a longer-acting agent after patient tolerance has been demonstrated. Outpatients may be started on low doses of long-acting ACEIs (eg, enalapril 2.5 mg) with gradual dose titration every 2 to 4 weeks until the maximum dose or desired response is achieved.[69] Kidney function indices and serum potassium concentrations must be monitored carefully, daily for hospitalized patients and every 2 to 3 days for outpatients. Monitoring may need to be more frequent during outpatient initiation of ACEI or ARB therapy for patients with preexisting kidney disease, congestive heart failure, or suspected renovascular disease. Use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (eg, NSAIDs, diuretics) should be discouraged and dehydration avoided.[69]

Management

Acute decreases in kidney function and the development of hyperkalemia usually resolve over several days after ACEI or ARB therapy is discontinued. Occasionally patients will require management of severe hyperkalemia, as described in detail in Chapter 70, "Potassium and Magnesium Homeostasis."

ACEIs or ARB therapy may frequently be reinitiated, particularly for patients with congestive heart failure, after intravascular volume depletion has been corrected or diuretic doses reduced. Slight reductions in kidney function (maintenance of a S_{cr} concentration of 2-3 mg/dL [177-265 µmol/L])

may be an acceptable trade-off for hemodynamic improvement in certain patients with severe congestive heart failure or renovascular disease not amenable to revascularization.

Nonsteroidal Anti-Inflammatory Drugs and Selective Cyclooxygenase-2 Inhibitors

The overall safety of NSAIDs is evidenced by the nonprescription availability in the United States of several drugs in the class (eg, ibuprofen, naproxen, ketoprofen). Although potential adverse renal effects from nonprescription NSAIDs had been a concern, conventional nonselective NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors are unlikely to acutely affect kidney function in the absence of renal ischemia or excess renal vasoconstrictor activity. Nevertheless, given their general safety and widespread availability, NSAIDs are among the most commonly used drugs, with approximately 111 million prescriptions worldwide and 30 billion over-the-counter doses of NSAIDs administered annually in the United States.[71]

Incidence

The incidence of NSAID-induced kidney injury is unclear. As many as 500,000 to 2.5 million people may develop some degree of NSAID nephrotoxicity in the United States annually.[72]

Clinical Presentation

NSAID- and COX-2-induced AKI usually occurs within 2 to 7 days of initiating therapy,[63,71] particularly with a short-acting agent such as ibuprofen, or within days of some other precipitating event (eg, intravascular volume depletion). Patients typically present with complaints of diminished urine output, weight gain, and/or edema. Urine sodium concentrations (less than 20 mEq/L [mmol/L]) and fractional excretion of sodium (less than 1% [0.01]) are usually low, and BUN, S_{cr}, potassium, and blood pressure are typically elevated. The urine sediment is usually bland and unchanged from baseline but may show occasional RTECs and granular casts.[63,71]

Pathogenesis

The pathogenesis of NSAID- and COX-2-induced AKI lies in the disruption of normal intraglomerular autoregulation.[63] Specifically, NSAIDs inhibit COX-catalyzed synthesis of vasodilatory prostaglandins, including prostaglandins I_2 (prostacyclin) and E_2, from arachidonic acid.[71] These prostaglandins are synthesized in the renal cortex and medulla by vascular endothelial and glomerular mesangial cells, and their effects are primarily local and result in net afferent arteriolar vasodilation. Vasodilatory prostaglandins have limited activity in states of normal renal blood flow, but in states of decreased renal blood flow, their synthesis is increased and they serve a vital autoregulatory role in the protection against renal ischemia and hypoxia by antagonizing renal arteriolar vasoconstriction due to angiotensin II, norepinephrine, endothelin, and vasopressin. Thus, administration of NSAIDs in the setting of reduced renal blood flow will blunt the usual compensatory increase in prostaglandin activity, altering the normal autoregulatory balance in favor of renal vasoconstrictors, thereby promoting renal ischemia and a reduction in glomerular filtration.[71]

Risk Factors

Risk factors for NSAID- and COX-2-induced AKI include age more than 60 years, preexisting kidney disease, hepatic disease with ascites, congestive heart failure, intravascular volume depletion/dehydration, systemic lupus erythematosus, or concurrent treatment with diuretics, ACEIs, or ARBs.[65,70,71] Use of ACEIs, diuretics, and NSAIDs concurrently is associated with a greater than 30% increased risk for AKI, which increases to greater than 60% in patients over age 75 or with preexisting kidney disease.[65,70] The elderly people are at higher risk because of multiple comorbidities, multiple-drug therapies, and reduced renal hemodynamics. Combined use of NSAIDs or COX-2 inhibitors and concurrent nephrotoxic drugs, particularly other drugs that affect intraglomerular autoregulation, should be avoided in high-risk patients.

Prevention

NSAID- and COX-2 inhibitor–induced AKI can be prevented by recognizing high-risk patients, avoiding potent compounds such as indomethacin and using analgesics with less prostaglandin inhibition, such as acetaminophen, nonacetylated salicylates, aspirin, and possibly nabumetone. Nonnarcotic analgesics (eg, tramadol) may also be useful but do not provide anti-inflammatory activity. When NSAID therapy is essential for high-risk patients, the minimal effective dose should be used for the shortest duration possible, and NSAIDs with short half-lives should be considered (eg, sulindac) along

with optimal management of predisposing medical problems and frequent kidney function monitoring. Moreover, use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (eg, ACEIs, ARBs, diuretics) should be discouraged in high-risk patients and dehydration avoided.[71]

Management

NSAID-induced AKI is treated by discontinuation of therapy and supportive care. Use of other nephrotoxic drugs should be avoided. Kidney injury is rarely severe, and kidney function generally recovers within 3 to 5 days.[63] Occasionally, the hemodynamic insult is sufficiently severe to cause ATN, which can prolong injury.

Cyclosporine and Tacrolimus

The calcineurin inhibitors cyclosporine and tacrolimus have dramatically enhanced the success of solid-organ transplantation. As many as 94% of kidney transplant patients are prescribed a calcineurin inhibitor–based immunosuppressive regimen.[73] Nephrotoxicity, however, remains a major dose-limiting adverse effect of both drugs. Although delayed chronic interstitial nephritis also is possible,[74] acute hemodynamically mediated kidney injury is an important mechanism of calcineurin inhibitor–induced nephrotoxicity.

Incidence

The reversible AKI occurred frequently in transplant recipients during the first 6 months of cyclosporine therapy. The five-year risk of CKD after transplantation of a nonrenal organ ranges from 7% to 21%, depending on the type of organ transplanted, and the occurrence of CKD in these patients is associated with more than a fourfold increase in the risk of death.[75]

Clinical Presentation

The clinical presentation of acute nephrotoxicity associated with calcineurin inhibitors (ie, hemodynamically mediated AKI) is quite different from the presentation of chronic nephrotoxicity (see "Chronic Interstitial Nephritis" section).[76] AKI may occur within days of initiating therapy, manifesting as a rise in S_{cr} concentration and a corresponding decline in creatinine clearance. Hypertension, hyperkalemia, sodium retention, oliguria, renal tubular acidosis, and hypomagnesemia are frequently observed in the absence of urine sediment abnormalities or morphologic lesions.[73] On the other hand, renal biopsy may reveal thickening of arterioles, mild focal glomerular sclerosis, proximal tubular epithelial cell vacuolization and atrophy, and interstitial fibrosis. Biopsy is most useful to distinguish acute calcineurin inhibitor nephrotoxicity from acute cellular rejection of the transplanted kidney, the latter being evidenced by interstitial infiltrates composed of activated lymphocytes (see Chapter 110, "Osteoarthritis").[77]

Pathogenesis

The acute hemodynamic changes associated with calcineurin inhibitor nephrotoxicity result from an increase in potent vasoconstrictors including thromboxane A_2 and endothelin, activation of the RAS and sympathetic nervous systems, as well as a reduction in the vasodilators nitric oxide, prostacyclin, and prostaglandin E_2.[73,75,76] The net effect is an imbalance in afferent and efferent tone, resulting in predominantly afferent vasoconstriction with reduced renal plasma flow and GFR. The mechanism of acute nephrotoxicity is generally thought to be dose related, since kidney function improves rapidly following dose reduction.[76]

Risk Factors

Risk factors include age over 65, higher dose, concomitant therapy with nephrotoxic drugs (particularly NSAIDs), and interacting drugs that inhibit calcineurin inhibitor metabolism and transport and thus increase systemic exposure, older kidney allograft age, salt depletion, diuretic use, and polymorphic expression of P-glycoprotein.[73,77]

Prevention

Because acute hemodynamically mediated kidney injury secondary to cyclosporine and tacrolimus is concentration related, pharmacokinetic and pharmacodynamic monitoring is an important means of preventing toxicity.[73] However, the persistent presence of therapeutic or low cyclosporine concentrations does not totally preclude the development of nephrotoxicity. Calcium channel blockers may antagonize the vasoconstrictor effect of cyclosporine by dilating glomerular afferent arterioles and preventing acute decreases in renal blood flow and glomerular filtration.[73] Lastly, decreased doses of cyclosporine or tacrolimus, primarily when used in combination with other nonnephrotoxic immunosuppressants, may minimize the risk of toxicity, but this may increase the risk of chronic rejection.

Management

AKI usually improves with dose reduction and treatment of contributing illness or the discontinuation of interacting drugs. CKD is usually irreversible, but progressive toxicity may be limited by discontinuation of cyclosporine (or tacrolimus) therapy or dose reduction, with the continuation of other immunosuppressants.[73,76] S_{cr} and BUN should be closely monitored (daily if possible), as should cyclosporine or tacrolimus concentrations, to ensure that serum concentrations are within the narrow therapeutic range.

SGLT-2 Inhibitors

The sodium-glucose co-transporter-2 (SGLT-2) inhibitors (eg, empagliflozin, canagliflozin, dapagliflozin) are now being employed frequently to enhance serum glucose control in patients with type 2 diabetes mellitus.[78] SGLT-2 inhibitor drugs are nephroprotective.[79,80] As such, they are FDA-approved and now used in addition to metformin to help with glucose control in patients with type 2 diabetes mellitus. The estimated GFR cutoffs for use of these drugs is <60 mL/min/1.73 m^2 for dapagliflozin and <45 mL/min/1.73 m^2 for empagliflozin and canagliflozin. However, AKI is one complication of canagliflozin and dapagliflozin that has been reported to the FDA Adverse Event Reporting System (FAERS). This led the FDA to issue an FDA Drug Safety Communication, http://www.fda.gov/downloads/Drugs/DrugSafety/UCM506772.pdf, for these two SGLT-2 inhibitors.

Incidence

There is no estimated incidence of AKI available for these drugs. However, over 100 cases of AKI associated with the SGLT-2 inhibitors have been reported to FAERS. This contrasts with the randomized controlled trials that do not note AKI as a complication of these drugs.[79,80] In addition, a propensity-matched analysis also showed no signal for AKI with these drugs.[81]

Pathogenesis

The increase in S_{cr} and development of AKI are likely related to a number of processes. As these drugs induce glucosuria due to inhibition of proximal tubular glucose reabsorption, they induce an osmotic diuresis (natriuresis) that can lead to volume depletion, especially when used along with diuretics. SGLT-2 inhibitor related volume depletion in the setting of RAS blocker therapy (ie, ACEI or ARB therapy) can lead to prominent hemodynamic (prerenal) AKI. When severe, acute tubular injury may develop leading to a classic form of ATN. In addition, the delivery of sodium chloride to the macula densa also induces a phenomenon known as tubuloglomerular feedback, which vasoconstricts glomerular afferent arterioles and reduces GFR, ultimately causing an increase in S_{cr}. The increase in S_{cr} may be interpreted by clinicians as indicative of AKI. However, over the long term, this effect is thought to be one of the major nephroprotective mechanisms of the SGLT-2 inhibitors by reducing hyperfiltration-related injury. The SGLT-2 inhibitors may cause direct tubular injury. Uricosuria induced by these drugs may cause both crystal-related tubular injury (crystal nephropathy) and crystal-independent mechanisms of injury.[82] Also, increased urinary glucose may promote intratubular oxidative stress by activating aldose reductase and sorbitol and fructose generation.[82]

Risk Factors

According to the FAERS reports, many patients developing AKI with these drugs were older, were also treated with RAS blockers and diuretics, and sometimes were also taking other nephrotoxins such as NSAIDs. Clearly, combining these drugs with the SGLT-2 inhibitors may lead to AKI when volume depletion occurs. Also, concurrent illness that leads to volume depletion (nausea, vomiting, diarrhea) may also increase risk for AKI.

Prevention

Prevention of AKI in patients with type 2 diabetes mellitus taking these drugs requires careful follow-up in patients who are also taking RAS blockers and diuretics. Patients should be counseled to avoid other nephrotoxins, in particular NSAIDs and COX-2 inhibitors, and contact their care provider when a concurrent illness develops. This will allow timely adjustment of the medications.

Management

When AKI develops, stopping the SGLT-2 inhibitor often is enough to allow kidney recovery. However, in patients with volume depletion on exam, holding the SGLT-2 inhibitor (and RAS blocker and diuretic if also prescribed) and giving intravenous fluids typically resolve AKI. In cases where ATN develops, the SGLT-2 inhibitor should be held and usual supportive care, including RRT when required, should be undertaken. The SGLT-2 inhibitor can likely be restarted in patients where kidney function recovers to baseline and eGFR is above the FDA-recommended threshold.

Chimeric Antigen Receptor T-Cells

Incidence

CAR T-cell therapy is a highly efficacious immunotherapy that employs the principle of adoptive cell transfer. T-cells are collected from patients and re-engineered to express selective tumor-targeted receptors (CARs) on cell surfaces. CARs function irrespective of any major histocompatibility complex restriction, making them immune to any T-cell evading mechanisms of tumor cells. The CAR T-cell therapy tisagenlecleucel is a CD-19 targeted therapy for B-cell acute lymphoblastic leukemia while axicabtagene ciloleucel is used to treat large B-cell lymphoma and brexucabtagene autoleucel is employed for relapsed/refractory mantle cell lymphoma.[83,84] CAR T-cell therapy is complicated by severe systemic inflammatory disorders that lead to AKI in 18.6% of patients, with up to 4.4% of patients developing AKI requiring dialysis.[85]

Pathogenesis

One of the most common toxicities observed with CAR-T therapy is CRS, which is characterized by high fever, hypotension, hypoxia, and multi-organ toxicity including AKI. CRS is triggered by a surge of cytokines and chemokines released by activated T-cells and by bystander immune cells. CRS typically manifests in the first week (median 2-3 days) after the CAR T-cell infusion and peaks within 1 to 2 weeks.[86] Patients at highest risk have bulky disease and multiple comorbidities. AKI is due to primarily to either hemodynamic (prerenal) kidney dysfunction or ischemic acute tubular injury (with severe hypotension and high grade CRS). Cytokine-mediated kidney injury, hemophagocytic lymphohistiocytosis (hyperactivation of lymphocytes and macrophages), and tumor lysis syndrome may also play a role, but have not been verified with kidney biopsy evidence. Infectious complications with sepsis and nephrotoxic medications (antibiotics, NSAIDs, etc.) may also contribute to AKI in these patients.[66,86]

Management

Management of AKI from CAR T-cell treatment is primarily focused on the severity (grade) of CRS with the overall goal to balance treatment of CRS complications and end-organ injury with beneficial effects of the anti-cancer therapy. Supportive care includes vasopressors and intravenous fluids for hypotension, while anti–interleukin-6 therapy with tocilizumab or siltuximab with/without corticosteroids is used for severe CRS.[66,86]

OBSTRUCTIVE NEPHROPATHY

Numerous medications may cause obstructive nephropathy, or kidney injury from deposition or precipitation within the renal tubules and/or collecting system. For example, the precipitation of drug crystals in distal tubular lumens can lead to intratubular obstruction, interstitial nephritis, and occasionally superimposed ATN, collectively termed “crystal nephropathy.” Nephrolithiasis, the formation of stones within the kidney, results from abnormal crystal precipitation in the renal collecting system, potentially causing urinary tract obstruction with kidney injury. Several medications that have been associated with development of obstructive nephropathy are listed in Table 65-1.

Crystal Nephropathy

Incidence

The incidence of crystal nephropathy is unclear for most of the implicated agents because histologically confirmed cases are rare, and many drugs cause kidney injury via multiple mechanisms.[87] For example, AKI develops in approximately 2% of patients who receive high-dose methotrexate, likely due to a combination of direct toxic effects and crystal nephropathy.[88,89] Similarly, crystalluria is observed in 20% of patients receiving indinavir, but the number of patients developing crystal nephropathy is unknown.[90]

Pathogenesis

Drugs may induce intratubular obstruction and AKI by direct (precipitation of the drug itself) and indirect means (ie, promoting release and precipitation of tissue-degradation products or cellular casts). For example, antineoplastic drugs may cause acute renal tubular obstruction indirectly by inducing tumor lysis syndrome, hyperuricemia, and intratubular precipitation of uric acid crystals.[50] The diagnosis is supported by a urine uric acid-to-creatinine ratio greater than 1. Uric acid precipitation can be prevented by vigorous hydration with normal saline, beginning at least 48 hours prior to chemotherapy, to maintain urine output 100 mL/hr in adults. Administration of allopurinol 100 mg/m^2 thrice daily (maximum of 800 mg/day) started 2 to 3 days prior to chemotherapy, and urinary alkalinization to pH 7 may also be of value. In patients at high risk of developing tumor lysis syndrome (ie, large tumor burden, preexisting kidney disease, and older age), a single fixed dose of 3 mg rasburicase may be beneficial.[91]

Drug-induced rhabdomyolysis is another form of indirect toxicity, which can lead to intratubular precipitation of myoglobin and, if severe, AKI.[92] The most common cause of drug-induced rhabdomyolysis is direct myotoxicity from 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins, including lovastatin and simvastatin.[93] The risk of rhabdomyolysis is increased when these drugs are administered concurrently with gemfibrozil, niacin, or inhibitors of the CYP3A4 metabolic pathway (eg, erythromycin and itraconazole).

Anticoagulant nephropathy, including warfarin-related nephropathy, is characterized by glomerular hemorrhage with subsequent intratubular obstruction by red blood cell casts. Patients with underlying CKD appear to be at greatest risk. The incidence of warfarin-related nephropathy may be as high as 33% in CKD versus 16.5% in non-CKD patients. Other risk factors included age, diabetes mellitus, hypertension, and cardiovascular disease.[94]

Intratubular precipitation of drugs or their metabolites can also directly cause AKI. Precipitation of drug crystals is due primarily to supersaturation of a low urine volume with the offending drug or relative insolubility of the drug in either alkaline or acidic urine.[90] Volume depletion is an important risk factor for the development of AKI. Urine pH decreases to approximately 4.5 during maximal stimulation of renal tubular hydrogen ion secretion. Certain solutes can precipitate and obstruct the tubular lumen at this acid pH, particularly when urine is concentrated, such as for patients with volume depletion. For example, several antiviral drugs have been associated with intratubular precipitation and AKI.[95,96] Acyclovir is relatively insoluble at physiologic urine pH and is associated with intratubular precipitation in dehydrated oliguric patients.[90] Foscarnet complexation with ionized calcium may result in precipitation of calcium-foscarnet salt crystals in renal glomeruli, causing primarily a crystalline glomerulonephritis. The salt crystals may then secondarily precipitate in the renal tubules causing tubular necrosis.[23] The protease inhibitors indinavir and atazanavir have been associated with symptomatic crystalluria or nephrolithiasis in 20% to 33% of patients receiving chronic treatment.[90,96] Intratubular indinavir or atazanavir crystal precipitation can be prevented in most patients if the patient consumes adequate hydration to obtain a urinary output of at least 1,500 mL/day.[95] Sulfadiazine, when used at high doses, and methotrexate may also precipitate in acidic urine and can cause oligoanuric kidney injury.[90] Massive administration of ascorbic acid can also result in obstruction of renal tubules with calcium oxalate crystals, leading to “oxalate nephropathy.”[90] Triamterene and the quinolone antibiotic ciprofloxacin may also precipitate in renal tubules and cause kidney injury.[23,87]

Kidney injury caused by intratubular precipitation of most tissue-degradation products or drugs and their metabolites can be largely prevented and possibly treated by administering the drug after vigorously prehydrating the patient, maintaining a high urine volume, and urinary alkalinization.[95,96]

Vancomycin Cast Nephropathy

Vancomycin-associated AKI may also be due to the formation of obstructive tubular casts composed of noncrystal nanospheric vancomycin aggregates admixed with uromodulin.[97] These distinctive casts are observed in some patients with AKI associated with high vancomycin trough concentrations. On kidney biopsy, acute tubulointerstitial inflammation is associated with these tubular casts. Co-precipitation of vancomycin and uromodulin occurs.[98]

Acute Phosphate Nephropathy

Nephrocalcinosis is a clinical pathologic condition characterized by extensive tubulointerstitial precipitation and deposition of calcium phosphate crystals leading to marked tubular calcification.[99] It is most commonly seen in clinical conditions associated with hypercalcemia and hypercalciuria, such as hyperparathyroidism, malignancy, and less frequently increased intake of calcium or vitamin D. However, nephrocalcinosis can also result from hyperphosphatemia and hyperphosphaturia in the absence of hypercalcemia, as is known to occur for patients who have received oral sodium phosphate solution (OSPS) as a bowel preparation.[100]

The term "acute phosphate nephropathy" was coined specifically to describe OSPS-induced nephrocalcinosis, as its pathogenesis is the result of increased phosphate intake rather than hypercalcemia.[100] Nephrocalcinosis is associated with use of OSPS for bowel preparation prior to GI procedures, and strong associations are present between exposure to OSPS and a decline in kidney function, particularly in the elderly and those with preexisting kidney disease.[100,101]

Incidence

The incidence of acute phosphate nephropathy is between 1 in 1,000 and 1 in 5,000 exposures, translating to roughly 1,400 to 7,000 new cases annually.[102]

Clinical Presentation

Patients usually present with AKI several days to months after exposure to OSPS. Low-grade proteinuria (less than 1 g/day), normocalcemia, and bland urinary sediment are usually observed. Extensive deposition of calcium phosphate in the distal tubules and collecting ducts without glomerular or vascular injury is the hallmark of acute phosphate nephropathy.[90]

Risk Factors

Risk factors include advanced age, preexisting kidney disease, female sex, hypertension, diabetes, bowel conditions associated with prolonged intestinal transit, high sodium phosphate dosage, volume depletion, and medications that affect renal perfusion or function (eg, diuretics, lithium, NSAIDs, ACEIs, or ARBs).[100]

Nephrolithiasis

Nephrolithiasis (formation of renal calculi or kidney stones) does not present as classic nephrotoxicity since GFR is usually not decreased. Drug-induced nephrolithiasis can be the result of abnormal crystal precipitation in the renal collecting system, potentially causing pain, hematuria, infection, or, occasionally, urinary tract obstruction with kidney injury. The overall prevalence of drug-induced nephrolithiasis is about 1% to 2% of all cases of nephrolithiasis.[96]

Kidney stone formation, possibly also accompanied by intratubular precipitation of crystalline material, has been a rare complication of drug therapy. Until the development of antiretroviral drugs, triamterene had been the drug most frequently associated with kidney stone formation, with a prevalence of 0.4%.[87] Sulfadiazine is a poorly soluble sulfonamide that may cause symptomatic acetylsulfadiazine crystalluria with stone formation and flank or back pain, hematuria, or kidney injury.[90] A high urine volume and urinary alkalinization to pH greater than 7.15 may be protective. Numerous other drugs have been implicated in the development of nephrolithiasis, including the antibacterial agents ciprofloxacin, amoxicillin, and nitrofurantoin, and various products containing ephedrine, norephedrine, pseudoephedrine, and melamine. Moreover, nephrolithiasis has become a well-known complication of antiretroviral agents, including the protease inhibitors indinavir, atazanavir, nelfinavir, amprenavir, saquinavir, ritonavir, and darunavir.[96]

GLOMERULAR DISEASE

Proteinuria, particularly nephrotic range proteinuria (defined as urine protein excretion greater than 3.5 g/day) with or without a decline in the GFR is a

hallmark sign of glomerular injury (see Chapter e66, "Glomerulonephritis"). Glomerular injury associated with drug exposure is broadly classified into either direct cellular toxicity or immune-mediated injury. Glomerular lesions associated with direct cellular toxicity include thrombotic microangiopathy (see "Renal Vasculitis" section), minimal change glomerular disease, and focal segmental glomerulosclerosis (FSGS). Lesions from immune-mediated injury include vasculitis (see "Renal Vasculitis" section) and membranous nephropathy.[103,104] Although drug-induced glomerular disease is uncommon, a variety of agents have been implicated.

Minimal Change Glomerular Disease

Drug-induced minimal change glomerular disease is frequently accompanied by interstitial nephritis and is most common during NSAID therapy. Lithium, pamidronate, interferon-α, and interferon-β have also been implicated.[103] Patients present abruptly with nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia and rarely with hematuria and hypertension. The pathogenesis is unknown, but nephrotic range proteinuria as a consequence of NSAID therapy is frequently associated with a T-lymphocytic interstitial infiltrate, suggesting disordered cell-mediated immunity.[71] Proteinuria usually resolves rapidly after discontinuation of the offending drug, and a course of corticosteroids (eg, prednisone) may help resolve the lesion. That said, the majority of adults with NSAID-induced minimal change glomerular disease achieve complete remission over the course of several months, even in the absence of corticosteroid treatment.[103]

Focal Segmental Glomerulosclerosis

FSGS is characterized by patchy areas (ie, only some glomeruli are partially affected by the disease) of glomerular sclerosis with interstitial inflammation and fibrosis (see Chapter e66). It represents a pattern of glomerular injury, not a disease per se, and is the final common pathway by which normal glomerular components are replaced by fibrous scar tissue. FSGS has been described in the setting of chronic heroin abuse (known as *heroin nephropathy*).[105] The pathogenesis is unknown but may include direct toxicity by heroin or adulterants and injury from bacterial or viral infections accompanying IV drug use. The bisphosphonates pamidronate and zoledronate, commonly used to treat osteoporosis, malignancy-associated hypercalcemia, and Paget's disease, are associated with the development of a particularly aggressive variant of FSGS called *collapsing glomerulopathy*.[103] It presents with massive proteinuria (greater than 8 g/day), and it is typically characterized by rising S_{cr} at diagnosis and rapid progression to ESKD. Patients receiving IV formulations, high doses, or prolonged therapy are at highest risk. Interferon-α, interferon-β, lithium, sirolimus, and anabolic steroids have also been associated with FSGS.

Membranous Nephropathy

Membranous nephropathy is the most common etiology of nephrotic syndrome in Caucasian adults.[104] It is characterized by subepithelial immune complex formation along glomerular capillary loops and, although rarely seen, has classically been associated with gold therapy, penicillamine, captopril, and NSAID use.[104] Patients present with nephrotic range proteinuria and microscopic hematuria, with hypertension and elevated S_{cr} apparent for patients with more advanced disease. The pathogenesis may involve damage to proximal tubule epithelium with antigen release, antibody formation, and glomerular immune complex deposition.[104] Proteinuria usually resolves slowly after discontinuing the offending drug. Patients who remain nephrotic after 6 months should be treated with a 6- to 12-month course of immunosuppressive therapy, which typically consists of prednisone with or without cyclophosphamide.

TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis refers to diseases in which the predominant changes occur in the renal interstitium rather than the tubules. The presentation may be acute and reversible with interstitial edema, rapid loss of kidney function, and systemic symptoms or chronic and irreversible, associated with interstitial fibrosis and minimal to no systemic symptoms.[106]

Acute Allergic Interstitial Nephritis

Incidence

5 The incidence of drug-induced acute allergic interstitial nephritis (AIN) is unclear and likely varies with clinical setting. For example, pathology

registries indicate AIN as the histologic lesion in only 2% to 5% of kidney biopsies, but from 10% to 27% of kidney biopsies performed in hospitalized patients with unexplained AKI demonstrate AIN.[63] Multiple drugs have been implicated in the development of AIN (Table 65-4). It usually manifests 2 weeks after exposure to a drug but may occur sooner if the patient was previously sensitized.[107]

TABLE 65-4

Drugs Associated with Allergic Interstitial Nephritis

Antimicrobials	
Acyclovir	Indinavir
Aminoglycosides	Rifampin
Amphotericin B	Sulfonamides
β-Lactams	Tetracyclines
Ciprofloxacin	Trimethoprim–sulfamethoxazole
Ethambutol	Vancomycin
Diuretics	
Acetazolamide	Loop diuretics
Amiloride	Triamterene
Chlorthalidone	Thiazide diuretics
Neuropsychiatric	
Carbamazepine	Phenytoin
Lithium	Valproic acid
Phenobarbital	
Nonsteroidal anti-inflammatory drugs	
Aspirin	Ketoprofen
Indomethacin	Phenylbutazone
Naproxen	Diclofenac
Ibuprofen	Zomepirac
Diflunisal	Cyclooxygenase-2 inhibitors
Piroxicam	

Miscellaneous	
Acetaminophen	Immune checkpoint inhibitors
Allopurinol	Lansoprazole
Interferon-α	Methyldopa
Aspirin	Omeprazole
Azathioprine	P-aminosalicylic acid
Captopril	Phenylpropanolamine
Cimetidine	Propylthiouracil
Clofibrate	Radiographic contrast media
Cyclosporine	Ranitidine
Glyburide	Sulfinpyrazone
Gold	Warfarin sodium

Clinical Presentation

Although methicillin-induced AIN is the prototype for AIN, AIN is associated with all β-lactam antibiotics (including cephalosporins) and numerous other antimicrobials. Clinical signs present approximately 14 days after initiation of therapy and include (with their approximate incidence) fever (27%-80%), maculopapular rash (15%-25%), eosinophilia (23%-80%), arthralgia (45%), and oliguria (50%).[107] The systemic hypersensitivity findings of the classic triad of fever, rash, and arthralgia, often along with eosinophilia and eosinophiluria, supported the diagnosis of AIN. However, this constellation of findings is not consistently reliable as one or more are frequently absent. In fact, the triad is seen in only 5% to 10% of patients with AIN, so caution is warranted in basing diagnosis on hypersensitivity findings alone.[108] Eosinophilia alone is insensitive, and eosinophiluria is insensitive and nonspecific, so urinary eosinophils are not considered a useful sign of AIN and are no longer recommended as a diagnostic test.[108] Anemia, leukocytosis, and elevated immunoglobulin E levels may occur. Tubular dysfunction may be manifested by acidosis, hyperkalemia, salt wasting, and concentrating defects.[107]

Nonsteroidal Anti-Inflammatory Drugs

NSAID-induced AIN has a different clinical presentation than that seen with most other drugs. Patients are typically over 50 years of age (reflecting NSAID use for degenerative joint disease), the onset is delayed a mean of 6 months from initiation of therapy compared with 2 weeks with β-lactams, and fever, rash, and eosinophilia are typically not observed in patients with NSAID-induced AIN.[100] Concomitant nephrotic syndrome (proteinuria greater than 3.5 g/day) occurs in more than 70% of patients. Prompt diagnosis of AIN is important as discontinuation of the offending drug may prevent irreversible renal damage. Renal biopsy is the most definitive method for diagnosis.

Proton Pump Inhibitors

The proton pump inhibitors (PPIs) are widely prescribed to treat acid-related gastrointestinal disease. While they are generally well tolerated and safe, AIN is a complication and it may lead to AKI, and rarely to CKD.[109] In contrast to the classic allergic presentation of AKI seen with the β-lactams, fever, rash, and eosinophilia are rarely seen with PPIs. In addition, the latent period from PPI exposure to AIN is much longer (weeks to months). Kidney

biopsy is often required to definitively diagnose PPI-related AIN due to the lack of diagnostic clinical and laboratory findings.[110]

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a novel class of cancer immunotherapy noted to be associated with AKI, which is due primarily to AIN.[66,111,112] The incidence of AKI associated with these drugs ranges between 1% and 5%, with kidney biopsy showing AIN in more than 80% of patients.[111] These drugs (monoclonal antibodies) target immune pathways, including the receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein-1 (PD-1), and the T-cell receptor ligand (PD-ligand-1), that dampen T-cell activation and effector responses to prevent autoimmunity. Cancer cells, however, use these pathways to escape targeting by the immune system. In inhibiting such pathways, immune checkpoint inhibitors stimulate T-cell responses against cancer cells. Off-target organ injury, termed "immune-related adverse events," including AIN has been described. AIN has been observed in patients receiving anti-PD-1 agents either as monotherapy or in combination with anti-CTLA-4 drugs.[66,111,112] The mechanism underlying immune checkpoint inhibitor–associated AIN is unknown, but may be similar to the previously described mechanisms behind AIN from other drugs. Immune checkpoint inhibitors may also favor development of autoantibodies or encourage a pro-inflammatory cytokine milieu.[66] Patients may present with either other immune-related adverse events or no symptoms. Clinical findings such as rash and eosinophilia may not be encountered, while laboratory tests such as pyuria and white blood cell casts are present only occasionally. Diagnosis of immune checkpoint inhibitor–associated AIN generally requires kidney biopsy.

Pathogenesis

The pathogenesis of the majority of cases of AIN is considered to be an allergic hypersensitivity response. This is supported by the fact that AIN is characterized as a diffuse or focal interstitial infiltrate of lymphocytes, eosinophils, and occasional polymorphonuclear neutrophils.[106] Granulomas and tubular epithelial cell necrosis are relatively common with drug-induced AIN. Occasionally a humoral antibody-mediated mechanism is implicated by the presence of circulating antibody to a drug hapten–tubular basement membrane complex, low serum complement levels, and deposition of immunoglobulin G and complement in the tubular basement membrane. More commonly, a cell-mediated immune mechanism is suggested by the absence of these findings and the presence of a predominantly T-lymphocyte.[106]

Risk Factors

Despite this being an idiosyncratic hypersensitivity reaction, recent studies suggest that underlying CKD, receipt of drugs such as PPIs and NSAIDs, and combination immune checkpoint inhibitor therapy increase risk for AKI.[111] Individuals with other drug allergies may have increased risk and warrant close monitoring.

Prevention

No specific preventive measures are known because of the idiosyncratic nature of these reactions. Patients must be monitored carefully to recognize the signs and symptoms because promptly discontinuing the offending drug often leads to full recovery.[107]

Management

Corticosteroid therapy may be beneficial and should be initiated immediately or soon after diagnosis of AIN along with discontinuance of the offending drug to avoid the risk of incomplete recovery of kidney function. While various regimens have been used, high-dose oral prednisone 1 mg/kg/day for 4 to 6 weeks with a stepwise taper over the next 4 weeks may be considered. However, if there is no significant improvement in kidney function after 3 to 4 weeks of treatment, then steroids should be discontinued.[106] Typical kidney function indices (eg, S_{cr}, BUN) and signs and symptoms of AIN should be monitored closely for improvement. In PPI-induced AIN, drug discontinuation and corticosteroids are effective in most but not all cases, with CKD occurring in a significant number.[109] Management of immune checkpoint inhibitor–associated AIN generally includes drug discontinuation and corticosteroids, although recommendations on dose and duration are lacking.[66] Rechallenge with an immune checkpoint inhibitor is associated with recurrent AKI in approximately 23% of patients.[111]

Chronic Interstitial Nephritis

Lithium, analgesics, calcineurin inhibitors, aristolochic acid, and only a few other drugs cause chronic interstitial nephritis, which is usually a progressive and irreversible lesion.

Lithium

Incidence

The prevalence of non-dialysis-dependent CKD stemming from chronic lithium nephrotoxicity in the general population of patients treated with lithium is approximately 1%.[113,114] The prevalence of lithium-induced ESKD among all ESKD patients is between 0.2% and 0.8%.[113] Although several renal tubular lesions are associated with lithium therapy, an impaired ability to concentrate urine (nephrogenic diabetes insipidus) is seen in 20% of all patients receiving lithium therapy.[115]

Clinical Presentation

Lithium-induced nephrotoxicity is typically asymptomatic and develops insidiously during years of therapy. Blood pressure is normal and urinary sediment is bland, making detection difficult until the disease progresses significantly.[116] It is usually recognized by rising BUN or S_{cr} concentrations or the onset of hypertension. Polydipsia (excessive thirst) and polyuria (excessive urination) are observed in 40% and 20%, respectively, of patients with nephrogenic diabetes insipidus (see Chapter 68, "Disorders of Sodium and Water Homeostasis"). Although interstitial fibrosis may be observed as early as five years after beginning therapy, lithium-induced CKD usually occurs after 10 to 20 years of lithium treatment.[116]

Pathogenesis

The precise mechanism of chronic lithium-induced nephrotoxicity is not well characterized. Impaired ability to concentrate urine is a result of a decrease in collecting duct response to antidiuretic hormone, which may be related to downregulation of aquaporin 2 water channel expression during lithium therapy.[116] Chronic tubulointerstitial nephritis attributed to lithium is evidenced most commonly by kidney biopsy findings of interstitial fibrosis, tubular atrophy, tubular microcysts, and glomerular sclerosis. The tubular microcysts can sometimes be visualized on imaging studies such as MRI. The pathogenesis may involve cumulative direct lithium toxicity, since duration of therapy correlates with the decline in the GFR.[116]

Risk Factors

The duration of lithium therapy and cumulative dose was considered the major determinants of chronic nephrotoxicity. However, this is now questionable, as long-term lithium therapy in the absence of episodes of acute intoxication may not be nephrotoxic.[117] Increased age may also be a risk factor, but daily dose is not.[114,116]

Prevention

Prevention of acute and chronic toxicity includes maintaining lithium concentrations as low as therapeutically possible, avoiding dehydration, and monitoring kidney function. It is unknown whether progression to CKD can be prevented by stopping lithium use when mild kidney injury is first recognized. This poses a dilemma as lithium is highly effective for affective disorders and the risks and potential benefits of discontinuing such a beneficial drug need to be carefully considered.[116] However, if lithium therapy is continued, kidney function must be monitored and therapy discontinued if it continues to decline. Amiloride has been used for prevention and treatment of lithium-induced nephrogenic diabetes insipidus, since it blocks epithelial sodium transport of lithium into the cortical collecting duct in the distal nephron.[116]

Management

Symptomatic polyuria and polydipsia can be reversed by discontinuation of lithium therapy or ameliorated with amiloride 5 to 10 mg daily during continued lithium therapy (see Chapter 68). If polyuria does not resolve within 7 to 10 days of therapy, then the amiloride dose should be increased to 20 mg daily. Progressive chronic interstitial nephritis is treated by discontinuation of lithium therapy, adequate hydration, and avoidance of other nephrotoxic agents. Lithium serum concentrations, as well as kidney function indices, including urine output, BUN, and S_{cr}, should be monitored

closely for resolution of signs and symptoms of toxicity.[116]

Cyclosporine and Tacrolimus

Delayed chronic tubulointerstitial nephritis, considered the Achilles' heel of calcineurin inhibitor–based immunosuppressive regimens, may occur after several months of therapy and can result in irreversible kidney disease.[73,74] Toxicity is progressive and usually manifests as a slowly rising S_{cr} concentration and decreased creatinine clearance that may not reflect the severity of histopathologic changes. All three compartments of the kidney can be affected, evidenced by typical biopsy findings that include arteriolar hyalinosis, glomerular sclerosis, and a striped pattern of tubulointerstitial fibrosis.[74] The pathogenesis involves sustained renal arteriolar endothelial cell injury and increased extracellular matrix synthesis, which ultimately result in chronic ischemia of the tubulointerstitial compartment because of increased release of endothelin-1, decreased production of nitric acid, and upregulation of transforming growth factor-β. Unlike acute nephrotoxicity, chronic toxicity is not dose dependent.[73,74]

Aristolochic Acid

Incidence

Although the true incidence of aristolochic acid nephropathy is unknown, approximately 3% to 5% of patients who consume the natural product develop interstitial fibrosis with tubular atrophy.[118]

Clinical Presentation

Patients with aristolochic acid nephropathy typically present with mild-to-moderate hypertension, mild proteinuria, glucosuria, and moderately elevated S_{cr} concentrations. Anemia and shrunken kidneys are also common on initial presentation.[119] The overwhelming majority of cases to date have been in women. The main pathologic lesions observed in the kidneys are interstitial fibrosis with atrophy and destruction of proximal tubules throughout the renal cortex; in general, the glomeruli are not affected. Perhaps the most remarkable feature of aristolochic acid nephropathy is the rate at which it progresses. In most individuals, ESKD requiring dialysis or transplantation develops within 6 to 24 months of exposure. An alarming high prevalence (approximately 40%-45%) of urothelial transitional cell carcinoma has been observed in Belgian patients who underwent renal transplantation.[118,119]

Pathogenesis

The precise mechanism of aristolochic acid nephropathy and urothelial carcinoma has yet to be characterized. The major components of aristolochic acid are metabolized to mutagenic compounds called *aristolactam I* and *aristolactam II*, respectively, which form aristolochic acid–DNA adducts in humans. These adducts cause direct DNA damage and may lead to proximal tubular atrophy and apoptosis.[119]

Prevention

The primary means of preventing aristolochic acid nephropathy is the limitation of exposure to compounds containing aristolochic acids. Several countries, including the United States, the United Kingdom, Canada, Australia, and Germany, have banned the use of herbs containing *Aristolochia*.[119] In patients that develop aristolochic acid nephropathy, treatment with corticosteroids along with toxin elimination have beneficial results.

Papillary Necrosis

Papillary necrosis is a form of chronic tubulointerstitial nephritis characterized by necrosis of the renal papillae, the regions of the kidney where the collecting ducts enter the renal pelvis, which leads to progressive kidney disease. Papillary necrosis is associated with diabetes, sickle cell disease, obstruction and infection of the urinary tract, and most commonly analgesic use.[120]

Analgesic Nephropathy

Incidence

Prototypical analgesic nephropathy is characterized by chronic tubulointerstitial nephritis with papillary necrosis.[120] Chronic excessive consumption of combination analgesics, particularly those containing phenacetin, was believed to be the major cause and led to the removal of phenacetin and phenacetin mixtures from most world markets. However, contemporary analgesics, particularly aspirin, acetaminophen, and NSAIDs, alone or in combination, are also associated with the development of analgesic nephropathy. The incidence of analgesic nephropathy has declined significantly since removal of phenacetin from many countries, with the prevalence now less than 5% in the US-adult ESKD population.[120]

Clinical Presentation

Analgesic nephropathy is a progressive disease that evolves slowly over several years.[120] It is difficult to recognize in the early stages of the disease because patients are often asymptomatic, and it may be underdiagnosed as a cause of ESKD. It is seen more commonly in women than men. Early manifestations are generally nonspecific and may include headache and upper GI symptoms; later manifestations include impaired urinary concentrating ability, dysuria, sterile pyuria, microscopic hematuria, mild proteinuria (less than 1.5 g/day), and lower back pain. As disease progresses, hypertension, atherosclerotic cardiovascular disease, renal calculi, and bladder stones are common, and pyelonephritis is a classic finding in advanced analgesic nephropathy. The most sensitive and specific diagnostic criteria include: (a) a history of chronic daily habitual analgesic ingestion (daily use for at least 3 to 5 years); (b) IV pyelography, renal ultrasound, or renal computed tomography imaging, which reveals decreased renal mass and bumpy renal contours; (c) elevated S_{cr}, that is, up to 4 mg/dL (354 µmol/L); and (d) papillary calcifications.[120]

Pathogenesis

Analgesic nephropathy originates in the papillary tip as a result of accumulated toxins, drugs and metabolites, decreased blood flow, and impaired cellular energy production. The metabolism of phenacetin to acetaminophen, which is then oxidized to toxic-free radicals that are concentrated in the papilla, is the initiating factor that causes toxicity by mechanisms analogous to acetaminophen hepatotoxicity via glutathione depletion.[121] Cortical interstitial nephritis develops secondary to papillary necrosis. Salicylates potentiate these effects by also depleting renal glutathione, and inhibiting prostaglandin-mediated vasodilation, thus further predisposing the renal medulla to ischemic injury.[121]

Risk Factors

The epidemiology of analgesic use and analgesic nephropathy continues to evolve. The classic concept persists that risk for ESKD increases with cumulative consumption of combination analgesics, phenacetin, or acetaminophen and aspirin or NSAIDs. Caffeine contained in combination analgesics may increase risk, but the role is not clear.[120] Chronic use of therapeutic doses of NSAIDs or high-dose acetaminophen, but not aspirin or salicylates alone, can cause analgesic nephropathy.

Prevention

Prevention has depended primarily on public health efforts to restrict the sale of phenacetin and combination analgesics. However, risk continues with ongoing availability of nonprescription combination analgesics containing aspirin, acetaminophen, and caffeine in the United States and throughout the world.

Individuals requiring chronic analgesic therapy may reduce risk by limiting the total dose, avoiding combined use of two or more analgesics, and maintaining good hydration to prevent renal ischemia and decrease the papillary concentration of toxic substances. Acetaminophen remains the preferred nonopiate analgesic for patients with preexisting kidney disease.

Management

Treatment of established nephrotoxicity requires cessation of analgesic consumption.[121] This can prevent progression and may improve kidney function. Kidney function indices, including urine output, BUN, and S_{cr}, should be monitored every several months. Patients should also be monitored for the development of transitional cell carcinoma of the renal pelvis, calyces, ureters, and bladder, which may present years after analgesic nephropathy is diagnosed.

RENAL VASCULITIS, THROMBOSIS, AND CHOLESTEROL EMBOLI

Renal Vasculitis

Drug-induced renal vascular disease commonly presents as vasculitis, thrombotic microangiopathy, or cholesterol emboli.[104,122] Vasculitis implies inflammation of the vessel wall, capillaries, or glomeruli and is typically classified according to vessel size (ie, small, medium, or large vessel vasculitis). Small vessel vasculitides usually affect multiple organ systems, including the kidneys and lungs, and are associated with nonspecific inflammatory symptoms such as fever, malaise, myalgias, arthralgias, and weight loss. Numerous drugs are associated with the development of renal vasculitis, including hydralazine, propylthiouracil, allopurinol, phenytoin, sulfasalazine, penicillamine, and minocycline (see Table 65-1).[104,122] Most drug-induced cases of vasculitis, including hydralazine, propylthiouracil, allopurinol, penicillamine, and the anti-TNF-α drug adalimumab, have been implicated in the development of antineutrophil cytoplasmic antibody–positive vasculitis.[104,122,123] Patients present with hematuria, proteinuria, oliguria, and red cell casts, frequently along with fever, malaise, myalgias, and arthralgias.[122] Treatment typically consists of withdrawing the offending drug and administration of corticosteroids or other immunosuppressive therapy, and usually leads to resolution of symptoms within weeks to months.

Thrombotic Microangiopathy

Thrombotic microangiopathy is characterized clinically by microangiopathic hemolytic anemia, fragmented red cells, and thrombocytopenia and pathologically by vascular endothelial proliferation, endothelial cell swelling, and intraluminal platelet thrombi in the small vessels, particularly affecting the renal and cerebral capillaries and arterioles.[103,124] The absence of inflammation in vessel walls distinguishes thrombotic microangiopathy from vasculitis. Numerous medications, including oral contraceptive agents, cyclosporine, tacrolimus, muromonab-CD3, many cancer chemotherapeutic agents including antiangiogenesis drugs (eg, bevacizumab, sunitinib, and sorafenib), mitomycin C, cisplatin, and gemcitabine, interferon-α, ticlopidine, clopidogrel, quinine, and several antimicrobial agents (eg, valacyclovir, penicillins, rifampin, and metronidazole) are associated with the development of thrombotic microangiopathy.[103,124] Patients may present with fever, neurological dysfunction, elevated S_{cr} and BUN, and hypertension, along with microangiopathic hemolytic anemia and thrombocytopenia. Kidney injury can be severe and irreversible, although corticosteroids, antiplatelet agents, plasma exchange, plasmapheresis, and high-dose IV immunoglobulin G have each induced clinical improvement.[124]

Cholesterol Emboli

Anticoagulants (particularly warfarin) and thrombolytics (eg, urokinase, streptokinase, and tissue-plasminogen activator) are associated with cholesterol embolization of the kidney.[125] These drugs act to remove or prevent thrombus formation over ulcerative plaques or may induce hemorrhage within clots, thereby causing showers of cholesterol crystals that lodge in small-diameter arteries of the kidney (renal arterioles and glomerular capillaries). Cholesterol crystal emboli induce an endothelial inflammatory response, which leads to complete obstruction, ischemia, and necrosis of affected vessels within weeks to months after initiation of therapy.[125] Purple discoloration of the toes and mottled skin over the legs are important clinical clues. Treatment is supportive in nature, since kidney injury is generally irreversible.

PHARMACOECONOMICS

The pharmacoeconomic implications of DIKD are enormous. In general, an episode of AKI leads to higher hospital resource use, with increases in the median direct hospital cost of $2,600 and the hospital length of stay by 5 days.[126] An increase in S_{cr} of greater than or equal to 0.5 mg/dL (44 µmol/L) is independently associated with a 6.5-fold increase in the odds of death, a 3.5-day increase in length of hospital stay, and nearly $7,500 in excess hospital costs even after adjusting for age, sex, and measures of comorbidity.[127] Amphotericin B–induced AKI leads to a mean increased length of hospital stay of 8.2 days and adjusted additional costs of $29,823 per patient.[128] The major driver of the increased costs associated with contrast-induced AKI was the cost of the longer initial hospital stay. The increased availability of automated clinical decision support systems and computer-guided medication dosing for hospital inpatients may improve the safety of potentially harmful drugs and minimize the occurrence of nephrotoxicity in this setting, thereby potentially lowering the corresponding economic consequences.[128]

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AIN	allergic interstitial nephritis
AKI	acute kidney injury
ARB	angiotensin II receptor blocker
ATN	acute tubular necrosis
BUN	blood urea nitrogen
CI-AKI	contrast media–induced AKI
CKD	chronic kidney disease
COX	cyclooxygenase
CRS	cytokine release syndrome
CTLA-4	cytotoxic T-lymphocyte antigen-4
DIKD	drug-induced kidney disease
ESKD	end-stage kidney disease
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
IGFBP7	insulin-like growth factor–binding protein 7
KIM-1	kidney injury molecule-1
NGAL	neutrophil gelatinase–associated lipocalin
NSAIDs	nonsteroidal anti-inflammatory drugs
OSPS	oral sodium phosphate solution
PD-1	programmed cell death protein-1
PPI	proton pump inhibitor
RAS	renin–angiotensin system

RTEC	renal tubular epithelial cell
S_{cr}	serum creatinine
SGLT-2	sodium-glucose co-transporter 2
TIMP-2	tissue inhibitor of metalloproteinase 2

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements regarding drug-induced kidney disease (DIKD) is CORRECT?
   A. A temporal relationship between DIKD and administration of the potentially toxic agent is rarely observed.
   B. The offending agent is rarely identified.
   C. DIKD is characterized by a slowly developing and transient reduction in GFR.
   D. The most common presentation of DIKD in the hospital setting is acute tubular necrosis.
2. Which of the following is associated with hemodynamically mediated kidney injury induced by angiotensin converting enzyme inhibitors?
   A. Enhanced efferent arteriolar dilation
   B. Patients with renal artery stenosis at decreased risk
   C. Increase in glomerular capillary hydrostatic pressure
   D. Increased glomerular ultrafiltration
3. Which of the following is the most common manifestation of drug-induced kidney disease?
   A. Proteinuria
   B. Pyuria
   C. Hematuria
   D. A decline in the glomerular filtration rate (GFR)
4. Which of the following statements regarding aminoglycoside-induced acute tubular necrosis is CORRECT?
   A. Risk factors include young age.
   B. Serum creatinine gradually increases 4 to 6 weeks after exposure to the drug.
   C. Patients typically present with non-oliguria, maintaining urine volumes greater than 500 mL/day.
   D. Toxicity of various aminoglycosides is related to anionic charge of the drug.
5. Which of the following drugs has been associated with chronic interstitial nephritis?
   A. Penicillin
   B. Radiographic contrast media
   C. Lithium
   D. Acyclovir
6. Which of the following drugs has been associated with nephrocalcinosis leading to obstructive nephropathy?
   A. Propylthiouracil
   B. Aminoglycosides
   C. Radiographic contrast media

D. Oral sodium phosphate solution

7. Which of the following is the preferred agent for prevention of cisplatin-induced nephrotoxicity?

   A. Fenoldopam

   B. Amifostine

   C. Dopamine

   D. Acetylcysteine

8. Which of the following segments of the nephron is associated with nephrotoxicity from pamidronate therapy?

   A. Glomerulus

   B. Proximal tubule

   C. Distal tubule

   D. Collecting duct

9. Which of the following strategies is used to prevent radiographic contrast media nephrotoxicity?

   A. Amifostine

   B. Avoid concurrent use of other nephrotoxins

   C. Use of high osmolality agents

   D. Diuretic therapy

10. Which of the following drugs is associated with cholesterol embolization of the kidney?

    A. Hydralazine

    B. Allopurinol

    C. Warfarin

    D. Propylthiouracil

11. Which of the following drugs would be the most likely culprit in a patient with newly diagnosed renal intratubular obstruction?

    A. Ibuprofen

    B. Losartan

    C. Amphotericin B

    D. Acyclovir

12. Which of the following is the preferred treatment for a patient with NSAID-induced minimal change glomerular injury accompanied by interstitial nephritis and proteinuria?

    A. Amifostine

    B. Pamidronate

C. Prednisone

D. Hydration

13. A 60-year old woman with a five-year history of NSAID use is prescribed enalapril and develops acute kidney injury. What is the most likely cause of her acute kidney injury?

A. Hemodynamically mediated kidney injury

B. Chronic interstitial nephritis

C. Focal segmental glomerulosclerosis

D. Acute allergic interstitial nephritis

14. Which of the following are signs and symptoms of methicillin-induced allergic interstitial nephritis?

A. Urinary crystals, fever, rash

B. Fever, eosinophilia, reduced intraglomerular pressure

C. Fever, rash, eosinophilia, oliguria

D. Rash, eosinophilia, pyuria, urinary crystals

15. Which of the following drugs is associated with chronic interstitial nephritis?

A. Cyclosporine

B. Ciprofloxacin

C. Cisplatin

D. Captopril

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** The most common presentation of DIKD in the hospital setting is acute tubular necrosis, characterized by an abrupt reduction in GFR. A temporal relationship between DIKD and administration of the potentially toxic agent is typically observed, and the offending agent is usually identified.

2. **A.** Angiotensin converting enzyme inhibitor therapy leads to a reduction in synthesis of angiotensin II, thereby preferentially dilating the efferent arteriole. This decreases outflow resistance from the glomerulus and decreases glomerular capillary hydrostatic pressure, which decreases intraglomerular pressure, glomerular ultrafiltration and GFR. Patients with renal artery stenosis are at increased risk.

3. **D.** The most common manifestation of drug-induced kidney disease, regardless of etiology, is a decline in the glomerular filtration rate. See the "Clinical Presentation" for more information.

4. **C.** Clinical evidence of aminoglycoside-induced nephrotoxicity is typically seen within five to seven days after initiation of therapy and manifests as a gradual progressive rise in Scr and BUN and decrease in creatinine clearance. Patients usually present with non-oliguria. Risk factors include increased age. The number of cationic groups on the drug molecule correlates with the degree of nephrotoxicity.

5. **C.** Lithium is associated with chronic interstitial nephritis. Penicillin is associated with acute allergic interstitial nephritis. Contrast media causes acute tubular injury, while acyclovir therapy is associated with obstructive nephropathy.

6. **D.** Oral sodium phosphate solution is associated with nephrocalcinosis. Aminoglycosides and contrast media cause acute tubular injury, and

propylthiouracil may cause renal vasculitis.

7. **B.** Amifostine chelates cisplatin in normal cells and reduces nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression. It serves as a thiol donor, thereby reducing intracellular reactive oxygen species and corresponding oxidative stress that plays a critical role in the development of cellular injury. See the "Cisplatin Nephrotoxicity" section for more information.

8. **A.** Pamidronate therapy is associated with two types of glomerular disease, minimal change disease and focal segmental glomerulosclerosis. See the "Glomerular Disease" section for more information.

9. **B.** It is critically important to avoid concurrent use of potentially nephrotoxic drugs (eg, NSAIDs, aminoglycosides) during administration and use of contrast media. Other strategies include use of low- or iso-osmolar contrast agents and hydration with isotonic sodium chloride.

10. **C.** Anticoagulants (particularly warfarin) and thrombolytics are associated with cholesterol embolization of the kidney. These drugs act to remove or prevent thrombus formation over ulcerative plaques or may induce hemorrhage within clots, thereby causing showers of cholesterol crystals that lodge in small-diameter arteries of the kidney.

11. **D.** Acyclovir is relatively insoluble at physiologic urine pH and is associated with intratubular precipitation and obstruction, particularly in dehydrated oliguric patients.

12. **C.** Proteinuria usually resolves rapidly after discontinuation of the offending drug and a course of corticosteroids (eg, prednisone), which is the preferred treatment. Amifostine is used to reduce the toxicities associated with cisplatin and carboplatin therapy, while hydration is commonly used for prevention of acute tubular necrosis associated with agents such as aminoglycosides, contrast media, and cisplatin.

13. **A.** When ACE inhibitor therapy (eg, enalapril) is initiated, the synthesis of angiotensin II is decreased, thereby preferentially dilating the efferent arteriole. This reduces outflow resistance from the glomerulus and decreases intraglomerular pressure and GFR. This in turn often leads to hemodynamically mediated kidney injury, particularly in the setting of reduced renal blood flow or concurrent NSAID use. See the "Hemodynamically Mediated Kidney Injury" section for more information.

14. **C.** Clinical signs present approximately 14 days after initiation of the offending drug and commonly include (with their approximate incidence) fever (27%-80%), maculopapular rash (15%-25%), eosinophilia (23%-80%), arthralgia (45%), and oliguria (50%).

15. **A.** Cyclosporine use is associated with development of chronic interstitial nephritis. Ciprofloxacin, cisplatin, and captopril are associated with acute allergic interstitial nephritis, acute tubular injury, and hemodynamically mediated kidney injury.