Acute Kidney Injury

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LEARNING OBJECTIVES

1. Evaluate a patient using diagnostic and physiologic classifications and risk factors for acute kidney injury (AKI).
2. Assess a patient for the presence of drug-related risk factors for AKI.
3. Design a plan to prevent or manage AKI in a patient.
4. Justify the pharmacist's role in preventing and managing AKI.

ABBREVIATIONS IN THIS CHAPTER

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
ESRD	End-stage renal disease
MI	Myocardial infarction
PPI	Proton pump inhibitor
RAS	Renin-angiotensin system
SGLT-2	Sodium-dependent glucose transporter-2

Table of common abbreviations.

INTRODUCTION

Epidemiologic studies documenting the incidence and prevalence of acute kidney injury (AKI) in the community setting are sparse. This is largely because of the lack of a common AKI definition, making generalization and evaluation of outcome measures difficult. Our current understanding of the epidemiology of AKI and its morbidity, mortality, and association with chronic kidney disease (CKD) is almost exclusively based on studies that evaluated patients who developed AKI while hospitalized. In these settings, AKI has been reported to be responsible for hospital mortality rates of 8%–26% (Hoste 2006). A more recent retrospective analysis of a large database from a single U.S. Veterans Affairs hospital showed that community-acquired AKI was more common than hospital-acquired AKI, accounting for about 80% of the patients with a discharge diagnosis of AKI (Schissler 2013).

Definition

Understanding the epidemiology of AKI has been limited by the absence of a broadly accepted definition of AKI. Recently, the importance of considering AKI more broadly as a clinical syndrome has been emphasized. This syndrome encompasses several etiologies of renal disease as well as extra-renal pathology involving functional changes and cellular damage. Unlike CKD, which has a well-established model for diagnosis, AKI definition and staging relies on laboratory values such as SCr, urinary output and imaging such as renal ultrasonography. Although more sensitive and specific biomarkers are needed, changes in SCr and/or urinary output form the basis of all current diagnostic criteria for AKI.

Diagnostic Classification

The standard options for calculating the CrCl with either the Cockcroft-Gault equation or the 4-variable Modification of Diet in Renal Disease (MDRD) equation are inappropriate for this syndrome

because these equations assume a stable SCr. Increasingly, the CKD Epidemiology Collaboration (CKD-EPI) equation is being reported by laboratories. The CKD-EPI equation is more accurate than the MDRD study equation for estimating the glomerular filtration rate (GFR) at higher GFR levels and allows for estimated GFR (eGFR) reporting throughout the GFR range (Stevens 2010). An evaluation of baseline SCr, which is not always known in the community setting, is needed to further estimate changes in kidney function. No standard approach to determining baseline kidney function exists, and ultimately, clinical judgment is necessary. Also of importance, SCr lags behind GFR and may therefore not provide an exact real-time assessment of kidney function, which helps explain the often-late diagnosis of AKI. As GFR decreases, the creatinine half-life increases from 4 hours to 24–72 hours, resulting in an SCr increase at least 24–36 hours after the initial insult (Ostermann 2016).

Consensus criteria that provide a method of diagnosing and describing AKI severity include the Acute Kidney Injury Network (AKIN) diagnostic criteria and the risk, injury, failure, loss, and end-stage renal disease (ESRD) (RIFLE) classification (Table 1).

According to the Kidney Disease: Improving Global Outcomes guidelines, AKI is an increase in SCr by 0.3 mg/dL or more within 48 hours; or an increase in SCr to 1.5 times baseline or more, which is known or presumed to have occurred within the prior 7 days; or urinary output less than 0.5 mL/kg/hour for 6 hours.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of renal anatomy and renal pathophysiology
- Concepts behind and interpretation of common measures of renal function: CrCl, eGFR, anuria, oliguria, non-oliguria, urinalysis findings
- Drug knowledge of pharmacologic agents commonly implicated in acute kidney injury
- General knowledge of disease states commonly encountered in the ambulatory care setting

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
- Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US Commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649-72.
- Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 workgroup. Nat Rev Nephrol 2017;13:241-57.

Physiologic Classification

The causes of AKI can be divided into three categories: prerenal, intrinsic, and postrenal AKI (Box 1). The most common classification in community-acquired cases is prerenal, which is caused by decreased renal perfusion that is typically volume related. Intrinsic AKI is characterized according to the structural component of the kidney that is affected by the histologic injury. Acute interstitial nephritis (AIN), a form of intrinsic AKI, results from lymphocytic infiltration of the interstitium. The classic triad of fever, rash, and eosinophilia is often present in a diagnosis of AIN and may help distinguish AIN from acute tubular necrosis, which is the most common cause of intrinsic AKI. Postrenal AKI results from obstruction of the urinary collecting system.

Pseudo AKI

Pseudo AKI is characterized by an acute increase in SCr independent of change in GFR. The most common mechanism for this phenomenon involves medications that decrease the tubular secretion of creatinine by inhibiting certain drug transporters required for its elimination. Notable examples of medications that decrease creatinine secretion include cimetidine, trimethoprim, dronedarone, and cobicistat (Duncker 2013; German 2012). Historically, certain medications such as cephalosporins and substances like bilirubin have been shown to interfere with creatinine assays, resulting in false elevations in SCr. However, this is less of a concern today because most clinical laboratories use assays traceable to these substances, which minimizes the impact of cross-sensitivity. Conversely, clinicians should pay attention to conditions in which SCr is falsely lowered, in which case a normal value may not rule out AKI.

Diagnostic workup should include urinalysis with microscopy, serial monitoring of blood and urinary indices (Table 2), and imaging such as renal ultrasonography. In patients with oliguria, the fractional excretion of sodium helps distinguish prerenal from intrinsic causes of AKI. Concomitant use of diuretics may decrease the usefulness of urine sodium measurements, thus masking a prerenal diagnosis. As a result, it is more appropriate to use the fractional excretion of urea (FEUrea) as a diagnostic measure in this setting. Low FEUrea can occur in the classic volume-depleted state, as well as in the volume-overloaded state that has decreased effective arterial blood volume such as congestive heart failure, cirrhosis, and sepsis.

Table 1. Comparison of RIFLE and AKIN Criteria for Diagnosing and Classifying AKI

RIFLE Classification		Urinary Output (common to both)	AKIN Criteria	
Classification	**SCr or GFR Criteria**	**Urinary Output**	**Stage**	**SCr Criteria**
Risk	Increase in SCr to 1.5 times baseline or GFR decrease > 25%	< 0.5 mL/kg/hr for > 6 hr	1	SCr increase 1.5–2 times baseline OR ≥ 0.3 mg/dL increase above baseline
Injury	Increase in SCr to 2 times baseline or GFR decrease > 50%	Less than 0.5 mL/kg/hr for > 12 hr	2	SCr increase ≥ 2.0–3 times baseline
Failure	Increase in SCr to 3 times baseline, or SCr > 4 mg/dL with an acute rise > 0.5 mg/dL or GFR decrease > 75%	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr	3	SCr increase > 3 times baseline OR Increase in SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL OR Initiation of renal replacement therapy
Loss	Need for renal replacement therapy for > 4 wk			
ESRD	Need for renal replacement therapy for > 3 mo			
Diagnostic and Staging Time Interval for Each Criterion				
Within 7 days			Within 48 hr	

AKI = acute kidney injury; ESRD = end-stage renal disease.

Information from: Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006;34:1913-7; Mehta RL, Kellum JA, Shah SV et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

Box 1. Common Causes Associated with AKI

Prerenal AKI (hemodynamically mediated AKI)

Decreased effective blood volume
- Cirrhosis
- Congestive heart failure

Intrarenal vasoconstriction
- Cardiorenal syndrome
- Drug induced: NSAIDs, ACEIs, ARBs, CNIs
- Hepatorenal syndrome

True hypovolemia
- GI loss (diarrhea, vomiting)
- Hemorrhage
- Renal loss (diuretic overuse)

Intrinsic AKI

Acute glomerulonephritis
- Poststreptococcal glomerulonephritis
- Thrombotic thrombocytopenic glomerulonephritis

Acute interstitial nephritis (AIN)
- Drug induced: Penicillins, cephalosporins, sulfonamides, proton pump inhibitors, NSAIDs
- Malignancy
- Systemic disease: Sarcoidosis, lupus

Acute tubular necrosis
- Cardiopulmonary arrest
- Drug induced: Aminoglycosides, cisplatin, amphotericin, methotrexate
- Hypovolemic shock
- Prolonged hypotension
- Radiocontrast media
- Sepsis

Acute vascular syndromes
- Renal artery thromboembolism
- Renal vein thrombosis

Postrenal AKI
- Malignancy
- Nephrolithiasis
- Urethral stricture

ACEI = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; CNI = calcineurin inhibitor.

Information from: Khalil P, Murty P, Palevsky P. The patient with acute kidney injury. Prim Care Clin Office Pract 2008;35:239-64; Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. Am Fam Physician 2012;86:631-9.

Table 2. Blood and Urinary Indices for Differential Diagnosis in AKI

	Prerenal AKI	Intrinsic AKI	Postrenal AKI
BUN/SCr ratio	> 20:1	10–15:1	10–15:1
FENa (%)	< 1	> 2	Variable
FEUrea (%)	< 35	< 60	
Urine osmolality (mOsm/kg)	> 500	< 350	
Urine sodium, mmol/L	< 20	> 40	> 40
Urine sediment	SG > 1.018, normal or hyaline casts	SG < 1.012, granular casts, cellular debris	Cellular debris
Urinary RBC	Negative	2–4+	1+
Urinary WBC	Negative	2–4+	Variable

FENa = fractional excretion of sodium = (urine sodium × SCr)/ (serum sodium × UCr) × 100; FEUrea = fractional excretion of urea = (UUN × SCr)/ (BUN × UCr) × 100; SG = specific gravity; UCr = urine creatinine; UUN = urine urea nitrogen.

RISK FACTORS ASSOCIATED WITH AKI

Patient-Related Risk Factors

Large epidemiologic studies have identified several risk factors associated with developing AKI. These predisposing factors include age older than 75, diabetes, heart failure, liver failure, and chronic kidney disease (Chawla 2014; Ishani 2011). The 2017 U.S. Renal Data System (USRDS) annual report underscored age as a major risk factor for developing AKI. The analysis showed that in those older than 60, the incidence of AKI was 46.6%–82%.

Comorbid conditions are important risk factors associated with AKI. A longitudinal follow-up of a large sample of patients with diabetes with an eGFR greater than 30 mL/minute/1.73 m^2 in a Veterans Affairs health care system over 10 years showed that each AKI episode was associated with doubling the risk of progression to stage 4 CKD (Thakar 2011). Other variables such as race and sex seemed to be less well established as independent risk factors associated with developing AKI (Leblanc 2005).

In addition, the relationship between AKI and CKD seems to be bidirectional because AKI is a major risk factor for developing CKD. Data analyses involving hospitalized Medicare beneficiaries have shown that AKI was associated with a 13 times higher risk of ESRD than in patients without AKI (Ishani 2009). This link between AKI and CKD needs to be more aggressively embraced in the community setting to correct its trend and decrease the high economic, societal, and personal burden associated with AKI.

Drug-Related Risk Factors

Medications account for about 20% of community- and hospital-acquired episodes of AKI, and the incidence in older adults has been reported to be as high as 66% (Naughton 2008). The kidneys are at elevated risk of drug toxicity because they receive a large amount of circulated blood (25% of the cardiac output) and are involved in drug metabolism and elimination.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are among the most common prescription and OTC medications used in the United States. Although patients may reach for NSAIDs because they are effective and seemingly benign, their use comes with risks. Some data suggest that NSAID use increases the odds of AKI in the general public by about 50% and increases the risk in older adults by 2- to 3-fold (Zhang 2017).

The mechanisms by which NSAIDs induce AKI are varied. The most common mechanism of injury is by alteration of renal hemodynamics, but this drug class can also cause acute or chronic interstitial nephritis as well as glomerulonephritis. A recent pooled meta-analysis showed that the odds of the general population, those with CKD, and older adults developing AKI from NSAIDs were increased by 1.73-, 1.63-, and 2.01-fold, respectively (Zhang 2017). The degree of cyclooxygenase-2 (COX-2) selectivity of NSAIDs did not affect the odds of developing AKI (Zhang 2017).

Prevention of NSAID-induced AKI should be multifaceted. An accurate medication history including OTC NSAID use should be obtained because patients may underreport use of these medications. The clinician should account for several sources of NSAIDs, including OTC, prescription, and combination products (e.g., cough/cold, sleep aids) and educate patients on the presence of NSAIDs in products and their kidney-related risks. Those using NSAIDs should be instructed to use them at the lowest dose and for the shortest duration possible. Alternative therapies such as acetaminophen, topical analgesic agents, adjuvant therapy, and nonpharmacologic

therapy can be considered for certain indications (e.g., headache, muscle ache, arthritis pain) and patient populations (e.g., those at increased risk of prerenal AKI, those at risk of cardiovascular- or GI-related adverse effects of NSAIDs, those without contraindications to alternative therapies). Outright avoidance of NSAIDs may be warranted in patients at high risk of developing prerenal AKI such as those with hepatic failure, heart failure, or preexisting renal impairment; those using agents affecting renal hemodynamics (e.g., diuretics, ACEIs, ARBs); and those at risk of volume depletion (e.g., older adults, acute illness, diarrhea, vomiting).

Patients with NSAID-induced AKI and intravascular volume depletion should receive volume repletion as clinically warranted (e.g., weigh the appropriateness of fluid resuscitation in heart failure). Prerenal AKI usually resolves promptly after discontinuing the NSAID.

A less common etiology of NSAID-induced AKI is AIN, an idiosyncratic immune-mediated hypersensitivity response. With NSAIDs, this reaction occurs an average of 6 months after initiation (Perazella 2010). Because the reaction is idiosyncratic and not dose-dependent, there are no preventive measures, and management initially consists of discontinuing the NSAID.

RAS Inhibitors

Prescription claims data show that ACEIs and ARBs are among the most commonly prescribed drug classes in the United States; in 2017, there were 106 million prescriptions for lisinopril alone (Aitken 2018).

Similar to NSAIDs, renin-angiotensin system (RAS) inhibition can induce AKI by altering renal hemodynamics and reducing glomerular capillary pressure. Because of this pharmacologic mechanism of action, an increase in SCr and a decrease in GFR are common within 3–5 days of initiating an ACEI or ARB. Typically, this RAS inhibition by ACEIs and ARBs is well tolerated in low-risk patients, but some recommend that ACEIs or ARBs be discontinued if the SCr increases by 30% or more above baseline after initiation or dose increase (Bakris 2000). However, one study argues that the 30% cutoff is based on weak evidence and suggests that continuing ACEIs or ARBs after more modest rises in SCr also carries risks (Schmidt 2017a). This cohort study of over 100,000 primary care patients showed statistically significant – and graduated – increases in ESRD, myocardial infarction (MI), heart failure, and all-cause mortality at all concentrations of increased SCr above 10% on initiation of an ACEI or ARB. For example, compared with the reference group with less than a 10% increase in SCr, the incidence rate ratio of ESRD was 1.73 for the 10%–19% increase group, 2.58 for the 20%–29% increase group, 3.80 for the 30%–39% increase group, and 4.04 for the 40% and greater increase group.

Prevention of RAS inhibitor–induced AKI can be undertaken through screening for susceptible patients, minimizing use of concomitant nephrotoxic agents, and monitoring all patients after initiation or dose increase. Concomitant use of agents affecting renal hemodynamics also places patients at risk (e.g., concomitant use of loop diuretics was associated with a 4-fold increase in the risk of SCr elevation of 30% above baseline) (Schmidt 2017a). Proper monitoring of renal function and action in response to change in renal function are often overlooked. In one retrospective study of over 200,000 patients, less than 50% of patients had baseline and follow-up monitoring of SCr, and 10% of patients had no monitoring at all (Schmidt 2017b). In addition, in those who had an SCr elevation of over 30% of baseline, only 20% had the ACEI or ARB discontinued (Schmidt 2017b). It is important to monitor the SCr before initiating RAS-blocking agents as well as within 1 week of initiation or dose increase. If RAS-blocking agents are deemed necessary in high-risk patients, initiation of a low dose of a short-acting agent with subsequent titration should be considered. An ACEI- or ARB-induced AKI is usually managed by discontinuing the offending agent; resolution of AKI occurs within several days, but its long-term impact requires additional study.

Loop Diuretics

Loop diuretics can induce AKI through prerenal or intrinsic causes. Two small studies found that patients with heart failure using loop diuretics had a greater risk of AKI if they were using higher doses of diuretics, had diabetes, were older, had negative fluid balance, had lower baseline kidney function, or had hyponatremia (Ricci 2013; Sun 2006). Although no guidelines exist, special care should be given to balance the need to maintain euvolemia with the risk of AKI in the ambulatory setting, especially in at-risk populations. Rarely, sulfonamide loop diuretics can cause AIN. Preventive measures are not possible because of the idiosyncratic nature of this reaction. However, AKI resolution typically occurs rapidly (days) on removal of the offending agent (Krishnan 2015).

Combination of NSAIDs, ACEIs/ARBs, and Diuretics – The "Triple Whammy"

Although AKI can be potentiated by NSAIDs, ACEIs/ARBs, and diuretics on their own, a special discussion of the risks of combined use is warranted. Each medication affects kidney function differently – diuretics can lead to decreased renal perfusion through hypovolemia, NSAIDs do so by constriction of afferent arterioles, and ACEIs/ARBs do so by dilation of efferent arterioles. Controlling the tone of the renal afferent and efferent arterioles is necessary to maintain perfusion pressure, especially during reduced renal blood flow. Several studies have identified an increased risk of AKI with the use of this combination of drugs. One retrospective cohort study of almost 500,000 subjects followed for almost 6 years identified a 31% higher rate of AKI with triple therapy than with treatment with only one agent (Lapi 2013). The subgroup analysis showed that the AKI risk doubled within the first 30 days of triple therapy. A smaller prospective cross-sectional study also found an increased risk of AKI in females taking

a two- or three-drug combination and males taking a three-drug combination compared with no NSAID, diuretic, or ACEI/ARB (Loboz 2005).

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs), namely cyclosporine and tacrolimus, have revolutionized the practice of transplant pharmacy and are essential components in many posttransplant maintenance immunosuppressive protocols. According to the latest Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients report, around 96% of adult kidney transplant recipients were discharged after transplantation on a CNI-based regimen (Hart 2017). One of the most common dose-limiting toxicities associated with cyclosporine and tacrolimus is nephrotoxicity. Acute CNI toxicity is described as renal dysfunction mediated by hemodynamic changes that is reversible and typically classified as prerenal AKI. The reversible functional impairment associated with CNI use is caused by vasoconstriction of the afferent arterioles, resulting in reduced renal blood flow (Naesens 2009). Long-term CNI use can also contribute to an irreversible and progressive tubulointerstitial injury and glomerulosclerosis labeled as chronic CNI nephrotoxicity (Naesens 2009).

Risk factors for CNI nephrotoxicity include systemic overexposure to cyclosporine or tacrolimus, concomitant NSAID use, and diuretic use (Naesens 2009). Strategies for preventing CNI nephrotoxicity should be aimed at lowering total drug exposure by therapeutic drug monitoring. Alternatively, dihydropyridine calcium channel blockers play a protective role in minimizing CNI nephrotoxicity because of their intrarenal vasodilatory effects offsetting the vasoconstrictive effects of the CNIs at the afferent arteriole (Naesens 2009; de Mattos 2000). In the renal transplant population when hypertension is a chronic issue, use of calcium channel blockers may offer a benefit, but care should be taken to assess for any drug-drug interactions with the CNI used in this population.

Oral Antimicrobials

β-Lactams

Penicillins and cephalosporins are among the most common antimicrobials implicated in AIN. In a case series of 133 patients with biopsy-proven AIN, penicillins caused 20% of drug-related AIN, whereas cephalosporins were implicated in 5% (Muriithi 2014). Acute interstitial nephritis caused by β-lactams often presents with the "classic" triad of symptoms – eosinophilia, rash, and fever (Pannu 2008). As discussed previously, because AIN is idiosyncratic, there are no preventive measures. A trial of glucocorticoids may be warranted.

Quinolones

Ciprofloxacin is the most commonly implicated fluoroquinolone in AIN as well as crystal nephropathy (Khan 2015). In one case series of 133 patients with biopsy-proven AIN, fluoroquinolones were implicated in 14% of drug-related causes (Muriithi 2014). In crystal nephropathy, fluoroquinolone crystals precipitate in alkaline urine, leading to obstructed urine flow and an interstitial reaction. Preventive measures include ensuring adequate hydration and using appropriate doses on the basis of renal function.

Sulfonamide Antibiotics

Mechanisms by which trimethoprim/sulfamethoxazole (co-trimoxazole) causes AKI include AIN, acute tubular necrosis, and crystal nephropathy. Like with NSAIDs, AIN with co-trimoxazole is caused by an idiosyncratic cell-mediated immune reaction. As with other drug-induced AIN, there is no dose relationship. Unlike with NSAIDs, AIN secondary to co-trimoxazole typically occurs more rapidly, within 7–10 days, of exposure and is managed by discontinuing the agent (Perazella 2010).

Tenofovir

Tenofovir is a nucleoside reverse transcriptase inhibitor most commonly used in combination with other antiretrovirals for the treatment of HIV. Tenofovir disoproxil fumarate was approved in 2001 and is co-formulated with several other antiretrovirals. Long-term renal and bone damage are well-known adverse effects of this tenofovir formulation, but the medication is also implicated in AKI through acute tubular necrosis, proximal tubulopathy, and Fanconi syndrome (Pazhayattil 2014; Pannu 2008). It is estimated that 20% of patients treated with tenofovir disoproxil fumarate have tubular dysfunction (Fernandez-Fernandez 2011). Although tenofovir disoproxil fumarate is metabolized to tenofovir and then to the active metabolite tenofovir-diphosphate, high circulating concentrations of tenofovir are responsible for its adverse effects (Sax 2015). Typically, tubular damage presents after 20 or more weeks of therapy (Izzedine 2005). Preventive measures such as renally dose-adjusting tenofovir disoproxil fumarate can be used. Once kidney injury occurs, it takes an average of 5 weeks after discontinuation for kidney function to return (Izzedine 2005). Another prevention and management strategy is to use the newer and less toxic formulation of tenofovir, tenofovir alafenamide. Tenofovir alafenamide was approved in 2015 and is currently part of four different co-formulations; it is not available on its own. As a novel prodrug of tenofovir, tenofovir alafenamide requires a much lower dose than tenofovir disoproxil fumarate to achieve higher concentrations of active metabolite; this mechanism is hypothesized to contribute to reduced renal adverse events because of the reduced exposure to nephrotoxic tenofovir (Sax 2015). Many studies have shown a reduction in adverse renal events, and national guidelines recommend substituting tenofovir disoproxil fumarate with tenofovir alafenamide to mitigate the risk of renal dysfunction and improve proteinuria and renal biomarkers (Wang 2016; Sax 2015, 2014).

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medication classes in the United States. Several PPIs are also available OTC. Documented PPI use occurred in 9.2% of all ambulatory visits in 2009 (Rotman 2013). A recent meta-analysis including over 2 million patients showed that PPI use was associated with a 61% increased risk of AKI (Yang 2017). On average, AIN took 11 weeks from PPI initiation to develop and did not present with the "classic" AIN symptoms of eosinophilia, rash, and fever. This adverse effect appears to be a class effect because all PPIs have been implicated in AIN (Brewster 2007). Beyond AKI, long-term PPI use has been associated with CKD, increased bone fractures, increased infections such as *Clostridium difficile* and community-acquired pneumonia, and electrolyte abnormalities such as hypomagnesemia. Because of emerging data on adverse effects, several initiatives to deprescribe PPIs are ongoing (Farrell 2017). One way to prevent PPI-associated AKI is to deprescribe PPIs in patients who no longer have an indication for a PPI or change to alternative acid-suppressive therapy (e.g., histamine-2 receptor antagonists).

Sodium-Dependent Glucose Transporter-2 Inhibitors

Sodium-dependent glucose transporter-2 (SGLT-2) inhibitors are a relatively new class of antidiabetic agents. These agents inhibit the SGLT-2 receptor in the proximal tubule to block glucose reabsorption, thereby lowering blood glucose concentrations. Although some members of the class slow the progression of kidney disease in patients with diabetes, over 100 AKI cases have been reported to the FDA involving canagliflozin and dapagliflozin (Wanner 2016). The mechanism by which SGLT-2 inhibitors cause AKI is uncertain, but some theorize that it is because of dehydration from osmotic diuresis and/or tubular injury from increased uric acid production (Hahn 2016). Postmarketing reports of AKI prompted the FDA to revise and intensify the warning of AKI for these medications. Before initiating an SGLT-2 inhibitor, risk factors for AKI such as dehydration, heart failure, CKD, and use of concomitant nephrotoxic agents should be considered and addressed, if possible. Most reported AKI cases occurred within 1 month of initiation and resolved on discontinuation, according to FDA reports. The FDA also recommends preemptive discontinuation of SGLT-2 inhibitors in the presence of reduced fluid intake or increased fluid losses.

Radiographic Contrast Media

Contrast-induced nephropathy (CIN) is a common iatrogenic complication associated with radiographic contrast media. Contrast-induced nephropathy is defined as an increase in SCr by greater than 25% or 0.5 mg/dL occurring within 3 days after intravascular administration of radiographic contrast media in the absence of an alternative etiology (Kitajima 2011). Typically, CIN is associated with an increase in SCr concentrations within 24–48 hours, often peaking at 3–5 days. If renal function returns to normal, it usually does so within 7–10 days (Kitajima 2011). For patients undergoing contrast-enhanced imaging procedures, patient-specific risk factors for developing AKI should be evaluated. In the ambulatory care setting, this can be performed by patient questionnaires. Historically, these questionnaires capture age, history of renal disease, prior kidney surgery, hypertension, diabetes, history of congestive heart failure, history of contrast media exposure, medication use (specifically metformin), and concomitant nephrotoxic medications. The incidence of CIN in such patients has been reported as 12%–50% (Brueck 2013).

The only intervention that has consistently decreased the risk of contrast-induced AKI is periprocedural intravenous isotonic crystalloids (Pavlesky 2013). Since the first randomized trial testing acetylcysteine for the prevention of CIN almost 2 decades ago, several subsequent trials have reached inconsistent results. Many of these studies have been limited by low statistical power and lack of blinding. Systematic reviews have yielded high heterogeneity across studies, precluding definitive conclusions regarding the efficacy of acetylcysteine. To this end, a large multicenter, randomized clinical trial called the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) with over 2300 patients evaluated the incidence of CIN 48–96 hours after angiography in patients receiving 1200 mg of acetylcysteine every 12 hours (two doses before and two doses after the procedure) compared with placebo (ACT Investigators 2011). Subjects with at least one risk factor for CIN such as age older than 70, SCr greater than 1.5 mg/dL, diabetes mellitus, congestive heart failure, left ventricular ejection fraction less than 45%, or hypotension were included, representing higher-risk subgroups than in previous studies. The incidence of CIN was identical in the acetylcysteine and placebo groups, 12.7% (p=0.97). Acetylcysteine had no statistically significant benefit in any subgroup, including those with a baseline SCr greater than 1.5 mg/dL, which consisted of around 16% of the study population (ACT Investigators 2011).

Ascorbic acid's ability to offer nephroprotection because of its antioxidant properties has been studied in randomized clinical trials with conflicting results. One single-center, randomized trial suggested ascorbic acid's benefit in preventing CIN (Spargias 2004). However, a second, large, two-center, randomized, double-blind study comparing intravenous saline plus acetylcysteine administration or intravenous sodium bicarbonate plus acetylcysteine or intravenous saline plus intravenous ascorbic acid plus acetylcysteine found that ascorbic acid provided no added benefit in reducing CIN (Briguori 2007).

Metformin should be held before contrast media administration and up to 48 hours post-administration. No strong data support discontinuing ACEIs, ARBs, or diuretics in this setting (Pavlesky 2013).

Patient Care Scenario

A 75-year-old man is brought to the urgent care clinic by his daughter with nausea, vomiting, and diarrhea occurring over the past 3 days. He has been unable to keep any food down, only liquids. The patient reports a decrease in urinary output and darker urine. Associated symptoms over the past few days include increased pain caused by osteoarthritis, for which he has been taking naproxen 200 mg by mouth three times daily. Home medications include enalapril 5 mg by mouth daily, atorvastatin 10 mg by mouth daily, pantoprazole 40 mg by mouth daily, docusate 100 mg by mouth twice daily, insulin glargine 20 units subcutaneously at bedtime, insulin lispro 5 units subcutaneously three times daily with meals, and aspirin 81 mg by mouth daily. On examination, the patient appears frail with dry mucous membranes. Blood pressure is 105/60 mm Hg with heart rate of 80 beats/minute when sitting and 80/55 mm Hg with heart rate of 100 beats/minute on standing. Laboratory tests consist of Na 137 mEq/L, K 4.1 mEq/L, Cl 101 mEq/L, HCO_3 21 mEq/L, BUN 52 mg/dL, SCr 2.3 mg/ dL, and glucose 98 mg/dL. Baseline renal function is unknown. What is the most likely etiology of this patient's AKI and what is the best recommendation for him?

ANSWER

The patient's history of decreased oral intake, vomiting, and diarrhea suggest volume depletion. The patient has also been taking an NSAID as well as an ACEI concomitantly, both of which can increase the risk of AKI, especially in a volume-depleted state. Physical findings of dry mucous membranes, orthostatic hypotension, and tachycardia further support a diagnosis of volume depletion. It is important to try to obtain this patient's historical laboratory information to determine the degree of change in kidney function and confirm the diagnosis of AKI. However, the patient reported a change in urinary output, and the change in color strongly suggests AKI. A urine sample should also be obtained to screen for urinary electrolytes and the presence/absence of urine sediments. Given the information provided, the most likely etiology for AKI in this patient would be altered renal hemodynamics secondary to volume depletion. This would likely lead to a diagnosis of prerenal AKI. Together with the patient's advanced age and diabetes, these events likely occurred because of his naproxen use in combination with enalapril while the patient was volume depleted because of a 3-day history of vomiting and diarrhea. Acute kidney injury secondary to PPI use cannot be ruled out, underscoring the need for a complete medication history. The patient may require hospital admission for intravenous fluid replacement and hydration, given that the oral route is not an option. Close monitoring of his renal function and electrolytes is necessary. The patient must avoid all NSAIDs, and enalapril should be held until blood pressure and renal function improve. Urinary output should be monitored closely.

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GENERAL PREVENTION AND MANAGEMENT

Prevention

The fundamental principle of preventing AKI is to treat the underlying cause or trigger. Primary prevention strategies involve identifying patients at high risk of AKI such as older adults, those with heart failure, and those with underlying kidney disease and avoiding exogenous renal insults, when possible. Clinicians should be cognizant of common nephrotoxins and their potential effects on kidney function to appropriately dose reduce or avoid these medications in patients at high risk of developing AKI. Clinicians should also consider correcting modifiable risk factors such as hypovolemia before initiating new therapy. Some organizations recommend discontinuing potentially harmful medications during periods of intercurrent illness, otherwise known as "sick day rules." Patients may be educated on sick day rules or provided with a "sick day rules card" instructing them to stop medications temporarily until they are eating or drinking normally for 24–48 hours. This includes medications such as NSAIDs, ACEIs, ARBs, diuretics, metformin, sulfonylureas, and co-trimoxazole during periods of vomiting, diarrhea, or fever. This practice is based on expert opinion and lacks evidence in the primary and secondary care settings (Whiting 2017; Griffith 2015). In addition, this practice can place patients at risk of harm if inappropriate self-management occurs (e.g., worsening control of hypertension, heart failure, or diabetes; inadvertent long-term discontinuation of maintenance medications). Educating at-risk patients is paramount in preventing AKI in the ambulatory care setting and is discussed in a subsequent section, Opportunities for the Pharmacist.

Management

Patients with AKI generally should be hospitalized unless the condition is mild and clearly results from an easily reversible cause. The focus on managing AKI in the ambulatory care setting is to restore renal blood flow and discontinue or adjust medications associated with nephrotoxicity.

Acute kidney injury caused by volume depletion requires volume resuscitation with isotonic crystalloids and a correction of the cause of volume loss to reverse or ameliorate AKI. Patients with congestive heart failure or cirrhosis may develop prerenal AKI because of reduced intravascular volume or

aggressive diuresis. In these situations of decreased effective arterial blood volume, the management strategy involves treating the primary organ failure.

Management of drug-induced AIN involves removing the suspected causative agent and providing supportive therapy. In most cases, AIN is self-limiting and reversible; however, recovery may take weeks to months (Pannu 2008). Use of corticosteroids in the treatment of drug-induced AIN is controversial. In a multicenter, retrospective study in Spain, researchers evaluated the influence of corticosteroids in 61 patients with biopsy-proven AIN (González 2008). Most patients (85%) who received corticosteroids (methylprednisolone 250–500 mg for 3–4 days followed by oral prednisone 1 mg/kg/day tapered over 8–12 weeks) had a significantly lower SCr at the end of follow-up (SCr 2.1 mg/dL vs. SCr 3.7 mg/dL in those who did not receive corticosteroids). Among treated patients, those who started corticosteroids within 7 days of withdrawing the offending drug were significantly more likely to recover renal function than those who received corticosteroids after this period (OR 6.6; 95% CI, 1.3–33.6) (González 2008). Conversely, a retrospective single-center analysis in the United States among 95 patients with biopsy-proven drug-induced AIN secondary to antibiotics (49%), PPIs (14%), and NSAIDs (11%) found that corticosteroid treatment (prednisone 40–60 mg daily) did not significantly affect recovery of kidney function at 6 months (Muriithi 2014). Factors correlated with poor recovery included longer drug exposure (15 vs. 30 vs. 130 days for complete, partial, and no recovery, respectively; p=0.04) and longer delay in starting steroid therapy (8 vs. 11 vs. 35 days, respectively; p=0.05). Lower baseline SCr concentration correlated with partial recovery versus no recovery (p=0.006) (Muriithi 2014).

In the ambulatory care setting, mild electrolyte abnormalities may accompany AKI. In general, attention should be paid to correcting hypo- or hyperkalemia, hypomagnesemia, and hyperphosphatemia.

Indications for renal replacement therapy include life-threatening electrolyte abnormalities – specifically, hyperkalemia, refractory metabolic acidosis, volume overload, diuretic resistance, uremia (defined as a BUN greater than 100 mg/dL), or encephalopathy. The absolute number of patients with AKI requiring dialysis more than doubled from 63,000 in 2000 to 164,000 in 2009, and about one-third of those who survived remained dialysis-dependent on hospital discharge (Gautam 2015; Hsu 2013). This creates a scenario for many patients to be treated in outpatient dialysis settings when their indication for dialysis is a diagnosis of AKI. Around 20%–60% of those who remained dialysis-dependent post-discharge were able to successfully come off dialysis (Cerda 2015). One recent Mayo Clinic analysis showed that most (73%) of these recoveries occurred within the first 3 months post-discharge (Hickson 2015). Of note, renal recovery is strongly influenced by individual patient comorbidities.

Prognosis

Community-acquired AKI has been associated with significant adverse long-term outcomes, including new-onset or progression of CKD similar to hospital-acquired AKI (Der Mesropian 2014; Wonnacott 2014). A meta-analysis of 13 cohort studies showed that compared with patients without AKI, those who recovered from AKI had almost a 10-fold higher risk of CKD, 3-fold higher risk of ESRD, and double the risk of death (Coca 2012). Another study showed a 67% increased risk of coronary events in patients who developed AKI requiring dialysis (Wu 2014). The 2017 USRDS reported that in 2013, of the Medicare patients older than 66 who were hospitalized for AKI, 28% were given an initial diagnosis of CKD in the year after that hospitalization and had a 35% cumulative probability of a recurrent AKI hospitalization. These studies and others report that most post-AKI adverse events occur in the first 3–6 months after an acute episode (Silver 2015; Bucaloiu 2012). Recent data analyses suggest that only 40% of patients with AKI requiring dialysis receive a nephrology referral within 90 days of hospital discharge (Harel 2013), and a separate study of patients who did not require dialysis post-discharge reported a follow-up rate of 11% within 30 days, with only 19% referred at 1 year (Siew 2012). These data represent an important care gap.

Evidence is lacking to guide the timing, frequency, and methods to evaluate kidney function in patients after an episode of AKI. The Acute Disease Quality Initiative workgroup recommends that the intensity of surveillance be proportionate to the risk of future outcomes. Those with comorbid conditions that increase the risk of future CKD progression may have greater benefit from earlier or more frequent surveillance than patients with a lower risk of future CKD (Siew 2016; Hickson 2015). One study prospectively evaluated over 35,000 patients with diabetes from over 100 Veteran Affairs medical centers in the United States who had their first noncardiac surgery. In this study, AKI was stratified by magnitude according to AKIN stage and duration – specifically, short duration was defined by less than 2 days, medium duration was defined by 3–6 days, and long duration was defined as 7 days or more (Coca 2010). Mortality rates in this analysis were greater for those with the lowest AKIN stage and with medium (3–6 days) or long (7 days or more) duration of AKI (21.5 and 29.3 deaths per 100 person-years, respectively) than for those with the most severe AKIN stage but short (2 days or less) duration of AKI (12.8 deaths per 100 person-years).

OPPORTUNITIES FOR THE PHARMACIST

Pharmacists can play a role in identifying patients at risk of AKI; providing early detection of AKI; optimizing medications for preventing and treating AKI; providing patient education, including providing sick day rules, maintaining hydration, and avoiding inappropriate use of OTC NSAIDs; and promoting adequate referral and follow-up. Quality improvement initiatives and other scholarly activities can help improve prevention and treatment of AKI.

Transitions of Care

In general, few patients with AKI have adequate follow-up after an episode of AKI (Siew 2012). Because of the lack of recognition of prior AKI and lack of follow-up, some authors advocate that a medical history of "episode of AKI" be documented in AKI survivors' medical records (Goldstein 2013). This could provide a method by which patients with a history of AKI are systematically identified. In addition, descriptions of AKI follow-up clinics exist; to date, no data support their impact on AKI morbidity or mortality (Silver 2015).

For patients who become dialysis-dependent after AKI, care coordination from the inpatient to the outpatient setting is critical. Before January 1, 2017, Medicare only provided payment to hospital-based dialysis units for patients with AKI requiring dialysis, which limited access and availability to these services. Adding community-based dialysis centers serves as a much-needed expansion of care. Pharmacists can play a crucial role in medication reconciliation and clinical follow-up as it relates to clinical laboratory results in these patients. Practical strategies to promote and monitor renal recovery in this unique population include avoiding hypotension during dialysis, minimizing nephrotoxins, having a regular clinical follow-up, and having regular laboratory evaluation.

Pharmacists in the ambulatory setting also play a role in medication optimization and patient education both during transitions of care and routine follow-up (Shaw 2015). Many patients with AKI may need referral for hospitalization and/or alterations in medications to prevent further insult. Those who are recovering from AKI may need referral to a nephrologist. According to the 2017 USRDS annual report, only 16% of Medicare patients surviving an AKI hospitalization had an outpatient nephrology follow-up within 6 months post-hospitalization, underscoring the lack of timely follow-up. Pharmacists can help bridge the gap regarding follow-up. Periodic assessment of renal function to assess prognosis is paramount in minimizing long-term risk and can be completed in pharmacist-run clinics. Once AKI has resolved, held medications (e.g., antihypertensives, antihyperglycemics) should be evaluated for reinitiation, when appropriate. Patients should be educated on their risks and advised on strategies they can use to minimize the risk, including sick day rules, hydration (if clinically appropriate), and general prescription and nonprescription medication education.

Initiatives and Resources

Globally, research and resources allocated to developing evidence-based, standardized approaches to preventing, diagnosing, and treating AKI are lacking. Similarly, limited efforts are in place to promote health professional and public awareness of AKI. As valuable members of the health care team, pharmacists should join the movement to reduce AKI morbidity and mortality.

The International Society of Nephrology developed the 0by25 campaign to reduce AKI mortality worldwide by promoting awareness to the public, health care professionals, and policy-makers (Mehta 2015). Five core elements have been developed to aid in these efforts: risk assessment, recognition, response, renal support, and rehabilitation.

Think Kidneys is a UK-based campaign funded through the National Health Service and the UK Renal Registry to improve care for those affected by or at risk of AKI. The website (thinkkidneys.nhs.uk) is a repository for completed and ongoing AKI research, news, and educational resources for physicians, pharmacists, nurses, community organizations, and the public. Specifically, there is guidance for pharmacists in optimizing medications during AKI and free patient education materials.

Although the National Kidney Foundation and the National Kidney Disease Education Program largely focus on CKD, other resources also target AKI. The Choosing Wisely initiative's mission is to decrease wasteful or unnecessary medical care – one initiative this initiative has championed is educating patients on the risks of NSAID use, for which a patient education handout has been created. Although a framework examines the effect of educational interventions on preventing AKI, more research is needed (Byrne 2015; Pai 2015).

CONCLUSION

Acute kidney injury is common in the community setting and is associated with high morbidity, high mortality, and increased health care costs. Early recognition and prevention are paramount to achieving good patient outcomes. Heightened screening and preventive management should occur for those at high risk, which includes adults older than 60, individuals with diabetes or preexisting CKD, and individuals with chronic medical problems such as heart failure or cirrhosis. Pharmacists in the ambulatory care setting are on the frontlines of educating patients on their risk and evaluating medications that can pose a risk of AKI.

Practice Points

- **AKI is characterized by many inciting causes that can complicate coexisting illnesses. AKI is common in the ambulatory care setting and is associated with high morbidity, high mortality, and increased health care costs.**
- **Risk factors for AKI include older age, preexisting CKD, heart failure, and liver failure.**
- **Main prevention strategies include avoiding or dose-reducing nephrotoxic agents, correcting for modifiable risk factors, and educating patients on agents that can negatively affect renal function.**
- **Management relies largely on treating the underlying cause and/or discontinuing the offending agent.**
- **Patients with a diagnosis of AKI should be evaluated within 3 months after resolution of renal injury and should have continued surveillance over 2–3 years to monitor for worsening of renal function or development of CKD.**

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

Z.K. is a 50-year-old man with a medical history of chronic kidney disease (CKD), diabetes, hypertension, and heart failure. Last week, he was discharged from the hospital after management and treatment of a myocardial infarction (MI). Z.K.'s BUN and SCr values on discharge were 26 mg/dL and 1.8 mg/dL, respectively (baseline). Today, his BUN is 32 mg/dL, SCr is 2.4 g/dL, serum sodium is 134 mEq/L, urine osmolality is 290 mOsm/kg, urine sodium is 40 mEq/L, and urine creatinine is 14.3 mg/dL, and there are granular casts in the urine. Renal ultrasonography is negative.

1. According to the AKIN classification scheme, which one of the following best assesses Z.K.'s stage of acute kidney injury (AKI)?

   A. 1
   B. 2
   C. 3
   D. 4

2. Given the patient's laboratory values, which one of the following best estimates Z.K.'s fractional excretion of sodium (FENa)?

   A. 0.8%
   B. 1.3%
   C. 2.3%
   D. 5.0%

3. Given his laboratory findings, which one of the following most likely caused Z.K.'s AKI?

   A. Postrenal AKI
   B. Prerenal AKI
   C. Acute interstitial nephritis (AIN).
   D. Acute tubular necrosis

4. Which one of the following patients has the highest risk of developing AKI from an acute illness resulting in volume depletion?

   A. 83-year-old man with diabetes prescribed losartan 50 mg by mouth once daily
   B. 77-year-old woman with diabetes and congestive heart failure prescribed losartan 50 mg by mouth once daily
   C. 65-year-old woman with diabetes and CKD prescribed losartan 50 mg by mouth once daily and furosemide 40 mg by mouth twice daily
   D. 56-year-old man with diabetes and congestive heart failure prescribed losartan 50 mg by mouth once daily and furosemide 40 mg by mouth twice daily

5. A 41-year-old man presents with uncontrolled hypertension. His medical history is significant for type 2 diabetes, hyperlipidemia, and renal transplantation (1 year ago). His current drugs include tacrolimus 3 mg by mouth every 12 hours, mycophenolate 1000 mg by mouth every 12 hours, prednisone 5 mg by mouth daily, metoprolol 50 mg by mouth twice daily, clonidine 0.2 mg by mouth twice daily, atorvastatin 10 mg by mouth daily, and aspirin 81 mg by mouth daily the past 3 days. His baseline SCr is 1.4 mg/dL (stable). Vital signs today include blood pressure 158/88 mm Hg, heart rate 62 beats/minute, respiratory rate 18 breaths/minute, and temperature 98.6°F. Tacrolimus trough concentration is 9.3 ng/mL (goal 8–10 ng/mL). Which one of the following is best to recommend to manage this patient's hypertension and reduce his risk of tacrolimus-related nephrotoxicity?

   A. Initiate enalapril 2.5 mg by mouth daily.
   B. Increase metoprolol to 100 mg by mouth twice daily.
   C. Initiate diltiazem CD 180 mg by mouth daily.
   D. Initiate amlodipine 5 mg by mouth daily.

6. A 67-year-old woman with a medical history of hypertension and diabetes is seen in the ambulatory care center for a workup of hematochezia and change in bowel habits. A CT scan of her abdomen and pelvis is scheduled for next week at one of your affiliated outpatient facilities. Her home drugs include enalapril 20 mg by mouth daily, metformin 850 mg by mouth twice daily, aspirin 81 mg by mouth daily, and atorvastatin 40 mg by mouth daily. The basic metabolic panel obtained today is as follows: Na 138 mEq/L, K 4.1 mEq/L, Cl 101 mEq/L, HCO_3 24 mEq/L, BUN 14 mg/dL, SCr 1.6 mg/dL, and glucose 105 mg/dL. As part of the coordinating care team preparing this patient for her outpatient procedure, you are discussing the role of oral acetylcysteine in preventing contrast-induced nephropathy (CIN) according to the ACT clinical trial. Which one of the following best describes the application of those clinical trial results to this patient case?

   A. Acetylcysteine was associated with a lower incidence of CIN than intravenous isotonic crystalloids and may be beneficial in this patient.
   B. Acetylcysteine was studied in patients undergoing intravascular angiography; therefore, this patient may have no clinical benefit.
   C. Acetylcysteine had a statistically similar incidence of CIN in patients with worsening degrees of kidney function and may add no benefit in this patient.
   D. Acetylcysteine did not reduce the risk of CIN statistically in the study population, but the clinical benefits may outweigh the risk in this patient.

7. A 47-year-old man presents to the clinic with a 2-day history of fever and rash. His medical history includes hypertension, type 2 diabetes, gastroesophageal reflux disease (GERD), and low back pain. His home drugs include enalapril 10 mg by mouth daily (× 8 years), pantoprazole 20 mg by mouth daily (× 8 years), metformin 1000 mg by mouth twice daily (× 7 years), glyburide 5 mg daily (× 5 years), ibuprofen 600 mg by mouth every 6 hours (× 6 months), and oxycodone 5 mg by mouth every 6 hours as needed for breakthrough pain (× 3 months). The patient receives a diagnosis of AIN. Which one of the following most likely caused this patient's AIN?

   A. Pantoprazole
   B. Ibuprofen
   C. Glyburide
   D. Enalapril

8. A 58-year-old woman has a medical history of intravenous drug abuse, alcohol abuse, hepatitis C virus infection, cirrhosis, and poor oral intake. Pertinent laboratory values include eGFR 72 mL/minute/1.73 m^2 and albumin 2.9 g/dL. Her home drugs include furosemide 40 mg by mouth daily, spironolactone 100 mg by mouth daily, propranolol 20 mg by mouth twice daily, thiamine 100 mg by mouth daily, lactulose 20 g by mouth twice daily, and elbasvir 50 mg/grazoprevir 100 mg by mouth once daily. Which one of the following poses this patient's greatest risk of AKI?

   A. Age
   B. Liver failure
   C. Poor oral intake
   D. Spironolactone use

9. A 66-year-old woman presents for a routine follow-up. She has a medical history of osteoarthritis, heart failure, and chronic obstructive pulmonary disease (COPD). Her home drugs include acetaminophen 650 mg by mouth every 8 hours as needed for pain, lisinopril 20 mg by mouth daily, carvedilol 12.5 mg by mouth every 12 hours, bumetanide 1 mg by mouth twice daily, and tiotropium inhaled one 18-mcg capsule by mouth daily. A review of systems and physical examination finds the patient in moderate pain, blood pressure 122/72 mm Hg, heart rate 64 beats/minute, lungs clear to auscultation and percussion, and positive hepatojugular reflex. Which one of the following is best to recommend to prevent AKI in this patient?

   A. Discontinue acetaminophen and initiate a COX-2 inhibitor.
   B. Discontinue bumetanide.
   C. Counsel the patient to avoid NSAID use.
   D. Counsel the patient to increase fluid intake.

Questions 10 and 11 pertain to the following case.

R.D., a 54-year-old man in your internal medicine clinic, was initiated on fosinopril 20 mg by mouth daily for hypertension last week. R.D.'s SCr was 0.9 mg/dL before initiation and is 1.1 mg/dL today.

10. The resident caring for R.D. asks you about the cardiorenal risks of RAS inhibitors. Which one of the following best interprets recent data for R.D.'s medical resident?

    A. An increase in SCr by more than 30% above baseline led to a statistically significant increase in the risk of MI and CKD but not in mortality compared with the reference group.
    B. An increase in SCr by more than 20% above baseline led to a nonstatistically significant increase in the risk of MI, CKD, and mortality compared with the reference group.
    C. An increase in SCr by more than 40% above baseline led to a statistically significant increase in the risk of CKD but not in MI or mortality compared with the reference group.
    D. An increase in SCr by more than 10% above baseline led to a statistically significant increase in the risk of MI, CKD, and mortality compared with the reference group.

11. Which one of the following is best to recommend to prevent future adverse effects from R.D.'s episode of AKI?

    A. Refer him to a nephrologist.
    B. Document "history of AKI" as a problem in the electronic medical record.
    C. Document a drug allergy to fosinopril in the electronic medical record.
    D. Develop a pharmacist-led post-AKI clinic.

12. A 74-year-old woman has a medical history of diabetes (A1C 8.7%), hypertension (blood pressure 128/74 mm Hg), and hyperlipidemia. Her eGFR is 68 mL/minute/1.73 m^2. Her home drugs include metformin 1000 mg by mouth daily, sitagliptin 100 mg by mouth daily, hydrochlorothiazide 25 mg by mouth daily, and rosuvastatin 20 mg by mouth daily. Her endocrinologist wants to initiate canagliflozin 100 mg by mouth daily for further A1C lowering. Which one of the following is best to recommend to prevent AKI in this patient?

    A. Counsel her to maintain adequate hydration.
    B. Monitor SCr within 1 week of initiation.
    C. Provide a prescription for fluconazole in the event of a genital mycotic infection.
    D. Avoid initiation of canagliflozin in reduced kidney function.

13. A 79-year-old Hispanic woman presents to your internal medicine clinic with a chief concern of aches and pains. She has a medical history of heart failure with reduced ejection fraction (ejection fraction 15%), MI (6 years ago), and COPD. Her home drugs include metoprolol XL 50 mg by mouth daily, lisinopril 20 mg by mouth daily, furosemide 40 mg by mouth twice daily, atorvastatin 40 mg by mouth daily, and umeclidinium 62.5 mcg/vilanterol 25 mcg 1 inhalation daily. Which one of the following would best prevent AKI in this patient?

    A. Perform a medication history and ask about home NSAID use.
    B. Refer the patient to nephrology.
    C. Educate the patient on "sick day rules."
    D. Develop a quality improvement initiative to reduce inappropriate medication use in older adults.

14. Which one of the following best exemplifies the practice of sick day rules?

    A. Patient who stops a loop diuretic while immobile after spinal surgery
    B. Patient who stops an ACEI while recovering from gastroenteritis
    C. Patient who stops metformin before receiving radiographic contrast media
    D. Patient who stops insulin aspart while fasting for a colonoscopy

15. A 27-year-old man presents to your clinic with concerns of low urinary output and peripheral edema. He has a history of hypertension (blood pressure 126/74 mm Hg), intravenous drug abuse (last use 1 year ago), HIV (initiated therapy 6 months ago; viral load undetectable 3 months ago), and GERD (asymptomatic today). His home drugs include valsartan 80 mg by mouth daily (× 6 months), elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg by mouth daily (× 6 months), omeprazole 20 mg by mouth daily (× 4 years), and naproxen 500 mg by mouth every 12 hours as needed for pain (× 4 years). His FENa is 3%; urinalysis +granular casts, 3+ RBC, 3+WBC. Which one of the following is best to recommend for this patient's AKI?

    A. Discontinue valsartan and change to hydrochlorothiazide 25 mg by mouth daily.
    B. Discontinue elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and change to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide by mouth daily.
    C. Discontinue omeprazole and initiate calcium carbonate 500 mg by mouth every 4 hours as needed for GERD.
    D. Discontinue naproxen and initiate acetaminophen 500 mg by mouth every 6 hours as needed for pain.