

Perioperative Acute Renal Failure: Diagnosis and Management

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Instructions

This study activity consists of 5 sections. Each section starts with a clinical question followed by pertinent didactic content. Explanations are provided for each answer to help identify areas you may need to focus on and increase your overall knowledge of the topic; they are not part of the CME test.

To participate, read each question and select your answer. If the answer is incorrect, a red box will appear with the explanation. When you select the correct answer, a green box will appear with the explanation, followed by the didactic content. The didactic content will not appear until the corresponding question(s) has been answered correctly. You may want to select the wrong answers as well to see the explanation for why they are incorrect.

All questions need to be answered correctly to move to the CME post-test and evaluation.

Section 1. Definitions, Epidemiology, and Risk Factors for the Development of ARF

You are called to see a 60-year-old male for management of hypertension. He has been admitted to the orthopedic surgery service for a right hip replacement. His medical history includes osteoarthritis, hypertension, and diabetes mellitus. His medical regimen includes metoprolol 25 mg twice a day and metformin 500 mg twice a day. The review of systems is unremarkable. Physical examination is notable for a blood pressure of 160/90 mm Hg with a heart rate of 78 bpm and a glucose finger-stick reading of 110 mg/dL. While performing your consultation, you notice that his serum creatinine was 0.8 mg/dL on admission and is now 1.9 mg/dL. What are the 2 most common causes of acute renal failure (ARF) occurring in the hospitalized patient?

A. Sepsis and post-renal obstruction

Incorrect. Sepsis is the fifth most common cause of ARF in hospitalized patients. Obstruction is a less common cause, ranking eighth. Obstruction as a cause of ARF in hospitalized patients is usually implicated in patients with conditions such as enlarged prostates or metastatic malignancies.

B. Radiographic contrast and sepsis

Incorrect. Radiographic contrast and sepsis are, respectively, the third and fifth most common causes of ARF in hospitalized patients.

C. Renal hypoperfusion and medications

Correct! Renal hypoperfusion and medications are the 2 most common causes of ARF among hospitalized patients.

D. Medications and glomerulonephritis

Incorrect. Medications are the second most common cause of ARF in hospitalized patients. However, glomerulonephritis is a less common cause, ranking twelfth. Most forms of glomerulonephritis cause deterioration in a patient's renal function over months to years. Renal failure from glomerulonephritis could be a presentation prompting admission, but is much less likely to occur in a patient who is already hospitalized for other reasons.

Definitions, Epidemiology, and Risk Factors for the Development of ARF

Acute renal failure is an important topic in hospital medicine because patients with even modest increases in their serum creatinine have increased mortality, length of stay, and costs.¹ The term "acute kidney injury" is starting to replace ARF because it is more accurate. In this module, we will use the older and still more widely accepted term, ARF. Many physicians and researchers define ARF differently, although recently there has been a movement to standardize the definition. The "RIFLE" criteria (Table 1) provide standardization and define a spectrum of renal dysfunction.²

Table 1. RIFLE Definitions

	GFR Criteria	UO Criteria
Risk	Increased serum creatinine $\times 1.5$ or GFR decrease $>25\%$	UO <0.5 mL/kg/hr $\times 6$ hr
Injury	Increased serum creatinine $\times 2$ or GFR decrease $>50\%$	UO <0.5 mL/kg/hr $\times 12$ hr
Failure	Increased serum creatinine $\times 3$ or GFR decrease $>75\%$ or a serum creatinine >4 mg/dL	UO <0.3 mL/kg/hr $\times 24$ hr or anuria $\times 12$ h
Loss	Complete loss of kidney function >4 weeks	
ESKD	Complete loss of kidney function >3 months	

ESKD = end-stage kidney disease; GFR = glomerular filtration rate; UO = urine output. Adapted with permission from Bellomo et al. *Intensive Care Med.* 2007;33:409-413.²

Among hospitalized patients, the RIFLE criteria predict in-hospital mortality.³ In a study of adults who were not receiving chronic dialysis, did not have a kidney transplant, and stayed in the hospital for more than 24 hours, patients with normal kidney function had a hospital mortality rate of 4.4%, whereas those in the "Risk," "Injury," and "Failure" categories had a 15.1%, 29.2%, and 41.1% hospital mortality rate, respectively.

Perioperative patients are a population at particularly high risk for hospital-acquired renal insufficiency. Nine percent to 25% of cases of renal insufficiency that develop in the hospital occur in the perioperative period.^{4,5} As listed in Table 2, specific surgeries associated with high rates of renal failure are coronary artery bypass graft, aortic, and valvular.^{5,6}

Surgical factors, such as cross-clamp time and time on cardiopulmonary bypass, are associated with a higher risk of ARF.⁶ Patient risk factors for postoperative ARF include baseline renal insufficiency, advanced age, left ventricular dysfunction, hypertension, diabetes mellitus, and the rupture of an aortic aneurysm.^{5,7}

Table 2. Risk Factors Associated with ARF

High-Risk Surgeries	Surgery-Specific Risk Factors	Patient-Specific Risk Factors
CABG	Cross-clamp time	Chronic renal insufficiency
Aortic	Time on cardiopulmonary bypass	Left ventricular dysfunction
Valvular		Hypertension
		Diabetes
		Aortic aneurysm rupture

ARF = acute renal failure; CABG = coronary artery bypass graft.

One study examining almost 32 000 patients undergoing cardiac surgery found that, as with hospitalized patients in general, even modest decrements in renal function are associated with significant increases in mortality.⁸ Patients with more than 30% decline in their glomerular filtration rate (GFR) postoperatively had a 5.9% mortality rate versus a mortality rate of 0.4% in those with a less than 30% decline in GFR. The deleterious effect of small decreases in GFR is especially pronounced among patients who have an elevated baseline creatinine preoperatively.^{6,8} Postoperative ARF requiring dialysis is associated with dismal outcomes, with reported mortality rates of 28%.⁹

Despite the clear importance of ARF in hospitalized patients, few studies have evaluated the causes of ARF in hospitalized patients outside of the intensive care unit (ICU) setting. Nash et al⁴ conducted a prospective study of 4622 inpatients, both medical and surgical, at a single center, to determine the causes of hospital-acquired renal insufficiency. Decreased renal perfusion and medications were the 2 most common causes of renal insufficiency in the inpatient population, accounting for 37% and 16% of cases, respectively. The third most common cause was intravenous (IV) contrast, followed by postoperative status. The most common culprit medications were aminoglycosides and nonsteroidal anti-inflammatory drugs (NSAIDs). Risk factors for renal insufficiency included elevated baseline creatinine and older age. The cause of renal failure associated with the highest mortality was sepsis. The greater the increase in creatinine, the higher the mortality rate. Among patients with more than 3 mg/dL increase in their creatinine, the mortality rate was 37.8%. Another prospective study that examined all the ARF cases in 13 tertiary care hospitals in Madrid, Spain, found similar results.¹⁰ The 2 most common causes of ARF were acute tubular necrosis (ATN), which included nephrotoxic ATN, and prerenal, which included volume-responsive ARF.

In summary, the RIFLE designations have standardized the ARF definitions and have prognostic significance for inpatients. One of the keys to avoiding ARF is to know what factors put patients at risk for it: certain high-risk surgeries, surgery-specific characteristics, and patient-specific characteristics. The most common inpatient causes of ARF are decreased renal perfusion and medications.

Section 2. Workup and Tests that Help Establish the Etiology of Hospital-Acquired ARF

A 58-year-old male, with a history of type 2 diabetes mellitus, hypertension, and a baseline serum creatinine of 1 mg/dL, is admitted to the orthopedic surgery service with a cellulitis over his prosthetic right knee. He is started on cefazolin and rapidly defervesces. On his third day of hospitalization, he develops profuse watery diarrhea. You are called 2 days later when his serum creatinine is up to 1.8 mg/dL. His daily urine output has decreased from 2200 mL on the day of admission to 700 mL currently. On examination, the patient's knee is only mildly red and there is no rash. The patient reports that he continues to have diarrhea. Urinalysis reveals a specific gravity of 1.025; trace ketones; and negative protein, blood, leukocyte esterase, and nitrite. The fractional excretion of sodium (FENa) is 0.4%. Urine eosinophils are pending. What is the most appropriate recommendation at this point?

A. Stop the cefazolin and switch to vancomycin pending the results of the urine eosinophils.

Incorrect. Acute interstitial nephritis (AIN) is in the differential. However, AIN is less likely than intravascular volume depletion given that the patient has no fever, no rash, and a history more compatible with volume depletion.

B. Order a stat renal ultrasound.

Incorrect. Obtaining a renal ultrasound is appropriate in most cases of ARF. However, there is nothing in the history to suggest a structural cause or post-renal obstruction (eg, a history of benign prostatic hyperplasia), and the decrease in the urine output could be due to the volume depletion. If volume repletion fails, a renal ultrasound would be reasonable. A bladder scan or in-and-out bladder catheter insertion are often more efficient means to evaluate for a post-void residual.

C. Obtain a 24-hour urine collection to more accurately assess the patient's creatinine clearance and proteinuria.

Incorrect. A 24-hour urine collection has almost no role in hospitalized patients. The patient's GFR can be estimated from an equation (MDRD [Modification of Diet in Renal Disease] 11 or Cockcroft-Gault 12). A spot urine protein-to-creatinine ratio is a good estimate of a patient's 24-hour proteinuria and should be used instead of a 24-hour urine collection.¹³

D. Give the patient a bolus of normal saline and then recheck his creatinine.

Correct! The data from this patient—including the low urine FENa, high specific gravity, and trace positive urine ketones—all point to this patient being volume depleted. The patient developed profuse diarrhea, likely secondary to *Clostridium difficile* colitis, leading to intravascular volume depletion and consequently ARF. An IV isotonic saline fluid bolus would likely improve his renal function.

Workup and Tests that Help Establish the Etiology of Hospital-Acquired ARF

A common and useful approach to categorizing ARF is to classify it into prerenal, intrarenal (also referred to as intrinsic renal), and post-renal causes as shown in Table 3.¹⁴⁻¹⁸

Table 3. Classification of the Major Causes of ARF

Cause	Examples
Pre-renal	
Hypovolemia	Hemorrhage (eg, from surgery), vomiting, and over diuresis
Hypotension	Cardiogenic shock, sepsis, and advanced chronic congestive heart failure
Pharmacologic	NSAIDs and ACEIs/ARBs
Vascular, large-vessel	Stenosis, thrombosis, and dissection
Intrarenal	
Acute tubular necrosis (ischemic)	Hypotension and sepsis
Acute tubular necrosis (toxic)	Aminoglycosides, IV contrast, amphotericin B, cisplatin, myoglobin, and tenofovir
Acute interstitial nephritis	
Glomerular	GN (eg, postinfectious GN, cryoglobulinemia, and lupus nephritis)
Vascular, small-vessel	Vasculitis, atheroemboli, thrombotic microangiopathy, and DIC
Post-renal	
Ureteral obstruction	Calculi, tumor, clot, lymphadenopathy, and retroperitoneal fibrosis
Bladder outlet obstruction	Neurogenic and tumor
Urethral obstruction	BPH, malpositioned or obstructed Foley catheter, and stricture

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARF = acute renal failure; BPH = benign prostatic hyperplasia; DIC = disseminated intravascular coagulation; GN = glomerulonephritis; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.
 Adapted from Albright RC Jr¹⁴; Hilton R¹⁵; Lameire et al¹⁶; Singri et al¹⁷; and Weisbord and Palevsky.¹⁸

Although valuable, the above scheme presents a broad array of potential etiologies, and it is critical to remember that a small number of diagnoses account for the vast majority of cases of ARF that develop in hospitalized patients. For example, based on the data from Nash et al,⁴ the top 5 causes of hospital-acquired renal failure—renal hypoperfusion, medications, radiographic contrast media, postoperative state, and sepsis—account for 82% of cases.

The initial assessment, in addition to the history and physical examination, should involve promptly evaluating urine studies, including urine sodium, urine creatinine, urine urea, a urinalysis (dipstick), urine microscopy analysis, and urine eosinophils. A full set of electrolytes, including calcium and phosphate, electrocardiogram, and in most cases, a renal ultrasound should also be obtained.¹⁹

Urine output needs to be determined, as anuria (<100 mL/day) implicates mechanical obstruction as a potential cause. Urine electrolytes can help with the diagnosis, as outlined in Table 4.^{14,17,18} The urine electrolytes are often used to differentiate between prerenal ARF and ATN.

Table 4. Urine Chemistry and Urinalysis Findings in ARF

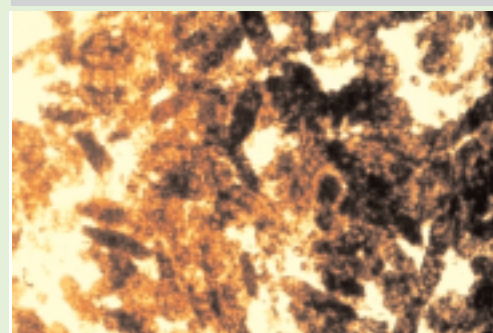
Etiology of ARF	Urine Na, mEq/L	FE _{Na}	FE _{Urea}	Proteinuria	Urine Sediment
Prerenal	<20	<1%	<35%	Minimal	Bland
Intrarenal					
ATN	>40	>2%	>50%	Minimal	Granular casts
AIN	Variable	Variable	Variable	Variable	Eosinophils
GN	<20	<1%	<35%	>300 mg/d	RBC casts
Post-renal	Variable	Variable	Variable	Minimal	Bland or RBCs

Useful as the FENa is, a number of caveats apply:

- In patients with completely normal renal function, a low FENa can represent nothing more than the maintenance of steady state with respect to sodium intake and excretion.
- Diuretics cause sodium wasting, making a high FENa uninterpretable. In cases of diuretic use, the fractional excretion of urea (FEUrea) can be used (<35% is low and >50% is high). Urea handling is less affected by diuretic use than sodium handling. However, the utility of FEUrea measurements has recently been called into question.²⁰
- Compared to other nephrotoxins that result in an elevated FENa, contrast-induced nephropathy (CIN) is often accompanied by a low FENa.²¹
- Urinary obstruction and sepsis are 2 conditions in which the urinary electrolytes are variable.²²

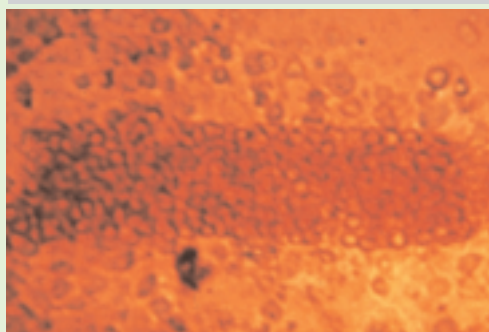
The results of the urinalysis and urine microscopy examination also provide useful diagnostic information. For instance, the presence of muddy brown granular casts (Figure 1)²³ supports a diagnosis of ATN. Red blood cell (RBC) casts (Figure 2)²⁴ and dysmorphic RBCs are highly suggestive of glomerulonephritis or vasculitis. White blood cell (WBC) casts (Figure 3)²⁴ are most commonly associated with pyelonephritis, though they can also be seen with AIN and glomerulonephritis. Urine eosinophils can be seen in AIN, as well as other conditions, such as renal atheroembolic disease and glomerulonephritis. The urinalysis is positive for blood in the presence of either hemoglobin or myoglobin. A urinalysis that is positive for blood in the absence of RBCs on microscopy suggests a diagnosis of rhabdomyolysis or hemolysis. The urinalysis, as measured with most dipsticks, tests for albumin but not non-albumin protein. In the case of ARF associated with a non-albumin proteinuria, such as myeloma kidney, there may be little or no protein on the urinalysis. The significance of urine eosinophils is discussed in a later section.

Figure 1. Image of Muddy Brown Granular Casts



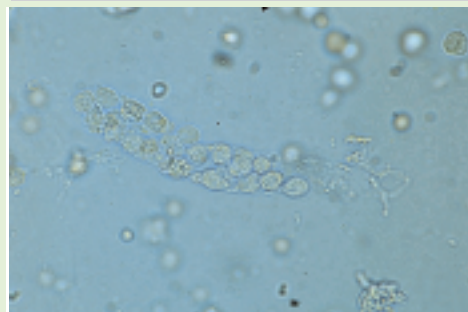
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Figure 2. Image of Red Blood Cell Casts



Post and Rose. Urinalysis in the diagnosis of renal disease-I. In: UpToDate. Rose BD, ed. UpToDate. Waltham, MA: 2008.24 Copyright © 2008 UpToDate, Inc. For more information visit www.uptodate.com.

Figure 3. Image of White Blood Cell Casts



Post and Rose. Urinalysis in the diagnosis of renal disease-I. In: UpToDate. Rose BD, ed. UpToDate. Waltham, MA: 2008.24 Copyright © 2008 UpToDate, Inc. For more information visit www.uptodate.com.

In summary, the ARF categories of prerenal, intrarenal, and post-renal help physicians to think about the differential diagnosis in an organized fashion. The differential diagnosis should take into account the causes that occur most often in the inpatient setting: renal hypoperfusion, medications, radiographic contrast media, postoperative state, and sepsis. A urinalysis, urine electrolytes, a urine microscopy examination, urine eosinophils, a renal ultrasound, and serum electrolytes all can add information to the history and physical examination when evaluating the causes of ARF.

Section 3. Analyze Evidence for Medical ARF Risk Reduction Therapies

You are called to perform a preoperative consultation on a 59-year-old male with a history of diabetes mellitus, hypertension, and a baseline serum creatinine of 1.6 mg/dL. He is about to undergo a partial bowel resection. The surgeon says he is concerned about the patient's kidneys "taking a hit" after the procedure, and he asks you what he can do to prevent this. Which of the following recommendations is most accurate?

A. The surgeon should use loop diuretics in this patient to maintain a good urine output.

Incorrect. Studies have not shown that loop diuretics, specifically furosemide, are beneficial.

B. The surgeon should use low "renal-dose" dopamine.

Incorrect. There is no evidence to support this practice.

C. The surgeon should use N-acetylcysteine (NAC).

Incorrect. Although NAC may be beneficial in preventing CIN, NAC does not provide a renoprotective effect in high-risk patients undergoing surgery.

D. The surgeon should avoid hypotension and nephrotoxins, but no specific pharmacologic measure is indicated.

Correct! No specific pharmacologic agent has clearly been shown to help prevent ARF postoperatively.²⁵⁻²⁷ It is appropriate to recommend avoiding hemodynamic insults to the kidney and nephrotoxins, such as NSAIDs, aminoglycosides, and contrast.

Analyze Evidence for Medical ARF Risk Reduction Therapies

Although several medicines have been tested in the perioperative setting for their ability to decrease the risk of postoperative ARF, none have clearly proven to be of benefit.²⁵⁻²⁷ Thus, the best approach is to provide supportive care, consisting of avoiding hypotension and renal hypoperfusion and limiting the kidney's exposure to nephrotoxic agents.

There is a certain logical appeal to using loop diuretics in post-surgical patients.²⁸ Patients with ATN who are nonoliguric have greater preservation of their renal function than patients who are oliguric.²⁹ However, this practice is not supported by the medical evidence.³⁰ In one cohort study looking at ICU patients with ARF on whom nephrologists consulted, 59% of the 326 patients received diuretics.³¹ The patients who received the diuretics actually had a significant increase in the risk of death or permanent renal insufficiency, 2 of the primary end points. In a randomized controlled trial (RCT) examining the effect of different pharmacologic treatments in preventing postoperative ARF among patients with normal preoperative creatinine undergoing cardiac surgery, furosemide, given as a constant infusion, appeared to be harmful compared to the placebo arm.³²

The use of low-dose (so-called renal-dose) dopamine to prevent ARF persists despite evidence refuting the efficacy of this practice. In a multicenter RCT to examine this issue, 328 ICU patients were randomized to receive either low-dose dopamine or placebo.³³ The primary end point was peak serum creatinine, and the dopamine group showed no significant advantage over the placebo group in this outcome, in the need for dialysis, or in duration of ICU stay. Two meta-analyses have attempted to synthesize the numerous studies on this matter. Both concluded that dopamine does not significantly prevent ARF.^{34,35}

N-acetylcysteine appears to be beneficial in preventing ARF in high-risk patients exposed to IV contrast (discussed in a subsequent section), but does it have a similar renoprotective benefit in patients at high-risk for ARF undergoing surgery? Small RCTs have not shown a clear benefit to NAC in patients undergoing surgery. The largest RCT involved 177 cardiac surgery patients with pre-existing renal insufficiency (estimated GFR

<60 mL/min). Eighty-nine patients received IV NAC perioperatively and the rest received placebo.³⁶ The post-operative estimated GFR in the NAC group was not significantly better than the placebo group, although there was a decrease in all-cause mortality in the NAC group. Two other trials showed no benefit with NAC treatment on renal function or overall mortality. One of the trials evaluated 45 patients undergoing elective aortic aneurysm repair who received oral and IV NAC.³⁷ The other study followed 80 patients with pre-existing renal insufficiency who received IV NAC before undergoing cardiac surgery.³⁸

When studied for its ability to prevent renal failure in surgical and ICU patients, the dopamine agonist fenoldopam has yielded conflicting results. The largest study, a prospective cohort in which 50% of the 218 patients undergoing cardiac surgery received fenoldopam, revealed a decrease in the incidence of ARF and mortality in a univariate analysis. That benefit, however, was not seen in a multivariate analysis.³⁹ An RCT enrolling 155 patients with early ATN found no benefit to fenoldopam in the primary end point of incidence of dialysis therapy and all-cause mortality at 21 days.⁴⁰ Two meta-analyses examining prevention of ARF with fenoldopam in at-risk patients concluded that fenoldopam may have benefits in these patients. Both recommended further study.^{41,42} Until additional large, well-powered RCTs have been conducted, the broad use of fenoldopam for ARF prophylaxis cannot be recommended.

In summary, despite the physiologic plausibility that specific pharmacotherapy might prevent ARF in patients at elevated risk, no medication has been proven to be of clear benefit. Thus, the most important measures that can be taken are supportive:

- Avoid hypotension and, when it develops, promptly correct fluid and blood losses
- Avoid the use of nephrotoxic drugs, monitor drug levels, and limit contrast studies
- Dose medications appropriately for patients' renal function
- Limit the use of central venous catheters and urinary catheters to situations that are absolutely necessary for diagnosis or treatment to decrease the likelihood of hospital-acquired infections

Section 4. Inpatient Medications that Commonly Cause ARF and How to Prevent It

A 28-year-old male with a history of AIDS was admitted to the general surgery service for incision and drainage of a right thigh abscess. You are called to see the patient for ARF after his serum creatinine has risen from a baseline of 0.7 mg/dL 3 days ago, up to 1.5 mg/dL today. His medications include trimethoprim-sulfamethoxazole, tenofovir, and ibuprofen as needed. Urine studies reveal 2+ protein, 2+ glucose, and a specific gravity of 1.01. Tests for urine eosinophils are negative. Serum electrolytes are notable for potassium of 3.1 mg/dL, HCO₃ of 18 mEq/L, and glucose of 98 mg/dL. Which of the following is the most appropriate next step?

A. Stop the trimethoprim-sulfamethoxazole

Incorrect. Although trimethoprim-sulfamethoxazole can cause AIN, it does not cause proximal tubular dysfunction, as is seen here.

B. Stop the tenofovir

Correct! This patient is displaying a type of medication-associated nephrotoxicity that is specific to tenofovir, in which there is proximal tubular dysfunction and renal failure.⁴³⁻⁴⁵ As part of the proximal tubular dysfunction, the patient wastes glucose (hence the glucosuria without hyperglycemia) and filtered bicarbonate (hence a proximal renal tubular acidosis). This condition of proximal tubular dysfunction is known as Fanconi syndrome, which also includes proteinuria and a decrement in GFR. Histologically, severe tubular necrosis is seen without significant glomerular damage.

C. Stop the ibuprofen

Incorrect. Although it is reasonable to discontinue ibuprofen due to its potential nephrotoxic effects, ibuprofen has not been associated with the type of proximal tubular dysfunction seen in this patient.

D. Hydrate the patient aggressively and recheck the serum creatinine

Incorrect. There is nothing in this presentation to suggest that intravascular volume depletion is the likely cause of this patient's ARF.

Inpatient Medications that Commonly Cause ARF and How to Prevent It

Medications are the second most common cause of ARF in hospitalized patients (after hypoperfusion).⁴ The most common culprit medications are found in Table 5.⁴

Table 5. Medications Associated with ARF

Medication	Medication-Associated ARF Events, %
Aminoglycosides	29.5
NSAIDs	21.3
Piperacillin/tazobactam	11.5
Amphotericin B	9.8
Trimethoprim-sulfamethoxazole	9.8
Cyclosporine	4.9
ACEIs	3.3

ACEI = angiotensin-converting enzyme inhibitor; ARF = acute renal failure; NSAID = non-steroidal anti-inflammatory drug.
Data adapted from Nash et al.⁴

Several general principles apply to minimizing medication-induced nephrotoxicity:

1. Review all the potential nephrotoxins a patient is receiving, so as to avoid a large cumulative burden of nephrotoxins. That is, one wants to avoid “piling on” the kidneys. For instance, avoid the addition of an aminoglycoside or NSAID to a patient who is receiving an angiotensin-converting enzyme inhibitor (ACEI) and was recently exposed to IV contrast.
2. Adjust the dose of medications for the patient’s GFR.
3. When appropriate (eg, aminoglycosides and calcineurin inhibitors), monitor the levels of the drug. Pharmacy support should be obtained in dosing medications appropriately.
4. Make systems-level changes to promote patient safety. Computer order sets that call for the administration of potentially nephrotoxic drugs should take into account the patients’ renal function. For instance, a postoperative care order set that calls for the use of ketorolac for pain control should have a caveat that this medication should be used with caution in patients whose serum creatinine is significantly elevated (ie, >2.5 mg/dL).⁴⁶

Aminoglycosides

Nephrotoxic medications commonly produce ATN.⁴⁷ Of all inpatient medications, aminoglycosides are the most common cause of ARF. Aminoglycoside nephrotoxicity is seen in 12% to 30% of patients receiving the drug.^{4,48} Generally, nonoliguric ARF typically develops several days after the initiation of the medication.⁴⁹ Risk factors for aminoglycoside nephrotoxicity include the presence of high trough levels, extended (>11 days) duration of treatment, and the presence of liver disease.^{50,51} Once-daily dosing of aminoglycosides and adequate hydration can help prevent nephrotoxicity.^{52,53} Consider whether an alternative antibiotic class is appropriate, especially if the patient has pre-existing renal insufficiency (Table 6).⁵⁴

Table 6. Aminoglycoside-Induced ARF

Mechanism	Risk Factors for ARF	Prophylactic Measures
ATN	High trough levels >11 days of treatment Liver disease Chronic kidney disease	Adequate hydration Once-daily dosing Alternative antibiotic

ARF = acute renal failure; ATN = acute tubular necrosis.

Nonsteroidal anti-inflammatory drugs

Another common cause of drug-induced ARF is NSAIDs, which can cause ARF via several mechanisms: decreased prostaglandin production (prostaglandins allow for afferent arterial vasodilatation), interstitial nephritis, papillary necrosis, and nephrotic syndrome. In most cases, appropriate treatment consists of discontinuing the NSAID. Risk factors for NSAID-induced ARF include underlying chronic kidney disease (CKD), dehydration, and older age (Table 7).^{46,55} Despite initial hopes to the contrary, the cyclooxygenase (COX)-2 inhibitors can be nephrotoxic.^{56,57}

Table 7. NSAID-Induced ARF

Mechanisms	Risk Factors for ARF	Treatment
Decreased prostaglandin production	Dehydration	Stop the NSAID
Interstitial nephritis	CKD	
Papillary necrosis	Administration with other nephrotoxins	
Nephrotic syndrome	Elderly	

ARF = acute renal failure; CKD = chronic kidney disease; NSAID = nonsteroidal anti-inflammatory drug.
Adapted with permission from Whelton. *Am J Med.* 1999;106:13S-24S.⁴⁶

β-lactam antibiotics

The nephrotoxicity associated with β-lactam antibiotics is generally due to AIN. Classically, this was associated with methicillin, but any β-lactam or cephalosporin antibiotic can be responsible, including piperacillin/tazobactam.⁵⁸ Further discussion of AIN is found in a subsequent section.

Amphotericin B

The antifungal agent amphotericin B commonly causes marked renal toxicity. In one study, 53% of patients treated with amphotericin B had a doubling of their serum creatinine.⁵⁹ Higher doses, and concomitant use of other nephrotoxins, such as cyclosporine, are associated with greater amphotericin B renal toxicity.⁶⁰ Measures to mitigate the renal toxicity of amphotericin B include prehydration and use of the lipid formulations of amphotericin B,⁶¹ among which liposomal amphotericin B may be the least nephrotoxic.⁶² Electrolyte abnormalities seen with amphotericin B include hypokalemia, hypomagnesemia, and a non-anion gap metabolic acidosis (Table 8).⁶³

Table 8. Amphotericin B-Induced ARF

Risk Factors for ARF	Prophylaxis Options	Associated Electrolyte Abnormalities
Higher doses	Prehydration	Hypokalemia
Administration with other nephrotoxins	Use lipid formulations	Hypomagnesemia Non-anion gap metabolic acidosis

ARF = acute renal failure.

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole, like any sulfonamide drug, can cause AIN. At higher doses, it can precipitate as crystals and lead to intratubular obstruction.^{64,65} Other clinically important effects of trimethoprim-sulfamethoxazole include a modest increase in serum creatinine that results from trimethoprim-induced inhibition of tubular creatinine secretion. Thus, the increase in creatinine does not reflect an actual change in GFR. Trimethoprim-sulfamethoxazole can also cause hyperkalemia by acting on the amiloride sensitive sodium channels, in a similar manner to the potassium-sparing diuretics like amiloride.⁶⁶ This action is most often clinically relevant when the patient has pre-existing renal insufficiency or is on another drug that can induce hyperkalemia.⁶⁵

Cyclosporine

Cyclosporine, and the related calcineurin inhibitor tacrolimus, can cause renal failure, likely due to renal vasoconstriction.^{67,68} The levels of the drug, which should generally be measured daily in inpatients, are associated with its toxicity. Goal levels, which should to be determined in collaboration with the transplant team, depend on various factors including when the transplant occurred. In addition to avoiding toxicity from high drug levels, consider treating the patient with a dihydropyridine calcium channel blockers (CCBs), such as long-acting nifedipine, in an effort to mitigate the vasoconstriction caused by cyclosporine.^{69,70} Many medications can increase calcineurin levels—including non-dihydropyridine CCBs, such as diltiazem; azoles, such as ketoconazole, fluconazole, and itraconazole; macrolides, such as clarithromycin and erythromycin more than azithromycin; and CYP3A4-metabolized statins, such as simvastatin and atorvastatin. Cyclosporine can also cause hyperkalemia.⁷¹

ACE inhibitors

Angiotensin-converting enzyme inhibitors produce ARF by decreasing activity of angiotensin II, resulting in decreased efferent (postglomerular) arteriolar tone. Less efferent tone leads to a lower intraglomerular pressure. ACEI-induced ARF is more likely to occur with any condition that produces kidney hypoperfusion, including volume depletion from diarrhea or vomiting,⁷² heart failure,⁷³ or bilateral renal artery stenosis.⁷⁴ Stopping the ACEI will usually lead to resolution of the ARF.

Acyclovir and indinavir

Uncommonly, acyclovir, given IV, can precipitate and form crystals. The crystals can cause intratubular obstruction and lead to ARF from an obstructive nephropathy. The crystals can sometimes also be seen in the urine. Similarly, the protease inhibitor indinavir can precipitate to form crystals and stones.^{75,76} Discontinue the offending drug and hydrate the patient.

Summary

In summary, medications are the second most common cause of ARF in the inpatient setting. Be aware of medications that are associated with ARF and avoid a cumulative burden of nephrotoxins. Adjust the dose of medications for the patient's GFR, and, when appropriate, monitor the levels of drugs. Make systems-level changes to avoid medication-induced nephrotoxicity and promote patient safety.

Section 5. Preventive Measures that Can Be Taken to Avoid Contrast-Induced Nephropathy

A 63-year-old male patient with a history of diabetes mellitus type 2 and angina is scheduled to undergo cardiac catheterization tomorrow due to a preoperative stress test showing moderate anterior wall ischemia. His baseline serum creatinine is 1.6 mg/dL. Which of the following treatment plans is the most appropriate?

A. Stop his metformin and give high-dose statin and fenoldopam

Incorrect. Although statins have been shown to reduce CIN, fenoldopam has not been shown to provide benefit.

B. Continue his metformin and give NAC and normal saline

Incorrect. Metformin levels can rise in the setting of CIN and should be held in patients receiving IV contrast.

C. Make sure the patient is euvolemic, but no additional specific intervention is indicated

Incorrect. Patients at risk for CIN should receive IV hydration with isotonic fluids (unless clearly contraindicated due to concerns about volume overload), and there are some data suggesting that isotonic sodium bicarbonate may be superior to normal saline. NAC is an additional measure that is indicated here.

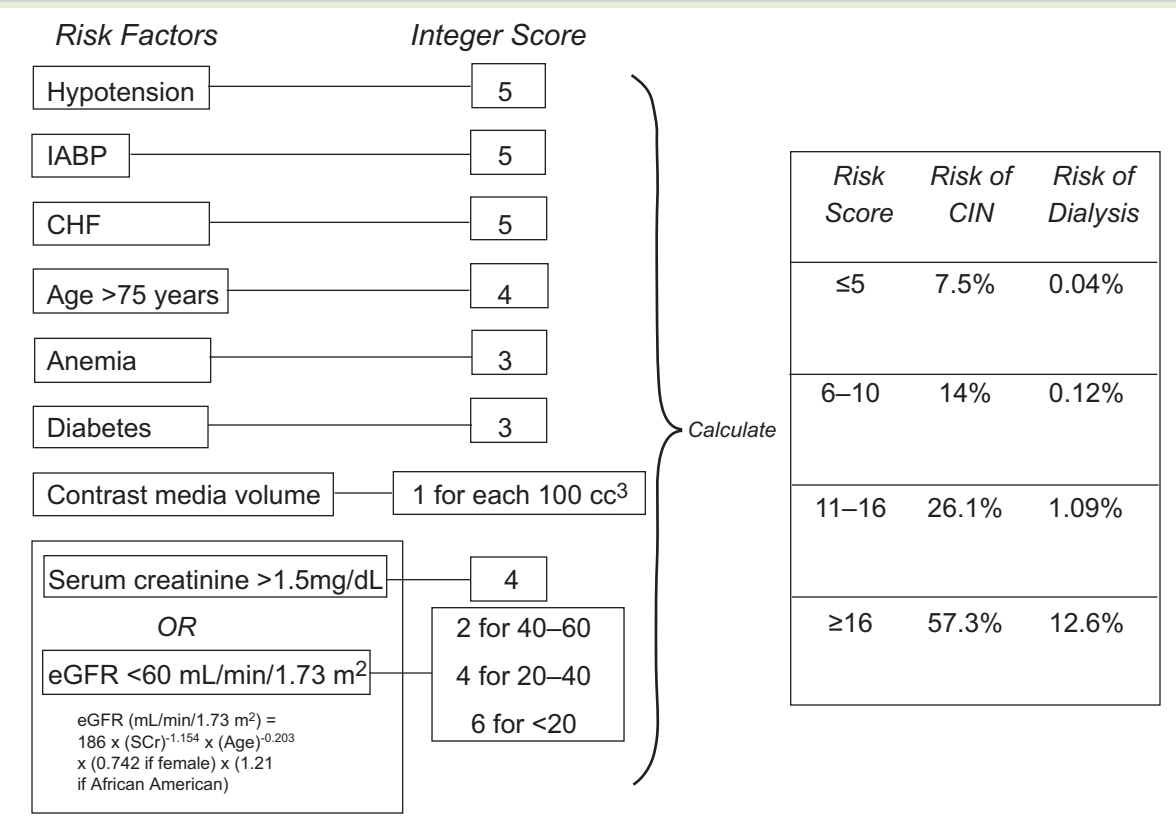
D. Stop his metformin and give NAC and isotonic bicarbonate-containing fluids

Correct! In patients with impaired baseline renal function, metformin should be held for at least 48 hours after the administration of contrast. Given its low cost and toxicity, oral NAC administration is an appropriate prophylactic measure, particularly for high-risk patients, such as those with diabetes and CKD. Hydration with IV isotonic fluids has also been shown to be of benefit in preventing CIN.

Preventive Measures that Can Be Taken to Avoid Contrast-Induced Nephropathy

Contrast-induced nephropathy risk factors identified in multivariate analyses include CKD (GFR <60 mL/min), diabetes mellitus, volume depletion, nephrotoxic medications, preprocedural hemodynamic instability, and other comorbidities, including anemia, chronic heart failure, and hypoalbuminemia.⁷⁷ One of the risk prediction models (Figure 4) that has been developed assigns weighted points to various risk factors.⁷⁸ The highest number of risk points is assigned for hypotension (systolic blood pressure <80 mm Hg), having an intra-aortic balloon pump, chronic heart failure (NY Heart Association class III or IV), and a very low estimated GFR. Other factors used in the model include age older than 75 years, anemia (hematocrit <39% for men and <36% for women), diabetes, and the volume of contrast media used. Based on those risk factors, the most important intervention is to minimize the dose of IV contrast (and avoid it when possible), especially in patients with risk factors, such as diabetes mellitus.^{79,80}

Figure 4. Scheme to Define CIN Risk Score



CHF = chronic heart failure; CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate; IABP = intra-aortic balloon pump. Reprinted with permission from Mehran et al. *J Am Coll Cardiol.* 2004;44:1393-1399.⁷⁸

Holding metformin

Metformin does not produce CIN. A reduction in GFR caused by IV contrast, however, could lead to an elevation in metformin levels and increase the risk of metformin-induced lactic acidosis. Although rare, there have been case reports of this occurring.^{81,82} Older guidelines recommended that metformin be held for 48 hours before and 48 hours after administration of contrast. More recent recommendations, including those published in the American College of Radiology Bulletin and the Canadian Association of Radiologists,^{83,84} state that patients with normal renal function should have metformin stopped on the day of the procedure and held for 48 hours after the procedure. In patients with impaired baseline renal function (ie, GFR <60 mL/min), metformin should be held for at least 48 hours after the administration of contrast and should not be restarted until it has been documented that the patient's renal function is not significantly above baseline. In patients with impaired baseline renal function, there is controversy regarding how far in advance of the contrast administration the metformin should be held. The European Society of Urogenital Radiology still recommends that it be held for 48 hours before contrast administration.⁸⁵

N-acetylcysteine

Two studies in the New England Journal of Medicine have looked at the ability of NAC to prevent CIN. One study enrolled 83 patients with significant baseline CKD, who had a mean serum creatinine of 2.4 mg/dL and were receiving IV contrast for computed tomography scans.⁸⁶ All patients received IV hydration, and 41 received NAC 600 mg orally twice a day on the day before and day of the examination involving contrast. The primary end point, an increase in serum creatinine of at least 0.5 mg/dL within 48 hours after contrast administration, was reached in 2% of the patients who received NAC (plus IV hydration) versus 21%

of the patients who received IV hydration alone ($P = .01$).

The other New England Journal of Medicine study evaluating NAC included 354 patients, most of whom had normal renal function, who received contrast for primary angioplasty.⁸⁷ In addition to IV hydration, patients were randomized to standard-dose NAC (600 mg IV and then 600 mg orally twice daily for the 48 hours postangioplasty), high-dose NAC (1200 mg IV and then 1200 mg orally twice daily for the 48 hours postangioplasty), or placebo. The primary end point, an increase in the serum creatinine of at least 25% within 72 hours of the angioplasty, occurred in 33% of control patients, 15% of those receiving standard-dose NAC, and 8% of patients receiving high-dose NAC ($P < .001$).

Another study that showed a dose-dependent benefit from NAC enrolled 224 patients with CKD (serum creatinine > 1.5 mg/dL) receiving IV contrast. Along with IV hydration, the patients were given either NAC 600 mg orally twice daily or NAC 1200 mg orally twice daily.⁸⁸ A creatinine increase of at least 0.5 mg/dL occurred in 11% of the standard-dose NAC group versus 3.5% in the high-dose NAC group ($P = .038$).

The data on NAC are not unequivocal. Negative studies have been published.⁸⁹⁻⁹¹ The largest meta-analysis of NAC concluded, however, that NAC may be beneficial. The trend toward benefit was more substantial in the higher quality studies.⁹² Especially given its low cost and low toxicity, oral NAC is an appropriate measure to employ to prophylax against CIN. Consider NAC therapy particularly for higher risk patients, such as those with diabetes and CKD.⁹³

IV hydration

The largest trial to examine the potential protective effects of IV hydration randomized 1620 patients undergoing coronary angioplasty to receive either normal saline or 5% dextrose in 0.45% sodium chloride at a rate of 1 mL/kg.⁹⁴ The rate of CIN was significantly reduced in the normal saline group (0.7%) versus the 5% dextrose in 0.45% sodium chloride group (2%) with an absolute risk reduction of 1.3% ($P = .04$). Subgroups that particularly benefited were patients with diabetes and patients receiving larger volumes of contrast. Merten et al⁹⁵ compared normal saline to isotonic sodium bicarbonate (154 mEq/L) in patients receiving contrast in a protocol of 3 mL/kg/hour for 1 hour before contrast administration followed by 1 mL/kg/hour for 6 hours after the patient received contrast. The rate of CIN was lower in the sodium bicarbonate group (1.7%) as compared to the normal saline group (13.6%; $P = .02$). Corroborating these results is the REMEDIAL (Renal Insufficiency Following Contrast Media Administration Trial) trial, which compared IV normal saline fluid plus NAC, versus IV sodium bicarbonate plus NAC, versus NAC plus ascorbic acid in 326 patients with CKD.⁹⁶ The rate of CIN was lowest in the IV sodium bicarbonate plus NAC group at 1.9%. The rates in the other 2 groups were similar at approximately 10% ($P = .019$). Thus, patients at risk for CIN should definitely receive IV hydration with isotonic fluids unless there is a clear contraindication due to concerns about volume overload. There are conflicting data as to whether isotonic sodium bicarbonate is superior to normal saline.⁹⁷⁻⁹⁹ Table 9 provides a summary of the various IV hydration studies for CIN prophylaxis.^{94-96,98-101}

Table 9. Summary of IV Hydration Studies for CIN Prophylaxis

Study (# of patients)	Design	Indication	Primary End Point	Intervention 1 (% Reaching End Point)	Intervention 2 (% Reaching End Point)	Absolute Risk Reduction
Mueller ⁹⁴ (1620)	RCT, open-label	Elective or emergency coronary angioplasty	Increase in SCr of ≥ 0.5 mg/dL within 48 hours	0.9% saline (0.7%)	0.45% NaCl with 5% glucose (2%)	1.3% ($P = .04$)
Merten ⁹⁵ (119)	RCT, partially blinded	Iopamidol administration	Increase of $\geq 25\%$ in SCr within 2 days	154-mEq/L NaCl (13.6%)	154-mEq/L sodium bicarbonate (1.7%)	11.9% ($P = .02$)
Recio-Mayoral ¹⁰⁰ (111)	RCT, patients blind	Emergency PCI	Absolute increase in SCr concentration of ≥ 0.5 mg/dL or within 3 days	Sodium bicarbonate plus pre- and post-PCI NAC (1.8%)	Isotonic saline plus post-PCI NAC (21.8%)	20% ($P < .001$)
Briguori ⁹⁶ (326)	RCT, double-blind	Coronary and/or peripheral procedures	Increase of $\geq 25\%$ in the SCr within 48 hours	0.9% saline infusion plus NAC (9.9%)	Sodium bicarbonate infusion plus NAC (1.9%)	8% ($P = .019$)
Masuda ¹⁰¹ (59)	RCT, open-label	Emergency coronary procedure	Increase > 0.5 mg/dL or $> 25\%$ in SCr concentration within 2 days	154-mEq/L sodium bicarbonate (7%)	154-mEq/L sodium chloride (35%)	28% ($P = .01$)
Maioli ⁹⁸ (502)	RCT, open-label	Planned coronary angiographic procedures	Absolute increase of ≥ 0.5 mg/dL over baseline serum creatinine within 5 days	Sodium bicarbonate plus NAC (10%)	0.9% sodium chloride plus NAC (11.5%)	1.5% ($P = .60$)
Brar ⁹⁹ (353)	RCT, patients blinded	Coronary angiography	$\geq 25\%$ reduction in the estimated GFR on days 1–4	Sodium bicarbonate (13.3%)	0.9% saline (14.6%)	1.3% ($P = .82$)

CIN = contrast-induced nephropathy; GFR = glomerular filtration rate; IV = intravenous; NAC = N-acetylcysteine; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SCr = serum creatinine. Data from Mueller et al⁹⁴; Merten et al⁹⁵; Briguori et al⁹⁶; Maioli et al⁹⁸; Brar et al⁹⁹; Recio-Mayoral et al¹⁰⁰; and Masuda et al¹⁰¹.

Statins and fenoldopam

Other pharmacologic agents that have been investigated as potential agents to prevent CIN include statins and fenoldopam. Two retrospective studies^{102,103} and one prospective observational study¹⁰⁴ of patients undergoing percutaneous coronary intervention found that statins reduced the risk of CIN. Fenoldopam, in contrast, has not been found to be of benefit in preventing CIN.^{105,106}

Summary

In summary, risk stratify patients who are to receive IV contrast. Those at high risk should be hydrated. There are conflicting data as to whether hydration with sodium bicarbonate is superior to normal saline. High-risk patients should also receive NAC. Limited studies indicate that high-dose NAC, 1200 mg orally twice daily, may provide more protection than low-dose NAC, 600 mg orally twice daily. Stop metformin for at least 2 days after contrast administration.

Section 6. Presenting Features and Management of Acute Interstitial Nephritis

A 56-year-old female is admitted with right-sided endocarditis and a serum creatinine of 1 mg/dL. Her blood culture grows *Staphylococcus aureus* that is sensitive to IV nafcillin, and she is discharged with a peripherally inserted central catheter line to complete a course of this antibiotic. Twelve days later, she develops ARF, with a serum creatinine of 3.1 mg/dL, and recurrent fever without an associated rash. She appears euvolemic on physical examination. Urine studies reveal 1+ protein, WBC casts, rare RBCs, and 3% eosinophils. What is the most appropriate next step?

A. Change the nafcillin to vancomycin and closely follow the serum creatinine

Correct! In this patient, who appears to have AIN, the appropriate measures are to stop the offending medication, change to an alternative medication that does not have allergic cross-reactivity, and closely follow the patient's renal function.

B. Change the nafcillin to cefazolin and promptly start oral prednisone¹

Incorrect. Because this patient appears to have AIN, you should substitute a medication that would be unlikely to cause any allergic cross-reactivity. Switching from a β -lactam antibiotic to a cephalosporin is not the best option.

C. Change the nafcillin to levofloxacin and obtain a prompt renal biopsy

Incorrect. Because this patient appears to have AIN, switching from nafcillin to another class of antibiotics is important. However, a renal biopsy is unnecessary unless the serum creatinine does not improve.

D. Continue the nafcillin and obtain a prompt renal gallium scan

Incorrect. This patient appears to have AIN, and the likely culprit medication, nafcillin, should be stopped immediately

Presenting Features and Management of Acute Interstitial Nephritis

This patient has signs and symptoms consistent with AIN, an immune-mediated form of ARF that is most often induced by medications. In addition to ARF, the cardinal findings associated with AIN are rash, fever, arthralgias, and eosinophilia/eosinophiluria.¹⁰⁷ Unfortunately, it is unusual to see all of these findings together, as was the case with the patient described in this case. In an AIN series consisting of 128 patients, at presentation, rash was present in 14.8% of patients, fever in 27.3%, and eosinophilia in 23.3%.¹⁰⁸ The combination of fever, arthralgias, and rash was present in only 10% of patients. In another smaller series, the combination of rash, fever, and eosinophilia was seen in only 1 of 13 patients.¹⁰⁹ Common presenting clinical features include fever, skin rash, arthralgias, and flank tenderness.¹¹⁰ Other associated non-specific symptoms include fatigue, nausea, and anorexia.¹⁰⁹

Laboratory abnormalities (Table 10) include eosinophilia, eosinophiluria, sterile pyuria, hematuria, and WBC casts classically, although granular casts can also be seen.^{109,110} Proteinuria is usually present at subnephrotic levels (ie, <3.5 g/24 hours¹¹¹) and usually less than 1 g/24 hours. The urine of patients with AIN often has a fixed specific gravity of 1.01 (isosthenuria), and tubular dysfunction leads to a urine sodium that is generally elevated (>40 mEq/L).

Table 10. Laboratory Findings in AIN

Serum	Urine
Elevated BUN and Cr	Eosinophiluria
Eosinophilia	WBC casts/pyuria
	Granular casts
	Hematuria
	Proteinuria (often <3.5 g/24 hrs)
	High urine sodium (>40 mEq/L)

AIN = acute interstitial nephritis; BUN = blood urea nitrogen; Cr = creatinine; WBC = white blood cell.

The time period from exposure to the inciting medication to the onset of symptoms is variable, but most commonly occurs approximately 2 weeks after starting the medicine.¹¹² Symptoms can occur, however, as early as 2 to 3 days after administration of a drug to which the patient has been previously sensitized/exposed.¹⁰⁷

The clinical and laboratory picture with NSAID-induced AIN is different. NSAID-associated AIN usually occurs after many months of drug exposure, and the resultant proteinuria is usually in the nephrotic range. Moreover, the kidney biopsy reveals a minimal change lesion. Fever, rash, and eosinophilia occur less often in patients with NSAID-induced AIN, and this condition responds poorly to steroid therapy.^{107,112} COX-2 inhibitors also can cause AIN.^{112,113}

Drugs that are associated with AIN include β -lactams (including cephalosporins), sulfonamides, vancomycin, rifampin, NSAIDs, cimetidine, proton pump inhibitors, carbamazepine, thiazide diuretics, and loop diuretics.^{107,110} Most cases of AIN are drug-related, especially those occurring in hospitalized patients. Less commonly, infections such as Streptococci, legionella, cytomegalovirus, Epstein-Barr virus, and syphilis can cause AIN.¹⁰⁷

Acute interstitial nephritis can be a challenging diagnosis. ARF that develops 3 weeks into a hospitalization can have numerous potential etiologies other than AIN. When all of the cardinal features are present (ie, rash, fever, arthralgias, and eosinophilia/eosinophiluria), AIN is the most likely diagnosis. Because the condition rarely presents classically, a high index of clinical suspicion is necessary to make the diagnosis. When AIN is suspected, it is appropriate to evaluate for the presence of urine eosinophils. The specificity and, especially, the sensitivity of eosinophiluria, are limited, however. One meta-analysis on the operating characteristics of eosinophiluria found a sensitivity for AIN of 67% and a specificity of 85%.¹¹⁴ A recent letter on this issue, based on 534 urine eosinophil tests, found a sensitivity of 25%.¹¹⁵ Eosinophiluria is not a finding specific to AIN. It can also be seen with atheroembolic disease, glomerulonephritis, and urinary tract infections.¹¹⁴

Because the absence of "classic" features like pyuria and eosinophilia cannot rule out AIN, this entity must remain on the differential diagnosis if no other more likely explanation for ARF has been found. Especially keep it in mind if a possible AIN-associated medication is still being prescribed.

A renal gallium scan may help diagnose AIN. The largest series, involving 108 patients who underwent renal gallium scans, found that all 11 patients with biopsy-proven AIN had positive gallium scans. Although sensitive, the scan was non-specific. Patients with glomerulonephritis, pyelonephritis, minimal change disease, and Henoch-Schonlein purpura also had positive scans.¹¹⁶ Another series of 12 patients with biopsy-proven AIN found that gallium scanning was positive in only 7 of the 12 patients.¹¹⁷ Thus the role of the gallium scan in diagnosing AIN is unclear.

Noninvasive tests are limited in their ability to establish a diagnosis of AIN. The diagnostic gold-standard test for AIN is renal biopsy. The indications for renal biopsy in AIN depend on a patient's response to withdrawing the purported culprit medication and to corticosteroids.

The management of AIN hinges on promptly discontinuing the suspected culprit medication. If the time

course and medication list point to a specific causative medication, then it should be stopped. If it is not clear what the offending agent is, then consider stopping any medication that could cause AIN. If the renal function does not improve within 3 days, then start corticosteroid treatment. The variable benefits of steroids on AIN have been evaluated mainly in retrospective series.^{107,118} Given the lack of evidence, a regimen of prednisone 1 mg/kg/day for 2 to 4 weeks, with a gradual taper, is reasonable.^{107,114} Perform a renal biopsy to confirm the diagnosis any time a patient with suspected AIN is going to be treated with steroids.^{107,114} If a renal biopsy cannot be promptly or safely performed and if the diagnosis seems clear, some clinicians will initiate steroids and assess the response before obtaining a renal biopsy.

In summary, AIN is an underappreciated cause of ARF in the inpatient setting. The classic features of ARF—fever, rash, arthralgias, and eosinophilia/eosinophiluria—uncommonly occur together. Medications usually cause AIN. Renal biopsy is the diagnostic gold standard. None of the noninvasive tests are particularly sensitive or specific. The cornerstone of AIN management is to discontinue the offending agent. Consider steroids if the renal function has not improved 3 days after withdrawing the medication. Before starting steroids, consider a renal biopsy.