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How to prevent, recognize, and treat drug-induced nephrotoxicity

ABSTRACT

Many drugs can injure the kidneys, but they cause renal injury via only a few common mechanisms. Many patients who develop renal injury after drug exposure have identifiable risk factors that could be modified or that should preclude the use of these drugs in the first place.

KEY POINTS

Pretreatment hydration can reduce the nephrotoxic potential of many drugs.

Renal injury can present as acute renal failure, nephrotic syndrome, renal tubular dysfunction, or chronic renal failure.

Early diagnosis is critical; therefore, physicians must be aware of the nephrotoxic potential of the medications they prescribe and the risk status of their patients. One must anticipate the problem and exclude drugs as possible causes of renal disease when no other obvious cause can be found.

MANY DRUGS have nephrotoxic potential, and some of them can cause more than one pattern of injury.[1,2] How, then, can one avoid nephrotoxicity?

In this review, we discuss the common nephrotoxic renal syndromes, the mechanisms of nephrotoxicity of specific commonly used drugs, the associated risk factors for renal injury, and strategies for preventing renal injury.

GENERAL PRINCIPLES

Be vigilant. Adverse renal effects of drugs are largely silent in the early stages, and only clinical vigilance can ensure early diagnosis. Monitor renal function closely when introducing any drug to a patient, especially drugs known to be nephrotoxic.

Identify patients at risk. Clinical risk factors for nephrotoxicity have been identified for some drugs. Approach the use of any potentially nephrotoxic drugs with caution in patients at high risk, and analyze the risks and benefits. Polypharmacy increases the risk.

Take precautions. Recommended measures to prevent or attenuate the toxicity of some common drugs are outlined in **TABLE 1**.

Manage the renal failure, as needed, by replacing fluid volume, starting dialysis, adjusting drug doses, trying steroids in cases of acute interstitial nephritis, and avoiding repeat exposure.

When in doubt about the cause of renal failure, hold all potentially offending drugs.

WHY THE KIDNEY IS VULNERABLE

Since the kidney excretes many drugs, it is routinely exposed to high concentrations of these drugs or their metabolites or both.

Prophylaxis of drug-induced renal failure

Amphotericin B
  Adjust dosage
  Hydrate with normal saline infusion
  Use liposomal formulation

Aminoglycosides
  Follow levels
  Correct potassium levels
  Give once-daily doses
  Adjust dosage for renal function
  Avoid use if possible in high-risk patients
  Possibly give calcium channel blockers

Intravenous contrast
  Hydrate with normal saline infusion
  Possibly give acetylcysteine

Cisplatin
  Hydrate with normal saline
  Possibly give thiosulfate

ACE inhibitors
  Avoid in bilateral renal artery stenosis
  Use with caution in hypovolemia

Acyclovir
  Avoid bolus doses
  Give intravenous fluids
  Adjust dose for renal function

Lithium
  Monitor levels
  Amiloride may prevent nephrogenic
    diabetes insipidus

Interleukin-2
  Intravenous saline, albumin infusion

Cyclosporine
  Follow levels
  Avoid drugs that raise levels
    (erythromycin, verapamil, ketoconazole)

Indinavir
  Hydrate
  Establish high urine flow

Furthermore, the kidney has several features that allow nephrotoxins to accumulate.[1] It is highly vascular, receiving about 25% of the resting cardiac output. The proximal renal tubule presents a large area for nephrotoxin binding and transport into the renal epithelium. Reabsorption of the glomerular filtrate progressively increases intraluminal nephrotoxin concentrations, while specific transport pathways in the kidney may engender site-specific toxicity.

■ **FOUR DRUG-RELATED RENAL SYNDROMES**

Drugs can cause four major renal syndromes:
• Acute renal failure
• Nephrotic syndrome
• Renal tubular dysfunction with renal potassium wasting and acidosis (not discussed in this review)
• Chronic renal failure.

■ **ACUTE RENAL FAILURE**

Acute renal failure is a rapid decrease in renal function associated with alterations in urine volume, azotemia, and derangement of biochemical homeostasis. An increase of creatinine by more than 0.5 mg/dL above a known baseline or a value higher than 1.5 mg/dL is generally considered significant. In severity, it can range from asymptomatic azotemia to severe acute renal failure that requires dialysis.

Drugs can cause acute renal failure by three mechanisms:
• Prerenal
• Intrinsic
• Obstructive.

Prerenal acute renal failure
Some drugs can cause acute renal failure by reducing the volume or pressure or both of blood delivered to the kidney; the resulting renal failure is therefore termed "prerenal."

Drugs implicated include diuretics, high-osmolar radiocontrast media,[3–5] the immunosuppressive drugs cyclosporine and tacrolimus, nonsteroidal anti-inflammatory drugs (NSAIDs), interleukin-2, and angiotensin-converting enzyme (ACE) inhibitors (**TABLE 2**).

Patients at risk are those who already have compromised renal blood flow such as with bilateral renal artery stenosis, or with decreased effective circulatory volume as with cirrhosis, nephrotic syndrome, or congestive heart failure.

Urinary findings. Because the kidneys are "good" but their blood supply is low, urine volume and sodium excretion are low while osmolality is high. The urine sediment is usually without casts, red blood cells, white blood

Acute renal failure can be asymptomatic or require dialysis

TABLE 2

Drug-induced toxic renal syndromes

DRUGS	PRERENAL	ACUTE RENAL FAILURE — INTRINSIC — ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	TTP-HUS*	OBSTRUCTIVE	NEPHROTIC SYNDROME	RENAL TUBULAR DYSFUNCTION	CHRONIC RENAL FAILURE
ACE inhibitors*	●							
Acyclovir			●		●			
Aminoglycosides		●					●	
Amphotericin B	●	●					●	
Analgesic abuse								●
Cephalosporins			●					
Chinese herbs							●	●
Cisplatin		●					●	
Ciprofloxacin			●					
Clopidogrel				●				
Cocaine		●	●	●				
COX-2 inhibitors*	●							
Cyclosporine	●		●					●
Diuretics	●		●					
Foscarnet		●			●		●	
Gold			●			●		
Ifosfamide							●	●
Immunoglobulin		●					●	
Indinavir			●	●	●			
Interferon	●							
Interleukin-2	●					●		
Lithium		●	●	●		●		●
Mannitol		●						
Mesalamine			●					
Mitomycin				●				
Nitrosureas								●
NSAIDs*	●		●			●		●
Penicillamine			●			●		
Penicillins			●					
Pentamidine		●					●	
Quinine				●				
Rifampin			●					
Sucrose		●						
Streptozocin		●					●	
Sulfonamides			●					
Tacrolimus	●			●				
Ticlopidine				●				
Triamterene			●		●			
Valproic acid			●					

*ACE—angiotensin-converting enzyme
 COX—cyclo-oxygenase
 NSAID—nonsteroidal anti-inflammatory drug
 TTP-HUS—thrombotic thrombocytopenic purpura-hemolytic uremic syndrome

cells, or protein.

Treatment. Stopping the offending drug usually resolves prerenal acute renal failure.

Three types of intrinsic acute renal failure

Drug-induced intrinsic acute renal failure falls into three types:
- Acute tubular necrosis
- Acute interstitial nephritis
- Thrombotic microangiopathy.

Drug-induced acute tubular necrosis

Drugs implicated. Most of the drugs that can cause acute tubular necrosis are excreted by the kidney; these include aminoglycoside antibiotics,[6] amphotericin B, cisplatin (causing renal failure in up to 25% of patients after a single dose[7]), radiocontrast agents (accounting for up to 20% of cases of hospital-acquired renal failure according to some studies[8,9]), pentamidine, cocaine, and intravenous immunoglobulins (**TABLE 2**).[10]

Acute tubular necrosis can also be induced by statin drugs given in combination with immunosuppressive agents such as cyclosporine; clinical features of rhabdomyolysis such as myalgias, elevated creatine kinase levels, and myoglobinuria may be seen. Similarly, the combination of cisplatin and aminoglycosides may be more nephrotoxic than either agent alone.

Mechanisms of injury are multiple but may overlap, including direct tubular toxicity, deranged cellular energy production, free radical injury, heme tubular toxicity, abnormal phospholipid metabolism, and intracellular calcium toxicity.[2,3] Osmolar changes in the kidney with vacuolization injury and acute tubular necrosis have been observed with intravenous immunoglobulin,[10] mannitol, and polyethylene glycol, which is a carrier in drugs such as lorazepam.[11] For most drugs that cause acute tubular necrosis, the target is predominantly either the early or late segments of the proximal tubule, though other segments may suffer variable injury. Perhaps the most critical determinant of nephrotoxicity is the extent of drug or toxin uptake within cellular targets in the kidney.[2]

Urinary findings. The onset of injury may not be readily detected because urine volume may be normal at first, but if the offending drug is continued, oliguria may ensue. Urine microscopy shows dark granular casts and renal epithelial cell casts, while the fractional excretion of sodium ([urine sodium / plasma sodium] / [urine creatinine / serum creatinine]) is often more than 2% to 3% (normal value < 1%).

Prevention. Nephrotoxicity from cisplatin can be reduced, though incompletely, by giving intravenous saline—about 150 to 250 mL/hour before, during, and after chemotherapy.

Acute allergic interstitial nephritis

Acute interstitial nephritis presents with systemic manifestations of a hypersensitivity reaction such as fever, rash, and arthralgias. The onset after drug exposure ranges from 3 to 5 days with a second exposure, to as long as several weeks with a first exposure. However, the latency period may be as short as 1 day with rifampin, or as long as 18 months with an NSAID.[12,13]

Drugs implicated include penicillins, cephalosporins, cocaine, sulfonamides, NSAIDs (especially fenoprofen, but so far not cyclo-oxygenase [COX-2] inhibitors), diuretics, lithium, ranitidine, omeprazole, captopril, lithium, phenytoin, valproic acid, amphotericin B, streptokinase, 5-aminosalicylates, allopurinol, rifampin, and some Chinese herbs.

Of note: some cases of acute interstitial nephritis are caused by systemic infections or connective tissue disease.

Urinary findings include white blood cells, red blood cells, and white cell casts. The fractional excretion of sodium is often above 1%, due to tubular damage, though lower values may be seen if there is associated volume depletion.[13] Protein excretion is mild in most cases, although some elderly patients and those with NSAID-induced acute interstitial nephritis may have proteinuria in the nephrotic range (> 3 g/24 hours). It is presumed that the glomerular permeability (podocyte) dysfunction in this case is mediated by cytokines released by infiltrating T cells.

Eosinophilia or eosinophiluria or both are present in more than 75% of cases, except in cases due to NSAIDs, in which fever, rash, and eosinophilia are typically absent.[13] Thus, the absence of eosinophilia does not exclude

In acute tubular necrosis, urine volume may be normal at first

the diagnosis. Hansel stain may increase the ability to demonstrate eosinophiluria.[14]

Some patients may have signs of tubulointerstitial damage such as those with Fanconi syndrome (tubular proteinuria, glucosuria, bicarbonaturia, phosphaturia, and aminoaciduria) and renal tubular acidosis.

Diagnosis. Although the clinical picture is highly suggestive, the diagnosis can be confirmed only by kidney biopsy, which is indicated if the diagnosis is uncertain or if the renal failure progresses or persists in spite of stopping the offending drug. The major histologic findings are interstitial edema and variable cellular infiltration by eosinophils, plasma cells, T lymphocytes, monocytes, and neutrophils. In rare cases, granulomas may be seen on kidney biopsy; patients with granulomas may also present with uveitis.

Treatment. In most cases, acute interstitial nephritis is reversible when the offending agent is stopped. Renal function typically begins to recover within 7 days of stopping the drug, and the serum creatinine concentration eventually returns to baseline values.

If renal failure persists, steroid therapy is indicated, although the reports that suggest that steroid therapy is beneficial are not from randomized studies.[15] Renal consultation is needed in this situation. Oral prednisone 1 to 2 mg/kg/day should be given for 4 to 6 weeks. If renal function does not recover after 4 to 6 weeks of steroids, immunosuppressive agents such as cyclophosphamide can be tried, though there are no randomized trial data to support their use in this situation.

Predictors of irreversible injury include use of the offending drug for more than 1 month, diffuse rather than patchy infiltrates, persistent acute renal failure, increased number of interstitial granulomas, and delayed response to steroids.

Thrombotic microangiopathy

Thrombotic microangiopathy can cause severe acute renal failure. In general, the pathologic hallmark of thrombotic microangiopathy is hyaline thrombi in the microvasculature of many organs. Changes in the kidney include afferent arteriolar and glomerular thrombosis and thickening of the glomerular capillary wall on electron microscopy due to the deposition of fibrin-like materials.

Drugs implicated include cyclosporine, tacrolimus,[16,17] chemotherapeutic agents (eg, mitomycin C, bleomycin, cisplatin),[18] ticlopidine, clopidogrel,[19] estrogen-containing oral contraceptives, quinine, and cocaine.[20] The incidence of thrombotic microangiopathy is higher with the combination of cisplatin and bleomycin than with cisplatin alone.[18]

Clinical manifestations. Thrombotic microangiopathy may manifest with fever, hemolytic anemia, thrombocytopenia, renal dysfunction, and central nervous system disease—the full pentad of symptoms of thrombotic thrombocytopenic purpura (TTP) most frequently seen in adults. However, not all patients present with the full pentad, and physicians should consider this possibility in any patient who develops Coombs-negative hemolytic anemia, thrombocytopenia, and renal failure after exposure to drugs.

In some patients, renal failure predominates in association with anemia and thrombocytopenia without central nervous system findings: the so-called hemolytic uremic syndrome (HUS). It is thought that in HUS, the microangiopathy is more localized. Mitomycin C is the drug most commonly associated with drug-induced HUS, which occurs in 2% to 10% of treated patients.[21] In mitomycin C-induced HUS, hypertension and pulmonary edema are common, but fever and neurologic abnormalities are not seen. Mitomycin C-associated HUS typically begins 1 to 2 months after the most recent dose, but a delayed response may also occur in patients who have received doses lower than 30 to 50 mg/m^2.[21]

No study has addressed the overall proportion of patients with the full syndrome of TTP vs HUS in drug-induced cases.

Although the pathologic findings are similar in drug-induced TTP and HUS, the pathogenesis, clinical course, and prognosis for each are different. It is believed that drug-induced endothelial damage or dysfunction activates platelets and leads to platelet aggregation. On the other hand, the antiplatelet agents ticlopidine and clopidogrel cause TTP-HUS through production of autoantibodies to the metalloproteinase that cleaves von Willebrand factor (vWF).[19] The decreased

Eosinophils are typically absent in NSAID-induced acute interstitial nephritis

enzymatic activity of vWF metalloproteinase can then lead to deficiency of high-molecular-weight normal vWF and accumulation of unusually large vWF (ULvWF). These ULvWF multimers can attach to activated platelets and promote platelet aggregation.

Urinary and blood findings. Urinalysis shows microscopic hematuria, subnephrotic proteinuria, hyaline, and few granular casts.

The reticulocyte count is elevated, haptoglobin levels are low, schistocytes are present in the peripheral blood smear, and the lactate dehydrogenase level is high.

Treatment. The most important first step in treating drug-induced TTP-HUS is to stop the offending drug. The role of plasma exchange therapy is controversial, although it has been shown to improve renal function in HUS associated with cyclosporine.[17] Some cases of TTP resolve if the patient is switched from cyclosporine to tacrolimus, though some patients also develop this reaction to tacrolimus.[17] Renal function often does not recover completely in drug-induced TTP-HUS due to hemolysis, though neurologic findings may resolve with stopping the offending drug with or without plasmapheresis. Overall mortality is high, though many patients may survive on chronic dialysis. Steroids are of no proven benefit in this syndrome.

Obstructive acute renal failure

Drug-associated obstruction of urine outflow can occur at several sites: within the tubules or the ureters (due to crystal formation), and outside the ureters (due to retroperitoneal fibrosis caused by agents such as methysergide).

Drugs implicated in crystal formation include acyclovir, sulfonamides, methotrexate, indinavir, triamterene, and vitamin C in large doses (due to oxalate crystals).[22–30] So far no cases of renal failure due to famciclovir have been reported, but dose reduction is advised in renal insufficiency. Guaifenesin and ephedrine can also cause stones to form in kidneys.[30]

Risk factors for crystal-induced acute renal failure include severe volume depletion (chronic diarrheal states, diuretic use, congestive heart failure, capillary leak syndromes), underlying renal insufficiency, bolus drug administration, and metabolic disorders such as metabolic acidosis or alkalosis. In addition,
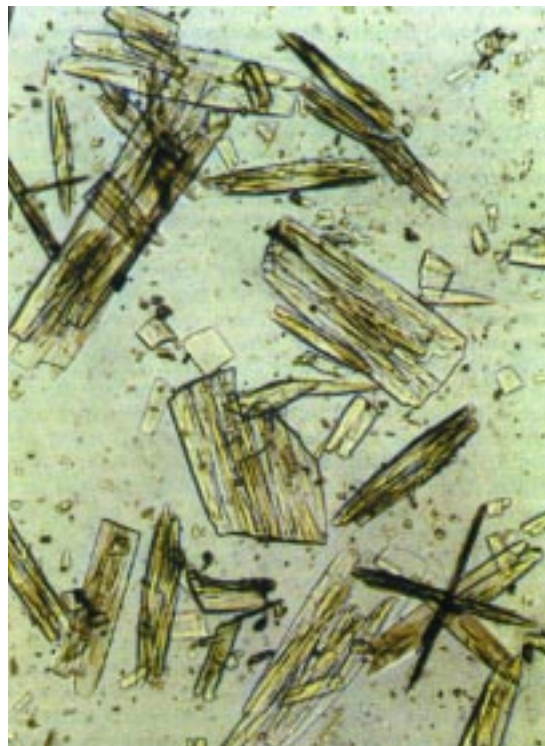
Indinavir crystals in urine

FIGURE 1. Rectangular indinavir crystals in urinary sediment on light microscopy.

FROM GAGNON RF, TSOUKAS CM, WALTERS AK. LIGHT MICROSCOPY OF INDINAVIR URINARY CRYSTALS [LETTER]. ANN INTERN MED 1998; 128:321.

patients with human immunodeficiency virus (HIV) infection may be at increased risk because they often have some of the above risk factors and often take multiple drugs. The solubility of some of these crystals is pH-dependent.[26,27] Acyclovir is mostly nephrotoxic at high doses (> 500 mg/m^2), and intravenous dosing appears to induce more nephrotoxicity, though acute renal failure has also been reported with oral acyclovir.[28,29]

Urinary findings. The urine sediment may contain red cells, white cells, and crystals. Acyclovir crystals are needle-shaped, while those of indinavir may appear as rectangular plates or as rosettes (**FIGURE 1**).[28] Triamterene crystals are spherical and birefringent on polarizing microscopy.

Treatment. Renal failure may be reversible when the drug is stopped, volume is replaced (with intravenous saline), and the urine alkalinized.

Prevention. Urine alkalinization can help

Urine alkalinization may prevent renal failure from sulfonamides, methotrexate, or triamterene

prevent crystalluria and acute renal failure in patients given sulfonamides, methotrexate, or triamterene.

■ CHRONIC RENAL INSUFFICIENCY

Chronic renal insufficiency caused by drugs generally presents as tubulointerstitial disease. This form of injury may be caused by chronic analgesic abuse, lithium, cisplatin, cyclosporine, nitrosourea, and Chinese herbs.

Of note: For some drugs (eg, cyclosporine, lithium), the mechanism of acute renal toxicity may be different from that of chronic renal injury.

Patients may present with slowly progressive elevation of creatinine, with or without renal tubular dysfunction syndromes. These syndromes may manifest as renal tubular acidosis, renal potassium wasting, concentration defects, and tubular proteinuria. These syndromes may also occur without renal failure.

In some cases, the renal damage is reversible when the offending drug is stopped, but in other cases it is irreversible. Frequently reversible forms include those due to 5-aminosalicylic acid,[31] mesalamine, and ifosfamide, while lithium and cyclosporine cause irreversible injury.[32]

■ NEPHROTIC SYNDROME

The nephrotic syndrome is due to glomerular dysfunction and marked by heavy proteinuria.

Drugs implicated include gold, NSAIDs, penicillamine, interferon, and captopril.

Manifestations. Patients may present with edema, proteinuria, and hypoalbuminemia. Membranous nephropathy is the most common form reported, though minimal-change nephropathy has also been seen with NSAIDs, as discussed below.

Treatment. Stopping the drug often leads to resolution of nephrotic syndrome, but irreversible injury has also been described.

■ NEPHROTOXICITY FROM ANALGESICS

The American public consumes large amounts of prescription and over-the-counter analgesics, which belong to three main classes: aspirin and other NSAIDs, inhibitors of cyclo-oxygenase-2 (COX-2 inhibitors), and acetaminophen and other nonnarcotic analgesics. Adverse renal effects can result either acutely or, in those who habitually take these agents, chronically (analgesic abuse nephropathy).

NSAID-induced renal syndromes

The recognized adverse renal effects of nonselective NSAIDs include acute renal failure, nephrotic syndrome, hypertension, hyperkalemia, and papillary necrosis.[33–35]

In a study from a hospital that serves indigent patients, acute renal failure occurred in 18% of patients receiving ibuprofen.[35] In a study of an elderly population (mean age 87 years), acute renal failure occurred in 13% of patients given NSAIDs.[36]

Though the risk of acute renal failure appears small in younger, healthy patients, the number of people who may develop acute renal failure is large since these drugs are widely used.

NSAID-induced prerenal acute renal failure

The most common type of NSAID-induced acute renal failure results from decreased synthesis of renal vasodilator prostaglandins, which can lead to reduced renal blood flow and reduced glomerular filtration. Normally, renal blood flow is not critically dependent on these eicosanoids, but patients become susceptible to acute renal failure if their renal blood flow is already reduced.

The reduction in sodium excretion that follows the reduction in renal prostaglandin synthesis can lead to elevation of systemic blood pressure, especially in elderly patients. In one study, ibuprofen, piroxicam, and sulindac all reduced urinary sodium in both young and elderly patients independent of their renal function.[37] However, ibuprofen use was associated with elevation of blood pressure in patients with renal insufficiency.

The recognized risk factors for NSAID-induced prerenal acute renal failure are impaired renal function, hypovolemia, congestive heart failure, cirrhosis, sodium and water depletion, anesthesia, advanced age, renal transplantation, and concomitant use of other drugs such as ACE inhibitors.

Even brief use of NSAIDs (eg, ketorolac), such as for postoperative pain or in the emer-

NSAID-induced renal failure can be acute or chronic

gency room, can cause acute renal failure.[38]

NSAID-induced
acute allergic interstitial nephritis

This complication appears to be an idiosyncratic reaction, particularly to the propionic acid derivatives (ibuprofen, naproxen, and fenoprofen), and is associated with nephrotic syndrome in about 90% of cases.[39–41]

In contrast to allergic interstitial nephritis induced by other drugs, acute interstitial nephritis associated with the use of NSAIDs tends not to present with systemic findings of hypersensitivity such as rash, eosinophilia, or eosinophiluria. Proteinuria may often be in the nephrotic range. In some cases, the renal interstitium shows a predominant lymphocytic infiltration rather than eosinophils. The release of mediators such as leukotrienes by these interstitial T lymphocytes is thought to cause the podocyte injury that leads to nephrotic syndrome.

NSAIDs may also alter potassium, sodium, and water homeostasis, causing hyperkalemia, hypertension, and hyponatremia.[41]

Renal failure from COX-2 inhibitors

It was initially hoped that the COX-2 inhibitors such as celecoxib and rofecoxib would be less nephrotoxic than regular NSAIDs. However, Perazella et al[42] recently reported the occurrence of renal failure after therapy with COX-2 inhibitors. The patients had some of the risk factors for NSAID-induced acute renal failure listed above. As more of these agents are used with an increasingly aging population, more cases are likely to be reported.

Acetaminophen-induced
acute tubular necrosis

It is commonly assumed that acetaminophen is less likely to cause acute renal failure than other analgesics because it lacks significant peripheral prostaglandin inhibition.[43] However, in some settings, renal failure may follow its use.

Acetaminophen is the most commonly reported cause of drug overdose in the United States.[44] Acute renal failure occurs in less than 2% of all acetaminophen poisonings, and 10% of severe cases of poisoning. Renal toxicity may also occur with regular therapeutic use of this drug in patients who are glutathione-

depleted (due to chronic alcoholism, starvation, or fasting), or in patients who take drugs that induce the cytochrome P-450 system, such as anticonvulsants.[43–45]

Acute renal failure due to acetaminophen manifests as acute tubular necrosis and may occur alone or in association with hepatic necrosis. The azotemia of acetaminophen toxicity is typically reversible, although it may worsen over 7 to 10 days before renal function recovers completely.

To recognize acetaminophen nephrotoxicity, one must take a thorough drug history (including use of over-the-counter agents), know the risk factors that reduce the margin of safety at therapeutic concentrations, and consider acetaminophen in the differential diagnosis of patients with combined hepatic and renal dysfunction. The controversial association between acetaminophen use and chronic analgesic abuse nephropathy is discussed below.

Analgesic nephropathy

The incidence of analgesic nephropathy varies by country, perhaps because different over-the-counter drugs are available in different countries. In Australia,[46] about 20% of patients starting dialysis had used analgesics daily until the sale of over-the-counter combination analgesics was stopped in 1980. In the United States, phenacetin, which was strongly associated with analgesic nephropathy, was withdrawn in 1983, while ibuprofen was introduced in 1984.

Risk factors. The relative risk of analgesic nephropathy (with end-stage renal disease) with use of several common analgesics based on studies between 1969 and 1992 are as follows[40]:
- Phenacetin 2.66–19.05
- Aspirin 1.0–2.5
- Acetaminophen 2.1–4.06
- NSAIDs 1.0.

Patients who abuse analgesics often have a history of some kind of chronic pain such as headache, backache, or arthritis. The condition is five times more common in women than men and has a peak incidence around 50 years of age.

Some studies reported an increased incidence of analgesic (acetaminophen) abuse in patients with other chronic nephropathies including hypertensive nephrosclerosis and

Suspect acetaminophen in combined renal and hepatic dysfunction

diabetic nephropathy.

Combinations of analgesics, especially those that include aspirin, are more nephrotoxic than single agents. Most studies agree that dehydration increases the nephrotoxicity of these agents. The contribution of caffeine, which is often present in analgesic combinations, is unclear, but its main role may be that it increases caffeine withdrawal headaches, which leads to increased use of analgesics.

Pathogenesis. The concepts of the pathogenesis of this condition are based on animal studies. Classically, the renal lesions show chronic interstitial nephritis and papillary necrosis. Phenacetin is metabolized to acetaminophen, the metabolism of which involves the cytochrome P-450 enzyme system located in the renal cortex and outer medulla, as well as prostaglandin endoperoxidase synthases in the renal papilla. Aspirin potentiates this toxicity by depletion of reduced glutathione needed for their detoxification. Papillary microangiopathy of obscure origin has also been implicated.

Presentation. The clinical expression of analgesic nephropathy is usually one of slowly progressive decline in renal function with acute episodes of worsening related to passage of papillae and subsequent urinary obstruction.

Diagnosis. The key to diagnosing analgesic nephropathy includes an accurate and detailed history of chronic pain or analgesic abuse. Patients may often deny using analgesics, though they might concede that they have chronic back pain or headache. The amount and the type of analgesic consumed is a critical element in making this diagnosis.

Laboratory findings include sterile pyuria and anemia (which may be out of proportion to the degree of azotemia in cases due to phenacetin), and renal sonography may show reduced kidney size with or without calcifications.

A recent European study[47] suggests that computed tomography (CT) without contrast may be useful in diagnosing analgesic nephropathy, with a sensitivity and specificity of 90% in patients with end-stage renal disease; and 87% and 100%, respectively, in patients with analgesic abuse and chronic renal failure.

Treatment. Successful therapy of analgesic abuse nephropathy requires stopping habitual analgesic abuse. Acetaminophen taken alone is probably safe for episodic use. If patients have chronic pain, tramadol (Ultram), a centrally acting analgesic with weak opioid activity, can be tried, as it has not yet been found to be nephrotoxic.[40]

In some patients, renal failure continues to progress even after stopping analgesic abuse. These patients should be referred to a nephrologist for dialysis or transplantation. Surveillance is also needed to detect urothelial cancers, which occur in high frequency in some of these patients.

■ AMINOGLYCOSIDE-INDUCED RENAL INJURY

Aminoglycoside antibiotics, used in severe gram-negative sepsis, cause nephrotoxicity in 10% to 20% of therapeutic courses.[48] The mechanism is proximal tubular injury leading to cell necrosis. Binding of these drugs to the proximal tubule depends on amino groups in each aminoglycoside agent.

Risk factors include a long duration of treatment, high trough concentrations (> 2 mg/L), repeated courses of aminoglycoside therapy a few months apart, advanced age, malnutrition, volume depletion, liver disease, preexisting renal disease, potassium and magnesium depletion, and concomitant exposure to other nephrotoxic drugs such as amphotericin B, cyclosporine, or diuretics.

Gentamicin is the most nephrotoxic of the aminoglycosides, followed in descending order by tobramycin, amikacin, netilmicin, and streptomycin. However, this ranking is not absolute, and all aminoglycosides can be nephrotoxic.[49] Careful monitoring of serum drug levels is helpful to avoid nephrotoxicity, although aminoglycoside nephrotoxicity can occur even with proper monitoring.

Presentation. Clinically, aminoglycoside-related renal toxicity presents primarily as nonoliguric acute tubular necrosis with granular casts in urinary sediments, and sometimes with Fanconi syndrome. The serum creatinine concentration characteristically rises 5 to 10 days after starting therapy, but this may occur earlier in the presence of sepsis, hypotension, or other nephrotoxic exposure.

With ACE inhibitors, a mild increase in creatinine may be an acceptable trade-off

Treatment. The initial therapy for aminoglycoside-related acute tubular necrosis is basically supportive, consisting of stopping the causative drug and other nephrotoxic agents, maintaining fluid and electrolyte balance, and controlling sepsis. Renal dysfunction is usually reversible after stopping aminoglycoside therapy, though hemodialysis may be required in some cases.

Prevention. Consolidated, high-dose aminoglycoside therapy (an infusion of 5–7 mg/kg/24 hours for 2–3 weeks or more depending on the site of infection) has recently gained favor, as this regimen seems to be as effective as the traditional regimen but less nephrotoxic.[49–51] Two unique pharmacodynamic properties—namely, postantibiotic effect (persistent bactericidal effect after removal of the drug) and concentration-dependent killing (the higher the drug level, the more rapid and efficient killing of the pathogens)—provide the basis for this dosing regimen.

Why this regimen is less nephrotoxic is not completely clear, but it is believed to be due to less accumulation of aminoglycosides in the renal tissue. Since the uptake of aminoglycosides at the proximal tubule is energy-dependent and saturable, a single large dose decreases the renal reabsorption substantially and is less nephrotoxic compared with the traditional divided dosing.

Critically ill patients are not ideal candidates for aminoglycoside therapy, though the clinician may not have a choice in patients with life-threatening sepsis.

■ RENAL FAILURE WITH ACE INHIBITORS

ACE inhibitors slow progressive renal injury, antagonize angiotensin II, and affect tissue remodelling in response to injury. Thus, they are particularly useful for congestive heart failure, diabetic nephropathy, sclerodermal renal crisis, and proteinuric nephropathies in general.

However, ACE inhibitors are a double-edged sword, as they can also cause renal failure under peculiar circumstances. Soon after ACE inhibitors were introduced, functional acute renal failure was reported in patients with renal artery stenosis receiving these drugs.[52,53] In some patients with renal artery stenosis, glomerular filtration may be critically dependent on the efferent arteriolar effects of angiotensin II. In these patients, acute renal failure results from loss of postglomerular efferent arteriolar vascular tone and is reversible if the drug is withdrawn; but in one reported case irreversible renal failure supervened.[54]

In some cases a mild increase in serum creatinine (< 30%) may be an acceptable trade-off for the potential benefits of these useful drugs, and might indeed be a good predictor of long-term preservation of renal function.[55–59]

Risk factors. The pretreatment glomerular filtration rate is the single best predictor of acute renal failure resulting from the use of ACE inhibitors, and studies suggest the incidence of renal failure in patients with renovascular hypertension who use ACE inhibitors varies from 20% to 38%.[55] Risk factors for ACE inhibitor-related acute renal failure include widespread atherosclerotic disease (with bilateral disease or unilateral disease in a solitary kidney), hypovolemia, concomitant diuretic or NSAID use, congestive heart failure, and renal insufficiency with serum creatinine concentrations higher than 1.6 mg/dL.

Prevention. Central to avoiding nephrotoxic effects of ACE inhibitors are recognition of risk factors, vigilant monitoring, and volume management. Some authorities recommend a "diuretic holiday" for several days before starting an ACE inhibitor. Another strategy in patients at high risk is to start with low doses of captopril (which is short-acting) and gradually titrate the dose upward in response to blood pressure and renal function. If renal function remains stable, one can switch to a long-acting ACE inhibitor.

■ RENAL FAILURE WITH ANGIOTENSIN II RECEPTOR BLOCKERS

Angiotensin II receptor blockers (ARBs) reduce blood pressure to a degree comparable to that achieved with ACE inhibitors, and like ACE inhibitors, they reduce proteinuria to a degree greater than would be expected from blood pressure reduction alone.

Early clinical experience with ARBs in patients with renal disease suggests that they might cause a lesser incidence of functional renal failure than do ACE inhibitors.[60] One recent report suggests that losartan, a selective

Some recommend a 'diuretic holiday' before starting an ACE inhibitor

ARB, is safe and effective in controlling hypertension in patients with renal insufficiency, but produced renal hemodynamic changes similar to those of an ACE inhibitor. In an anecdotal report of a crossover trial in two patients with chronic renal failure, a switch from ARB to an ACE inhibitor in one patient led to deterioration of renal function, which reversed when the ARB was restarted.[60]

One situation in which an ARB or an ACE inhibitor can be used in the face of acute renal failure is in sclerodermal renal crisis.[61] In a case reported recently, blood pressure was controlled successfully and renal failure was reversed by losartan.

An unresolved question is whether the combination of an ACE inhibitor and an ARB is better than either agent alone. In a European study,[62] the combination of candesartan 16 mg daily and lisinopril 20 mg daily was well tolerated and controlled blood pressure better than either agent alone. However, the decrease in creatinine clearance after 24 weeks was most significant in the patients receiving lisinopril alone, followed by the group that received both lisinopril and candesartan. Renal function was unchanged in the patients who received candesartan alone over the study period.

Until more studies are completed, it would be prudent to monitor renal function closely in patients started on ARBs and avoid volume depletion and NSAIDs as described with ACE inhibitors.

■ AMPHOTERICIN B NEPHROTOXICITY

Amphotericin B is still the gold standard therapy for life-threatening systemic fungal sepsis, but many patients develop acute renal failure associated with urinary magnesium and potassium wasting, hypokalemia, renal tubular acidosis, and polyuria due to nephrogenic diabetes insipidus.[63–66] The nephrotoxicity is related to direct tubular damage by deoxycholate—used as a solubilizing agent for amphotericin B—as well as renal vasoconstriction. The renal toxicity is reversible on cessation of therapy.

Liposomal amphotericin B is as effective as conventional amphotericin B in empirical therapy of fungal infections in febrile neu-

tropenic patients, and it is associated with less infusion-related toxicity and less nephrotoxicity.[66] However, it is very expensive, limiting its widespread use.

Risk factors for nephrotoxicity with amphotericin B include a high dose (toxicity is rare at < 0.5 mg/kg/day or a cumulative dose < 600 mg). Volume replacement with normal saline has been shown to prevent nephrotoxic acute renal failure, though it has no effect on the electrolyte imbalance.[64]

■ NEPHROTOXICITY OF HERBAL MEDICINES

There has been a global resurgence in the use of alternative medicines. Unfortunately, many plants contain substances toxic to the kidney.[67]

For example, herbal medicine use has been suggested to cause 35% of all cases of acute renal failure in some African countries.[68–70] Furthermore, since 1993, several reports documented rapidly progressive kidney failure leading to end-stage renal disease in women who had taken diet pills that contained Chinese herbs.[71] This so-called Chinese herb nephropathy was characterized by an extensive fibrosis of the renal interstitium. The toxic agent in these herbs is thought to be aristolochic acid.[72] About 50% of patients with end-stage renal disease due to Chinese herb nephropathy also develop urothelial cancers,[73] while some have valvular heart disease.[74]

Ask your patients specifically about their use of alternative medicines if they present with unexplained renal failure: patients often do not consider alternative therapies when asked about their medications.[75]

■ COCAINE NEPHROTOXICITY

Cocaine abuse can induce several forms of renal damage,[76] including acute tubular necrosis due to rhabdomyolysis. It can also cause accelerated or malignant hypertension, renal failure, and allergic interstitial nephritis (probably mediated by additives in the "crack" formulation of cocaine).

Physicians caring for inner-city patients must be alert to the possibility that cocaine may contribute to acute renal failure in some of their patients.

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