Drug-Induced Nephrotoxicity

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Drugs are a common source of acute kidney injury. Compared with 30 years ago, the average patient today is older, has more comorbidities, and is exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function. Drugs shown to cause nephrotoxicity exert their toxic effects by one or more common pathogenic mechanisms. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of pathogenic mechanisms of renal injury, patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention. Some patient-related risk factors for drug-induced nephrotoxicity are age older than 60 years, underlying renal insufficiency (e.g., glomerular filtration rate of less than 60 mL per minute per 1.73 m^2), volume depletion, diabetes, heart failure, and sepsis. General preventive measures include using alternative non-nephrotoxic drugs whenever possible; correcting risk factors, if possible; assessing baseline renal function before initiation of therapy, followed by adjusting the dosage; monitoring renal function and vital signs during therapy; and avoiding nephrotoxic drug combinations. *(Am Fam Physician.* **2008;78(6):743-750. Copyright © 2008 American Academy of Family Physicians.)**

Drugs cause approximately 20 percent of community- and hospital-acquired episodes of acute renal failure.[1-3] Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent.[4] Compared with 30 years ago, patients today are older, have a higher incidence of diabetes and cardiovascular disease, take multiple medications, and are exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function.[5] Although renal impairment is often reversible if the offending drug is discontinued, the condition can be costly and may require multiple interventions, including hospitalization.[6] This article provides a summary of the most common mechanisms of drug-induced nephrotoxicity and prevention strategies.

Pathogenic Mechanisms

Most drugs found to cause nephrotoxicity exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy.[7-9] Knowledge of offending drugs and their particular pathogenic mechanisms of renal injury is critical to recognizing and preventing drug-induced renal impairment *(Table 1*[10-31]*)*.

ALTERED INTRAGLOMERULAR HEMODYNAMICS

In an otherwise healthy young adult, approximately 120 mL of plasma is filtered under pressure through the glomerulus per minute, which corresponds to the glomerular filtration rate (GFR). The kidney maintains or autoregulates intraglomerular pressure by modulating the afferent and efferent arterial tone to preserve GFR and urine output. For instance, in patients with volume depletion, renal perfusion depends on circulating prostaglandins to vasodilate the afferent arterioles, allowing more blood flow through the glomerulus.

At the same time, intraglomerular pressure is sustained by the action of angiotensin-II–mediated vasoconstriction of the efferent arteriole. Drugs with antiprostaglandin activity (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) or those with antiangiotensin-II activity (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) can interfere with the kidneys' ability to autoregulate glomerular pressure and decrease GFR.[10,32] Other drugs, such as calcineurin inhibitors (e.g., cyclosporine [Neoral], tacrolimus [Prograf]), cause dose-dependent vasoconstriction of the afferent arterioles, leading to renal impairment in at-risk patients.[11]

TUBULAR CELL TOXICITY

Renal tubular cells, in particular proximal tubule cells, are vulnerable to the toxic effects

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Patients at highest risk of drug-induced nephrotoxicity are those with one or more of the following: age older than 60 years, baseline renal insufficiency (e.g., GFR < 60 mL per minute per 1.73 m^2), volume depletion, multiple exposures to nephrotoxins, diabetes, heart failure, and sepsis.	C	1-3, 7, 34, 35
Assess baseline renal function using the MDRD or Cockcroft-Gault GFR estimation equation and consider a patient's renal function when prescribing a new drug.	C	7, 33, 41-43
Monitor renal function and vital signs after starting or increasing the dose of drugs associated with nephrotoxicity, especially when used chronically.	C	7, 10, 32, 48
Drug-induced renal impairment is generally reversible, provided the nephrotoxicity is recognized early and the offending medication is discontinued.	C	52

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

of drugs because their role in concentrating and reabsorbing glomerular filtrate exposes them to high levels of circulating toxins.[12] Drugs that cause tubular cell toxicity do so by impairing mitochondrial function, interfering with tubular transport, increasing oxidative stress, or forming free radicals.[8,13] Drugs associated with this pathogenic mechanism of injury include aminoglycosides, amphotericin B (Fungizone; brand not available in the United States), antiretrovirals (adefovir [Hepsera], cidofovir [Vistide], tenofovir [Viread]), cisplatin (Platinol), contrast dye, foscarnet (Foscavir), and zoledronate (Zometa).[12-14]

INFLAMMATION

Drugs can cause inflammatory changes in the glomerulus, renal tubular cells, and the surrounding interstitium, leading to fibrosis and renal scarring. Glomerulonephritis is an inflammatory condition caused primarily by immune mechanisms and is often associated with proteinuria in the nephrotic range.[12] Medications such as gold therapy, hydralazine (Apresoline; brand not available in the United States), interferon-alfa (Intron A), lithium, NSAIDs, propylthiouracil, and pamidronate (Aredia; in high doses or prolonged courses) have been reported as causative agents.[12,13,15]

Acute interstitial nephritis, which can result from an allergic response to a suspected drug, develops in an idiosyncratic, non–dose-dependent fashion.[16] Medications that cause acute interstitial nephritis are thought to bind to antigens in the kidney or

Table 1. Drugs Associated with Nephrotoxicity

Drug class/drug(s)	*Pathophysiologic mechanism of renal injury*
Analgesics	
Acetaminophen, aspirin	Chronic interstitial nephritis
Nonsteroidal anti-inflammatory drugs	Acute interstitial nephritis, altered intraglomerular hemodynamics, chronic interstitial nephritis, glomerulonephritis
Antidepressants/mood stabilizers	
Amitriptyline (Elavil*), doxepin (Zonalon), fluoxetine (Prozac)	Rhabdomyolysis
Lithium	Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines	
Diphenhydramine (Benadryl), doxylamine (Unisom)	Rhabdomyolysis
Antimicrobials	
Acyclovir (Zovirax)	Acute interstitial nephritis, crystal nephropathy
Aminoglycosides	Tubular cell toxicity
Amphotericin B (Fungizone*; deoxycholic acid formulation more so than the lipid formulation)	Tubular cell toxicity
Beta lactams (penicillins, cephalosporins)	Acute interstitial nephritis, glomerulonephritis (ampicillin, penicillin)
Foscarnet (Foscavir)	Crystal nephropathy, tubular cell toxicity
Ganciclovir (Cytovene)	Crystal nephropathy
Pentamidine (Pentam)	Tubular cell toxicity
Quinolones	Acute interstitial nephritis, crystal nephropathy (ciprofloxacin [Cipro])
Rifampin (Rifadin)	Acute interstitial nephritis
Sulfonamides	Acute interstitial nephritis, crystal nephropathy
Vancomycin (Vancocin)	Acute interstitial nephritis

(continued)

Table 1. *(continued)*

Drug class/drug(s)	*Pathophysiologic mechanism of renal injury*
Antiretrovirals	
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	Tubular cell toxicity
Indinavir (Crixivan)	Acute interstitial nephritis, crystal nephropathy
Benzodiazepines	Rhabdomyolysis
Calcineurin inhibitors	
Cyclosporine (Neoral)	Altered intraglomerular hemodynamics, chronic interstitial nephritis, thrombotic microangiopathy
Tacrolimus (Prograf)	Altered intraglomerular hemodynamics
Cardiovascular agents	
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	Altered intraglomerular hemodynamics
Clopidogrel (Plavix), ticlopidine (Ticlid)	Thrombotic microangiopathy
Statins	Rhabdomyolysis
Chemotherapeutics	
Carmustine (Gliadel), semustine (investigational)	Chronic interstitial nephritis
Cisplatin (Platinol)	Chronic interstitial nephritis, tubular cell toxicity
Interferon-alfa (Intron A)	Glomerulonephritis
Methotrexate	Crystal nephropathy
Mitomycin-C (Mutamycin)	Thrombotic microangiopathy
Contrast dye	Tubular cell toxicity
Diuretics	
Loops, thiazides	Acute interstitial nephritis
Triamterene (Dyrenium)	Crystal nephropathy
Drugs of abuse	
Cocaine, heroin, ketamine (Ketalar), methadone, methamphetamine	Rhabdomyolysis
Herbals	
Chinese herbals with aristocholic acid	Chronic interstitial nephritis
Proton pump inhibitors	
Lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix)	Acute interstitial nephritis
Others	
Allopurinol (Zyloprim)	Acute interstitial nephritis
Gold therapy	Glomerulonephritis
Haloperidol (Haldol)	Rhabdomyolysis
Pamidronate (Aredia)	Glomerulonephritis
Phenytoin (Dilantin)	Acute interstitial nephritis
Quinine (Qualaquin)	Thrombotic microangiopathy
Ranitidine (Zantac)	Acute interstitial nephritis
Zoledronate (Zometa)	Tubular cell toxicity

**—Brand not available in the United States.*

Information from references 10 through 31.

act as antigens that are then deposited into the interstitium, inducing an immune reaction.[16] However, classic symptoms of a hypersensitivity reaction (i.e., fever, rash, and eosinophilia) are not always observed.[13,16] Numerous drugs have been implicated, including allopurinol (Zyloprim); antibiotics (especially beta lactams, quinolones, rifampin [Rifadin], sulfonamides, and vancomycin [Vancocin]); antivirals (especially acyclovir [Zovirax] and indinavir [Crixivan]); diuretics (loops, thiazides); NSAIDs; phenytoin (Dilantin); proton pump inhibitors (especially omeprazole [Prilosec], pantoprazole [Protonix], and lansoprazole [Prevacid]); and ranitidine (Zantac).[13,16-19]

Chronic interstitial nephritis is less likely than acute interstitial nephritis to be drug induced; it is also insidious in onset, and signs of hypersensitivity are often lacking.[20] Drugs associated with this mechanism of nephrotoxicity include calcineurin inhibitors (e.g., cyclosporine, tacrolimus), certain chemotherapy agents, Chinese herbals containing aristocholic acid, and lithium.[11,20,21] Chronic interstitial nephritis has been reported with analgesics such as acetaminophen, aspirin, and NSAIDs when used chronically in high dosages (i.e., more than 1 gram daily for more than two years) or in patients with preexisting kidney disease.[22,23] Early recognition is important because chronic interstitial nephritis has been known to progress to end-stage renal disease.[20] Diagnosis may be difficult because most patients do not consider over-the-counter preparations to be medications and tend to underreport frequency of use.

CRYSTAL NEPHROPATHY

Renal impairment may result from the use of drugs that produce crystals that are insoluble in human urine. The crystals precipitate, usually within the distal tubular lumen, obstructing urine flow and eliciting an interstitial reaction.[13] Commonly prescribed drugs associated with production of crystals include antibiotics (e.g., ampicillin, ciprofloxacin [Cipro], sulfonamides); antivirals (e.g., acyclovir, foscarnet, ganciclovir [Cytovene]); indinavir; methotrexate; and

triamterene (Dyrenium).[12,13,24] The likelihood of crystal precipitation depends on the concentration of the drug in the urine and the urinary pH.[24] Patients most at risk of crystal nephropathy are those with volume depletion and underlying renal insufficiency.[24]

Chemotherapy for lymphoproliferative disease, leading to tumor lysis syndrome with uric acid and calcium phosphate crystal deposition, has also been associated with renal failure.[25]

RHABDOMYOLYSIS

Rhabdomyolysis is a syndrome in which skeletal muscle injury leads to lysis of the myocyte, releasing intracellular contents including myoglobin and creatine kinase into the plasma. Myoglobin induces renal injury secondary to direct toxicity, tubular obstruction, and alterations in GFR.[26] Drugs may induce rhabdomyolysis directly secondary to a toxic effect on myocyte function, or indirectly by predisposing the myocyte to injury.[26,27] Clinical manifestations of rhabdomyolysis include weakness, myalgia, and tea-colored urine.[27]

Statins are the most recognizable agents associated with rhabdomyolysis, but more than 150 medications and toxins have been implicated.[26] Rhabdomyolysis with statin monotherapy is rare, with an average reported incidence of 0.44 per 10,000 person-years of therapy.[28] Many drugs of abuse, such as cocaine, heroin, ketamine (Ketalar), methadone, and methamphetamine, have been reported to cause rhabdomyolysis.[26,27] Drugs and alcohol are causative factors in up to 81 percent of cases of rhabdomyolysis, and up to 50 percent of patients subsequently develop acute renal failure.[29]

THROMBOTIC MICROANGIOPATHY

In thrombotic microangiopathy, organ damage is caused by platelet thrombi in the microcirculation, as in thrombotic thrombocytopenic purpura.[30] Mechanisms of renal injury secondary to drug-induced thrombotic microangiopathy include an immune-mediated reaction or direct endothelial toxicity.[30] Drugs most often associated with this pathogenic mechanism of nephrotoxicity include antiplatelet agents (e.g., clopidogrel [Plavix], ticlopidine [Ticlid]), cyclosporine, mitomycin-C (Mutamycin), and quinine (Qualaquin).[30,31]

Preventing Drug-Induced Renal Impairment

Drug-induced nephrotoxicity tends to occur more frequently in certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention.[7,33] Prevention strategies should target the prescribing and monitoring of potential nephrotoxins in at-risk patients. Whenever possible, risk factors should be corrected before drugs associated with nephrotoxicity are prescribed.

Table 2. Patient-Related Risk Factors for Drug-Induced Nephrotoxicity

"Absolute" or "effective" intravascular volume depletion
Age older than 60 years
Diabetes
Exposure to multiple nephrotoxins
Heart failure
Sepsis
Underlying renal insufficiency (glomerular filtration rate < 60 mL per minute per 1.73 m^2)

Information from references 1 through 3, 7, 34, and 35.

PATIENT-RELATED RISK FACTORS

Patient-related risk factors vary somewhat depending on the offending drug. However, some risk factors are common to all nephrotoxins and include age older than 60 years, underlying renal insufficiency (e.g., GFR of less than 60 mL per minute per 1.73 m^2), intravascular volume depletion, exposure to multiple nephrotoxins, diabetes, heart failure, and sepsis *(Table 2)*.[1-3,7,34,35] There are conflicting reports about the influence of race and genetic variation, as well as whether men are at greater risk of developing acute renal failure compared with women.[34] The risk of acute renal failure increases with the presence of each additional risk factor. Patients with any of these risk factors, especially those who have more than one risk factor (e.g., a patient with diabetes and heart failure), should be closely monitored for changes in renal function when a medication is added or a dosage is increased.

Both "absolute" and "effective" intravascular volume depletion are risk factors for drug-induced renal impairment. Absolute intravascular volume depletion may occur in patients who have gastroenteritis, chronic diarrhea, aggressive diuresis, or poor oral intake.[10] Effective intravascular volume is the volume of blood perceived by baroreceptors located in the right atrium and the kidney. Decreased effective circulating blood volume results from sequestration of fluid into third-space compartments and is associated with sepsis, heart failure, ascites, or pancreatitis.[7,36]

DRUG-RELATED RISK FACTORS

Certain drugs are inherently nephrotoxic and include aminoglycosides, amphotericin B, cisplatin, contrast dye, and cyclosporine.[7,34] For others, such as those associated with chronic interstitial nephritis and crystal deposition,

Table 3. Patient-Related Risk Factors and Specific Prevention Strategies for Selected Agents

Medications	*Risk factors*	*Prevention strategies*
Drugs altering intraglomerular hemodynamics[10-12,23,32]		
ACE inhibitors, ARBs, NSAIDs	Underlying renal insufficiency; intravascular volume depletion; age older than 60 years; concomitant use of ACE inhibitors, ARBs, NSAIDs, cyclosporine (Neoral), or tacrolimus (Prograf)	Use analgesics with less prostaglandin activity (acetaminophen, aspirin, sulindac [Clinoril], nabumetone [Relafen; brand not available in the United States]) Correct volume depletion before initiation of drug, especially if used on a chronic basis Monitor renal function and vital signs following initiation or dose escalation, especially if used in at-risk patients
Cyclosporine, tacrolimus	As above, plus: excessive dose, concomitant use with other nephrotoxic drugs or drugs that inhibit cyclosporine or tacrolimus metabolism	Monitor serum drug concentrations and renal function Use lowest effective dose
Drugs associated with tubular cell toxicity[7,12,13,37,38]		
Aminoglycosides	Underlying renal insufficiency, duration of therapy > 10 days, trough concentrations > 2 mcg per mL, concomitant liver disease, hypoalbuminemia	Use extended-interval dosing Administer during active period of day Limit duration of therapy Monitor serum drug levels and renal function two to three times per week Maintain trough levels ≤ 1 mcg per mL
Amphotericin B (Fungizone; brand not available in the United States)	Underlying renal insufficiency, rapid infusion, large daily dosage, deoxycholate formulations more so than lipid formulations, prolonged duration of therapy	Saline hydration before and after dose administration Consider administering as a continuous infusion over 24 hours Use liposomal formulation Limit duration of therapy
Contrast dye	Underlying renal insufficiency, age older than 70 years, diabetes, heart failure, volume depletion, repeated exposures	Use low-osmolar contrast in the lowest dose possible and avoid multiple procedures in 24 to 48 hours 0.9% saline or sodium bicarbonate (154 mEq per L) infusion before and after procedure Withhold NSAIDs and diuretics at least 24 hours before and after procedure Monitor renal function 24 to 48 hours postprocedure Consider acetylcysteine preprocedure
Drugs associated with chronic interstitial nephropathy[11,20-23]		
Acetaminophen, aspirin, NSAIDs	History of chronic pain, age older than 60 years, female sex, cumulative consumption of analgesic > 1 gram per day for more than two years	Avoid long-term use, particularly of more than one analgesic Use alternate agents in patients with chronic pain
Lithium	Elevated drug levels	Maintain drug levels within the therapeutic range Avoid volume depletion
Drugs associated with crystal nephropathy[12,13,24]		
Acyclovir (Zovirax), methotrexate, sulfa antibiotics, triamterene (Dyrenium)	Volume depletion, underlying renal insufficiency, excessive dose, intravenous administration	Discontinue or reduce dose Ensure adequate hydration Establish high urine flow Administer orally

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NSAID = nonsteroidal anti-inflammatory drug.

Information from references 7, 10 through 13, 20 through 24, 32, 37, and 38.

nephrotoxicity is dose dependant or related to prolonged duration of treatment.[24] Combination therapy with multiple nephrotoxins can result in synergistic nephrotoxicity, thus increasing the risk of renal injury.[7] Specific preventive measures unique to some of these drugs are highlighted in *Table 3*.[7,10-13,20-24,32,37,38]

Contrast-induced nephropathy is reported to be the third most common cause of acute renal failure in hospitalized patients.[2] The exact incidence, however, varies depending on study design, type and dose of contrast used, and presence of acute renal failure risk factors and other comorbidities.[37] The risk of contrast-induced

Table 4. General Measures to Prevent Drug-Induced Nephrotoxicity

Adjust medication dosages using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children).
Assess baseline renal function using the MDRD equation, and consider patient's renal function when prescribing a new drug.
Avoid nephrotoxic combinations.
Correct risk factors for nephrotoxicity before initiation of drug therapy.
Ensure adequate hydration before and during therapy with potential nephrotoxins.
Use equally effective non-nephrotoxic drugs whenever possible.

MDRD = Modification of Diet in Renal Disease.

Information from references 7, 10, and 33.

nephropathy is highest in patients with chronic kidney disease (i.e., a GFR of less than 60 mL per minute per 1.73 m^2), especially in the presence of diabetes.[39] Other risk factors include dehydration, heart failure, age older than 70 years, and concurrent use of nephrotoxic drugs.[37] Patients with risk factors for contrast-induced nephropathy, especially those who have multiple risk factors, require prophylactic interventions before imaging.[37] Prophylactic interventions studied have included normal saline or sodium bicarbonate infusions and acetylcysteine before and after imaging.[38,40] However, the role of acetylcysteine has yet to be defined because clinical trial results have been inconsistent.[37]

Table 5. Formulas to Assess Renal Function and Adjust Medication Dosages

Author	*Estimation formula*	*Purpose*
MDRD[41]	eGFR = 186 × serum creatinine (mg per dL)$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742 if patient is female) × (1.210 if patient is black)	To assess renal function and stage chronic kidney disease[44]
Cockcroft and Gault[42]	Male: eCrCl = ([140 – age (years)] × ideal body weight [kg]) ÷ (serum creatinine [mg per dL] × 72) Female: male eCrCl × 0.85	To adjust drug dosing for renal function in adults[45]
Schwartz[43]	eCrCl = (length [cm] × k) ÷ serum creatinine (mg per dL) k = 0.45 (infants one to 52 weeks of age) 0.55 (children one to 13 years of age) 0.70 (males 14 to 17 years of age) 0.55 (females 14 to 17 years of age)	To adjust drug dosing for renal function in children

eCrCl = estimated creatinine clearance; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

Information from references 41 through 45.

PREVENTIVE MEASURES

General preventive measures include using equally effective but non-nephrotoxic drugs whenever possible, correcting risk factors for nephrotoxicity, assessing baseline renal function before initiating therapy, adjusting the dose of medications for renal function, and avoiding nephrotoxic drug combinations *(Table 4)*.[7,10,33] Baseline renal function can be estimated at the bedside using the Modification of Diet in Renal Disease (MDRD) formula or the Cockcroft-Gault formula in adults and the Schwartz formula for children *(Table 5)*.[41-45] The National Kidney Foundation advocates using the MDRD formula for the detection and staging of chronic kidney disease.[44] GFR estimation equations are included in programs for handheld computers such as MedCalc, Archimedes, InfoRetriever, Epocrates, and Micromedex. The MDRD is accessible online at http://nkdep.nih.gov/professionals/gfr_calculators/index.htm.

Most drugs that are eliminated renally do not require dosage adjustment until the creatinine clearance falls below 50 mL per minute.[46] The preferred formula advocated by the U.S. Food and Drug Administration to guide drug dosing in adults is the Cockcroft-Gault formula because it has been used in nearly all pharmacokinetic studies to generate drug-dosing guidelines.[45,47] Compared with the MDRD, the Cockcroft-Gault equation tends to overestimate the GFR and may yield different results depending on the patient.[41] For example, the estimated GFR of a 64-year-old, 190-lb (86-kg) woman with a serum creatinine level of 1.3 mg per dL (110 μmol per L; normal: 0.8 to 1.4 mg per dL [70 to 120 μmol per L]) is 59 mL per minute using the Cockcroft-Gault formula and 44 mL per minute per 1.73 m^2 according to the MDRD. In this example, both formulas indicate renal insufficiency, but the patient's medications most likely would not require a dose adjustment.

Adequate hydration is important to maintain renal perfusion and avoid drug-induced renal impairment. Whenever possible, volume status should be assessed and corrected, if necessary, before initiation of nephrotoxic agents. This is particularly true when prescribing medications such as ACE inhibitors, ARBs, and NSAIDs, which induce alterations in renal hemodynamics in patients who are significantly volume depleted.[10,32] Signs of significant intravascular volume depletion include orthostatic hypotension, blood pressure of less than 90/60 mm Hg, and decreased

skin turgor accompanied by a loss of more than 5 percent of baseline body weight.[1-4] Currently, there is no consensus on the optimal solution, volume, or timing of fluids to restore renal perfusion.[7]

A systems approach involving computerized physician order entry and clinical decision support may reduce the danger of exposing at-risk patients to nephrotoxins, but such systems are greatly underused in the ambulatory setting.[48] Forming collaborations between those who prescribe drugs and clinical pharmacists is a good option and should be pursued and developed, although funding such efforts may be a challenge.[48] Two reports from the Institute of Medicine recognized that pharmacists are an essential resource in safe medication use and that pharmacist-physician-patient collaboration is important.[49,50] The clinical and economic impact of clinical pharmacists in other settings has been extensively reviewed and summarized in the literature.[51]

VIGILANCE

In one large cohort study of Medicare enrollees in the ambulatory setting, inadequate laboratory monitoring played a role in 36 percent of all preventable adverse drug events.[48] In addition, when assessing baseline renal function, physicians should consider monitoring serum creatinine levels after starting or increasing the dosage of drugs associated with nephrotoxicity, especially those used chronically in patients with multiple risk factors for renal impairment. A systems approach toward adopting an electronic medical record may provide a practical method for automated monitoring of all patients in general, and patients at risk of nephrotoxicity in particular.

RECOGNITION AND EARLY INTERVENTION

Most episodes of drug-induced renal impairment are reversible. Renal function generally returns to baseline provided the impairment is recognized early and the offending medication is discontinued.[52] Failure to act on available information relating to clinical findings or laboratory results was the most common monitoring error, occurring in 37 percent of preventable adverse drug events, including those affecting the kidney, in older ambulatory patients.[48]

A decrease in renal function as evidenced by a rise in serum creatinine levels following the initiation of a drug signals the possibility of drug-induced renal injury. An exception to this is an increase in serum creatinine following the initiation of cimetidine (Tagamet) or trimethoprim (Proloprim), because they compete with creatinine for tubular secretion and are not associated with kidney damage or urine abnormalities.[52] Although there are no standard guidelines used to interpret changes in serum creatinine, a 50 percent rise from baseline, an increase of 0.5 mg per dL (40 μmol per L) or more when baseline serum creatinine is less than 2 mg per dL (180 μmol per L), or an increase of 1 mg per dL (90 μmol per L) or more if baseline creatinine is greater than 2 mg per dL have been used as biochemical criteria of acute renal failure.[1,2,32]

At the first sign of renal dysfunction, the patient's medication list should be reviewed to identify offending agents. If multiple medications are present and the patient is clinically stable, physicians should start by discontinuing the drug most recently added to the patient's medication regimen. Attention should then be directed at avoiding further renal insults by supporting blood pressure, maintaining adequate hydration, and temporarily discontinuing all other possible nephrotoxins.[53]

This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

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