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ROLE OF PHARMACIST IN MANAGEMENT OF DRUG INDUCED NEPHROTOXICITY

Mohamed Ashraf PT* and Nehal Ahmed ElKilany

*Pharmacist, SEHA - AHS, Abu Dhabi, UAE.

***Corresponding Author: Dr. Mohamed Ashraf PT**

Pharmacist, SEHA - AHS, Abu Dhabi, UAE.

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ABSTRACT

Drug induced kidney injury is a frequent adverse event which can be costly and may require multiple interventions even leading to hospitalization.[4] A growing number of patients are developing drug-induced nephrotoxicity due to a number of factors including polypharmacy and exposure to potentially nephrotoxic therapeutic & diagnostic procedures. Pharmacists can play a key role in identifying possible causes of drug-induced kidney injury and limit their toxic effect by identifying causative agents and suggesting appropriate substitutions.[6]

INTRODUCTION

Although the majority of drugs in common usage have low nephrotoxic potential, specific certain patients and clinical situations seem to be susceptible to nephrotoxicity.[5] Patients with underlying renal insufficiency, defined as glomerular filtration rate less than 60 mL/min/1.73 m^2, heart failure, sepsis, and intravascular depletion are particularly vulnerable to developing nephrotoxicity. The recognition of the factors that predispose to nephrotoxicity of drugs would enable attempts at limiting or preventing the same. Recommendation for renal drug adjustment is one of the common interventions provided by pharmacists to avoid unwanted complications.

Pharmacists as members of the health care team are appropriately trained to make rational drug-dose adjustments in patients with acute and chronic kidney disease.[7] In this article, the most common drug induced nephrotoxicity that can be recognized at outpatient settings due to the prevalence of the offending drugs will be highlighted and the key role of pharmacists recommendation for management or therapeutic substitutions will be discussed.

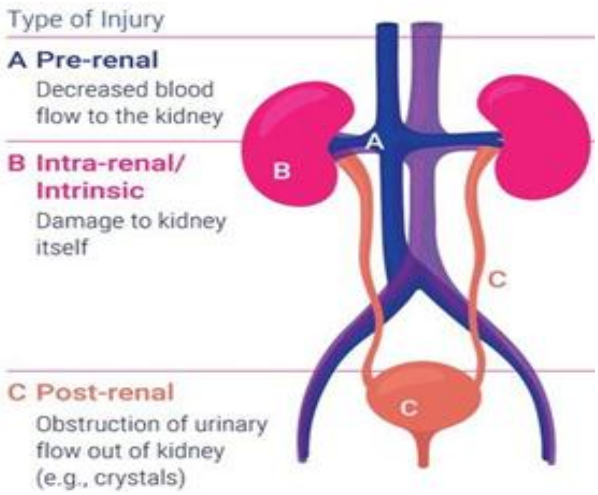


Figure 1: Site of renal injury.

Table 1: Nephrotoxic medications site of action.

Nephrotoxicity	Drugs
Pre-renal	ACE inhibitors Angiotensin receptor blockers Iodinated contrast agents NSAIDs
Intra-renal	Sulfa drugs (sulfamethoxazole, thiazide diuretics) Penicillin analogues (nafcillin, oxacillin) Aminoglycoside antibiotics Proton-pump inhibitors Iodinated contrast agents Cephalosporins Amphotericin B Ciprofloxacin NSAIDs
Post-renal	Acyclovir Analgesics Methotrexate

COMMON DRUG INDUCED NEPHROTOXICITY

Nephrotoxicity can be classified into pre-renal, intra-renal (which includes interstitial nephritis & tubular necrosis) or post-renal.

Aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), contrast agents, and angiotensin converting enzyme inhibitors (ACEIs) are the most common cause of AKI.[7] The risk of contrast-induced nephropathy is highest in diabetics and chronic kidney disease.[8]

Certain drugs such as ampicillin, ciprofloxacin, sulfonamides, acyclovir, ganciclovir, methotrexate and triamterene are associated with crystal nephropathy. Crystal nephropathy may also results from the use of chemotherapy due to uric acid and calcium phosphate crystal deposition.[9,10]

Drugs associated with tubular cell toxicity and acute interstitial nephropathy include aminoglycosides, amphotericin B, cisplatin, beta lactams, quinolones, rifampin, sulfonamides, vancomycin, acyclovir, and contrast agents.[14,15,16] These agents induce renal tubular cell injury by impairing mitochondrial function and interfering with tubular transport and increasing oxidative stress and free radicals.[15,17] Chronic use of acetaminophen, aspirin, diuretics and lithium is associated with chronic interstitial nephritis leading to fibrosis and renal scarring.[13,16,18-20]

Acute Tubular Necrosis

ATN refers to a generally reversible deterioration of kidney function associated with a variety of renal insults; the most common precipitant of ATN is renal ischemia. The primary agents associated with this type of injury are aminoglycosides, radio contrast media, cisplatin, amphotericin B, and osmotically active agents such as Immunoglobulin, dextran, and Mannitol.[2]

A. Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Normally, the kidney attempts to maintain GFR by dilating the afferent arteriole and constricting the efferent arteriole in response to a decrease in renal blood flow. During states of reduced blood flow, the juxtaglomerular apparatus increases renin secretion.

Plasma renin converts angiotensinogen to angiotensin I, and ultimately angiotensin II by angiotensin-converting enzyme. Angiotensin II constricts the afferent and efferent arterioles, but has a greater effect on the efferent arterioles, resulting in a net increase in intraglomerular pressure.[34] When ACEI therapy is initiated, RAAS inhibitors prevent the formation or action of angiotensin II and abolish this protective mechanism, the efferent arterioles dilates, which leads to fall intraglomerular pressure and GFR, this in turn often leads to nephrotoxicity.

A common strategy for at-risk patients is to initiate therapy with very low doses of a short-acting ACEI (e.g., captopril 6.25 mg-12.5 mg), then gradually titrate the dose upward and convert to a longer-acting agent after patient tolerance has been demonstrated. Outpatients may be started on low doses of long-acting ACEIs with gradual dose titration every 2 to 4 weeks until the maximum dose or desired response is achieved.[35] ACEI are contraindicated in patient with renal artery stenosis, and also when dehydration, over diuresis, poor fluid intake, and low sodium diet can increase the dependency of the efferent arterioles on AT II. When ACEI given in these situations, GFR can fall dramatically and S_{Cr} rises.

AKI can be averted by withholding the ACE inhibitor (or diuretics, or both) for a day and repleting the intravascular fluid volume with a saline containing fluid (normal saline, or 0.45% saline). The ACE inhibitor can be restarted at the same dose after adequate hydration. ACE inhibitor may precipitate AKI in patients who are taking concomitant drugs with renal afferent arteriole vasoconstricting effect, most notably NSAID and cyclosporine. Patients who receiving ACEI should be monitored judiciously with regards to their serum creatinine, and electrolyte concentrations. Once ACEI is initiated, an increase in S_{Cr} of 20% to 30% can be expected. Because it typically normalizes within 2 to 3 months. Serum creatinine increases greater than this along with reduced urine output is a signal of AKI.

B. Non-steroidal Anti-inflammatory Drugs & Selective Cyclooxygenase-2 Inhibitors

Non-steroidal anti-inflammatory drug- and COX-2-induced AKI usually occurs within 2 to 7 days of initiating therapy, particularly with a short-acting agent such as ibuprofen, or within days of some other precipitating event (e.g. intravascular volume depletion). Patients typically present with complaints of diminished urine output, weight gain, and/or edema.[51-53]

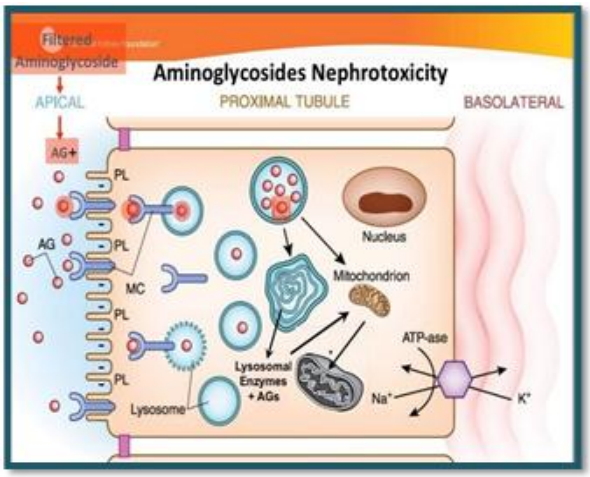
Acetaminophen is considered one of the safest agents to use for the treatment of pain, in renal patients and otherwise, as long as dosing is below the minimal daily dose. It is metabolized in the liver to five inactive metabolites. The terminal elimination half- life of its sulfate and glucuronide metabolites are prolonged in patients with renal failure; therefore, the dosing interval should be increased to six to eight hours in renally impaired patients.[42,45,54]

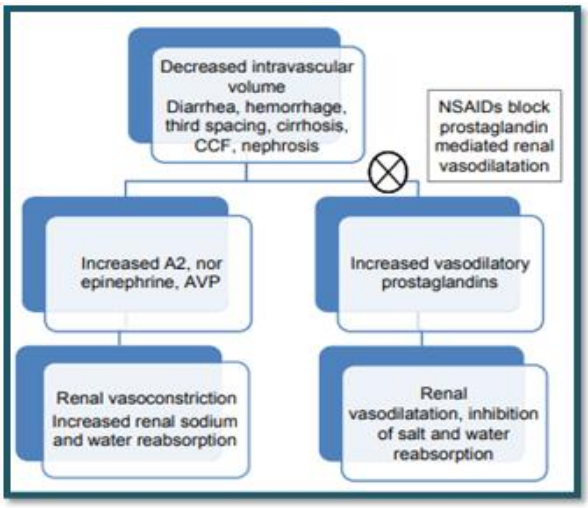
Mefenamic acid is metabolized in the liver. It can further deteriorate renal function in patients with underlying renal disease.[55] However, the nephrotoxic potential of this agent is of little consideration in ESRD patients on dialysis, and therefore no dosage adjustments are necessary in these patients.[45]

Cox-2 specific NSAID have similar effects on renal function as the nonselective NSAID and thus are not safer with respect to AKI. NSAID related AKI is most

often due to a hemodynamically mediated reduction in GFR that occurs in patients who are particularly dependent on vasodilatory prostaglandin to maintain renal perfusion. Risk factors for NSAID and COX-2 induced AKI include age more than 60 years, preexisting kidney disease, hepatic disease with ascites, congestive heart failure, intravascular volume depletion or dehydration. The use of ACEIs, diuretics, and NSAIDs concurrently is associated with a greater than 30% increased risk for AKI, which increases to greater than 60% in patients over age 75 or with preexisting kidney disease.[52,53]

This form of AKI is usually reversible in 2 to 7 days on discontinuation of the drug and rarely occurs in healthy individuals. Non-steroidal anti-inflammatory drug- and COX-2 inhibitor-induced AKI can be prevented by recognizing high-risk patients,[51] avoiding potent compounds such as indomethacin and using analgesics with less prostaglandin inhibition, such as acetaminophen, nonacetylated salicylates, aspirin, and possibly nabumetone. Non-narcotic analgesics (e.g. Tramadol) may also be useful but do not provide anti-inflammatory activity. When NSAID therapy is essential for high-risk patients, the minimal effective dose should be used for the shortest duration possible and use of other nephrotoxic drugs should be avoided.





C. Aminoglycoside Nephrotoxicity

Aminoglycoside-associated ATN is primarily due to accumulation of high drug concentrations within proximal tubular epithelial cells, and subsequent generation of reactive oxygen species that produce mitochondrial injury, which leads to cellular apoptosis and necrosis.[22] The mechanism of aminoglycoside induced ATN is complex, approximately 5% of filtered aminoglycoside is actively reabsorbed by the proximal tubules, which is polycationic and bind to the negatively charged brush border cells within the tubule lumen. The number of cationic groups on the drug molecule appears to correlate with the degree of nephrotoxicity, which is consistent with the observation of higher rates of toxicity with neomycin versus gentamicin, followed by tobramycin, then amikacin.[23]

Clinical evidence of aminoglycoside-associated nephrotoxicity is typically seen within 5 to 7 days after initiation of therapy and manifests as a gradual progressive rise in S_{cr} and BUN and decrease in creatinine clearance.[23]

Dehydration, sepsis, hypotension, ischemia, and use of other nephrotoxic drugs frequently contribute to AKI in patients who are receiving aminoglycosides. Aminoglycoside nephrotoxicity is a function of drug exposure, and it might be minimized with extended interval dosing, (administration of one large daily aminoglycoside dose, minimize time depended toxicity, because of saturable uptake kinetics in the proximal tubules).

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

D. Radio contrast Media- Induced Acute Tubular Necrosis

This is defined as a rise in the serum creatinine by >25% during the first 3 days following the administration of IV contrast medium. The primary mechanisms by which contrast media induces nephrotoxicity are renal ischemia and direct cellular toxicity.[24] Renal ischemia likely results from systemic hypotension and simultaneous acute vasoconstriction caused by disruption of normal prostaglandin synthesis and the release of adenosine, endothelin, and other renal vasoconstrictors.

Subsequently, a sustained reduction in renal blood flow of up to 25% that lasts for several hours immediately following contrast administration may be evident.[24] This reduced renal blood flow leads to a 50% reduction in oxygen partial pressure and renal ischemia, along with increased concentrations of contrast in the renal tubules, which exacerbates the direct cytotoxicity.[24,25] Therefore, preexisting kidney disease, particularly in those with estimated GFR less than 60 mL/min/1.73 m^2 (less than 0.58 mL/s/m^2), is the most important risk factor.

Volume expansion and correction of dehydration prior to contrast administration is a mainstay of preventive therapy.[24] parenteral hydration with isotonic saline before and after contrast administration reduces the incidence of toxicity, particularly in high-risk patients. Stopping nephrotoxic drugs 48 hour before CM exposure and limiting CM volume will be beneficial for reducing CIN. High osmolality contrast media cause a marked diuresis with excretion of increased amount of sodium, this activate the tubuloglomerular feedback mechanism, leading to vasoconstriction of the afferent arterioles and a reduction of the GFR. Low-osmolar (600- 800 mOsm/kg [mmol/kg]) nonionic (iohexol and iopamidol) and ionic (ioxaglate) contrast agents may be used to minimize the incidence of nephrotoxicity.

E. Cisplatin Nephrotoxicity

Cisplatin (Cis-platinum) a platinum based antineoplastic drugs for the treatment of solid tumors, is commonly associated with nephrotoxicity.[27] Within the kidney, Cisplatin and metabolites are localized to the juxtamedullary cortical region with a greater degree of injury seen in the S3 segments of the proximal tubules.[27,28,29,30] Tubular cell exposure to cisplatin then activates a series of cell signaling pathways, including generation of reactive oxygen species that collectively promote tubular cell injury and death via necrosis or apoptosis.

Carboplatin, a second-generation platinum analog, is associated with a lower incidence of nephrotoxicity than cisplatin and thus is the preferred agent in high-risk patients. Amifostine, an organic thiophosphate that is converted to an active metabolite, chelates cisplatin in normal cells and reduces the nephrotoxicity, associated with cisplatin and carboplatin therapy. Classic antioxidants such as ascorbic acid, thiol-based antioxidants such as α-lipoic acid and N-acetylcysteine, which reduce oxidative damage by acting as a sulfhydryl donor. AKI caused by cisplatin therapy is usually partially reversible with time and supportive care, including dialysis, Serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.

F. Amphotericin B Nephrotoxicity

The mechanism of Amphotericin nephrotoxicity is afferent arteriolar vasoconstriction leading to a reduction in renal blood flow and GFR, and ischemic tubular injury.[33] Nephrotoxicity can be minimized by limiting the cumulative dose, increasing the infusion time, ensuring the patient is well hydrated, and avoiding concomitant administration of other nephrotoxins.[33]

Administration of 1 L IV 0.9% sodium chloride daily during the course of therapy appears to reduce toxicity and a single infusion of saline 10 to 15 mL/kg prior to administration of each dose of amphotericin B are generally recommended.[33] A number of other antifungal agents such as itraconazole, voriconazole, and caspofungin are viable alternatives and are now routinely used in lieu of amphotericin B for patients at high risk of developing nephrotoxicity.

Analgesic Nephropathy

Chronic use of therapeutic doses of NSAIDs or high-dose acetaminophen, but not aspirin or salicylates alone, can cause analgesic nephropathy.[61] Individuals requiring chronic analgesic therapy may reduce risk by limiting the total dose, avoiding combined use of two or more analgesics, and maintaining good hydration to prevent renal ischemia and decrease the papillary concentration of toxic substances.

Cholesterol Emboli

Anticoagulants (particularly warfarin) and thrombolytics (e.g., urokinase, streptokinase, and tissue-plasminogen activator) are associated with cholesterol embolization of the kidney. These drugs act to remove or prevent thrombus formation over ulcerative plaques or may induce hemorrhage within clots, thereby causing showers of cholesterol crystals that lodge in small diameter arteries of the kidney (renal arterioles and glomerular capillaries). Cholesterol crystal emboli induce an endothelial inflammatory response, which leads to complete obstruction, ischemia, and necrosis of affected vessels within weeks to months after initiation of therapy.[62] Purple discoloration of the toes and mottled skin over the legs are important clinical clues. Treatment is supportive in nature, since kidney injury is generally irreversible.

Drug Induced acute interstitial Nephritis

A. Proton Pump Inhibitors

PPI are the most used medications worldwide, often for prolonged period, initially recognized in 1992 with Omeprazole administration, they are known risk factor for acute kidney injury and CKD.[38,45] With PPI use those 60 years or older at a 10 fold higher risk compared with those aged 15 to 49 years.[39,43]

The incidence of AIN in patients taking PPIs is difficult to determine accurately. Although histamin-2 receptor blockers also have been linked to AIN, no such increased risk of CKD has been noted with this class of medications compared with PPI.[40] Renal dysfunction in drug associated AIN usually improve after withdrawal of the offending drug. Glucocorticoids have been shown to promote earlier recovery of renal function and reduce fibrosis.

B. Antibiotics

The kidney is a common target for toxic xenobiotics, due to its specific capacity to clearance of toxic substances.[47] Kidney inflammation with hypersensitivity drug reactions including eosinophilia, rash, and fever was first recognized in the 1940s associated with Sulphonnamides.

A variety of Antibiotics, such as penicillin's, Cephalosporin's, quinolones, rifampicin, cause drug induced AIN. Pathophysiology of this reaction is suspected that either humoral or cell-mediated immune mechanism. The drug-protein antigens become lodged in the renal tubules, which initiate the inflammatory cascade.

Ceftriaxone induced AKI when administered concomitantly with aminoglycosides was reported.[48] Also crystalluria and frank nephrolithiasis with ceftriaxone has been noted in the literature.[49,50]

Crystal Nephropathy

Several medications that are insoluble in human urine are known to precipitate within the renal tubules. Intratubular precipitation of either exogenously administered medications or endogenous crystals (induced by certain drugs) can promote chronic and acute kidney injury, termed crystal nephropathy. Volume depletion, certain metabolic disturbances that promote changes in urinary pH favoring crystal precipitation. For example, AKI develops in approximately 2% of patients who receive high dose methotrexate, likely due to a combination of direct toxic effects and crystal nephropathy.[57]

Similarly, crystalluria is observed in 20% of patients receiving indinavir, but the number of patients developing crystal nephropathy is unknown.[63] Drug-induced rhabdomyolysis is another form of indirect toxicity, which can lead to intratubular precipitation of myoglobin and if severe, AKI.[59] The most common cause of drug-induced rhabdomyolysis is direct myotoxicity from (HMG-CoA) reductase inhibitors or statins, including lovastatin and simvastatin.[60] The risk of rhabdomyolysis is increased when these drugs are administered concurrently with gemfibrozil, niacin, or inhibitors of the CYP3A4 metabolic pathway (e.g. erythromycin and itraconazole).

Some sulfonamide antibiotics are relatively insoluble in acid urine, particularly sulfadiazine and sulfamethoxazole, because this drug is highly insoluble in urine with a pH of ≤5.5, May cause crystalluria with stone formation. Urinary alkalization to pH greater than 7.15 may be protective. The widely used fluoroquinolone antibiotic, ciprofloxacin, is known to cause AKI from acute interstitial nephritis. Ciprofloxacin has also been reported to cause crystalluria in experimental animals and both crystalluria and crystal-induced AKI in humans, Ciprofloxacin crystals typically precipitate in an alkaline pH, (urine pH greater than 7.3). To prevent ciprofloxacin crystal-induced AKI, should be dose adjusted for level of glomerular filtration rate (GFR), the patient should be volume replete, and alkalinization of the urine should be avoided.

AKI from drug-induced crystalline nephropathy requires the presence of a significant amount of drug crystal within tubular lumens that favor crystal insolubility in a low urinary flow state. This is accomplished by supersaturation of constituent molecules, low or high urine pH (depending on the drug), volume depletion. Acyclovir can precipitate in the setting of hypovolemia, rapid IV bolus administration, and with excessive dosing. IV fluids and slower IV administration are employed to prevent/reduce the occurrence. IV methotrexate and its metabolites can precipitate within the tubules when given in high doses, with acid urine, and in the setting of hypovolemia.

Role of Pharmacists in managing renal toxicity

Pharmacist can play a pivotal role in identifying possible causes of drug induced renal toxicity and limit their toxic effect by identifying those most likely to cause or contribute to injury.

Dose adjustment is critical during changes in renal function, and the pharmacist can ensure that optimal therapy is provided during the critical time.

Pharmaceutical interventions include correcting/ clarifying orders, providing drug information, suggesting alternative therapies, identifying drug interactions, and therapeutic drug monitoring. Pharmacist possess unique knowledge of pharmacokinetics and pharmacodynamics so they can evaluate patient's individual status and recommend the most appropriate drugs, and dosing to prevent nephrotoxicity. If the pharmacist encountered any drug-related problems, they would communicate with the physician or other health care professionals to achieve the best clinical outcome (proper renal dosage, efficacy, ADR, interactions). It is beneficial for the patients that physicians and pharmacist work together as therapy team to provide personally effective, efficient, and safe medication therapy.

Pharmacist often perform these tasks while the patient is hospitalized, and plan should be developed for continued monitoring as transitions occur or to other facilities or the patient is discharged home if the risk or injury still persist.

Table 2: The Most Commonly Used Nephrotoxic Drug.

Medication	Drug Category	Renal toxicity	Medication	Drug Category	Renal toxicity
Acetaminophen	Non-narcotic analgesic	Chronic interstitial nephritis / Acute tubular necrosis	D-penicillamine	Antirheumatic	Chronic interstitial nephritis
Acetazolamide	Carbonic-anhydrase inhibitor	Proximal renal tubular acidosis	Diphenhydramine	Antihistamine	Rhabdomyolysis
Acyclovir	Antiviral	Chronic interstitial nephritis / Acute tubular necrosis	Furosemide	Loop diuretic	Acute interstitial nephritis
Allopurinol	Hypouricemic agent	Acute interstitial nephritis	Methotrexate	Antineoplastic	Crystal nephropathy
Aspirin	Non-narcotic analgesic	Chronic interstitial nephritis	Naproxen	Nonsteroidal anti-inflammatory	Acute /chronic interstitial nephritis Acute tubular necrosis Glomerulonephritis
Amitriptyline	Antidepressant	Rhabdomyolysis	Omeprazole	Proton pump inhibitor	Acute interstitial nephritis
Aminoglycosides	Antimicrobial	Acute tubular necrosis	Pantoprazole	Proton pump inhibitor	Acute interstitial nephritis
Amphotericin B	Antifungal	Acute tubular necrosis Distal renal tubular acidosis	Penicillin G	penicillin	Glomerulonephritis
ACEI	Antihypertensive	Acute kidney injury	Phenytoin	Anticonvulsant	Acute interstitial nephritis Diabetes insipidus
ARB	Antihypertensive	Acute kidney injury	Quinolones	Antimicrobial	Chronic interstitial nephritis / Acute tubular necrosis
Benzodiazepines	Sedative-Hypotonic	Rhabdomyolysis	Rifampin	Antimicrobial	Acute interstitial nephritis
Beta lactams	Antimicrobial	Acute interstitial nephritis	Statins	Lipid- lowering	Rhabdomyolysis
Cephalosporin	Antimicrobial	Acute tubular necrosis	Sulfonamides	Antimicrobial	Chronic interstitial nephritis / Acute tubular necrosis
Contrast agents	Contrast medium	Acute tubular necrosis	Tetracycline	Antimicrobial	Acute tubular necrosis
Cisplatin	Antineoplastic	Chronic interstitial nephritis	Thiazides	Diuretic	Acute interstitial nephritis

CONCLUSION

The expertise of a pharmacist in pharmacotherapy, and medication management along with good communications with physicians and the members of the care team provide the optimum set-up for offering most effective and safe management of patients with renal disease. Besides reviewing the patients' entire medication list, including over-the-counter drugs and herbal products, pharmacists evaluation of suspected drugs includes consideration of the temporal sequence between the event and drug administration, objective evidence including drug concentrations when appropriate, prior knowledge of the event to support the nephrotoxin as a culprit, and ruling out the other non–drug-related causes.

Moreover, updated knowledge in the pharmaceutical field as well as communication with patients, the patient's caregivers, and other health professionals involved in the patient care regarding new medication information, in both verbal and written forms can be helpful.

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