Clinical Focus: Antibiotic-induced acute kidney injury

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Acute kidney injury (AKI) is not an uncommon diagnosis. It affects an estimated 13.3 million people per year [2] with 1 in 5 of all hospitalized patients having this diagnosis.[1] AKI increases all-cause morbidity and mortality and can occur for many reasons including direct trauma to the kidney, burns, shock, and blood loss. Numerous medications such as NSAIDS, ACE-inhibitors, diuretics, antifungals, antivirals, and antibiotics can also lead to AKI. [3] The CDC estimates about 47 million prescriptions of antibiotics are written each year in the outpatient setting for infections that do not require antibiotic therapy. This equates to about 30% of all antibiotics prescribed [12]. Antibiotics are one of the most prescribed medications in the inpatient setting as well, with over half of all inpatients receiving antibiotics during their admission.[5] With this prevalence of antibiotic usage, antibiotic-induced kidney injury should be on all clinicians' minds. However, AKI is an often-overlooked adverse outcome associated with antibiotic therapy which can cause significant morbidity in unsuspecting patients.

The incidence of antibiotic-induced AKI has been reported to be up to 36%, which varies according to class and setting.[3] Commonly prescribed antibiotics within the outpatient setting that carry an increased risk of AKI include sulfamethoxazole-trimethoprim (TMP/SMX), ciprofloxacin, and penicillin. Antibiotics that carry an increased risk of AKI and are common to the inpatient setting include aminoglycosides and vancomycin.

Trimethoprim/sulfamethoxazole (TMP/SMX), the most prescribed sulfonamide antibiotic, carries an increased risk of AKI, but also can cause an elevation of creatinine without acute kidney injury. In a study of 573 patients who were treated with TMP/SMX for a minimum of six days, 64 (11.2%), patients were found to have elevated serum creatinine and BUN consistent with AKI. AKI in patients taking TMP/SMX is most commonly a result of acute interstitial nephritis, but it can also affect the epithelia sodium channel in the distal convoluted tubule, resulting in hyperkalemia. Research suggests that both renal function and potassium levels should be monitored while patients are receiving TMP/SMX and discontinued if there is a suggestion of AKI. This is especially important in those patients with underlying renal impairment. In patients with TMP/SMX-induced AKI, cessation of the medication results in prompt return of normal renal function.[14]

Ciprofloxacin, the fluoroquinolone that carries the highest risk of AKI, is capable of injuring the kidney via multiple mechanisms, often due to acute interstitial nephritis mediated by an acute allergic reaction and inflammation of the renal interstitium.[6,2,8] Other causes of ciprofloxacin-induced AKI include granuloma formation and crystal deposition. Granuloma formation can occur in the renal interstitium by infiltration of histocytes and T lymphocytes in a hypersensitivity reaction to the fluoroquinolone. Crystal deposition can occur in the kidney with administration of ciprofloxacin when urine pH is more than 6.8 and results in acute renal tubular damage. [8,11] This risk can be reduced by IV hydration, which prevents alkalization of the urine and crystal formation.[2] An additional risk factor for fluoroquinolone-induced AKI is concomitant use of renin-angiotensin-aldosterone-system blockers, which can increase the risk four-fold. [11] Concomitant use of fluoroquinolones with RAAS modifying drugs should be avoided if possible, but if given together, it is suggested that providers closely monitor serum creatinine.

Onset of fluoroquinolone-induced AKI typically occurs 7-14 days after initiation of treatment. Findings include pyuria, eosinophiluria, inflammatory infiltrate in the renal interstitium, and granuloma formation.[6] Treatment of fluoroquinolone-induced AKI consists of cessation of the offending agent and administration of IV hydration. [2,6] Most cases of fluoroquinolone-induced AKI are reversible and mild, with kidney function returning to baseline in a few weeks to months after initial injury. In more severe cases, prednisone 1mg/kg/day for four weeks has been shown to speed recovery times. [2,6]

Beta-lactams carry risk of causing AKI as well, although the incidence is unknown. The relative risk of AKI is highest with carbapenems and decreases with cephalosporins, penicillins, and monobactams, respectively. There are two main mechanisms by which the kidney is injured by beta-lactams. The first, a hypersensitivity reaction resulting in interstitial nephritis, is found in the penicillins and results in inflammation of the renal interstitium and loss of kidney function similar to the flouroquinolones. [6,9] Cephalosporins, carbapenems, and monobactams can cause AKI by a second mechanism resulting in acute tubular necrosis, thought to be due to an accumulation of the antibiotic within the cell. Typically, beta-lactams are actively transported into the proximal tubule epithelial cells and then secreted from the cell into the luminal fluid, resulting in excretion. However, in AKI it has been proposed that instead of secretion into the lumen of the nephron, the beta-lactam is transported back into the cell which results in destruction of the mitochondria and subsequent cell death with loss of kidney function. [9] Studies have shown that should beta-lactam-induced AKI occur, IV hydration and early corticosteroid administration have a protective effect against long term complications. In severe cases, as with the other AKI-inducing dialyzable substances, hemodialysis is effective in clearing beta-lactams from the body. [2]

Aminoglycosides are a tempting class of antibiotics for prescribers due to their relatively broad-spectrum coverage. When clinicians hear "antibiotic-induced AKI", or nephrotoxic antibiotics, the first drug class that usually comes to mind are the aminoglycosides. However, there is a voluminous amount of research demonstrating their predilection to cause AKI. The incidence of aminoglycoside-induced AKI ranges between 8% and 26%.[7] The aminoglycosides associated with the highest risk of AKI are neomycin, gentamicin, tobramycin, amikacin, netilmicin, and streptomycin. [2,6,8] Onset of AKI typically occurs 5-10 days after initiation of treatment via acute tubular necrosis. [3,6] Risk factors include advanced age, obesity, volume depletion, preexisting liver disease, diabetes, hypertension and/or decreased renal perfusion, and the use of concomitant nephrotoxic drugs. [2,3,6,7]

Numerous preventative measures exist for aminoglycoside-associated AKI, including concomitant use of statins and/or beta-lactam antibiotics, administration of antioxidants, and interval dosing and limiting exposure. [2,6] Concomitant use of beta-lactam antibiotics has been proven to have a protective effect against AKI, although the mechanism of this protection is unknown. Concomitant statin usage has been shown to decrease accumulation of gentamicin in the epithelial cells of the proximal renal tubules, thus lowering the risk of cellular injury and death. [2] Most commonly, clinicians minimize risk and exposure by opting to limit administration duration to less than seven days, use once daily dosing, and monitor trough levels. Most cases of aminoglycoside-induced AKI are reversible with cessation of the offending agent and IV hydration. Of note, these injuries do not cause long term damage and ordinarily will heal with full recovery in roughly 20 days for mild to moderate cases.[8] In severe cases, hemodialysis may be needed to clear aminoglycosides from the body.

Vancomycin, an often-used glycopeptide, has been the subject of numerous studies addressing vancomycin-induced AKI with varied results. Incidence has been reported anywhere between 6-40%. [2,6] In comparing the risk of vancomycin to other antibiotics, it can be classified as a moderate risk; its risk is significantly lower than aminoglycosides, slightly higher than beta-lactams, and much higher than that of fluoroquinolones. [1,8] Despite extensive research, the exact mechanism of vancomycin-induced AKI is still unknown. The common proposed mechanisms of injury include those already discussed with other antibiotic classes - hypersensitivity reactions resulting in acute interstitial nephritis and pro-inflammatory oxidative stress causing acute tubular necrosis. [2] Vancomycin carries other specific risk factors for the development of AKI including concomitant usage of aminoglycosides, broad-spectrum penicillins like piperacillin-tazobactam, cefepime, high trough levels , and extended duration of therapy. [2,3,6,7] While there is no maximum duration of vancomycin therapy, onset of vancomycin-induced AKI is typically seen 12 days after the first administration and cessation should be considered around this time. [3,6] Treatment for vancomycin-induced AKI includes cessation of the drug and hemodialysis. Within four hours of hemodialysis, 30 to 46% of the administered vancomycin can be cleared out of the body. [2] Return to full

renal function is possible, but there is a higher rate of long term morbidity with vancomycin-induced AKI compared with fluoroquinolones or beta-lactams. [2,3]

Antibiotic-induced acute kidney injury is a prevalent concern with the use of antibiotics across virtually all classes and settings. Clinicians should be aware of this risk and utilize appropriate mitigation strategies, including laboratory monitoring, limiting duration of therapy, IV hydration, medication adjustments, and even hemodialysis when appropriate. With prompt recognition and corrective measures, the morbidity and mortality risk of antibiotic-induced AKI can be limited and patients have potential to maintain near-baseline renal function.

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