

# Patient Safety Tip of the Week

February 4, 2020

## Drugs and Chronic Kidney Disease

Medication use is an important aspect of management of CKD (chronic kidney disease). There are at least 5 important issues:

- medications that should be avoided because they may worsen CKD
- medications that should be avoided because they may worsen complications of CKD
- medications that need dosage adjustment in the presence of CKD
- medications that should be used because they may prevent CKD progression
- other agents that may need avoidance or dose reduction in patients with CKD (eg. contrast agents)

In the last couple months there have been several studies pertinent to these issues. First, there was an excellent recent review of the management of CKD by Chen et al. in JAMA ([Chen 2019](#)). Then there was a study ([Tuttle 2019](#)) showing, in patients at risk for CKD, low rates of prescribing potentially beneficial medications (eg. ACE inhibitors or ARB's) but common use of potentially nephrotoxic agents (eg, NSAID's and PPI's). Yet another study ([Lefebvre 2020](#)) found that potentially nephrotoxic medications are prescribed at high rates to children with CKD. And, then, an expert panel published in the Annals of Pharmacotherapy ([Taji 2020](#)) a consensus-based pragmatic list of medications used in primary care that require dosage adjustment or avoidance in people with CKD.

The Tuttle study ([Tuttle 2019](#)) mined detailed patient-level EHR data from more than 600,000 adults and over 12,000 children with CKD in the CURE-CKD registry. 33.7% of adults with CKD received potentially nephrotoxic agents nonsteroidal anti-inflammatory drugs (NSAID's) or proton pump inhibitors (PPI's), compared to renoprotective drugs like renin-angiotensin system inhibitors, which were prescribed to only 20.6%. Although nearly two-thirds of the adults with CKD had diabetes, hypertension, or prediabetes, rates of laboratory testing for albuminuria or proteinuria and of prescribing ACE inhibitors or ARBs were low. Given the most common cause of death in CKD is cardiovascular disease, the low use of cardiovascular preventive agents, such as statins and aspirin, is also concerning. The Tuttle study did not report prescription rates for other potentially nephrotoxic drugs.

Though the CURE-CKD data registry included children, the Tuttle study reported primarily on adults with CKD. On the other hand, Lefebvre and colleagues ([Lefebvre 2020](#)) looked at use of potentially nephrotoxic medications in patients aged <18 years in a large research database of patients in primary care practices in the UK, matching patients with CKD to those without CKD. The overall rate of nephrotoxic medication prescriptions was 71 prescriptions per 100 person-years in patients with CKD and eight prescriptions per 100 person-years in patients without CKD (adjusted rate ratio, 4.1). One would actually have expected the CKD group would have lower rates of nephrotoxic medication prescriptions, so the findings were particularly bothersome.

One of the most important things in management of CKD is to avoid potential nephrotoxins. NSAID's (non-steroidal anti-inflammatory drugs) are probably the biggest offender that are commonly used. The Chen review ([Chen 2019](#)) notes "Routine administration of NSAID's in CKD is not recommended, especially among individuals who are taking ACE-I or ARB therapy."

The Chen review also discussed common medications that require dose reductions in the presence of CKD, including most antibiotics, direct oral anticoagulants, gabapentin and pregabalin, oral hypoglycemic agents, insulin, chemotherapeutic agents, and opiates, among others. Most of these categories also made the Taji ([Taji 2020](#)) consensus-based final list of 24 medications routinely used in the primary care setting that should be avoided or dose adjusted based on a patient's eGFR:

- antibiotics (ciprofloxacin, co-trimoxazole, levofloxacin, nitrofurantoin)
- anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban)
- anticonvulsants (gabapentin, pregabalin)
- antivirals (acyclovir, valacyclovir)
- antidiabetic agents (canagliflozin, dapagliflozin, empagliflozin, glyburide, metformin),
- other medications (baclofen, digoxin, colchicine, lithium, spironolactone, fibrates, duloxetine)

The Taji study also produced a list of 12 medications that could be considered for dose adjustment or avoidance, including:

- solifenacin
- tolterodine
- famciclovir
- oseltamivir
- gliclazide
- saxagliptin
- sitagliptin
- bisphosphonates
- escitalopram
- metoclopramide
- rosuvastatin,
- venlafaxine

The Taji lists do not include over-the-counter medications or commonly used herbal or alternative medication remedies. The Chen review notes, in particular, those herbal remedies containing aristolochic acid or anthraquinones have been associated with a variety of adverse renal effects.

Not included in the list compiled by Taji et al. ([Taji 2020](#)) are drugs that should be avoided because they may aggravate some complications of CKD. For example, the Chen review notes that phosphate-based bowel preparations (both oral and enema formulations), which are readily available over-the-counter, can lead to acute phosphate nephropathy.

The Chen review also clarified some issues about the use of PPI's (proton pump inhibitors) in patients with CKD. Though it concludes that uniform discontinuation of proton pump inhibitors in CKD is not necessary, it does suggest that indications for use of PPI's should be addressed at each primary care visit. (Of course, in our many columns on polypharmacy and deprescribing, we've frequently discussed that PPI's are often inadvertently continued without clear-cut indications in all patients, not just those with CKD.)

The Chen review notes that gadolinium-based contrast agents are contraindicated in individuals with acute kidney injury, eGFR less than 30 mL/min/1.73 m<sup>2</sup>, or end-stage kidney disease, given the risk of nephrogenic systemic fibrosis (NSF). It goes on to note that newer macrocyclic chelate formulations (eg, gadoteridol, gadobutrol, or gadoterate) are much less likely to cause nephrogenic systemic fibrosis, but that the best prevention may still be to avoid gadolinium altogether. They recommend that, if administration of gadolinium is deemed essential, the patient must be counseled on the potential risk of nephrogenic systemic fibrosis and a nephrologist may be consulted for consideration of postexposure hemodialysis.

Other contrast dyes, such as those used in CT scanning and angiography, may rarely be associated with Contrast Induced Nephropathy (CIN). About 2 percent of people receiving dyes can develop CIN ([NKF 2019](#)). However, the risk for CIN can increase for people with diabetes, a history of heart and blood diseases, and chronic kidney disease (CKD). The risk of CIN in people with advanced CKD (GFR below 30 mL/min/1.73m<sup>2</sup>) increases to 30 to 40 percent. And the risk of CIN in people with both CKD and diabetes is 20 to 50 percent.

Clearly, caution must be used when using such contrast agents in patients with CKD. The most important consideration is whether contrast is absolutely necessary for the study. If it is necessary, steps should be taken to minimize the risk of CIN, such as ensuring adequate hydration, using the least amount of contrast necessary, and avoiding repeat contrast administration too soon.

It's also important to monitor the patient for CIN or NSF after studies utilizing each type of contrast agent, respectively.

CPOE (computerized physician order entry) and e-Prescribing systems offer clinical decision support (CDSS) tools that should help avoid both inappropriate medications and inappropriate medication dosages in patients with CKD. The eGFR is readily available in the electronic medical record of almost every patient so the CDSS should be able to check the eGFR and alert the clinician of the need to adjust the dose of one of these medications or avoid their use altogether. Now is a good time for you to utilize the information in these recent studies to investigate whether your CPOE system (if you are a hospital) or your e-Prescribing system (in your practice or clinic setting) have up-to-date clinical decision support tools that can aid your prescribing medications to patients with CKD.

Similarly, your CPOE and e-Prescribing systems and radiology information systems (RIS) should have decision support tools that automatically check the eGFR when any study is ordered using contrast or gadolinium contrast and issue alerts as appropriate.

**Update:** After we posted this column, Wooden and colleagues ([Woolen 2020](#)) published a systematic review and meta-analysis on the incidence of the risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent. Agents in the American College of Radiology classification group II GBCA are: gadobenate dimeglumine, gadobutrol, gadoterate meglumine, and gadoteridol. They found that the risk of NSF from group II GBCA administration in stage 4 or 5 CKD is likely less than 0.07%. They suggest that the potential diagnostic harms of withholding group II GBCA for indicated examinations may outweigh the risk of NSF in this population.

The accompanying editorial ([Maripuri 2020](#)) concurs that the strength of the evidence favors a more permissive approach to using group II GBCAs in patients with CKD, especially when contrast-enhanced MRI is the superior imaging modality. It points out a disconnect between the more conservative approach still maintained by the FDA and the more permissive guidelines from the ACR. It notes a probable similar disconnect between nephrologists and radiologists, with the former concerned that the lack of cases may be driven by avoidance of GBCAs in high-risk patients and the latter more convinced by the biochemical case for safety of newer GBCAs.

### **Some of our prior columns on dialysis, CKD, and ESRD:**

March 26, 2007	<a href="#">“Alarms Should Point to the Problem”</a>
February 2009	<a href="#">“Unintended Consequences of eGFR Reporting”</a>
May 2009	<a href="#">“Erythropoiesis-Stimulating Agents and Mortality”</a>
September 20, 2011	<a href="#">“When Practice Changes the Evidence: The CKD Story”</a>
September 2013	<a href="#">“Is Nephrologist Caseload Related to Dialysis Mortality?”</a>
September 2014	<a href="#">“New Tubing Connections”</a>

June 23, 2015 “[Again! Mistaking Antiseptic Solution for Radiographic Contrast](#)”  
November 1, 2016 “[CMS Emergency Preparedness Rule](#)”  
April 25, 2017 “[Dialysis and Alarm Fatigue](#)”  
July 16, 2019 “[Avoiding PICC’s in CKD](#)”  
December 10, 2019 “[Dialysis Line Dislodgements](#)”

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