Appendix K. Nephrotoxic Agents and Medication Dose Adjustments in CKD

A. Background

It has been estimated that approximately 1 in 5 episodes of AKI in hospitalized patients are related to medication,(260) and during an inpatient episode of critical care, approximately a third of patients receive multiple potentially nephrotoxic medications.(261) In the outpatient environment of care, approximately half of patients with stage G3-G5 CKD are using a potentially inappropriate medication.(262) AKI/CKD states represent complex clinical conditions with often limited therapeutic alternatives. As such, this appendix is not intended to provide an exhaustive list of drugs that could be nephrotoxic or need adjustment with changing kidney function but rather, to provide the front-line clinician with a conceptual approach to the assessment of a drug's nephrotoxic potential and management of pharmacotherapy in patients with CKD.

B. Nephrotoxic Medications

The kidney is a relatively small organ but receives 20% of cardiac output and has a role in the filtration, secretion, reabsorption, and biotransformation of medications. As such, it has a greater exposure to the risk of toxic drug effects than other organ systems.(263) Despite the commonness of drug-related harm to the kidney, there is, interestingly, not an agreed upon nomenclature or specific definition of drug-induced nephrotoxicity. For this guideline targeted towards the PCP, we highlight the approach developed during the KDIGO 2019 Controversies in Acute Kidney Injury conference as it organizes drugs into two major categories by which they can cause harm: kidney dysfunction or kidney injury.(264) This allows the prescribing provider to consider any drug, or combination of drugs, as to its manner of causing direct kidney injury, dysfunction, both, or neither in the context of patient specific risk mitigation or exacerbating factors.(264)

Although the 2-grouping format of the KDIGO controversies model may have some affinity for the PCP, organizing drug-induced nephrotoxicity in this manner is not without limitations. First, all the systems are grounded with a focus on hospital-acquired AKI of which drug-induced kidney injury is a significant contributor. Unfortunately, there is a paucity of information on community acquired AKI, which is epidemiologically distinct.(265) Consequently, the ambulatory care provider must borrow from evidence obtained in the hospital setting and intuit risk factors for community-acquired drug-induced nephrotoxicity (see Table K-1). Also, while these models can help with risk versus benefit assessment for drug toxicity that accumulates with dose and duration of exposure, there is not a good means for estimating the risk of drug-induced nephrotoxicity that occurs idiopathic or immune-mediated mechanisms, such as acute interstitial nephritis (AIN) that may occur with proton pump inhibitors (PPI). Per the FDA Adverse Event Reporting System (FAERS) from 2019-2023, there were 77,000 reports of serious AKI suspected to be caused by a drug. Seven of the top 10 suspect generic drugs reported were in the PPI class representing 86% of all reported cases of serious, drug-induced AKI.(266) These findings are similar to global surveillance reports where the PPI class occupies 4 of 5 drugs suspected of causing nephrotoxicity.(267) Thus, the PCP must have a high degree of clinical suspicion of drugs may be causative when an acute decline in kidney function is detected, especially since cessation of the offending agent is the first step in reversing drug-induced AKI. While rapid detection and removal of the offending drug or nephrotoxin is important, prevention is key. Kurani et al. (2019)(262) demonstrated that patient knowledge of their having CKD was associated with a protective effect, reducing exposure