Keep Children with CKD Safe from Inappropriate Prescribing

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Medical advancements over the past decades have led to improved survival rates and longevity for children with a number of acute and chronic illnesses, including sepsis, cancer, congenital heart disease, and cystic fibrosis. The interventions associated with these improvements include the reliance on nephrotoxic medications, which in and of themselves can lead to AKI and resultant CKD. In fact, our team previously demonstrated that children with noncritical illnesses who were exposed to a high nephrotoxic-medication burden and then developed AKI had a high rate of decreased GFR and/or proteinuria 6 months after the AKI episode (1). Importantly, none of these children had CKD or proteinuria before the nephrotoxic-medication exposure. The American Society of Nephrology AKI Working Group has highlighted a broader association of AKI to CKD and admonished clinicians regarding the 10% and 40% rates of follow-up for CKD after an AKI episode in adults and children, respectively (2). Furthermore, the Acute Disease Quality Initiative has recently codified the time period between AKI and CKD as "acute kidney disease" to focus attention on ensuring active follow-up of patients after an AKI episode for CKD development (3). It is inexcusable to lose these patients when their risk for CKD is so high.

Recognition of CKD in children is especially important given their relatively longer life expectancy compared with adults and the progressive rate of GFR decline observed in children with CKD (4). Although successful interventions to slow CKD progression in adults and children are limited, including angiotensin-converting enzyme inhibition and good BP control, avoidance of unnecessary nephrotoxic-medication exposure represents a potential method to preserve kidney function. Increasing awareness of nephrotoxic medication–associated AKI and avoidance of unnecessary nephrotoxic-medication burden can lead to a sustained decrease in AKI rates in children with noncritical illness (5). The rates of nephrotoxic-medication exposure in children with CKD, however, has not been reported extensively.

In this issue of *CJASN*, Lefebvre and colleagues (6) report the results of their interrogation of a large diagnostic code database, housed in the United Kingdom, to ascertain nephrotoxic-medication prescribing rates in children <18 years of age. They examined data from a 20-year period (1997–2017) and matched nephrotoxic-medication prescribing rates in children with versus without a diagnosis of CKD (1:4 match) and assessed patients for up to 5 years after the diagnosis of CKD was first recorded. In their comparison, the investigators adjusted for sex, age, Index of Multiple Deprivation quintile, general practice region, number of hospitalizations in 12 months before cohort entry, prematurity, diabetes, hypertension, cancer, and history of heart surgery or heart failure.

After starting with >15 million patients in the database, the investigators were able to confidently match about 1000 patients with CKD to 4000 patients without CKD. Overall, 26% of children with CKD versus 15% of children without CKD were prescribed at least one nephrotoxic medication over the period of study, using a list widely regarded to comprise nephrotoxic medications. Nonsteroidal inflammatory drugs (NSAIDs) were the most commonly prescribed medications for these cohorts. The exposure rates increased to 71% versus 50% when an expanded medication list was used; cephalosporin/penicillin antibiotics accounted for the most common exposures from this expanded list. After their multiple adjustments, the investigators observed a relative rate of nephrotoxic-medication prescription for patients with CKD of 4.1 and 2.7 from the first and expanded medication lists, respectively.

These results are of great concern for the pediatric CKD population. One could potentially expect that knowledge of CKD and the risk for more rapid CKD progression from nephrotoxic-medication exposure would yield a lower rate of nephrotoxic-medication prescription, not a rate that is two- to fourfold higher. Clearly, many of these patients with CKD could have other underlying systemic illnesses that require the use of nephrotoxic medications; yet, in their secondary analyses, the investigators demonstrate that some medications classes, such as NSAIDs and proton pump inhibitors, have suitable less nephrotoxic alternatives and are therefore potentially avoidable. These exposures were also consistent over the 5 years of follow-up, revealing a persistent nephrotoxic-medication burden that likely has cumulative effects. NSAIDs are of particular concern, because children who are hospitalized and receive an appropriate dose of an

NSAID still have a high rate of AKI (7). Given that nephrotoxic medication–associated kidney injury is usually nonoliguric, the damage caused by these medications in any patient, not only children with CKD, may go unrecognized unless rigorous, systematic surveillance of kidney function by serum creatinine or cystatin C is undertaken.

This study has many strengths, including a robust database with sufficient information to assess for confounding variables that were rightly included in the adjustments, detailed medication prescription data, a long duration of follow-up, and the included matching of patients with versus without a CKD diagnosis. The major limitation, which the authors note, is the reliance on administrative coding data, which is well known to underestimate AKI and CKD rates, including in children. The database also does not contain information regarding prescription indication or the medical specialty of the prescribing practitioner, both of which would calibrate the interpretation of the necessity of the medications being prescribed.

Nevertheless, the results from this study should serve to stimulate the pediatric medical community to insist on developing systems to identify appropriate and inappropriate nephrotoxic-medication prescribing to children with CKD, with a goal of protecting children from the latter. AKI survivor clinics cannot only be used to assess for CKD development, but also to educate children and their caregivers regarding nephrotoxic medications and medication classes to avoid (8). This type of program represents just one small, initial step toward a goal of achieving zero preventable harm to children with CKD.

Disclosures

Dr. Goldstein has nothing to disclose.

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See related article, "Primary Care Prescriptions of Potentially Nephrotoxic Medications in Children with CKD," on pages 61–68.