ACKD Advances in Chronic Kidney Disease
A Journal of the National Kidney Foundation®
Vol 27, No 1, January 2020

EDITORIAL

Toxicology and Kidney: Not so Innocent Bystander

Check for updates

Patients are exposed to numerous prescribed and over-the-counter medications. Unfortunately, drugs remain a relatively common cause of acute and chronic kidney injury. By some estimates, up to 1-in-3 cases of acute kidney injury (AKI) can be attributed to the effect of prescribed drugs and endogenous/exogenous toxins. However, establishing causality in drug-induced kidney disease is challenging and requires knowledge of the biological plausibility of the agent, mechanism of injury, time course, and assessment of competing risk factors. To date, there are no widely accepted standards to identify and characterize the spectrum of these disorders. A recent consensus publication proposed standardizing "phenotypes" for drug-induced kidney disease as delineated by the International Serious Adverse Events Consortium. This opinion-based publication proposed phenotypes based on the primary compartment of tissue damage: tubular injury, glomerular injury, interstitial inflammation, and nephrolithiasis.[1]

AKI is usually diagnosed during acute care hospitalizations. Yet, it may be "community-acquired," whereby the illness associated with AKI is triggered before acute care admission, or "hospital-acquired", where it is typically considered as a complication of an illness after hospitalization. A Veterans Administration intensive care unit cohort — observational cohort using a central infrastructure to support learning and improvement — described the natural history of AKI in critically ill patients. From over 195 intensive care units across the country, the study recorded that approximately 75% of participants who met the criteria for AKI did so within first 48 hours of admission (median time, 15.6 hours; interquartile range, 8.5 to 27.6 hours). Another 25% of AKI subjects reached that threshold at a median time of 87.2 hours (interquartile range, 53 to 147 hours). Importantly, the odds of hospital mortality for the community acquired group were 2.52 (95% confidence interval, 2.45 to 2.60) but was 4.66 (95% confidence interval, 4.47 to 4.85) in the hospital acquired group.[2] In both instances, there are possible links to prescribed agents.[2]

A combination of factors including the innate nephrotoxicity of drugs, underlying patient characteristics that increase their risk for kidney injury, and the metabolism and pathway of excretion by the kidneys of the various agents administered enhance risk for drug-induced nephrotoxicity.[3] A keen understanding of these domains is necessary to be able to approach the diagnosis and management of these disorders. Although AKI as a syndrome does not have any specific therapies, the cause of AKI due to a drug or a toxin provides a unique opportunity to either prevent or treat these exposures, including application of specific extra-corporeal therapies.

In addition to the mechanisms of action and specific targets of kidney damage (e.g., tubular epithelium, endothelium, blood vessels, podocytes, and so on), there is an opportunity to prevent or manage these types of disorders via an improvement in processes of care. For instance, a nicely compiled review in this issue, which covers various nephrotoxins, highlights the fact that many of such drug exposures overlap multiple disciplines that deliver care to our patients.[4] For instance, radio-contrast exposures can be primarily prescribed in association with diagnostic studies or cardiovascular interventions; antidiabetic therapies are usually managed by primary care or endocrine specialists, whereas vitamins and herbal supplements can be consumed by patients without any directed prescriptions. Thus, a multipronged approach of prevention includes increased awareness of both the providers and patients. In addition, once an exposure occurs, and a nephrologist is involved in the care of the patient, a high index of suspicion of a potential toxic exposure remains one of the cornerstones of early recognition and treatment.

As for therapies, including antidotes or extracorporeal removal, time is the essence once a patient has already set on a cascade of vital organ injury. Thus, institution of therapies to preserve organ function and prevent ongoing damage remain the overarching principles of

1548-5595/$36.00
https://doi.org/10.1053/j.ackd.2020.01.001

the initial approach to management. Many anecdotal reports in the literature suggest that the morbidity and mortality associated with these syndromes could be mitigated by more timely diagnosis and early institution of therapies.

The burden of diagnosis of treatment is that much more when there is potential harm due to a prescribed agent. As we develop novel therapies to treat complex life-threatening diseases, the discussion about risks and benefits of kidney injury as an "innocent bystander" becomes that much more relevant given the established connections between kidney injury and mortality as well as long-term risk of progressive kidney disease. The patients deserve our meticulous attention towards the possible adverse events and toxicities of prescribed therapies and counseling them in instances of other exposures that could cause harm to vital organs.

Charuhas V. Thakar, MD
Professor of Medicine

Division of Nephrology
University of Cincinnati
Renal Section, Cincinnati VAMC
Cincinnati, OH

Financial Disclosure: The author declares that he has no relevant financial interests.

REFERENCES

1. Mehta RL, Awdishu L, Davenport A, et al. Phenotype standardization for drug-induced kidney disease. *Kidney Int.* 2015;88(2):226-234.
2. Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med.* 2009;37(9):2552-2558.
3. Perazella M. Pharmacology behind common drug toxicites. *Clin J Am Soc Nephrol.* 2018;13(12):1897-1908.
4. Harbord N. Poisoning, toxicology, and the nephrologist. *Adv Chronic Kid Dis.* 2020;27(1):3-4.