Nephron

Clinical Practice: Mini-Review

Nephron
DOI: 10.1159/000531916

Received: March 31, 2023
Accepted: June 30, 2023
Published online: August 22, 2023

Challenges in Pharmacovigilance: Variability in the Criteria for Determining Drug-Associated Acute Kidney Injury in Retrospective, Observational Studies

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Keywords
Acute kidney injury · Medication errors · Patient harm · Patient safety · Pharmacovigilance

Abstract

Background: Drug-associated acute kidney injury (D-AKI) accounts for 19–26% of acute kidney injury (AKI) events in hospitalized patients and results in outcomes similar to patients with AKI from other etiologies. Diagnosing D-AKI is complex and various criteria have been used. ***Summary:*** To highlight the variability in D-AKI determination, a review was conducted between January 2017 and December 2022 using PubMed. Search terms included adaptations of "drug associated kidney injury" to identify a sampling of literature discussing definitions and criteria for D-AKI evaluation. The search yielded 291 articles that were uploaded to Rayyan, a software tool used to screen and select studies. Retrospective, observational electronic health record (EHR) studies conducted in hospitalized patients were included. The final sample contained 16 studies for data extraction, representing mostly adult populations (n = 13, 81.3%) in noncritical or unspecified inpatient settings (n = 12, 75%). Nine studies (56.3%) utilized the recommended Kidney Disease: Improving Global Outcome guidelines (KDIGO) criteria to define AKI. Baseline creatinine or laboratory criteria for kidney function were provided in 10 studies (62.5%). Eleven studies (68.8%) established a temporal sequence assessment linking nephrotoxin drug exposure to an AKI event, but these criteria were inconsistent among studies using time frames as soon as 3 months prior to AKI. ***Conclusion:*** This review highlights the substantial variability in D-AKI criteria in select studies. Minimum expectations about what should be reported and criteria for the elements reported are needed to assure transparency, consistency, and standardization of pharmacovigilance strategies.

Introduction

Drug-associated acute kidney injury (D-AKI), a phenotype of acute kidney injury (AKI), accounts for 19–26% of inpatient AKI events [1]. A study conducted across five academic hospitals in the USA reported in-hospital

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mortality rates from nephrotoxic causes ranging from 18% to 50% [2]. A single-center AKI surveillance study among children reported that 70% of the patients presented with residual kidney damage during a follow-up visit that was 6 months after the AKI event associated with high nephrotoxic medication exposure [3]. Patient outcomes related to D-AKI are similar to outcomes for patients with AKI due to other etiologies [2].

It is important to identify and manage D-AKI promptly to avoid negative outcomes. Still, the diagnosis of D-AKI is a complex process and various criteria have been used to make this determination. The criteria are complicated further when real-time assessments in clinical practice are compared to retrospective evaluations using electronic health record (EHR) data. The heterogeneity in D-AKI assessment criteria creates confusion and inconsistency. This can prevent proper identification and overlooking drugs as a contributor or cause of an AKI event [1, 4]. Further, it creates challenges in pharmacovigilance.

D-AKI requires standardized definitions to facilitate detection, consistency in interpretation, opportunities for prevention, and ensuring pharmacovigilance surveillance strategies. This review highlights the variability in D-AKI criteria in a select representation of recent retrospective, observational EHR studies conducted in hospitalized patients.

Methods

A PubMed search was conducted between January 2017 and December 2022 to identify a recent sampling of literature discussing definitions and criteria for D-AKI using the following terms: "drug" or "medication" or "nephrotoxin" mentioned in the title, and "associated" or "induced" and "acute kidney injury" or "acute kidney failure" or "acute kidney disease" or "acute renal failure" or "acute renal disease" or "acute renal injury" or "AKI" or "ARF" or "AKD" mentioned in any aspect of the article (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000531916). Additionally, the search included the following filters: full-text, humans, and English. The PubMed search yielded 291 articles.

Rayyan, a software tool to facilitate screening and selecting studies, was used. The 291 publications were uploaded to Rayyan for title and abstract review. Inclusion criteria were observational studies conducted in hospitalized patients. Case reports or series, prospective studies, meta-analyses, reviews, letters, editorials, and commentaries were excluded (n = 102). Furthermore, studies that were not available as full-text (n = 4), irrelevant to the review (n = 125), and of an inappropriate study population (n = 19) were excluded. Articles were evaluated by three reviewers (N.A., I.Z., C.S.). Two additional reviewers (B.S., S.L.K.-G.) were available to resolve any discrepancies. Forty-one articles remained for full-text review. Of these studies, there were further exclusions because 18 were not EHR studies, four did not define D-AKI and three described illicit drug use, drug abuse, or unregulated substances as a cause for D-AKI. The final sample contained 16 studies for data extraction (online suppl. Fig. 2).

The following information was extracted from each article: patient population and care setting, D-AKI definition used, if D-AKI criteria were derived from AKI guidelines, utilization of urine output criteria for AKI, management of missing serum creatinine (SCr) data, definition of baseline SCr and related criteria, temporal sequence conditions for D-AKI, assessment of creatinine stability and other AKI causes including drugs prior to an AKI event, plausibility of drug as a cause, utilization of a causality tool, and evaluation of recovery.

Results

Of the 16 articles, the patient populations mainly consisted of adults (n = 13, 81.3%) with the remaining studies conducted in the pediatric population (n = 3, 18.8%). A majority were denoted as noncritical inpatient or unspecified inpatient (n = 12, 75%), three (18.8%) were completed in intensive care units, and one (6.3%) study evaluated patients who transferred from the emergency department to the ward.

Table 1 provides the exact definitions for D-AKI and highlights the variability. Definitions differed between articles with some lacking any temporal relation of nephrotoxin exposure to AKI development and others deviating from guidelines. For example, one study mentions D-AKI development with nephrotoxin exposure within the 3 months prior to AKI; whereas another describes AKI development within 48 h prior to nephrotoxin exposure. Table 2 provides a detailed list of the criteria applied for determining AKI and the criteria applied for assessing causality. Nine studies (56.3%) utilized Kidney Disease: Improving Global Outcome guidelines (KDIGO) for AKI determination while the others utilized Acute Kidney Injury Network (AKIN) (n = 3, 18.8%), Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) (n = 1, 6.3%), or alternative criteria (n = 3, 18.8%). Only 10 studies (62.5%) provided a baseline definition for SCr or other laboratory result to describe kidney function before drug administration. In cases of missing SCr values, only 10 studies (62.5%) mentioned a method to account for this in the data analysis (i.e., excluding subjects or adjusting for this statistically post-data collection). A total of 11 studies (68.8%) established a temporal sequence linking nephrotoxin drug exposure to an AKI event, but variation among the studies existed. One (6.3%) study used an adverse drug-event causality tool (i.e., Naranjo) for an objective assessment of nephrotoxin association to an AKI event.

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Table 1. Definitions provided for baseline kidney function, drug associated AKI, and temporal sequence

Author (Year)	Guidelines referenced for definitions	Definition of D-AKI	Baseline criteria	Temporal sequence
Ye et al. [5] (2022)	RIFLE	"The RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria, which are based on the highest serum creatinine value observed during polymyxin B therapy and compared with the baseline, were used to evaluate whether the patients had developed renal injury and the severity of nephrotoxicity."	"Baseline serum creatinine was that measured on the day that polymyxin B was initiated."	During polymyxin B therapy
Qiao et al. [6] (2022)	2018 recommendations of the European Society of Urogenital Radiology	". . .PC-AKI is defined as an increase in SCr levels >26.5 mol/L (0.3 mg/dL), or to a value 1.5 times the baseline value, in the 48–72 h following PCI."	N/A	48–72 h following PCI
Salerno et al. [7] (2021)	KDIGO (AKI)	"Based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, we defined AKI as an increase in serum creatinine ≥0.3 mg/dL or ≥1.5 times the baseline creatinine which was considered to be the most recent serum creatinine value within 2 days of first drug combination exposure."	". . .baseline creatinine which was considered to be the most recent serum creatinine value within 2 days of first drug combination exposure."	". . .after the first day of exposure through 6 days after last day of drug combination exposure."
Jeon et al. [8] (2021)	KDIGO (AKI)	". . .(1) an increase in serum creatinine (SCr) to ≥150% within 7 days from baseline or (2) an increase in SCr by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 h at any time during follow-up, according to the Kidney Disease Improving Global Outcomes (KDIGO) SCr-based criteria."	"The index date for the exposed group was the first day of use of any NSAID during the hospital stay... The baseline period included the index date and up to 2 days before the index date. . .Baseline SCr was defined as the closest SCr to index date, which was measured during the baseline period."	". . .(1) an increase in serum creatinine (SCr) to ≥150% within 7 days from baseline or (2) an increase in SCr by ≥ 0.3 mg/dL (26.5 μmol/L) within 48 h at any time during follow-up. . ." The follow-up period was for 5 days after the last day of NSAID administration.
Roberts et al. [9] (2021)	KDIGO (AKI)	". . .developed AKI within 30 days after surgery as defined by the Kidney Disease: Improving Global Outcomes criteria (a ≥26 μmol/L absolute increase in serum creatinine within 48-h or ≥50% relative increase in serum creatinine within 7 d)."	"Baseline estimated glomerular filtration rate (eGFR) was calculated using the closest serum creatinine measurement before surgery as per the Chronic Kidney Disease Epidemiology Collaboration equation."	"Temporal associations between prior medication exposures and AKI were also examined within four mutually exclusive first exposure time periods defined relative to the index date for each case and matched controls. These included the first exposure to medication on the day immediately before the index date, first exposure 2–3 d prior to the index date, first exposure 4–5 d before the index date, and first exposure greater than 5 d before the index date."
Oda et al. [10] (2020)	AKIN	". . .an increase in SCr level >0.3 mg/dL or >50% in at least two consecutive measurements during vancomycin therapy."	N/A	During vancomycin therapy
Hinson et al. [11] (2020)	KDIGO (AKI)	"AKI was defined as an absolute increase in sCr concentration of ≥0.3 mg/dL or 1.5 times increase over baseline within the previous 7 days according to the Kidney Disease Improving Global Outcomes (KDIGO) sCr-based criteria."	"The first sCr measured during the index ED encounter was used as baseline, and an interval of 24–168 h was selected based on previously published consensus-based definitions for DIKD."	N/A; The evaluation of SCr was conducted from 24 to 168 h after admission to the ED and nephrotoxins prescribed in the ED were considered for D-AKI. It is unclear if these drugs were a continuation of home medications.

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Table 1 (continued)

Author (Year)	Guidelines referenced for definitions	Definition of D-AKI	Baseline criteria	Temporal sequence
Yu et al. [12] (2020)	KDIGO (AKI)	"According to the AKI SCr definition criteria of 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury, the inclusion criteria were as follows:. . . (3) an increase in SCr by at least 0.3 mg/dL within 48 h or an increase in SCr to at least 1.5 times higher than baseline within the prior 7 days. . .The Naranjo Adverse Drug Reaction Probability Scale (Naranjo Scale) was used to determine whether AKI could be caused by drugs. The ADR was assigned to a probability category from the total score as follows: definite ≥9, probable 5–8, possible 1–4, and doubtful ≤0. Patients with scores ≥1 were defined as D-AKI."	"We defined the SCr baseline as the last laboratory measurement between 7 days before and 2 h after administration of the suspected drug."	N/A; Temporality was assessed inherent to the grading in the Naranjo criteria, but the time frame was N/A in the methods.
Wang and Chen [13] (2020)	Clinical practice guideline for drug-induced kidney injury in Japan 2016	"The diagnosis of drug-induced kidney injury was based on the 2016 clinical guidelines in Japan."	N/A	". . .patients with acute kidney injury (AKI) with a drug exposure history within 3 months. . ."
Yamamoto et al. [14] (2019)	KDIGO (CKD)	"The following categories were included in the definition of RAS inhibitor–related kidney injury: (a) RAS inhibitor–related eGFR decline of greater than or equal to 30% defined as an eGFR decline that recovered by greater than or equal to 30% within 3 months of discontinuation of the RAS inhibitor and (b) RAS inhibitor–related hyperkalemia of greater than or equal to 6.0 mEq/L defined as a potassium level greater than or equal to 6.0 mEq/L that normalized after discontinuation of the RAS inhibitor."	"The patients' eGFR and potassium levels at 3 months after discontinuation of the RAS inhibitors were regarded as baseline levels."	Within 3 months of discontinuation of the RAS inhibitor
Jeon et al. [15] (2019)	KDIGO (AKI)	"Following the Kidney Disease International Global Organization (KDIGO) stage 2 AKI criteria, AKI was defined as the first day with an increase of serum creatinine (SCr) ≥200% of a baseline SCr within 1–5 days."	"Baseline SCr was defined as the most recent SCr within 2 days prior to a given (D-AKI) risk model day."	"Because AKI manifestation may take several days after a renal insult, we followed a patient up to 5 days after a (D-AKI) risk model day to ascertain onset."
Delzer et al. [16] (2018)	KDIGO (AKI)	"The presence of AKI was determined by an increase in SCr ≥0.30 mg/dL or an increase in SCr to ≥1.5 times baseline within 48 h after initiation of NSAID therapy. The severity of AKI was graded as follows: stage 1: equivalent to an increase in SCr ≥0.30 mg/dL or 1.5–1.9 times baseline; stage 2: equivalent to an increase in SCr of 2.0–2.9 times baseline; and stage 3: equivalent to an increase in SCr to ≥4.00 mg/dL or ≥3.0 times baseline or initiation of renal replacement therapy."	"Comparator patients were excluded from primary and secondary analyses if they did not have an initial or baseline SCr measured within 24 h after hospital admission."	48 h after initiation of NSAID therapy

Table 1 (continued)

Author (Year)	Guidelines referenced for definitions	Definition of D-AKI	Baseline criteria	Temporal sequence
Uber et al. [17] (2018)	KDIGO (AKI)	"Acute kidney injury was diagnosed and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria during the first 7 days of CVICU stay. . . The creatinine criteria were applied with complete temporal components (7 days for relative changes and 48 h for the 0.3 mg/dL absolute change). AKI was defined as the presence of any KDIGO AKI stage; severe AKI was defined as the presence of KDIGO AKI stage ≥2."	"Baseline creatinine was determined to be the serum creatinine most proximal to the surgical procedure. If one was not available in the immediate preoperative phase, baseline was assessed to be the lowest creatinine in the 3 months prior to surgery."	N/A; Nephrotoxin exposure within 7 days after cardiovascular surgery and AKI within the 7 days postoperatively but the temporality between drug and event was N/A.
Duceppe et al. [18] (2018)	AKIN	"The primary outcome was postoperative AKI at 48 h after surgery. AKI was defined by the stage 1 criterion of the Acute Kidney Injury Network (AKIN), that is, an absolute increase in serum creatinine concentration ≥26 μmol/L or a ≥50% increase in baseline serum creatinine concentration."	N/A	N/A; Antihypertensive initiation date N/A. Evaluated antihypertensive medications continued on the morning of surgery and evaluation of AKI at 48 h postoperatively.
Branch-Elliman et al. [19] (2017)	AKIN	"Stage 1 AKI was defined as an increase in serum creatinine ≥26.5 μmol/L (0.3 mg/dL) and/or an increase to 1.5- to <2.0-fold the baseline level. Stage 2 AKI was defined as an increase in serum creatinine to 2.0- to <3.0-fold the baseline level, and Stage 3 AKI was defined as an increase of serum creatinine to ≥3.0-fold the baseline level or an increase in creatinine from <353.6 μmol/L (4.0 mg/dL) to ≥353.6 μmol/L (4.0 mg/dL) with at least a 44.2-μmol/L (0.5-mg/dL) rise."	N/A	"The association between receipt of 2 drugs versus 1 drug and the post operative incidence of AKI (any AKI and AKI stages 1, 2, and 3 as defined by the Acute Kidney Injury Network) within 7 days was evaluated."
Constance et al. [20] (2017)	KDIGO (AKI)	"Specifically, AKI was defined as an increase in SCr ≥0.3 mg dL^{-1} (≥26 μmol L^{-1}) within a 48 h time period or an increase in SCr to ≥1.5 times baseline, known or presumed to have occurred within the prior 7 days. In addition, SCr measurements ≥1.5 mg dL^{-1} persisting ≥48 h were considered an AKI."	N/A	N/A; However, data provided suggest 15 days. Median (IQR) age of first NSAID administration was 4.9 (3.7–7.7) days in neonates; median (IQR) doses of NSAID was 3 (3–6); AKI events were evaluated in first 30 days of life and the median (IQR) day of life for first AKI event was 15.5 (6.3–34.8).

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; D-AKI, drug-associated acute kidney injury; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcome; N/A, not available; NSAID, nonsteroidal anti-inflammatory drug; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SCr, serum creatinine.

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Table 2. Criteria for assessing AKI and drug causality

	Ye et al. [5] (2022)	Qiao et al. [6] (2022)	Salerno et al. [7] (2021)	Jeon et al. [8] (2021)	Roberts et al. [9] (2021)	Oda et al. [10] (2020)	Hinson et al. [11] (2020)	Yu et al. [12] (2020)	Wang and Chen [13] (2020)	Yamamoto et al. [14] (2019)	Jeon et al. [15] (2019)	Delzer et al. [16] (2018)	Uber et al. [17] (2018)	Duceppe et al. [18] (2018)	Branch-Elliman et al. [19] (2017)	Constance et al. [20] (2017)
Used urine output criteria																
Missing data for SCr discussed			X	X	X		X	X			X	X		X	X	X
Baseline SCr or lab value definition provided	X		X	X	X		X	X		X	X	X	X			
Explicit temporal sequence established	X	X	X	X	X	X			X	X	X	X			X	
Creatinine stability prior to AKI assessed																
Other causes of AKI discussed	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Discussed known nephrotoxicity of potentially causal agent (plausibility)		X	X	X	X	X	X	X		X	X	X	X	X	X	X
Causality tool used to aid in assessment of drug-associated event								X								
Assessed more than one medication			X	X	X		X	X	X	X	X	X	X	X	X	X
Concomitant drugs considered	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Recovery/ resolution evaluated													X			

Used urine output criteria: $n = 0$, 0%; missing data for SCr discussed: $n = 10$, 62.5%; baseline definition provided: $n = 10$, 62.5%; temporal sequence established: $n = 11$, 68.8%; creatinine stability prior to AKI assessed: $n = 0$, 0%; other causes of AKI discussed: $n = 15$, 93.8%; discussed known nephrotoxicity of potentially causal agent: $n = 14$, 87.5%; causality tool used to aid in assessment of drug-associated event: $n = 1$, 6.3%; assessed more than one medication: $n = 13$, 81.3%; concomitant drugs considered: $n = 15$, 93.8%; recovery/resolution evaluated: $n = 1$, 6.3%.

Discussion

There is lack of consistency in D-AKI definitions and causality assessment criteria provided in retrospective observational studies representing challenges in detection, assessment, understanding, and prevention. Even studies that provided a definition for D-AKI were dissimilar, indicating a lack of standardization. Drug-event causality tools are recommended to aid in assessment and provide reliability among evaluators and between studies but were utilized in only one of the 16 selected articles. Causality criterion most frequently assessed across the 16 studies was plausibility of the drug as a cause, temporal sequence, and other causes. While this may appear favorable at first glance, it is highly discouraging that not only did definitions vary, but baseline SCr definition, temporal sequence consideration between AKI event and drug, evaluation of other drug causes, and other nondrug causes also lacked consistency between studies. This lack of standardization explains why variability in incidence and prevalence rates of D-AKI exists.

The three main criteria used to identify AKI are KDIGO, RIFLE, and AKIN. Although all of these definitions have similarities, the more recent and preferred definition is KDIGO [21]. Of the 16 articles evaluated, only nine (56.3%) applied KDIGO and of those, not all employed the full KDIGO definition or variations of the definition were utilized. Additionally, the 10 studies (62.5%) that provided a baseline definition for SCr or other laboratory result to describe kidney function before drug administration, a concept mentioned in the mainstay guidelines, used time windows for determination of baseline SCr ranging from within 30 days prior to drug insult to 3 months after (i.e., 3 months after discontinuation of the RAS inhibitors were regarded as baseline levels) [9, 14]. Establishing a baseline laboratory measurement for comparison to fluctuations post-nephrotoxin insult is essential to determining the presence of D-AKI.

Further discrepancies exist, with only 11 studies (68.8%) establishing a temporal relation between the nephrotoxin administration and AKI onset. Temporal sequences were described as "after the first day of exposure through 6 days after last day of drug combination exposure" and "patients with AKI with a drug exposure history within 3 months" [7, 13]. Assessing temporal sequence is an essential gauge for causality because the drug must be administered before the rise in functional or damage biomarkers. Also, the drug should be administered at least 24 h prior to the rise in SCr because it takes at least that long for the increase to reflect the insult. Temporal sequence is a minimum characteristic to consider for causality.

There are several other items that should be reported for transparency in causal determination. The management of missing data such as SCr needs to be discussed as with any study involving EHR data. Deliberating other causes of AKI such as other drugs, diseases, or conditions, including sepsis or surgery, are relevant causality criterion and critical in D-AKI determination. Consideration to the stability of the baseline SCr provides evidence of the contribution of the drug to the change of functional kidney status. When a drug is administered while the SCr is rising, this suggests an association more than an induced event. In contrast, if the drug is administered while the SCr is stable then this enhances consideration of causality. Baseline SCr stability prior to drug administration was not discussed in any article we evaluated. Knowing recovery status following a D-AKI event is useful in understanding the impact but was only reported in one study. All of these criteria are important to disclose in D-AKI assessment.

This review focused on retrospective studies to provide homogeneity in the evaluation because there are expectations that real-time and retrospective studies may have inherent variability in the assessment measures. We limited our review to studies over the past 6 years for an evaluation of contemporary approaches. The search terms used could have been more thorough, but the goal was to provide a sampling of the variability in the literature and not a comprehensive systematic review. A further description of elements to report in studies evaluating D-AKI is highlighted in online supplementary Table 1.

Conclusion

The variability in the criteria for assessing D-AKI and causality is substantial, creating challenges in pharmacovigilance surveillance strategies. For purposes of transparency and consistency, there should be a minimum expectation about what should be reported and criteria for the elements reported in retrospective observational EHR studies designed to evaluate D-AKI.

Conflict of Interest Statement

Dr. Kane-Gill receives grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases R01 DK121730 and U01DK130010, the National Center for Complementary and Integrative Health U54AT008909, and the Jewish

Healthcare Foundation. A.B. was supported R01 GM110240 from the National Institute of General Medical Sciences (NIH/NIGMS), R01 EB029699 and R21 EB027344 from the National Institute of Biomedical Imaging and Bioengineering (NIH/NIBIB), R01 NS120924 from the National Institute of Neurological Disorders and Stroke (NIH/NINDS), and by R01 DK121730 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK). T.O.-B. was supported by K01 DK120784, R01 DK123078, and R01 DK121730 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), R01 GM110240 from the National Institute of General Medical Sciences (NIH/NIGMS), R01 EB029699 from the National Institute of Biomedical Imaging and Bioengineering (NIH/NIBIB), R01 NS120924 from the National Institute of Neurological Disorders and Stroke (NIH/NINDS), and UL1TR001427 from the National Center For Advancing Translational Sciences of the National Institutes of Health.

Dr. Kane-Gill holds an executive position in the Society of Critical Care Medicine. The content of this manuscript is solely the responsibility of the author and does not represent the official views of the Society of Critical Care Medicine.

Funding Sources

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award number R01 DK121730. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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