Effect of Tiered Implementation of Clinical Decision Support System for Acute Kidney Injury and Nephrotoxin Exposure in Cardiac Surgery Patients

Christopher M. Justice II[1,2,3,#] Connor Nevin[4,#] Rebecca L. Neely[5] Brian Dilcher[6] Nicole Kovacic-Scherrer[7] Heather Carter-Templeton[8] Aaron Ostrowski[2,9] Jacob Krafcheck[1] Gordon Smith[10] Paul McCarthy[11] Jami Pincavitch[12,13] Sandra Kane-Gill[14] Robert Freeman[15] John A. Kellum[16] Roopa Kohli-Seth[17] Girish N. Nadkarni[18,19,20] Khaled Shawwa[21] Ankit Sakhuja[17,19,20]

[1] Heart and Vascular Institute, JW Ruby Memorial Hospital, West Virginia University, Morgantown, West Virginia, United States
[2] Nurse Anesthesia Program, School of Nursing, West Virginia University, Morgantown, West Virginia, United States
[3] Department of Anesthesia, Summersville Regional Medical Center, West Virginia University, Summersville, West Virginia, United States
[4] Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, United States
[5] Department of Information Technology, West Virginia University, Morgantown, West Virginia, United States
[6] Department of Emergency Medicine, West Virginia University, Morgantown, West Virginia, United States
[7] School of Pharmacy, West Virginia University, Morgantown, West Virginia, United States
[8] Department of Adult Health, School of Nursing, West Virginia University, Morgantown, West Virginia, United States
[9] Department of Anesthesia, West Virginia University, Morgantown, West Virginia, United States
[10] Department of Epidemiology and Biostatistics, West Virginia University, Morgantown, West Virginia, United States
[11] Division of Cardiovascular Critical Care, Department of Cardiovascular and Thoracic Surgery, West Virginia University, Morgantown, West Virginia, United States
[12] Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, United States
[13] Department of Orthopedics, West Virginia University, Morgantown, West Virginia, United States
[14] Department of Pharmacy and Therapeutics, University of Pittsburgh, Pittsburgh, Pennsylvania, United States
[15] Institute for Health Care Delivery Science, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[16] Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States
[17] Institute for Critical Care Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States
[18] Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States
[19] Division of Data Driven and Digital Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States
[20] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States
[21] Section of Nephrology, Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, United States

Address for correspondence Ankit Sakhuja, MBBS, MS, Division of Data Driven and Digital Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States (e-mail: ankit.sakhuja@mssm.edu).

Appl Clin Inform 2025;16:1–10.

Abstract

Background Nephrotoxin exposure may worsen kidney injury and impair kidney recovery if continued in patients with acute kidney injury (AKI).

Objectives This study aimed to determine if tiered implementation of a clinical decision support system (CDSS) would reduce nephrotoxin use in cardiac surgery patients with AKI.

Methods We assessed patients admitted to the cardiac surgery intensive care unit at a tertiary care center from January 2020 to December 2021, and August 2022 to September 2023. A passive electronic AKI alert was activated in July 2020, followed by an electronic nephrotoxin alert in March 2023. In this alert, active nephrotoxic medication orders resulted in a passive alert, whereas new orders were met with an

Keywords
- nephrotoxin
- clinical decision support
- acute kidney injury
- electronic alert
- nephrotoxic medication

[#] *equally contributed as first author.*

received
May 29, 2024
accepted after revision
September 19, 2024

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0044-1791822.
ISSN 1869-0327.

interruptive alert. Primary outcome was discontinuation of nephrotoxic medications within 30 hours after AKI. Secondary outcomes included AKI-specific clinical actions, determined through modified Delphi process and patient-centered outcomes. We compared all outcomes across five separate eras, divided based on the tiered implementation of these alerts.

Results A total of 503 patients met inclusion criteria. Of 114 patients who received nephrotoxins before AKI, nephrotoxins were discontinued after AKI in 6 (25%) patients in pre AKI-alert era, 8 (33%) patients in post AKI-alert era, 7 (35%) patients in AKI-alert long-term follow up era, 7 (35%) patients in pre nephrotoxin-alert era, and 14 (54%) patients in post nephrotoxin-alert era ($p = 0.047$ for trend). Among AKI-specific consensus actions, we noted a decreased use of intravenous fluids, increased documentation of goal mean arterial pressure of 65 mm Hg or higher, and increased use of bedside point of care echocardiogram over time. Among exploratory clinical outcomes we found a decrease in proportion of stage III AKI, need for dialysis, and length of hospital stay over time.

Conclusion Tiered implementation of CDSS for recognition of AKI and nephrotoxin exposure resulted in a progressive improvement in the discontinuation of nephrotoxins.

Background and Significance

Acute kidney injury (AKI), defined as an abrupt rise in serum creatinine,[1] is a common complication in critically ill patients. AKI is especially common in patients after cardiac surgery, where one in three patients develop AKI.[2] AKI in these patients is an independent predictor of morbidity and mortality.[1–3] Even a small rise in serum creatinine after cardiac surgery has been associated with worse outcomes.[1–3] AKI after cardiac surgery has a multifactorial etiology, including ischemia–reperfusion injury, neurohumoral activation, activation of inflammatory mediators, oxidative stress, and use of nephrotoxic agents.[4] The persistence of these factors can also lead to continued AKI progression. Among these, nephrotoxin use is a relatively easily modifiable risk factor. Nephrotoxin burden worsens AKI, and avoidance of nephrotoxins has been shown to decrease the incidence and progression of AKI in critically ill patients.[1–3,5–19] Additional measures to reduce AKI severity after cardiac surgery include volume optimization, maintenance of adequate end-organ perfusion, glycemic control, and workup for and management of underlying causes.[1–3,7,17,18,20] The management of AKI relies on early recognition and preventing its progression by providing clinical interventions early in its course.[1–3,5,6,8–19,21–23]

Informatics tools have provided a new opportunity to alert clinicians about the presence of AKI. Such measures have shown an impact on enhanced recognition and improved outcomes of patients with AKI.[5,8,16,24–26] They can, however, be hindered by the development of alert fatigue. Our previous work has led to the development of an electronic AKI alert designed to increase the awareness of AKI, which has shown over 90% end user acceptance 1 year after the implementation.[21] Initially, this alert was evaluated for its impact on discontinuation of nephrotoxins after AKI. To further enhance its effectiveness, and based on the feedback from key stakeholders, we have since enhanced this alert by incorporating an additional, nephrotoxin alert for patients with AKI who are prescribed potentially nephrotoxic medications.

Objectives

Our primary objective for the present study was to evaluate the impact of this tiered implementation of the clinical decision support system (CDSS) on the use of nephrotoxins in patients with AKI after cardiac surgery. Our secondary aims were to evaluate the impact of this tiered CDSS on other AKI-specific clinical actions and exploratory clinical outcomes.

Methods

The Clinical Decision Support System

Electronic Acute Kidney Injury Alert

We implemented the electronic AKI alert in the electronic health record on July 1, 2020, as an initial effort to improve early recognition of AKI.[21] We displayed this electronic AKI alert to physicians, advanced practice providers (APP), and pharmacists in a noninterruptive manner in the Epic[27] storyboard for 48 hours after the development of AKI (►Fig. 1A). The storyboard is a vertical bar on the left side of a patient's chart in Epic, which is the electronic health record at the institution. The storyboard includes patient information such as name, photo, age, date of birth, and allergies. The alert was triggered upon admission if an increase in serum creatinine of 50% or more was detected compared with baseline serum creatinine. For subsequent serum creatinine values within the same admission, the alert activated when there was an increase of at least 0.3 mg/dL

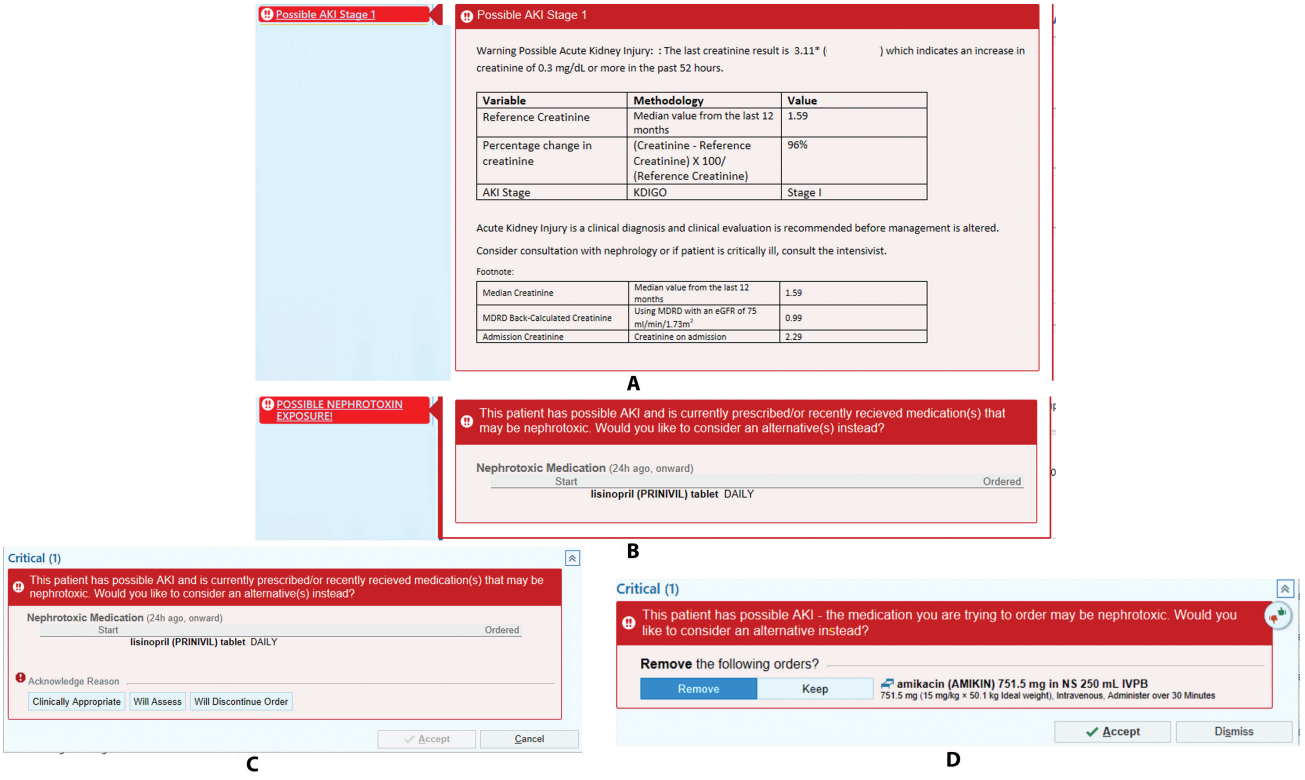

Fig. 1 Electronic alerts (©2024 Epic Systems Corporation). (**A**) Electronic acute kidney injury alert. (**B**) Passive electronic nephrotoxin alert for already ordered nephrotoxins. (**C**) Additional details shown on clicking the passive nephrotoxin alert. (**D**) Interruptive electronic nephrotoxin alert for new nephrotoxin orders.

within 52 hours from the baseline serum creatinine. Our previous work has shown high sensitivity, specificity,[28] and acceptance rates by end users caring for patients after cardiac surgery.[21]

Electronic Nephrotoxin Alert

We developed the electronic nephrotoxin alert such that it was activated for patients with AKI who were prescribed nephrotoxic medications. The nephrotoxic medication list for this alert was developed by the West Virginia University AKI Committee, a committee established to improve the processes and outcomes of patients with and at risk for AKI. The committee has multidisciplinary representation including intensivists, nephrologists, nurses, and pharmacists. The nephrotoxic medication list was created through a combination of comprehensive literature review,[9,29,30] input from content experts, and consideration for available formulary at the institution. We have shown the resultant nephrotoxic medication list in ►**Supplementary Table S1** (available in the online version). This alert was also displayed to physicians, APPs, and pharmacists caring for these patients. The alert was displayed in a noninterruptive fashion in the Epic storyboard[27] for patients with AKI who had active orders for a nephrotoxic medication (►**Fig. 1B**). Clicking the alert provides additional details about the triggering nephrotoxin and three options for the resolution of the alert (►**Fig. 1C**): (1) "Clinically Appropriate," which silences the alert for 12 hours; (2) "Will Assess," which silences the alert for 1 hour; and (3) "Will Discontinue Order," which does not silence the alert for that user, and thus, the user would continue to see the alert, until the active nephrotoxin order is discontinued. The time intervals for silencing the alert were determined through a collaborative process involving our informatics team members (A.S., R.L.N., B.D., J.P.) and feedback from end users. When a new order for a nephrotoxic medication was entered into the chart of a patient with AKI, the nephrotoxin alert was displayed as an interruptive alert (►**Fig. 1D**). This interruptive alert provided the end users the option to continue with the order or the default option to discontinue the unsigned order. This alert was initially implemented in our electronic health record in February 2023 but needed enhancements due to technical issues. The alert was then reimplemented in March 2023.

Study Design and Population

The study was conducted at a large, academic, tertiary care center's high-acuity cardiac surgery intensive care unit. We included all critically ill adult (≥18 years old) patients who developed AKI after cardiac surgery. We analyzed AKI events across five eras according to the timeline of the tiered implementation of CDSS with patient inclusion in each era determined by the timing of the AKI diagnosis/alert (►**Table 1**).

The diagnosis of AKI was based on the Kidney Disease Improving Global Outcome's (KDIGO) serum creatinine-based criteria.[1] In congruence with previous literature, we used the patient's median serum creatinine levels from the past 12 months to determine the baseline serum

Table 1 The eras based on implementation of the tiers of clinical decision support system

Era	Description	Timeline	AKI alert present	Nephrotoxin alert present
Era 1	Included patients within 6 mo before the implementation of the passive electronic AKI alert	January 2020–June 2020	No	No
Era 2	Included patients within 6 mo after the implementation of the electronic AKI alert	July 2020–December 2020	Yes	No
Era 3	Included patients for a year after the post AKI-Alert Era to assess the alert's long-term impact	January 2021–December 2021	Yes	No
Era 4	Included patients within 6 mo before the first implementation of the electronic nephrotoxin alert	August 2022–January 2023	Yes	No
Era 5	Included patients within 6 mo after the revised implementation of the electronic nephrotoxin alert	March 2023–September 2023	Yes	Yes

Abbreviation: AKI, acute kidney injury.

creatinine.[21,24,28] When prior serum creatinine values were unavailable, we estimated the baseline serum creatinine based on back-calculation using the Modification of Diet in Renal Disease equation.[31] Although race-free equations are now recommended for estimation of kidney function, they have not been validated for this application. For patients with a history of chronic kidney disease and no documented prior serum creatinine values, we used admission serum creatinine as the baseline serum creatinine. We excluded patients with end-stage kidney disease, those already on dialysis before cardiac surgery, and those with baseline creatinine ≥ 4 mg/dL.

Data Collection

We collected demographics (age and sex), medications, and clinical actions performed for up to 30 hours after AKI as per the AKI checklist. We chose the 30-hour time frame to capture actions performed early (approximately within the first day) after AKI. The clinical actions included the use or discontinuation of nephrotoxins, use of vasopressors, measurement of urine output, maintenance of mean arterial pressure (MAP) not less than 65 mm Hg for two consecutive hours, insertion or maintenance of an arterial line for patients requiring vasopressors, targeting of MAP goal of 65 mm Hg or greater (per the documentation in progress notes), initiation or maintenance of intravenous fluid infusion, use of diuretics, hourly urine output measurement, documentation of assessment of volume status in progress notes, documented use of bedside point of care echocardiogram, performance of formal transthoracic echocardiogram, performance of renal ultrasound, measurement and trending of serum lactate values if the first value was above 2 mmol/L, workup for sepsis (measurement of procalcitonin or collection of blood cultures), and maintenance of glycemic control (serum glucose values < 180 mg/dL). To evaluate the discontinuation of nephrotoxins within 30 hours after AKI, we assessed and compared nephrotoxins administered within 30 hours before and after AKI. As iodinated contrast is not ordered as a recurring medication, we did not include it as part of the nephrotoxins discontinued after AKI. We did, however, include the use of iodinated contrasts as a new nephrotoxin if administered within 30 hours after AKI development. We also collected information regarding the maximum AKI stage during hospital stay, need for dialysis, and length of hospital stay.

Outcomes

Our primary outcome was the discontinuation of nephrotoxins after AKI among patients who have undergone cardiac surgery. Secondary outcomes included AKI-specific clinical actions and exploratory clinical outcomes. The AKI-specific clinical actions were determined through consensus among 22 faculty members, including nephrologists, intensivists, and cardiac surgeons taking care of these patients at the institution. The consensus for these clinical actions was derived by a modified Delphi procedure involving two rounds of questionnaires (►**Supplementary Tables S2** and **S3**, available in the online version). The questions in the first round were developed based on literature review[1,9,17,19] and the content expertise of the investigators. These included 26 questions with answers in a 5-point Likert scale format and five open-ended questions. The clinical actions that had at least 70% consensus were considered approved. The second round consisted of questions that did not achieve consensus and questions developed based on the responses to the open-ended questions in the first round. Based on these two rounds, we achieved consensus on clinical actions specific to patients with AKI after cardiac surgery. Removal of nephrotoxins was one of the consensus clinical actions that served as our primary outcome. The rest of the clinical actions served as the secondary outcomes for this study. We provided a list of these clinical actions as a physical, pocket-sized Cardiac Surgery AKI Checklist to all end users at the time of the implementation of the electronic nephrotoxin alert (►**Fig. 2**). The exploratory clinical outcomes in this study were maximum AKI stage during the hospital stay, need for dialysis, and hospital length of stay.

Statistical Analysis

We have reported categorical variables as percentages and shared mean values for continuous variables. Chi-square or Fisher's exact test were utilized as appropriate to compare

- Perform medication review
  - Discontinue/adjust dosing for nephrotoxic and renally cleared medications as appropriate
- Perform point of care ultrasound to assess heart, lungs, kidney, and bladder
- Assess fluid volume status
  - Treat with diuretics if hypervolemic; utilize balanced crystalloids if hypovolemic
- Initiate vasoactive medications to maintain MAP >65 mmHg for patients refractory to fluid resuscitation
  - Individualize inotrope/vasopressor choice
  - Place arterial line if vasoactive medications are required or noninvasive monitoring is unreliable
- Measure urine output every hour and weight daily
  - Place indwelling bladder catheter if accurate measurement is not otherwise feasible
- Maintain serum glucose values <180 mg/dL
- Work up for hemolysis, sepsis, intra-abdominal hypertension, and bleeding

Fig. 2 Consensus AKI-specific clinical actions. AKI, acute kidney injury.

proportions and analysis of variance to compare means. We utilized the Cochran Armitage trend test to assess trends.[32,33] Additionally, to assess adjusted trends of outcomes across different eras, we performed logistic and linear regression analyses adjusted for age, sex, history of chronic kidney disease, type of surgery, and time from start of deployment of each tier of CDSS to the actual diagnosis of AKI or activation of alert. We considered a *p*-value threshold of <0.05 as statistically significant. We performed all analyses using JMP software 17 (SAS Institute Inc., Cary, North Carolina, United States).

Results

Out of 1,303 eligible cardiac surgery patients, 503 developed AKI and were included in this study. The baseline characteristics of patients are shown in ►Table 2. When broken down by era, era I (pre AKI-alert) included 104 patients (AKI rate 54%), era II (post AKI-alert) included 85 patients (AKI rate 42%), era III (AKI-alert long-term follow-up) included 158 patients (AKI rate 38%), era IV (pre-nephrotoxin-alert) included 75 patients (AKI rate 36%), and era V (post-nephrotoxin-alert) included 81 patients (AKI rate 28%). Overall, the mean age of patients was 64 years (±13.27 years) and 350 (70%) were male. In total, 114 (23%) patients received nephrotoxins within 30 hours before AKI, and 72 (14%) patients continued to receive nephrotoxins within 30 hours after the development of AKI. New nephrotoxins were ordered for 44 (9%) patients within 30 hours after AKI development.

When analyzed by eras based on the tiered implementation of CDSS, nephrotoxins were actively being used within 30 hours before the development of AKI in 24 (23%) patients in era I, 24 (28%) patients in era II, 20 (13%) patients in era III, 20 (27%) patients in era IV, and 26 (32%) patients in era V. Among these, nephrotoxins were discontinued within 30 hours of AKI among 6 (25%) patients in era I, 8 (33%) patients in era II, 7 (35%) patients in era III, 7 (35%) patients in era IV, and 14 (54%) patients in era V ($p=0.047$ for trend) (►Fig. 3). On adjusted analysis, the odds ratio for discontinuation of nephrotoxins for each era with era I as base was 1.50 (95% CI: 1.08–2.10). There was, however, no significant change in the initiation of new nephrotoxins within 30 hours of AKI over the eras (12 [12%] in era I, 7 [8%] in era II, 12 [8%] in era III, 8 [11%] in era IV, and 5 [6%] in era V; $p=0.338$ for trend).

Among the secondary outcomes studied, although we found a decrease in the documentation of volume status assessment over time ($p=0.001$ for trend), there was a decrease in administration of intravenous fluids after development of AKI ($p<0.001$ for trend) (►Table 3). There was also an increase in the documentation of a MAP target goal of ≥65 mm Hg ($p<0.001$ for trend), an increase in documented performance of bedside echocardiograms ($p=0.02$ for trend), and trending of serum lactate levels over the studied eras ($p<0.001$ for trend).

Among the exploratory clinical outcomes, we found a decrease in the proportion of stage III AKI (severe AKI) development ($p=0.037$ for trend), need for dialysis ($p=0.004$ for trend), and average length of stay ($p<0.001$ for trend; ►Fig. 3). On adjusted analysis, the odds ratio for

Table 2 Baseline characteristics of patients

		Era 1	Era 2	Era 3	Era 4	Era 5	*p*-Value
Age (y), mean (standard deviation)		62 (1.3)	60 (1.4)	65 (1)	65 (1.5)	65 (1.5)	0.04
Male sex, count (%)		73 (70%)	61 (72%)	97 (61%)	50 (74%)	62 (81%)	0.02
Type of surgery[a]—CABG valve	CABG surgery	52 (50%)	36 (42%)	86 (54%)	34 (45%)	40 (49%)	0.05
	Valve surgery	42 (40%)	43 (51%)	49 (31%)	27 (36%)	26 (32%)	
	Others	10 (10%)	6 (7%)	23 (15%)	14 (19%)	15 (19%)	
History of chronic kidney disease, count (%)		18 (17%)	17 (20%)	24 (15%)	15 (20%)	26 (32%)	0.05

Abbreviation: CABG, coronary artery bypass graft.
[a]Duplicate numbers are due to multiple surgery types in same patients.

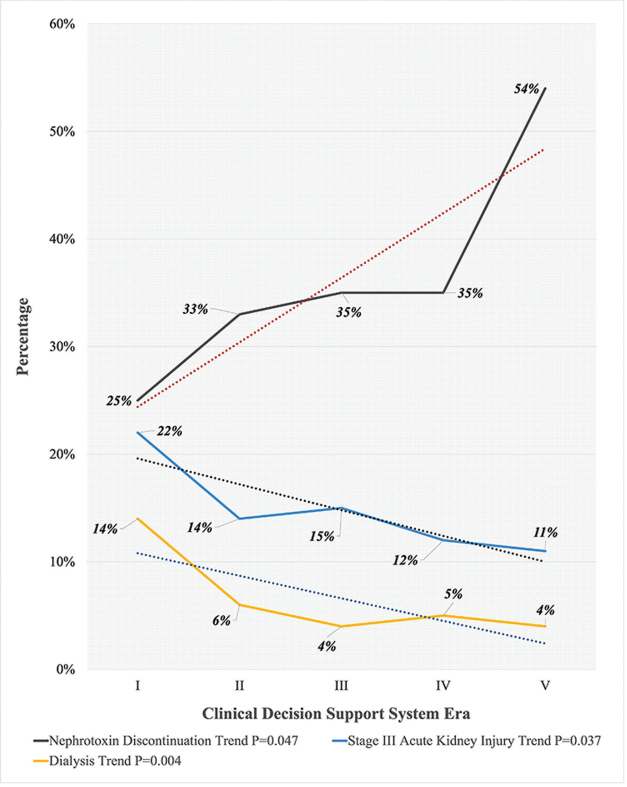

Fig. 3 Outcomes.

development of stage III AKI was 0.83 (95% CI: 0.66–1.03), for need for dialysis was 0.60 (95% CI: 0.40–0.80), and the adjusted coefficient for length of stay was 1.30 (95% CI: −2.30 to −0.30) for each era with era I as base.

Discussion

In this study, we evaluated the impact of tiered implementation of CDSS on the care of patients who develop AKI after cardiac surgery. We have demonstrated that the tiered implementation of this CDSS resulted in a stepwise increase in the discontinuation of nephrotoxic medications following AKI. We also noted some improvements in the completion of other AKI-specific clinical actions identified by a consensus of experts who are actively involved in the care of these patients.

The utilization of electronic alerts for AKI has been shown to increase the rates of diagnosis of AKI and decrease the time to first medical review of the chart.[16] However, their impact on the improvement of care processes[15,16,34,35] and exploratory clinical outcomes[15,24,34,36] has been mixed. Cardiac surgery-associated AKI is usually multifactorial and is associated with the release of cytokines and chemokines due to the entire cardiac output being exposed to the cardiac bypass circuit during surgery, nonpulsatile blood flow while on cardiac bypass, low cardiac output states, reperfusion injury after unclamping at the completion of surgery, use of nephrotoxic medications, and complications of cardiac function specific to surgeries that adversely affect hemodynamics and require additional surgeries.[37–40] The goal of therapy rests on the prevention of further progression by minimizing any further injury to the kidneys and the management of AKI complications. Based on these principles, KDIGO has provided general guidelines for AKI management, including treating the original cause of AKI, optimizing hemodynamic and volume status, and avoiding nephrotoxic medications and iodinated contrast media.[1] The KDIGO guidelines when adopted as a care bundle have been associated with improved outcomes.[20] However, compliance with bundle implementation is low.[41] A potential reason for reduced compliance and mixed results in care process improvements when implementing electronic AKI alerts is that KDIGO's guidelines for managing AKI are general principles rather than recommendations for specific actions. In this study, we identified and implemented clinical actions specific to the management of patients with AKI after cardiac surgery. These clinical actions were established by a consensus among multidisciplinary providers caring for these patients. Thus, by identifying consensus-driven clinical actions like nephrotoxin discontinuation, we have a better chance to see which actions are actually implemented in clinical practice. Understanding this will also guide the design of future trials aimed at optimizing AKI management.

Discontinuation of nephrotoxic medications is an important, established clinical action for the management of patients with AKI.[9,29,30] A recent randomized clinical trial[42] showed that implementation of an electronic nephrotoxin alert for hospitalized patients with AKI led to discontinuation of nephrotoxic medications within 24 hours of randomization in 61.1% of patients in the alert group versus 55.9% of patients in the control group ($p < 0.001$). This is similar to our study, in which electronic alerts led to an improvement in the discontinuation of nephrotoxic medications. This study was, however, a randomized trial performed among all hospitalized patients with an already high rate of nephrotoxin discontinuation among patients with AKI in the control group, decreasing the effect size achieved by implementing an electronic alert. Our study, in comparison, was a real-world, tiered implementation of a CDSS targeted toward patients after cardiac surgery. Patients undergoing cardiac surgery are at a much higher risk for AKI and its complications. We showed that the rate of nephrotoxin discontinuation within 30 hours after AKI was 25% before any alerts, 33% after implementation of the electronic AKI alert, and 54% after implementation of the electronic nephrotoxin alert. Furthermore, the rate of nephrotoxin discontinuation was 35% just prior to the implementation of the electronic nephrotoxin alert and more than a year after the implementation of the electronic AKI alert. Thus, there was no indication that secular trends alone accounted for the improvement in nephrotoxin discontinuation following the implementation of the nephrotoxin alert. Another major difference between the study by Wilson and colleagues and ours was that the former only used an interruptive alert for nephrotoxins. In contrast, we used a combination of passive and interruptive alerts, the latter only during active order entry, with the default option to discontinue the unsigned nephrotoxic medication order. Passive alerts are

Table 3 Completion of acute kidney injury specific consensus clinical actions across eras

Era	I $N=104$	II $N=85$	III $N=158$	IV $N=75$	V $N=81$	Total $N=503$	Trend p
Nephrotoxin pre-AKI[a]	24 (23%)	24 (28%)	20 (13%)	20 (27%)	26 (32%)	114 (23%)	0.311
Nephrotoxin post-AKI[b]	27 (26%)	20 (24%)	17 (11%)	16 (21%)	17 (21%)	97 (19%)	0.264
New nephrotoxin-ordered post-AKI[c]	12 (12%)	7 (8%)	12 (8%)	8 (11%)	5 (6%)	44 (9%)	0.338
Use of vasopressors	51 (49%)	43 (51%)	67 (42%)	28 (37%)	41 (51%)	230 (46%)	0.529
Maintenance of MAP not less than 65 mm Hg for 2 consecutive hours	85 (82%)	66 (78%)	120 (76%)	58 (77%)	68 (84%)	397 (79%)	0.857
Documented MAP goal of 65 mm Hg or higher	65 (63%)	56 (66%)	110 (70%)	68 (91%)	78 (96%)	377 (75%)	<0.001
Placement of arterial line	45 (43%)	36 (42%)	57 (36%)	35 (47%)	40 (50%)	213 (42%)	0.39
Use of intravenous fluids	96 (92%)	79 (93%)	149 (94%)	37 (49%)	41 (51%)	402 (80%)	<0.001
Use of diuretics	66 (64%)	54 (64%)	88 (56%)	42 (56%)	44 (54%)	294 (58%)	0.115
Hourly urine output measurement	36 (35%)	35 (41%)	53 (34%)	11 (15%)	15 (19%)	150 (30%)	<0.001
Documented volume assessment	101 (97%)	82 (97%)	157 (99%)	66 (88%)	72 (89%)	478 (95%)	0.001
Bedside point of care echocardiogram	5 (5%)	5 (6%)	16 (10%)	10 (13%)	10 (12%)	46 (9%)	0.02
Formal echocardiogram	18 (17%)	20 (24%)	27 (17%)	9 (12%)	20 (25%)	94 (19%)	0.766
Renal ultrasound	1 (1%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	3 (1%)	0.885
Lactate measurement	51 (49%)	48 (57%)	97 (61%)	39 (52%)	45 (56%)	280 (56%)	0.494
Lactate trend	28 (27%)	25 (30%)	52 (33%)	33 (44%)	40 (50%)	178 (35%)	<0.001
Sepsis workup	34 (33%)	25 (30%)	38 (24%)	10 (13%)	14 (17%)	121 (24%)	0.001
Glucose < 180 mg/dL	61 (59%)	59 (70%)	86 (54%)	48 (64%)	48 (59%)	302 (60%)	0.818

Abbreviations: AKI, acute kidney injury; MAP, mean arterial pressure.
[a]Nephrotoxin pre-AKI: patients that were on modifiable nephrotoxins before development of AKI. As iodinated contrast is usually ordered only once, it was not included in this list.
[b]Nephrotoxin post-AKI: patients that were on modifiable nephrotoxins after development of AKI. As iodinated contrast is usually ordered only once, it was not included in this list.
[c]New nephrotoxin ordered post AKI: patients who did not receive nephrotoxic medications before AKI but received nephrotoxic medications after AKI. This column includes new orders for iodinated contrast following AKI. This also includes cases where a new nephrotoxin was started in a patient already on nephrotoxin before AKI (in the nephrotoxin pre-AKI).

associated with less alert fatigue and increased compliance,[43,44] potentially contributing to greater improvement in the nephrotoxin discontinuation observed in our study.

Additionally, our study showed greater attention to keeping MAP > 65 mm Hg as assessed through documentation in progress notes over the time period of the study. We also noted increasing attention to repeating lactate measurements if the initial one was elevated, increased utilization of bedside point of care echocardiograms, and workup for sepsis in patients with AKI. All these actions were part of the specific clinical actions developed by the consensus among multidisciplinary providers caring for these patients. Interestingly, we found less documentation of volume status assessment throughout the study. However, we noted a decline in the rate of intravenous fluid administration to patients with AKI after cardiac surgery, which, in conjunction, may reflect increased attention to assessment of volume status despite less documentation. Similarly, we did not see a consistent improvement in hourly urine output measurement with these alerts. This could be a reflection of the practice to minimize indwelling urinary bladder catheter time after cardiac surgery. It is important to note that neither alert of our CDSS was explicitly geared to guide clinicians toward any of these clinical actions. Our only intervention for these clinical actions was to provide clinicians with a list of expert consensus clinical actions as a physical, pocket-sized AKI checklist when the electronic nephrotoxin alert was implemented. Further research is needed to determine if targeted CDSS focused on these specific clinical actions could lead to more consistent improvements.

Although our focus with this study was on discontinuation of nephrotoxins after AKI, we also noted some improvement in exploratory clinical outcomes during the time period of the study. Implementation of a CDSS with high user acceptance[21] and the development of specific clinical actions via expert consensus may have contributed to improved outcomes. This, however, needs to be interpreted with caution due to nonrandomized nature of the study and the fact that these exploratory outcomes can be affected by other things beyond the scope of this study, including the impact of the pandemic during the earlier eras. Although the sustained increase in discontinuation of nephrotoxins since the implementation of AKI alert argues against a significant impact of Hawthorne effect, a longer-term follow-up since implementation of nephrotoxin alert is needed to further validate its impact. Additionally, this was a single-center study performed at a tertiary care, high-volume cardiac surgery center, which may limit the generalizability of the results to other populations. Although our primary focus was on the discontinuation of nephrotoxins after AKI, we also evaluated secondary clinical actions developed through a modified Delphi process. Since the action list was created by a consensus group from a single institution, it may affect its generalizability, underscoring the need for multicenter validation to confirm its broader applicability. Finally, we did not evaluate the end user acceptance of the nephrotoxin alert. However, it was developed and implemented by the same team that developed the electronic AKI alert, which had high rates of end user acceptance.

Conclusion

In conclusion, our study demonstrated a progressive improvement in the discontinuation of nephrotoxic medications by implementing a tiered CDSS. The results of our study need to be confirmed in prospective multicenter studies.

Clinical Relevance Statement

Electronic AKI alerts have shown varying impacts on care processes and exploratory clinical outcomes, partly explained by the development of alert fatigue. Our previous work has led to the development of an electronic AKI alert with a high level of user acceptance, which we have since enhanced by incorporating a nephrotoxin alert for patients with AKI. In this work, we show that careful development and implementation of electronic alerts can enhance care processes and possibly clinical outcomes, offering a solution to this highly critical issue through effective application of clinical informatics.

Multiple-Choice Questions

1. Which of the following statements is true regarding the impact of AKI alerts?
   a. Studies uniformly show improvement in care processes by implementation of AKI alerts.
   b. Studies uniformly show improvement in patient-centered outcomes by implementation of AKI alerts.
   c. Studies uniformly show improvement in both care processes and patient-centered outcomes by implementation of AKI alerts.
   d. Studies show mixed results for improvement in care processes and patient-centered outcomes by the implementation of AKI alerts.

   Correct Answer: The correct answer is option d. The literature has shown inconsistent findings regarding the effectiveness of AKI alert implementation in enhancing care processes and clinical outcomes.

2. Which of the following statements is true regarding how the electronic nephrotoxin alert was displayed in the EPIC electronic health record?
   a. As an interruptive alert that popped up every time the chart was accessed.
   b. Only as a passive alert.
   c. A carefully crafted combination of both passive and interruptive alert.
   d. It was only displayed in the results tab.

   Correct Answer: The correct answer is option c. The electronic nephrotoxin alert was displayed as a passive alert for already active nephrotoxic medication orders and an interruptive alert when actively ordering a potentially nephrotoxic medication in a patient with AKI.

Protection and Human and Animal Subjects

The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical

Principles for Medical Research Involving Human Subjects and was reviewed by West Virginia University Institutional Review Board. Participants were informed of the contents prior to study participation and voluntarily consented to participate.

Funding

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases Grant no.: 5K08DK131286 (A.S.). U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Conflict of Interest

G.N.N. is a founder of Renalytix, Pensieve, Verici and provides consultancy services to AstraZeneca, Reata, Renalytix, Siemens Healthineer and Variant Bio, serves a scientific advisory board member for Renalytix and Pensieve. He also has equity in Renalytix, Pensieve and Verici. S.K.G. receives grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases R01DK121730 and U01 DK130010. the National Center for Complementary and Integrative Health U54AT008909 and the Jewish Healthcare Foundation. J.A.K. reports receiving consulting fees from Astute Medical/bioMerieux, Astellas, Alexion, Chugai Pharma, Novartis, Mitsubishi Tenabe and GE Healthcare and is a Full time employee of Spectral Medical. All remaining authors have declared no conflicts of interest.

References

1 International Society of Nephrology. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2(01):141
2 Schurle A, Koyner JL. CSA-AKI: incidence, epidemiology, clinical outcomes, and economic impact. J Clin Med 2021;10 (24):5746
3 Machado MN, Nakazone MA, Maia LN. Prognostic value of acute kidney injury after cardiac surgery according to kidney disease: improving global outcomes definition and staging (KDIGO) criteria. PLoS One 2014;9(05):e98028
4 Bellomo R, Auriemma S, Fabbri A, et al. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). Int J Artif Organs 2008;31(02):166–178
5 Arias Pou P, Aquerreta Gonzalez I, Idoate García A, Garcia-Fernandez N. Improvement of drug prescribing in acute kidney injury with a nephrotoxic drug alert system. Eur J Hosp Pharm 2019;26 (01):33–38
6 Engelman DT, Crisafi C, Germain M, et al. Using urinary biomarkers to reduce acute kidney injury following cardiac surgery. J Thorac Cardiovasc Surg 2020;160(05):1235–1246.e2
7 Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. Curr Opin Anaesthesiol 2017;30(01):60–65
8 Haase M, Kribben A, Zidek W, et al. Electronic alerts for acute kidney injury. Dtsch Arztebl Int 2017;114(1–2):1–8
9 Hickman RJ. Ninja program successfully reduces AKI from nephrotoxic medications. KNO 2020;12(05):1–3
10 Hodgson LE, Roderick PJ, Venn RM, Yao GL, Dimitrov BD, Forni LG. The ICE-AKI study: impact analysis of a clinical prediction rule and electronic AKI alert in general medical patients. PLoS One 2018;13(08):e0200584
11 Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006;10(03):R73
12 Kolhe NV, Reilly T, Leung J, et al. A simple care bundle for use in acute kidney injury: a propensity score-matched cohort study. Nephrol Dial Transplant 2016;31(11):1846–1854
13 Kolhe NV, Staples D, Reilly T, et al. Impact of compliance with a care bundle on acute kidney injury outcomes: a prospective observational study. PLoS One 2015;10(07):e0132279
14 Sakhuja A, Kumar G, Gupta S, Mittal T, Taneja A, Nanchal RS. Acute kidney injury requiring dialysis in severe sepsis. Am J Respir Crit Care Med 2015;192(08):951–957
15 Selby NM, Casula A, Lamming L, et al. An organizational-level program of intervention for AKI: a pragmatic stepped wedge cluster randomized trial. J Am Soc Nephrol 2019;30(03):505–515
16 Spencer S, Dickson F, Sofroniadou S, Naudeer S, Bhandari S, Hazara AM. The impact of e-alerts on inpatient diagnosis and management of acute kidney injury. Br J Hosp Med (Lond) 2021;82(02): 1–11
17 Vives M, Hernandez A, Parramon F, et al. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis 2019;12:153–166
18 Zarbock A, Küllmar M, Ostermann M, et al. Prevention of cardiac surgery–associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: the prevAKI-multicenter randomized controlled trial. Anesth Analg 2021;133(02):292–302
19 Zhao Y, Zheng X, Wang J, et al. Effect of clinical decision support systems on clinical outcome for acute kidney injury: a systematic review and meta-analysis. BMC Nephrol 2021;22(01):271
20 Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 2017;43(11):1551–1561
21 Nevin C, Shawwa K, Pincavitch J, et al. Acceptance of acute kidney injury alert by providers in cardiac surgery intensive care unit. Appl Clin Inform 2023;14(01):119–127
22 Thomas ME, Sitch A, Baharani J, Dowswell G. Earlier intervention for acute kidney injury: evaluation of an outreach service and a long-term follow-up. Nephrol Dial Transplant 2015;30(02):239–244
23 West Midlands Acute Medicine Collaborative. The impact of the NHS electronic-alert system on the recognition and management of acute kidney injury in acute medicine. Clin Med (Lond) 2019;19 (02):109–113
24 Al-Jaghbeer M, Dealmeida D, Bilderback A, Ambrosino R, Kellum JA. Clinical decision support for in-hospital AKI. J Am Soc Nephrol 2018;29(02):654–660
25 Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal Rwith the HITEC Investigators. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. BMC Med Inform Decis Mak 2017;17(01):36
26 Oh J, Bia JR, Ubaid-Ullah M, Testani JM, Wilson FP. Provider acceptance of an automated electronic alert for acute kidney injury. Clin Kidney J 2016;9(04):567–571
27 Epic Systems Corporation. Epic. September 7, 2023. Accessed December 1, 2023 at: https://www.epic.com/software/
28 Sakhuja A, Bataineh A, Dealmeida D, et al. Creating a high-specificity acute kidney injury detection system for clinical and research applications. Am J Kidney Dis 2021;78(05):764–766
29 Goldstein SL, Kirkendall E, Nguyen H, et al. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. Pediatrics 2013;132(03):e756–e767
30 Goldstein SL, Mottes T, Simpson K, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int 2016;90(01):212–221
31 MDRD study equation. National Kidney Foundation. October 26, 2015. Accessed December 20, 2023 at: https://www.kidney.org/content/mdrd-study-equation

32 Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11(03):375–386
33 Cochran WG. Some methods for strengthening the common χ2 tests. Biometrics 1954;10(04):417–451
34 Li T, Wu B, Li L, et al. Automated electronic alert for the care and outcomes of adults with acute kidney injury. JAMA Netw Open 2024;7(01):e2351710
35 Colpaert K, Hoste EA, Steurbaut K, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. Crit Care Med 2012;40 (04):1164–1170
36 Wilson FP, Shashaty M, Testani J, et al. Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial. Lancet 2015;385(9981): 1966–1974
37 Carmona P, Mateo E, Casanovas I, et al. Management of cardiac tamponade after cardiac surgery. J Cardiothorac Vasc Anesth 2012;26(02):302–311
38 Muresian H. Prevention of systolic anterior motion after mitral valve repair. Tex Heart Inst J 2005;32(03):453, author reply 453–454
39 Estrada VHN, Franco DLM, Moreno AAV, Gambasica JAR, Nunez CCC. Postoperative right ventricular failure in cardiac surgery. Cardiol Res 2016;7(06):185–195
40 Nadim MK, Forni LG, Bihorac A, et al. Cardiac and vascular surgery–associated acute kidney injury: the 20th international consensus conference of the ADQI (acute disease quality initiative) group. J Am Heart Assoc 2018;7(11):e008834
41 Küllmar M, Weiß R, Ostermann M, et al. A multinational observational study exploring adherence with the kidney disease: improving global outcomes recommendations for prevention of acute kidney injury after cardiac surgery. Anesth Analg 2020; 130(04):910–916
42 Wilson FP, Yamamoto Y, Martin M, et al. A randomized clinical trial assessing the effect of automated medication-targeted alerts on acute kidney injury outcomes. Nat Commun 2023;14(01):2826
43 Fallon A, Haralambides K, Mazzillo J, Gleber C. Addressing alert fatigue by replacing a burdensome interruptive alert with passive clinical decision support. Appl Clin Inform 2024;15(01):101–110
44 Olakotan OO, Mohd Yusof M. The appropriateness of clinical decision support systems alerts in supporting clinical workflows: a systematic review. Health Informatics J 2021;27(02):14604582211007536