Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury

abstract

BACKGROUND AND OBJECTIVE: Nephrotoxic medication exposure represents a common cause of acute kidney injury (nephrotoxin-AKI) in hospitalized children. Systematic serum creatinine (SCr) screening has not been routinely performed in children receiving nephrotoxins, potentially leading to underestimating nephrotoxin-AKI rates. We aimed to accurately determine nephrotoxin exposure and nephrotoxin-AKI rates to drive appropriate interventions in non–critically ill hospitalized children.

METHODS: We conducted a prospective quality improvement project implementing a systematic electronic health record (EHR) screening and decision support process (trigger) at a single quaternary pediatric hospital. Patients were all noncritically ill hospitalized children receiving an intravenous aminoglycoside for ≥3 days or ≥3 nephrotoxins simultaneously (exposure). Pharmacists recommended daily SCr monitoring in exposed patients. AKI was defined by the modified pediatric Risk, Injury, Failure, Loss and End-stage Renal Disease criteria (≥25% decrease in estimated creatinine clearance). We developed 4 novel metrics: exposure rate per 1000 patient-days, AKI rate per 1000 patient-days, AKI rate (%) per high nephrotoxin admission, and AKI days per 100 exposure days (AKI intensity).

RESULTS: This study included 21 807 patients accounting for 27 711 admissions. A total of 726 (3.3%) unique exposed patients accounted for 945 hospital admissions (6713 patient-days). AKI occurred in 25% of unique exposed patients and 31% of exposure admissions (1974 patient-days). Our EHR-driven SCr nephrotoxin-AKI surveillance process was associated with a 42% reduction in AKI intensity.

CONCLUSIONS: Nephrotoxin-AKI rates are high in noncritically ill children; systematic screening for nephrotoxic medication exposure and AKI detection was accomplished reliably through an EHR based trigger tool. Pediatrics 2013;132:e756–e767

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KEY WORDS acute kidney injury, nephrotoxic medications, electronic health record, children

ABBREVIATIONS
AKI—acute kidney injury
CCHMC—Cincinnati Children’s Hospital Medical Center
EHR—electronic health record
IV AG—intravenous aminoglycoside
nephrotoxin-AKI—nephrotoxic medication exposure and associated acute kidney injury
NSAID—nonsteroidal antinflammatory drug
pRIFLE—pediatric modified Risk, Injury, Failure, Loss and End-stage Kidney Disease criteria
SCr—serum creatinine

(Continued on last page)
The changing disease distribution in tertiary and quaternary medical centers has led to therapies required to promote survival but that increasingly put patients at risk for iatrogenic injuries including kidney damage.\(^1\)–\(^4\) Nephrotoxic medication exposure and associated acute kidney injury (nephrotoxin-AKI) occur commonly in hospitalized children. Eighty-six percent of noncritically ill children at a large children’s hospital received at least 1 nephrotoxin.\(^5\) Nephrotoxin-AKI was cited as the primary cause of 16% of pediatric AKI cases\(^3\) and is associated with significant morbidity and increased length of stay and costs.\(^5,6\)

Intravenous amino-glycoside (IV AG) exposure for >5 days is associated with nephrotoxin-AKI rates of 19% to 31%.\(^8\) Thus, nephrotoxin-AKI represents a significant health care burden for hospitalized children.

Nephrotoxin-AKI is usually diagnosed by a serum creatinine (SCR) level increase, because nephrotoxin-AKI is generally nonoliguric in nature. Although monitoring kidney function with SCR is inexpensive and widely available, SCR was measured infrequently (at least every 4 days only 50% of the time) in the aforementioned studies. A larger AKI cohort may therefore be undetected because SCR is not monitored systematically in at-risk patients. We hypothesized an unrecognized iatrogenic epidemic of nephrotoxin-AKI may exist, which is a potentially modifiable adverse safety event if systematic SCR assessment detects AKI reliably. The electronic health record (EHR), which contains medication prescription and administration data, could potentially offer the opportunity to screen patients exposed to nephrotoxins and therefore at risk for nephrotoxin-AKI.

Use of the EHR to detect iatrogenic harm retrospectively is, in fact, well described. EHR-based safety tools include kidney injury triggers, such as the Institute for Healthcare Improvement’s Global Trigger Tool,\(^7\) a recent tool using Acute Kidney Injury Network definition,\(^8\) or dosing tools to improve compliance with renal-dosing of medications.\(^9\) EHR-based AKI detection expedites time to interventions and yields a higher percentage of patients returning to baseline kidney function.\(^10,11\) Matheny used retrospective EHR data to develop a risk stratification model to predict hospital-acquired AKI.\(^12\) However, no literature exists regarding implementation of a predictive risk stratification trigger to prospectively identify patients exposed to nephrotoxins and provide timely intervention strategies to minimize AKI.

We believe predicting, preventing, and/or mitigating nephrotoxin-AKI has the potential to improve safety and outcomes. The first step toward minimizing nephrotoxin-AKI requires a reliable system to identify exposure and AKI development. We report on a hospital-wide quality improvement initiative to (1) characterize nephrotoxin-AKI epidemiology comprehensively compared with previously published literature and (2) test if an EHR-generated predictive trigger successfully identifies noncritically ill children exposed to nephrotoxic medications (compared with manual screening by pharmacists) and would be accepted to direct standardized SCR screening in these patients. We hypothesized we would find a high rate of nephrotoxin-AKI with the current quality improvement protocol.

**METHODS**

This prospective project was undertaken after presentation to all Medical and Surgical Service Chiefs at Cincinnati Children’s Hospital Medical Center (CCHMC) via collaboration among the CCHMC Center for Acute Care Nephrology, James M. Anderson Center for Health Systems Excellence, and Division of Pharmacy Services. The project was initiated June 1, 2011; data reported are derived through June 2, 2012. The project was approved by the CCHMC Institutional Review Board with a waiver of informed consent.

**Screening Algorithm and Trigger Process**

Each weekday morning, pharmacists assigned to inpatient teams screened the CCHMC EHR (EpicCare Inpatient, Epic Systems, Verona, WI) to assess for noncritically ill patients with high nephrotoxin exposure (“exposure”; defined subsequently). The screening process occurred in 2 phases during the study: (1) daily manual screening from pharmacists’ patient lists (June 1–September 16, 2011) was replaced by (2) an automated daily EHR-generated screening report, developed at CCHMC (September 17–June 2, 2012). Data managers and pharmacists verified all exposure cases manually on the automated report daily to ensure data validity.

Because we sought to identify nephrotoxic medication exposure as a primary cause of AKI, patients admitted to ICUs were excluded as AKI is multifactorial in critically ill children commonly resulting from hypotension or sepsis.\(^1,3,5\) Patients with chronic kidney disease, kidney transplant, or urinary tract infection were excluded.

On the basis of the surveillance algorithm (Fig 1), pharmacists recommended daily SCR monitoring for all exposed patients during morning rounds with the medical team, and then substitution of a nonnephrotoxic or less nephrotoxic medication and/or
pharmacokinetic drug concentration monitoring if appropriate. Recommendations were made within 12 hours of the patient appearing on the trigger report. Daily Scr monitoring orders were placed immediately in the EHR by the resident physician if agreed to by the attending physician. Medication substitution recommendations included substitutions of nonsteroidal antiinflammatory drugs (NSAIDs) with oral/intravenous acetaminophen or less nephrotoxic antimicrobial agents for aminoglycosides or vancomycin. Adherence to recommendations was recorded daily and reported to the principal investigator (SLG). SLG contacted primary attending physicians who did not agree to daily Scr monitoring to discuss their rationale.

**Operational Definitions**

**High Nephrotoxin Exposure Patient**

A patient was deemed at high nephrotoxin exposure (exposed) at the time they received an IV AG ≥3 days or ≥3 nephrotoxins derived from a list used from previous study2 (Table 1), adding iodinated contrast agents for the current study16. This list included all members of a nephrotoxin class (eg, angiotensin-converting enzyme inhibitors) available in our formulary. Patients were considered exposed for 48 hours after stopping IV AG or reducing to <3 nephrotoxins. Patients were newly identified if placed back on IV AG for ≥3 days or ≥3 nephrotoxins

**TABLE 1 List of Nephrotoxic Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Supplemental Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Ambisome*</td>
<td>Foscarinet</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Gadopentetate dimeglumine*</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Gadoxetate disodium*</td>
</tr>
<tr>
<td>Captopril</td>
<td>Ganciclovir</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Iofosamide</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Iodixanol*</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>Iopamidol*</td>
</tr>
<tr>
<td>Colistimethate</td>
<td>Ioversol*</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Ketorolac</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Lithium</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Nafcilin</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Ticarcillin/clavulanic acid</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Valganciclovir</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

* Medications counted for 7 days after administration toward exposure.

**TABLE 2 pRIFLE Scr-Based AKI Criteria**

<table>
<thead>
<tr>
<th>Risk</th>
<th>eCCI decrease by 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>eCCI decrease by 50%</td>
</tr>
<tr>
<td>Failure</td>
<td>eCCI decrease by 75% or eCCI &lt;35 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure ≥4 wk</td>
</tr>
<tr>
<td>End stage</td>
<td>End-stage renal disease (persistent failure ≥3 mo)</td>
</tr>
</tbody>
</table>

eCCI, estimated creatinine clearance.

* eCCI derived for the Schwartz equation as previously described.13
simultaneously after the 48-hour window.

**AKI**

AKI was defined by 3 strata (R, I, and F) of the SCr-based pediatric modified Risk, Injury, Failure, Loss and End-Stage Kidney Disease criteria (pRIFLE; Table 2), which uses changes in estimated creatinine clearance (calculated by the modified Schwartz estimation equation). Because nephrotoxin-AKI is usually nonoliguric in nature, we did not use the pRIFLE urine output criteria. AKI by pRIFLE has been associated with worse outcomes in critically ill and noncritically ill children with AKI.

**Outcome Measures**

We developed 4 a priori weekly outcome measures to ascertain the impact of exposure and AKI development. Table 3 details the measure name definitions, their underlying calculations, and their clinical context. To calculate weekly rates, patients were clustered to the calendar week they became exposed. For instance, if a patient received 3 nephrotoxins simultaneously in week 1 of the study but developed AKI in week 2, the AKI days were attributed to week 1. We grouped nephrotoxins by class to identify classes with highest exposure and AKI prevalence rates.

**Statistical Analysis**

To characterize nephrotoxin-AKI epidemiology, we report demographic variables descriptively and compare groups using analysis of variance or $\chi^2$ analysis as appropriate using Stata Version 12 (College Station, TX). The Tukey multiple comparison test was used to assess differences between medication class proportions in the exposure and AKI patient groups. A $P$ value of $<0.05$ was considered significant. To assess for the prospective trigger algorithm’s effect on AKI epidemiology, we used statistical process control methods to identify changes from baseline rates for each metric. A priori we set a standard of 8

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**TABLE 3 Outcome Measures and Definitions**

<table>
<thead>
<tr>
<th>Measure Name</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Clinical Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>High NTMx exposure prevalence rate (per 1000 patient-days)</td>
<td>Number of new patients with high NTMx exposure in the calendar week of study</td>
<td>The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study</td>
<td>This measure generates a normalized rate of high NTMx exposure cases per study week.</td>
</tr>
<tr>
<td>AKI prevalence rate (per 1000 patient-days)</td>
<td>Number of patients with high NTMx exposure who developed AKI in the calendar week of study</td>
<td>The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study</td>
<td>This measure generates a normalized rate of AKI cases per study week.</td>
</tr>
<tr>
<td>Rate of patients with high NTMx exposure who develop AKI (%)</td>
<td>Number of patients who develop AKI</td>
<td>Number of new patients with high NTMx exposure in the calendar week of study</td>
<td>This measure generates the fraction of patients with high NTMx exposure who develop AKI.</td>
</tr>
<tr>
<td>AKI intensity rate (per 100 susceptible patient days)</td>
<td>Number of days patients have AKI</td>
<td>The total number of susceptible patient days standardized per 100 susceptible-days</td>
<td>This measure depicts a normalized duration of AKI per susceptible days.</td>
</tr>
</tbody>
</table>

NTMx, nephrotoxic medication.

* AKI development factors into the numerator of the week that the patient became susceptible if AKI develops in a different calendar week than when a patient became susceptible.
consecutive weekly metric rates below the baseline rate to qualify as a statistical change, or special cause, which corresponds to 99.7% likelihood that the change observed resulted from the improvement intervention.22 Statistical process control methodology has served as the primary quality improvement assessment measurement to track the serious safety event rates for the past 7 years at CCHMC.23

RESULTS

Characterizing the Epidemiology of Nephrotoxin-AKI

During the study period, 21,807 unique patients accounted for 27,711 admissions to the noncritical care floors; 726 (3.3%) unique children (384 male [53%], mean age 8.9 ± 7.2 years) had exposure, accounting for 945 separate

| TABLE 4 Distribution of High NTMx Exposure Admissions and AKI Rates by Specialty Service |
|-----------------------------------------------|----------------|----------------|--------|--------|--------|--------|
| Services                        | High NTMx Case | AKI Cases | Gender |
|                                | Count | %a | No | Yes | %b | Female | Male |
| Bone marrow transplant         | 263   | 27.83 | 142 | 121 | 46.01 | 108 | 155 |
| Liver transplant               | 131   | 13.86 | 84 | 47 | 35.88 | 81 | 50  |
| Oncology                       | 105   | 11.11 | 68 | 37 | 35.24 | 47 | 58  |
| Pulmonary (excluding cystic fibrosis) | 77 | 8.15 | 54 | 23 | 29.87 | 32 | 45  |
| Cystic fibrosis                | 71    | 7.51 | 65 | 6  | 8.45  | 43 | 28  |
| General pediatrics             | 64    | 6.77 | 60 | 4  | 6.25  | 35 | 29  |
| Gastrointestinal surgery, trauma | 39 | 4.13 | 28 | 11 | 28.21 | 19 | 20  |
| Oncology                       | 30    | 3.17 | 25 | 5  | 16.67 | 21 | 9   |
| Cardiology                     | 27    | 2.86 | 18 | 9  | 33.33 | 13 | 14  |
| Urology                        | 27    | 2.86 | 25 | 2  | 7.41  | 12 | 15  |
| Neurosurgery                   | 26    | 2.75 | 22 | 4  | 15.38 | 10 | 16  |
| Gastroenterology lumen         | 25    | 2.65 | 18 | 7  | 28.00 | 10 | 15  |
| Otolaryngology                 | 21    | 2.22 | 15 | 6  | 28.57 | 9  | 12  |
| Neurology                      | 20    | 2.12 | 18 | 2  | 10.00 | 9  | 11  |
| Nephrology                     | 11    | 1.16 | 6  | 5  | 45.45 | 4  | 7   |
| Cardiotoracic surgery          | 2     | 0.21 | 2  | 0  | 0.00  | 1  | 1   |
| Ophthalmology                  | 2     | 0.21 | 2  | 0  | 0.00  | 1  | 1   |
| Physical medicine and rehabilitation | 2 | 0.21 | 2  | 0  | 0.00  | 2  | 0   |
| Rheumatology                   | 2     | 0.21 | 1  | 1  | 50.00 | 2  | 0   |
| Total                          | 945   | 655  | 290 | 459 | 486   |      |

NTMx, nephrotoxic medication.

a Represents the percentage of high NTMx cases by each specialty service.

b Represents the AKI rates for each specialty service.

FIGURE 3

Distribution of medications/medication classes prescribed to high-exposure patients and patients who developed AKI. The Tukey multiple comparison test was used to test differences between groups of proportions. The steps include transformation of input proportion, ranking of these transformed proportions, and then pairwise comparisons. Only NSAIDs were more frequently prescribed (*P < .05) in the AKI versus high-exposure patients compared with amphotericin, antiviral agents, calcineurin/mammalian target of rapamycin inhibitors (CIN/mTOR), and angiotensin-converting enzyme (ACE) inhibitors. IV, intravenous; NTMx, nephrotoxic medication.
hospital admissions. Exposed patients accounted for 6713 days (8.5%), and patients with AKI accounted for 1974 (2.5%) days out of 78731 noncritically ill admission days. The flow diagram outlining the screening, inclusion, and exclusion distributions is shown in Fig 2. Neither mean age nor age distribution differed between the exposed versus nonexposed patients. Patients with bone marrow transplantation, pulmonary disease, gastrointestinal disease, liver/multivisceral transplantation, and oncologic disease comprised the majority of exposed patients (Table 4). AKI rates varied greatly among subspecialty services with >10 exposed patients (6%–46%). We observed no patient mortality while patients remained on noncritical care unit floors.

AKI occurred in 290 of 945 (30.7%) exposure admissions. The AKI pRIFLE maximum severity distribution was 148 admissions with pRIFLE-R, 114 with pRIFLE-I, and 28 with pRIFLE-F. Aggregate days per pRIFLE strata were 1264 for pRIFLE-R, 578 for pRIFLE-I, and 132 days for pRIFLE-F.

Antivirals, calcineurin/mammalian target of rapamycin inhibitors, amphotericin, piperacillin/tazobactam, or angiotensin-converting enzyme inhibitors were prescribed in nearly 90% of exposure admissions (Fig 3). There was a wide distribution of nephrotoxins prescribed in AKI admissions, including NSAIDs, aminoglycosides, and vancomycin observed in addition to antiviral agents, calcineurin/mammalian target of rapamycin inhibitors, piperacillin/tazobactam, and angiotensin-converting enzyme inhibitors (Fig 3). Only NSAIDs were statistically more prevalent in the AKI versus exposure group.

**Effect of Automated Trigger Tool and SCr Monitoring**

We achieved a 99% daily SCr monitoring adherence rate for high nephrotoxin-exposed patients. We observed a stable rate of exposure of 7.6 admissions per 1000 patient days from June 1 through September 17, 2011, which increased to 11.6 admissions per 1000 patient days, coinciding with

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**FIGURE 4**

Weekly average high nephrotoxic medication (NTMx) exposure rates as measured by high NTMx exposure patients per 1000 noncritically ill patient hospital days. The rate increased from 7.6 to 11.6 patients per 1000 patient days, coinciding with EHR detection reports replacement of manual chart data extraction. Each data point represents 1 week beginning from Monday to the following Sunday.

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the change from manual pharmacist screening to EHR-generated reports (Fig 4). Neither patient demographics nor primary admitting service distributions differed between the manual and EHR-trigger implementation cohorts (data not shown). We observed an initial AKI rate of 2.6 per 1000 patient days, which increased to 4.3 per 1000 patient days but then subsequently decreased to 1.9 per 1000 patient days over the year of observation (Fig 5).

The mean weekly AKI rate was stable at 25.5% (range 6%–62%) for the entire year among unique high-nephrotoxin exposed patients (Fig 6) and 31% for all patient admissions (including repeated admissions). We observed a 42% decrease in AKI intensity from 33.6 to 19.5 days in AKI per 100 exposure days (Fig 7). The medication class exposure distribution did not differ between the months before and after the observed decrease in AKI intensity (Fig 8). We did observe a decrease of 43 to 23 days of exposure per 1000 non-ICU days for patients with AKI that preceded the drop in AKI intensity, suggesting the earlier withdrawal of nephrotoxins in AKI patients led to the decrease in AKI intensity.

**DISCUSSION**

We were able to develop, implement, and automate a screening method and several novel metrics to detect and track patients with nephrotoxin exposure and ascertain AKI rates reliably. We observed high rates (25.5% in unique patients, 31% of all admissions) of AKI in patients receiving an IV AG for ≥3 days or ≥3 nephrotoxic medications. This led to an initial average of >30 AKI days per 100 exposure days.

Several patient populations had a high prevalence of exposure and/or AKI cases, which is undoubtedly related to the population spectrum admitted to CCHMC as well as nephrotoxins routinely prescribed on those services. In identifying these populations, we will be able to target improvement interventions to decrease potentially unnecessary exposure and further reduce AKI severity and intensity. One planned intervention is to increase antibiotic stewardship and vigilance for services in which patients have substantial and

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**FIGURE 5**

Weekly average AKI development rates as measured by patient number with AKI per 1000 noncritically ill patient hospital days. The AKI rates initially increased above, and then decreased below, the baseline rate. Each data point represents 1 week beginning from Monday to the following Sunday. BMT, bone marrow transplantation.
predictable nephrotoxin exposure (eg, the cystic fibrosis population) and who demonstrate high rates of exposure and AKI. By instituting this near-real-time AKI risk-reporting system (pharmacists make recommendations within 12 hours of exposure), we can now implement and inform interventions in an agile and timely manner to health care teams.

Interestingly, we observed a 42% decrease in AKI intensity (days in AKI per 100 exposure days), and we estimate that this improvement would be associated with >900 AKI days avoided annually. We speculate the decrease in AKI intensity resulted from earlier detection of SCr rise and associated withdrawal of nephrotoxins based on the decrease in exposure days per 1000 non-ICU days in AKI patients, but this was not one of our a priori metrics. Also, we did not direct care with the exception of daily SCr monitoring recommendation and substitution of a nonnephrotoxic or less nephrotoxic medication and/or pharmacokinetic drug concentration monitoring. Nonetheless, the primary objective of this quality improvement project was to reliably characterize nephrotoxic medication prescription and associated AKI epidemiology, not necessarily to detect an improvement in outcomes at this point.

Our project underscores the importance of timely feedback across various disease services, which was executed by the pharmacists participating and making recommendations on rounds, when the entire team could evaluate and implement them in real time. It is possible the improvement observed resulted from the teams becoming more familiar with the process, and, if such a process can be sustained, it will demonstrate an efficient model to drive change with complex patients that is congruent with Lee’s recently proposed care redesign model, which is wholly unaffected by changes in payment models.

**Lessons From the Project**

Although detecting AKI is seemingly simple on the surface, we needed to develop novel workflows, algorithms, and metrics to accomplish our quality improvement goals. The exposure and
AKI surveillance algorithm is complex, which results in part from the natural history and progression of AKI. For instance, the delayed presentation of AKI led to prolonged deliberation regarding metric construction and which week attribution of nephrotoxin exposure and AKI development should occur. Development of our outcome measures and definitions was therefore paramount to the success of the project and to calculate accurate statistics.

The initial stages of our efforts required presentations to the CCHMC Safety Committee and medical and surgical division chiefs to highlight the potential unrecognized epidemic of nephrotoxin-AKI framed in the context of a potentially modifiable adverse safety event to gain stakeholder buy-in. These efforts yielded uniform enterprise commitment to the project and patient safety in terms of resources and agreement to systematic SCr monitoring; recommendations for daily SCr monitoring were followed 99% of the time and continue as part of our standard practice today. The execution of the project initially relied on manual data collection, largely shouldered by our pharmacy and analytics teams. The subsequent automated reports, once validated, offered several potential advantages: (1) more timely, consistent, and thorough survey of our patient population and (2) a more accurate determination of exposure and AKI development because our initial nephrotoxin list contained 45 medications and was difficult to cross-check on each patient on a busy service, which can be difficult to track manually. Use of automated reports correlated with increased ability to detect exposed patients from mid-September through the duration of the project. We did not see a simultaneous increase or decrease in AKI prevalence rates with the increased exposure detection. We cannot explain the transient higher then subsequently lower AKI prevalence rates per 1000 noncritically ill hospital admission days, although it is possible that the 8 nephrotoxins prescribed in 90% of AKI cases were prescribed more to the increased bone marrow transplantation cohort (Fig 5) initially and

FIGURE 7
Weekly average AKI intensity rates measured as days in AKI by the pRIFLE per 100 days of high nephrotoxic medication (NTMx) exposure. The mean AKI intensity rate decreased by 42% from 33.6 to 19.5 days as revealed by 8 consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents 1 week beginning from Monday to the following Sunday.
then subsequently less often over these time periods. Although we rigorously evaluated 45 potential nephrotoxins, we identified a high-priority list of 8 medication classes that account for >90% of exposures and association with AKI. The medications on these lists are not surprising but could serve as a guide to initiate similar projects at other centers more efficiently.

Strengths

Our study’s strengths include a large population size, similar to other large quaternary pediatric institutions, novel yet rigorous metrics, a commitment of the entire hospital organization to follow pharmacists’ screening recommendations based on patient risk profile, and the use of statistical process control methods to track changes over time. Although a major strength of the study was the >99% adherence to daily SCr monitoring in exposure patients and detection of the AKI development and intensity rates we observed, this must be balanced with the associated cost and discomfort of daily blood draws.

Limitations

This was a single-site study, which somewhat limits our generalizability to other centers, adults, and ICU patients; however, our study validates the speculation that AKI may have gone unrecognized in previous work performed at a similar pediatric center.5,6 Future research will build on this work to examine the epidemiology of AKI at other centers. Our patient populations and prescribing practices may differ from other institutions. We cannot extrapolate our data to ICU populations because AKI is usually multifactorial in critically ill children. Our decision to not use the urine output criteria could have led to underestimation of AKI rates. We empirically chose to follow SCr to detect AKI for 48 hours after high nephrotoxic medication exposure ceased, and if AKI developed after this window, we may have underestimated AKI rates. Finally, it is possible that some patients had AKI resulting from causes in addition to nephrotoxin exposure. We suggest this does not invalidate the benefit of our screening algorithm because we detected a high rate of AKI in exposed patients, which would lead to appropriate interventions (dose reduction, medication change) irrespective of AKI cause, a strategy recommended by the Kidney Disease Improving Global Outcomes AKI Guidelines.25 Future

FIGURE 8

Comparison of monthly distribution of medication class exposures in patients with AKI before and after the observed decrease in AKI intensity. No difference was observed in medication class distribution between the 2 time periods ($\chi^2 = 1.67, P = .98$). ACE, angiotensin-converting enzyme; CIN/mTOR, calcineurin/mammalian target of rapamycin inhibitors.
work can focus on enriching the nephrotoxin-AKI clinical model with other causes to improve risk stratification. The primary objective of this current report was to identify high nephrotoxic medication exposure and associated AKI rates reliably, so the more intensive work to identify causality is the subject of ongoing quality improvement efforts on a disease-specific basis. This project shifts the current use of trigger tool methodology from documenting adverse drug events that have already occurred to predicting harm and providing timely feedback. Because 31% of exposure admissions develop AKI, we can test the EHR ability to provide recommendations for alternative medications with pharmacy services input. Finally, the nephrotoxins we assessed are not uniquely prescribed to children, so our methodology may be generalizable to other health care settings with EHR capabilities, including adult hospitals, home care, and outpatient infusion centers.

REFERENCES

Dr Goldstein was responsible for the entire project including conception and design, data acquisition, analysis and interpretation of data, drafting the initial draft of and editing subsequent drafts the article, and approval of the version to be published; Dr Kirkendall participated in conception and design, data acquisition, analysis and interpretation of data, edited the first and subsequent drafts of the article, and approval of the version to be published; Mr Nguyen participated in data acquisition, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis and approved the final version of the manuscript; Dr Schaffzin participated in analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript; Dr Bucuvalas contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding and approved the final version of the manuscript; Ms Bracke contributed to conception and design and data acquisition, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript; Ms Foertmeyer contributed to conception and design and data acquisition, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript; Ms Brunner contributed to data acquisition, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript; Drs Lesko and Barclay contributed to conception and design and data acquisition, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript; Dr Lannon contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and obtaining funding and approved the final version of the manuscript; and Dr Muething contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and technical support and approved the final version of the manuscript.

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