Adverse Drug Events during AKI and Its Recovery

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Summary

Background and objectives The impact of AKI on adverse drug events and therapeutic failures and the medication errors leading to these events have not been well described.

Design, setting, participants, & measurements A single-center observational study of 396 hospitalized patients with a minimum 0.5 mg/dl change in serum creatinine who were prescribed a nephrotoxic or renally eliminated medication was conducted. The population was stratified into two groups by the direction of their initial serum creatinine change: AKI and AKI recovery. Adverse drug events, potential adverse drug events, therapeutic failures, and potential therapeutic failures for 148 drugs and 46 outcomes were retrospectively measured. Events were classified for preventability and severity by expert adjudication. Multivariable analysis identified medication classes predisposing AKI patients to adverse drug events.

Results Forty-three percent of patients experienced a potential adverse drug event, adverse drug event, therapeutic failure, or potential therapeutic failure; 66% of study events were preventable. Failure to adjust for kidney function (63%) and use of nephrotoxic medications during AKI (28%) were the most common potential adverse drug events. Worsening AKI and hypotension were the most common preventable adverse drug events. Most adverse drug events were considered serious (63%) or life-threatening (31%), with one fatal adverse drug event. Among AKI patients, administration of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antibiotics, and antithrombotics was most strongly associated with the development of an adverse drug event or potential adverse drug event.

Conclusions Adverse drug events and potential therapeutic failures are common and frequently severe in patients with AKI exposed to nephrotoxic or renally eliminated medications.

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Introduction

AKI increases the risk of death and serious morbidity in hospitalized patients (1–3). Among several pathways to adverse outcomes, AKI can lead to therapeutic failure or toxicity from rapid changes in drug elimination (1,4–8). Although the rate of adverse drug events (ADEs) during AKI is not known, the ADE rate in patients with a stable, elevated serum creatinine (SCr) is significantly higher than the general inpatient population (9–11). Improving drug management during AKI includes avoiding nephrotoxins, selecting and dosing drugs based on estimated GFR, and increasing the frequency of therapeutic drug monitoring (12). However, the extent to which these measures are followed and the frequency of preventable adverse patient outcomes are not yet well described.

In this study, we characterized both ADEs and therapeutic failures (TFs) among hospitalized patients experiencing either AKI (rise in SCr) or recovery from AKI (return of SCr to a pre-AKI baseline) with exposure to nephrotoxic or renally eliminated medications. All study events were prespecified as part of a quality improvement program to improve drug safety, and data were collected prospectively from detailed electronic documentation.

Materials and Methods

Setting

Vanderbilt University Hospital (VUH) is a 648-bed academic, tertiary care facility with computerized physician order entry (CPOE) and integrated clinical decision support (13–15). Clinical pharmacists round with most intensive care teams and selected medical and surgical teams on weekdays. Study data were collected as part of a quality improvement program with Institutional Review Board approval to improve drug safety (16). Briefly, the program featured CPOE-based clinical decision support (17,18), prospective monitoring, and as necessary, intervention by a clinical pharmacist through an electronic surveillance tool. Data for this observational study were collected at discharge by an independent outcome assessor. The effect of the quality improvement intervention on study outcomes is reported separately (16).

Patient Population

We enrolled patients hospitalized between June 1, 2010 and August 31, 2010 who met the study criteria: a minimum 0.5 mg/dl SCr change during a rolling 48-hour period (Figure 1) and an order for a nephrotoxic

or renally eliminated drug (Supplemental Table 1). Patients with both increasing and decreasing SCr changes were included in the study and classified as AKI or AKI recovery based on the direction of the initial SCr change. The threshold of 0.5 mg/dl was selected by an internal committee of expert nephrologists in 2005 before the publication of standard AKI stages by the Acute Kidney Injury Network (AKIN), and it is intended to represent the threshold above which medication use needs to be reassessed (17,19). We calculated AKI severity using AKIN staging, which compares a baseline creatinine (SCr before minimum 0.5 mg/dl rise) with a 7-day peak (19). Because a prior SCr was not always available for staging AKI recovery patients, the nadir during admission was substituted (20). We excluded patients receiving chronic dialysis for ESRD, organ transplantation, palliative care, transient SCr changes (return to baseline within 24 hours), or erroneous SCr values from spurious blood samples. Medications that prompted inclusion are listed in Supplemental Table 1. Because there is no standard consensus of medications to adjust or avoid in AKI, a committee of nephrologists, internists, and pharmacists reviewed medication package inserts, textbooks (21,22), and primary literature. The committee created Supplemental Table 1 to

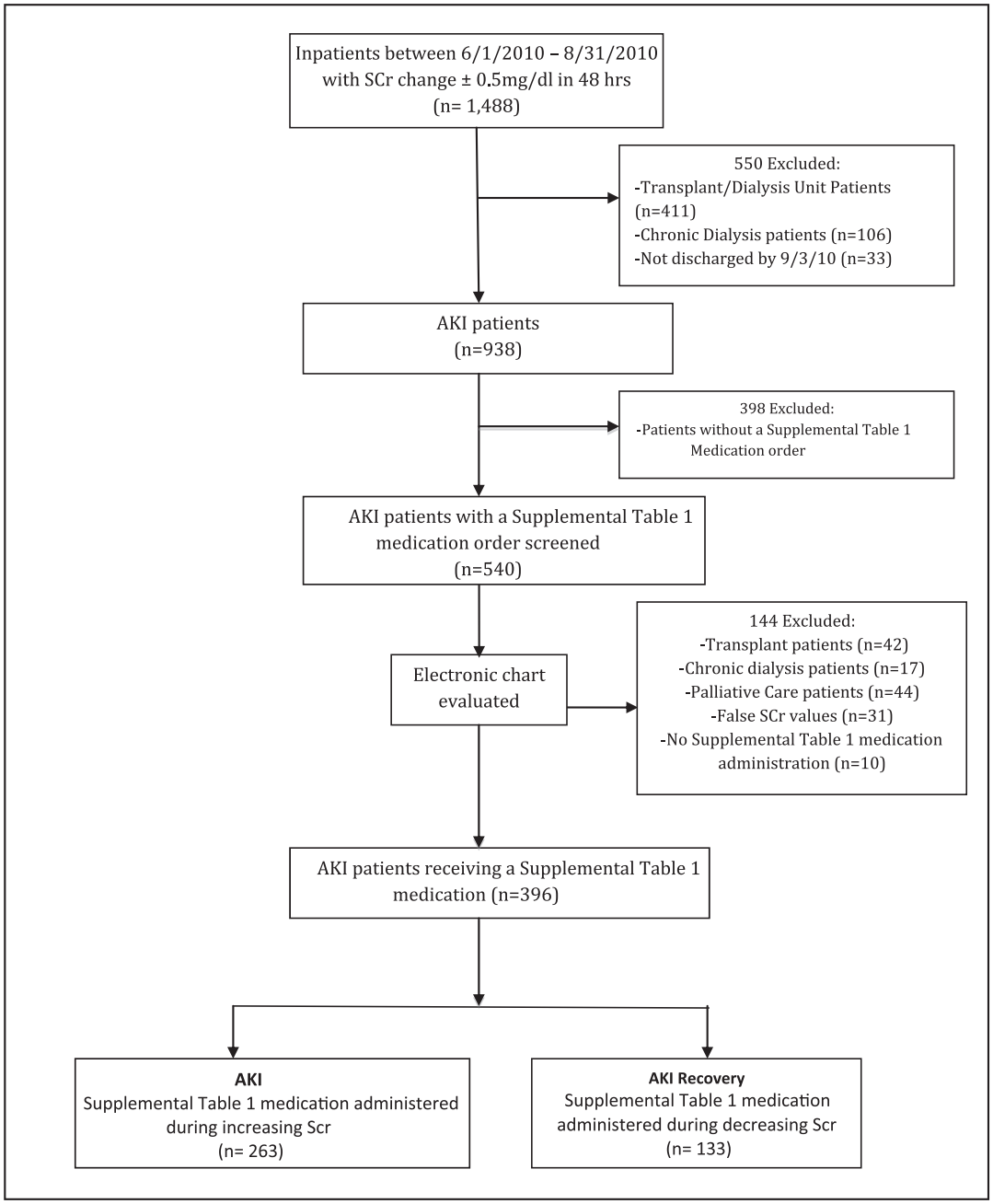

Figure 1. | **Flow diagram of patients.**

include medications that could contribute to AKI or have the potential for adverse effects with accumulation in AKI. It is limited to medications on VUH's formulary, and it is not intended to include all medications available. Some medications triggered inclusion in the study only if administered during increasing SCr, whereas antibiotics with a wide therapeutic window triggered inclusion only when exceeding a prespecified dose threshold.

Identification and Evaluation of Study Events

At hospital discharge or death of an enrolled patient, a clinical pharmacist reviewed the electronic medical record to determine whether one of the prespecified study events was present (Figure 2). A blinded outcomes assessment adjudication committee, consisting of a nephrologist and internal medicine physician, independently reviewed cases with at least one potential ADE (pADE), ADE, TF, or potential TF (pTF). We performed pilot reviews of initial cases to ensure that the adjudicating reviewers were in agreement in grading the severity and preventability of events and that all potential errors were identified. When discrepancies between reviewers occurred, reviewers met together with a tie-breaker nephrologist to reach a consensus.

Definition and Classification of Outcome Measures

The primary outcome measures were incidence, type, and severity of pADEs, ADEs, TFs, and pTFs. Secondary outcomes included drug classes that were associated with ADEs during AKI and the impact of ADEs in the AKI subset on length of stay (LOS) weighted by the Medicare Diagnosis Related Group (DRG). A committee of nephrologists, internists, and pharmacists compiled a list of possible ADEs using previous ADE literature, medication package inserts, and textbooks (21–26). Detailed criteria for each outcome are listed in Supplemental Table 2 using previous definitions (11,23–27) when possible. Briefly, we defined pADEs as events with the potential for injury related to a drug but during which no injury occurred. We defined ADEs relevant to AKI patients as injuries resulting from a medication listed in Supplemental Table 1. Laboratory-only ADEs, a subcategory of ADEs, included critical value laboratory values attributable to a medication listed in Supplemental Table 1 that are associated with morbidity (25).

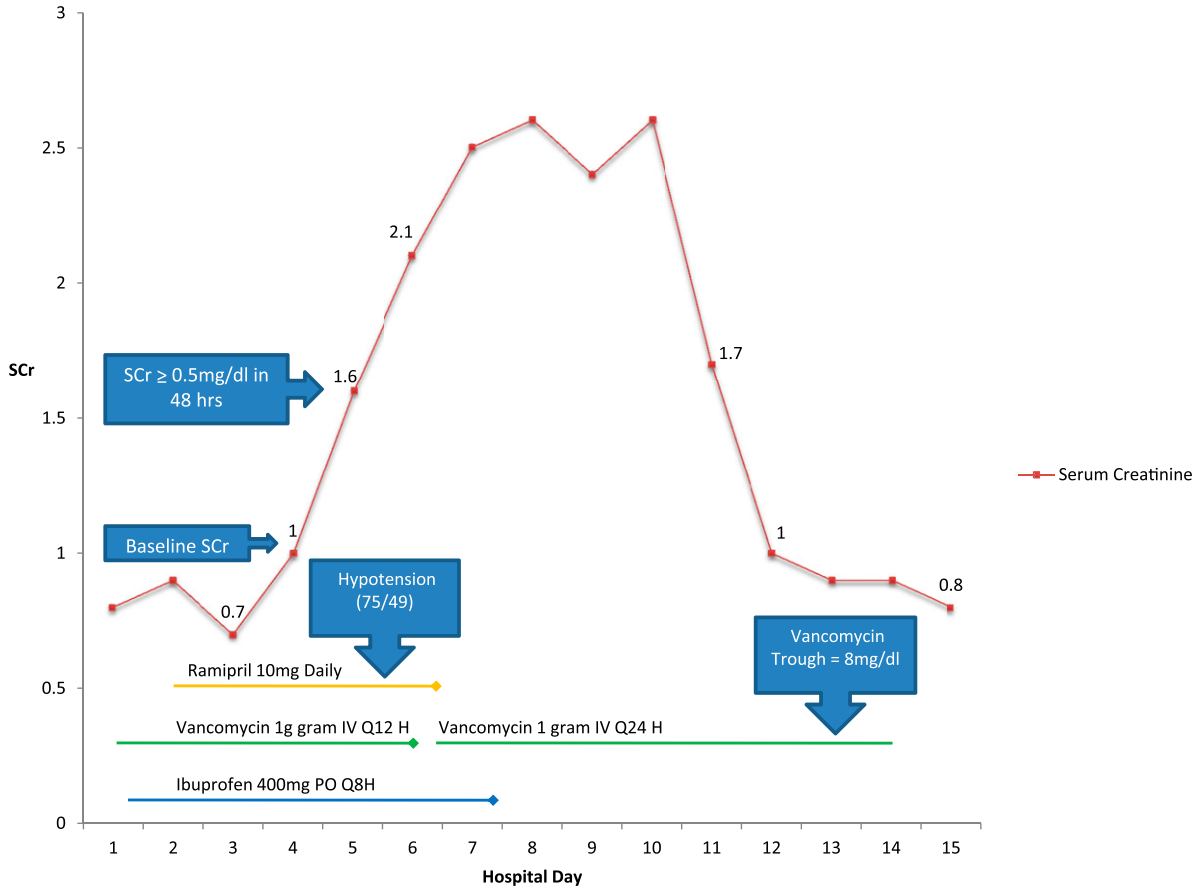

Figure 2. | **Timeline of AKI and adverse drug event evaluation legend.** Patient X met inclusion criteria on hospital day 5 when the serum creatinine (SCr) increased >0.5 mg/dl within 48 hours while receiving a medication from Supplemental Table 1 (ramipril, vancomycin, and ibuprofen). An adverse drug event (hypotension) was recorded for ramipril during AKI. Vancomycin was changed to one time daily administration during AKI but was not adjusted for AKI recovery. A potential therapeutic failure was recorded for vancomycin when the trough was <10 mg/dl during AKI recovery. A potential adverse drug event was recorded for continuing a nonsteroidal anti-inflammatory drug agent until hospital day 7, which was >24 hours during AKI.

Thresholds for antibiotic supratherapeutic and subtherapeutic concentrations were selected based on prior publications (28–30). During AKI recovery, we defined substantial subtherapeutic drug levels (Supplemental Table 2) and underdosing of medications with serum concentrations that are not clinically monitored as pTFs. Medication underdosing or subtherapeutic drug levels that were linked to morbidity or mortality based on clinical adjudication were categorized as TFs. We counted an event consisting of both a laboratory abnormality and an ADE as a single event. Severity was categorized as significant, serious, life-threatening, or fatal (26). Severity of pADEs was graded based on the potential severity. Categories of preventability were classified as definitely preventable, probably preventable, probably not preventable, and definitely not preventable (11,24,31). For analysis, we collapsed preventability into preventable (definitely and probably preventable) or not preventable (definitely and probably not preventable). Quantification of the contribution of a nephrotoxic medication to the genesis or severity of AKI when continued during SCr rise is difficult. For ADEs where the medication was associated with AKI, medication contribution was graded by two nephrologists as certain, probable, possible, or unlikely (32).

Statistical Analyses

Descriptive statistics were presented as frequencies for categorical variables and means with SD (mean ± SD) or medians with interquartile range (IQR) according to the distribution of the continuous variables. Demographic and clinical factors were compared between patients with and without ADEs using Wilcoxon rank-sum test or a Pearson chi-squared test as appropriate. κ-Statistics and bootstrapped 95% confidence intervals (CIs) were used to describe the agreement between outcome evaluators. Bootstrapped CIs account for repeated measurements within a patient. A proportional odds model was used to assess the effect of ADE on AKI stage.

The association of each drug class with ADEs was assessed using a multivariable Poisson regression model to compute the incidence rate ratio with adjustment for age, sex, admitting service, number of scheduled medication orders, baseline creatinine level, intensive care unit (ICU) admission, mechanical ventilation, patient comorbidities, major surgery this admission, SCr at the time of qualifying for AKI, and allocation to the intervention arm in the quality improvement trial. To avoid overfitting, a propensity score incorporating 12 variables (race, sex, comorbidities, major surgery, and creatinine timing) was computed using logistic regression. Multivariable linear regression was used to assess the association of ADE with the actual LOS with adjustment for the DRG-expected LOS, age, admitting service, number of scheduled medication orders, baseline SCr, intensive care, and mechanical ventilation. Actual LOS and expected LOS were natural logarithm-transformed to improve normality. Statistical analysis was performed using R version 2.10.0 (http://www.r-projecct.org). A two-sided significance level was set as 0.05.

Results

During the study period, 938 patients experienced a minimum 0.5 mg/dl SCr change, of which 396 patients received a targeted medication (Supplemental Table 1). The baseline SCr was 1.1 mg/dl (IQR=0.8, 1.6), with a baseline GFR of 63 ml/min per 1.73 m^2 (IQR=42, 97) (Table 1). For AKI patients, the median increase in SCr from baseline to peak was 0.9 mg/dl (IQR=0.6, 1.4). AKIN criteria classified 61% of patients as stage 1, 18% of patients as stage 2, and 21% of patients as stage 3. AKI recovery patients experienced a median decrease of 1.2 mg/dl (IQR=0.7, 2.1) from their peak SCr. Patients with AKI had multiple comorbidities (mean=2.4±1.4) and frequently received intensive care (57%). Of 396 study patients, 170 patients (43%) experienced 200 study events, consisting of 52 ADEs, 21 laboratory-only ADEs, 93 pADEs, 1 TF, and 33 pTFs. The κ-statistic for inter-rater reliability of the initial physician rating before consensus adjudication was 0.93 (95% CI=0.87 to 0.97) for pADE versus no pADE, 0.95 (95% CI=0.9 to 0.99) for ADE versus no ADE, and 0.58 (95% CI=0.49 to 0.66) for preventable ADE versus nonpreventable ADE.

Severity and Preventability of ADEs and pADEs

Of pADEs, 33 were significant (35%), 56 were serious (60%), and 4 were life-threatening (5%). Patients experienced a total of 73 ADEs (18 events/100 patients), consisting of 52 ADEs and 21 laboratory-only ADEs (Table 2). Most laboratory-only ADEs were serious (90%) or life-threatening (10%). Most ADEs were either serious (63%) or life-threatening (31%). The one drug-related fatality resulted from a gastrointestinal bleed during intravenous ketorolac therapy. A small proportion of ADEs (6%) were documented after SCr had returned to baseline but were judged to originate from drug exposures during AKI.

Types of ADEs and pADEs

Potential ADEs were comprised mostly of failure to adjust medication for decreased renal elimination (63%) or continued use of a nephrotoxic medication (28%) for greater than 24 hours after AKI onset (Table 3). Supplemental Table 3 contains descriptions of example ADEs. Laboratory-only ADEs included both supratherapeutic drug levels (90%) and hyperkalemia (10%). Worsening AKI was the most common outcome judged to be at least partially related to an ADE (n=24) and resulted in acute hemodialysis in three patients. Medications contributing to AKI were started a median of 48 hours (IQR=35, 72) before the initial SCr rise and continued for a median of 24 hours (IQR=11, 27) after. In addition to standard rating method for ADEs, two nephrologists used separate criteria (32) and graded the certainty of the drug causing or contributing to AKI as possible in 38% of patients, probable in 54% of patients, and certain in 8% of patients (32). Hypotension occurred often (n=11) along with bleeding (n=6), cognitive changes (n=4), and oversedation (n=6). Five ADEs required a rapid response team evaluation, and four ADEs required transfer to an ICU.

Medications Associated with ADEs and pADEs

The medications most frequently associated with ADEs with adjustment for frequency of use are detailed in Table 4. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) most commonly

Table 1. Baseline characteristics of study population

Baseline Characteristics	All Patients (*n*=396)	AKI[a] (*n*=263)	AKI Recovery[b] (*n*=133)
Age (yr), mean ± SD	60±16	59±16	60±16
Sex, *n* (%)			
Women	171 (43)	111 (42)	60 (45)
Men	225 (57)	151 (57)	74 (56)
Race, *n* (%)			
White	321 (81)	206 (57)	115 (86)
Black	54 (14)	46 (17)	8 (6)
Other	9 (2)	1 (0.3)	8 (6)
Unknown	12 (3)	10 (4)	2 (2)
Admitting service, *n* (%)			
Medicine	249 (63)	156 (59)	93 (70)
Surgery	147 (37)	107 (41)	40 (30)
Intensive care unit, *n* (%)[c]	224 (57)	161 (61)	63 (47)
Comorbidities, *n* (%)			
Cancer	101 (26)	64 (24)	37 (28)
Cerebrovascular disease	52 (13)	31 (12)	21 (16)
Congestive heart failure	100 (25)	75 (29)	25 (19)
Coronary artery disease	132 (34)	94 (36)	38 (29)
Diabetes	153 (39)	104 (40)	49 (37)
End stage liver disease	17 (4)	12 (5)	5 (4)
Hypertension	256 (65)	169 (64)	86 (65)
Mechanical ventilation	109 (28)	90 (34)	19 (14)
Peripheral vascular disease	22 (6)	14 (5)	8 (6)
Baseline serum creatinine (mg/dl), median ± IQR[d]	1.1 (0.8, 1.6)	1.1 (0.9, 1.6)	1.1 (0.8, 1.6)
Baseline estimated GFR (ml/min per 1.73 m^2), median ± IQR[e]	63 (42, 97)	62 (43, 88)	67 (39, 109)

IQR, interquartile range.
[a]Patients experiencing a 0.5 mg/dl increase in serum creatinine (SCr) during a 48-hour window while receiving a medication listed in Supplemental Table 1.
[b]Patients experiencing a 0.5 mg/dl decrease in SCr during a 48-hour window while receiving a medication listed in Supplemental Table 1.
[c]Intensive care unit admission at any time during hospitalization.
[d]SCr before the initial 0.5 mg/dl rise in AKI and as the SCr nadir in patients admitted in AKI who experience recovery during hospitalization.
[e]Calculated by four-variable Modification of Diet in Renal Disease equation using baseline SCr.

Table 2. Adverse drug events by type and severity

Event	ADE[a]	Laboratory-Only ADE[a]	Potential ADE	TF	Potential TF
Event, *n*	52	21	93	1	33
Number of patients with an event, *n* (%)	51 (13)	21 (5)	69 (17)	1 (0.3)	29 (7)
Rate/100 medication orders[b]	1.9	0.8	3.4	0.04	1.2
Preventable, *n* (% of orders)[c]	35 (67)	13 (62)	NA	1 (100)	NA
Severity of event, *n* (%)					
Significant	2 (4)	0 (0)	33 (35)	0 (0)	13 (40)
Serious	33 (63)	19 (90)	56 (60)	0 (0)	12 (36)
Life-threatening	16 (31)	2 (10)	4 (5)	0 (0)	8 (24)
Fatal	1 (2)	0 (0)	0 (0)	1 (100)	0 (0)

ADE, adverse drug event; TF, therapeutic failure; NA, not applicable.
[a]Total ADEs (*n*=73) are separated into two subgroups: ADEs and laboratory-only ADEs. Definitions are in Supplemental Table 2.
[b]Inpatient medication orders (2699 total orders) on 396 study patients.
[c]Preventability defined by assessments of definitely not preventable and probably not preventable.

Table 3. Description of potential adverse drug events and adverse drug events

Event	Incidence *n* (%)
pADE (*n*=93)	
Contraindicated use for >24 hours	26 (28)
No dose adjustment for >24 hours	15 (16)
No interval adjustment for >24 hours	44 (47)
Ineffective at low creatinine clearance	2 (2)
No drug level monitoring	5 (5)
No creatinine monitoring	3 (3)
Other	6 (6)
Laboratory-only ADE (*n*=21)	
Hyperkalemia	2 (10)
Supratherapeutic drug levels	19 (90)
Vancomycin	18
Tobramycin	1
ADE (*n*=52)	
Hypotension	11 (21)
QT prolongation	2 (4)
Cognitive changes/somnolence	4 (8)
Delirium	1 (2)
Extrapyramidal symptoms	1 (2)
Oversedation	6 (11)
Rash	1 (2)
Major bleed	1 (2)
Minor bleed	5 (10)
Worsening AKI	24 (46)
Crystalurea	1 (2)
Respiratory depression	2 (4)
Hemodialysis	3 (6)
Colitis	1 (2)
Death	1 (2)

Subcategory numbers and percentages may exceed the total *n* or 100%, because one event could be composed of multiple adverse drug events (ADEs) or potential ADEs (pADEs). Supplemental Table 2 has definitions of each ADE and laboratory-only ADE.

caused ADEs followed by nonsteroidal anti-inflammatory agents, opiate analgesics, and parenteral antithrombotic agents. ADEs from ACEI/ARBs comprised 11 symptomatic hypotensive events and 12 events causing or contributing to AKI. All antithrombotic ADEs involved bleeding during enoxaparin or fondaparinux therapy. Antibiotics, particularly β-lactams, fluoroquinolones, and vancomycin, were responsible for the majority of pADEs and laboratory-only ADEs. ACEI/ARBs (P=0.004), antibiotics (P=0.005), and parenteral antithrombotics (P=0.004) were associated with ADEs and pADEs in the multivariate analysis. When ADEs alone were analyzed, only ACEI/ARBs (P=0.004) and parenteral antithrombotics (P=0.001) were significant in the multivariate analysis.

TF and pTF

Of pTFs, 33 occurred in 29 patients, with 85% resulting from antibiotics; 13 pTFs (40%) were significant, 12 pTFs were serious (36%), and 8 pTFs were life-threatening (24%). One fatal TF occurred in a patient treated with levofloxacin monotherapy (750 mg every 48 hours) for a sensitive *Stenotrophomonas* ventilator-associated pneumonia during AKI. Levofloxacin was not adjusted during AKI recovery. After 4 days of subtherapeutic antibiotic dosing, the patient died of hypoxic respiratory failure on maximal ventilator support.

Outcomes Associated with ADE and pADEs

Patients with an ADE or pADE were more likely to have greater severity of AKI, which was represented by higher AKIN stage, than patients without an event (P value for trend=0.02). After adjustment for patient characteristics and drug indications, patients with an ADE did not have a longer LOS compared with patients without an ADE (1.79 days; 95% CI=−0.28 to 3.86, P=0.09). We found similar nonsignificant differences after excluding those patients who died before discharge from the analysis.

Discussion

Our study is the first, to our knowledge, to characterize the rates of ADEs and TFs and the corresponding near misses among hospitalized patients experiencing AKI and exposure to a nephrotoxic or renally eliminated medication. One of eight patients in this high-risk cohort was found to have an adverse therapeutic outcome, and an additional one fourth of the cohort was put at risk of an adverse outcome from a medication error. Two thirds of the ADEs were judged preventable, primarily because of failure to adjust drug dosing in the setting of changing renal function. Two medication classes (ACEI/ARBs and parenteral antithrombotics) showed an increased risk of injury during AKI compared with other therapeutic classes. Finally, a trend to increased hospital length of stay was observed in patients with ADEs after adjusting for multiple other clinical factors in a multivariable analysis.

Previous reports of hospitalized patients with reduced creatinine clearance from any cause found kidney dysfunction to be a risk factor for ADEs (33,34). Hug *et al.* (11) found that patients with impaired kidney function (both acute and chronic) in a community hospital setting experienced a 10% rate of ADEs, of which 91% were preventable, and a 55% rate of potential ADEs. Among the population (*n*=938) identified in our study period (Figure 1), 21% experienced or had the potential to experience an ADE or TF, with an 8% ADE rate. Patients in the general hospitalized population (ADEs rates=0.6%–6%) (23,24,35) and critically ill patients (ADE rates=2.7%–9.5%) have comparable rates; however, we only examined for ADEs with a known biologic relationship to AKI (36,37). Although one half of the pADEs and ADEs reported by previous studies occurred during other stages of the medication pathway (transcription, administration, or dispensing), all of the events in our study were linked to the ordering and monitoring stages managed by medical providers and pharmacists.

Our multivariable analysis identified ACEI/ARBs and parenteral antithrombotics as independent predictors of ADEs in AKI. Antibiotics were also an independent predictor when pADEs were included. Similar to prior studies, we found that antibiotics and analgesics were common causes of ADEs and pADEs (23,24,34,37–39). However, antivirals and ACEI/ARBs also were associated with

Table 4. Drug classes involved in potential adverse drug events and adverse drug events

Drug or Drug Class	Event Rate (No./100 Medication Orders)[a]	ADE (*n*=52)	Laboratory-Only ADE (*n*=21)	pADE (*n*=93)	TF (*n*=1)	pTF (*n*=33)
Opiate analgesics	2.3	7	—	1	—	—
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	12.2	19	2	14	—	—
Antithrombotics	4.8	5	—	4	—	—
Antifungals	2.8	1	—	1	—	1
Antibiotics	8.1	5	19	53	1	28
Vancomycin	8.4	2	19	10	—	15
β-Lactams	5.6	1	—	25	—	7
Aminoglycosides	2.9	1	—	1	—	—
Quinolones	5.1	—	—	14	1	3
Other antibiotics	14.2	1	—	3	—	3
Nonsteroidal anti-inflammatory drugs	29.8	7	—	10	—	—
Anticonvulsants	6.2	2	—	1	—	—
Antivirals	16.7	2	—	3	—	2
Antiarrhythmics	6.8	2	—	3	—	—
Vasodilators	4.7	0	—	3	—	—
Other	—	2	—	0	—	2

[a]Event rate is the sum of adverse drug events (ADEs), laboratory-only ADEs, potential ADEs (pADEs), therapeutic failures (TFs), and potential TFs (pTFs) for each drug class divided by the total number of orders for that drug class in our study population during our study period. The event rate is shown to control for a drug class having a larger number of events based on the volume of orders.

ADEs in AKI patients. Previous literature has reported AKI as the most common ADE, and studies of ICU populations confirm ADEs as the cause of up to 25% of AKI cases (11,40–43). Based on detailed review of AKI events by the outcomes committee using two independent methods of rating ADEs (24,32), ACEI/ARBs seemed to trigger AKI by causing systemic hypotension during a renin-dependent dehydrated state and decreasing intraglomerular pressure in the setting of other renal perfusion insults. Clinicians should be vigilant with ACEI/ARB, antithrombotic, and antibiotic orders during AKI because of their high risk of ADEs, including worsening AKI with ACEI/ARBs (11). Although previous literature has focused on ADEs when SCr is elevated, the AKI recovery phase also increases the risk of adverse therapeutic outcomes. The severity and incidence of pTFs highlight the vigilance needed not only during AKI but also during AKI recovery.

We found that greater severity of AKI is associated with ADEs, representing both the effect of nephrotoxic drugs administered before the peak SCr and also, the greater impact of severe AKI on renally eliminated medications. The impact of AKI on patient outcomes, including mortality and length of stay, has already been well described (2,3,44,45); in this cohort, ADEs contributed to the high AKI-associated mortality. Among the 24 deaths in our cohort, 2 deaths were judged to be at least partially related to a preventable ADE—1 death during AKI and 1 death during resolution. In contrast to previous studies (11), we did not find an increase in LOS in the context of an ADE. However, our analysis was limited to AKI patients who already have longer than average admissions and controlled for other patient characteristics in addition to the DRG.

Our study highlights the challenges of caring for patients with AKI and was conducted in a medical center with many medication safety strategies, including electronic medical records, CPOE with clinical decision support (17), and rounding clinical pharmacists. We could not quantify the impact of these safeguards on our outcome rates, but previous studies suggest substantial improvement (4,46–48). Our study's ADE rates may be lower than in hospitals with fewer ADE prevention strategies. The frequency of improper medication adjustment, despite existing strategies, illustrates the difficulty of monitoring a fluctuating target drug dose. Furthermore, such targeting depends on serum markers and mathematical estimates of kidney function that are inaccurate during AKI (49,50). AKI patients may be at higher risk of ADEs, because therapeutic decisions are based on inaccurate markers that lag behind acute changes in GFR.

Our study has several limitations. We identified AKI-related adverse events using clinical documentation and a list of prespecified ADEs. Prehospital, unrecognized, or undocumented ADEs are not included. We did not collect data on patients postdischarge, consistent with the quality improvement design that lacked informed consent to contact patients directly. Medications discontinued more than 1 day before AKI onset were not included because of the uncertainty of the relationship between drug, changing creatinine, and outcome. We did not include patients with

AKI who died before a 0.5 mg/dl SCr change. The presence, severity, and preventability of adverse events were based on implicit review by a committee of clinicians. Although agreement was not complete, our inter-rater reliability was comparable with previous studies. Finally, our findings are pertinent for medical centers with high-acuity patients. Rates of AKI-related adverse therapeutic outcomes may differ significantly across clinical environments.

In conclusion, ADEs and pTFs were common and frequently severe in AKI patients exposed to nephrotoxic or renally eliminated medications. Documented TFs were uncommon. Most events were preventable during both AKI onset and AKI recovery. AKI patients receiving ACEI, ARBs, antithrombotics, and antibiotics are at highest risk and should receive more intensive monitoring.

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Disclosures

None.

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