BIOMEDICAL INFORMATICS

A SYSTEM TO MONITOR AND IMPROVE MEDICATION SAFETY IN THE SETTING OF ACUTE KIDNEY INJURY

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Thesis under the direction of Professor Lemuel R. Waitman

Clinical decision support systems can decrease common errors related to inadequate dosing for nephrotoxic or renally cleared drugs. Within the computerized provider order entry (CPOE) system, we developed, implemented, and evaluated a set of interventions with varying levels of workflow intrusiveness to continuously monitor for and alert providers about acute kidney injury. Passive alerts appeared as persistent text within the CPOE system and on rounding reports, requiring no provider response. Exit check alerts interrupted the provider at the end of the CPOE session, requiring the provider to modify or discontinue the drug order, assert the current dose as correct, or defer the alert. In the intervention period, the number of drugs modified or discontinued within 24 hours increased from 35.7% to 50.9%, and the median time to modification or discontinuation decreased from 27.1 hours to 12.9 hours. Providers delayed decisions by repeatedly deferring the alerts. Future enhancements will address frequent deferrals by involving other team members in making mid-regimen prescription decisions.

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A SYSTEM TO MONITOR AND IMPROVE MEDICATION SAFETY IN THE SETTING OF ACUTE KIDNEY INJURY

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LIST OF ABBREVIATIONS

ADQI .....acute dialysis quality initiative

AKI .....acute kidney injury

AKIN ..... acute kidney injury network

ARF .....acute renal failure

CPOE .....computerized provider order entry

EMR.....electronic medical record

GFR .....glomerular filtration rate

RIFLE ..... Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease

VUMC ..... Vanderbilt University Medical Center

CHAPTER I

INTRODUCTION

Medication safety is a major target for recent hospital efforts to reduce iatrogenic complications. Many adverse drug events that hospitalized patients experience result from errors in drug selection, dosing, administration, and monitoring. Admitted patients often experience significantly reduced renal function during their stay, and many receive inappropriate medications or excessive doses. The causes of acute kidney injury (AKI) are well known, and with some attention to associated medication safety, complications can be significantly reduced.

Clinical decision support within computerized provider order entry (CPOE) systems can reduce medication errors. Interventions to suggest initial doses tailored to individual patients, especially geriatric patients or those with worsening physical conditions, can decrease the number of sub-therapeutic and toxic doses. Changes that patients experience while admitted to the hospital may cause the initially prescribed dose to be inappropriate. In particular, patients who experience a decline in renal function may require a discontinuation or a reduced dose for drugs that are nephrotoxic or renally cleared. While the initial dosing interventions prevent some errors, much room for improvement exists. A system to monitor for and alert providers about significant changes in renal function in patients on renally dosed drugs can improve both provider response to changes and resulting patient renal function.

Leveraging existing informatics frameworks at Vanderbilt University Medical Center (VUMC) and adopting methods proven successful in reviewed literature, we developed a set of interventions to detect AKI in patients receiving nephrotoxic or renally cleared medications and to alert providers about the change in renal function and appropriate medication safety recommendations. We began our interventions with a pilot project, detecting changes in renal function sufficient to require a change in the dose of vancomycin. To further improve medication safety, we developed our main intervention to include detection of more significant changes in renal function in the presence of numerous target nephrotoxic and renally cleared drugs.

In developing our intervention, we incorporated successful aspects from reviewed systems not previously evaluated together. Our system alerted providers directly in real time about significant changes in renal function that potentially affected existing orders. Within the CPOE system, a passive alert allowed providers to act on the given advice with minimal workflow interruption. If the provider did not take any actions prior to the end of the session, the system interrupted the workflow, presenting an additional alert that required a response.

We evaluated the interventions using as our primary outcome the rate at which providers modify or discontinue orders within 24 hours of a significant change in renal function. As a secondary outcome, we evaluated the total time between a significant change and a modification or discontinuation of the drug. We also analyzed the actual provider responses to the intervention using descriptive statistics. Our provider response outcomes included the method for provider action, passive alert clicks, exit check alert option selection frequency, and alert deferrals.

Finally, we described in detail the steps we have planned for future work. Included in these steps are passive alert improvements, refined alerting criteria, and additional levels of medication safety monitoring. We also plan to further evaluate our interventions, including analysis of patient outcomes and the effect of the intervention on improving renal function.

CHAPTER II

BACKGROUND

Acute Kidney Injury

Definition

Acute Kidney Injury (AKI), often referred to as acute renal failure (ARF) when severe, occurs when a patient rapidly loses kidney function such that elimination of metabolic byproducts decrease [1]. AKI commonly occurs in hospitalized patients, with the inciting event occurring prior to hospital admission or during the hospital stay. Causes can be classified into prerenal causes such as extracellular fluid volume loss and impaired cardiac function, intrinsic renal causes such as glomerulonephritis, interstitial nephritis, or acute tubular necrosis, or postrenal causes such as obstruction of urine flow. Acute tubular injury is the most common at 45%, resulting from ischemia, nephrotoxins, or pigment disposition [1-5].

For many years, a consensus numerical value necessary to merit AKI classification, whether measured as blood urea nitrogen or serum creatinine, did not exist within the nephrology community. Investigators use various criteria to classify AKI and ARF, including changes across a threshold value for serum creatinine or estimated glomerular filtration rate (GFR), or relative changes in serum creatinine or GFR within a given time period. GFR may be estimated with one of several methods, including the Cockcroft-Gault formula [6] or the Modification of Diet in Renal Disease formula [7].

Medical literature reports more than 30 criteria for defining AKI [8]. Threshold values most often range from serum creatinine values greater than 1.5 mg/dl to 4.0 mg/dl or estimated creatinine clearance less than 40 ml/min to 80 ml/min. Relative change criteria range from serum creatinine increases of 0.5 mg/dl to 1.0 mg/dl or 25% to 100% from baseline or creatinine clearance decreases of 50% to 100% from baseline within 24 hours to two weeks.

Recently, several groups developed formal criteria to better classify renal insufficiency. In 2004, the Acute Dialysis Quality Initiative (ADQI) developed the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) criteria to classify levels of renal dysfunction based on glomerular filtration rate (GFR) or urine output [9].

Table 1 summarizes the RIFLE criteria. A subsequent study found that the RIFLE criteria outperformed previously used indicators to predict mortality in patients with AKI [10].

Table 1: RIFLE criteria for risk of renal dysfunction, injury to the kidney, and failure of kidney function

Level	GFR* Criteria	Urine Output Criteria
Risk	Increased serum creatinine x 1.5	Urine output < 0.5 ml/kg/h x 6 hrs
	or GFR decrease > 25%	
Injury	Increased serum creatinine x 2	Urine output < 0.5 ml/kg/h x 12 hrs
	or GFR decrease > 50%	
Failure	Increased serum creatinine x 3	Urine output < 0.3 ml/kg/h x 24 hrs
	or GFR decrease > 75%	or Anuria x 12 hrs
	or Serum creatinine ≥ 4 mg/dl with acute rise ≥ 0.5 mg/dl	

*GFR = glomerular filtration rate

ADQI along with representatives from nephrology and intensive care medicine societies more recently introduced the term AKI to encompass a broader spectrum of ARF and established the Acute Kidney Injury Network (AKIN). AKIN developed a new classification system for AKI by defining stages of injury based on more sensitive changes in serum creatinine [11]. The AKIN system mirrors the RIFLE criteria for percentage increases in serum creatinine and absolute in urine output, but it changes the earliest stage criteria to include a more sensitive 0.3 mg/dl increase in serum creatinine . Table 2 summarizes the AKIN system. Alternative methods to determining acute renal failure include absolute increases in serum creatinine or estimated creatinine clearance levels below a certain threshold.

Table 2: AKIN criteria for acute kidney injury

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increased serum creatinine ≥ 0.3 mg/dl	Urine output < 0.5 ml/kg/h x 6 hrs
	or Increase to ≥ 150% to 200% from baseline	
2	Increased serum creatinine to > 200% to 300% from baseline	Urine output < 0.5 ml/kg/h x 12 hrs
3	Increased serum creatinine to > 300% from baseline	Urine output < 0.3 ml/kg/h x 24 hrs
	or Serum creatinine ≥ 4.0 mg/dl with an acute increase ≥ 0.5 mg/dl	or Anuria x 12 hrs

Effect on Drug Administration

Significant changes in renal function have a considerable effect on drug pharmacokinetics and pharmacodynamics [12-14]. The most important factor that AKI may affect is reduced glomerular filtration, which causes renally cleared drugs to accumulate. A 50% reduction in filtration can double the half-life of a drug [14]. Such changes do not typically affect loading doses, but maintenance drug doses and

frequencies often require alterations. Other pharmacological parameters altered by AKI include altered drug absorption and bioavailability, distribution, and metabolism. Also, when AKI is severe enough to require renal replacement therapy, drug management should change substantially to allow for periodic re-dosing of medications removed by hemodialysis.

Significance

AKI occurs frequently among inpatients and is most often hospital-acquired. Various studies estimate an incidence for AKI in adults of 5% to 17% in hospitalized patients [2, 5, 15-18]. In adult patients who develop AKI during hospitalization, risk of mortality rates may be significantly increased. Within intensive care units, mortality rates for patients with AKI range from 62% to 86% [10, 18]. Studies of hospital-wide mortality associated with AKI estimate rates from 15% to 64% [2, 16, 19, 20]. International, multicenter studies estimate AKI associated mortality rates from 45% to 60% [3, 5, 21].

Many factors contribute to AKI, including dehydration, surgical procedures, and administration of medications or contrast dyes [1, 2, 16, 18, 19, 22]. In particular, nephrotoxic drugs are the most common cause of AKI, and aminoglycosides account for a large percent of medication-induced episodes [2, 19, 22]. Careful renal function monitoring with avoidance or reduction of nephrotoxic medications may contribute to increased AKI prevention or amelioration.

Studies report that up to 50% of patients with AKI receive inappropriate doses of nephrotoxic or renally cleared medications [17, 23-29]. Providers with minimal clinical

experience in renal dosing must rely on expertise from consulting pharmacists and nephrologists or refer to published dosing guidelines. Such resources are often unavailable at the time of initial dosing, contributing to the high error rates in renally dosed drugs. Immediate feedback, whether provided by an expert during rounds or decision support during a CPOE session, can reduce the frequency of renal dosing errors [23-27, 29].

Informatics Solutions for Medication Safety

Clinical decision support embedded in CPOE systems may reduce large numbers of medication errors [30-33]. While various types of decision support may result in positive outcomes, systems implementing support including guided dosing algorithms and monitors for out-of-range lab values hold the highest potential to improve error rates [34-37].

Several studies evaluated the effects of computer-assisted dosing at the initial order time. Chertow, et al. measured the improvement on drug prescribing and patient outcomes of a system to adjust drug dose and frequency in patients with renal insufficiency. When applicable, the CPOE intervention notified providers ordering one of about 500 nephrotoxic or renally cleared medications of a patient's impaired renal function, suggesting drug dose amount and frequency from a knowledge base developed by the expert panel. The intervention system also suggested substitute drugs when initially selected medications were considered to be harmful. The results showed that 15% of orders written for renally cleared or nephrotoxic medications in patients with renal insufficiency had at least one parameter modified by the system. The fraction of

prescriptions written appropriately in the intervention and control periods was 67% versus 54% for dose and 59% versus 35% for frequency. While the fraction of inappropriate doses decreased during the intervention period, the large number of doses still deemed inappropriate may be due to noncompliance [23].

In response to the system developed by Chertow, et al. and in an attempt to maintain educational opportunities through entering orders, Oppenheim, et al. developed a CPOE intervention to check the drug dose and interval and alert providers after submission and only when the entered dose is inappropriate. During the intervention period, 23% of orders generated an alert prompting a change in the entered dose or frequency. Providers adjusted 52% of orders that received the alert [29].

Galanter, et al. created a set of CPOE alerts to reduce administration of medications contraindicated due to renal insufficiency. The authors designed the alerts to prompt providers not to complete an order for a drug if the minimum safe creatinine clearance was greater than the patient's most recent estimated creatinine clearance. Following implementation, the likelihood of patients receiving one or more doses of a contraindicated medication after the order was initiated decreased from 89% to 47%. Staff provider compliance with the alert was 42%, and compliance increased in patients with worsening patient renal function [26].

Recognizing that patients often experience changing renal function during their admission, other studies developed surveillance systems to monitor for and alert providers about renal function changes. Rind, et al. evaluated the effect on physicians' behavior and patient outcomes of computer-based alerts for rising serum creatinine levels in the presence of nephrotoxic and renally cleared drugs. The alert appeared in an

electronic mailbox to the attending physician and all additional physicians who had accessed the patient record within three days of the event. A prospective time-series study showed discontinued or modified doses an average of 21.6 hours sooner than without the alerts. The most noticeable change occurred with the renally cleared drugs, with a difference in 34.7 hours. The authors attribute the smaller improvement in nephrotoxic drugs to the attentiveness of physicians without an alert to renal function changes in the presence of nephrotoxins. The relative risk of a patient developing serious renal impairment in the intervention period compared to the control period was 0.45. In addition, the mean serum creatinine levels after detected events dropped significantly during the intervention period. When questioned about the alerts, 44% of physicians categorized the alerts as helpful in the care of their patients, 28% found them annoying, and 65% wished to continue receiving alerts [38].

In a later approach, Evans, et al. developed a surveillance system to monitor for excessive doses based on renal function for patients receiving any of five targeted antibiotics. The system generated a printed list of patients daily, including for each patient the change in renal function, and for each drug a suggested dose and the drug level if available. Pharmacists reviewed the list each morning, contacting the provider as necessary to prompt an alteration to the order. The authors measured a decrease in both the number of patients receiving excessive doses (50% versus 44%) and the number of days patients received excessive doses (4.7 days versus 2.9 days) between the pre-intervention and intervention periods [24].

Extending surveillance to all types of ADEs, Kilbridge, et al. implemented a monitoring system to alert providers about rules-based intervention and ADE triggers.

The system evaluates admitted patients each morning, displaying those patients that may require intervention to clinical pharmacists using a web-based application. Rules including drug-induced nephrotoxicity resulted in frequent ADE and intervention triggers [39].

Vanderbilt University Medical Center

Vanderbilt University Hospital, the Monroe Carrell Jr. Children's Hospital at Vanderbilt, and the Psychiatric Hospital at Vanderbilt make up Vanderbilt University Medical Center (VUMC), a large, urban, tertiary care facility and Level 1 trauma center in Nashville, Tennessee. VUMC has an 832 bed capacity and admits 42,611 patients each year [40].

Providers at VUMC utilize a variety of internally developed and purchased computerized systems, including an electronic medical record (EMR), CPOE, laboratory reporting, nursing documentation, and medication administration. The EMR integrates communication between members of the health care team and provides aggregated patient information from numerous institutional resources [41].

Developed internally and continuously enhanced and evaluated by the department of biomedical informatics, the CPOE system provides various levels of integrated decision support [42-44]. In one example, the CPOE system displays pharmacy warnings for drug-drug and drug-allergy interactions. In addition to interaction alerts, providers may receive decision support for initial dosing of some medications. Guidelines-based renal dosing nomograms assist providers in ordering renally excreted drugs such as

vancomycin, significantly improving the rate at which patients achieve therapeutic drug levels [45].

Summary

As demonstrated in numerous studies, hospital-acquired AKI is a widespread problem among inpatients. Those patients with nephrotoxic or renally cleared drug orders are at an even greater risk for associated mortality or morbidities. Fortunately, with close renal function monitoring and avoidance or adjusted dosing of targeted drugs, medication safety for patients experiencing AKI can be significantly improved. Solutions including dosing experts rounding with providing teams and decision support within CPOE systems have demonstrated the success of such efforts, reducing percentages of incorrect dosing and times during which patients are receiving excessive doses.

Despite the reported success of previous solutions in improving medication safety, no solution provides optimal support in reducing errors. Systems providing initial dosing advice reduce many errors, but they do not account for changes in renal function experienced later in a patient's hospital stay. While the system developed by Rind, et al. [38] monitored for and alerted providers about changing renal function, the alerts appeared in a separate system, outside of the provider's workflow. The surveillance systems developed by Evans, et al. [24] and Kilbridge, et al. [39] also delivers alerts outside of the CPOE system and provider workflow, providing alerts to pharmacists. While notifying pharmacists has some advantages, displaying alerts to providers at order entry time may allow for the timeliest responses. In addition, alerts displayed to providers remove the potentially high costs associated with additional pharmacy staffing.

A system to alert providers directly in the CPOE system at order entry time of changes in renal function in patients with nephrotoxic or renally cleared drug orders may further reduce medication errors with AKI.

CHAPTER III

PILOT VANCOMYCIN DOSING MONITOR

Introduction

Pharmacy and informatics staff members at VUMC implement and maintain guidelines-based renal dosing nomograms to assist providers in ordering renally excreted drugs such as vancomycin. Figure 1 displays the vancomycin nomogram. The nomogram always suggests a 1000 milligram dose and adjusts the frequency of administration. The nomogram was not designed to apply to dialysis, burn, paralysis, liver failure, transplant, and cystic fibrosis patients, or for patients with extreme weight. The order advisor shown in Figure 2 appears when the provider initially prescribes vancomycin and recommends the correct dose amount and frequency based on the patient's age, weight, and Cockcroft-Gault estimated creatinine clearance. The use of the nomogram improves the rate at which patients achieve therapeutic range of vancomycin (85.2% versus 67.1%) [45].

While the dosing advisor improves initial vancomycin dosing, the large percent of inpatients who experience changing renal function may require an adjusted dose [1]. Of these, less than half receive appropriate doses [17, 23-29]. A system to continuously monitor for medication errors may act as a safety net, enhancing computer-based guidelines [33, 39].

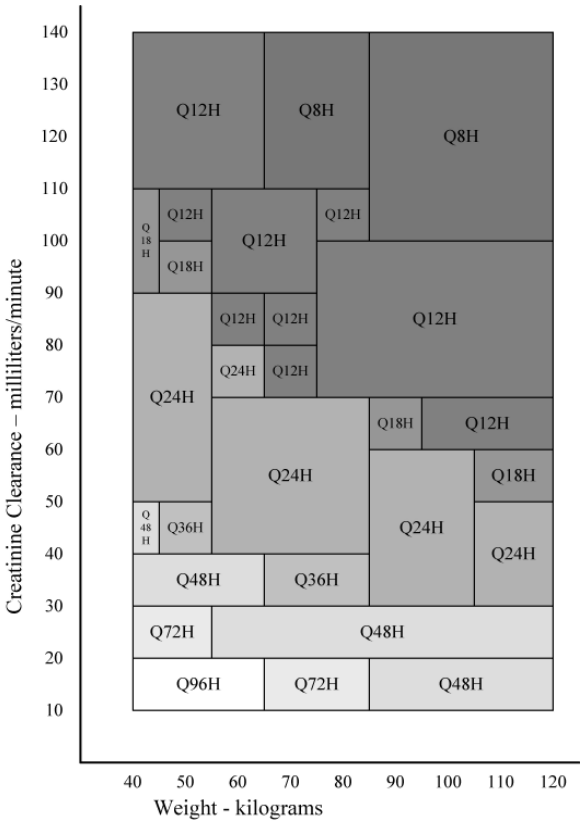

Figure 1: Vancomycin dosing nomogram

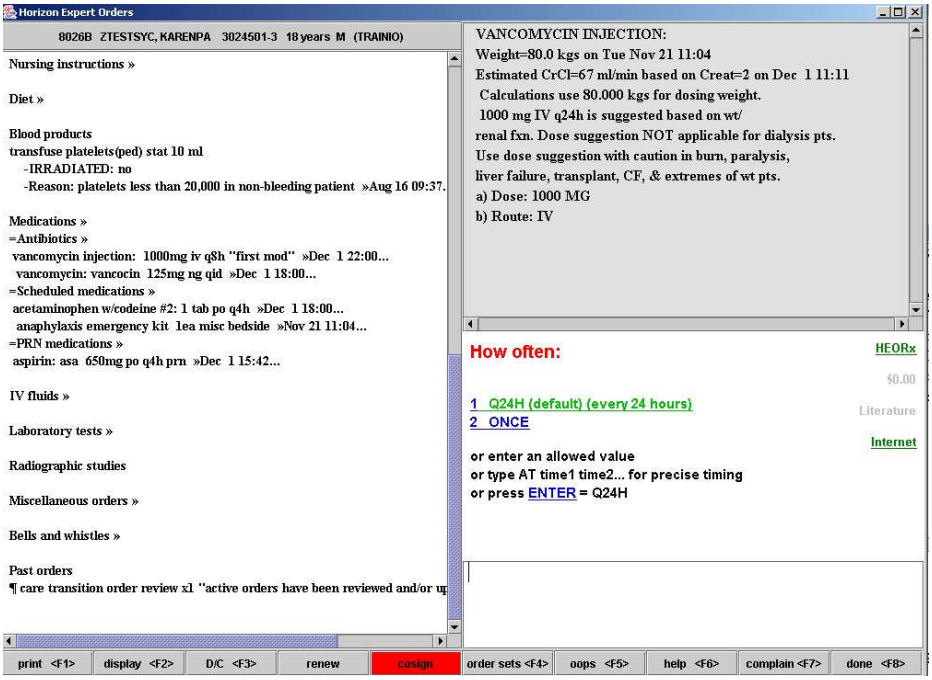

Figure 2: Vancomycin dosing advisor

We evaluated the efficacy and yield of the pilot monitoring orders after initial order entry in a retrospective study. The initial alert appeared in the pharmacy alert section of the CPOE system to delivering targeted decision support for medication adjustment based on estimated creatinine clearance.

Methods

System Description

We developed a monitor that detects vancomycin dose altering changes in a patient's serum creatinine or creatinine clearance levels. The system retrieved the original dosing parameters at the session initiation time, and it compared dosing recommendations based on these initial values with the recommendations based on current values. If the advice differed, a pharmacy alert appeared, informing the provider that the values had changed and a new dosing recommendation may be available. The provider could click on the text to view detailed information, including relevant lab values. The system stored a record of the alert in the user activity log and printed the display text on the current medications and results sheet, which providers printed and referred to when rounding. Figure 3 shows a screenshot of the vancomycin monitor alert.

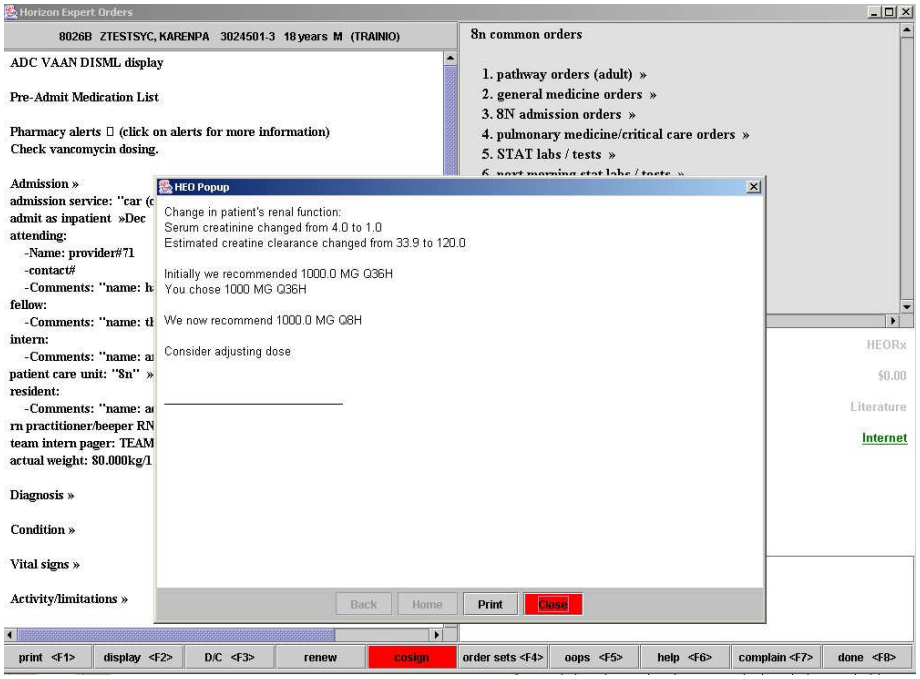

Figure 3: Pilot vancomycin therapeutic dosing alert

Study Population and Data Collection

To perform our retrospective analysis, we retrieved data for all adult cases in 2006 as the pre-intervention group. For the intervention group, we collected adult cases between 2/20/07 and 3/12/07, which encompasses the first three weeks of implementation.

We first excluded patients who were not admitted as inpatients and patients who received only one-time vancomycin doses. We did not analyze patients without a recorded baseline serum creatinine level, age, weight, and sex to limit the population to only orders based on the nomogram. We also excluded patients who did not have at least one serum creatinine lab result following the vancomycin order to potentially trigger the alert. Because the nomogram is inappropriate for dialysis patients, we attempted to remove them from the study population by eliminating those who received dialysis prior

to receiving vancomycin, those admitted to the nephrology service, and those who received dialysis after the vancomycin order but before an event occurred. We created an additional group for a subanalysis of patients who had at least one recorded vancomycin trough level.

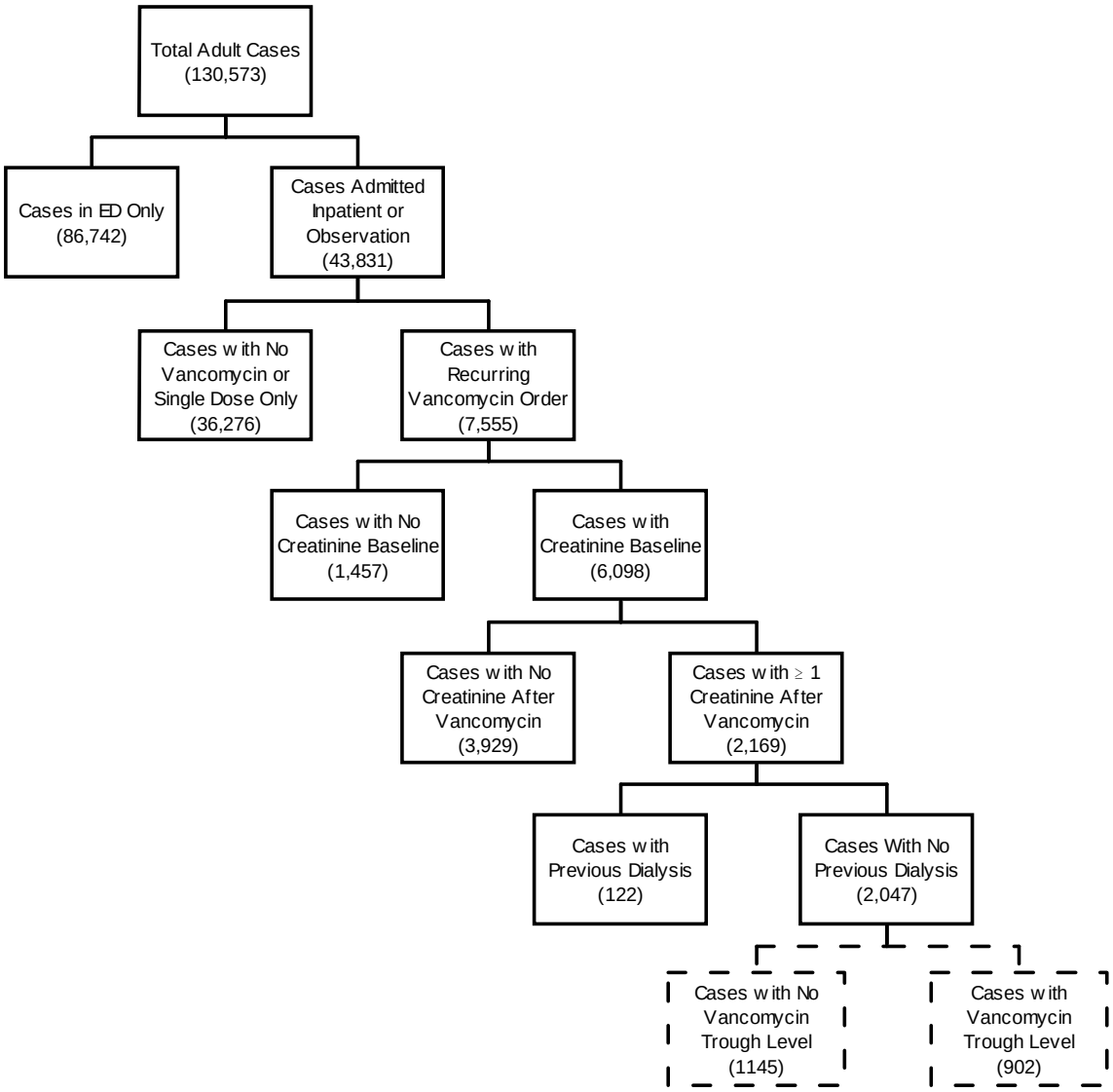

Figure 4: Pre-intervention study population for vancomycin dosing monitor

Our study populations consisted of 2047 cases in the pre- intervention group and 138 cases in the intervention group. The pre-intervention and intervention vancomycin trough level subgroups contained 902 and 113 cases respectively. Figure 4 illustrates the pre-intervention study population relative to all patients admitted to the medical center. To analyze each patient in the population, we retrieved start times for new, modified, or discontinued vancomycin orders; dialysis unit orders; serum creatinine levels; and vancomycin levels.

Procedures

We applied the vancomycin nomogram to the data at each change in serum creatinine level or dose modification. Each time our monitor would have produced an alert (i.e. the nomogram recommended a different dose), we logged the time of the event. At the next change, if reapplication of the nomogram confirmed a corrected dose, we calculated the time in between the initial event detection and the correcting change. We summed the time that the patient was receiving a non-optimal dose and the total time the patient was on a recurring vancomycin dose. We recorded the number of times the nomogram detected an event, including whether the dose was too high or too low. For the subgroup of patients with vancomycin trough levels, we tracked for each case whether the level dropped below 5 mcg/dl or reached a value greater than 25 mcg/dl.

For preliminary analysis of the intervention data, we accessed the user activity log files to determine how many times the monitor actually displayed the alert for a patient.

Data Analysis

To assess the alert's value on past data, we calculated the median time while on vancomycin that the patient was receiving a non-optimal dose. We also calculated the total frequency of events and observed whether the events were for too high or low doses. We tracked the number of patients who experienced more than one event. For patients who had a vancomycin trough level, we recorded whether a level was less than 5 mcg/dl or greater than 25 mcg/dl. We performed the same analysis on the intervention data.

Results

The pre-intervention group included 2047 cases. For these cases, the median time patients spent receiving the non-optimal dose was 23.2 hours. The total number of events detected was 2922; 1795 high events occurred, and 1127 low events occurred. These events affected 1414 patients, with 756 patients experiencing more than one event. There were 112 patients with vancomycin trough levels less than 5 and 165 patients with levels greater than 25.

The intervention group included 138 cases. Patients experienced a median time of 8.5 hours receiving a non-optimal dose. There were 163 total events; 95 events were high, and 68 events were low. A total of 88 patients experienced events, and 42 patients experienced more than one event. There were 10 patients with vancomycin trough levels less than 5 and 17 patients with levels greater than 25. Table 3 shows these results. During the three-week time period, the monitor displayed an alert to providers in 3018 separate CPOE session.

Table 3: Vancomycin pilot study results

	Pre-intervention	Intervention
Total Patients in Study Population	2047	138
Median Total Dosed Hours [IQR *]	291.83 [114.4, 1157.5]	137.5 [72.2, 233.6]
Median Hours Non-Optimal Dose [IQR]	23.2 [0, 105.4]	8.5 [0, 54.1]
Total Alerts	2922	163
High Alerts (%)	1795 (61.4)	95 (58.3)
Low Alerts (%)	1127 (38.6)	68 (41.7)
Patients With 1 or More Alerts (%)	1414 (69.1)	88 (63.8)
Patients with > 1 Alerts (%)	756 (36.9)	42 (30.4)
Vancomycin Trough < 5 (%)	112 (12.4)	10 (8.8)
Vancomycin Trough > 25 (%)	165 (18.3)	17 (15.0)

* Interquartile range

Discussion

We developed, simulated, and implemented a decision support system that monitors patients' renal function for changes in order to alert providers when a more optimal dose is recommended. By applying the system to pre-intervention data, we determined that more than half of patients (69.1%) had an opportunity to receive a more optimal dose. Non-optimal dosing occurs frequently in both directions; patients are both being overdosed and underdosed.

Decision support within the system at the LDS Hospital included a similar system to monitor antibiotic dosing [33]. The study found that implementing the monitor reduced rates and lengths of excessive dosage. Our monitor does not limit detection to doses exceeding the recommendation by also including underdosed amounts. In addition, we focus on alerting the provider directly with this data rather than only informing the pharmacists.

Our study had several limitations. Some indications, such as pneumococcal meningitis, have higher target trough levels. This limitation supports the monitoring based on the vancomycin level rather than strictly following the nomogram. We

excluded patients who were not started on the nomogram to restrict our analysis to patients with typical indications for vancomycin. The Cockcroft-Gault formula for estimating renal function [6] is less accurate for rapidly changing renal function, limiting our calculated non-optimal dose time for cases. However, alerting physicians is still appropriate. Our analysis does not include patients who start vancomycin without a baseline creatinine, which is common in patients arriving to the emergency department. These patients may still benefit from a monitor that alerts based on renal function.

While this research showed potential for improving medication safety, changes in serum creatinine are often severe enough to indicate AKI. These changes demand more than a simple reduction in dose, and involve many targeted drugs in addition to vancomycin. An enhanced intervention, including more sensitive detection of changes in creatinine and responding to all nephrotoxic or renally cleared drugs will likely have a stronger effect in reducing associated morbidities.

CHAPTER IV

MAIN INTERVENTION

Introduction

To further improve medication use in patients with changing renal function, we developed an enhanced set of interventions, including alerts similar to the vancomycin dose monitor. The interventions monitored for more significant changes in renal function in the presence of target nephrotoxic and renally cleared drugs. The interventions also utilized more intrusive methods of alerting providers. With this enhanced intervention, we aimed to improve provider response to changing renal function.

Methods

Intervention Description

The set of interventions includes a passive text display alert and a more intrusive, interactive exit check alert. Providers may receive one or both of the alert types for non-dialysis adult patients when a change in renal function may be linked to one of three classes of drugs as defined by a team of nephrologists, pharmacists, and infection control physicians. Table 4 shows the complete list of target drugs for each drug class. Drugs in class A are nephrotoxic and should be avoided with AKI, drugs in class B should be adjusted with AKI, and drugs in class C should be reviewed and possibly adjusted or discontinued with prolonged AKI.

Table 4: Target drug list

Class A Drugs Avoid with AKI*	Class B Drugs Adjust with AKI*	Class C Drugs Review with Prolonged AKI*
Acarbose	Acyclovir	Amoxicillin
Acetazolamide	Adefovir	Ampicillin
Acetohexamide	Allopurinol	Azithromycin
Amikacin	Carboplatin	Bretylium
Amphotericin B	Cisplatin	Cefaclor
Capreomycin	Colchicine	Cefazolin
Celecoxib	Cycloserine	Cefepime
Chlorpropamide	Didanosine	Cefotaxime
Cidofovir	Digitoxin	Cefotetan
Diclofenac sodium	Digoxin	Cefoxitin
Diflunisal	Eptifibatide	Ceftazidime
Enoxaparin	Etoposide	Cefuroxime
Etodolac	Famciclovir	Cephalexin
Fenoprofen	Flucytosine	Chloroquine
Flurbiprofen	Foscarnet	Ciprofloxacin
Gallamine	Ganciclovir	Clarithromycin
Gentamicin	Imipenem-cilastatin	Clofibrate
Glyburide	Itraconazole	Daptomycin
Ibuprofen	Meropenem	Disopyramide
Immune globulin	Mitomycin	Doxacurium
Indomethacin	Penicillin-VK	Ertapenem
Ketoprofen	Pentostatin	Ethambutol
Ketorolac	Procainamide	Flecainide
Meloxicam	Pyridostigmine	Fluconazole
Meperidine	Stavudine	Gemfibrozil
Metformin	Temozolomide	Hydroxyurea
Methotrexate	Topotecan	Idarubicin
Nabumetone	Valacyclovir	Indinavir
Naproxen	Valganciclovir	Lamivudine
Nitrofurantoin	Vancomycin	Levofloxacin
Nitroprusside	Voriconazole	Melphalan
Pancuronium		Metocurine
Piroxicam		Mivacurium
Radiology exams		Morphine
with contrast dye		Neostigmine
Rofecoxib		Norfloxacin
Sotalol		Ofloxacin
Streptomycin		Penicillin-G
Sulindac		Piperacillin
Tenofovir		Pyrazinamide
Tetracycline		Quinidine
Tobramycin		Quinine
Tolmetin		Rifampin
Trimetrexate		Ticarcillin
Tubocurarine		Tocainide
Valdecoxib		Zidovudine

*AKI = acute kidney injury

We defined a significant change in renal function as an increase or decrease in serum creatinine of 0.5 mg/dl within 48 hours. The critical difference for a lab value is the minimum change measured that is not a result of chance [46]. Our team of nephrologists recognizes a change in serum creatinine of three times the critical difference as significant, which for a wide range of measured values averages to 0.5 mg/dl.

The improved passive alert (Figure 5) appeared in the case of a significant increase or decrease in renal function coupled with class A, B, or C drug that was ordered or last modified prior to the change. Patients receiving dialysis, identified by providers using a dialysis flag order, did not receive the alert. The passive alert displayed as descriptive text in the Pharmacy Alert section of the information pane and as a simple alert notification next to the trigger drug in the Medication List section. In addition, the text appeared in the Pharmacy Alert section of printed rounding reports. Within the CPOE system, when a provider clicked the Pharmacy Alert text, a popup window appeared with detailed information about the order, including initial patient data, and relevant lab results. The popup window also contained advice about what action to take with the drug, depending on the drug classification: avoid, adjust, or review. When available for drugs requiring an adjustment, the system provided updated dosing advice. The Medication List text opened an order modification dialog window when clicked, which providers frequently used to modify or discontinue orders. The alert persisted for 48 hours or until the patient's renal function improved such that no significant change was detected. The provider could suppress the alert by modifying or discontinuing the

order or the asserting the current dose as correct within the exit check alert (described below).

The exit check alert (Figure 6) interrupted the provider when he or she tried to exit the CPOE system on a patient with a significant decrease in renal function coupled with a class A or B drug that that was ordered or last modified prior to the change and not modified or discontinued within the current session. As with the passive alert, patients with the dialysis flag order did not receive the alert. In addition, the alert excluded drugs that were ordered when the patient's estimated creatinine clearance was less than 30 ml/min. A popup window appeared, requiring the provider to act on the alert by choosing to modify or discontinue the drug, to suppress the alert by confirming that the dose was correct, or defer the alert until the next CPOE session. The provider could also select to identify the patient as receiving dialysis, suppressing all renal dosing alerts for future sessions. Similar to the passive alert, the alert displayed detailed information about the order and related lab values. Deferred alerts persisted for 48 hours or until the patient's renal improved such that no significant change was detected.

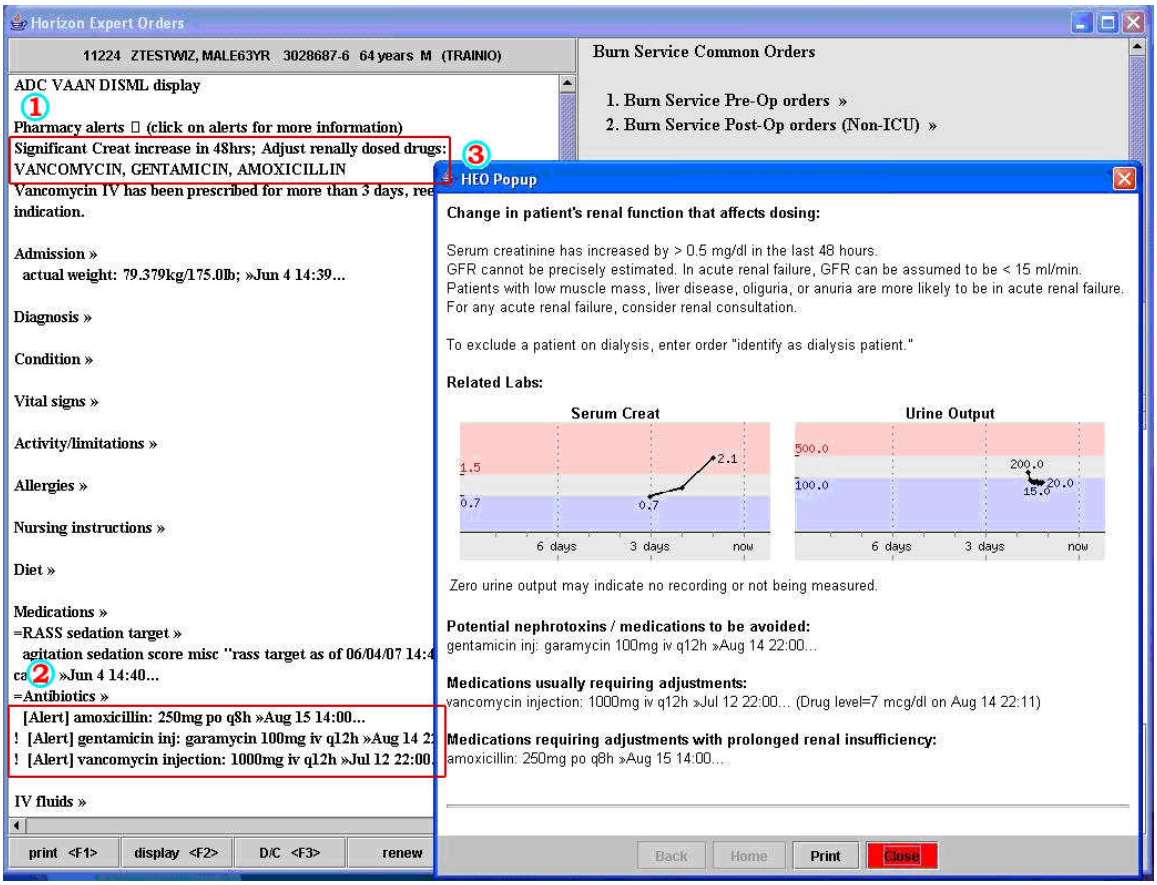

Figure 5: Passive intervention alert

1) Pharmacy alert text
   - Informative text about the change in renal function and prescribed target drug
   - Opens pharmacy alert popup when clicked.
2) Medication alert text
   - Alert text about prescribed target drugs
   - Denotes class A or class B target drug with "!" symbol
   - Opens order modification dialog window when clicked.
3) Pharmacy alert popup
   - Opens with pharmacy alert text click
   - Displays detailed information about the change in renal function and prescribed target drugs

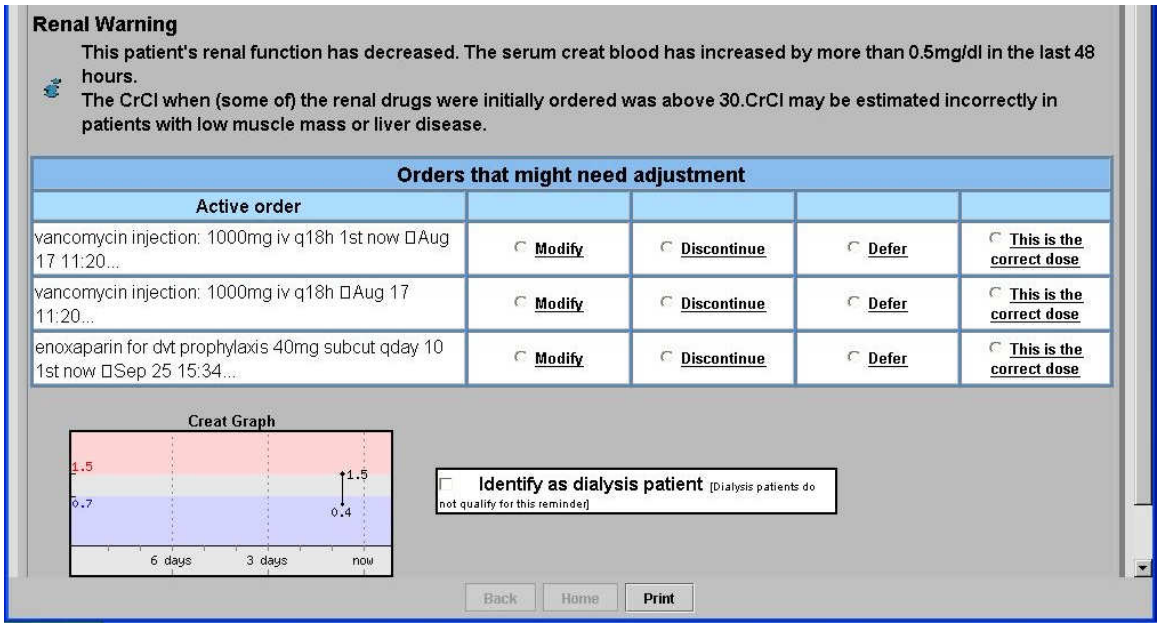

Figure 6: Exit check intervention alert

- Displays change in renal function with graph of serum creatinine over time
- Requires providers for each alerting drug to modify the order, discontinue the drug, defer the alert, or assert the dose as correct
- Allows option to identify patient as receiving dialysis, suppressing future alerts

Timeline for Implementation

Implementation of the intervention in the CPOE system began in June 2007 with a pilot exit check alert for vancomycin. On August 13, 2007, we released a preliminary version of the both the passive and exit check alerts. After reviewing the user activity log files and user feedback, we made final adjustments and fixed all reported issues. We implemented the final version on October 12, 2007.

Study Population

We included all adult cases that could have received an exit check alert. Eligible cases had two or more measured serum creatinine levels within 48 hours, where the second level is 0.5 mg/dl greater than the first level, with an active order for a class A or class B target drug. To exclude dialysis patients from analysis, for whom the intervention does not apply, cases with a dialysis order preceding the significant change in serum creatinine were not included. We analyzed only the first significant creatinine change within a drug regimen. The patient demographics (Table 5) and target drug orders (Table 6) were similar for the pre-intervention and intervention periods.

In the 301-day pre-intervention period, we recorded 10,822 significant serum creatinine changes, with 4209 changes in the presence of a target drug. We evaluated 1369 initial events. Of these, 54 drugs were discontinued because the patient was discharged within 24 hours of the event. In the 126-day intervention period, we recorded 3984 significant serum creatinine changes, with 1994 in the presence of a target drug. We evaluated 629 initial events, including 25 drugs that were discontinued due to patient discharge within a 24 hour period.

Table 5: Study population

	Pre-Intervention 10/15/06 – 8/11/07 (301 days, 43 weeks)	Intervention 10/14/07 – 2/16/08 (126 days, 18 weeks)	p-value
Admitted adult patients (patients per day)	29849 (99.17)	13138 (104.27)	< .01
Age, mean, year (s.d.)	53.46 (21.62)	53.30 (20.56)	.47
Sex			
Females, %	51.72	51.87	.77
Males, %	48.63	48.46	.75
Unknown, %	0.35	0.33	.74
Race, %			
White	76.79	77.39	.17
Black	16.03	15.65	.32
Hispanic	1.87	1.75	.39
Other	2.13	6.34	< .01
Unknown	23.35	22.58	.08
Admitting service, %			
Cardiology	10.56	10.64	.80
Critical Care	4.29	4.66	.09
Dermatology	0.02	0.03	.53
Gastroenterology	1.37	1.69	.01
Geriatrics	1.29	1.80	<.01
Hematology/Oncology	4.77	5.15	.09
Infectious Disease	1.58	1.64	.65
Medicine	9.86	10.87	<.01
Neurology	2.84	3.68	<.01
Neurosurgery	4.45	4.24	.33
Ob-Gyn	9.91	8.57	<.01
Orthopedics	6.11	5.89	.38
Other	1.97	1.81	<.01
Otolaryngology	1.60	1.55	.70
Psychiatry	7.96	7.28	.02
Pulmonary	1.95	2.18	.12
Renal	1.92	2.15	.12
Surgery	27.55	26.16	< .01
ICU, %	22.62	22.56	.89
Dialysis, %	3.07	3.19	.51
Creatinines per patient per day	1.73	2.91	< .01

Table 6: Target drug use by drug class in study population

Drug group (N), %	Pre-Intervention 10/15/06 – 8/11/07 (301 days, 43 weeks)	Intervention 10/14/07 – 2/16/08 (126 days, 18 weeks)	p-value
Any target drug (152)	70.33	70.15	.71
Analgesics (4)	3.72	4.96	<.01
Antiarrhythmics (8)	1.27	1.44	<.01
Antibacterials – Aminoglycosides (4)	5.55	4.36	<.01
Antibacterials – Carbapenems (3)	3.07	2.57	<.01
Antibacterials – Glycopeptides (1)	16.65	17.07	.28
Antibacterials – Other (3)	1.27	1.29	.86
Antibacterials – Penicillins (1)	0.18	0.14	.35
Antibacterials – Tetracyclines (1)	0.05	0.06	<.01
Antibodies (5)	0.45	0.37	.24
Anticholinesterases (3)	0.19	0.15	.36
Anticonvulsants (4)	0.73	0.75	82
Antidiabetics (7)	2.53	2.24	.07
Antifungals (5)	0.42	0.32	.13
Antigouts (4)	2.80	2.96	.36
Antimycobacterials (2)	0	0	-
Antineoplastics (14)	0.85	0.59	<.01
Antiparasitics (1)	0	0	-
Antithrombotics (3)	17.80	17.01	.04
Antivirals (14)	4.65	4.87	.32
Cardiac Glycosides (4)	3.75	3.60	.45
Muscle Relaxants (5)	0	0.02	.01
NSAIDs (23)	30.75	30.11	.18
Radiology Exams with Contrast Dye (28)	4.67	4.22	.04
Vasodilators (5)	1.72	1.80	.56

Data Collection

For each initial significant increase in serum creatinine detected, we recorded a unique case event for all active class A or class B drugs when the change occurred. For example, a patient with two active orders at the time of the change would have two events recorded. We also recorded actions for each drug, including modifications and discontinuations of the order. We defined a successful action for each event as a modification or discontinuation of the order within 24 hours of the significant change. From the user activity log files, we collected the number of alerts displayed, the number of clicked passive alerts, and the exit check alert responses.

We did not contact patients or physicians during the study, so informed consent was waived. The local institutional review board approved this study through an expedited review, considering it to be of minimal risk to participants.

Data Analysis

We conducted a comparative analysis using the rate of actions per detected event as our main outcome. We completed a chi-square test to evaluate for a significant difference in the action rate between the intervention periods for all drugs and for class A and B drugs separately. We also evaluated the overall time taken to modify or discontinue an event-causing drug as secondary outcome. We calculated the median time between an event occurrence and a drug modification or discontinuation, excluding drug orders that were discontinued for the reason of patient discharge. Using a Mann-Whitney ranksum test, we evaluated for a significant difference in the median time outcome between the intervention and control periods.

We further evaluated the data using an interrupted time series analysis [47, 48], assessing the weekly action rate multiple ways to account for various outcomes. To account for a potential secular trend, we included in our model the number of weeks since the start of the study period. We included a parameter to allow a hinge point after the intervention. We tested for correlation between weeks by adding lags of one and two weeks to the model. We also evaluated the number of events, or the number of potential actions. Because both the lags and number of events did not significantly predict the outcome, we excluded the variables from our final model. We considered an alternate model with the number of actions per week as our dependent variable and evaluated the

number of events in addition to the variables described in the previous model. The effect of the intervention as an interaction variable did not differ significantly from the previous model, so did not pursue the analysis. Our final regression model evaluated the weekly rate of action against variables for time and intervention.

In addition to evaluating the rate of provider action before and after the intervention, we analyzed actual provider responses to the intervention alerts. We first evaluated the action rates for alerted medications after the passive alert, through the exit check alert, and in subsequent sessions after initially overriding the alert. To exclude the effect of the exit check alert for class A and class B drugs and evaluate the passive alert, we measured the action rate prior to the end of a CPOE session, which would suppress the exit check alert.

Our secondary provider responses analysis outcomes included the number of times providers clicked on the passive alert to open the more informative popup window and the frequency at which each exit check option was selected. For the exit check selection frequency, we disregarded deferrals and included only the terminal response for each significant change and drug pair. We also quantified the number of times providers chose the “defer” option before making a final selection.

Results

Comparative Analysis

Action Rate

We compared the rate of provider action, modifications or discontinuations within 24 hours, for events, initial serum creatinine significant changes in the presence of a target drug, before and after implementation of the intervention. In the pre-intervention period, 894 patient cases with a class A or class B drug order experienced at least one significant change in creatinine. We recorded 1315 events, with 470 actions (35.7 actions per 100 events). In the intervention period, 416 cases with a nephrotoxic or renally cleared drug order experienced events. The action rate increased to 50.9 actions per 100 events, with 629 events and 320 actions ($p < 0.001$).

The intervention appeared to have a more profound effect when we stratify the results by drug severity group. We saw the most significant impact with the class A, or nephrotoxic, drugs. In the pre-intervention period, we recorded 498 events with 194 actions (39.0 actions per 100 events). The intervention period action rate increased to 63.6 actions per 100 events, with 239 events and 152 actions ($p < 0.001$). The action rate for class B drugs also increased in the post-intervention period ($p = 0.002$). In the pre-intervention period we recorded 817 events with 276 actions (33.8 actions per 100 events), and in the intervention period we recorded 390 events with 168 actions (43.1 actions per 100 events). Table 7 summarizes the comparative analysis results.

Table 7: Comparative analysis results of action rate

	Pre-intervention	Intervention	p-value
Cases with an Event (%)	894 (3.00)	416 (3.16)	.37
Total Events	1315	629	.08
Nephrotoxins (%)	498 (37.9)	239 (38.0)	.27
Renally Cleared (%)	817 (62.1)	390 (62.0)	.18
Total Actions (%)	470 (35.7)	320 (50.9)	<.001
Nephrotoxins	194 (39.0)	152 (63.6)	< .001
Renally Cleared	276 (33.8)	168 (43.1)	.002

Time to Action

We also evaluated the overall time to action between the pre-intervention and intervention periods. In the pre-intervention period, 992 event-triggering medications resulted in a drug modification or discontinuation before patient discharge. The median time between an event occurrence and an action in the pre-intervention period was 27.1hours. The median time in the intervention period was 14.2 hours sooner at 12.9 hours. The difference between intervention and pre-intervention periods for nephrotoxin discontinuation or modification was 14.6 hours sooner (23 hours vs. 8.4 hours), and the difference between periods for renally cleared drugs was 9.8 hours sooner (28.8 hours vs. 19.0 hours). Table 8 summarizes the time to action results.

Table 8: Comparative analysis results of time to action

	Pre-intervention	Intervention	p-value
Total Events with Actions (%)	992 (72.5)	514 (78.6)	.003
Median Hours to Action (IQR)*	27.1 (7.8, 57.1)	12.9 (5.8, 38.5)	< 0.001
Nephrotoxins	23 (7.5, 41.3)	8.4 (4.5, 21.2)	< 0.001
Renally Cleared	28.8 (8.3, 61.8)	19.0 (6.7, 55.1)	0.012

* IQR = Interquartile ranges

Time-Series Analysis

Our time-series analysis confirmed our previous finding that the intervention significantly increased the action rate ($p = 0.03$). Time was not a significant factor in the regression model before or after the intervention ($p = 0.34$ and 0.28 respectively). Figure 7 illustrates the significant increase in weekly action rate after intervention for all target drugs. As in the comparative analyses, we found a greater effect of the interventions for the nephrotoxic drugs. The change in action rate for nephrotoxic drugs remained significant ($p = 0.02$), while the change in action rate for renally cleared drugs was not significant ($p = 0.32$).

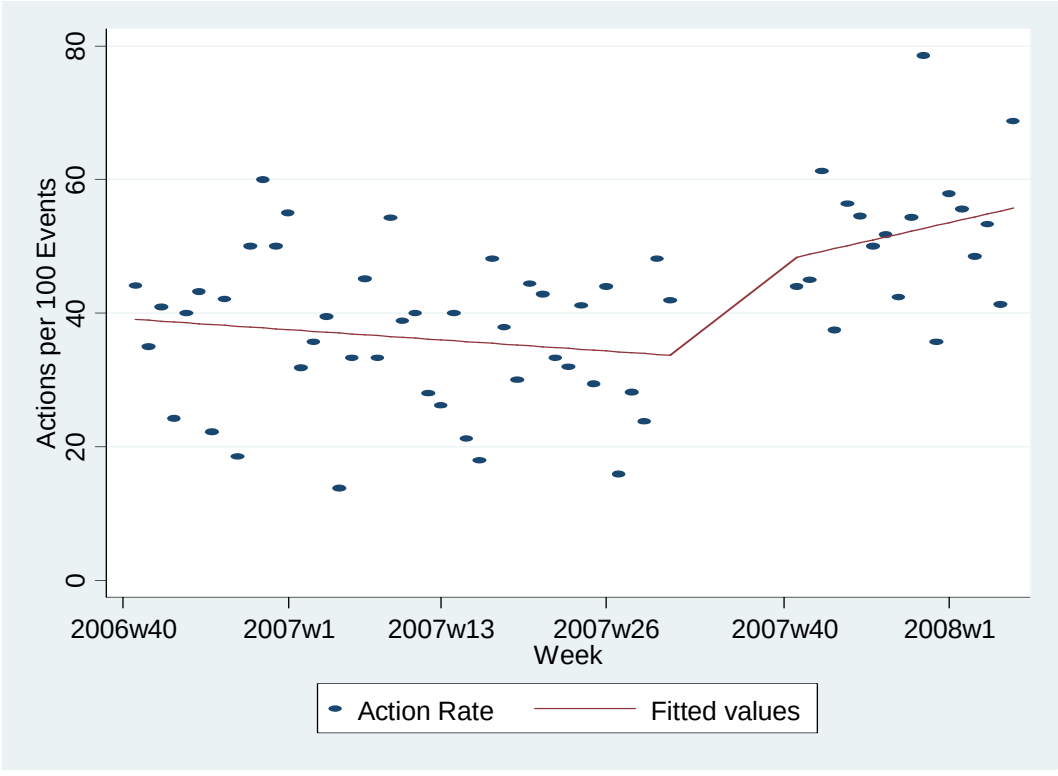

Figure 7: Time-series analysis

Provider Response Analysis

Provider Actions

We evaluated 516 initial alerted AKI events. For each event-drug pair, the passive alerts displayed a median of 14 times, often to multiple providers. The overall action rate for orders that generated a passive or exit check alert was 58.9 actions per 100 events. Of these, providers modified or discontinued 69 drugs (13.4%) after only viewing a passive alert, suppressing the exit check alert. After viewing the exit check alert, providers acted on 116 drugs (22.5%) by selecting the "modify" or "discontinue" option. Providers modified or discontinued 119 drugs (23.1%) in a subsequent CPOE session after initially selecting the "correct dose" option or choosing to defer the alert. Providers performed the largest percentage of actions after initially deferring the alert (15.1%). Table 9 summarizes these results.

Table 9: Action rate for alerted medication orders

Alert Type	**Action Rate, N (%)**
All Orders (N = 516)	304 (58.9)
After viewing passive alert only	69 (13.4)
Through the exit check alert	116 (22.5)
"Modify" option selected	63 (12.2)
"Discontinue" option selected	53 (10.3)
Within a subsequent CPOE session	119 (23.1)
"Defer" option selected	78 (15.1)
"Correct Dose" option selected	41 (7.9)

After receiving the passive alert, providers clicked on 21 alerts to view the additional details. Of these, 13 were in response to increasing serum creatinine events, and 8 were in response to decreasing serum creatinine events. Five clicks in response to

increasing serum creatinine included class A or B drugs, and the remaining clicks involved a class C target drug. In addition to clicks on the Pharmacy Alert text, providers also clicked on the Medication List text to display a prompt to change the order. After receiving an alert, providers clicked on the text 713 times. However, this number may over-represent provider acknowledgement of the alert, as providers typically click the medication list to modify or discontinue drugs, regardless of a displayed alert.

Exit Check Alert Selections

For each event triggering an exit check intervention, we determined the terminal response selected by providers. The most frequent option selected was "correct dose", in 37.8% of cases, followed by "defer", in 34.7% of cases. The "modify" option was selected in 15.0% of cases, and the "discontinue" option was selected in 12.5% of cases.

Table 10: Exit check alert responses by drug

		Selection Rate, %			
Drug (Drug Class)	**Total Events**	**Modify**	**Discontinue**	**Defer**	**Correct Dose**
Vancomycin (B)	101	21.8	4.0	37.6	36.6
Enoxaparin (A)	78	19.2	11.5	34.6	34.6
Acyclovir (B)	71	1.4	0	74.6	23.9
Meperidine (A)	39	5.1	12.8	76.9	5.1
Digoxin (B)	35	5.7	2.9	45.7	45.7
Allopurinol (B)	17	23.5	11.8	17.6	47.1
Ibuprofen (A)	17	11.8	47.1	23.5	17.6
Imipenem (B)	16	25.0	0	37.5	37.5
Valganciclovir (B)	15	6.7	0	53.3	40.0
Gentamicin (A)	12	25	8.3	50	16.7

The ten drugs that generated the most alerts are shown in Table 10. Of the 42 nephrotoxic or renally cleared drugs that generated an alert, 29 had less than 10 alerts

appear to providers in the intervention period. Of the ten drugs that triggered the highest number of alerts, the drugs most often deferred were meperidine (76.9%) and acyclovir (74.6%). On the contrary, allopurinol and ibuprofen were deferred much less frequently.

We also determined how often providers chose the "defer" option before making a final selection. The terminal response was selected as the first response for 45% of alerts. Figure 8 shows how often exit check alerts were deferred prior to the terminal response. When the "defer" option was selected at least once before the terminal response, the median number of prior alerts was 3. The maximum number of deferrals prior to the terminal response selected was 18, 22, 56, and 32 for the "modify," "discontinue," "correct dose", and "defer" responses respectively.

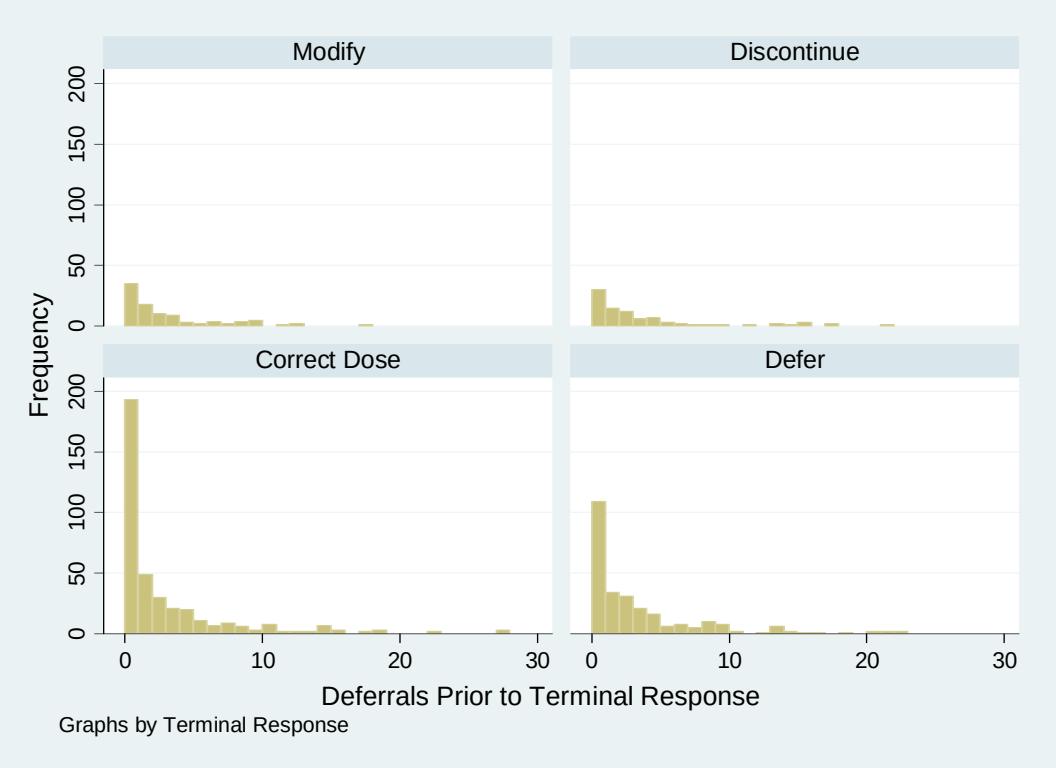

Figure 8: Number of deferred exit check alerts prior to terminal response

As time progressed and providers became more familiar with the interventions, the number of deferred alerts decreased. Figure 9 shows the median number of deferred alerts for each week, stratified by terminal exit check response.

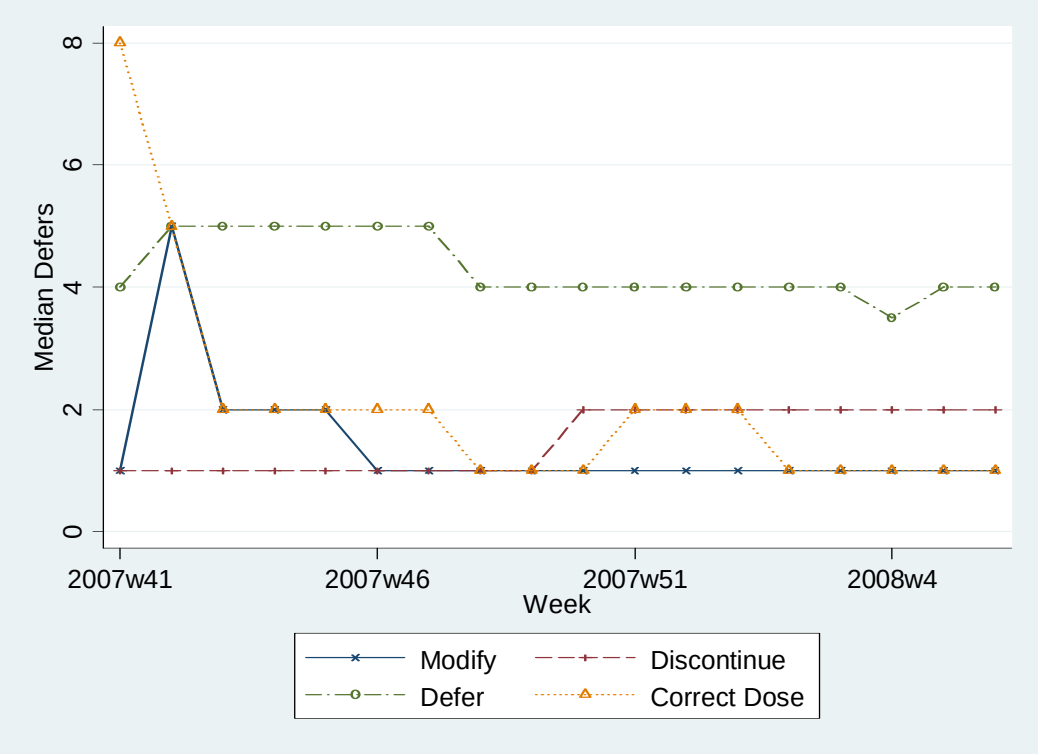

Figure 9: Median exit check defers before terminal response by week

Discussion

We developed a set of CPOE interventions with varying levels of workflow intrusiveness to continuously monitor for and alert providers about AKI. Through a comparative analysis of AKI events before and after implementation of the interventions, we discovered that the interventions significantly improved provider response to AKI events. Providers modified or discontinued nephrotoxic and renally cleared drugs more frequently and quickly with the interventions. Despite the success in improving provider

response, evaluation of actual provider usage showed low response rates to passive alerts and high override and deferral rates for the exit check alerts.

The findings of our evaluation are important in reducing errors. Improved dosing of nephrotoxic and renally cleared drugs in patients with AKI may reduce associated patient morbidity and represents improved compliance with standard of care for hospitalized patients. A better understanding of how providers respond to the available alert types allows us to build further enhanced intervention systems and further improve medication safety.

The interventions we developed utilize decision support capabilities not previously combined in a single system. Many evaluated systems provide guidance for renally dosed drugs when providers initially prescribe the medications [23, 26, 29]. Because patients often experience changes in renal function, these doses may become inappropriate later during a patient's hospital stay. Rind, et al. implemented a surveillance system to alert providers about renal function changes [38], however the alerts appeared to providers as e-mail messages outside of the workflow. The systems developed by Evans, et al. [24] and Kilbridge, et al. [39] also include a surveillance approach, however the systems assess for changes only once daily, and the alerts appear to pharmacists rather than ordering providers. Alerts displayed to pharmacists require additional pharmacy staffing, which may be expensive. By continuously monitoring for updated lab results and alerting ordering providers directly in the CPOE system, we eliminate associated pharmacy costs and give providers the opportunity to make dosing changes more quickly.

Rind, et al. measured a reduction in the time to action of 21.6 hours, while we recorded a reduction of 14.2 hours. The authors also found that the reduction in time to action for renally cleared drugs exceeded the reduction for nephrotoxic drugs, while we found the greatest reduction in nephrotoxic drugs. The disparity in the results may be due to the differing intervention criteria, both for the change in renal function and target drugs.

The high rate of deferred and overridden alerts that we measured matches the results of previous studies. Chertow, et al. [23] and Galanter, et al. [26] also found high rates of alert overrides and noncompliance (42%, 48%) with their decision support systems. Some of the overrides are likely appropriate due to sufficiently low initial dosing as a result of guided dosing decision support. Additionally, some renal dysfunction may result from patient dehydration, and may be easily reversed with fluid administration. As with the disparate time to action results we observed compared to previous studies, the higher override rate may result from differing alert criteria. Providers choose to defer or override some drugs more often than others. Through additional evaluation of alerting criteria, we can improve the specificity of the alert and increase compliance.

Our study had some limitations. Although we tried to account for confounders through our time-series analysis, some factors in addition to the intervention may have caused the improved provider response. In one example, pharmacists began to use a surveillance tool to monitor aminoglycoside dosing during the intervention period. Improved aminoglycoside prescribing as a result of the pharmacy tool may have biased our results.

Another limitation is our analysis of action rate. For this study, we counted any discontinuation or modification to an order as an event, and we did not check that dose modifications were appropriate or in the correct direction. Some modifications that we counted as compliant responses in our analysis may have included incorrectly increased doses by providers who ignored the alert advice.

CHAPTER V

FUTURE WORK

Introduction

These interventions had a significant effect in improving provider response to AKI events. However, responses to the passive alerts were low, and providers deferred more than half of the exit check alerts. By making changes to the intervention, including an improved passive alert, adjusting the alerting criteria, and adding a monitoring system that includes other team members, provider response can be further improved.

Improved Passive Alert

The current passive alert in the CPOE system allows providers to respond to alerts in their normal workflow and avoid interruptions. However, low response rates with passive alerts indicate that the alerts may remain unnoticed in the busy user interface. The pharmacy alert section of the CPOE system often displays numerous text alerts that providers frequently override. To increase the effectiveness of the alert, we propose modifications to make the alert more visible. One method to accomplish this includes prioritizing alerts and changing the text of higher priority alerts from black to an alternative color. Alerts displayed in the alternative color may stand out and increase provider response.

Another method to improve the passive alert is to enhance the order modification window that opens with the medication list alert click. Providers click on the medication

list alert more often than the pharmacy alert, but at present this alert does not show the detailed information included with the pharmacy alert popup window. By adding this data to the order modification window, providers may make better decision about the target drugs.

Adjusted Alerting Criteria

The effect of the intervention varied for the numerous target drugs. Vancomycin triggered the most number of alerts and had a high action rate. However, other drugs that received numerous alerts, including meperidine and acyclovir, had a much lower action rate. In addition, many drugs received very few alerts. We can further evaluate the target drugs that may not always merit an action, either eliminating the drugs from our target list or placing the drugs into a different alert class. In addition, we can evaluate the passive alerts generated for significant serum creatinine increases with class C drugs and significant serum creatinine decreases. As a result, we can decrease the noise level of the alerts and reduce the high provider deferral and override rates.

We can also improve the alerting criteria by checking for correct dosing of prescribed medications when patients experience AKI. Providers often anticipate AKI events and reduce doses of target medications at the time of initial prescription. When this is the case, the alerts may be unnecessary. By suppressing alerts for sufficiently low doses of target drugs, we can further reduce noisy alerts.

Higher Level Surveillance

The high alert deferral rate may be due to ordering providers' lack of experience in dosing drugs according to renal function. By involving other team members, such as pharmacists, we can potentially allow for quicker decisions about dosing. In particular, alerts that are repeatedly deferred may be escalated to a higher priority for additional review. Many other groups have adopted the method of alerting pharmacists instead of providers directly [24, 39]. We have begun to develop tools allowing pharmacists to monitor for adverse drug events resulting from aminoglycoside and warfarin use. Extensions of these tools, in addition to team-level monitoring tools, such as patient management dashboard, incorporated into the EMR may improve provider responses to the alerts.

Further Intervention Evaluation

While the intervention currently alerts providers about declining and improving renal function, we only evaluated declining renal function for this study. Patients frequently experience improved renal function while admitted, and initially low doses may need to be increased to allow for optimal therapy. We can evaluate the effect of the interventions in the presence of improving renal function using methods similar to those we employed to evaluate the effect of the interventions in AKI.

In addition to evaluating provider responses to the interventions, we plan to evaluate the effect of the interventions on patient outcomes. Potential outcomes include patient serum creatinine levels at the time of discharge, incidence of AKI, duration of AKI, the number of patients with unanticipated dialysis, mortality rates, and patient

lengths of stay. However, due to the complexity of AKI and illness severity of patients who experience AKI, patient outcomes may be difficult to measure.

CHAPTER VI

CONCLUSION

We developed, implemented, and evaluated a set of interventions to continuously monitor for and alert providers about AKI in the presence of target nephrotoxic or renally cleared drugs. Through comparative and time-series analyses, we determined the interventions to be significantly effective in both increasing the rate of provider modification or discontinuation of target drugs within 24 hours and decreasing the total time to modification or discontinuation following an AKI event. Evaluation of actual provider responses to alerts revealed high rates of provider overrides and deferrals. We plan to improve future responses by enhancing the alerting methods and criteria and developing additional interventions to be used by other team members.

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