ABSTRACT

The utilization of clinical decision support (CDS) is increasing among healthcare facilities that have implemented computerized physician order entry or electronic medical records. Formal prospective evaluation of CDS implementations rarely occurs, and misuse or flaws in system design are often not recognized or corrected. Through retrospective nephrologist adjudication of acute kidney injury (AKI) CDS alerts, we identified patient and knowledgebase factors that contributed to inappropriate or false positive, alerts. We also estimated the rate of inappropriate provider responses, which occurred in the setting of both true and false positive alerts. We found that few alerts were determined to be inappropriate. Unintended adverse consequences, or inappropriate provider responses resulting from inappropriate alerts, were rare.

Retrospective review often occurs too late to make critical corrections or initiate redesign efforts. We developed a real-time, web-based surveillance tool for nephrotoxic and renally cleared medications that integrates provider responses to CDS recommendations with relevant medication ordering, administration, and therapeutic monitoring data. The surveillance view displays all currently admitted, eligible patients and provides brief demographics with triggering order, laboratory, and CDS interactions to facilitate the identification of high-risk patient conditions, such as an imminent adverse drug event (ADE) or potential ADE (pADE). The patient detail view displays a detailed timeline of orders, order administrations, laboratory values, and CDS interactions for an individual patient and allows users to understand provider actions and patient condition changes occurring in conjunction with CDS interactions.

We evaluated the surveillance tool with a randomized trial, where intervention patients were monitored on the surveillance tool daily by a clinical pharmacist and control patients received only

existing CDS and standard of care. Despite interventions made by the study pharmacist from the surveillance tool, we found no significant change in the timeliness of provider modifications or discontinuations of targeted medications or occurrence of pADEs or ADEs. We concluded that clinical pharmacist surveillance of AKI-related medication alerts did not improve the timeliness or quality of provider responses or patient outcomes.

ACHIEVING MEDICATION SAFETY DURING ACUTE KIDNEY INJURY:

THE IMPACT OF CLINICAL DECISION SUPPORT AND

REAL-TIME PHARMACY SURVEILLANCE

By

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LIST OF ABBREVIATIONS

Abbreviation   Definition

ADE .... adverse drug event

AKI .... acute kidney injury

BCMA .... bar coded medication administration

CDS .... clinical decision support

CPOE .... computerized provider order entry

DPV .... Dynamic Pharmacovigilance

eMAR .... electronic medication administration record

EMR .... electronic medical record

IQR .... interquartile ranges

NSAID .... non-steroidal anti-inflammatory drug

pADE .... potential adverse drug event

PAML .... pre-admission medication list

VUH .... Vanderbilt University Hospital

VUMC .... Vanderbilt University Medical Center

CHAPTER I

INTRODUCTION

In response to new financial incentives within the United States, healthcare facilities are accelerating the adoption of clinical information systems, including electronic medical records (EMRs), computerized provider order entry (CPOE), pharmacy management, and medication administration systems (1). Many of these systems feature clinical decision support (CDS) functionality to assist providers by promoting correct order entry and providing patient-specific recommendations (2). Although CDS improves patient care in many settings, CDS failures, such as unjustified provider overrides and error-producing conditions within the technology, are frequently documented (3-7). Understanding the cause and consequences of these failures is critical to avoiding user dissatisfaction with the systems and preventing other unintended adverse consequences, such as patient harm (8,9).

To further reduce errors, many facilities are implementing surveillance methods, such as e-mail messages to notify care team members about changes in patient conditions or computer-generated patient lists that are monitored daily by pharmacists (10-12). Surveillance tools have also been implemented to evaluate CDS in real-time, but these have typically evaluated usage in the aggregate and not in detail at the patient level (13). Failures are not often readily apparent outside the context of an individual patient care episode, and it can be difficult to differentiate a technical failure from a usage failure without sufficient clinical detail presented in tandem with the CDS triggers and user response.

This project aimed to integrate externalized provider CDS interactions with a real-time patient care surveillance tool in order to improve the overall response of the medical team to medication safety alerts and improve patient outcomes with reduced adverse drug events (ADEs) and potential ADEs

(pADEs). The study was performed in the clinical domain of acute kidney injury (AKI), which affects a large number of patients at various points across all hospital units and services and has numerous opportunities for intervention.

In the first aim (Chapter III), we retrospectively evaluated the appropriateness of existing CPOE alerts for medication safety in AKI. Using these results, we determined characteristics of CDS failures and made recommendations for improving drug-laboratory alerting systems. In the second and third aims (Chapter IV), we developed and piloted a web-based pharmacy surveillance tool to allow real-time monitoring of at-risk patients and CDS failures. The iterative process allowed us to create more specific criteria for selecting patients eligible for an intervention.   In the final aim (Chapter V), using a randomized trial, we evaluated real-time use of the surveillance tool and interventions by a clinical pharmacist compared to existing CPOE alerts and standard of care. We classified occurrence, preventability, and severity of pADEs and ADEs to measure an effect on patient outcomes, and we evaluated the timeliness and rate of provider modification or discontinuation of targeted medications to measure an effect on provider behavior.

CHAPTER II

BACKGROUND

Failures in the Medication Management Process

Many institutions have implemented computerized systems with clinical decision support (CDS), which can prevent errors in all phases of medication management. However, these systems do not always function as intended, and numerous failures have been described. We define failures as instances in which the CDS systems were ineffective, which may be related to provider usage or may be technical in nature. Usage failures are defined broadly as cases in which providers do not adopt the advice provided by the CDS (whether justified or unjustified), or misuse the CDS. Examples include disregarding dosing recommendations, overriding interaction alerts, or misinterpreting user interface elements leading to an entry error. Technical failures are defined as errors within the clinical system source code, CDS rules or algorithms, or a clinical content, such as an incorrect dose configuration for a medication order. Technical failures are especially common when quality test scenarios inadequately simulate live scenarios, such as unexpected missing or out of range input values for calculations and alerting logic. Classen, et al. describe a methodology for evaluating systems that uses simulated test patients and scenarios in an attempt to reduce such failures (14).

Medication errors resulting from CDS failures are common in both inpatient and outpatient care settings, and occur at all stages of the medication management process (3-7). According to Kilbridge and Classen, the medication management process has six major segments, each having a distinct purpose and list of tasks involved (15). These segments and tasks are depicted in Figure 1 (15). Within

each segment of the medication management process exist distinct opportunities for CDS systems and failures.
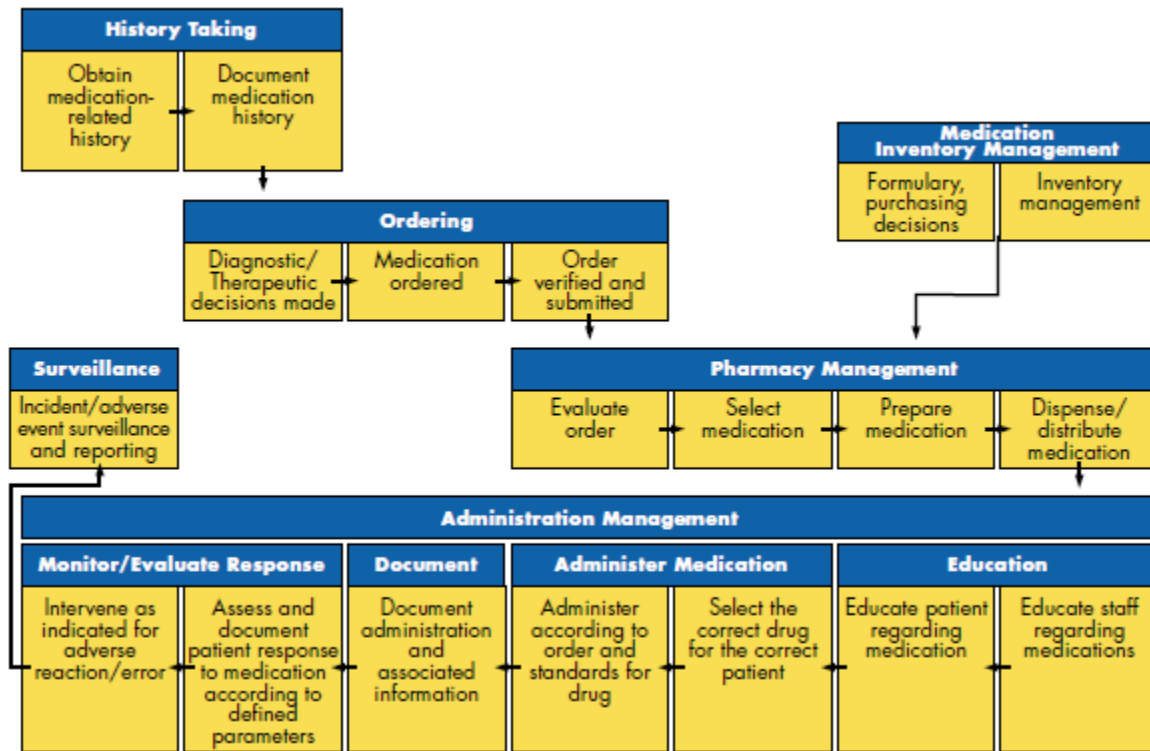
Figure 1: Inpatient medication management process (15)

Medication Reconciliation

The first step in the medication management process is history-taking and medication reconciliation, "the process of comparing a patient's medication orders to all of the medications that the patient has been taking (16)." Discrepancies or errors in medication lists are common, occurring in 10% to 67% of patients (17-25).   Of these discrepancies, 11 % to 59% had the potential to cause harm to the patient (19,23-25). Errors of omission, where a currently prescribed medication does not appear on a patient's medication list, are the most common form of discrepancy (18,19,22-24).   Medication reconciliation has been shown to reduce discrepancies, particularly when completed by clinical

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pharmacists (17,18,20,21,25-28). For this reason, the Joint Commission began mandating inpatient medication reconciliation in 2006 (16). In 2006, medication reconciliation had been reportedly implemented in 71.7% of surveyed hospitals; however the effectiveness of these implementations is unknown (29).

Computerized tools to facilitate reconciliation can reduce errors (17,26-28). In one approach by Partners HealthCare, a Pre-Admission Medication List (PAML) Builder tool facilitates medication reconciliation by displaying lists of medication information collected automatically from multiple data sources and allowing providers to quickly select items to be added to the PAML. The tool is used at both admission and discharge to maintain accurate lists for patients throughout the entire care process, and it has been successful in both decreasing the time and effort required for medication reconciliation and reducing discrepancies (26-28). In a similar approach at Kings County Hospital Center, reported by Agrawal and Wu, an electronic tool allows a nurse or physician to complete the medication history step, a physician to document the intended action for each medication and generate admission orders, and a pharmacist to perform medication reconciliation. However, to increase compliance, computerized alerts reminded physicians to complete documentation, giving a hard-stop if greater than 24 hours have passed since the patient's admission (17).

Despite the improved outcomes with medication reconciliation and computerized tools, discrepancies still occur. One cause of failure, as demonstrated by Agrawal and Wu, is lack of compliance by care team members (17).

Ordering

Errors frequently occur in the prescribing or ordering phase of medication management. Among orders placed, 4% to 6% contain an error, with rates varying by medication class and patient or provider

factors. Common errors include wrong or missing dose, frequency, or route. These errors are most frequently caused by a knowledge deficit, such as an unknown patient allergy, decline in hepatic or renal function, drug interaction, or other contraindication. Patient harm is possible in many of identified prescribing errors (3-5).

Numerous studies have shown that medication errors are preventable by CPOE (30-35). In one landmark study, Bates, et al. evaluated medication errors before and after implementation of a CPOE system with decision support that required complete orders; limited orders to hospital-approved standard doses, names, and frequencies; displayed relevant laboratory results; and alerted providers about drug-allergy, duplicate order, and other interactions. The authors found that rate of medication errors, excluding missed dose errors, fell 81 percent (142 per 1,000 patient-days to 26.6 per 1,000 patient-days) (35).

Multiple approaches for providing effective CDS in medication ordering exist (2). Clinical systems commonly employ passive alerts that display additional text, change existing text colors, or show images, without interrupting the workflow, and interruptive alerts, which require that providers acknowledge or respond to the alert before resuming order entry. These types of alerts may notify providers of drug interactions, changing laboratory values, or other information relevant to the patient's medical condition.

Order sets, a collection of pre-instantiated orders, are an approach for promoting adherence to clinical guidelines and efficiency in order entry. Order sets may ensure that patients with a given condition receive appropriate medications and promote drug level monitoring for high-risk medications (36). In some CPOE systems, providers interact with sophisticated computerized modules that generate orders that adhere to guidelines and protocols. These advisors may assist providers with calculations, administration intervals, and appropriate laboratory test monitoring (31,37).

Failures are common for all approaches to CDS. Both passive and interruptive alerts may fail from usage errors, for example alerts that are ignored or unnoticed by busy providers due to suboptimal placement, or frequently overridden (38-43). Technical failures occur when alerting logic or the data sources are flawed such as failures of drug safety alerts to incorporate a history of patient tolerance to a drug (38-41,8,44).   For order sets, usage failures occur when providers do not use applicable order sets for a given patient condition or deviate from recommendations. For example, providers may fail to order an appropriate drug or monitoring laboratory tests from the order set, or select a reoccurring laboratory test from an order set in order to bypass interventions that discourage excessive test ordering (45). Technical failures may include missing, incorrectly configured, or erroneous medications, laboratory tests, or other items within an order set; faulty logic that fails to account for existing orders and generates duplicate orders; or pre-defined doses that are inappropriate for a patient with comorbidities. Common usage failures for ordering advisors include incorrect inputs for calculation, unclear or confusing user interfaces, and incomplete use of the advisor. Failures can also be technical, such as errors in calculations and other logic within the advisors. CPOE systems can also introduce new errors, including more or new work issues, workflow issues, never-ending demands, paper persistence, communication issues, emotions, new kinds of errors, changes in the power structure, and overdependence on technology (8,9).

Medication Inventory and Pharmacy Management

The medication inventory and pharmacy management phases of medication management include pharmacy verification, preparation, and dispensing of ordered medications in addition to packaging, storage, and formulary management. Errors may occur due to illegible orders or mistakes in the preparation and dispensing of medications. CPOE systems have played a large role in reducing

errors related to illegible handwriting (3,30). Cina, et al. determined that 3.6% of filled orders contained errors, and 79% were undetected by pharmacists (46). To eliminate some dispensing errors, a large number of pharmacies have implemented computerized systems such as carousels, bar coding, automated dispensing cabinets (47). Oswald and Caldwell evaluated the use of a pharmacy carousel system and found a decrease in errors with filling automated cabinets, but no immediate effect on other errors (48). Studies by Cochran, et al. and Poon, et al. measured reduced errors and adverse drug events (ADEs) in the pharmacy management phase from bar coding systems (49-51).

Although some positive outcomes have been noted, errors or failures occur with the implementation of computerized systems for pharmacy management. In the first six weeks after implementation of the carousel, Oswald and Caldwell found an increase in filling error rates (48). Likewise, Cochran, et al. found a large percent of errors caused by bar coding in the pharmacy, including incorrect or missing bar codes on medications and overrides of warnings (49).

Administration

The next phase in the medication management process is medication administration. Errors in this phase occur in 7% to 54% of administrations (52-56). Types of errors that have been measured in medication administration include wrong patient, drug, dose, route, or time (49,52,55,57). The rate and type of error varies by administration day or time, drug class, drug route, and patient location (53,56,58,59). While some errors cause little or no harm to patients, many have the potential to be life-threatening (49,51,55,58).

Many errors associated with medication administration can be eliminated with computerized systems. "Bar coded medication administration (BCMA) is point-of-care system that requires positive patient identification and electronic verification of medications at the bedside before their

administration (60)." A survey conducted in 2008 found that 25% of hospital had implemented BCMA, and use of technology in the medication administration phase is increasing (47). BCMA has been demonstrated to reduce more than half of administration errors (51,53,54,59,61). In one example, Helmons, et al. measured medication errors before and after implementation of BCMA. The BCMA system was integrated with both the pharmacy and CPOE systems, allowing automatic updates of the electronic medication administration record (eMAR) and displays within BCMA of medications due at a certain time. Nurses used a bedside computer in each patient's room to select the eMAR and scan the bar code on the patient's wristband to confirm his or her identity, then scanned the bar code on each dosage form to verify the medication, dosage form, dose, and administration time on the patient's eMAR. Excluding wrong-time errors, the rate of medication errors decreased by 58% (59).

Computerized infusion pumps, or smart pumps, for intravenous medications may also detect and reduce errors occurring in the medication administration phase (62-64). Husch, et al. report that 66.9% of medications observed infusing through an IV pump had an associated error (62). Wilson and Sullivan describe the implementation and use of smart pumps, highlighting the relative ease in implementation, the resulting increased safety for patients with heparin infusions, and the use by continuing quality improvement to monitor output data and further prevent errors (63). In a prospective, randomized time-series trial, Rothschild, et al. found that, although the rate of medication errors did not change, the rate of detection increased with the use of smart pumps (64). Fifty-nine percent of hospitals use smart infusion pumps (47).

Despite the potential for success of BCMA and smart infusion pumps, errors still occur, and many are introduced by the technology, including discrepancies between systems, non-compliance, and workarounds (49,52,57,65,66). Helmons, et al. found that more distractions of the nursing staff occurred, patient education decreased, and wrong-time errors increased in some units following BCMA

(59). As described by Flynn, et al. smart infusion pumps can be inappropriately programmed by providers as a result of poor design (67).

Surveillance as a Solution to Preventing Medication Management Failures

Although surveillance comprises the final phase of the medication management process, it allows monitoring for failures in all phases. Initial methods for understanding failures or unintended adverse consequences relied on voluntary reporting of errors by medical personnel and retrospective manual chart review. Bates, et al. identified errors retrospectively using voluntary reporting, solicitation, and chart review (4). However, because of the inadequacy of voluntary reporting and manual chart review, and because data necessary for surveillance has become increasingly available in electronic formats from CPOE and EMR systems, computerized tools have become useful in performing surveillance for medication errors (10-12).

Classen, et al. developed a computerized system to print a daily ADE report based on components for voluntary reporting and automated detection algorithms. A clinical pharmacist reviewed the reports and verified the occurrence of ADEs. The authors found that the computerized system markedly increased ADE detection (11). Jha, et al. used a similar approach, finding that the computer monitor identified 45% of ADEs, manual chart review identified 65%, and voluntary reporting identified only 4% (12). Adapting rules from the previous studies, Kilbridge, et al. developed a monitoring system that displaying admitted patients that may require intervention to clinical pharmacists using a web-based application instead of a printed report. The automated system detected 90% of ADEs, indicating that computerized methods may be sufficient to replace voluntary reporting and manual review (10).

Commercial systems also exist to facilitate surveillance. Jha, et al. evaluated the Vigilanz Corporation's Dynamic Pharmacovigilance (DPV), a computerized tool that uses preset rules to monitor laboratory and pharmacy data and detect ADEs. During the trial, 11.3% of 516 high-severity alerts generated by DPV were considered clinically important, and 23% of these were associated with an ADE (68).

Similar systems can also be used to evaluate CDS effectiveness (13,69). Zimmerman, et al. displayed retrospective CDS interaction data in a spreadsheet with a dashboard format, allowing a rules and alerts committee to evaluate alert effectiveness and make improvements to the system (69). Reynolds, et al. developed a web-based graphical dashboard using a commercially available business analytics application, which allowed monitoring of order and alert volume by patient location, prescriber type, and alert type. Monthly review of the dashboard by a Physician Informatics Group provided opportunities to identify poorly performing alerts and later make system improvements (13). Despite the benefit of these methods, neither allows real-time evaluation of CDS usage at the patient level. Data may be difficult for institutions to obtain and use, monitoring personnel may not be available, or institutions may not realize the value of implementing such a system.

Medication Safety in Acute Kidney Injury

Definition and Significance

Acute kidney injury (AKI) is a common domain for CDS system development and evaluation. AKI occurs when a patient rapidly loses kidney function such that elimination of metabolic byproducts decreases (70). 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 (71-76). 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% (76,77). Studies of hospital-wide mortality associated with AKI estimate rates from 15% to 64% (72,74,78,79). International, multicenter studies estimate AKI associated mortality rates from 45% to 60% (71,80).

Many factors contribute to AKI, including dehydration, surgical procedures, and administration of medications or contrast dyes (70,72,74,76,78,81). In particular, nephrotoxic drugs are a common cause of AKI, and aminoglycosides account for a large percent of medication-induced episodes (72,78,81). 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 (61,75,82-87). 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 (61,82-85,87).

Clinical Decision Support Systems

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 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 and recommending 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 (82). 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, and 52% of alerted orders were adjusted (87). 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% (84). Field, et al. found similar results in a study measuring initial dosing advice in a long-term care facility, where the relative risk of appropriate final drug orders in intervention units compared to control units was 1.2 (88).

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 e-mail alerts for rising serum creatinine levels in the presence of nephrotoxic and renally cleared drugs, finding discontinued or modified doses an average of 21.6 hours sooner than without the alerts. The relative risk of a patient developing serious renal impairment and the mean serum creatinine levels also improved significantly

during the intervention period (89). In a later approach, Evans, et al. developed a surveillance system to monitor for excessive doses based on renal function for patients receiving targeted antibiotics, which generated a printed list of patients daily that included each patient's change in renal function, therapeutic drug levels, and suggested drug doses. 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% to 44%) and the number of days patients received excessive doses (4.7 days to 2.9 days) between the pre-intervention and intervention periods (83).

Implications for Real-Time Patient Surveillance

AKI is a clinical area of interest for real-time patient surveillance for several reasons. Hospitalized patients across all units and under the care of providers in different specialties and roles are susceptible to AKI. Occurrence of AKI is also likely to occur at any point during a patient's admission, often more than once, and it is not often identified. At every stage of AKI, there are potential opportunities for intervention to prevent worsening patient conditions. In addition, medications that may need to be discontinued or adjusted in AKI are given at widely varying intervals. Finally, treatment of AKI is not standardized.

Other patient conditions have similar implications for surveillance, such as renally dosed medications in chronic kidney disease or warfarin treatment for anticoagulation. However, chronic kidney disease dosing and monitoring is standardized such that specific alterations are recommended for given out-of-range monitoring levels. Likewise, because warfarin is most commonly dosed once a day, in the evening, the time between resulting labs and the next dose to be given is often large, allowing providers much time to identify the problem and make changes.

Vanderbilt University Medical Center Strategies

Dosing Guidance for Nephrotoxic and Renally Cleared Medications

Pharmacy and informatics staff members at Vanderbilt University Medical Center (VUMC) implement and maintain guidelines-based renal dosing nomograms to assist providers in ordering renally excreted drugs such as vancomycin. The order advisor 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. In an early study, use of the nomogram improved the rate at which patients achieve therapeutic range of vancomycin (85.2% versus 67.1%) (90).

Interactive advisors for aminoglycosides are also in use at VUMC. The advisors support extended interval dosing and traditional dosing, providing custom doses and frequencies calculated via a pharmacokinetic model using automatically imported demographic and laboratory data, drug level monitoring and the opportunity to initiate Infectious Disease or Pharmacy consultations. All values in the advisor may be edited by ordering providers to incorporate information that is not electronically available. An electronic chart review of a random cohort of patients found a significant increase in proportion of order dosing and frequency consistent with the expert recommendations (40% to 80% dosing, 63% to 87% frequency). Therapeutic drug monitoring also improved, with a significant increase in proportion of trough levels in the goal range (59% to 89%) (91).

Computerized Provider Order Entry Interventions

Intervention Description

In addition to dosing guidance, early efforts to improve medication safety in AKI included intervention alerts that warned care providers about existing inpatient medication orders that potentially required a dose adjustment or discontinuation in the setting of a changing serum creatinine (42). The target list of drugs that triggered the intervention included a comprehensive list of medications in the hospital formulary affected by renal function, as determined by an expert team of nephrologists, pharmacists, and infectious disease specialists. The expert panel divided target medications into three toxicity levels: drugs that were directly nephrotoxic or should be avoided with AKI, those requiring dose adjustments to avoid potentially toxic accumulation, and drugs with a low potential for toxicity but which should be reviewed for possible dose adjustments during prolonged episodes of AKI.

The first alerting mechanism, an initial passive alert, displayed when providers launched an order entry session on a patient who had a 0.5 mg/dl increase or decrease in serum creatinine and were prescribed a medication on the target list. The second alert was interruptive, and it appeared as providers attempted to exit from an ordering session when the provider had not adjusted medications in the manner suggested by the passive alert. However, the interruptive alert was limited to patients experiencing increasing creatinine levels, prescribed medications with moderate or high potential for toxicity, and a baseline creatinine clearance greater than 30 ml/min, as estimated by the Cockcroft-Gault equation (92). Thus, providers might receive one or both alert types when a change in a patient's renal function occurred in the presence of targeted drugs.

Results

For patients experiencing increasing creatinine events, the provider response rate increased significantly post-intervention for both high and moderate toxicity medications. The greatest improvement in provider response occurred for high toxicity drugs, increasing from 40.1 (226 of 564 events) to 61 (316 of 518 events) modifications or discontinuations per 100 events (p < 0.001). For patients with decreasing creatinine events and moderate or low toxicity level medications, the response rate to what were only passive alerts did not significantly change from the pre-intervention rate.

We also compared the time to provider response between the pre-intervention and post-intervention periods. The median time between a changing creatinine event and provider response in the pre-intervention period for patients with increasing creatinine events decreased significantly for all toxicity levels. The greatest improvement in time to response occurred with the high toxicity drugs, where medications were modified or discontinued 18.1 hours sooner in the post-intervention period than the pre-intervention period (p < 0.001). With decreasing creatinine events, the time to response did not significantly change between pre- and post-intervention periods.

Improvements in the timing of order modifications or discontinuations varied among the multiple target drugs evaluated. Medications for gout, non-steroidal anti-inflammatory drugs (NSAIDs), and diuretics were most frequently altered due to the intervention; each showed a 25% increase rate of dose modification or discontinuation. While the net change for most antimicrobials was low, ranging from decreasing by 3 responses per 100 events to increasing by 13 responses per 100 events, the rate of dose modifications increased for each group.

We evaluated the provider response to alerts generated by eligible medication orders in the 31 week post-intervention period. Study events (rise or fall in serum creatinine) triggered 1956 passive alert/interruptive alert pairs and an additional 886 passive alerts without an accompanying interruptive

alert. After viewing only a passive alert, providers modified or discontinued 26.9% of alerted medication orders. Providers clicked the passive alert to view the detailed information screen for less than 1% of passive alerts.

For those orders not immediately modified or discontinued following the passive alerts, providers most frequently (78.1%) chose to defer response within the interruptive alert. Providers selected the "modify" or "discontinue" options during 4.2% and 3.7% of initial interruptive alerts respectively, and selected the "correct dose" option for 14% of initial interruptive alerts. Following an initial deferral, providers subsequently modified or discontinued 59% of medication orders and marked 36.5% as correct; 4.1% of orders were not modified or discontinued prior to patient death or discharge.

Alerts were often viewed and deferred by multiple team members over the course of hours to days. For each event-drug pair, the passive alert displayed to one or more providers a median of 24 times. For those orders eligible for an interruptive alert, the median number of deferred alerts was 4 (interquartile ranges: 2-10; range: 1-56) prior to a more definitive response.

Pharmacy Surveillance of Aminoglycosides

Intervention Description

Real time surveillance tools were developed for aminoglycosides as a complement to the other decision support mechanisms, to synthesize patient data for a content expert to evaluate, and as a final safety net to ensure malformed prescriptions of high-alert medications were not propagated and that appropriate dose adjustments and monitoring were conducted in a timely manner (93). The surveillance tool was developed as a python based web application that organizes patients onto dashboards based on provider-entered orders for high alert medications. Messages from clinical and administrative

systems are parsed and loaded into a MySQL relational database. Scheduled tasks analyze new data for patient eligibility, calculate alerts, and compile the appropriate patient characteristics for the dashboards. User activity is also logged to the database.

Results

During the study period, 12,919 adult inpatient and observation cases were admitted and had orders written. Of these, 405 cases (3%) had orders for an aminoglycoside. On average, there were 27 patients with 8 alerts on the aminoglycoside dashboard. We recorded 16 individual pharmacists using the aminoglycoside dashboard, with nine using it for more than ten days. Distribution of monitoring responsibility distributed as 45, 45, 39, 35, 40, 33, 19, 12, 10 days per pharmacist. The dashboard was predominantly checked between 0700 and 1600, and coverage was excellent with both monitoring 89 (99%) of the days.

At the patient level, 405 cases (100%) were reviewed. The total number of times a case was reviewed was 2807 (6.9 times/case reviewed). Pharmacists marked 402 (99%) cases as checked and made comments for 373 (92%) cases. Total comments created were 1219 (3.3 times/case commented). Official pharmacy recommendations were generated 161 times for 98 distinct cases. The capability to launch CPOE directly from the tool was used on 40 distinct cases (46 times).

Summary and Conclusion

Despite the success of current implementations to improve medication safety in AKI, room for improvement still exists. Continual overrides of interventions and other CDS failures highlight the need for surveillance efforts. Successful implementation and pharmacy use of an existing dashboard for

patient surveillance indicate the likelihood that a similar approach for monitoring AKI and CDS will

continue to reduce errors.

CHAPTER III

INAPPROPRIATENESS OF ACUTE KIDNEY INJURY MEDICATION SAFETY ALERTS AND

PROVIDER RESPONSES COMPARED TO EXPERT NEPHROLOGY REVIEW

Introduction

Interruptive alerts are frequently used, in addition to other clinical decision support (CDS) solutions, to reduce medication errors and adverse drug events (ADEs) (2,31,30,32-35). These alerts require that providers acknowledge or respond to the alert before resuming order entry, notifying providers of drug interactions, changing laboratory values, or other information relevant to the patient's medical condition. An alert intervention in use at Vanderbilt University Hospital (VUH) was successful in improving the rate and timeliness of provider response to medication safety in acute kidney injury (AKI) (42). Despite the success of the intervention, high rates of alert overrides suggested room for further improvement. Prior research has found that many alert overrides are clinically justifiable (40,41). Researchers have also found that clinical systems often lead to new errors or unintended adverse consequences (8,9).

With this study, we aimed to define the characteristics of medication-related AKI alerts determined to be clinically appropriate by expert nephrology review and, using these characteristics, suggest methods for improving future drug-laboratory alerting systems. We hypothesized that alert inappropriateness was explained by patient, drug, and laboratory test factors not accounted for by the alerting algorithm. We anticipated finding disqualifying patient conditions, medication dosing that was appropriate prior to alert display, and transient or errant laboratory values. We also hypothesized that

inappropriately displayed alerts may have led to new errors or unintended adverse consequences in the form of inappropriate provider responses.

Methods

Study Setting

VUH is an academic, tertiary care facility with over 500 adult beds and 34,000 admissions annually at which care providers have used locally-developed and maintained inpatient CPOE and inpatient/outpatient EMR systems for more than a decade. These systems include extensive integrated decision support, including dosing advice and alerts about drug-allergy, drug-laboratory, and drug-drug interactions (2,94,95). CPOE alerts about potential AKI appear to providers for patients with a 0.5 mg/dl increase in serum creatinine over 24 hours following an active, recurring order for a targeted nephrotoxic or renally cleared medication (42).

Study Population

Eligible cases were admitted as inpatients to VUH between November 2007 and October 2008 and received at least one AKI medication alert. Patients who were identified as a dialysis patient by the primary physician or who received hemodialysis prior to the first alert were excluded. From this cohort, 300 cases were randomly selected for expert review. As multiple alerts may have displayed for each alerted medication, adjudications were performed on distinct patient-medication pairs, and subsequent alerts on the same pair were ignored. This study was approved by the Vanderbilt Institutional Review Board.

Study Design

Two study nephrologists (DC, JW) performed a retrospective electronic chart review of study patients. Each nephrologist reviewed 200 cases, 100 of which overlapped (300 cases total). When the reviewers disagreed, responses were determined by consensus with a third nephrologist (JL). Prior to evaluating the 300 study cases, we performed multiple pilot evaluations of 10 to 15 cases. The pilot evaluations allowed us to measure initial interrater reliability and to identify scenarios that frequently resulted in disagreement. Throughout this process, we iteratively developed instructions for completing the adjudications. The resulting instructions for this review are presented in Appendix A. All data were entered into a web-based data collection tool that displayed patient orders, laboratory results, and alerts together and saved responses in a separate research database.

Outcomes

The primary outcome for the study was the rate of inappropriate alerts.   Reviewers first determined whether an alert display was inappropriate, which we defined as an instance in which the information was not clinically relevant and a change of care was inappropriate.   Reviewers then determined whether alerts adjudicated as appropriate to display were urgent, defined as requiring a response within 48 hours of display. If an alert should not display or it was not urgent, reviewers selected determinants of the inappropriate alerts, including patient, medication, and laboratory characteristics.

A secondary outcome was inappropriate provider responses to the displayed alerts. Independent of the reviews, we determined actual provider response and timing electronically using a PHP script and MySQL queries. Reviewers determined whether the provider's response to the alert was acceptable or unacceptable, and recorded the response that they would have expected to be

appropriate at the time. With this data, we evaluated factors associated with responses determined to be inappropriate, including inappropriateness of the alert displayed. We also evaluated factors associated with the timing of the response.

Statistical Analysis

Interrater reliability for adjudicated variables was calculated using the kappa statistic. A kappa statistic of 0 to 0.20 has been considered slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.6 moderate agreement, 0.61 to 0.8 substantial agreement, and 0.81 to 1 almost perfect agreement (96). Univariate comparisons were made with the Pearson chi-square test for categorical variables and the t-test for continues variables.

We performed exploratory analyses, using multivariate logistic regression to evaluate the effect of demographics and drug characteristics on our primary outcome, alert inappropriateness. We also used multivariate logistic regression to evaluate the effect of alert inappropriateness, demographics, drug characteristics, and expected response on the inappropriateness of provider responses to alerts. All statistical analyses were performed using Intercooled Stata 9.2.

Results

Study Population

Demographics for the cases included in the study are described in Table 1. For these 300 cases, alerts for 487 initial medication-case pairs that appeared to providers were adjudicated by the reviewers. As indicated in Table 2, though 67.35% of alerts were initially deferred, providers selected modify in 13.76%, discontinue in 14.99%, correct dose in 34.5%, and defer in 36.76% of final responses.

Actual final responses, independent of the final alert selection, included 30.18% modify and 49.49% discontinue. The median time to response for all alerts was 24.05 hours, and 62.63% of responses occurred within 48 hours.

Table 1: Study population demographics for acute kidney injury alerts

Age (y)	60.82 ± 18.15
Sex (%)	
Women	35.00
Men	60.67
Unknown	4.33
Race (%)	
White	62.67
Black	15.00
Hispanic	2.00
Other	1.00
Unknown	18.33
Admitting Service (%)	
Cardiology	17.00
Critical Care	12.00
Geriatrics	1.33
Hematology/oncology	8.33
Hepatology	1.00
Infectious disease	4.00
Medicine	8.00
Orthopedics	5.33
Other	3.00
Renal	0.33
Surgery	29.33
Trauma	10.33
Intensive Care Unit (%)	52.67

Table 2: Descriptive evaluation of acute kidney injury alerts

	Total Alerts n=487	Inappropriate Alerts n=96
Medications to Avoid (%)	206 (42.30%)	40 (41.67%)
Medications to Adjust (%)	281 (57.70%)	56 (58.33%)
Initial deferral (%)	328 (67.35%)	72 (75.00%)
Medications to Avoid	117 (56.80%)	25 (62.5%)
Medications to Adjust	211 (75.09%)	47 (83.93%)
Final alert response (%)		
Modify	67 (13.76%)	10 (10.42%)
Discontinue	73 (14.99%)	7 (7.29%)
Correct dose	168 (34.5%)	33 (34.38%)
Defer	179 (36.76%)	46 (47.92%)
Actual response (%)		
Modify	147 (30.18%)	25(26.04%)
Discontinue	241 (49.49%)	52 (54.17%)
Response within 24 hours	240 (49.28%)	33 (34.38%)
Median hours to response (IQR)		
Medications to Avoid	10.7 (3.97, 45)	15.83 (5.22, 100.43)
Medications to Adjust	41.33 (9.4, 131.25)	53.62 (14.08, 168.5)
Drug or Drug Group (%)		
Aminoglycosides	25 (5.13%)	10 (10.42%)
Antiarrhythmics	8 (1.64%)	1 (1.04%)
Antifungals	6 (1.23%)	2 (2.08%)
Antigouts	28 (5.75%)	5 (5.21%)
Antineoplastics	1 (0.21%)	0 (0.00%)
Antithrombotics	102 (20.94%)	21 (21.88%)
Antivirals	57 (11.70%)	11 (11.46%)
Carbapenems	29 (5.95%)	6 (6.25%)
Digoxin	35 (7.19%)	7 (7.29%)
Meperidine	8 (1.64%)	1 (1.04%)
Nitroprusside	16 (3.29%)	2 (2.08%)
NSAIDs	36 (7.39%)	4 (4.17%)
Other Antibacterials	2 (0.41%)	0 (0.00%)
Sulfonylureas	2 (0.41%)	0 (0.00%)
Vancomycin	130 (26.69%)	26 (27.08%)

IQR = interquartile ranges

NSAIDs = non-steroidal anti-inflammatory drugs

Table 3: Multivariate analysis of patient demographic and drug factors on acute kidney injury alert display inappropriateness

	Odds Ratio	95% Confidence Interval	p
Sex			
Men	Reference		
Women	0.62	0.31, 1.22	0.17
Unknown	0.31	0.64, 1.53	0.15
Race			
White	Reference		
Black	0.81	0.32, 2.01	0.64
Hispanic	0.15	0.31, 0.69	0.02
Other	2.53	0.34, 18.87	0.37
Unknown	0.76	0.31, 1.87	0.55
Admitting Service			
Surgery	Reference		
Cardiology	0.35	0.13, 0.91	0.03
Critical Care	0.56	0.18, 1.79	0.33
Geriatrics	1.13	0.94, 13.52	0.92
Hematology/oncology	0.79	0.27, 2.32	0.66
Hepatology	1.66	0.14, 20.13	0.69
Infectious disease	0.99	0.15, 6.62	0.99
Medicine	1.40	0.46, 4.29	0.55
Orthopedics	1.40	0.43, 4.50	0.57
Other	0.29	0.03, 2.88	0.29
Trauma	2.04	0.80, 2.57	0.13
Drug or Drug Group			
Antithrombotics	Reference		
Aminoglycosides	2.37	0.92, 6.11	0.08
Antiarrhythmics	0.82	0.10, 6.64	0.85
Antifungals	2.98	0.52, 17.25	0.22
Antigouts	1.52	0.46, 4.95	0.49
Antivirals	0.93	0.37, 2.34	0.88
Carbapenems	1.22	0.45, 3.36	0.70
Digoxin	1.75	0.66, 4.65	0.27
Meperidine	0.67	0.72, 6.21	0.72
Nitroprusside	0.75	0.17, 3.40	0.71
NSAIDs	0.56	0.19, 1.63	0.29
Vancomycin	1.13	0.59, 2.16	0.71

Alert Inappropriateness and Non-Urgency

Interrater reliability for alert inappropriateness was moderate; reviewers agreed for 84.62% of alerts (kappa=0.46).   After reaching consensus, the reviewers selected 391 (80.29%) alerts as appropriate to display; the positive predictive value was 4.07. All appropriate alerts were determined to

be urgent, requiring a response within 48 hours, so we excluded non-urgency from further analysis. Multivariate logistic regression analysis results are shown in Table 3. For those alerts determined to be inappropriate, contributing factors most commonly included no AKI or previously adjusted doses (Table 4).

Table 4: Contributing factors for acute kidney injury alert inappropriateness

	Inappropriate Alerts (%) n=96
Dialysis patient	9 (9.38)
Transplant patient	0 (0.00)
Palliative care patient	0 (0.00)
Dose already adjusted for acute kidney injury	29 (30.21)
Dose is already low and for prophylaxis	4 (4.17)
Drug levels are in therapeutic range	0 (0.00)
Primary team has documented AKI risk and drug benefit	21 (21.88)
Transient AKI	31 (32.29)
No AKI - lab error	10 (10.42)
No AKI - drug interference with serum creatinine assay	16 (16.67)
No AKI - insufficient change in GFR	37 (38.54)
Other	3 (3.13)

Note: Percentages add up to greater than 100, as multiple factors may have been selected for each alert.
AKI = acute kidney injury
GFR = glomerular filtration rate

Table 5: Expected responses for inappropriate acute kidney injury alerts and provider responses

	Total Responses n=487	Inappropriate Alerts n=96	Inappropriate Responses n=82
Should not have changed therapy	114 (23.41%)	61 (63.54%)	8 (9.76%)
Modify the dose or interval	230 (47.23%)	22 (22.92%)	43 (52.44%)
Discontinue	161 (33.06%)	13 (13.54%)	32 (39.02%)
Documentation of indication	88 (18.07%)	21 (21.88%)	22 (26.83%)
Monitor drug levels	189 (38.81%)	42 (43.75%)	19 (23.17%)
Monitor other levels	3 (0.62%)	0 (0.00%)	3 (3.66%)
Other	7 (1.44%)	2 (2.08%)	4 (4.88%)

Note: Percentages add up to greater than 100, as multiple responses may have been selected for each alert.

Table 6: Multivariate analysis of acute kidney injury alert appropriateness, patient demographic, and drug factors on provider response inappropriateness

	Odds Ratio	95% Confidence Interval	p
Inappropriate alert	0.35	0.15, 0.83	0.02
Sex			
Men	Reference		
Women	0.90	0.45, 1.79	0.76
Unknown	0.76	0.20, 2.94	0.69
Race			
White	Reference		
Black	0.33	0.09, 1.19	0.09
Hispanic	2.19	0.60, 7.92	0.23
Other	2.58	0.33, 20.17	0.36
Unknown	1.86	0.01, 4.30	0.15
Admitting Service			
Surgery	Reference		
Cardiology	0.40	0.98, 1.65	0.21
Critical Care	0.80	0.10, 1.65	0.69
Hematology/oncology	1.19	0.41, 3.47	0.75
Hepatology	3.66	0.24, 56.60	0.35
Infectious disease	0.23	0.05, 0.97	0.05
Medicine	1.18	0.28, 5.06	0.82
Orthopedics	2.61	0.79, 8.65	0.12
Other	1.62	0.37, 7.06	0.52
Trauma	2.09	0.77, 5.64	0.15
Drug or Drug Group			
Antithrombotics	Reference		
Aminoglycosides	0.60	0.14, 2.59	0.49
Antiarrhythmics	2.91	0.44, 19.28	0.27
Antigouts	2.04	0.56, 7.38	0.28
Antivirals	3.35	1.42, 7.92	0.006
Carbapenems	1.26	0.40, 4.00	0.69
Digoxin	0.96	0.21, 4.50	0.96
Meperidine	11.63	1.60, 84.62	0.02
Nitroprusside	1.35	0.30, 6.15	0.70
NSAIDs	1.60	0.60, 4.27	0.35
Vancomycin	0.74	0.33, 1.66	0.46

Alert Response Inappropriateness

Interrater reliability for response inappropriateness was fair; reviewers agreed for 78.06% of alerts (kappa=0.37). After reaching consensus, reviewers adjudicated provider responses to alerts as inappropriate for 82 (16.84%) of alerts. Of these, only 8 (9.76%) resulted from an alert adjudicated as

inappropriate. Table 5 shows the distribution of expected responses that the reviewers selected for all

alerts and for those alerts and responses considered to be inappropriate.

Multivariate logistic regression found that inappropriate alerts were significantly less likely to

result in an inappropriate responses with an adjsted odds ratio of 0.35 (p=0.02). Alerts for patients

admitted to the infectious disease service were also less likely to be inappropriate, having an odds ratio

of 0.23 (p=0.05).   Drugs that were more likely to result in an inappropriate response included antivirals,

having an odds ratio of 3.35 (p=0.006), and meperidine, having an odds ratio of 11.63 (0.02). These

results are described in Table 6.

Discussion

Summary of Findings

Using retrospective chart review and consensus by a team of nephrologists, we evaluated CPOE

alerts for patients with AKI, which, despite a previously demonstrated positive effect on provider

behavior, had high override rates (42). We found that reviewers determined most alerts displayed to

providers were not inappropriate (80.29%), and all alerts displayed were urgent. The factors most

frequently listed by reviewers as reasons for alert inappropriateness included no AKI or previously

adjusted doses. These results have multiple implications for development of future alerting systems and

reducing false positive alerts. Some factors of alert inappropriateness, including chronic dialysis,

transplant, and palliative care patient status could be used to prevent patients from receiving alerts if

the data was properly coded in the EMR and queriable by all clinical systems. Advanced algorithms that

are able to factor in sufficiently adjusted doses, low prophylactic doses, and drug levels for therapeutic

monitoring within the normal range may also increase the specificity of alerts. Finally, alerting systems

could be improved by the ability to identify laboratory values that are false due to drug interference, laboratory error, or bad draws or to detect changes that may be transient. Improved specificity of alerts is crucial to preventing alert fatigue.

Though we hypothesized that inappropriate alerts were likely to result in inappropriate responses, we found that most inappropriate responses resulted from appropriate alerts. This indicates that most inappropriate responses were errors of omission (e.g. failure to modify or discontinue a targeted medication) rather than errors of commission (e.g. incorrectly modifying or discontinuing a medication that should not be changed); unintended adverse consequences were rare compared to true overrides of the alerts.

Comparison to Literature

Prior studies have described and evaluated overrides of alerts, and other work has applied qualitative methods to understand rationale behind some failures in CDS systems. In one systematic review, van der Sijs, et al. reported that alerts were frequently overridden for low severity, irrelevance, or repeated display (38). Weingart, et al. found that common justifications for inappropriate alerts included clinical insignificance of alert, patient tolerance of drug, benefit of drug outweighing disadvantages, and limited course of treatment; 95.6% of reviewed overridden alerts were justified (40). Ash, et al. and Koppel, et al. found that introduction of clinical systems frequently caused unintended adverse consequences, or the occurrence of new errors (8,9). Our results, however, show that only 9.76% of inappropriate responses occurred for alerts that were inappropriate. Understanding the appropriateness of alerts and downstream responses is important for improving patient safety and preventing errors, and too few studies have performed such analyses.

Challenges in the Evaluation of Alerts

Numerous issues arose in the process of evaluating the AKI alerting system. One significant issue was the lack of gold standards available for adjudication. One source of disagreement for reviewers was heterogeneity in nephrology training and published evidence, which contributed to differing treatment philosophies and expectations. For example, some reviewers had a higher tolerance for risk than others, willing to wait for further changes in serum creatinine before determining alert appropriateness or urgency. Similarly, lack of gold standard in treatment caused disagreement among the reviewers. No standards exist for prescribing and dosing nephrotoxic and renally cleared medications in the setting of AKI, where estimates of glomerular filtration rate are often inaccurate; various methods are deemed acceptable in practice, and determining whether resulting orders are appropriate or should be urgently corrected is often difficult. With multiple responses determined to be acceptable during adjudication, reviewers frequently disagreed.

Another challenge for evaluation is the presence of information bias. The nephrologists reviewed the alerts retrospectively, and adjudication depended on the availability of information in the EMR. The EMR is typically comprehensive with respect to orders and laboratory values, but narrative information, such as patient comorbidities, indication, or historical tolerance was not always readily available. This information gives necessary patient context to the reviewers, describing the thought process and methodology for medication ordering and dosing. Without the necessary patient context, reviewers were required to make assumptions, which frequently led to disagreement in the adjudications.

Finally, because of the subjectivity in reviews, lack of gold standards, and missing information, it was difficult to create completely objective criteria for evaluating appropriateness and urgency of the alerts. We performed several iterations of pilot reviews to assess completeness and clarity of the

questions and agreement among the reviewers. The final instruction set attempted to unify the different approaches taken by the nephrologists in reviewing cases and overcome many of the challenges by including methods for determining the patient's baseline renal function, variables that could be used and time limits for evaluating appropriateness of the alert and responses, and frequently encountered exceptions to the rules.

Limitations

Our study has a number of limitations. Because we evaluated only a limited number of alerts for medication safety in AKI, our findings may not be generalizable to other CDS settings or clinical scenarios. However, commercial or other custom clinical systems may have similar alerts for changing serum creatinine values in the setting of renally dosed medications, and methods applied in our study are likely to result in similar findings. It is also likely that an evaluation of other drug-laboratory alerts, such as those for anticoagulant or glucose management, would have similar findings. Despite these assumptions, we cannot determine how well our results externalize to other types of alerts and CDS systems.

Our results are also limited by the type and training of the reviewers performing the adjudications. Because of the many challenges faced in evaluating the alerts, we only assigned nephrologists to review the alerts and provider responses for appropriateness. Perceptions of alert and provider response appropriateness may differ by reviewer role and background. Attending physicians may view some alerts as unnecessary at the time of display while interns may find value in the alert and deem a lack of response as appropriate. Similarly, nephrologists may view all renal alerts as clinically significant, while internal medicine physicians or surgeons may see the alert as noisy. Additional adjudication of the alerts by reviewers with a variety of different roles and backgrounds would improve

the generalizability of the results, perhaps highlighting additional frequently encountered contributing factors for alert and response inappropriateness.

Finally, the retrospective bias and other challenges involved in evaluating the alerting system limited the findings. A prospective study evaluating the alerts and provider responses in real time would allow reviewers to collect detailed narrative data about patients and orders, including indication, rationale, and methods for ordering and dosing. This additional data would provide more informative insight on the appropriateness of the alerts and responses, though it is unknown whether we would find an increase in appropriateness due to correct provider behavior or a decrease in appropriateness due to provider error. However, such findings might also bias the inappropriateness findings for provider responses, as providers may be more likely to respond quickly and appropriately while being observed. Our finding of few inappropriate responses resulting from inappropriate alerts may be due to sensitivity in the adjudication of alert and response appropriateness by the reviewers.

Conclusion

Success of CDS systems is often hindered by high rates of overrides and low rates of adherence, though it may increase with improvements to alerting systems. We developed a novel approach to evaluating CDS systems that identifies factors accounting for alert inappropriateness, measures alert inappropriateness, includes downstream actions in evaluating provider responses to alerts, and incorporates alert inappropriateness in determining provider response inappropriateness. With this approach, we identified contributing factors to alert inappropriateness that could be used to improve alerting systems, including consideration of false laboratory values; documented indication, understanding of risk, and medication benefit; previously adjusted doses or interval; and therapeutic

drug values. However, because most inappropriate responses did not result from inappropriate alerts,

other approaches are necessary to further reduce errors.

CHAPTER IV

DEVELOPMENT AND IMPLEMENTATION OF A REAL-TIME PHARMACY SURVEILLANCE

TOOL FOR MEDICATION SAFETY IN ACUTE KIDNEY INJURY

Introduction

Computerized provider order entry (CPOE) systems and electronic medical records (EMRs) that embed clinical decision support (CDS) can improve patient care by providing patient-specific recommendations and promoting correct orders (2). However, CDS failures are common, particularly during implementation. Failures include unjustified provider overrides and error-producing conditions within the technology (38,39,9). Rapid proactive response to failures can increase user satisfaction and prevent other unintended adverse consequences.

Many facilities have implemented surveillance methods to reduce errors. Some surveillance systems utilize e-mail messages to notify care team members about changes in patient conditions or to inform supervisors about alert overrides, while others create reports of patient drug orders that are monitored by clinical pharmacists (10,83,89). Real-time surveillance tools have also been implemented to monitor aggregate CDS use (13,69).

However, CDS failures are difficult to interpret without the context of the patient care episode. The workflow of existing implementations, depicted in Figure 2, has a number of limitations. The informatics personnel developing the systems are disconnected from the clinician. The need for CDS monitoring increases with frequent source code updates, CDS rule modifications, or user interface changes. Also, pharmacist consultations are independent and often contradictory with clinical decision support, or they are delayed.
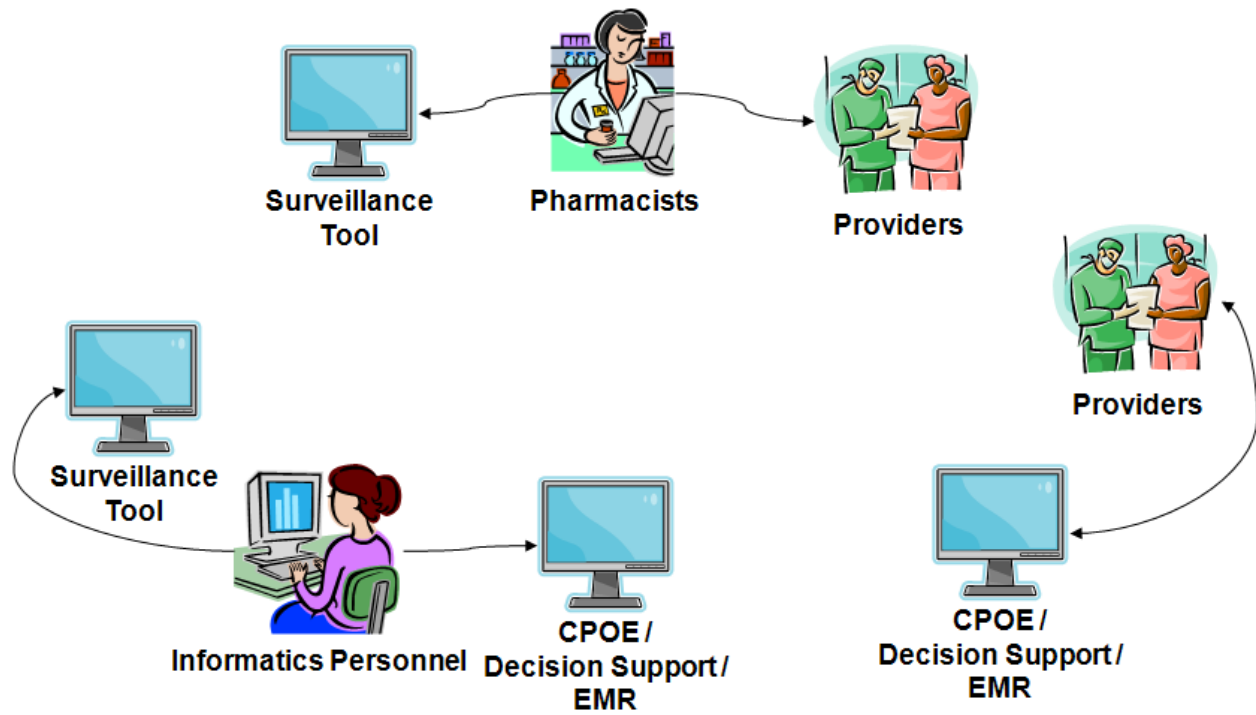
Figure 2: Traditional model of surveillance
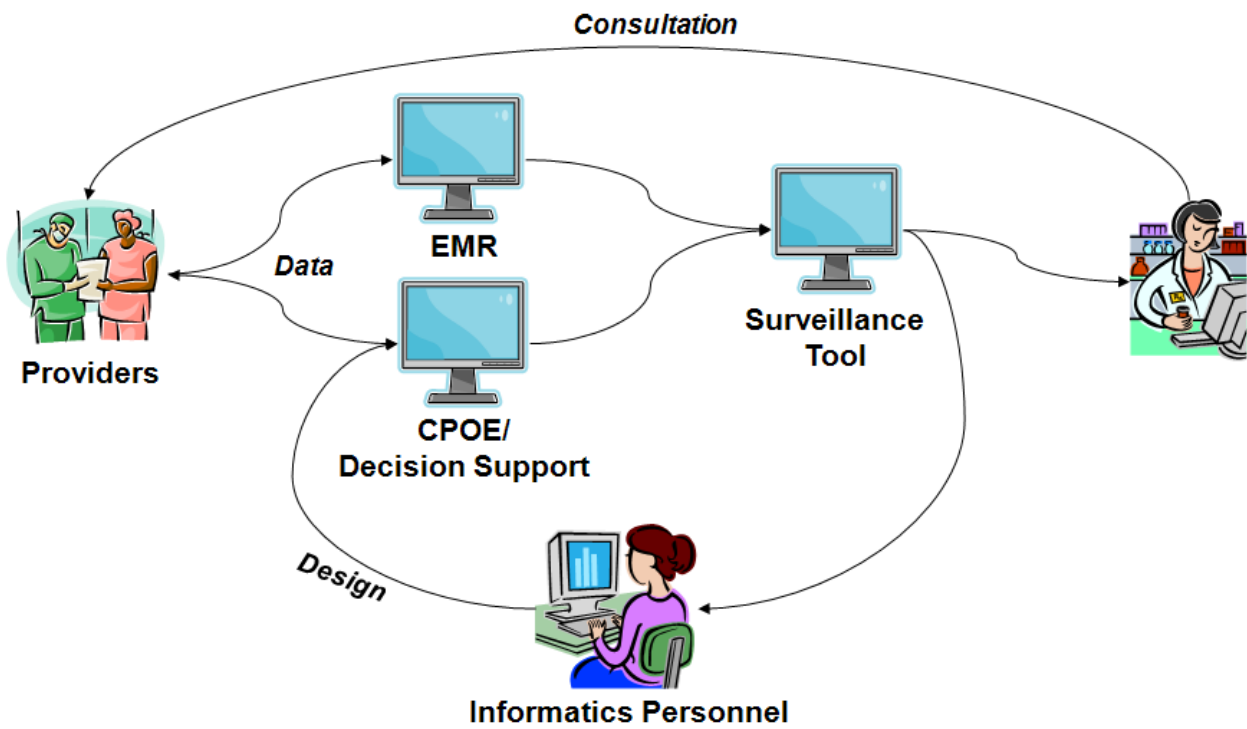
Figure 3: Novel model of surveillance

A new, novel model of surveillance, depicted in Figure 3, connects pharmacists to providers and decision support interactions, and it also allows informatics personnel to view actual interactions in the context of an individual patient. We applied this model in developing a web-based surveillance tool for monitoring acute kidney injury (AKI) patients and CDS interactions.

Surveillance Tool Development

Surveillance Tool Infrastructure

Providers at VUMC use a locally developed and maintained EMR and CPOE system along with vendor supplied pharmacy management, laboratory, and medication administration systems, each with multiple levels of CDS. Additional locally developed CDS capabilities, such as a laboratory alert paging engine for providers and a web-based surveillance tool for clinical pharmacists, supplement monitoring of high-risk patients. These systems rely on an interface engine to synchronize clinical data and prevent overload of primary data sources for clinical systems (97). Log files that are generated by the CPOE and other clinical systems record provider interactions with CDS, and data about patient demographics, medication orders, medication administrations, and laboratory values are parsed into relational databases, which clinical systems or researchers can query.

The pharmacy surveillance tool is a Python web application backed by a MySQL database that contains parsed clinical and administrative messages. Scheduled tasks query data routed through the interface engine from the clinical systems for patient demographics, provider-entered orders, laboratory values, and medication administrations. The tasks then analyze the data to determine patient eligibility, calculate alerts, and collect additional patient data to display on the surveillance tools. A queue parses

CDS log files and stores them in a separate database, which is also used by the scheduled tasks to

populate the surveillance tool. Figure 4 shows a diagram of the surveillance tool infrastructure.
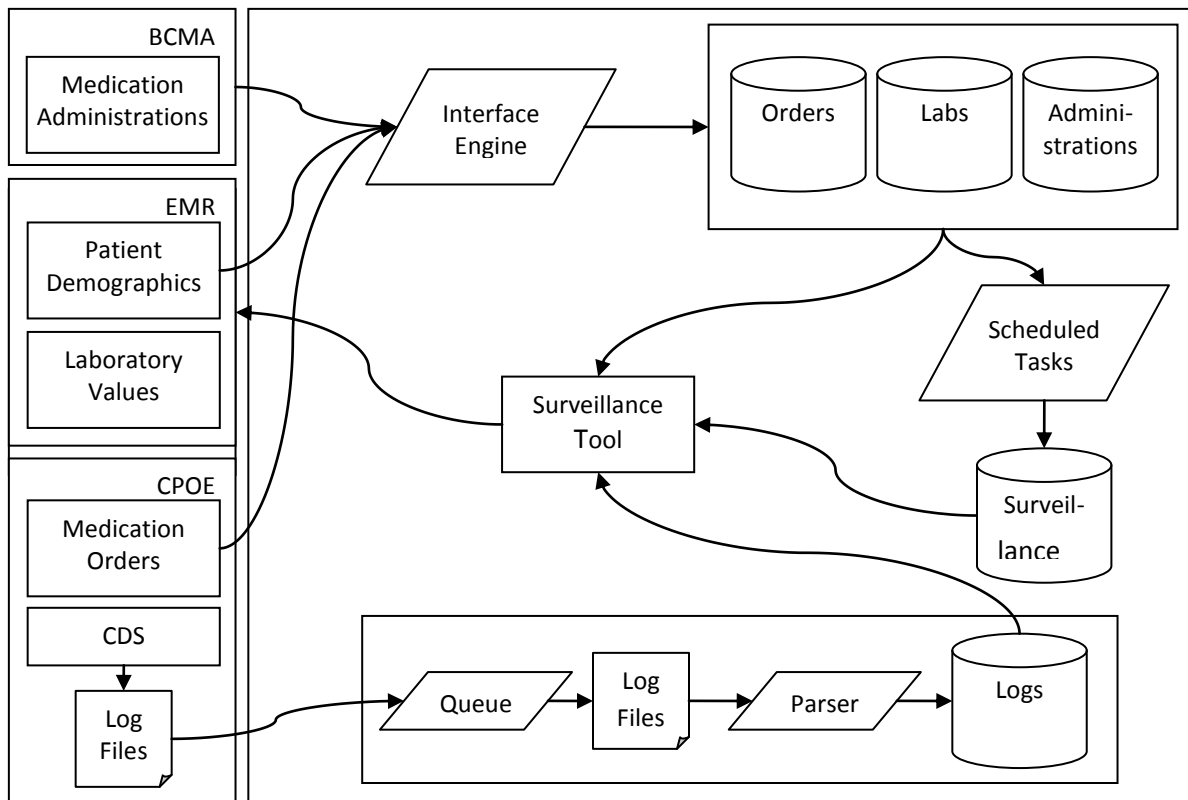
Figure 4: Pharmacy surveillance tool infrastructure

BCMA = Bar coded medication administration
CPOE = computerized provider order entry
CDS = clinical decision support
EMR = electronic medical record

Developers can configure new individual surveillance and patient detail views based on a variety

of patient conditions or medication orders. The developer first creates a utility file that evaluates

patients for inclusion criteria, such as drug exposure or lab results, determines when and for how long a

patient appears on the tool, and defines patient alerts and other data elements to be calculated or

collected, such as inappropriate or out of range orders and laboratory results. The utility files are executed by the scheduled tasks each time the surveillance tool is updated. Next, the developer creates display files, specifying the data elements, display order, and patient prioritization for both the summary and patient views. The display files are parsed by the system each time users view the surveillance tool.

Surveillance Workflow

The surveillance tool consists of two primary view types: the surveillance view and the patient detail view. The surveillance view displays all currently admitted patients eligible for surveillance. In the case of AKI, all patients meeting the alert criteria of a 0.5 mg/dl increase in serum creatinine within 48 hours following an order for a nephrotoxic or renally cleared drug are displayed. This view allows pharmacists or other staff to identify patients at high risk for harm. As depicted in Figure 5, the AKI surveillance view shows patient details such as name, medical record number, providing service, hospital location, age, and sex, in addition to creatinine values of interest and alert deferral data.

The second view type, depicted in Figure 6, shows a patient detail view, which displays a graph of events of interest and a detailed timeline for an individual patient in reverse chronological order to give context for the CDS interaction events. The timeline includes all orders, order administrations, laboratory values, and CDS interactions during the patient's admission. The display can be resorted by type, description, value, start time, or stop time to meet the need or preference of the user. Surveillance team members can use the patient detail view to understand provider actions and patient condition changes occurring in conjunction with CDS failures without having to redirect to and search a patient's EMR. This view also allows staff to enter comments for reference to viewers at a later time; these notes are only available within the surveillance tool and are not a permanent component of the

patient's EMR. Staff can also use this view to enter notes directly into the EMR; these notes are pre-populated with patient information that can be edited before submission.

Pilot Implementation and Evaluation of Acute Kidney Injury Surveillance Tool

Prior to formally evaluating the surveillance tool for AKI, we performed a pilot implementation. The study pharmacists (EN, ZC) and a nephrologist (ES) reviewed select cases during the initial four months of implementation (February 2010 to May 2010). We held weekly meetings to discuss the reviewed cases, evaluate the potential for intervention based on various patient and drug factors, and assess the usefulness of the surveillance tool. Changes to the inclusion criteria and surveillance tool display were iteratively implemented until team members were satisfied with the product.

Based on the feedback from the pilot implementation, we made changes to the targeted medication list and the inclusion criteria for both the surveillance tool and AKI CDS. From the targeted medication list, we removed tubocurarine. We added sitagliptin and exenatide as medications to avoid and aztreonam as a medication to adjust. We also recategorized temozolomide and adefovir from medications to adjust into medications to review, enoxaparin from a medication to avoid into a medication to adjust, and tenofovir from a medication to avoid into a medication to review. Some medications that were ordered frequently for prophylaxis (enoxaparin, acyclovir, allopurinol, co-trimoxazole, colchicine, valganciclovir, and fluconazole) were excluded when the dose was sufficiently low. Beyond the toxicity classification, all medications were further categorized as targeted for increasing serum creatinine, decreasing serum creatinine, both, or neither (i.e. to be displayed to provide context only). The final list of targeted medications is presented in Table 7.

Acute Kidney Injury

(Back | Demo Mode [Off] | All ADEs | Logout)

Pro Tip: To sort on multiple columns, hold down shift while you click!

Toxic Drugs [List]	Direction	Defers [CDS]	C	Last Checked	Name	MRN	Casenumber	Height (in)	Weight (kg)	Age [DOB]	Service	Unit [Room]	Pre-Trigger Creat (mg/dL) [Time]	Trigger Creat (mg/dL)	Trigger CrCl	Trigger Time	Updated	Following [Time]
1 Avoid 1 Adjust 1 Review	INC	3		-NEVER				67	54.431	34	TRA	10N	0.51	1.14	59.74	2010-08-07 09:30:00	2010-08-09 13:27:18	YES
1 Avoid	INC	0		-NEVER						50	OTO	9NSM	3.01	3.78	NA	2010-08-09 09:10:00	2010-08-09 13:25:53	YES
2 Review	INC	0	C	2010-08-06 11:13:12					101.18	74	GMD	8S	1.16	1.75	45.04	2010-08-05 04:35:00	2010-08-09 13:25:42	YES
2 Review	INC	1	C	2010-08-06 10:57:13				68	99.1	81	CSX	5N	5.42	6.04	9.27	2010-08-07 04:10:00	2010-08-09 13:27:14	YES
3 Adjust	DEC	0	C	2010-08-06 10:46:46				65	181.8	66	NES	6T3	1.57	0.82	49.79	2010-08-02 02:15:00	2010-08-09 13:25:36	YES
3 Adjust	DEC	0		2010-08-06 11:18:22				70	69.57	55	PUL	8T3	2.15	1.24	66.23	2010-08-07 06:17:00	2010-08-09 13:26:06	YES
1 Adjust	DEC	1	C	2010-08-06 14:20:56				74	100.0	58	GMD	S74	2.57	1.39	67.35	2010-08-08 05:30:00	2010-08-09 13:25:17	YES
2 Review	DEC	9	C	2010-08-06 11:19:03				66	87.0	44	GMD	8T3	2.94	2.16	39.38	2010-08-09 05:45:00	2010-08-09 13:25:13	YES
2 Review	DEC	3		2010-08-05 09:21:45				70	68.06	67	URO	9T3	2.38	1.79	38.55	2010-08-05 02:00:00	2010-08-09 13:27:18	YES
Toxic Drugs [List]	Direction	Defers [CDS]	C	Last Checked	Name	MRN	Casenumber	Height (in)	Weight (kg)	Age [DOB]	Service	Unit [Room]	Pre-Trigger Creat (mg/dL) [Time]	Trigger Creat (mg/dL)	Trigger CrCl	Trigger Time	Updated	Following [Time]
	DEC	0		2010-08-04 18:43:34				60	71.0	85	CAR	7N	2.62	1.58	29.17	2010-08-08 03:45:00	2010-08-09 13:27:22	YES
	DEC	0		-NEVER				69	80.0	58	GMD	8T3	1.81	0.67	120.17	2010-08-08 06:00:00	2010-08-09 13:27:27	YES
	INC	0		2010-07-30 16:44:03				69	88.48	74	ORT	9NSM	2.87	3.37	19.23	2010-07-29 02:15:00	2010-08-09 13:26:47	NO
1 Adjust	DEC	0	C	2010-07-22 12:23:54				71	122.0	61	GMD	10S	1.95	1.28	64.54	2010-07-06 02:00:00	2010-08-09 13:25:19	NO
	DEC	0	C	2010-07-31 15:04:10				60	61.235	48	PUL	S74	2.38	1.86	42.06	2010-07-25 18:20:00	2010-08-09 13:25:04	NO
	DEC	2	C	2010-07-26 13:50:45				75	95.0	47	INF	8S	1.97	1.26	86.62	2010-08-04 06:30:00	2010-08-09 13:25:28	NO

Figure 5: Surveillance view of real-time tool for monitoring acute kidney injury patients and clinical decision support interactions
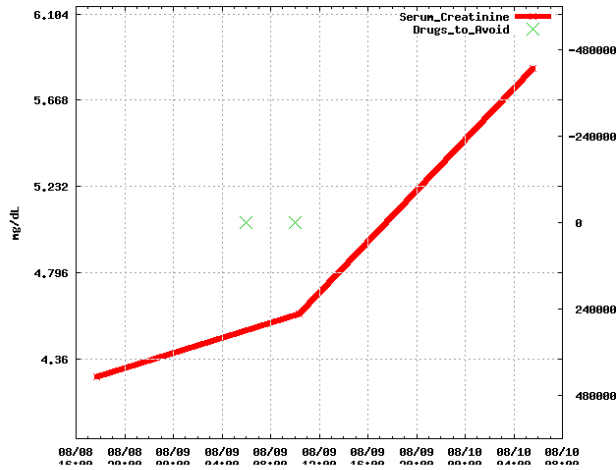
AKI Patient Information

Name:		MRN:	Age: 53	Sex: F	Weight: 70.0	Height: 0
Service: **HEM**	Unit: **8S**	Room: **8227B**	Updated: **2010-08-10 08:25:35**	Case:		
TEAM PAGER:						

Graph ▾

Relevant Orders

PID	Order	Type	Description	Lab Value	Comment	Start	Stop
12680	85	O	FUROSEMIDE: LASIX 20. MG PO QDAY 06			2010-08-10 06:00:00	
		L	Creat	5.83		2010-08-10 05:35:00	
		L	K	5.2	Plasma potassium reference range = 3.3-4.8 mEq/L Serum potassium reference range = 3.5-5.1 mEq/L Almost all samples are plasma	2010-08-10 05:35:00	
12680	85	OA	FUROSEMIDE 1.0 TAB 20 MG		U	2010-08-10 05:19:00	
7244	33	OA	LISINOPRIL 1.0 TAB 20 MG		U	2010-08-10 05:19:00	
5214	93	O	MORPHINE PCA 5MG/ML: BASAL: 5 MG/HR DEMAND: 2MG Q15MIN X 3 D		BASAL: 5 MG/HRDEMAND: 2MG Q15MINTO START AT NEXT SYRINGE CHANGE	2010-08-09 20:00:00	2010-08-12 19:59:00
		L	Creat	4.59		2010-08-09 10:20:00	
		L	K	4.4	Plasma potassium reference range = 3.3-4.8 mEq/L Serum potassium reference range = 3.5-5.1 mEq/L Almost all samples are plasma	2010-08-09 10:20:00	
20809	79	O	ENOXAPARIN FOR DVT PROPHYLAXIS 30. MG SUBCUT Q24H			2010-08-09 10:00:00	
20809		DS	ORDERING ADVISOR (ENOXAPARIN FOR DVT PROPHYLAXIS)		Recommend dose for DVT prophylaxis for CrCl * Enoxaparin 30mg SC q24hDo NOT use for dialysis patients RECOMMENDED 30 MGQ24H USING CRCL = 14.1948 BY	2010-08-09 08:35:00	
7244	33	O	LISINOPRIL: ZESTRIL 20. MG PO QDAY 06			2010-08-09 06:00:00	
5231	27	O	RVS # 26 MORPHINE PCA 1MG/ML: BASAL: 5 MG/HR DEMAND: 2MG Q15		BASAL: 5 MG/HRDEMAND: 2MG Q15MINLOCKOUT MG / 4 HOURS ;	2010-08-08 18:46:00	2010-08-09 19:26:00
		L	Creat	4.27		2010-08-08 17:42:00	
		L	K	5.1	Plasma potassium reference range = 3.3-4.8 mEq/L Serum potassium reference range = 3.5-5.1 mEq/L Almost all samples are plasma	2010-08-08 17:42:00	
5231	26	O	MORPHINE PCA 1MG/ML: BASAL: 3 MG/HR DEMAND: 1MG Q15MIN 1ST S		BASAL: 3 MG/HRDEMAND: 1MG Q15MINLOCKOUT MG / 4 HOURS ;	2010-08-08 16:32:00	2010-08-08 18:46:00
9836	25	O	MORPHINE INJECTION: 5 MG IV STAT X 1			2010-08-08 16:32:00	2010-08-08 16:32:00
5214	93	OA	U 0.0 U U		^please send	1800-01-01 00:00:00	

Figure 6: Patient detail view of real-time tool for monitoring acute kidney injury patients and clinical decision support interactions

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This Page Last Checked: Never — [Update Last Checked Time]

Baseline SCr: 4.59	Time: 2010-08-09 10:20:00
Last SCr: 5.83	Time: 2010-08-10 05:35:00
Last CrCl: 12.33	

Intervention Review ▾

Is an intervention required?
- ○ Yes
- ○ No

If no intervention required, why?

No AKI
- ○ Chronic Dialysis Patient
- ○ Transplant Patient
- ○ False Lab Measurement

AKI
- ○ Transient AKI
- ○ No Active Orders
- ○ Palliative Care
- ○ No Dose Change Required
- ○ Other

Intervention Recommendation:
- ☐ Monitor Serum Creatinine Daily
- ☐ Monitor Serum Potassium Daily
- ☐ Other Monitoring
- ☐ Other

Intervention Contact:

Contacted Provider:
- ☐ Intern
- ☐ Resident
- ☐ Attending
- ☐ Nurse Practitioner
- ☐ Pharmacist
- ☐ Nephrologist
Provider Name(s):

Contact Method:
- ☐ Text Page
- ☐ Verbal Communication
- ☐ Starpanel Note

Provider Response:
- ☐ Provider Agreed to Make Changes
- ☐ Provider Did Not Agree to Make Changes
- ☐ Pharmacist to Make Changes
- ☐ Provider and Pharmacist Compromised

Continue to Follow Patient?
- ⦿ Yes
- ○ No

[Submit Intervention Review]

Previous Pharmacy Comments ▾
No previous comments

Pharmacy Comment Box ▾
Previous Star Comments ▾
Star Comment Box ▾

```
AGE:   53
HEIGHT:   0
WEIGHT:   70.0
IBW:
SEX:  F
Pre-Trigger SCr (mg/dL):  4.59
Trigger SCr (mg/dL):   5.83
```

[Submit StarPanel Comment]

(Within Morphine PCA order row — Intervention Review ▾)

Response Required?
- ○ Yes ○ No

Recommended Response
- ☐ Increase Dose
- ☐ Increase Interval
- ☐ Decrease Dose
- ☐ Decrease Interval
- ☐ Discontinue Medication
- ☐ Consider Alternate Medication
- ☐ Monitor Therapeutic Drug Levels
- ☐ Other

Table 7: Targeted nephrotoxic or renally cleared medications for surveillance

Medications to Avoid		Medications to Adjust	Medications to Review	
ACARBOSE*	METFORMIN*	ACYCLOVIR (>400mg Q12H)	ADEFOVIR*	MORPHINE*
ACETAZOLAMIDE*	METHOTREXATE*	ALLOPURINOL (>100mg Q24H)	ALENDRONATE+	NEOSTIGMINE*
ACETOHEXAMIDE*	MOEXIPRIL*	AMANTADINE	AMOXICILLIN+	NORFLOXACIN
AMIKACIN	NABUMETONE*	AZTREONAM	AMOXICILLIN-CLAVULANATE	OFLOXACIN
AMPHOTERICIN B*	NAPROXEN*	BACTRIM (>1 DS tablet BID)	AMPICILLIN	PAMIDRONATE+
BENAZEPRIL*	NITROFURANTOIN*	CARBOPLATIN*	AZITHROMYCIN+	PENICILLIN-G
CANDESARTAN*	NITROPRUSSIDE*	CISPLATIN*	BRETYLIUM	PIPERACILLIN
CAPREOMYCIN*	OLMESARTAN*	COLCHICINE (>0.6mg Q24H)	BUMETANIDE+	PYRAZINAMIDE
CAPTOPRIL*	PANCURONIUM*	CYCLOSERINE	CEFACLOR+	QUINIDINE
CELECOXIB*	PERINDOPRIL*	DAPTOMYCIN	CEFAZOLIN	RIFAMPIN+
CHLORPROPAMIDE*	PIROXICAM*	DIDANOSINE	CEFEPIME	RISEDRONATE+
CIDOFOVIR*	QUINAPRIL*	DIGITOXIN	CEFOTAXIME	TEMOZOLOMIDE*
CYCLOPHOSPHAMIDE*	RAMIPRIL*	DIGOXIN	CEFOTETAN	TENOFOVIR*
CYCLOSPORINE*§	ROFECOXIB*	DOFETILIDE	CEFOXITIN	TICARCILLIN
CYTARABINE*	SITAGLIPTIN+	DORIPENEM	CEFTAZIDIME	TOCAINIDE
DICLOFENAC SODIUM*	SOTALOL*	EPTIFIBATIDE	CEFUROXIME	TORSEMIDE+
DIFLUNISAL*	STREPTOMYCIN*	ERTAPENEM	CEFUROXIME+	ZIDOVUDINE
ENALAPRIL*	SULINDAC*	ETOPOSIDE*	CEPHALEXIN+	ZOLEDRONIC ACID+
ENALAPRILAT*	TACROLIMUS*§	FAMCICLOVIR	CHLOROQUINE	
ENOXAPARIN* (>30mg Q24H)	TELMISARTAN*	FLUCYTOSINE	CIPROFLOXACIN	
ETODOLAC*	TETRACYCLINE*	FOSCARNET	CLARITHROMYCIN+	
EXENATIDE*	TOBRAMYCIN	GANCICLOVIR	CLOFIBRATE	
FENOPROFEN*	TOLMETIN*	GANCICLOVIR	Contrast Dye+	
FLURBIPROFEN*	TRANDOLAPRIL*	IMIPENEM-CILASTATIN	DISOPYRAMIDE	
FONDAPARINUX	TRIMETREXATE*	ITRACONAZOLE	DOXACURIUM INJ	
FOSINOPRIL*	VALDECOXIB*	LACOSAMIDE*	ETHACRYNATE+	
GALLAMINE*	VALSARTAN*	MEROPENEM	ETHAMBUTOL	
GENTAMICIN INJ		METOCLOPRAMIDE*	FLECAINIDE	
GLYBURIDE*		MITOMYCIN*	FLUCONAZOLE (>100mg Q24H)	
IBUPROFEN*		PENICILLIN-VK	FUROSEMIDE+	
IFOSFAMIDE*		PENTOSTATIN*	GEMFIBROZIL+	
IMMUNE GLOBULIN*		PRAMIPEXOLE*	HYDROMORPHONE+	
INDOMETHACIN*		PREGABALIN*	HYDROXYUREA*	
IRBESARTAN*		PROCAINAMIDE	IBANDRONATE+	
KETOPROFEN*		PYRIDOSTIGMINE	IDARUBICIN*	
KETOROLAC*		STAVUDINE	INDINAVIR	
LISINOPRIL*		TOPOTECAN*	LAMIVUDINE	
LITHIUM		VALACYCLOVIR	LEVOFLOXACIN	
LOSARTAN*		VALGANCICLOVIR (>450mg Q24H)	MELPHALAN*	
MELOXICAM*		VANCOMYCIN	METOCURINE	
MEPERIDINE*		VORICONAZOLE	MIVACURIUM	

* Medication only targeted for increasing serum creatinine intervention.
+ Medication was not targeted for intervention, displayed only on surveillance tool for context.
§ Medication was not targeted for patients admitted to a transplant unit.

To avoid conflicting recommendations by the study pharmacist, we also refined the inclusion criteria by excluding patients on selected services that were already closely monitored by specialized, trained clinicians. Patients admitted to the renal service are cared for by nephrologists, who have already adjusted targeted medications. Patients admitted to the renal, liver, or bone marrow transplant

services are monitored by a designated pharmacist.   In these cases, the study pharmacist was not necessarily more qualified to adjust treatment regimens for medications such as immunosuppressants.

Because some patients who met eligibility criteria were determined to be low risk or falsely alerted, and because patients could recover from an AKI event, we added functionality to allow the intervention pharmacist to categorize patients as "no longer following." These patients were sorted to the bottom of the display on the surveillance view of the tool to facilitate determination of higher risk patients by the intervention pharmacist. Patients with this categorization remained at the bottom of the list for the duration of their admission unless a new trigger medication or change in serum creatinine was detected.

Conclusion

Traditional methods for surveillance are not sufficient for monitoring patients and CDS failures in real-time, but existing systems are easily extended to facilitate such needs. Using a new model for surveillance, we developed a web-based surveillance tool that allows pharmacists and other surveillance team members to evaluate patients with AKI in real-time for potential ADEs or CDS failures. Iterative implementation with continual feedback ensured that the surveillance tool worked as expected and met the needs of the study surveillance team members prior to a formal evaluation.

CHAPTER V

EVALUATION OF A REAL-TIME PHARMACY SURVEILLANCE TOOL FOR REDUCING

ADVERSE DRUG EVENTS IN ACUTE KIDNEY INJURY: A RANDOMIZED TRIAL

Introduction

Computerized systems for surveillance can further reduce errors when clinical decision support

(CDS) within computerized provider order entry (CPOE) systems and electronic medical records (EMRs)

is insufficient (2,38,39,9,10,13,69,83,89). However, no prior study has evaluated the use of a real-time

surveillance tool for medication errors that incorporates provider interactions with CDS. We developed

a web-based surveillance tool for use by clinical pharmacists to monitor patients with acute kidney

injury (AKI), which affects patients across all hospitalized units and for which care and medication

prescribing is not standardized. With a randomized controlled trial, we evaluated the effect of daily

monitoring with the surveillance tool by a clinical pharmacist on the rate, timeliness, and severity of

intercepted adverse drug events (ADEs) compared to standard care in a setting with wide use of an EMR

and CPOE with extensive integrated CDS.

Methods

Study Setting

Vanderbilt University Hospital (VUH) is an academic, tertiary care facility with over 500 adult

beds and 50,000 admissions annually at which care providers have used locally-developed and

maintained inpatient CPOE and inpatient/outpatient EMR systems for more than a decade. Also in place

are pharmacy management, bar coded medication administration, and pharmacy automation systems. These systems include extensive integrated decision support, such dosing advice and alerts about drug-allergy, drug-laboratory, and drug-drug interactions (2,94,95). CPOE alerts about potential AKI appear to providers for patients with a 0.5 mg/dl increase in serum creatinine over 24 hours following an active, recurring order for a targeted nephrotoxic or renally cleared medication (42). In addition to CDS within the CPOE system, pharmacy surveillance of renally cleared drugs occurred during rounds with multidisciplinary teams. This study was approved by the Vanderbilt Institutional Review Board.

Study Population

The study included all admitted adult patients who experienced a 0.5 mg/dl change in serum creatinine over 48 hours of hospitalization following an eligible active, recurring order for one or more targeted nephrotoxic or renally cleared medications. Patients who were dialyzed prior to the first serum creatinine change event or identified as a dialysis patient through a dialysis flag order, in addition to those admitted to renal transplant, liver transplant, or nephrology services were excluded.

Targeted medications were categorized into three toxicity groups: medications to avoid, medications to adjust, and medications to review in AKI. These medications were further classified as requiring intervention in increasing serum creatinine, in decreasing serum creatinine, both, or neither (displayed on the surveillance for context only). A select number of medications were excluded if the dose was sufficiently low for prophylaxis, as these medications were ordered frequently and had low potential for harm. Some medications were also excluded for patients admitted to a transplant service, as these patients were monitored frequently by clinical pharmacists. Patients with only low toxicity medication triggers were excluded. Targeted medications are listed in Table 7.

Study Design

Patients were randomly assigned to appear on a pharmacy surveillance tool at the time that he or she first met eligibility criteria. The patient remained in the assigned intervention or control group for the remainder of his or her hospital admission. The surveillance tool system evaluated all patients for internal alerts and inclusion criteria to ensure that comparable data was collected for both groups, but only those patients randomized to the study group appeared on the surveillance tool. All patients received previously existing CDS, which included CPOE advisors for initial medication prescribing, CPOE alerts for changing serum creatinine in the setting of nephrotoxic or renally cleared medications, and pharmacy surveillance of aminoglycosides. The triggering criteria for CPOE alerts for changing serum creatinine mirrored those used for the surveillance tool; all eligible cases received the CPOE alerts.

The surveillance tool was monitored by the clinical pharmacist for internal medicine (EN). The protocol for making patient interventions is described in Figure 7. Interventions could be medication specific (e.g. for example decreasing the dose) or patient specific (e.g. monitoring the serum creatinine). Each workday, the study pharmacist reviewed the patients appearing on the surveillance tool for potential AKI, using both the surveillance and patient detail views with CDS interaction data to determine the each patient's level of risk. For patients determined to be experiencing AKI and needing an intervention, the study pharmacist contacted the primary provider to recommended changes in care. Patients remained on the tool until discharged; though the study pharmacist could classify patients as "no longer following," and sort them to the bottom of the display. Patients with this classification who experienced another triggering creatinine or who were prescribed a new triggering medication were automatically classified as "following" again until the pharmacist re-checked "no longer following." All interactions, including patient's classification of AKI, communication with provider, recommendations provided, and actions taken, were recorded within the surveillance tool for later analysis.
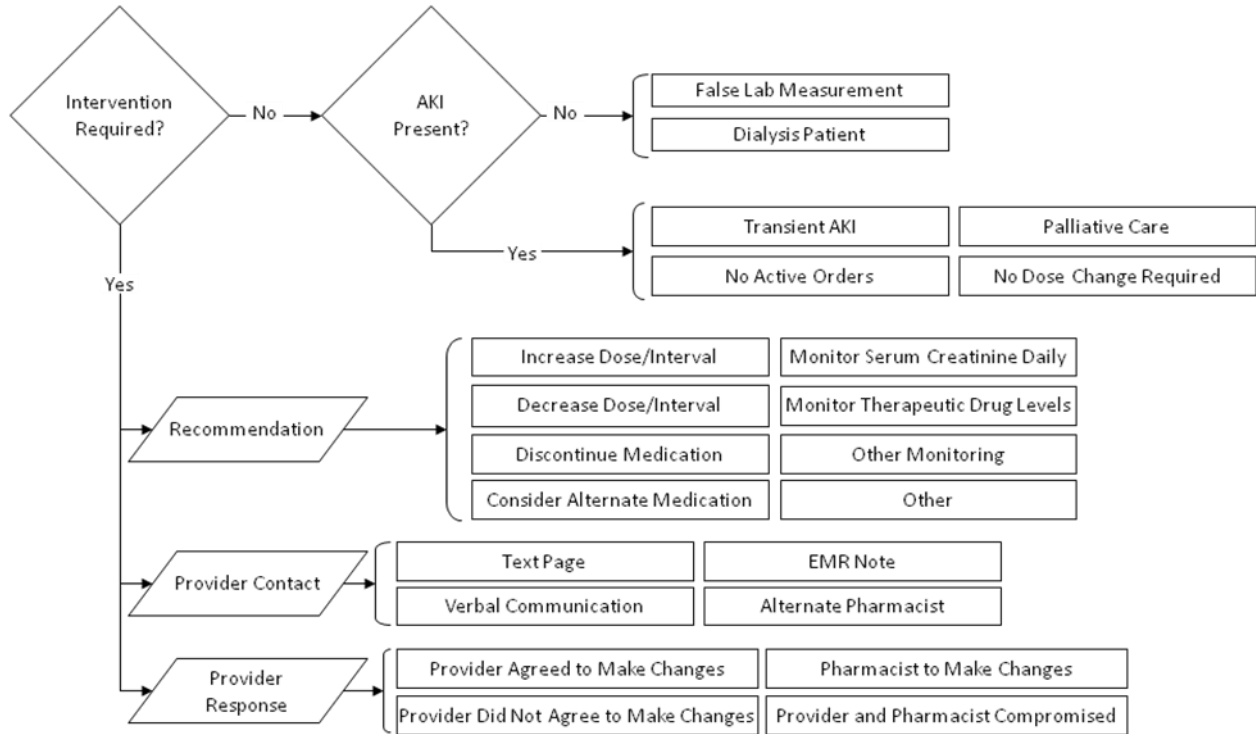
Figure 7: Pharmacy surveillance intervention protocol

AKI = acute kidney injury
EMR = electronic medical record

Outcomes

We measured a variety of outcomes to evaluate changes in patient safety and provider behavior. We conformed to an intent-to-treat analysis, where cases randomized to the intervention group remained in the intervention group whether or not the study pharmacist reviewed the patient and recommended a change in care. Our primary outcome measured the rate of ADEs and potential ADEs (pADEs) in the intervention group compared to the concurrent control group. Based on work by Bates, et al., we defined pADEs as incidents with the potential for injury related to a drug, such as use of a non-steroidal anti-inflammatory drug for at least 24 hours. We defined ADEs as injuries resulting from the administration of a drug; these included lab-only ADEs, such as a toxic vancomycin trough level, and

actual ADEs, such as a bleed after administration of enoxaparin (4). We limited measurement of pADEs and ADEs to those specific to AKI medications; Appendix B includes a detailed list of pADEs and ADEs measured. We measured outcomes after completion of the inpatient encounter (either by death or discharge), evaluating only data existing in the EMR at that time, as outpatient information is not routinely available for all patients; pADEs or ADEs occurring after patient discharge were not included in the analysis.

The initial outcomes assessment pharmacist (ZC), blinded to patient intervention status, reviewed all cases that met the eligibility criteria using an electronic tool similar to the surveillance tool. If no exclusion criteria were determined, the pharmacist recorded patient comorbidities and dialysis, if present. The pharmacist also reviewed each targeted medication order for an associated error, following instructions to include record any potential error. An outcomes assessment adjudication committee then independently reviewed cases categorized as having at least one pADE or ADE, using methods previously applied to rate preventability and severity (4,23,98). The adjudication committee included a nephrologist (GB) and an internal medicine physician (NP) for initial reviews and an additional nephrologist (ES) to break ties when disagreement occurred. We performed pilot reviews of initial cases to ensure that the adjudicating reviewers were in agreement and that the initial outcomes assessment pharmacist had identified all potential errors.

We evaluated provider behavior as our secondary outcome, measuring the time to provider response. We electronically calculated the time from the first change in serum creatinine to modification or discontinuation of targeted medications ordered prior to the change (42) and the time from the initial order to modification or discontinuation of targeted medications ordered after the change.

We also measured outcomes describing the use of the surveillance tool. These included number of patients appearing on the tool, number of data items (e.g. drugs, labs, and CDS interactions of interest) for patients, time of day the tool was viewed, duration of views, number of patients with comments or EMR notes submitted, and the number of patients for which pharmacists intervened. Using direct observation and interviews, we collected qualitative data on pharmacists' use of the surveillance tool. We also evaluated comments and EMR notes recorded through the tool.

Randomization

For allocation of cases to intervention or control groups, a pseudo-random number function (Python Random) assigned cases a number in the range [0.0, 1.0) during the first update for which the case met inclusion criteria. Cases with an assigned number greater than 0.5 were allocated to the intervention group, and cases with a number less than or equal to 0.5 were allocated to the control group. Cases remained in the assigned control or intervention group until discharge.

Blinding

All outcomes assessment pharmacists and physicians were blinded to patient intervention status. The intervention pharmacist was aware of patients that were assigned to the intervention group but blinded to the list of patients assigned to the control group. To ensure that outcomes assessors were not made aware of intervention status by viewing notes in a patient's EMR made by the intervention pharmacist, outcomes assessors accessed the web-based EMR using Mozilla Firefox (99) and the Greasemonkey Firefox Add-on (100) with an installed user script that removed notes generated by the study pharmacist from the intervention surveillance tool (Appendix C).

Statistical Analysis

We used the Pearson chi-square test for categorical variables and the t-test for continuous variables to perform univariate comparisons between the control and intervention groups. To evaluate provider behavior, we applied survival analysis methods for time to provider response. We defined an event or failure as a provider modification or discontinuation. We censored cases if providers did not modify or discontinue the medication until patient discharge. For medications ordered prior to the triggering event, follow-up started at the time of the triggering serum creatinine change, and for medications ordered after the triggering event, follow-up started at the time the medication was ordered. We used the log-rank test to measure the difference between control and intervention groups and provided Kaplan-Meier plots for visualization of the data. Analyses were conducted with Intercooled Stata 9.2.

Results

Study Population

Figure 8 is a diagram of the allocation and follow-up of control and intervention cases. During the trial period, 1,767 of 11,128 adults admitted to VUMC experienced a triggering change of serum creatinine over 48 hours. Of these, we excluded 9 cases that had a triggering change prior to the start of the trial, 398 patients without targeted medications, 106 cases identified before the triggering event as having chronic dialysis, and 411 cases admitted to a renal service or renal, liver, and bone marrow transplant unit. We enrolled 540 cases; 278 were randomized to the control group, and 262 were randomized to the intervention group. During analysis, the initial outcomes assessment pharmacist, blinded to intervention status, marked patients for exclusion when they were determined to be chronic

dialysis patients (9 control, 8 intervention), transplant patients (28 control, 14 intervention), palliative care patients (26 control, 18 intervention), triggered by a false lab measurement (14 control, 17 intervention), and not have received administrations of targeted medications (5 control, 5 intervention).

We compared demographic characteristics, including age, sex, race, admitting service, and admission to an intensive care unit, and comorbidities, which the initial outcomes assessment study pharmacist classified, between the control and intervention groups to ensure that the study groups were similar (Table 8). We found no statistical difference between groups for any variable evaluated.
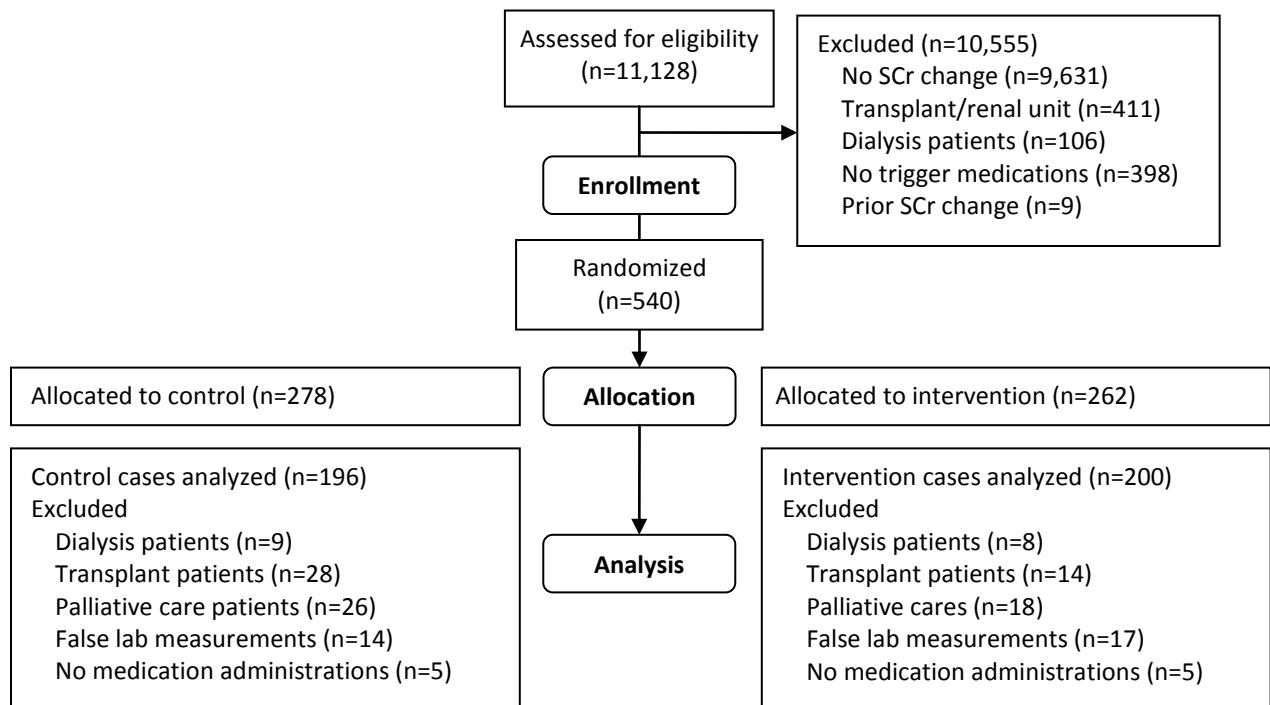
Figure 8: Flow diagram of control and intervention cases

Table 8: Study population demographics for analyzed acute kidney injury surveillance cases

	Control Cases n = 196	Intervention Cases n = 200	P
Age (y)	61.48 (17.74)	63.44 (18.30)	0.28
Sex (%)			
Women	39.29	45.50	0.21
Men	59.18	51.50	0.12
Unknown	1.53	3.00	0.33
Race (%)			
White	72.96	69.00	0.39
Black	10.2	16.50	0.06
Hispanic	1.53	0.50	0.31
Other	2.04	0.50	0.17
Unknown	13.27	13.50	0.95
Admitting Service (%)			
Cardiology	20.92	15.00	0.13
Critical Care	11.22	17.50	0.08
Geriatrics	2.55	2.50	0.97
Hematology/oncology	8.16	7.50	0.81
Hepatology	2.55	1.50	0.46
Infectious disease	1.53	3.00	0.33
Medicine	12.76	12.50	0.94
Orthopedics	5.10	6.00	0.70
Other	2.04	4.50	0.17
Surgery	26.02	22.50	0.41
Trauma	7.14	7.50	0.89
Intensive Care Unit (%)	52.04	57.00	0.32
Comorbidities (%)			
Cancer	28.57	22.50	0.17
Cerebrovascular disease	11.73	14.50	0.42
Congestive heart failure	24.49	26.00	0.73
Coronary artery disease	32.65	34.00	0.78
Diabetes	35.71	41.50	0.24
End-stage liver disease	4.59	4.00	0.77
Hypertension	62.24	67.00	0.32
Mechanical ventilation	29.59	25.50	0.36
Peripheral vascular disease	3.57	7.50	0.09

Evaluation of Adverse Drug Events

Initial outcomes assessment included 196 control cases with 1303 medication orders and 200 intervention cases with 1396 medication orders. The initial outcomes assessment pharmacist indicated that 77 (39.29%) control and 70 (35%) intervention cases had experienced a pADE or ADE. For individual orders, the initial outcomes assessment pharmacist indicated that 111 (8.52%) control and 115 (8.24%) had an associated pADE or ADE.

Agreement between the two initial outcomes adjudication physicians was 92.19% for pADEs and 91.84% for ADEs. After reaching consensus, the adjudication committee determined that zero control and two intervention cases (one control and six intervention medications) selected in the sensitive initial outcomes phase did not have a pADE or ADE; 77 (39.29%) control and 68 (31.00%) intervention cases had pADEs or ADEs (RR=0.87, p=0.28) for 110 (8.44%) control and 109 (7.81%) intervention orders (RR=0.92, p=0.55), indicating that the adjudication committee agreed with the initial outcomes assessment pharmacist for most cases.

The adjudication committee determined that 44 (22.45%) control and 45 (22.61%) intervention cases experienced a pADE (RR=1.01), and 59 (4.53%) control and 63 (4.52%) intervention medication orders had an associated pADE (RR=1.00). Distribution of pADE types is described in Table 9. Frequent responses for pADEs categorized as "other" by the study pharmacist included "dose and interval change inappropriate for trough level" and "interacted with another prescribed medication". We found no statistically significant differences between control and intervention groups (p=0.99 and 0.97 for cases and medications respectively).

The adjudication committee determined that 14 (7.14%) control and 16 (8.00%) intervention cases experienced a lab-only ADE (RR1.12), and 16 (1.23%) control and 16 (1.15%) intervention medication orders had an associated lab-only ADE (RR=0.93). Also, 32 (16.33%) control and 24 (12.00%)

intervention cases experienced an actual ADE (RR=0.74), and 36 (2.76%) control and 30 (2.15%) intervention medication orders had an associated actual ADE (RR=0.78). The occurrence of lab-only ADEs and actual ADEs was not statistically different between study groups for cases (p=0.75 and 0.22 respectively) or medication orders (p=0.84 and 0.30 respectively). However, documentation of AKI was significantly higher for control orders compared to intervention orders; 52.78% of control orders resulted in AKI, and 26.67% of intervention orders resulted in AKI (p=0.03). Table 10 describes the distribution of ADE and lab-only ADE types that occurred.

Severity and preventability of pADEs and ADEs are described in Table 11. Most pADEs were significant or serious, and most ADEs were serious or life-threatening. We collapsed "definitely" and "probably" determinations for preventability and found that 7 (43.75%) of control and 4 (25.00%) of intervention lab-only ADEs, and 9 (25.00%) of control and 13 (43.33%) of intervention ADEs were determined to be preventable.

Among drugs or drug groups with at least ten orders in the control and intervention groups, errors most commonly occurred for angiotensin II receptor antagonists (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), vancomycin, and carbapenems, 22.8%, 20.9%, 12.4%, and 11.7% of orders resulting in a pADE or ADE respectively. Table 12 describes these results.

Table 9: Evaluation of potential adverse drug events

	Control n=1303	Intervention n=1396	P
Potential adverse drug events	59 (4.53%)	63 (4.52%)	0.99
Contraindicated use for > 24 hours	15	12	0.40
No dose adjustment for > 24 hours	9	16	0.17
No interval adjustment for > 24 hours	30	31	0.86
Ineffective at low creatinine clearance	1	3	0.34
Administration error	2	1	0.52
No drug level monitoring	5	5	0.91
No creatinine monitoring	1	3	0.34
Other	5	1	0.08

Table 10: Evaluation of adverse drug events

	Control n=1303	Intervention n=1396	p
Lab-only adverse drug events	16 (1.23%)	16 (1.15%)	0.84
Hyperkalemia	2	1	0.54
Hypokalemia	0	0	--
Hypernatremia	0	0	--
Hyponatremia	0	0	--
Toxic drug levels	9	9	1.00
Subtherapeutic drug levels	6	6	1.00
Hypoglycemia (asymptomatic)	0	0	--
Adverse drug events	36 (2.76%)	30 (2.15%)	0.30
Bradyarrhythmia	1	0	0.36
Hypotension	7	7	0.70
QT Prolongation	1	2	0.45
Cognitive changes/somnolence	2	7	0.04
Delirium	1	0	0.36
Extrapyramidal symptoms/movement disorders	0	2	0.12
Oversedation	4	5	0.51
Seizure	0	0	--
Rash	0	1	0.27
Hypoglycemia (symptomatic)	0	0	--
Pancreatitis	0	0	--
Diarrhea	0	0	--
Anemia	0	0	--
Lactic acidosis	0	0	--
Major bleed	0	1	0.27
Minor bleed	3	2	0.80
Neutropenia	0	0	--
Thrombocytopenia	0	0	--
Neuromuscular control	0	0	--
Vision changes	0	0	--
Hearing loss	0	0	--
Tinnitus	0	0	--
Acute kidney injury	19	8	0.03
Crystalurea	0	1	0.27
Renal replacement therapy	0	0	--
Volume overload	0	0	--
Respiratory depression	1	3	0.22
Death	0	0	--

Table 11: Evaluation of potential adverse drug event and adverse drug event severity and preventability

	Control	Intervention
Potential adverse drug events	59 (4.53%)	63 (4.52%)
Significant	26 (44.07%)	27 (42.86%)
Serious	30 (50.85%)	27 (42.86%)
Life-threatening	3 (5.08%)	9 (14.29%)
Fatal	0 (0.00%)	0 (0.00%)
Lab-only adverse drug events	16 (1.23%)	16 (1.15%)
Preventable	7 (43.75%)	4 (25.00%)
Significant	0 (0.00%)	1 (6.25%)
Serious	9 (56.25%)	11 (68.75%)
Life-threatening	7 (43.75%)	4 (25.00%)
Fatal	0 (0.00%)	0 (0.00%)
Adverse drug events	36 (2.76%)	30 (2.15%)
Preventable	9 (25.00%)	13 (43.33%)
Significant	2 (5.56%)	4 (13.33%)
Serious	25 (69.44%)	13 (43.33%)
Life-threatening	9 (25.00%)	12 (40.00%)
Fatal	0 (0.00%)	1 (1.52%)

Table 12: Evaluation of potential adverse drug events and adverse drug events by drug or drug group

| Drug or Drug Group	n	Potential Adverse Drug Events		Lab-Only Adverse Drug Events		Adverse Drug Events	
		Control	Intervention	Control	Intervention	Control	Intervention
Vancomycin	371	14 (8.9%)	16 (7.5%)	13 (8.2%)	15 (7.0%)	1 (0.6%)	1 (0.5%)
Analgesics	353	5 (2.6%)	7 (4.4%)	0 (0.0%)	0 (0.0%)	5 (2.6%)	7 (4.4%)
Quinolones	350	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ACE Inhibitors	231	9 (7.9%)	9 (7.7%)	2 (1.8%)	1 (0.9%)	7 (6.1%)	8 (6.8%)
Penicillins	195	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Antithrombotics	187	3 (3.1%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	3 (3.1%)	2 (2.2%)
Carbabenems	157	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cephalosphorins	109	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antifungals	108	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Aminoglycosides	70	1 (2.5%)	1 (3.3%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
Vasodilators	64	1 (3.9%)	2 (5.3%)	0 (0.0%)	0 (0.0%)	1 (3.9%)	2 (5.3%)
ARBs	57	6 (25.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	6 (25.0%)	1 (3.0%)
NSAIDs	57	7 (13.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (13.2%)	0 (0.0%)
Digoxin	51	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other Antibacterials	49	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)
Anticonvulsants	48	1 (4.8%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (3.7%)
Antivirals	42	1 (4.4%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (4.4%)	1 (5.3%)
Anticholinesterases	26	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Antigouts	23	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sotalol	22	1 (9.1%)	3 (27.3%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	3 (27.3%)

Evaluation of Provider Responses

For medications active at the time of patient's triggering serum creatinine change or ordered after the event, we compared the time to provider response, defined as drug modification or discontinuation, using the log-rank test. We did not find any statistically significant differences between the control and intervention groups. Table 13 shows the resulting median times to response, hazard ratios, and p-values. Kaplan-Meier curves for these results are shown in Figure 9 for medications ordered prior to AKI and Figure 10 for medications ordered after AKI.

Table 13: Evaluation of surveillance and provider response

	Control		Intervention			
		Median Hours to		Median Hours to	Hazard	
	n	Response (IQR)	n	Response (IQR)	Ratio	P
Ordered prior to AKI						
Medications to avoid	106	27.89 (5.13, 76.87)	115	14.17 (3.65, 48.8)	1.12	0.45
Medications to adjust	100	26.21 (4.43, 71.38)	110	24.93 (5.17, 65.16)	1.00	0.98
Medications to review	126	27.5 (7.8, 51.63)	149	26.57 (8.31, 51.53)	0.94	0.60
Ordered after AKI						
Medications to avoid	179	27.82 (13.58, 70)	152	40.28 (14.78, 81.7)	0.95	0.70
Medications to adjust	146	46.53 (20.47, 96.68)	207	32.12 (13.82, 76.23)	1.22	0.09
Medications to review	237	47.5 (20.02, 76.63)	257	47.5 (22.27, 78.33)	1.07	0.48

AKI = acute kidney injury
IQR = interquartile ranges
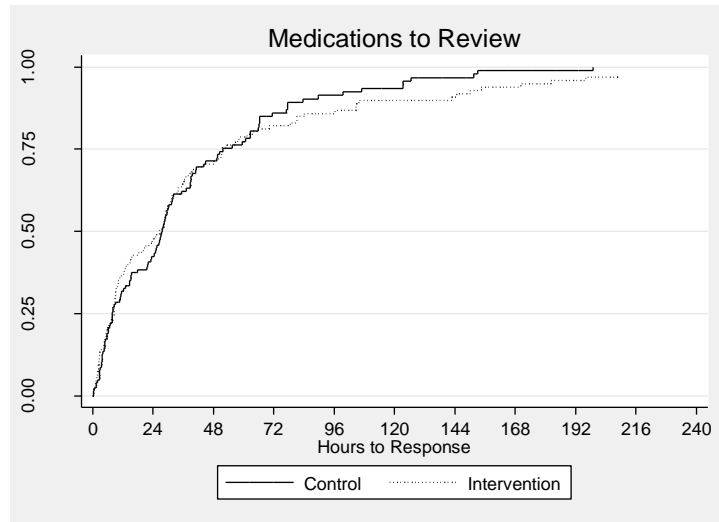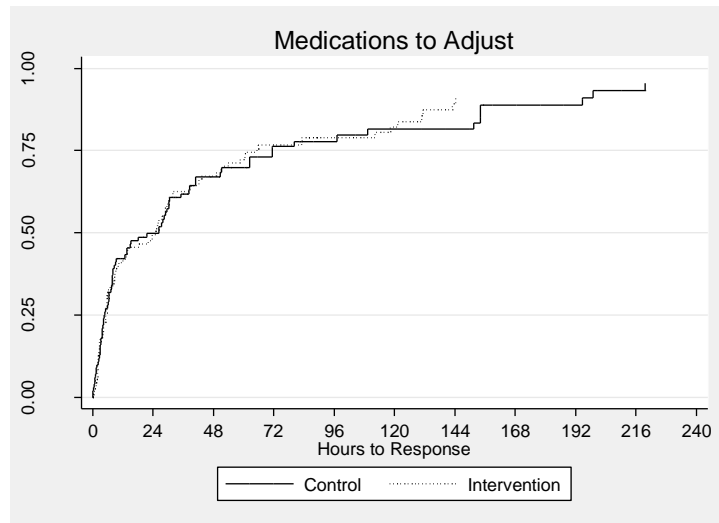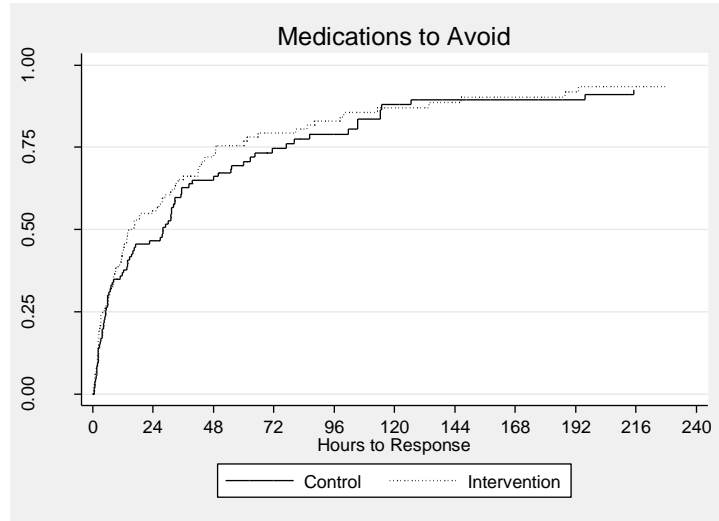
Figure 9: Kaplan-Meier curves for time to provider response by intervention group for medications ordered prior to acute kidney injury
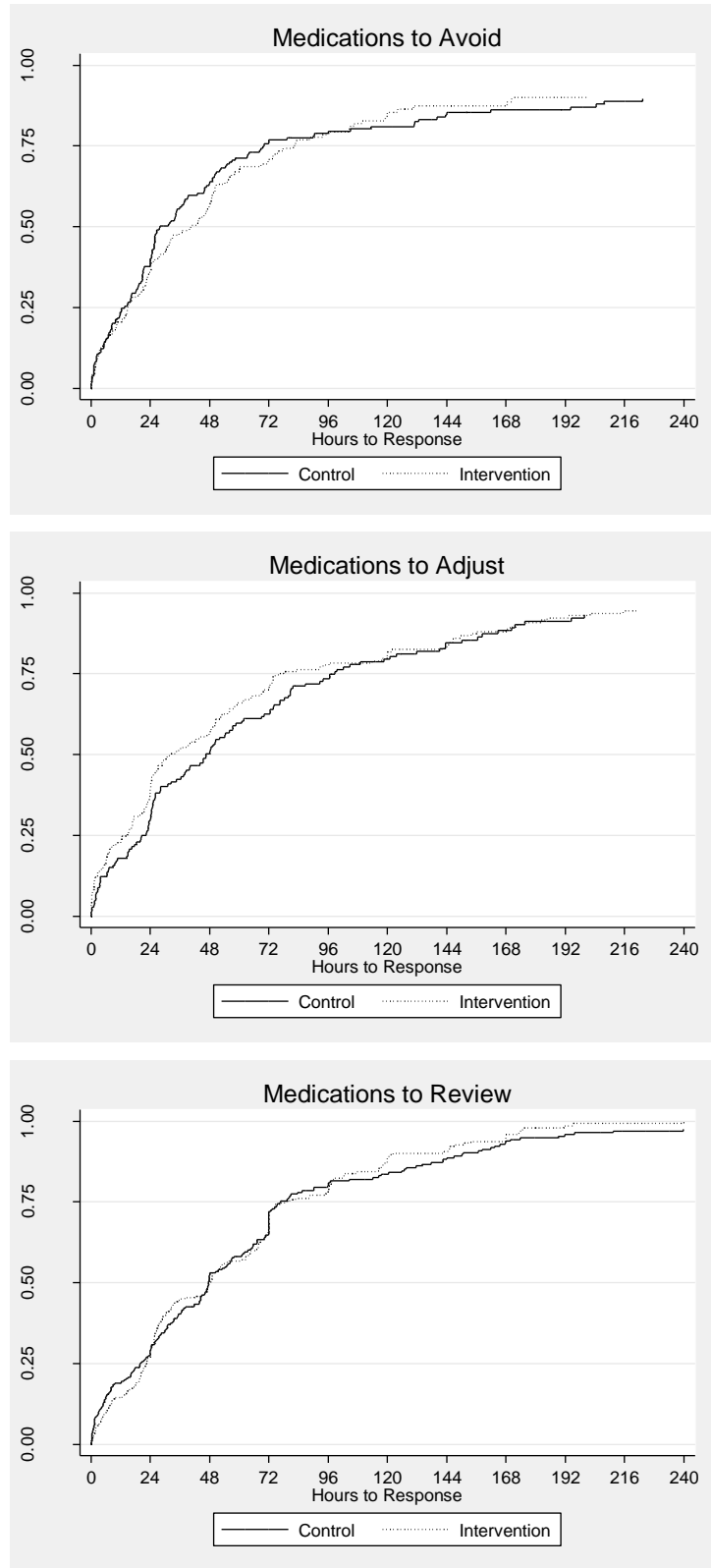
Figure 10: Kaplan-Meier curves for time to provider response by intervention group for medications ordered after acute kidney injury

Study Pharmacist Interactions with the Surveillance Tool

Using both quantitative analyses of surveillance tool usage logs and qualitative analysis using observation, we evaluated the study pharmacist's interactions with the surveillance tool. During the 3-month study period, 262 intervention patients appeared on the surveillance tool. The study pharmacist viewed the surveillance tool on 67 days, 56 of which (83.58%) were weekdays. Although monitoring occurred often between 08:00 and 16:00, the study pharmacist preferred to check the surveillance tool in the afternoon once providing teams had completed rounds, updated medication orders, and entered EMR notes, and laboratory results had returned. On Mondays or other days for which the surveillance tool had not been monitored for days prior, full review took longer, as more new patients who did not require following appeared. During the week for which times were recorded, the pharmacist spent 71 minutes monitoring the surveillance tool on Monday, and a mean of 16.75 minutes on the remaining days (25 on Tuesday, 9 on Wednesday, 15 on Thursday, and 18 on Friday).

When reviewing patients, the study pharmacist evaluated the serum creatinine trend, the most recent creatinine clearance estimate, and the active orders. The EMR served as a reference for verification of administrations and discontinued medications, and it provided additional patient information, including vital signs (e.g. urine output, blood pressure, mental status), cultures, and rationale for orders. In some instances, the patient's nurse or providing team were contacted for additional information. Though the integrated CDS interactions on the surveillance tool indicated which prescribing advice and alerts the provider had previously received, this information did not often impact the workflow of the study pharmacist.

Of the displayed intervention patients, 230 (87.79%) were reviewed by the study pharmacist. Patients with no active orders were frequently checked first, as these patients required less time for review. The study pharmacist reviewed an average of 10.75 patients each day the surveillance tool was

monitored. Of the reviewed intervention patients, 102 (44.35%) of the patients remained active for

monitoring. Patients were most often removed from the monitoring list if there were no active orders

and all laboratory levels were in the normal range and not trending towards worse.

The study pharmacist recommended an intervention for 40 (17.39%) cases (49 total intervention

recommendations). Reasons indicated when no intervention was required are described in Table 14.

Most cases without an intervention did not require a dose change. The study pharmacist made patient

recommendations (i.e. recommendations that were not medication specific) for 8 cases.   Patient

recommendations categorized as "other" (2 cases) included redrawing serum creatinine, monitoring for

sedation and treatment failure, discontinuing oral potassium, and adding height and weight. The study

pharmacist recommended interventions for 71 medications (43 cases). Medication recommendations

categorized as "other" (9 medications) included correcting the patient's weight, holding the medication,

and monitoring for sedation. Frequencies of recommended patient and medication intervetnions are

described in Table 15 and Table 16.   The study pharmacist most frequently used indicated use of text

pages and verbal communication to contact the providing team; of 52 recorded contact events 28

included text pages (53.85%), 32 verbal communications (61.54%), and 1 an EMR note (1.92%)

Providers most often agreed with the recommended changes, and the study pharmacist frequently

made changes directly in the CPOE system.

The study pharmacist submitted 157 surveillance tool comments for 102 cases. The comments

frequently summarized patient comorbidities, laboratory values and trends, and indications; served as

reminders for continued monitoring; and elaborated recommendations. These comments remained

within the surveillance tool and did not appear in the patient's EMR. Examples of these types are listed

in Table 17. EMR notes were written for 3 cases (4 notes total). These were most commonly used when

the providing team was unavailable (e.g. providing team does not have an attending on campus, or provider did not respond to text page).

Table 14: Study pharmacist justifications for no recommended surveillance interventions

Reason	Total Responses (%) n=503	Cases (%) n=217
Dialysis	2 (0.40)	2 (0.86)
Transplant	0 (0.00)	0 (0.00)
False lab measurement	15 (2.98)	10 (4.29)
Transient acute kidney injury	8 (1.59)	7 (3.00)
No active orders	80 (15.90)	68 (32.19)
Palliative care	4 (7.95)	4 (1.72)
No dose change required	392 (97.81)	175 (80.26)
Other	2 (0.40)	2 (0.86)

Table 15: Study pharmacist patient recommendations for surveillance

	Total responses (%) n=8
Monitor serum creatinine	3
Monitor serum potassium	0
Monitor other	3
Other	2

Table 16: Study pharmacist medication recommendations for surveillance

	Total responses (%) n=99
Increase dose	14 (14.14)
Increase interval	9 (9.09)
Decrease dose	14 (14.14)
Decrease interval	13 (13.13)
Discontinue medication	17 (17.17)
Consider alternate medication	7 (7.07)
Monitor therapeutic drug levels	16 (16.16)
Other	9 (9.09)

Table 17: Examples of study pharmacist surveillance comments

Type	Examples
Summary of patient comorbidities	"baseline SCr 1.7-2, zosyn dose okay. Severe CAD and NSTEMI medically managed- ACEI acceptable." "Pt with heart failure, on milrinone, amiodarone, dopamine. Rec dcing levaquin dt qtc prolongation. Cultures back, enterococcus, vanc should be sufficient. Will need level at steady state tomorrow."
Summary of laboratory values and trends	"SCr of 0.48 is outlier." "CrCl= 42 today."
Summary of indication	"patient just had urological surgery, sotalol home dose ok for now, lower dose. levaquin should prob go to Q48 if aki persists, can address tomorrow before morning dose given. no changes today. will recheck tomorrow." "SCr improved... CrCl calculates to 50-60 ml/min. Macrobid okay due to limited [IV] access and suspected MDR UTI."
Reminders for continued monitoring	"may need to incr vanc if scr cont to decrease." "Will rec decr lovenox to 30 Qd if SCr any higher tomorrow."
Elaboration of recommendations	"Pt with heart failure, on milrinone, amiodarone, dopamine. Rec dcing levaquin dt qtc prolongation. Cultures back, enterococcus, vanc should be sufficient. Will need level at steady state tomorrow." "talked with team about adjusting sotalol. Doses have been held due to hypotension. Rec Qd administration or told them to consider cards consult."

Surveillance Interactions and Adverse Drug Events

Of the 33 patients that received an intervention, 15 (45.5%) experienced a pADE, and 14 (42.4%) experienced an ADE. These rates are significantly higher than those for patients not receiving an intervention, with 30 (18.1%) experiencing a pADE and 26 (15.6%) experiencing an ADE ($p=0.001$ and $p < 0.001$ respectively). Qualitative feedback indicated that ADEs occurring after study pharmacist review frequently resulted from patients with borderline criteria for intervention.

Discussion

Summary of Findings

We performed a prospective, randomized trial of the monitoring of a real-time, web-based patient surveillance tool and interventions by a clinical pharmacist to improve medication safety in AKI compared to existing CDS and standard of care. During analysis, despite a number of interventions made by the study pharmacist, we found no significant improvements in total patient outcomes, including occurrence, preventability, and severity of pADEs and ADEs, or in process outcomes, including rate and timeliness of provider modifications or discontinuations of targeted medications. Documented AKI resulting from targeted medications was significantly lower in the intervention group compared to the control group, though this finding may have be biased from providers being more aware of AKI after pharmacist intervention; 7 of 8 documented AKI intervention group patients received an actual intervention from the study pharmacist.

Many factors may have contributed to our negative findings. Existing CDS for initial dosing of nephrotoxic and renally cleared drugs, CDS for monitoring of these medications within CPOE, and surveillance by other pharmacists in the event of changing laboratory values results in a large percentage of prevented errors. Because of this, the number of interventions made by study pharmacist was relatively low. Many of the medication orders for patients who appeared for review on the surveillance tool had already been adjusted for decreased renal function and did not require an additional change. Though we were able to exclude some medication orders that were sufficiently low for prophylaxis, an algorithm that could evaluate orders for appropriate dose and interval for the patient's renal function might improve specificity of eligible patients. Because errors still occurred for patients that received an intervention, the timing of the surveillance and resulting alterations to therapy

may not have been appropriate. An alternate workflow, such as use of the surveillance tool by front-line

pharmacists approving and dispensing medication orders or by a pharmacist or other provider

participating in rounds might allow earlier prevention of medication errors and reduction of ADEs.

Finally, we did not have sufficient power to detect a difference between groups with a low prevalence of

pADEs and ADEs. While a difference of 8.39% in cases with pADEs or ADEs was observed between

control and intervention groups, a sample size with 703 cases in each study group would be required to

achieve 90% power.

Qualitative assessment of the benefit of the integrated CDS on the surveillance tool was

inconclusive, as the study pharmacist did not frequently incorporate the data in the surveillance

workflow. Further research is necessary to determine whether inclusion of the data on the surveillance

tool has an effect on surveillance and outcomes.

Comparison to Literature

Many prior studies have evaluated the use of surveillance to prevent pADEs and ADEs, finding

that systems successfully identify 45% to 90% of ADEs, though these studies have not evaluated the

effect of systems on actual prevention of ADEs (10-12,68). Though some investigators have evaluated

the use of retrospective CDS surveillance and real-time aggregate CDS surveillance (13,69), no prior

study has evaluated the effect of surveillance of CDS in real time on patient or process outcomes. The

restriction of our intervention and analysis to ADEs only related to AKI also makes it difficult to compare

our results to these studies, which measured all types of ADEs. However, pharmacy use of the

surveillance tool for monitoring AKI patients and CDS was similar to use described for a similar tool for

aminoglycosides and anticoagulants (93). Our study also differs from prior research in that we

evaluated the surveillance tool in a setting with extensive existing CDS.

Limitations

A number of factors limit the generalizability of our results. First, development of the real-time surveillance tool required integration with several advanced clinical systems, which many facilities have not implemented. However, a similar tool may be developed, or a commercial system may be installed, requiring access to commonly patient census, laboratory, and medication ordering data. These systems have been implemented in most facilities, and data may be shared with HL7 messages or existing data repositories. With external collection of surveillance interaction data, the methods from out study could be applied to evaluate alternate systems for surveillance.

Our results are also limited by evaluation in the single domain of AKI. Other clinical scenarios, including anticoagulant prescribing and glucose management, may also benefit from real-time surveillance with CDS, as they depend on laboratory results for proper dosing, and prior work shows similar results with effects of CDS in these scenarios.

Conclusion

We evaluated the use of a real-time surveillance tool of AKI patients and CDS interactions with a randomized trial, where intervention patients were monitored daily by a clinical pharmacist and control patients received only existing CDS and standard of care. Despite interventions made by the study pharmacist from the surveillance tool, we found no statistically significant improvements in provider responses or occurrence or severity of potential ADEs or ADEs between control and intervention study groups. Further research is necessary to determine whether a larger sample size, improved inclusion criteria, or alternate workflow would have led to positive findings.

CHAPTER VI

DISCUSSION

Summary of Findings

With this research, we aimed to identify failures associated with medication-related clinical decision support (CDS) for acute kidney injury (AKI) and reduce further errors with real-time surveillance. In the first aim, nephrologists performed retrospective adjudication of AKI alerts, determining appropriateness of alerts that displayed to providers of provider responses to the alerts. We found that most alerts were appropriate but identified a number of factors contributed to false alerting that could be improved in future alerting systems, including checks for appropriate drug dosing and therapeutic drug levels. Likewise, most alert responses were appropriate, and those that were inappropriate most often occurred for appropriate alerts; providers frequently committed errors or omission in the form of unjustified overrides rather than committing errors of commission, or unintended adverse consequences.

In an attempt to further improve timeliness of provider responses and reduce errors, we developed and implemented a real-time web-based surveillance tool, which integrates provider responses to CDS recommendations with relevant medication ordering, administration, and therapeutic monitoring data. We evaluated the surveillance tool with a randomized trial, where intervention patients were monitored on the surveillance tool daily by a clinical pharmacist and control patients received only existing CDS and standard of care. The study pharmacist made some interventions through the surveillance during the trial, but we found no statistically significant improvements in provider responses or occurrence or severity of adverse drug events (ADEs) or potential ADEs between

control and intervention study groups. This negative finding was likely due to a high baseline of error

prevention from existing CDS in the CPOE system and surveillance by alternate pharmacists, which we

previously found to be beneficial and appropriate, and an ineffective workflow for further preventing

errors. Further research is necessary to determine whether the surveillance tool would be beneficial in

clinical settings without extensive CDS or whether an alternate surveillance workflow could have further

prevented errors.

Implications

The findings from both of phases of this research have implications on CDS and medication

safety. It is important that CDS is thoroughly evaluated both prior to and after implementation to

continually improve systems and prevent errors, and our approach is novel in many aspects. First, we

evaluated patient factors for triggered alerts to determine appropriateness, which is frequently not

accounted for in studies of CDS systems. Prior research has typically described prevalence of alerts,

ignoring those that may be clinically irrelevant. Identification of these scenarios and attempts to

improve the specificity of alerts is crucial in preventing alert fatigue. Next, we allowed for downstream

responses to alerts outside of the initial alert context. Traditional evaluations of alerts report provider

overrides to the initially displayed alerts and do not account for changes to care made at a later time.

This is significant, as we have found that providers frequently override alerts for the first display but

make changes after discussing therapy with the care providing team or consulting with a pharmacist or

other provider. Finally, we accounted for the alert appropriateness measure in evaluating responses to

alerts instead of assuming that all alert overrides are unjustified. Typical evaluations measure only

adherence to CDS advice and fail to acknowledge that alerts to not apply to all patients and scenarios.

These methods for evaluation could be adapted to fit a variety of CDS implementations, including drug-laboratory, drug-drug, and other alerting systems, for a number of clinical scenarios.

The surveillance system that we developed could be implemented in other settings. Though we did not find a statistically significant difference in patient or process outcomes with the surveillance system, research conducted in settings without extensive CDS or monitoring, or in different clinical scenarios, might result in positive findings. For example, warfarin doses are frequently administered in the evenings, and surveillance during the day would occur in time to identify errors and make changes to therapy prior to the administration. Likewise, an institution without guided renal dosing or alerts about decreases in renal function or existing monitoring may not have had a high rate of already adjusted therapy prior to pharmacy surveillance. It is important to identify settings for research and workflows for interventions that have a high potential for improving patient care.

Limitations

As described in the previous chapters, this research has a number of limitations. In the first aim, we retrospectively evaluated appropriateness of alerts for AKI with nephrologists serving as reviewers. These results were limited, as physicians with other roles and training may perceive alerts very differently. While we were not able to evaluate reviews by other physicians for the retrospective aim, we did evaluate reviews of ADEs in our prospective aim by a pharmacist, nephrologists, and internal medicine physician. Because we found that these reviewers were able to reach consensus in reviews, we believe that additional reviewers of the retrospective alerts may produce similar results, despite the difference in content of the reviews. Our results also depend on implementations of numerous clinical systems. Implementation of solutions for many contributing factors to inappropriate alerts would require a CPOE system with integrated laboratory and coded EMR data, which are frequently difficult to

obtain and rarely accurate or complete.   Creating and managing a knowledge base with such alerting

criteria would also be challenging. Finally, because we completed our research in the clinical domain of

AKI, our results may also have limited generalizability.

CHAPTER VII

CONCLUSION

Through retrospective expert adjudication of medication-safety clinical decision support (CDS) alerts for acute kidney injury (AKI), we identified contributing factors to alert inappropriateness that could be used to improve alerting systems, including consideration of false laboratory values; documented indication, understanding of risk, and medication benefit; previously adjusted doses or interval; and therapeutic drug values. Evaluation of provider responses to the alerts found that most responses were appropriate, and inappropriate responses were most often true overrides; unintended adverse consequences rarely occurred. Additional research is necessary to further improve both CDS systems and resulting outcomes, and the framework we developed for evaluating alerts can support this research.

We developed, implemented, and evaluated the use of a real-time, web-based surveillance tool for AKI patients and CDS interactions with a randomized trial, where intervention patients were monitored daily by a clinical pharmacist and control patients received only existing CDS and standard of care. Despite interventions made by the study pharmacist from the surveillance tool, we found no statistically significant improvements in the timing of provider responses or in the occurrence or severity of adverse drug events or potential adverse drug events between control and intervention study groups. Though we established feasibility of real-time surveillance that incorporates CDS, further research is necessary to determine whether a larger sample size, a different clinical scenario with less prevalent or effective CDS, improved specificity of inclusion criteria that accounted for therapy that was already

appropriate or an alternate workflow that better matched the clinical scenario would have led to

positive findings, and to determine whether inclusion of the CDS benefits the surveillance.

APPENDIX A

INSTRUCTIONS AND PROTOCOL FOR ACUTE KIDNEY INJURY ALERT ADJUDICATION

I. Alert Appropriateness Scale

Definition: Adjudicator's determination of the appropriateness of the alert displayed for a patient-drug pair. Adjudication is made at the time that the alert was first displayed for each eligible medication order given the patient's serum creatinine compared to baseline. Serum creatinine measurements within 48 hours of the alert may be used to identify transient changes and lab errors. Drug indication and dosing is assumed to be appropriately determined by the providing team.

a. Alert Display Axis

    i. Should not display – response would be unacceptable

    ii. Should display – response would be acceptable

b. Alert Urgency Axis

    i. Response is expected within 48 hours of initial display

    ii. Response may be delayed greater than 48 hours after initial display

I. Contributing Factors to Inappropriate or Non-Urgent Alerts

Definition: Adjudicator's determination of patient, medication, or laboratory characteristics that may indicate that a patient-drug alert is inappropriate or not urgent. Determinations are made at the time that the alert was first displayed for each eligible medication order using resources available at that time.

c. Patient Characteristics

    i. Dialysis patient

      ii.   Transplant patient

      iii.   Palliative care patient

  d. Medication Characteristics

      i.   Dose already adjusted for AKI

      ii.   Dose is already low and for prophylaxis

      iii.   Drug levels are in therapeutic range

      iv.   Primary team has documented AKI risk and drug benefit

  e. Laboratory Characteristics

      i.   Transient AKI

      ii.   No AKI – lab error

      iii.   No AKI – drug interference with serum creatinine assay

      iv.   No AKI – insufficient change in GFR

I. Provider Response

Definition: Actual provider response and expected provider response by nephrologist to alerted medication, regardless of alert appropriateness or urgency. Determinations are made by first evaluating for responses made in the context of the final displayed alert (i.e. provider selected modify, discontinue, defer, correct dose). If alerts were continually deferred and no response was made through the alert, determinations are made by evaluating the patient's ordering history for a response made in a later ordering session, within 24 hours of the final displayed alert.

Type (Select all that apply) (Determined Electronically)

      i.   Provider did not respond (i.e. continued deferral)

      ii.   Provider selected "Correct Dose"

      iii.   Provider modified the drug dose

    iv.   Provider modified the drug interval

    v.   Provider discontinued the drug

    vi.   Provider monitored drug levels

    vii.   Provider monitored serum creatinine levels

    viii.   Provider monitored other levels

Timing (Determined Electronically)

    ix.   Provider did not respond

    x.   Provider responded immediately

    xi.   Provider responded within 24 hours

    xii.   Provider delayed response for > 24 hours

b.   Adjudication

    i.   Provider response was unacceptable

    ii.   Provider response was acceptable

c.   Expected Response Type (Select all that apply)

    i.   Provider should not have changed therapy

    Example: If dose is sufficiently low or already adjusted, no change is necessary.

    ii.   Provider should have modified the drug dose or interval

    iii.   Provider should have documented indication

    iv.   Provider should have discontinued the drug

    Example: Absolute contraindications should always be discontinued

    v.   Provider should have monitored drug levels

    Example: Drugs in which levels can be checked and used for monitor purposes

    should always have levels monitored

vi. Provider should have monitored serum creatinine levels

Example: Serum creatinine should always be monitored on a daily basis.

vii. Provider should have monitored other levels

INSTRUCTIONS FOR ADVERSE DRUG EVENT ADJUDICATION

I. Potential Adverse Drug Event (pADE)

    Definition: an incident with potential for injury related to a drug

    a. Type

        i.   Contraindicated use for > 24 hours

        ii.   No dose adjustment for > 24 hours

        iii. No interval adjustment for > 24 hours

        iv.   Ineffective at low CrCl

        v.   Administration error

        vi.   No drug level monitoring

        vii. No potassium monitoring

        viii. No creatinine monitoring

        ix.   No other monitoring

        x.   Other

I. Adverse Drug Event (ADE) or Lab-Only ADE (Intermediate Outcome)

    Definition: an injury resulting from a medical intervention related to a drug

    b. Preventability

        i.   Definitely preventable

        ii.   Probably preventable

        iii. Probably not preventable

  iv. Definitely not preventable

c. Lab-Only ADE Type

  i. Hyperkalemia (K > 5.3 mEQ/L)

  ii. Hypokalemia

  iii. Hypernatremia

  iv. Hyponatremia

  v. Toxic Drug Levels

  Examples:

   1. Vancomycin Trough < 10mg/dl or > 25mg/dl

   2. Amikacin Extended Interval Dosing Trough > 2mcg/ml OR Traditional Dosing Trough > 10mcg/ml

   3. Gentamicin/Tobramycin Extended Interval Dosing: Trough> 0.5mcg/ml OR Traditional Dosing: Trough > 2mcg/ml

   4. Digoxin > 1.7 ng/ml

   5. Lithium > 1.2 mmol/L

   6. Procainamide > 12 mcg/ml

  vi. Subtherapeutic Drug Levels

  vii. Hypoglycemia (Asymptomatic)

  viii. Other

d. ADE Type

  i. Bradyarrhythmia – Heart Rate < 60 beats/min OR Administration of Atropine with documented reason of bradycardia

ii. Hypotension – Systolic < 90mmHg OR Diastolic < 60mmHg OR MAP < 65mmHg OR Receipt of systemic vasopressor (Norepinephrine, Phenylephrine, Dopamine > 5mcg/kg/min, Epinephrine, Vasopressin)

iii. QT Prolongation – QTc interval on EKG > 440msec

iv. Cognitive Changes/Somnolence – CAM-ICU+ OR Documented Cognitive changes in chart

v. Delirium

vi. EPS/Movement Disorders

vii. Oversedation – RASS below daily set goal OR RASS < -3 (moderate sedation: Movement but no eye contact to voice) OR Receipt of Opiate antagonist or Flumazenil OR Documented oversedation in chart

viii. Seizure

ix. Rash

x. Hypoglycemia (Symptomatic) – < 70mg/dl OR Administration of D50W for documented symptoms OR <40mg/dl (severe)

xi. Pancreatitis – (N/V AND Amylase) AND/OR (Lipase > Upper limit of normal range AND chart documentation)

xii. Diarrhea

xiii. Anemia – Men: Hgb < 13g/dl; Women: Hgb < 12g/dl

xiv. Lactic Acidosis – Lactate >4mmol/L OR Lactate >5mmol/L + ABG pH< 7.35

xv. Major Bleed – Known or suspected Bleed site AND Hgb decrease >5 g/dl

xvi. Minor Bleed – Known Bleed site AND Hgb decrease > 3 g/dl but <5g/dl

xvii. Neutropenia – Platelets <150,000 cells/mm3 OR 50% decrease in Platelets from

admission

xviii. Thrombocytopenia

xix. Neuromuscular Control

xx. Vision Changes

xxi. Hearing Loss

xxii. Tinnitus

xxiii. Acute Kidney Injury

xxiv. Crystalurea

xxv. Renal Replacement Therapy

xxvi. Volume Overload

xxvii. Respiratory Depression

xxviii. Death

xxix. Other

e. Severity of pADE or ADE

Definition: this is the degree of patient harm that could be caused by the above pADE or

ADE

i. Significant: an error that can cause patient symptoms that, while harmful to the

patient, pose little or no threat to the patient's life function

Examples:

1. Dose of the drug with low therapeutic index is too high (i.e. ½ to 4x the

normal dose)

2. Dose is too low for a patient with the condition being treated

3. Wrong laboratory studies to monitor a specific side effect of the drug are ordered

4. The wrong route of administration for the condition being treated is ordered

ii. Serious: an error that can cause signs/symptoms that are associated with a serious level of risk that is not high enough to be life-threatening. In addition, it is serious if it can cause persistent alteration of daily function

Examples:

1. Route is inappropriate with the potential of causing a severe toxic reaction

2. Dose is too low for a patient with serious disease who is in acute distress

3. Dose with low therapeutic index is too high (i.e. four to ten times the normal dose)

4. Dose of the drug would result in serum drug levels in the toxic range

5. Drug could exacerbate the patient's condition (e.g. drug-drug interaction or drug-disease interaction)

iii. Life-threatening: an error that can cause signs/symptoms that if not treated would put the patient at risk of death

Examples:

1. Drug level is likely to be in the severe toxicity range based on common dosage guidelines

2. Drug order has a high potential to cause cardiopulmonary arrest or life-threatening adverse reaction (e.g. anaphylaxis)

3. Dose of potentially life-saving drug is too low for a patient having the disease treated

4. Dose of a drug with a very low therapeutic index is too high (i.e. 10x the normal dose)

iv. Fatal: an error that caused the patient's death

APPENDIX C

GREASEMONKEY SCRIPT FOR BLINDED STUDY PERSONNEL CHART REVIEW

```
// ==UserScript==

// @name           Hide Notes

// @namespace      http://dbmi.mc.vanderbilt.edu/

// @include        https://*.mc.vanderbilt.edu/cgi-bin/sp/*

// ==/UserScript==


unsafeWindow.hideAKINotes = function() {

    var s = document.getElementsByTagName('span');

    for (i = 0; i < s.length; i++) {

       if (s[i].getAttribute('styp') == 'Pharmacy Recommendation') {

          s[i].style.display="none";

          s[i].previousSibling.style.display="none";

       }

    }

}


var chart = document.getElementById('PC2');

if (chart != null) {

   chart.addEventListener('load', function() {
```

```javascript
var s = chart.contentDocument.getElementsByTagName('span');

for (i = 0; i < s.length; i++) {

    if (s[i].getAttribute('styp') == 'Pharmacy Recommendation') {

        s[i].style.display="none";

        s[i].previousSibling.style.display="none";

    }


    if (s[i].getAttribute('class') == 'Tab') {

        var oc = s[i].getAttribute('oc').replace(/"/g, "'");

        s[i].setAttribute('oc', oc + '; hideAKINotes();');

    }

  }

} , false);

}
```

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