Grant Final Report

Grant ID: 5R18HS017010

Surveillance for Adverse Drug Events in Ambulatory Pediatrics

Inclusive Dates: 09/01/07 – 02/28/11

Principal Investigators:
Thomas C Bailey (07/15/09 – 02/28/11)
Peter M. Kilbridge (09/01/07 – 07/14/09)

Team Members:
Laura A. Noirot
Richard M. Reichley
Kathleen M. Berchelmann
Courtney Schneider
Kevin M. Heard
Miranda Nelson
Karissa Burroughs
Susan Dusenberry
Michael Gysbers
Danielle Bartolomucci
Rakesh Nagarajan

Performing Organization:
Washington University School of Medicine

Project Officer:
Amy Helwig

Submitted to:
The Agency for Healthcare Research and Quality (AHRQ)
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Abstract

Purpose: The objective was to evaluate automated detection methods for adverse drug events (ADEs) in pediatric patients with sickle cell anemia, cystic fibrosis, and cancer in the ambulatory setting.

Scope: We developed an automated system for measuring the frequency of ADEs in pediatric patients with specific chronic diseases that result in the need for emergency department care or hospital admission.

Methods: A rule based expert system was used for discrete data, and a natural language processing method for text data. We determined the positive predictive value (PPV) of alerts based on these methods, and compared the sensitivity and PPV to manual chart review by an expert pharmacist.

Results: The automated system detected 156 ADEs in 1983 patients. The systems issued 726 unique signals for possible ADEs, for a positive predictive value (PPV) of 21.5%. A pharmacist reviewed the charts of a random sample of 392 patients. Compared to a composite gold standard, the sensitivity of the automated system was 43%, while the PPV was 16%. The chart review sensitivity was 86%, with a PPV of 59%. The automated method took 66.7 hours of pharmacist review time, whereas the chart review took 565 hours.

Key Words: Drug toxicityc, expert systems, pediatrics, sickle cell anemia, cystic fibrosis, neoplasms

Final Report

Purpose

The principal objective of the proposed work is to implement and evaluate information technology (IT) – based measures of the incidence of adverse drug events (ADEs) in pediatric patients with sickle cell anemia, cystic fibrosis, and cancer in the ambulatory setting, and during transitions in care to and from the ambulatory setting. We will employ several automated methods to accomplish this objective and to evaluate the success of the project. We will pursue this objective by addressing the following specific aims.

1. To implement an automated surveillance system for measuring the incidence of ADEs occurring in the outpatient setting (including the emergency department) in pediatric patients with specific chronic diseases, that result in the need for emergency department care or admission to the St. Louis Children's Hospital. For this Aim, we will use an event detection computer system, and will build upon our prior experience and existing expert systems for inpatient event detection.(1-4)

2. To utilize the automated surveillance system for measuring the incidence of ADEs occurring in these patient populations during the transition in care from outpatient to inpatient setting, e.g., originating during the admission process. For this Aim, we will employ a rules base similar to that which we have employed previously, (3) with modifications for pediatric patients.

3. To utilize the automated surveillance system for measuring the incidence of ADEs in the target pediatric populations within 4 weeks of discharge from SLCH. We will accomplish this using outpatient clinic-based information plus data generated by any other encounter (e.g., emergency department visit, rehospitalization, phone calls documented in clinic, etc.).

4. To evaluate the performance of the event detection system as employed in Aims 1-3. We will evaluate the performance of the system as determined by positive predictive value for ADE detection; assess the resource requirements for rule evaluation; and compare the overall sensitivity and specificity of the system with findings from focused chart review following implementation and refinement of the system.

Scope

Patient Population

We focused our investigation on populations of pediatric patients with specific chronic illnesses: sickle cell disease, cystic fibrosis, and cancer. There were several reasons for this. Children and patients with special healthcare needs are identified as priority populations for AHRQ-supported research under the Healthcare Research and Quality Act of 1999 (http://www.ahrq.gov/hrqa99a.htm). In addition, children with chronic illnesses constitute a significant portion of the population of children with special healthcare needs,(5;6) one of the 20 groups identified by the Institute of Medicine as priority areas for improvement in health care quality.(7) They constitute a population facing numerous challenges to effective management of care across the continuum, with particular challenges around medication management. These patients receive multiple medications in inpatient and outpatient settings, many of them potentially toxic, and are thus at significant risk for adverse drug events (ADEs). In addition, little is known about the incidence of ADEs and associated morbidity in these patients, and few practical methods exist for measuring and tracking these events. As an academic center with responsibility for large numbers of chronically ill children, we were well positioned to extend our existing expertise with informatics to the study of these patients, who receive virtually all of their outpatient care in our specialty clinics, and whose medical record data were accessible to us from ambulatory as well as inpatient settings.

Background and Significance

ADEs, defined as harm to patients by drugs,(8) comprise one of the largest categories of adverse events in studies examining the epidemiology of patient safety.(9-12) Measurement of ADEs was identified as critical patient safety metric in the Institute of Medicine's 2004 report on patient safety(12) and in their National Healthcare Quality Report. Measuring the incidence of ADEs in care environments is essential to (1) establish a baseline performance metric against which to measure improvement, (2) separate medication errors and system failures that result in harm to patients from the many that do not, and (3) accurately direct interventions toward preventing those failures that harm patients. Despite the extensive literature on medication safety, medication errors, and adverse drug events in adult populations, little is known about the frequency and nature of these events in children, and less is known about ADE incidence in children with chronic disease.

Adverse Drug Events in Ambulatory Care. Factors that affect medication safety – pediatric and adult – in the ambulatory environment are many and complex. They include: reliance on patients and families to understand and adhere to medication regimens; frequent use by patients of multiple providers; multiple and sometimes overlapping insurance and pharmacy benefit plans; use of multiple pharmacies; and numerous settings of care provision, often with poor communication of patient information across settings.

With so many opportunities for problems, it is not surprising that ADEs are a significant problem in outpatients. A number of studies have examined ADEs in adult ambulatory patients,

and estimates of event incidence vary significantly. Hutchinson et al (13) conducted detailed telephone interviews with 1026 internal medicine patients to estimate the frequency and severity of ADEs. They scored the reports for causality and found an overall incidence of 5% "probable" or "definite" ADEs. Darnell et al. conducted in-person interviews with elderly patients, and estimated an ADE incidence of 29.1%.(14) Gandhi employed a combination of telephone interviews and chart reviews to prospectively study ADEs in outpatients from four internal medicine practices; they reported 27 ADEs per 100 patients.(15) Chart review-based studies have reported various measures of the incidence of outpatient ADEs. One study employing surveillance of cause of injury in outpatient settings reported an average of 15 ADE related visits per 1000 population.(16) Using techniques similar to more recent "trigger"-type chart review methods, Schneider et al. at the University of Utah audited 463 adult outpatient charts from two hospital-based clinics and found documented adverse drug reactions in 21% of the patients.(17) Several groups have recently reported studies employing computer-based methods to detect ADEs in ambulatory patients. Using computerized surveillance methods, Honigman found an incidence of 5.5 ADEs per 100 patients cared for out of 15,665 patients seeking outpatient care.(18) Using a similar methodology, Gurwitz et al. studied over 30,000 older adults cared for under a single HMO, and reported an incidence of 50.1 ADEs per 1000 patient-years.(19)

ADEs occurring in the ambulatory setting are a well recognized cause of emergency department (ED) visits and hospitalizations. For example, one retrospective chart review of 13,004 ED records at an academic medical center ED found that 1.7% of encounters were due to ADEs; these patients had a higher probability of requiring hospitalization than matched controls.(20) In another study, Raschetti et al. found that 4.3% of visits to one hospital emergency room over one year were attributable to ADEs; 19% of these patients required hospitalization.(21) A large scale surveillance study by the National Electronic Injury Surveillance System-All Injury Program (NEISS-AIP) estimated that 2.5% of ED visits, and 6.7% of hospitalizations for unintentional injuries are due to ADEs.(22) In this study approximately 40% of ADEs were due to medications that require monitoring (e.g., blood levels, blood sugar, etc.) Others have estimated that 3-5% of all acute care admissions to general hospitals result from ADEs.(18;23-26) Consistent with these findings, in our previous work we have shown that ambulatory ADEs related to high-alert medications – particularly anticoagulants – are a frequent cause of hospitalization.(4) ADEs occur in patients while they are in the ED, resulting in requirement for hospitalization or increased length of ED stay, additional therapies, and other complications.(20) Most of the literature on in-ED ADEs has focused on strategies for error reduction, particularly in pediatric settings; (27-34) little has been reported on the incidence of ADEs originating in the ED.

Medication Safety during Transitions in Care. There is significant evidence that transitions in care, particularly between outpatient and inpatient settings, are high risk events from the point of view of medication safety. Upon admission to the hospital patients are exposed to additional risks associated with care – and information– transfer. Cornish et al.(35) examined unintended medication discrepancies upon hospital admission. Studying patients admitted to an internal medicine service who reported taking four or more medications at home, and comparing the patient's home medication list with the admission medication orders the authors found that 53.6% of patients had one or more unintended discrepancies, the most common of which was omission of a medication. They estimated that 32.9% of these discrepancies had the potential to cause moderate harm, and 5.7%, potential to cause severe harm. Discharge from the hospital

represents another high risk process for medication safety.(36) Providers may fail to restart outpatient medications that were discontinued on admission; medications started during hospitalization may be continued without adequate outpatient monitoring (e.g., oral anticoagulants); and communication failures between hospital and community providers may lead to duplicate or conflicting therapies. One study found that approximately 11% of patients suffered adverse drug events during the 4 weeks following discharge from the hospital.(37)

Pediatric Adverse Drug Events. Studies of pediatric ADEs have focused largely on adverse effects associated with specific medications(38) and immunizations;(39;40) and specific environments (e.g., non-operative procedural sedation).(41-44) Studies of hospitalized patients have used methodologies including voluntary reporting (45;46) and analysis of diagnostic and therapeutic codes;(47;48) neither of these methods yields a comprehensive analysis of patient care data.(49;50) A large collaborative recently reported a "trigger tool"-based chart review study of all types of adverse events in neonatal intensive care patients; however these investigators did not report the specific incidence of drug related events.(51)

Several investigators have taken more comprehensive approaches to data gathering and measurement of the incidence of medication-based harm to children. One study of pediatric inpatients utilizing chart review and voluntary reporting (52) measured medication errors and adverse events, and detected an overall rate of ADEs of 2.3 per 100 admissions, comparable to lower end estimates from studies of adult inpatients. (53-55) The NEISS-AIP study of ED visits for ADEs found that children aged 5 years and under had an estimated population rate of 4.3 ADE-related ED visits per 1000 population, or almost double the overall population rate.(22)

Another study examining adverse drug reactions (WHO definition: "an effect which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis and therapy; " excludes dosage error-related events) on a pediatric ward with a selected patient population (e.g., immunosuppression, cystic fibrosis, sickle cell anemia) found an overall rate of 21.5 ADRs per 100 admissions.(56)

There is also reason to suspect that harm due to medications in pediatrics may be under-recognized, or incorrectly attributed. Many medications have not been evaluated for safety in pediatric use and are routinely prescribed off label. In tertiary care settings in particular, pediatricians use medications with which there is little experience in children, and whose safety profile is thus even less well understood. The range of possible ADE types and offending drugs is therefore potentially greater in pediatrics than has been appreciated to date.(57)

Children with Chronic Disease: Medication Safety Challenges. Among children with chronic diseases ADEs may be as significant a source of harm in the ambulatory setting and during care transitions as in the adult population. In addition to their chronic medication burdens, they are subjected to the peculiar hazards associated with pediatric medication management. The requirement for weight-based dosing in most instances introduces an important opportunity for error. In some settings dose adjustments need to take into account, adjusting for gestational age, chronologic age, ideal weight, renal function, and/or body surface area.(58) In preparing medications for dispensing pediatric pharmacists frequently need to repackage adult preparations, thus adding more opportunities for errors to occur. Some of the medication safety challenges associated with three diseases are listed here.

Children with Chronic Disease: Medication Safety Challenges—Cystic Fibrosis. Most of these patients are receiving chronic therapy with such medications as nebulized tobramycin, Pulmozyme, hypertonic saline, and home therapy with intravenous aminoglycoside antibiotics. Comorbidities requiring therapy include diabetes, intestinal obstructive syndromes, hemoptysis, and heart failure. Well recognized ADEs in these patients include aminoglycoside-induced renal failure and high frequency hearing loss. While there is considerable literature demonstrating the benefits of many of these therapies, there are few data on the incidence and severity of such ADEs in CF patients.(59-61)

The Division of Pulmonary Medicine at St. Louis Children's Hospital follows approximately 300 patients with cystic fibrosis. The Division maintains its own database of these patients, and tracks numerous aspects of their care including medications, allergies, laboratory values, radiology studies, and medical problems. Clinic visits are documented via dictation plus structured data capture using this database; the clinic notes are stored in the BJC Healthcare clinical data repository.

Children with Chronic Disease: Medication Safety Challenges—Sickle Cell Disease. Patients with hemoglobin SS and SC disease take multiple medications in the ambulatory setting including hydroxyurea, antibiotics, non-steroidal anti-inflammatory agents (NSAIDS), narcotics, and others. Toxicities of these medications include myelosuppression due to hydroxyurea, oversedation due to narcotics, and renal disease due to NSAIDs. Narcotics overdoses occur in both inpatient and outpatient settings with some frequency due to clinician confusion around dosing parameters for hyromorphone versus morphine and oxycontin versus oxycodone. While these drug-related morbidities are well recognized, little is known about the actual incidence of ADEs in sickle cell patients.(62;63) The Hematology-Oncology Division at St. Louis Children's Hospital follows a stable population of approximately 425 patients with symptomatic sickle cell syndromes. Clinic visits are documented via dictation and the clinic notes are stored in the BJC clinical data repository.

Children with Chronic Disease: Medication Safety Challenges—Oncology. While there has been much research into improving the safety of chemotherapy there has been relatively little work demonstrating the frequency and nature of ADEs in oncology patients.(64) In part this is because of the well recognized toxicity inherent in many chemotherapy regimens and the consequent belief that ADEs in these patients are an unavoidable feature of therapy. However, greater knowledge and better medications to modify the side effects of antineoplastics have in recent years resulted in reductions in chemotherapy-induced morbidity, making it important to understand the degree to which medication-related harm to cancer patients is preventable. In addition, several studies have shown that many ADEs in cancer patients are due not to antineoplastic agents, but to other medication types such as sedatives and narcotics. Thus there is much room to improve our understanding of the frequency and nature of ADEs in pediatric cancer patients.

The Hematology-Oncology Division at St. Louis Children's Hospital follows a population of approximately 1000 patients with many different tumor types and stem cell transplants. Of these approximately 300 are receiving active treatment, and receive a wide variety of medications in the ambulatory setting, many toxic. The remainder are tracked in long term follow-up. The Division maintains a database containing data pertinent to the ongoing care of these patients;

clinic visits are documented via dictation and the clinic notes are stored in the BJC clinical data repository.

Automated Surveillance for Detection of ADEs. The power of automated surveillance methods for detecting adverse events, particularly ADEs, has become clear.(4;8;12;65-67) This methodology employs computer systems to analyze data collected in the normal course of patient care, looking for signals that suggest the occurrence of an ADE. Such signals range from detection of toxic serum medication levels and orders for antidotes to combinations of medication and laboratory data suggesting an evolving ADE. More complete descriptions of different surveillance systems and signal types may be found elsewhere.(26;65;66) In an evidence-based review of technologies for improving patient safety, AHRQ classified automated ADE surveillance as having a "high strength of evidence" for impact and effectiveness. (AHRQ Publication 01-E058 July 20, 2001) Such systems require a fraction of the resources of chart review,(66) utilize explicit detection criteria and methods for analysis, and unlike chart review, are capable of ongoing, comprehensive surveillance of a study population. Automated surveillance systems are able to detect far more adverse events – four to twenty-fold – compared with voluntary reporting systems, (4;65) and importantly, detect ADEs that are undetected by, and more serious than those detected by chart review. (66;68) The sensitivity of ADE surveillance can be greatly increased by incorporation of such methods as keyword and phrase identification in text documents, and use of diagnostic and therapeutic code data. (18;19;66;69)

Surveillance methods have been applied to studies of medication safety in adult ambulatory settings. Many of these same factors that make the ambulatory environment a complex one contribute to the challenges of studying medication safety in outpatients. With the exception of certain single payer-provider environments where all patient care data (clinical, financial, and demographic) is managed by a single organization,(19) it is extremely difficult to assemble a complete set of patient data to permit comprehensive, cross-continuum study.

In an important cohort study of older ambulatory patients, Gurwitz et al. examined ADEs in Medicare patients at a multispecialty group practice during a one year period using multiple methods, including review of discharge summaries and emergency department notes, provider event reports, computerized text key word scanning, and computerized signals (such as ICD-9 codes, drug levels, laboratory results, and antidote orders).(19) They found an overall ADE incidence of 5% per year in this population. An important element of their methodology was the establishment of associations between medications and terms describing specific adverse effects of the medication; this mapping served as the basis for automated free text scanning of the outpatient clinic notes for potential ADE signals. Among all methods used, this keyword scanning technique yielded the most ADEs (37%), followed by the computer-generated signals (29%).

This study underlines the need for an emphasis upon different data types and sources from those that prove most useful in the inpatient setting. There are several reasons for this. Laboratory monitoring of medications and physiologic function, while frequently occurring on a near-daily basis in the hospitalized patient, occurs far less frequently in the ambulatory setting. Thus, patients are more likely to present with symptoms suggestive of an ADE in the absence of supporting laboratory data; and they will frequently receive corrective therapy without laboratory information being obtained. The clinician may however document the associated signs and symptoms of the event in a text note. Specific antidotes are far less frequently administered in the outpatient setting than in the hospital; and rarely are both medication administration and

laboratory data available simultaneously in a fashion that permits combination drug-lab rules to be used. The Gurwitz study has important implications for the current proposal, as we plan to implement similar technologies for automated ADE detection in pediatric patients.

There is no published experience with the use of automated surveillance in pediatric populations, and building a pediatric-oriented automated surveillance system would require some adjustments to the methodologies used in adult populations. Surveillance systems implemented thus far utilize many signal detection algorithms that look for adverse events due to hazardous medications that are used heavily in adults, but much less frequently in children – such as anticoagulants and insulin. By contrast, pediatric ADEs may more commonly involve electrolyte solutions, antiinfectives, immunomodulating drugs and others.(56) In addition, it is likely that some categories of pediatric ADEs are not well recognized due to the relatively infrequent use of some agents in children.

Little is known about medication safety in pediatrics in general, and even less about the incidence of harm to children from medications in ambulatory settings and during transitions in care. We developed and implemented an automated surveillance-based system with which to measure the incidence of adverse drug events (ADEs) in pediatric patients with chronic illnesses occurring in the outpatient setting (including the emergency department) that require emergency care or hospital admission, and during transitions in care to and from the inpatient hospital setting.

Methods

The project was divided into a “validation period” and a “study period”. The validation period was conducted on inpatients due to the ready accessibility of data, while we simultaneously established outpatient data feeds in anticipation of the study period. The validation period provided an assessment of a wide range of rules executed by the automated system. This period was used to evaluate the positive predictive value (PPV) of rules, and the following summarizes our methods and findings for the validation period. Following this, we discuss the methods and findings of the study period.

Validation Period

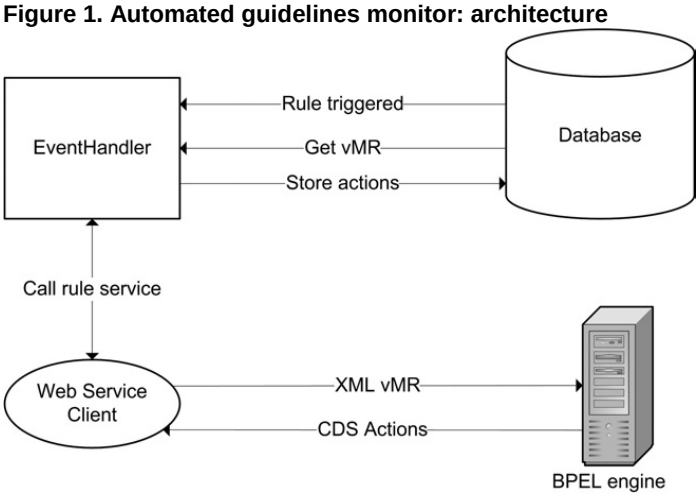
St Louis Children’s Hospital (SLCH) is a 250-bed hospital specializing in the care of acutely ill pediatric patients. The SLCH is a member of BJC HealthCare, a 13 hospital integrated delivery system headquartered in St Louis. The hospital has approximately 14,500 admissions annually, with an average length of stay of 3.4 days. The SLCH is the principal pediatric teaching hospital for the Washington University School of Medicine (WUSM), and is located with Barnes-Jewish Hospital on the WUSM-BJC academic medical center campus in St Louis. Our study population included all patients admitted between Feb 1 and Jul 31, 2008, with the exception of oncology patients, for reasons described below. The study was approved by Washington University School of Medicine’s Human Research Protection Office.

Building upon our previous work with expert systems,(70-72) we modified a rules-based computer program to perform real-time surveillance of patient data from SLCH clinical systems,

searching for combinations of demographic, encounter, laboratory and pharmacy data that suggest that an ADE may have occurred.

Data from SLCH systems is sent in near-real time by HL7 interfaces to a relational database. Triggers for rule evaluations are identified as data are stored in the database, which prompts our Automated Guideline Monitor (AGM) to evaluate these data against rules. The AGM manages the rule base and database queries in the following manner.(73) An application called event handler queries the database and constructs a Virtual Medical Record (VMR) for any patient on whom one or more rules have been triggered. The VMR is translated into an eXtensible Markup Language (XML) message and sent via HTTP to an open source Active BPEL (Business Process Execution Language) engine that employs Web services Business Process Execution Language (BPEL). The BPEL engine executes the given rule and returns a list of one or more clinical decision support actions (e.g., alert, no action, etc). Rules use XPath expression language, a W3C standard for extracting and evaluating XML data. This architecture is shown in Figure 1.

Figure 1. Automated guidelines monitor: architecture



Alerts generated by AGM are displayed on a Web-based user interface for evaluation by pharmacists. For the purposes of this study, the interface was modified to allow for two independent assessments and a final assessment interface for a third reviewer (PMK) that showed all alert details and the two independent assessments.

Our rule set was constructed based on our previous work in adult hospitals,(3) but expanded for the pediatric environment. Additional rules were included in an effort to detect certain ADEs that we suspect to be more common in the pediatric environment than in general hospitals, based on previous experience, event reports, and the frequency and use of different medication classes in our hospital. For example, we hypothesized that a rule for detecting seizures secondary to medications might be useful. Also, we suspected that medication-induced electrolyte abnormalities requiring intervention represent a common and potentially under-appreciated type of pediatric ADE. We altered our previous rule for insulin-induced hypoglycemia, requiring a glucose level of 40 mg/dL or less, in response to the large number of clinically insignificant values between 40 and 50 that we detected in our previous work. (4) We also tested a number of rules targeting medication-induced GI dysfunction. The rule set employed during the study period is shown in Figure 2.

Figure 2. The ADE surveillance rules

Rule Description
Amikacin > 35 Post
Anti-Xa laboratory test result > 2
Carbamazepine > 14
Clostridium difficile infection
Digoxin > 2.5
Flumazenil administered
Gentamicin > 40 and cystic fibrosis; gentamicin > 15 all other patients
Gentamicin trough > 3
Hepatotoxicity: elevated liver function test (2.5x ULN)
Hyperkalemia: potassium > 6.5 and age > 1 yr
Hyperphosphatemia: phosphorus > upper limit of normal
Hypocalcemia: calcium < 8.6 with drug cause
Hypoglycemia: glucose < 40 and insulin
Hypokalemia: potassium < 3
Hypomagnesemia: Mg^{2+} < 1.6
Hyponatremia: sodium < 135 with drug cause
Hypophosphatemia: phosphorus < lower limit of normal
INR > 4.5
Metabolic acidosis: anion gap > 11 with drug cause
Naloxone administered
Nephrotoxicity: (Scr 2× increase over past 2 days) or (Scientific Review > 1.5x ULN)
Neutropenia: ANC < lower limit of normal
Pancreatitis: elevated pancreatic enzymes (1.5x ULN)
Phenobarbital > 50
Phenytoin > 18 and <= 20 and albumin < 3.3
Phenytoin > 20
Seizures (as indicated by admin. Of lorazepam or diazepam)
Tacrolimus > 20
Thrombocytopenia (HIT): platelets > 100,000 with 50% decline from baseline
Tobramycin > 40 and cystic fibrosis; tobramycin > 15 all other patients
Tobramycin trough > 3
Vancomycin trough elevated > 25

ADE = adverse drug event; INR = international normalized ratio; ULN = upper limit of normal.

Using this “broad spectrum” rule set we anticipated a high level of false-positive alerts in our oncology population, due to the high incidence of well-recognized and currently unavoidable adverse events from antineoplastic medications. Therefore, for purposes of this initial validation investigation, we excluded all oncology patients from our data collection and subtracted their numbers from our admission and hospital-day data. Each of the two study pharmacists (CS, MN) independently reviewed all the resulting alerts using training and evaluation methodologies described previously.(3;4) To review current alerts, they accessed the system’s Web site approximately three times per week. The Web site displays all alerts fired by the system that have not yet been reviewed. Selecting an alert from the list displays the information screen containing information about the alert plus critical patient data, including current medication lists, relevant laboratory values, patient weight, and demographic data. The pharmacists had access to other online systems including the hospital pharmacy system and the enterprise clinical data repository to assist them in their evaluation of alerts. They examined every alert independently, reviewing the patient’s record to determine whether an ADE had occurred. Each alert was scored

for causality using the Naranjo algorithm for determining probability of causality;(74) events with causality scores 5 or higher (probable or definite ADEs) were then scored for severity using the NCC-MERP scoring system (http://www.nccmerp.org). They also recorded the responsible medications, and a narrative of the event. All pharmacist findings were then reviewed and adjudicated by a physician expert (PMK), whose evaluation served as the gold standard. Events scoring 5 or higher on the Naranjo scale (probable or definite causation), and with NCC-MERP scores of E or higher (indicating harm to the patient) were considered ADEs in this study.

Results for Validation Period. During the six month validation study period, 6,889 non-oncology patients were admitted to the St Louis Children's Hospital, generating 40,250 patient-days. The automated detection system generated 1226 alerts, and detected 160 true ADEs, representing 4 ADEs per 1,000 patient-days, or 2.3 ADEs per 100 admissions. One hundred thirty-five of the events represented temporary harm to the patient (NCC MERP score E); 20 patients suffered temporary harm that required prolonged hospitalization (F), 4 patients suffered permanent harm (G), and one patient died of multisystem disease complicated by drug-induced nephrotoxicity from gentamicin and vancomycin (I) (Table 1). The most common true positive alerts were hypokalemia (66), hypomagnesemia (19), nephrotoxicity (18), and naloxone administration (9). The medications most frequently implicated were diuretics, antibiotics, immunosuppressants, narcotics, and anticonvulsants.

Table 1. ADEs and severity by rule

Rule	E	F	G	I	Total
Hypokalemia	64	2			66
Hypomagnesemia	19				19
Nephrotoxicity	13	2	2	1	18
Naloxone administered	9				9
Hepatotoxicity	7		2		9
C. difficile infection	5	2			7
INR > 4.5	4	1			5
Vancomycin trough elevated	3	2			5
Carbamazepine > 14		4			4
Phenytoin > 20	1	2			3
Digoxin > 2.5	1	1			2
Phenobarbital > 50	1	1			2
Flumazenil administered		2			2
Neutropenia	2				2
Hyperkalemia	1	1			2
Hypoglycemia	1				1
Metabolic acidosis	1				1
Hypophosphatemia	1				1
Tobramycin trough elevated	1				1
Tacrolimus > 20	1				1
Total	135	20	4	1	160

ADE = adverse drug event; INR = international normalized ratio.

The ADEs and Severity by Rule. The average age of patients suffering ADEs was 6.3 years, compared with an average age of 6.8 years for all nononcology patients admitted during this period. The greatest number of ADEs occurred in the hospital's critical care units, with 56 (35%) in cardiac intensive care, 43 (27%) in general pediatric intensive care, and 12 (7.5%) in newborn intensive care. The composite positive predictive value (PPV) of the rule set (e.g., total # ADEs/total # alerts) was 13%; PPV ranged from 100% to 0 (Table 2). Only three of the 160 ADEs were reported by clinicians through our hospital's voluntary reporting system.

Table 2. ADE rules: positive predictive value (rules with no ADEs not listed)

Rule Description	ADEs	Alerts	PPV
Carbamazepine > 14	4	4	1.00
Digoxin > 2.5	2	2	1.00
Flumazenil administered	2	2	1.00
Hypoglycemia: glucose < 40 and insulin	1	1	1.00
Naloxone administered	9	14	0.64
Clostridium difficile infection	7	14	0.50
Phenobarbital > 50	2	6	0.33
INR > 4.5	5	16	0.31
Hypokalemia: potassium < 3	66	223	0.30
Tacrolimus > 20	1	4	0.25
Tobramycin trough > 3	1	4	0.25
Hypomagnesemia: Mg^{2+} < 1.6	19	80	0.24
Vancomycin trough elevated	5	24	0.21
Phenytoin > 20	3	17	0.18
Nephrotoxicity: (Scr 2× increase over past 2 days) or (Scientific Review > 1.5x ULN)	18	149	0.12
Metabolic acidosis: anion gap > 11 with drug cause	1	9	0.11
Hyperkalemia: potassium > 6.5 and age > 1 yr	2	25	0.08
Hepatotoxicity: elevated liver function test (2.5x ULN)	9	159	0.06
Neutropenia: ANC < lower limit of normal	2	67	0.03
Hypophosphatemia: phosphorus < lower limit of normal	1	85	0.01

ADE = adverse drug event; INR = international normalized ratio; ULN = upper level of normal.

The ADE Rules: Positive Predictive Value. The study pharmacists were able to evaluate most (80%) of the alerts using just the information available on the Web page. A minority of alerts required them to refer to other online systems (pharmacy system, clinical data repository); only occasionally was it necessary to examine the patient's paper chart. The pharmacists spent an average of 7 hours per week each evaluating the alerts.

Discussion for Validation Period. The rate of ADEs detected in validation period study is comparable to that found in pediatric inpatients by Kaushal et al.(75) using manual chart review. It is roughly half the rate that we detected in adults in a general hospital with similar methods and a more limited rule set;(4) however, it is 50% higher than the rate detected in pediatric patients by others using the limited rule set.(76) Seventy percent of ADEs occurred in critical

care units, presumably due to the higher per-patient use of hazardous medications in these settings. The average age of patients affected was similar to that of the overall patient population. The nature of ADEs that we found, however, differs from previous studies in several ways. The proportion of ADEs due to electrolyte-wasting medications (diuretics, antimicrobials, antirejection drugs) is significant. We believe that this represents an important observation, as drug-induced electrolyte depletion severe enough to result in total body deficits requiring intervention qualify as temporary harm, and if not carefully managed can have serious consequences in pediatric patients.

We found few ADEs due to anticoagulation or insulin. This is not surprising given the relatively infrequent use of these medications in pediatrics compared with adult populations. We also found fewer incidences of C. difficile colitis than in our previous work;(4) this may reflect better infection control practices, or other unknown factors. Some of our new "experimental" rules for detection of drug-induced seizures, pancreatitis, and hyponatremia proved to be of no value; they generated 216 false-positive alerts and no true ADEs.

We detected no instances of true heparin-induced thrombocytopenia (HIT) during the study period, despite generating 82 alerts from this rule. This is consistent with literature suggesting HIT is less common in children than in adults.(77;78) We also found that one group of previously useful "traditional" rules, those for elevated aminoglycoside levels, were less useful in our population, detecting only one ADE during the study period. It may be that in the current era of routine pharmacokinetic monitoring of these agents, as practiced at our hospital, these rules will be of less value. Similarly, as many young children carry C. difficile and have clinically insignificant C. difficile toxin in their stool, a positive C. difficile toxin test does not always denote antibiotic-associated colitis. In this study, 50% of patients with positive C. difficile toxin tests suffered ADEs.

Conclusions for the Validation Period. Automated surveillance for ADEs detects harm from medications in pediatric inpatients, and the nature of ADE types in children may differ significantly from adults. Consistent with previous studies, only a tiny fraction of the ADEs detected by automated surveillance were detected by voluntary reporting. There were several limitations to this validation period study. The intentional exclusion of oncology patients deprived us of information about ADE rates in this high risk population. An inherent limitation of automated surveillance is that the number and types of ADEs that can be detected is limited by the range of data types available to the rule engine.

Study Period

1983 patients under age 21 with sickle cell disease, cancer or cystic fibrosis with at least one admission to SLCH hospital, ER or outpatient clinics between November 1, 2008 and May 16, 2009 were included in the study population. 83% of patients were in the study for all study days (all 6 months).

Table 3. Study period demographics

Race	Sex : F	Sex: M	Grand Total
Asian	6	5	11
Black	269	303	572
Caucasian	675	705	1380
Hispanic	5	14	19
Native American	1		1
Grand Total	**956**	**1027**	**1983**

Methods for Study Period. Following the validation period of the study described above, all rules with a PPV lower the 5% were eliminated or modified with the goal of striking a better balance between review effort and ADE detection. We also incorporated a natural language processing component into the detection system, enabling us to search discharge summaries, inpatient consult notes, nursing documentation, and other narrative sources for words and phrases suggestive of ADEs. We adapted Cancer Text Information Extraction System (caTIES), a publicly available natural language processing tool (NLP). All inpatient and outpatient text documents for the study population were encoded for the following UMLS concepts and their associated synonyms: oversedation, diarrhea, drug fever, hemorrhage, oto-toxicity, gingival hyperplasia, interstitial nephritis, itching/pruritis, neurologic tremor, prolonged QTc interval, rhadomyolysis, serum sickness, cataract, severe allergic reaction, and generalized ADE. Each automated system alert was independently reviewed by two pharmacists who were blinded to the other's assessments which included a Naranjo causality score and National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) severity classification. A physician reviewer (PMK) resolved differences between the two reviewers. An ADE was defined as NCCMERP classification of "E" or higher with Naranjo score >=5.

Alerts and ADEs can be described as duplicates of another alert or ADE, indicating that the same criteria was met more than once. The NLP rule category called "NLP – General Adverse Event" could potentially overlap with all other rules. The criteria for this rule had terms including "adverse drug event", "adverse drug reaction", "adverse drug effect", "drug reaction", "drug side effects". Due to the potential overlap, we excluded this rule from some analyses. In addition, there were incidental ADEs discovered during the process of reviewing records prompted by the alerts, which we also excluded from many analyses. For the oncology patient population, we excluded the well described and often unavoidable adverse effects of chemotherapeutic agents (e.g. neutropenia, elevated LFTs, and nausea/vomiting). It was determined prior to initiation of the study that we would not include these types of ADEs since they are accepted risks in that patient population.

Results

The demographics for the 1983 patients included in the study are shown in Table 3. There were 1871 alerts among 457 patients in this study population. Table 4 depicts these alerts and adjudicated ADE assessments.

Table 4. Automated system results

	# Alerts	# ADEs	# NLP Invalid	# No ADE	#Patients
All	1871	291	684	896	457
w/o duplicates	1287	156	561	570	456
Excluding incidental & General ADE	1621	237	524	860	429
Excluding incidental, General ADE & duplicates	1076	117	417	542	427

Unique Signal Results for the Automated System

In order to look at the automated system's ability to detect a unique signal, the performance with invalid alerts and duplicate alerts were excluded. In this analysis, the automated system issued 726 unique signals. Of these, 156 were determined to be ADEs, for a PPV of 21%. Table 5 depicts the automated system rules, the number of unique signals associated with each rule, the number of adverse drug events detected, and the corresponding PPV.

Table 5. Automated system signals by rule

Rule Description	No ADE	ADE	Signals	PPV
Hypoglycemia: Glucose < 40 and insulin		3	3	1.00
Naloxone Administered		2	2	1.00
NLP - Gingival hyperplasia (phenytoin)		2	2	1.00
User Entered Adverse Drug Event (Incidentals)	2	24	26	0.92
Hypophosphatemia: Phosphorus < lower limit of normal with drug cause	1	1	2	0.50
Hypomagnesemia: Mg++ < 1.6	31	30	61	0.49
Clostridium difficile infection	3	2	5	0.40
NLP - General Adverse Drug Events	26	15	41	0.37
NLP - Allergic or Infusion Reaction	13	6	19	0.32
Nephrotoxicity: (Scr 2x increase over past 2 days) or (Scr > 1.5x ULN)	12	4	16	0.25
Hypokalemia: Potassium < 3	45	14	59	0.24
Vancomycin trough elevated	7	2	9	0.22
NLP - Itching / Pruritis	71	16	87	0.18
NLP – Ototoxicity	16	3	19	0.16
NLP – Diarrhea	144	20	164	0.12
NLP - Altered mental status	101	9	110	0.08
NLP - Excessive anticoagulation	25	2	27	0.07
NLP - Neurologic (tremors)	15	1	16	0.06
Anti-Xa lab test result > 2	1		1	0.00
Cyclosporine > 600	2		2	0.00
Hyperkalemia: (Potassium > 6.5 or kayexalate ordered) and Age > 1 yr	6		6	0.00
Hypocalcemia: Calcium < 8.6 with drug cause	2		2	0.00
Neutropenia: ANC < lower limit of normal	7		7	0.00
NLP – Cataract	4		4	0.00
NLP - GI bleed	12		12	0.00
NLP - Interstitial nephritis	3		3	0.00
NLP - Prolonged QTc	4		4	0.00
PTT > 100sec X2 consecutive results within 24hr period	3		3	0.00
Tacrolimus > 20	12		12	0.00
Tobramycin trough > 3	1		1	0.00
Vancomycin > 60 POST	1		1	0.00
Grand Total	570	156	726	

Rule Type

Table 6 depicts unique signals by discrete vs NLP rule types. Incidental signals were those that happened to be detected by the pharmacist when they were prompted by a rule based alert to do a chart review.

Table 6. Unique signals by discrete vs. NLP rule types

Alert Type	No ADE	ADE	Signals	PPV
Discrete	134	58	192	0.30
NLP	434	74	508	0.15
Incidentals	2	24	26	0.92
Grand Total	570	156	726	

Patient Condition

Because it was possible for one patient to be represented in more than one patient condition, Table 7 describes patient condition with multiple condition categories listed. For example, if a patient had Malignancy and Cystic Fibrosis, he/she would be counted once.

Table 7. ADEs by patient condition

Condition Type	No ADE	ADE	Signals	PPV
Malignancy Cystic Fibrosis	15	6	21	0.29
Cystic Fibrosis	98	31	129	0.24
Malignancy	356	98	454	0.22
Sickle Cell Disease	84	18	102	0.18
Malignancy Sickle Cell Disease	15	3	18	0.17
Cystic Fibrosis Sickle Cell Disease	2	0	2	0.00
Grand Total	570	156	726	

Origin of Adverse Event

Table 8. ADEs by location of origin

Origin of Adverse Event	ADE Count	% of Total
Inpatient (no transition)	76	48.7%
Outpatient (detected in ED, Clinic, or Hospital)	72	46.2%
ED	8	5.1%
Grand Total	156	

Since the completion of the study, several ADE surveillance rules have been implemented across all BJC hospitals for adults and for pediatrics, with some modifications from the study rules to accommodate other hospitals' available data and preferences. The rules that were implemented are in table 9 below.

Table 9. ADE Surveillance rules implemented across BJC Healthcare

Rule Description
{Kayexalate and K > 6.0} OR {K > 6.5 and drug}
Digoxin level > 2 or Digibind
Flumazenil ordered
Glucose < 40 and hypoglycemic agent
INR > 5 with Vitamin K or INR > 6
Naloxone ordered
Nephrotoxin with rising SCr

Chart Review

The final Aim of the study was to compare the performance of the automated system to manual chart review. However, since neither the automated system nor chart review represent a 'perfect' standard we have analyzed performance (PPV, sensitivity) of the automated system and chart review methods as compared to a consensus gold standard. Secondarily, we determined the amount of effort involved with both systems.

Population

Based upon the validation period study, we estimated an overall annual ADE incidence of 15.7 per 100 patients per year for our study population. We determined a sample of 392 patients would provide an ADE incidence of 15.7 +/-3.2 with 95% confidence. The sample was randomly selected from the study population, stratified by patient condition. Demographics for the chart review population are included in Tables 10 and 11.

Table 10. Demographics for the chart review

Race	Female	Male	Total
Asian	1	1	2
Black	57	52	109
Caucasian	135	142	277
Hispanic	1	3	4
Grand Total	**194**	**198**	**392**

Table 11. Patient conditions for the chart review

Patient Condition	
Cystic Fibrosis	67
Malignancy	241
Malignancy Sickle Cell Disease	9
Sickle Cell Disease	75
Grand Total	**392**

Methods for Chart Review

A study pharmacist (KB) who was blinded to the assessments of the automated system used a trigger tool to screen the selected patients' charts. The criteria in the trigger tool matched the criteria used by the automated system. The identified ADEs were manually matched to the automated system, when a match could be found, by a separate study pharmacist (RR). All ADEs found by the chart review but not by the automated system were reviewed by a study physician (PK). ADEs found by the automated system had been previously reviewed as described above.

Results for Chart Review

For the automated system and chart review, there were 42 ADEs found in this sample of patients. There were 12 ADE's found by both methods, 6 ADE's found only by the automated system, and 24 ADEs were found only by chart review (shown in the Figure). Overall, chart review found 36 ADEs and the automated system found 18 ADEs.

Figure 3. ADEs found by the automated system versus chart review

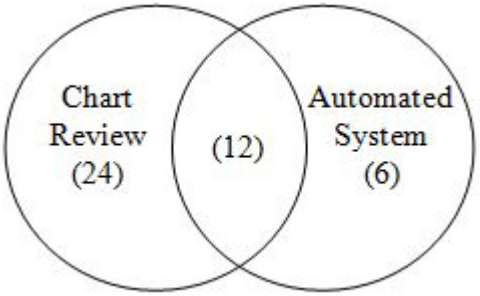


Table 12. Summary table of Sensitivity and PPV

Table 12a.

	Automated System Signals versus Gold Standard – All Rules	Chart Review versus Gold Standard – All Rules
Sensitivity	43%	86%
PPV	16%	59%

Table 12b.

	Automated System Signals versus Gold Standard – Discrete Rules	Chart Review versus Gold Standard – Discrete Rules
Sensitivity	71%	79%
PPV	26%	42%

Table 12c.

	Automated System Signals versus Gold Standard – NLP Rules	Chart Review versus Gold Standard – NLP Rules
Sensitivity	29%	89%
PPV	11%	71%

Automated System Signals versus Gold Standard

Comparison of the automated system's PharmD & MD assessments compared to a combination of the PharmD & MD assessment for both the automated system and chart review.

In order to assess signals, NLP Invalid alerts and duplicate alerts are excluded. In order to accurately compare the automated system to chart review, incidental alerts and ADEs and NLP-General Adverse Drug event alerts and ADEs are excluded. This produces the following results:

Table 13. Automated system with PharmD & MD assessment

	Gold Standard*: Combination of automated system & chart review PharmD & MD assessments **+**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **-**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **Totals**
Automated system With PharmD & MD assessment: **+**	18	95	113
Automated system With PharmD & MD assessment: **-**	24		
Automated system With PharmD & MD assessment: **Totals**	42		

Sensitivity=18/42=0.43
PPV =18/113=0.16

Table 14. Automated system signals versus gold standard for discrete rules

	Gold Standard*: Combination of automated system & chart review PharmD & MD assessments **+**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **-**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **Totals**
Automated system With PharmD & MD assessment: **+**	10	29	39
Automated system With PharmD & MD assessment: **-**	4		
Automated system With PharmD & MD assessment: **Totals**	14		

Sensitivity=10/14=0.71
PPV =10/39=0.26

Table 15. Automated system signals versus gold standard for NLP rules

	Gold Standard*: Combination of automated system & chart review PharmD & MD assessments **+**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **-**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **Totals**
Automated system With PharmD & MD assessment: **+**	8	66	74
Automated system With PharmD & MD assessment: **-**	20		
Automated system With PharmD & MD assessment: **Totals**	28		

Sensitivity=8/28=0.29
PPV =8/74=0.11

Chart Review PharmD Assessment vs Gold Standard

Chart review PharmD assessment compared to a combination of the PharmD & MD assessment for both the automated system and chart review.

In order to assess signals (versus alerts), NLP Invalid alerts and duplicate alerts are excluded. In order to accurately compare the automated system to chart review, incidental alerts and ADEs and NLP-General Adverse Drug event alerts and ADEs are excluded. This produces the following results:

Table 16. Chart review PharmD assessment

	Gold Standard*: Combination of automated system & chart review PharmD & MD assessments **+**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **-**	Gold Standard: Combination of automated system & chart review PharmD & MD assessments **Totals**
Chart Review PharmD assessment: **+**	36	25	61
Chart Review PharmD assessment: **-**	6		
Chart Review PharmD assessment: **Totals**	42		

Sensitivity=36/42=0.86
PPV =36/61=0.59

The Amount of Effort Involved with Each System

Our study found that it took an average of 1.43 hours for a chart review and 10 minutes / trigger for the automated system. For the chart review sample of patients, the automated method took a total review time of 66.7 hours whereas the chart review took 565 hours.

Of the 24 ADEs that the automated system missed, below is a table that summarizes the reasons.

Table 17. Summary

Reasons Automated System missed Chart Review ADEs	Count	%
Allergy Lists and search term of 'rash' (in documents) and/or use of Benadryl or Nubain were excluded from the automated system rules because they created too many false positives during the validation period.	12	50.00%
Handwritten/scanned notes not available to automated system	6	25.00%
Outpatient lab data, not available to automated system	3	12.50%
Missing POC Glucose labs	1	4.17%
"fogginess" and "dizziness" not included in NLP trigger terms.	1	4.17%
Ambulance note not available to automated system.	1	4.17%
Grand Total	**24**	**100.00%**

For the 6 ADEs that chart review missed, we verified that the information existed in the electronic patient chart.

Overall Conclusions

Our study documented a high rate of ADEs in pediatric patients with sickle cell disease, cystic fibrosis, or cancer. By definition in this study, these ADEs resulted in harm to patients, and were associated with a high degree of causality with the associated drugs. Nearly 50% of these ADEs originated in the outpatient setting. Because neither the automated system nor the manual chart review represent a gold standard for judging performance characteristics of either method for detecting these ADEs, an adjudicated composite of the automated system and manual chart review was constructed to serve as the gold standard. Compared to this gold standard, the PPV of automated system signals for ADEs, as defined in this study, in a random sample of study population patients, was16% and the sensitivity was 43%. The automated system consisted of two types of rules: those based upon discrete data, and those based upon text data (NLP). When looked at separately, these rules had differing PPV and sensitivity. The PPV for discrete data rules was 26%, while the sensitivity was 71%. On the other hand, the PPV for NLP rules was 11%, and the sensitivity was 29%.

As expected, a highly trained expert study pharmacist using chart review outperformed the automated system. Chart review had a positive predictive value of 59%, and a sensitivity of 86% However, while chart review had a higher positive predictive value, and was more sensitive than the automated system, it took nearly eight times as long to perform a chart review when compared to the automated system. Further, the reasons for ADEs being missed by the automated system indicate that nearly half were discovered in documentation that was not available to the automated system, and half were the result of rashes that were detected by the

chart review, but rules for detecting these were eliminated from the automated system because of poor PPV. There was no difference in the level of harm in ADEs found by the automated system vs manual chart review (data not shown). Both the automated system and manual chart review outperform voluntary reporting systems for ADE surveillance. Thus, automated detection of ADEs represents an efficient and feasible means of detecting ADEs in high risk pediatric populations in both the inpatient and outpatient settings that would otherwise go undetected in the absence of labor intensive chart review.

Reference List

1. Bailey TC, Noirot LA, Christensen EM, Milligan PE, Kimmel NL, Fraser VJ et al. Validation of automated event triggers using laboratory values related to two problem-prone drugs. *AMIA Annu Symp Proc* 2003;781.

2. Huang C, Noirot LA, Reichley RM, Bouselli DA, Dunagan WC, Bailey TC. Automatic detection of spironolactone - related adverse drug events. *AMIA Annu Symp Proc* 2005;989.

3. Kilbridge P. Implementation of a System for Computerized Adverse Drug Event Surveillance and Intervention at an Academic Medical Center. *Journal of Clinical Outcomes Management (JCOM)* 2006; 13(2):94-100.

4. Kilbridge PM, Campbell UC, Cozart HB, Mojarrad MG. Automated surveillance for adverse drug events at a community hospital and an academic medical center. *J Am Med Inform Assoc* 2006; 13(4):372-377.

5. Newacheck PW, Strickland B, Shonkoff JP, Perrin JM, McPherson M, McManus M et al. An epidemiologic profile of children with special health care needs. *Pediatrics* 1998; 102(1 Pt 1):117-123.

6. McPherson M, Arango P, Fox H, Lauver C, McManus M, Newacheck PW et al. A new definition of children with special health care needs. *Pediatrics* 1998; 102(1 Pt 1):137-140.

7. Karen Adams and Janet M.Corrigan e. *Priority Areas for National Action: Transforming Health Care Quality*. National Academies Press; 2003.

8. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care* 2004; 13(4):306-314.

9. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324(6):377-384.

10. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care* 2000; 38(3):261-271.

11. Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ* 2004; 170(11):1678-1686.

12. Aspden P, Corrigan JM, Wolcott J, Erickson SM. *Patient safety: Achieving a new standard for care*. Washington, DC: The National Academies Press; 2004.

13. Hutchinson TA, Flegel KM, Kramer MS, Leduc DG, Kong HH. Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective study. *J Chronic Dis* 1986; 39(7):533-542.

14. Darnell JC, Murray MD, Martz BL, Weinberger M. Medication use by ambulatory elderly. An in-home survey. *J Am Geriatr Soc* 1986; 34(1):1-4.

15. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E et al. Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348(16):1556-1564.

16. Zhan C, Arispe I, Kelley E, Ding T, Burt CW, Shinogle J et al. Ambulatory care visits for treating adverse drug effects in the United States, 1995-2001. *Jt Comm J Qual Patient Saf* 2005; 31(7):372-378.

17. Schneider JK, Mion LC, Frengley JD. Adverse drug reactions in an elderly outpatient population. *Am J Hosp Pharm* 1992; 49(1):90-96.

18. Honigman B, Lee J, Rothschild J, Light P, Pulling RM, Yu T et al. Using computerized data to identify adverse drug events in outpatients. *J Am Med Inform Assoc* 2001; 8(3):254-266.

19. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 289(9):1107-1116.

20. Hafner JW, Jr., Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med* 2002; 39(3):258-267.

21. Raschetti R, Morgutti M, Menniti-Ippolito F, Belisari A, Rossignoli A, Longhini P et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. *Eur J Clin Pharmacol* 1999; 54(12):959-963.

22. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006; 296(15):1858-1866.

23. Caranasos GJ, Stewart RB, Cluff LE. Drug-induced illness leading to hospitalization. *JAMA* 1974; 228(6):713-717.

24. Miller RR. Hospital admissions due to adverse drug reactions. A report from the Boston Collaborative Drug Surveillance Program. *Arch Intern Med* 1974; 134(2):219-223.

25. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329(7456):15-19.

26. Jha AK, Kuperman GJ, Rittenberg E, Teich JM, Bates DW. Identifying hospital admissions due to adverse drug events using a computer-based monitor. *Pharmacoepidemiol Drug Saf* 2001; 10(2):113-119.

27. Kozer E, Scolnik D, Macpherson A, Keays T, Shi K, Luk T et al. Variables associated with medication errors in pediatric emergency medicine. *Pediatrics* 2002; 110(4):737-742.

28. Kozer E, Seto W, Verjee Z, Parshuram C, Khattak S, Koren G et al. Prospective observational study on the incidence of medication errors during simulated resuscitation in a paediatric emergency department. *BMJ* 2004; 329(7478):1321.

29. Croskerry P, Shapiro M, Campbell S, LeBlanc C, Sinclair D, Wren P et al. Profiles in patient safety: medication errors in the emergency department. *Acad Emerg Med* 2004; 11(3):289-299.

30. Peth HA, Jr. Medication errors in the emergency department: a systems approach to minimizing risk. *Emerg Med Clin North Am* 2003; 21(1):141-158.

31. Bizovi KE, Beckley BE, McDade MC, Adams AL, Lowe RA, Zechnich AD et al. The effect of computer-assisted prescription writing on emergency department prescription errors. *Acad Emerg Med* 2002; 9(11):1168-1175.

32. Kozer E, Scolnik D, Macpherson A, Rauchwerger D, Koren G. The effect of a short tutorial on the incidence of prescribing errors in pediatric emergency care. *Can J Clin Pharmacol* 2006; 13(3):e285-e291.

33. Kozer E, Scolnik D, Macpherson A, Rauchwerger D, Koren G. Using a preprinted order sheet to reduce prescription errors in a pediatric emergency department: a randomized, controlled trial. *Pediatrics* 2005; 116(6):1299-1302.

34. Taylor BL, Selbst SM, Shah AE. Prescription writing errors in the pediatric emergency department. *Pediatr Emerg Care* 2005; 21(12):822-827.

35. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN et al. Unintended medication discrepancies at the time of hospital admission. *Arch Intern Med* 2005; 165(4):424-429.

36. Triller DM, Clause SL, Hamilton RA. Risk of adverse drug events by patient destination after hospital discharge. *Am J Health Syst Pharm* 2005; 62(18):1883-1889.

37. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. Adverse drug events occurring following hospital discharge. *J Gen Intern Med* 2005; 20(4):317-323.

38. Carroll MC, Yueng-Yue KA, Esterly NB, Drolet BA. Drug-induced hypersensitivity syndrome in pediatric patients. *Pediatrics* 2001; 108(2):485-492.

39. Abramson JS, Baker CJ, Fisher MC, Gerber MA, Meissner HC, Murray DL et al. Possible association of intussusception with rotavirus vaccination. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics* 1999; 104(3 Pt 1):575.

40. McPhillips HA, Davis RL, Marcuse EK, Taylor JA. The rotavirus vaccine's withdrawal and physicians' trust in vaccine safety mechanisms. *Arch Pediatr Adolesc Med* 2001; 155(9):1051-1056.

41. Cravero JP, Blike GT, Beach M, Gallagher SM, Hertzog JH, Havidich JE et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. *Pediatrics* 2006; 118(3):1087-1096.

42. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. *Acad Emerg Med* 2005; 12(6):508-513.

43. Hoffman GM, Nowakowski R, Troshynski TJ, Berens RJ, Weisman SJ. Risk reduction in pediatric procedural sedation by application of an American Academy of Pediatrics/American Society of Anesthesiologists process model. *Pediatrics* 2002; 109(2):236-243.

44. Cote CJ, Notterman DA, Karl HW, Weinberg JA, McCloskey C. Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. *Pediatrics* 2000; 105(4 Pt 1):805-814.

45. Upperman JS, Staley P, Friend K, Neches W, Kazimer D, Benes J et al. The impact of hospitalwide computerized physician order entry on medical errors in a pediatric hospital. *J Pediatr Surg* 2005; 40(1):57-59.

46. Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ. Reported adverse drug events in infants and children under 2 years of age. *Pediatrics* 2002; 110(5):e53.

47. Miller MR, Elixhauser A, Zhan C. Patient safety events during pediatric hospitalizations. *Pediatrics* 2003; 111(6 Pt 1):1358-1366.

48. Miller MR, Zhan C. Pediatric patient safety in hospitals: a national picture in 2000. *Pediatrics* 2004; 113(6):1741-1746.

49. Cullen DJ, Bates DW, Small SD, Cooper JB, Nemeskal AR, Leape LL. The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Jt Comm J Qual Improv* 1995; 21(10):541-548.

50. Weingart SN, Iezzoni LI. Looking for medical injuries where the light is bright. *JAMA* 2003; 290(14):1917-1919.

51. Sharek PJ, Horbar JD, Mason W, Bisarya H, Thurm CW, Suresh G et al. Adverse events in the neonatal intensive care unit: development, testing, and findings of an NICU-focused trigger tool to identify harm in North American NICUs. *Pediatrics* 2006; 118(4):1332-1340.

52. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001; 285(16):2114-2120.

53. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991; 266(20):2847-2851.

54. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. *Arch Intern Med* 2005; 165(10):1111-1116.

55. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; 5(3):305-314.

56. Weiss J, Krebs S, Hoffmann C, Werner U, Neubert A, Brune K et al. Survey of adverse drug reactions on a pediatric ward: a strategy for early and detailed detection. *Pediatrics* 2002; 110(2 Pt 1):254-257.

57. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. *Pediatrics* 2006; 118(2):555-562.

58. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349(12):1157-1167.

59. Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med* 1996; 335(3):179-188.

60. Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *J Pediatr* 2006; 148(2):259-264.

61. Rowe SM, Clancy JP. Advances in cystic fibrosis therapies. *Curr Opin Pediatr* 2006; 18(6):604-613.

62. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; 103(6):2039-2045.

63. Hankins JS, Ware RE, Rogers ZR, Wynn LW, Lane PA, Scott JP et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood* 2005; 106(7):2269-2275.

64. Gandhi TK, Bartel SB, Shulman LN, Verrier D, Burdick E, Cleary A et al. Medication safety in the ambulatory chemotherapy setting. *Cancer* 2005; 104(11):2477-2483.

65. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991; 266(20):2847-2851.

66. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; 5(3):305-314.

67. Silverman JB, Stapinski CD, Huber C, Ghandi TK, Churchill WW. Computer-based system for preventing adverse drug events. *Am J Health Syst Pharm* 2004; 61(15):1599-1603.

68. Kilbridge PM, Classen DC. Automated surveillance for adverse events in hospitalized patients: back to the future. *Qual Saf Health Care* 2006; 15(3):148-149.

69. Honigman B, Light P, Pulling RM, Bates DW. A computerized method for identifying incidents associated with adverse drug events in outpatients. *Int J Med Inform* 2001; 61(1):21-32.

70. McMullin ST, Reichley RM, Kahn MG, Dunagan WC, Bailey TC. Automated system for identifying potential dosage problems at a large university hospital. *Am J Health Syst Pharm* 1997; 54(5):545-549.

71. McMullin ST, Reichley RM, Watson LA, Steib SA, Frisse ME, Bailey TC. Impact of a Web-based clinical information system on cisapride drug interactions and patient safety. *Arch Intern Med* 1999; 159(17):2077-2082.

72. Reichley RM, Seaton TL, Resetar E, Micek ST, Scott KL, Fraser VJ et al. Implementing a commercial rule base as a medication order safety net. *J Am Med Inform Assoc* 2005; 12(4):383-389.

73. Huang Y, Noirot LA, Heard KM, Reichley RM, Dunagan WC, Bailey TC. Migrating toward a next-generation clinical decision support application: The BJC Healthcare experience. *AMIA Annu Symp Proc* 2007;344-348.

74. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30(2):239-245.

75. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001; 285(16):2114-2120.

76. Ferranti J, Horvath MM, Cozart H, Whitehurst J, Eckstrand J. Reevaluating the safety profile of pediatrics: a comparison of computerized adverse drug event surveillance and voluntary reporting in the pediatric environment. *Pediatrics* 2008; 121(5):e1201-e1207.

77. Boning A, Morschheuser T, Blase U, Scheewe J, von der BM, Grabitz R et al. Incidence of heparin-induced thrombocytopenia and therapeutic strategies in pediatric cardiac surgery. *Ann Thorac Surg* 2005; 79(1):62-65.

78. Frost J, Mureebe L, Russo P, Russo J, Tobias JD. Heparin-induced thrombocytopenia in the pediatric intensive care unit population. *Pediatr Crit Care Med* 2005; 6(2):216-219.

List of Publications and Products

Gysbers,M.; Reichley,R.; Kilbridge,P.M.; Noirot,L.; Nagarajan,R.; Dunagan,W.C.; Bailey,T.C. Natural language processing to identify adverse drug events. *AMIA.Annu.Symp.Proc*. 2008: 961. PMID:18999130

Kilbridge,P.M.; Noirot,L.A.; Reichley,R.M.; Heard,K.M.; Dunagan,W.C.; Bailey,T.C. Computerized surveillance for adverse drug events in a pediatric hospital. *AMIA.Annu.Symp.Proc*. 2008: 1004. PMID:18998917

Reichley, R.M; Gysbers, M; Noirot, L.A.; Rogers, C; Nelson, M; Bailey, T.C. Kilbridge, P.M. Pediatric Adverse Drug Event Surveillance with Natural Language Processing. *AMIA.Annu.Symp.Proc*. 2009:1015.

Kilbridge,P.M.; Noirot,L.A.; Reichley,R.M.; Berchelmann,K.M.; Schneider,C.; Heard,K.M.; Nelson,M.; Bailey,T.C. Computerized surveillance for adverse drug events in a pediatric hospital. *J.Am.Med.Inform.Assoc.* 2009; 16(5):607-612. PMID: 19567791