Adverse Drug Event Detection in Pediatric Oncology and Hematology Patients: Using Medication Triggers to Identify Patient Harm in a Specialized Pediatric Patient Population

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Objective To investigate the use of a trigger tool for the detection of adverse drug events (ADE) in a pediatric hospital specializing in oncology, hematology, and other catastrophic diseases.

Study design A medication-based trigger tool package analyzed electronic health records from February 2009 to February 2013. Chart review determined whether an ADE precipitated the trigger. Severity was assigned to ADEs, and preventability was assessed. Preventable ADEs were compared with the hospital's electronic voluntary event reporting system to identify whether these ADEs had been previously identified. The positive predictive values (PPVs) of the entire trigger tool and individual triggers were calculated to assess their accuracy to detect ADEs.

Results Trigger occurrences (n = 706) were detected in 390 patients from 6 medication triggers, 33 of which were ADEs (overall PPV = 16%). Hyaluronidase had the greatest PPV (60%). Most ADEs were category E harm (temporary harm) per the National Coordinating Council for Medication Error Reporting and Prevention index. One event was category H harm (intervention to sustain life). Naloxone was associated with the most grade 4 ADEs per the Common Terminology Criteria for Adverse Events v4.03. Twenty-one (64%) ADEs were preventable, 3 of which were submitted via the voluntary reporting system.

Conclusion Most of the medication-based triggers yielded low PPVs. Refining the triggers based on patients' characteristics and medication usage patterns could increase the PPVs and make them more useful for quality improvement. To efficiently detect ADEs, triggers must be revised to reflect specialized pediatric patient populations such as hematology and oncology patients. *(J Pediatr 2014;165:447-52)*.

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Multiple event detection methods are needed to reliably and completely identify medication errors and adverse drug events (ADEs) across all phases of the medication use system.[1-7] The 4 primary event-detection methods are voluntary event (incident) reports, direct observation, chart review, and trigger tools.[1] These methods capture more events when used in combination than if used alone.[1-6] The time and labor costs of direct observation and extensive chart review limit their utility for continuous adverse event monitoring. Although incident reporting is widely used and can identify clinically significant events, underreporting is a common challenge of this method.[1,3] Of the currently available event detection tools, incident reporting and trigger tools have been suggested to be the most optimal combination.[1]

Triggers are defined as an "occurrence, prompt, or flag (eg, laboratory values or medication orders) found on review of the medical chart that 'triggers' further investigation to determine the presence or absence of an adverse event."[8-10] Trigger tools can be an effective and efficient method for identifying ADEs.[1,7,11,12] Although trigger tools have proven effective for identifying more ADEs than other methods alone, the positive predictive value (PPV) of triggers for accurately identifying adverse events is often low and limits their utility and efficiency.[7,10,13-16] To justify resources to incorporate this event detection method into regular use, trigger tool PPVs need to be improved. Low PPVs have been reported across triggers designed for both the general adult and pediatric populations as well as for specific subsets of pediatric patients, such as those in neonatal intensive care units (NICUs).[16] The pediatric-focused trigger tool developed by the Child Health Corporation of America to accurately identify

ADE	Adverse drug event
CPOE	Computerized prescriber order entry
CTCAE	Common Terminology Criteria for Adverse Events
EHR	Electronic health record
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NICU	Neonatal intensive care unit
PPV	Positive predictive value
St. Jude	St. Jude Children's Research Hospital
TLS	Tumor lysis syndrome

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ADEs in general pediatric patients reported a PPV of only 3.7%.[10] The NICU population trigger tool designed by Sharek et al[16] has a greater PPV (38%) than that of the Child Health Corporation of America trigger tool, which emphasizes the benefit of considering patient subpopulations to increase a trigger tool's ability to detect ADEs.

The purpose of this study was to investigate the effectiveness and efficiency of using a trigger tool to detect ADEs in a pediatric hospital specialized in treating oncologic, hematologic, and other catastrophic diseases in children. The primary objectives of the study were to determine the PPVs of the overall trigger tool and the individual triggers to accurately identify ADEs. In this study we also assessed the ability of the trigger tool to identify unique ADEs that were not submitted in the hospital's electronic voluntary event reporting system.

Methods

St. Jude Children's Research Hospital (St. Jude) primarily cares for children with cancer, infectious diseases, and sickle cell disease. St. Jude contracts with the Cerner Corporation (Kansas City, Missouri) to provide a highly integrated electronic health record (EHR) system that includes laboratory, pharmacy, electronic medication administration record, computerized prescriber order entry (CPOE), and documentation functions. CPOE was fully implemented using a phased approach during the study. Before the implementation of CPOE, medication orders were handwritten by prescribers and transcribed into the pharmacy system. After May 2010, prescribers entered all medication orders electronically and medications were electronically verified in the pharmacy system. St. Jude's EHR implementation, especially CPOE for chemotherapy, was completed in 2010.[9]

St. Jude participates in the Automated Adverse Event Detection Collaborative,[17] a consortium working to facilitate the use of triggers in pediatric hospitals by the use of EHRs. The electronic trigger tool package was obtained from the Automated Adverse Event Detection Collaborative and incorporated into St. Jude's EHR system. The software program conducts an extensive search of patient medical records for any type of order containing specific medications and laboratory values. For example, in the case of medication orders, both pharmacy orders and CPOE orders are retrieved. This information is generated into a report that also contains patient-specific information and can be used to determine the presence of a potential ADE. An ADE was defined as an unintended injury or complication resulting from the use of a drug that requires additional monitoring, treatment, or hospitalization, or that results in death.[11] Approximately 200-300 medication-related safety events per month are reported in the hospital's electronic voluntary event-reporting system. The inpatient and specialty pharmacies dispense approximately 70 000 doses a month; the outpatient pharmacy dispenses an estimated 7500 prescriptions per month. The rate of ADEs reported during the period in which the triggers were reviewed was mostly constant.

We investigated the use of the following triggers (medications) for possible ADEs: hyaluronidase, flumazenil, naloxone, sodium polystyrene sulfonate, protamine, and vitamin K. These medication triggers were selected because of their wide use in other pediatric patient populations and their likelihood of identifying ADEs in pediatric oncology and hematology patients. The software package was used to identify triggers between February 16, 2009 (the date the hospital's new electronic voluntary event reporting system was implemented), and January 31, 2013 (**Figure 1**; available at www.jpeds.com). If it was determined that a trigger was associated with an ADE, the severity of harm was assigned to the ADE according to the classification of both the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and an adapted version of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Medication Error Index.[11,17,18] The CTCAE v4.03 is organized by system organ class, and within each class adverse events are listed and accompanied by grades of severity ranging from mild (grade 1) to death (grade 5).[17] The adapted NCC MERP Index uses categories E, F, G, H, and I for grading the range of severity. These categories represent adverse events that reached the patient (ie, not categories A-D, "near-misses" or events that did not result in harm) and caused harm (with E denoting temporary patient harm and I denoting patient death).[11,18] The study was approved by the St. Jude institutional review board for exempt status.

The potential ADEs detected by medication triggers were reviewed by a pharmacist (R.C.) and a physician (S.H.). Detected ADEs that were agreed on by both reviewers were retained for further analysis. Data collection on the following variables was documented for each ADE: date, area of the hospital in which it occurred, medication(s) contributing to the ADE, intervention(s), severity of ADE, and preventability of the ADE.

The preventability of the ADE was assessed with the 6-point scale for determination of causation, which has been previously used in pediatric trigger tool research (**Table I**; available at www.jpeds.com).[19] The scale was used to assess the likelihood that an ADE was the result of medical error, one of the purposes it was originally designed.[20] The possible responses for this measurement tool range from "virtually no evidence for management causation" (ie, a score of 1) to "virtually certain evidence for management causation" (ie, a score of 6). If an ADE had a causation rating of 4 or greater (ie, a greater than 50/50 chance that it was caused by health care management) the medication use process phase (eg, prescribing/ordering, transcribing, dispensing, administering, monitoring) was recorded (**Table II**).

Time to complete the chart review process and identify whether an ADE occurred was recorded to assess the personnel requirements for ADE identification from medication triggers. The hospital's electronic voluntary event reporting system was reviewed to determine whether the preventable ADEs identified by use of the trigger tool had