Published in final edited form as:

J Pediatr. 2014 September ; 165(3): 447–452.e4. doi:10.1016/j.jpeds.2014.03.033.

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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Abstract

Objective—To investigate the use of a trigger tool for adverse drug event (ADE) detection 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 six medication triggers, 33 of which were ADEs (overall PPV = 16%). Hyaluronidase had the highest PPV (60%). Most ADEs were category E harm (temporary harm) per the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) 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 (CTCAE) v4.03. Twenty-one (64%) ADEs were preventable; 3 of which were submitted via the voluntary reporting system.

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The authors declare no conflicts of interest.

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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.

Keywords

trigger tools; event detection methods; adverse drug event; electronic health record; pediatric diseases; medication safety; pediatric medication errors

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 four 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 (e.g., 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 PPV's 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 (CHCA) to accurately identify ADEs in general pediatric patients reported a PPV of only 3.7%.¹⁰ The NICU population trigger tool designed by Sharek et al has a higher PPV (38%) than that of the CHCA trigger tool, which emphasizes the benefit of considering patient sub-populations to increase a trigger tool's ability to detect ADEs.¹⁶

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 in order to accurately identify ADEs. Additionally, the study 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, MO) to provide a highly integrated EHR system that includes laboratory, pharmacy, electronic medication administration record (eMAR), computerized prescriber order entry (CPOE), and documentation functions. CPOE was fully implemented using a phased approach during the study. Before CPOE implementation, 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 (AAEDC),¹⁷ a consortium working to facilitate the use of triggers in pediatric hospitals using electronic health records (EHRs). The electronic trigger tool package was obtained from AAEDC and incorporated into St. Jude's EHR system. This 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 to 300 medication 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 7,500 prescriptions per month. The rate of ADEs reported over 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 due to 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 version 4.03 (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 (i.e., 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 (RC) and a physician (SH). Detected ADEs that were agreed upon 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.

ADE preventability was assessed with the six-point scale for determination of causation, which has been previously used in pediatric trigger tool research (Table V; 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” (i.e., a score of 1) to “virtually certain evidence for management causation” (i.e., 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 healthcare management) the medication use process phase (eg, prescribing/ordering, transcribing, dispensing, administering, monitoring) was recorded (Table IV).

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 using the trigger tool had been voluntarily reported. The PPVs of the trigger tool and the individual triggers were calculated as the fraction of triggers that identified ADEs. This was defined as the number of triggers that detected ADEs divided by the total number of triggers.

Results

A total of 706 triggers were detected in 390 patients between February 16, 2009, and January 31, 2013. The majority of the patients were white (N = 273, 70%), the mean age was 11 years, and the sample was 55% male. Roughly half of the patients were diagnosed with leukemia (N = 211, 54%) and almost a quarter of the sample was diagnosed with some form of solid tumor (N = 93, 24%). The sample was representative of the overall population of the study hospital. Furthermore, the sample’s cancer diagnosis distribution is similar to U.S. national pediatric data reported by the National Cancer Institute (NCI) (e.g., 48.5% of U.S. patients with cancer between the ages of 0 and 19 were diagnosed with leukemia).² Two authors (RC and SH) determined that 114 triggers detected 33 unique ADEs (Table I). Figure 2 (available at www.jpeds.com) represents the ADEs by medication trigger type over time. Table V contains primary diagnosis, medication(s) involved, ADE description, intervention, and causation ratings for each identified ADE. The PPVs for individual triggers ranged from 0% to 60%, and the PPV of the entire tool was 16% (Table I). Hyaluronidase had the highest PPV (60%).

The time required to investigate if a trigger was associated with an ADE was approximately 3 minutes (mean 2.55, SD = 1.58) per event. The time in minutes to determine if an ADE

occurred for each trigger was as follows: hyaluronidase (mean 3.00, SD = 2.00), flumazenil (mean 4.41, SD = 2.32), naloxone (mean 2.29, SD = 1.51), sodium polystyrene sulfonate (mean 1.84, SD = 1.92), protamine (mean 2.48, SD = 1.51), and vitamin K (mean 1.30, SD = 1.05).

Of the 33 ADEs, 27 (82%) events were classified as NCCP MERP category E (temporary harm), four events as category F (temporary harm requiring initial or prolonged hospitalization), one (3%) event as category G (permanent harm), and one (3%) event as category H (intervention to sustain life). None of the ADEs resulted in death. Regarding the CTCAE classifications, the naloxone trigger identified the most grade 4 ADEs (Table II).

The sodium polystyrene sulfonate trigger identified the most ADEs (Table III), with CTCAE hyperkalemia grade 2 being the most frequently encountered ADE (Table II). The primary cause of hyperkalemia in our patients varied. Forty-four (17%) of the 257 triggers for sodium polystyrene sulfonate use occurred in patients with tumor lysis syndrome (TLS) and did not represent ADEs. Of the 14 ADEs identified by sodium polystyrene sulfonate, cyclosporine was implicated in 9 (64%) cases (Table V).

Neither vitamin K nor protamine identified any ADEs in our patients. None of the patients received vitamin K for warfarin reversal. The majority of protamine orders were for prophylactic use during extracorporeal photophoresis in patients with severe coagulopathies.

Of the 33 identified ADEs, 21 (63.6%) were considered to have a greater than 50/50 chance that they were caused by healthcare management (i.e., a six-point causation rating of 4 or above) (Table V).¹⁹ Three of the greater than 50/50 chance of being caused by management (i.e., preventable) ADEs were reported to the hospital's electronic voluntary event reporting system. Sixteen (76.2%) of these 22 ADEs occurred in the prescribing phase of medication delivery (Table IV). reporting system.

Discussion

This study reports the use of trigger tools to detect ADEs specific to pediatric hematology and oncology patients. The medications hyaluronidase, flumazenil, naloxone, sodium polystyrene sulfonate, protamine, and vitamin K were specifically selected as the most relevant triggers for this patient population. Diphenhydramine and promethazine were excluded due to the frequent use of these medications as chemotherapy-related antiemetics in pediatric cancer patients. Other common triggers used in general pediatric populations (eg, antiemetics, laxatives/stool softeners) were not selected as these agents are commonly used in hematology and oncology patients, and they were expected to have limited utility for ADE detection in our setting.¹⁰ However, we found that even selectively chosen triggers did not efficiently identify ADEs in this specialized patient population.

The disease states unique to our patients complicated the use of some triggers. Traditionally, the sodium polystyrene sulfonate trigger is used to identify cases in which excessive potassium is administered, yet the poor PPV (27%) of sodium polystyrene sulfonate may in part be due to its recommended and appropriate use in TLS.²¹ Hyperkalemia is a potentially life-threatening consequence of TLS, and frequent potassium measurements and oral

administration of sodium polystyrene sulfonate are recommended.²¹ Additionally, multiple nephrotoxic agents are often used in the treatment of oncology patients, and even careful monitoring may not prevent renal impairment with resultant hyperkalemia. Vitamin K was not ordered for patients on warfarin experiencing an ADE but instead was prescribed for patients experiencing chemotherapy or disease-induced thrombocytopenia, veno-occlusive disease, or malabsorption. Similarly, orders for protamine were not related to heparin use.

These results indicated various opportunities that remain to improve trigger sensitivity. For example, the vitamin K trigger can be improved by limiting it to patients with a previous or current order for warfarin. Another study made similar modifications to the vitamin K trigger, which resulted in substantial improvements in the PPV (from 12.5% to 46%).⁶ In our study, none of the patients from the 301 vitamin K trigger occurrences were prescribed warfarin.

Our initial experience with trigger tools designed for a general pediatric population illustrates that they do not efficiently identify ADEs in a specialized patient population. Previous studies have demonstrated the benefit of developing triggers for a specialty pediatric population. For example, Sharek et al designed a manual trigger tool to detect NICU-specific ADEs. The tool had a PPV of 38% and was effective and efficient for identifying ADEs.¹⁶ Although general pediatric triggers can identify ADEs in hematology and oncology patients,¹⁰ the complex therapies and disease states of these patients must be considered to develop an effective trigger tool for medication surveillance.

Consistent with results from earlier studies,^{10, 13–16} the PPV of our trigger tool varied widely and was relatively low overall. However, the tool did detect some events that had not been voluntarily reported, which reinforces the notion that multiple event detection methods are needed to fully capture a hospital's ADEs. However, compared with other studies, we identified only two events not reported to our hospitals voluntary event reporting system, which may be due to a healthy reporting culture as demonstrated by consistent scores above the benchmark on the reporting dimensions of the Agency for Quality Research and Quality's Hospital Survey on Patient Safety Culture.²²

To evaluate the usefulness and resource implications for each trigger, we collected both PPV and the time needed to determine if an ADE occurred. Even though these are useful metrics, it is also important to consider the frequency of trigger occurrences when evaluating their utility. For example, protamine's PPV was 0% and flumazenil had a relatively low PPV of 39%, but as these antidotes are often used in response to an ADE they may still be valuable triggers. These medications were prescribed only 41 times in the 4-year study period, and it took only about 3 minutes to identify whether an ADE was associated with a trigger. Therefore, the use of protamine and flumazenil as triggers would not require substantial organizational resources for event detection.

Although our primary focus was ADE detection, we also assessed preventability using a six-point scale that has been validated in other trigger tool research.¹⁵ Assigning preventability of ADEs identified through trigger tools has been operationalized in various ways. Some have used a binary decision^{10, 13, 16} and others have characterized it on a continuum.¹⁹

Others, such as the Institute for Healthcare Improvement Global Trigger Tool, have questioned the value of assessing the preventability of ADEs identified through trigger tools.^{6, 11} To recognize the potential subjectivity of evaluating preventability, we choose to rate on a continuum. We found that over half of the ADEs identified through trigger tools were likely preventable, which is consistent with the use of trigger tools in other specialized pediatric populations.¹⁶

A limitation identified during the study was that the trigger tool did not query some specific order types. For example, orders for naloxone drips (e.g., to relieve itching from morphine) and for total parenteral nutrition (TPN) containing vitamin K were not captured. This exclusion would not have affected the PPV of vitamin K because use of vitamin K in TPN does not represent an ADE, but naloxone ADEs may have been missed. Also, the electronic identification of ADEs associated with naloxone and flumazenil was complicated by anesthesia's limited use of electronic medication documentation on the eMAR during much of the study period. To account for this limitation, naloxone and flumazenil triggers in post-anesthesia care unit received additional review. Electronic pre and post procedure notes were assessed and if the note did not mention any complications or use of naloxone or flumazenil, it was assumed that these medications were ordered for as needed use but were not administered. This experience shows the importance of careful evaluation of trigger tools during implementation.

Ultimately, more comprehensive detection of ADEs is intended to contribute to improvements in the medication-use process and patient care. Traditionally, the trigger tool approach relies on retrospective review and identification of ADEs, which can delay improvements. With the wide introduction of EHRs, it is possible for the trigger tool approach to identify ADEs rapidly at the point of order entry. Such integration could result in trigger tools taking a role similar to clinical decision support functions (e.g. dose range checking alerts, drug-drug interaction alerts).^{23, 24} Trigger tools could be used to alert staff when a certain medication is ordered prompting immediate investigation. However, given the widespread challenge of alert fatigue with clinical decision support, refining triggers to be highly predictive for identifying ADEs in the desired population is an essential prerequisite for real-time implementation of medication surveillance.^{25–27}

Acknowledgments

Supported by the Cancer Center Core through the National Institutes of Health (CA 21765) and the American Lebanese Syrian Associated Charities.

List of abbreviations

ADE	Adverse drug event
EHR	Electronic health record
PPV	Positive predictive value
TLS	Tumor lysis syndrome

References

1. Meyer-Massetti C, Cheng CM, Schwappach DLB, Paulsen L, Ide B, Meier CR, et al. Systematic review of medication safety assessment methods. *American Journal of Health-System Pharmacy*. 2011; 68:227–40. [PubMed: 21258028]
2. Howlader, N.; Noone, A.; Krapcho, M.; Garshell, J.; Neyman, N.; Aletkruse, S., et al. SEER Cancer Statistics Review, 1975–2010, [Online]. National Cancer Institute; Bethesda, MD: http://seer.cancer.gov/csr/1975_2010/
3. Hartwig S, Denger S, Schneider P. Severity-indexed, incident report-based medication error-reporting program. *American Journal of Health-System Pharmacy*. 1991; 48:2611–6.
4. Neubert A, Dormann H, Weiss J, Criegee-Rieck M, Ackermann A, Levy M, et al. Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? *European journal of clinical pharmacology*. 2006; 62:959–65. [PubMed: 17021890]
5. Eriksson R, Jensen PB, Frankild S, Jensen LJ, Brunak S. Dictionary construction and identification of possible adverse drug events in Danish clinical narrative text. *Journal of the American Medical Informatics Association*. 2013
6. Classen DC, Lloyd RC, Provost L, Griffin FA, Resar R. Development and evaluation of the Institute for Healthcare Improvement global trigger tool. *Journal of Patient Safety*. 2008; 4:169–77.
7. Classen DC, Resar R, Griffin F, Federico F, Frankel T, Kimmel N, et al. ‘Global trigger tool’ shows that adverse events in hospitals may be ten times greater than previously measured. *Health Affairs*. 2011; 30:581–9. [PubMed: 21471476]
8. Resar R, Rozich J, Classen D. Methodology and rationale for the measurement of harm with trigger tools. *Quality and Safety in Health Care*. 2003; 12:ii39–ii45. [PubMed: 14645894]
9. Rozich J, Haraden C, Resar R. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Quality and safety in Health Care*. 2003; 12:194–200. [PubMed: 12792009]
10. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children’s hospitals. *Pediatrics*. 2008; 121:e927–e35. [PubMed: 18381521]
11. Griffin, F.; Resar, R. IHI Global Trigger Tool for measuring adverse events. 2. Institute for Healthcare Improvement; 2009.
12. Kirkendall ES, Kloppenborg E, Papp J, White D, Frese C, Hacker D, et al. Measuring adverse events and levels of harm in pediatric inpatients with the global trigger tool. *Pediatrics*. 2012; 130:e1206–e14. [PubMed: 23045558]
13. Burch KJ. Using a Trigger Tool to Assess Adverse Drug Events in a Children’s Rehabilitation Hospital. *The Journal of Pediatric Pharmacology and Therapeutics*. 2011; 16:204–9. [PubMed: 22479163]
14. 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:e1201–e7. [PubMed: 18450863]
15. Matlow A, Flintoft V, Orrbine E, Brady-Fryer B, Cronin C, Nijssen-Jordan C, et al. The Development of a Canadian Paediatric Trigger Tool for Identifying Potential Adverse Events. *Health Care Quarterly*. 2005; 8:90–3.
16. 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; 118:1332–40. [PubMed: 17015521]
17. Stockwell DC, Kirkendall ES, Muething SE, Kloppenborg E, Vinodrao H, Jacobs BR. Automated Adverse Event Detection Collaborative: Electronic Adverse Event Identification, Classification and Corrective Actions Across Academic Pediatric Institutions. *Journal of Patient Safety*. 2013 in-press.
18. [Access date January 10] National Coordination Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>

19. Matlow AG, Cronin CMG, Flintoft V, Nijssen-Jordan C, Fleming M, Brady-Fryer B, et al. Description of the development and validation of the Canadian Paediatric Trigger Tool. *BMJ quality & safety*. 2011; 20:416–23.
20. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. *New England journal of medicine*. 1991; 324:370–6. [PubMed: 1987460]
21. Kova evi A, Dehghan A, Filannino M, Keane JA, Nenadic G. Combining rules and machine learning for extraction of temporal expressions and events from clinical narratives. *Journal of the American Medical Informatics Association*. 2013
22. Sorra, J.; Nieva, V. *Hospital Survey on Patient Safety Culture*. Rockville, MD: Agency for Healthcare Research and Quality; 2004.
23. Bennett JW, Glasziou PP. Computerised reminders and feedback in medication management: a systematic review of randomised controlled trials. *Medical Journal of Australia*. 2003; 178:217–22. [PubMed: 12603185]
24. Garg AX. Effects of Computerized Clinical Decision Support Systems on Practitioner Performance and Patient Outcomes. *Journal of American Medical Association*. 2005; 293:1223–8.
25. Embi PJ, Leonard AC. Evaluating alert fatigue over time to EHR-based clinical trial alerts: findings from a randomized controlled study. *Journal of the American Medical Informatics Association : JAMIA*. 2012; 19:e145–8. [PubMed: 22534081]
26. Lin CP, Payne TH, Nichol WP, Hoey PJ, Anderson CL, Gennari JH. Evaluating clinical decision support systems: monitoring CPOE order check override rates in the Department of Veterans Affairs' Computerized Patient Record System. *Journal of the American Medical Informatics Association : JAMIA*. 2008; 15:620–6. [PubMed: 18579840]
27. van der Sijs H, Aarts J, van Gelder T, Berg M, Vulto A. Turning off frequently overridden drug alerts: limited opportunities for doing it safely. *J Am Med Inform Assoc*. 2008; 15:439–48. [PubMed: 18436915]

Table I

Trigger occurrences, triggers associated with and ADE, number of distinct ADEs, and PPVs of individual medication triggers and the total trigger tool

Trigger	Number of Triggers	Number of Triggers Corresponding to an ADE	Number of Distinct ADEs	PPV (%) ^a
Protamine	23	0	0	0
Vitamin K	301	0	0	0
Sodium polystyrene sulfonate	257	70	14	27
Naloxone	102	34	12	33
Flumazenil	18	7	5	39
Hyaluronidase	5	3	2	60
Total Trigger Tool	706	114	33	16

^aPPV was calculated as the number of triggers that detected ADEs divided by the total number of triggers.

Table IISeverity of ADEs according to the CTCAE classification^a

Trigger	Grade 1	Grade 2	Grade 3	Grade 4
Protamine	N/A ^b	N/A ^b	N/A ^b	N/A ^b
Vitamin K	N/A ^b	N/A ^b	N/A ^b	N/A ^b
Sodium polystyrene sulfonate	0	10	3	1
Naloxone	0	3	7	5
Flumazenil	1	4	3	1
Hyaluronidase	0	1	0	1

^aIn some cases, multiple “adverse events” were associated with the ADE (e.g., nausea grade 1 and depressed level of consciousness grade 2 documented as symptoms of a single ADE identified by the flumazenil trigger). Therefore, the total number of CTCAE adverse events ($n = 38$) does not equal the number of distinct ADEs ($n = 33$).

^bNo ADEs were identified

Table III

Six-point scale for determination of causation for identified ADEs

Trigger	Virtually no Evidence Caused by Management	Slight to Modest Evidence Caused by Management	Less than 50/50 Chance Caused by Management	Greater than 50/50 Chance Caused by Management	Moderate to Strong Evidence Caused by Management	Virtually Certain Evidence Caused by Management
Protamine	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a
Vitamin K	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a	N/A ^a
Sodium polystyrene sulfonate	1(7.1%)	9(64.2%)	0	3(21.4%)	1(7.1%)	0
Naloxone	2(16.6%)	0	0	0	1(8.3%)	9(75.0%)
Flunazetil	0	0	0	1(20.0%)	2(40.0%)	2(40.0%)
Hyaluronidase	0	0	0	0	1(50%)	1(50%)
Total	3(9.1%)	9(27.2%)	0	4(12.1%)	5(15.2%)	12(36.3%)

^aNo ADEs were identified

Table IV

Phase of medication use system for ADEs that were more than 50% chance caused by healthcare management

Trigger	Prescribing	Dispensing	Administering	Monitoring
Protamine	N/A ^a	N/A ^a	N/A ^a	N/A ^a
Vitamin K	N/A ^a	N/A ^a	N/A ^a	N/A ^a
Sodium polystyrene sulfonate	3	1	0	0
Naloxone	8	0	1	1
Flumazenil	4	0	0	1
Hyaluronidase	0	0	1	1

^a No ADEs were identified

Table V
Primary diagnosis, involved medications, ADE description and intervention, and preventability rating

Primary Diagnosis	Medications Involved	ADE Description	Intervention	Preventability Rating
Hyaluronidase				
B Cell acute Lymphoblastic Leukemia (ALL)	acyclovir	IV infiltrated into left forearm	Increased monitoring of the patient was required.	5
Neuroblastoma	total parenteral nutrition	The patient came into hospital because CADD pump was beeping. However, it stopped prior to arriving at hospital and patient was sent home. Nurse did not assess the patient's line before sending her home. Her line had detached and her TPN extravasated into the surrounding tissue.	The patient was transferred to ICU and admitted as an inpatient. She received skin grafts and plastic surgery.	6
Flumazenil				
acute myeloid leukemia (AML)	lorazepam	The lorazepam dose was increased from 0.5 to 1mg. The patient developed syncope and became unresponsive.	The lorazepam dose was decreased and patient was transferred to the ICU for increased monitoring. A CT scan and chest xray were performed.	5
medulloblastoma	lorazepam	The patient had ataxia, slurred speech, and unsteady gait.	The lorazepam dose was decreased and a CT scan performed.	4
medulloblastoma	lorazepam, diphenhydramine	The patient had nausea, vomiting, and increased sedation.	The anti-emetic doses were decreased.	5
osteosarcoma	lorazepam	Prior to discharge the patient had syncope and was readmitted. The patient had syncope the night before when given same dose of lorazepam per nursing note in chart.	The patient was readmitted required increased monitoring.	6
rhabdomyosarcoma	lorazepam	The patient had increased sedation when lorazepam was given around the same time as hydromorphone.	The patient required increased monitoring	6
Naloxone				
AML	hydromorphone	After receiving hydromorphone, patient had an anaphylactic reaction (confusion, sensation of throat closing, tongue swelling, tachypnea).	The patient was treated with hydrocortisone and epinephrine for anaphylaxis.	1
AML	lorazepam	The lorazepam dose was increased from 0.5 to 1mg. The patient developed syncope and became unresponsive.	The lorazepam dose was decreased and patient was transferred to the ICU for increased monitoring. A CT scan and chest xray were performed.	1
atypical teretoid rhabdoid tumor (ATRT)	hydromorphone	Patient was started on patient controlled analgesia (PCA) with hydromorphone at 0.1mg q15min bolus. This did not control his pain, so he was changed to 0.2mg basal with 0.2mg bolus q30min with a clinician dose of 0.2mg q30min. At 0905 on 11/30/11, he gave himself a bolus of 0.2mg and then about a half an hour later, he received a clinician dose of 0.2mg. He rapidly went into respiratory depression, received naloxone and responded well.	The CADD pump was stopped and 0.2 mg of naloxone was given. The hydromorphone was restarted at the correct dose.	6

Primary Diagnosis	Medications Involved	ADE Description	Intervention	Preventability Rating
glioblastoma	morphine	The patient received 0.2 mg morphine intravenous for pain and had an episode of decreased responsiveness, decline in function, constricted pupils, and poor tone.	The patient responded quickly to naloxone administration and was monitored closely.	6
medulloblastoma	lorazepam, diphenhydramine	The patient experienced oversedation with anti-emetics	The medication does was changed.	6
neuroblastoma	hydromorphone	The patient had apnea after multiple boluses of hydromorphone. Father gave boluses "to stay ahead of pain" even though patient was sleeping.	The patient required bagging and naloxone administration along with increased monitoring. The hydromorphone CADD bolus dose was decreased and changed to clinician administration only.	6
neuroblastoma	hydromorphone, morphine	The patient was given one dose of oral morphine in clinic and then an IV morphine dose with no relief. He was admitted and given a total of three hydromorphone doses. In the early morning he was noted to have shallow respirations and decreased respiratory rate.	The patient was administered naloxone and improved.	6
neuroblastoma	fentanyl, hydromorphone	Patient experienced mild intermittent hypoxia. She then became progressively apneic but would recover with stimulation. She had received hydromorphone and a bolus of fentanyl within an hour of the event. She had also received an antibody infusion about 2 hours prior to the event.	Her hydromorphone was discontinued and she was monitored more closely.	5
Non-Hodgkin's lymphoma	hydromorphone	The hydromorphone PCA dose was increased and patient then received a dose of lorazepam. The patient had decreased respiratory effort and increased sedation.	The patient was administered naloxone and improved. The hydromorphone and lorazepam doses were decreased.	6
osteosarcoma	lorazepam	The patient was difficult to arouse post-MRI.	The lorazepam dose was decreased.	6
thabomyosarcoma	hydromorphone, lorazepam	The patient was on a hydromorphone PCA and received a dose of 2 mg lorazepam when his respiratory rate was noted to be 3.	The patient responded well to flumazenil and naloxone. The hydromorphone PCA was stopped. However, his pain was 10/10 in the morning and the pain team was consulted.	6
sickle cell	hydromorphone, morphine	The patient was difficult to arouse while using a hydromorphone PCA. The concentration of the hydromorphone was 1 mg/mL but the settings on the CADD pump were 0.1 mg/mL.	medication dose change, increased monitoring	6
Sodium polystyrene sulfonate				
Adrenocortical carcinoma	cisplatin	There was concern that too much potassium was administered with cisplatin.	The patient's cisplatin was held. The patient was treated for hyperkalemia and her labs improved.	4
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase. It was noted that patient may also have been dehydrated due to little oral intake.	The patient's discharge was delayed. She was treated for hyperkalemia and her labs improved.	2

Primary Diagnosis	Medications Involved	ADE Description	Intervention	Preventability Rating
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
AML	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
Fanconi anemia	cyclosporine & vancomycin	The patient was receiving vancomycin and cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and her labs improved.	2
pre B ALL	spironolactone	The patient was receiving spironolactone which may have led to potassium increase.	The spironolactone was discontinued and the patient's labs improved.	4
pre B ALL	foscarnet	The patient had electrolyte disturbances following initiation of foscarnet therapy.	Upon completion of foscarnet the patient's labs improved.	2
relapsed ALL	cyclosporine	The patient was receiving cyclosporine which may have led to potassium increase.	The patient was treated for hyperkalemia and his labs improved.	2
severe aplastic anemia	cyclosporine	The patient had cyclosporine-induced nephrotoxicity which led to a potassium increase.	The patient received sodium polystyrene sulfonate daily to keep potassium within normal range.	1
severe aplastic anemia	ACE-inhibitor	The patient was started on an ACE-inhibitor for renal protection and then his potassium increased. The chart noted that tacirolimus and nephritis may also have caused the potassium to increase.	The ACE-inhibitor was discontinued and the patient was placed on a low potassium diet.	4
severe aplastic anemia	potassium chloride & potassium phosphate	The patient received oral potassium chloride and potassium phosphate for low potassium. Within 4 days of starting oral therapy her potassium was higher than normal. Engraftment syndrome may also have caused this spike in potassium.	The potassium supplements were discontinued and that patient was treated for hyperkalemia with improvement.	5