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ORIGINAL RESEARCH ARTICLE

Evaluation of an Automated Surveillance System Using Trigger Alerts to Prevent Adverse Drug Events in the Intensive Care Unit and General Ward

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Abstract

Introduction Adverse events in the intensive care unit (ICU) may be associated with several possible causes, so determining a drug-related causal assessment is more challenging than in general ward patients. Therefore, the hypothesis was that automated trigger alerts may perform differently in various patient care settings. The purpose of this study was to compare the frequency and type of clinically significant automated trigger alerts in critically ill and general ward patients as well as evaluate the performance of alerts for drug-related hazardous conditions (DRHCs).

Methods A retrospective cohort study was conducted in adult ICU and general ward patients at three institutions (academic, community, and rural hospital) in a health system. Automated trigger alerts generated during two nonconsecutive months were obtained from a centralized database. Pharmacist responses to alerts and prescriber response to recommendations were evaluated for all alerts. A clinical significant event was defined as an actionable intervention requiring drug therapy changes that the pharmacist determined to be appropriate for patient safety and where the physician accepted the pharmacist's recommendation. The positive predictive value (PPV) was calculated for each trigger alert considered a DRHC (i.e., abnormal laboratory values and suspected drug causes).

Results A total of 751 alerts were generated in 623 patients during the study period. Pharmacists intervened on 39.8 and 44.8 % alerts generated in the ICU and general ward, respectively. Overall, the physician acceptance rate of approximately 90 % was comparable irrespective of patient care setting. Therefore, the number of clinically significant alerts was 88.9 and 83.4 % for the ICU and non-ICU, respectively. The types of drug therapy changes were similar between settings. The PPV of alerts identifying a DRHC was 0.66 in the ICU and 0.76 in general ward patients.

Key Points

Trigger alerts are a time-effective strategy to prevent adverse drug events. They perform equally well in an intensive care unit (ICU) and a general ward population.

Alert performance was similar irrespective of teaching, community, or rural hospital setting.

Clinical pharmacists could utilize this strategy as a component of their daily patient care responsibilities.

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Conclusions The number and type of clinically significant alerts were similar irrespective of patient population, suggesting that the alerts may be equally as beneficial in the ICU population, despite the challenges in drug-related event adjudication. An opportunity exists to improve the performance of alerts in both settings, so quality improvement programs for measuring alert performance and making refinements is needed.

1 Introduction

Adverse drug events (ADEs) are common in the critically ill patient population [1]. The incidence of ADEs is more common and severe in intensive care unit (ICU) patients than in non-ICU patients [2–4]. Critically ill patients have multiple risk factors for experiencing ADEs, including acuity of illness, exposure to 'high-risk' medications, potential drug–drug interactions, and the overall number of medications administered [5, 6]. Preventable and potential ADEs are twice as likely to transpire in the ICU as in general medical–surgical ward patients as a result of receiving twice the number of medications [2]. Fortunately, 20–68 % of ADEs occurring in the ICU are considered to be preventable, thus providing an opportunity for intervention [4, 7].

Although several ADE surveillance methods currently exist, most are aimed at detection rather than prevention [8]. Previous studies demonstrate that clinical decision support using trigger alerts results in a higher rate of ADE detection than with voluntary reporting methods and is more time efficient and less costly than direct observation or medical record review [8–10]. Trigger alerts have the potential to prevent ADEs by alerting the clinician before patient harm occurs and at a minimum should mitigate severity [11–14]. Automated medication monitoring systems using trigger alerts based on logic-based rules are a form of ADE prevention. This preventive approach focuses on identifying the intermediate step before drug-induced patient harm occurs, known as an ADE [15]. A drug-related hazardous condition (DRHC) is an antecedent to injury resulting from an abnormal laboratory or physiologic parameter with the potential for harm [15]. Trigger alerts targeted at identifying DRHCs can allow clinicians to make drug therapy changes in the intermediate step before injury occurs [16].

Trigger alerts are typically generated from laboratory abnormalities, supra- or sub-therapeutic serum drug concentrations, or orders for antidotes of drug-induced complications (e.g., phytonadione, protamine, naloxone, etc.) [17]. However, surveillance of antidotes is limited to only detection since drug-induced sequela has already transpired [17]. Clinical decision support systems designed for prevention have focused more on laboratory abnormalities, including drug serum concentrations, using triggers based on logic-based criteria to alert the clinician to evaluate the clinical scenario and possibly intervene [18]. These trigger alerts compare laboratory data with information such as medication administration/ordering information, procedures, location within a hospital, and diagnoses indicating presence of a DRHC [10, 14, 18–21]. As triggers continue to advance, they will soon incorporate possible drug-induced physiologic changes such as hypotension [16].

Only a couple of studies have evaluated the impact of pharmacists utilizing automated trigger alert systems on intervention rates accepted by physicians [19, 22]. Previous work demonstrates that pharmacists intervene on 12–19 % of all trigger alerts generated and result in most recommendations for drug therapy changes being accepted by the provider [19, 22]. Both studies demonstrated the potential of trigger alerts to improve patient safety by incorporating this ADE surveillance strategy into the pharmacists' daily responsibilities. These studies were limited to single-center evaluations conducted at university hospitals. Furthermore, the performance of trigger alerts evaluated was not specific to an ICU population, nor was a comparison made to non-ICU patients. Also, the severity of DRHCs was not evaluated in either of these studies. We hypothesized that ICU patients, with a higher acuity and more complexity, would generate a higher rate of false-positive trigger alerts, resulting in lower pharmacist intervention and physician acceptance rates than in general ward patients. Therefore, the purpose of this study was to compare the frequency and type of clinically significant automated alerts in critically ill and general ward patients. The secondary objective was to determine the positive predictive value (PPV) of alerts at identifying DRHCs.

2 Methods

This retrospective cohort study was approved by the Institutional Review Board. The automated trigger system alerts generated during two non-consecutive months (May and December 2012) at three medical centers (733-bed teaching hospital, 214-bed community hospital, and 53-bed rural hospital) within the same health system (Banner Health, Phoenix, AZ) were collected from a centralized database. We excluded patients aged <18 years, those for whom an electronic medical record (EMR) was not accessible, and duplicate alerts that were generated for the same medication during a single admission. Trigger alerts at all study institutions do not focus on mere detection of actual ADEs (e.g., antidotes), but rather aim to prevent ADEs by identifying clinical circumstances with the potential for medication-related harm and are considered

actionable in order to prevent harm or ameliorate severity. These alerts are generated in real time based on criteria of logic-based rules being met. The triggers utilized were developed based upon proprietary clinical decision support software (Cerner). The clinical decision support software enables institutions to add, remove, and make modifications in the rules to meet the needs of the specific institution. A multidisciplinary team within our health system is responsible for evaluating and changing alerts based on performance. This multidisciplinary team consists primarily of information technology personnel, pharmacists, nurses, and physicians. The team periodically monitors alert performance and modifies triggers based on clinician feedback as well as results from our ADE surveillance program. All study sites utilized the same set of alerts within our health system. All trigger alerts ($n = 93$) generated at each study site were reviewed by a pharmacist as part of their daily responsibilities (see Electronic Supplementary Material [ESM] 1). After review of the patient's EMR to adjudicate the alert for significance and ADE potential, pharmacists documented their response to each alert, including whether the physician was contacted and if any change to therapy was made. Physicians were not notified for selected drug dosing adjustments based on renal function as each site followed an institution-approved protocol that allowed pharmacists to make these changes. The pharmacist still evaluated these alerts for appropriateness in the change of dose.

2.1 Definitions

The pharmacists' intervention was defined as contacting the physician to make a recommendation in a change of therapy or request monitoring in response to an alert. Physician acceptance of the intervention recommendation was obtained from the pharmacists' documentation. A clinically significant event was defined as an actionable intervention requiring drug therapy changes that the pharmacist determined to be appropriate for patient safety, and the physician accepted the pharmacist's recommendation. Pharmacist interventions resulting in increased monitoring without any changes in drug therapy and accepted by the physician were not considered clinically significant. A medication error occurring without any deleterious events experienced by the patient was defined as a 'potential ADE' [23].

Alerts were categorized as 'inappropriate therapy/monitoring', 'dosing related', 'laboratory abnormality', or 'other' (see ESM 1). For those alerts ($n = 19$) with an abnormal laboratory value as an intermediate step before patient harm (ADE), a causality assessment between the drug and event was completed by the pharmacist. The association of a DRHC with a medication was evaluated using three objective, validated causality instruments by one investigator (JPD) for the purposes of this evaluation [24–26]. The algorithms developed by Kramer et al. [25], Naranjo et al. [24], and Jones [26] assist clinicians in determining the probability of an ADE occurring from a specific medication. These different instruments contain assessment categories, including documentation of a similar adverse reaction in the literature, other possible non-drug etiologies of the reaction, timing of the reaction in relation to the suspected medication, availability of objective evidence, ADE resolution following discontinuation of suspected drug, and similar reaction if the same medication was reintroduced to the patient [24–26]. The Kramer et al. [25] and Naranjo et al. [24] tools utilize a numeric scoring system, while the Jones [26] instrument follows an assessment algorithm corresponding to the likelihood of an ADE. A DRHC was considered medication-related when at least two of the three causality assessment instruments concluded the correlation was 'possible', 'probable', or 'definite'. This method has been used by previously published studies [9, 18, 27]. The severity of potential harm at the time the alert was generated was classified using the National Cancer Institute's Common Terminology Criteria for Adverse Events [28]. This 5-point grading scale ranks the severity of a specific adverse event symptom ranging from mild (1) to death (5) [28]. The specific abnormal symptom, laboratory value, or disease for a broad range of adverse events (bleeding, cardiac arrhythmia, etc.) corresponds to a numeric value of severity based on the significance for each event. For example, hypothermia with temperatures ranging from 32 to 35 °C would correspond to a severity score of 2, while 28 to 32 °C would result in a score of 3.

2.2 Analysis

The primary endpoint was a comparison of the frequency and type of clinically significant events between ICU and non-ICU patients. Chi-squared tests and Fisher's exact tests were used as appropriate using a web-based program named Social Science Statistics [29]. A p-value <0.05 was considered to be statistically significant. To calculate the PPV for each trigger related to a DRHC, we divided the number of times that a signal fired and correlation with a medication was confirmed (i.e. the number of true positives), by the number of times the signal fired with or without confirmed correlation with a medication (i.e. the sum of true positives and false positives).

3 Results

3.1 Overall Results

A total of 751 alerts (623 unique patients) were generated from a total list of 93 logic-based trigger rules in our

healthcare system (see ESM 1). The distribution of all trigger alerts among the teaching, community, and rural hospitals was 72.6, 24, and 3.4 %, respectively. Patient characteristics are illustrated in Table 1. The majority of alerts involved inappropriate dosing and inappropriate therapy/monitoring parameters (Fig. 1). The most common therapeutic drug classes associated with trigger alerts were antithrombotic agents (35.6 %), antibacterial agents (20.2 %), and antipyretic/analgesic agents (11.9 %). These therapeutic drug classes were similar in both ICU and general ward patients.

3.2 Pharmacist Interventions

The overall rate of pharmacist interventions in the ICU and the general ward were 39.8 and 44.8 %, respectively (Table 2). Pharmacists intervened more in general ward patients at the teaching hospital, while the community and rural institutions showed similar rates (Table 2). The rates of physician acceptance of the pharmacist intervention recommendations were similar irrespective of ICU or general ward location as well as type of hospital (Table 2). Interventions resulting in actual drug therapy changes were also similar between ICU and general ward patients, irrespective of hospital setting (Table 2). The most common drug therapy changes in the ICU and general ward cohorts were discontinuation of the medication, dose reduction, and decrease in dosing frequency (Table 3).

Table 1 Alert and patient characteristics of those triggering an alert

Variable	ICU	General ward
Total alerts (*n*)	226	525
Teaching hospital	170 (75.2)	375 (71.4)
Community hospital	38 (16.8)	142 (27.1)
Rural hospital	18 (8.0)	8 (1.5)
Male	139 (61.5)	266 (50.7)
Age, years [mean (SD)]	57.7 (16.4)	60.2 (17.3)
Length of hospital stay, days	11 (6–20)	7 (4–14)
APACHE II score	15 (11–24)	NA
Days first alert was generated following hospital admission	2 (1–5)	2 (0–5)

Data are presented as *n* (%) or median (IQR) unless otherwise indicated

APACHE Acute Physiology and Chronic Health Evaluation, *ICU* intensive care unit, *IQR* interquartile range, *NA* not applicable, *SD* standard deviation

3.3 Causality Assessment

Of the 93 trigger alerts, 19 (20.4 %) were assessed for causality between the suspected medication and adverse event. Subgroup analysis of 161 trigger alerts from those 19 logic-based rules with a high risk of drug-induced laboratory abnormalities was conducted (see ESM 1). Rules targeting drug-induced thrombocytopenia generated the greatest number of such alerts for both ICU (35.6 %) and non-ICU (29.5 %) settings. Alerts generated from the other rules were observed to occur at similar rates in the ICU and non-ICU, with the exception of those targeting increased international normalized ratio values, for which fewer alerts were generated in the ICU than in the non-ICU (2.7 vs. 17 %, respectively). Overall, 115 (71.4 %) of these alerts were considered as DRHCs per causality assessment. General ward patients had a higher PPV for alerts associated with a DRHC than those in the ICU (0.76 vs. 0.66, respectively) (Table 4). No differences in the DRHC severity at the time of alert generation were found between ICU and general ward patients (Fig. 2).

4 Discussion

Our study evaluated pharmacist interventions in response to medication-related automated trigger system alerts in

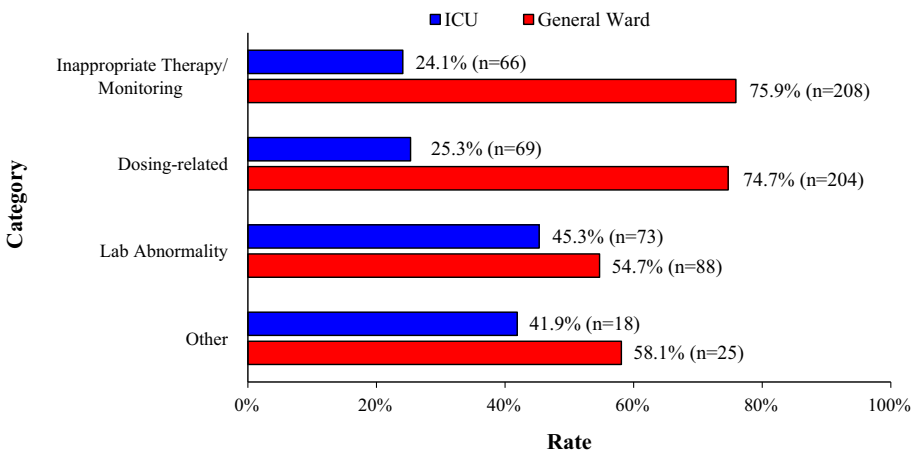

Fig. 1 Comparison of trigger alerts rates by category between intensive care unit and general ward patients. The total number of unique logic-based trigger alert rules at all study institutions for each category was 29 inappropriate therapy/monitoring, 41 dosing-related, 19 laboratory abnormality, and four other. *ICU* intensive care unit, *lab* laboratory

Table 2 Outcomes associated with intensive care unit and general ward trigger alerts

Outcome	Population		*p* value
	ICU	General ward	
Pharmacist intervention[a]	39.8 (90/226)	44.8 (235/525)	0.21
Physician acceptance[b]	90 (81/90)	86 (202/235)	0.33
Clinically significant event[c]	88.9 (80/90)	83.4 (196/235)	0.22

Data are presented as % (*n*) unless otherwise indicated

[a] Percentage was calculated from number of pharmacist interventions/total number of alerts generated

[b] Percentage was calculated from number of pharmacist interventions accepted by physician/number of pharmacist interventions

[c] Percentage was calculated from number of medication therapy changes completed as a result of pharmacist intervention with physician acceptance/number of pharmacist interventions

Table 3 Types of medication changes resulting from clinically significant events: intensive care unit and general ward trigger alerts

Variable	ICU ($n = 87$)	General ward ($n = 216$)	*p* value
Discontinue medication	25 (31.3)	53 (27.0)	0.45
Decrease dose	22 (27.5)	44 (22.4)	0.35
Decrease frequency	9 (11.3)	27 (13.8)	0.60
Decrease dose and decrease frequency	7 (8.8)	16 (8.2)	0.85
Hold or reschedule dose	4 (5.0)	17 (8.7)	0.45
Change medication	3 (3.8)	11 (5.6)	0.76
Order laboratory test	0 (0)	14 (7.1)	0.01
Increase dose	5 (6.3)	5 (2.6)	0.14
Start medication	2 (2.5)	4 (2.0)	1.00
Increase frequency	2 (2.5)	3 (1.5)	0.63
Increase dose and decrease frequency	1 (1.3)	1 (0.5)	0.49
Increase dose and increase frequency	0 (0)	1 (0.5)	1.00

Data are presented as *n* (%) unless otherwise indicated

Table 4 Positive predictive values for trigger alerts ($n = 19$) possibly associated with drug-related hazardous conditions

Patient population	No. of trigger alerts[a]	No. of DRHCs associated with trigger alerts[b]	PPV
ICU	73	48	0.66
General ward	88	67	0.76

DRHC drug-related hazardous condition, *ICU* intensive care unit, *PPV* positive predictive value

[a] These alerts were generated from 19 of the logic-based rules associated with drug-related laboratory abnormalities determined a priori to have a high probability of resulting in a DRHC

[b] Considered a DRHC after the application of a causality assessment

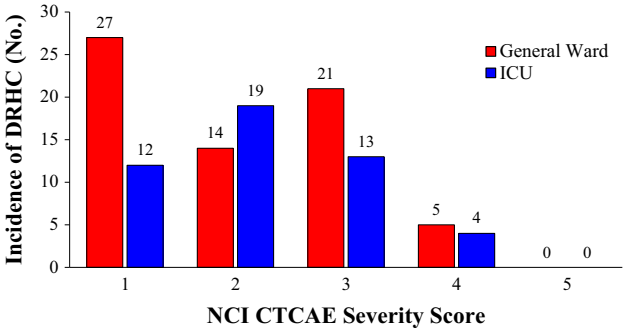

Fig. 2 Severity of drug-related hazardous conditions. *DRHC* drug-related hazardous condition, *ICU* intensive care unit, *NCI CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events (*1* mild, *2* moderate, *3* severe, *4* life-threatening, *5* death)

ICU and general ward patients. Similarly, we also examined physician acceptance of pharmacist recommendations and changes in drug therapy. Our results showed pharmacist intervention rates were slightly higher in the general ward population than in the critically ill, while the physician acceptance rates were more common in the ICU. Also, the rate of drug therapy changes resulting from pharmacist intervention was similar in both populations. The performance of these alerts, as measured by the PPV, for a subset of trigger alerts ($n = 19$) suggested that DRHCs were correctly identified more frequently in the general ward than in the ICU. Our study was unique in that we compared the clinical significance for trigger alerts between ICU and general ward patients, and stratified the severity of potential DRHCs. It is important to evaluate pharmacists' management of alerts, as this is one approach to more effective alerts, since alert generation within electronic charting and order entry systems has been identified as a reason for clinical decision support failure [30].

Two previously published studies evaluated the rates of pharmacist interventions and physician acceptance from automated trigger system alerts. Rommers et al. [22] evaluated the number of alerts and pharmacist intervention rates between two ADE surveillance strategies. A conventional ADE surveillance system consisting of pharmacists evaluating only drug–drug interactions and drug-overdose alerts overridden by physicians was compared with a more comprehensive system using logic-based clinical rules to detect potential ADEs. Overall, the total alerts generated by the conventional versus logic-based systems were 248 and 177, respectively. The investigators observed that 19.4 % of trigger alerts resulted in pharmacist intervention, with 71 % of pharmacist recommendations accepted by the physician at a university hospital.

Silverman et al. [19] evaluated trigger alerts utilized by pharmacists in preventing ADEs over a 3-year period at a tertiary care teaching facility. The logic-based rules in the automated surveillance trigger alerting system at this

institution were intermittently modified throughout the study period to improve alert performance, resulting in a high PPV. The total number of alerts generated each year over the study period was 25,995, 17,706, and 15,787. These investigators found a progressive increase in pharmacist intervention rates from 5.4 to 12.9 % in response to an automated trigger alert system, with a similar increase seen in physician acceptance of those interventions from 78.7 to 92.2 % over the study period.

The overall rate of pharmacist intervention (43.3 %) observed in our study was significantly higher than in the two previously mentioned studies. This finding may be explained by differences in the overall number of alerts as well as the potential for false-positive triggers from the logic-based rules customized at each respective institution. Also, approximately 36 % of all alerts assessed in our study were primarily directed at medication dosing, particularly renally eliminated drugs in patients with renal dysfunction. Furthermore, alerts evaluated in our study were generated in real time. Silverman et al. [19] noted a significant lag time between alert generation (24-h period extending to midnight of each day) and pharmacist evaluation of the alerts (beginning of each day shift). This lag time provides physicians time to react and possibly make changes prior to pharmacist evaluation. However, the lag time is concerning from a patient care perspective as it creates opportunities for ADEs and/or heightened ADE severity.

The physician acceptance rates and specific changes to drug therapy we observed were similar to those reported by Silverman et al. [19]. The higher physician acceptance rates observed in our study for the ICU may be attributed to dedicated pharmacists covering these units, with whom the physicians are familiar and confident in recommendations they make. Furthermore, differences in pharmacist available coverage (day and evening shifts) to address the trigger alerts, which were generated in real time, might explain this difference. We did not find that hospital setting significantly impacted the physician acceptance or change in therapy rates (data not shown). This also may be explained by the fact that all logic-based rules were exactly the same for all three study sites within our health system.

The subgroup analysis determining the performance of high probability alerts for drug-related laboratory abnormalities in our study found a higher PPV (0.76) in the general ward patient population. This was slightly lower than previously reported in a non-ICU setting by Rommers et al. [22] (PPV 0.85). However, the overall number of alerts in our study was significantly higher, which may have resulted in more opportunity for firing false-positive alerts [22]. To our knowledge, only one other study has evaluated the performance of alerts for drug-related events in real time in the ICU, but this was limited to five alerts [18]. Our data suggest that the performance of trigger alerts in identifying DRHCs, specifically drug-induced laboratory abnormalities, was not as successful in the critically ill as in the general ward population. These patients often have multisystem organ failure, which may mimic drug-induced clinical manifestations, making it more challenging to decipher between drug and disease causes.

Continuous process improvement of alert performance should be carried out to minimize false-positive alerts, which can be achieved by modifying logic-based rules or eliminating those associated with a low PPV so clinicians can focus their efforts on high-performance alerts. Unfortunately, several non-drug-related causes may contribute to the generation of a high incidence of false-positive trigger alerts [23]. Therefore, modifying logic-based rules to exclude such non-medication causes would improve the performance of trigger alerts preventing ADEs. Equally important is the scrupulous consideration that should be given to the creation of new alert triggers. Institutions may prematurely implement an action plan in response to significant ADEs as a 'knee-jerk' reaction by creating new trigger alerts without appropriately considering their performance.

Limitations of this study were primarily due to its retrospective nature, as we were dependent on documentation in the EMR. Although all events were assessed for severity using a validated scale, actual injury or harm was not evaluated. Clinical endpoints were not evaluated, so pharmacist intervention resulting from trigger alerts leading to improved outcomes remains unknown. Also, future studies should focus on the PPV of trigger alerts, the potential severity of DRHCs, and the clinical sequelae should pharmacist judgment determine that no intervention is required.

5 Conclusion

Automated surveillance methods involving trigger alerts in identifying DRHCs and preventing ADEs is a feasible strategy for pharmacists to incorporate into their patient care responsibilities. Pharmacists' interventions based on alerts and physician acceptance or recommendations were similar in ICU and general ward settings. The number and type of clinically significant alerts resulting in actual changes to drug therapy were similar irrespective of patient population, suggesting that these triggers may be equally beneficial in the ICU population, despite the challenges in drug-related event adjudication. Medical facilities utilizing this technology should regularly assess the performance of implemented trigger alerts as part of a continuous quality improvement strategy to ensure that they remain efficient at identifying potentially preventable ADEs.

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