MINIREVIEWS

Clinical decision support for drug related events: Moving towards better prevention

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Abstract

Clinical decision support (CDS) systems with automated alerts integrated into electronic medical records demonstrate efficacy for detecting medication errors (ME) and adverse drug events (ADEs). Critically ill patients are at increased risk for ME, ADEs and serious negative outcomes related to these events. Capitalizing on CDS to detect ME and prevent adverse drug related events has the potential to improve patient outcomes. The key to an effective medication safety surveillance system incorporating CDS is advancing the signals for alerts by using trajectory analyses to predict clinical events, instead of waiting for these events to occur. Additionally, incorporating cutting-edge biomarkers into alert knowledge in an effort to identify the need to adjust medication therapy portending harm will advance the current state of CDS. CDS can be taken a step further to identify drug related physiological events, which are less commonly included in surveillance systems. Predictive models for adverse events that combine patient factors with laboratory values and biomarkers are being established and these models can be the foundation for individualized CDS alerts to prevent impending ADEs.

Key words: Drug-related side effects and adverse reactions; Decision support systems; Clinical; Medication errors; Patient safety; Clinical pharmacy information systems; Intensive care units; Critical care; Adverse drug event; Clinical decision support systems

Core tip: Drug related events in the intensive care unit are associated with higher medical costs and dire patient outcomes. Clinical decision support (CDS) systems are the most important component to aid in adverse drug event (ADE) surveillance and improve in medication safety. Institutions are increasing the use of CDS systems for event detection and CDS systems that combine patient factors with laboratory values, drug information and biomarkers are key to effective ADE prevention.

INTRODUCTION

Medication errors (ME) occur at median rate of 106 per 1000 patient days in adult intensive care unit (ICU) patients[1]. ME are concerning because of the prospect of impending injury, known as a preventable adverse drug event (ADE). Table 1 provides definitions of drug related events[2-6]. Approximately one-third of ME result in ADEs[7,8]. Examples of ME resulting in ADEs include missed doses, wrong administration technique, duplicate therapies, drug interactions, equipment failure, inadequate monitoring and preparation errors[9].

Critically ill patients are at greater risk for MEs and ADEs compared to non-ICU patients because of the complexity of their drug regimens, sheer volume of medications that they receive, in particular, the volume of intravenous drugs received and acute changes in organ function that can alter the pharmacokinetics[8,10,11]. Prevention of ME and ADEs is important and the significance can resonate to a greater degree in critically ill patients because the severity of ADEs and related outcomes are worse compared to patients in other settings[8,12-14].

Institutions need to commit to an active medication safety surveillance system to detect and prevent drug related events and ensure the safest care possible[15]. Active medication safety surveillance systems use methods that can be categorized as: (1) retrospective approaches that are conducted after drug related events occur and often after the patient is discharged from the hospital; or (2) prospective approaches that capture events in real-time or as close to real-time as possible allowing for interventions to prevent the event from progressing to harm[16]. Voluntary reporting or incident reporting is the most commonly used retrospective surveillance method[17]. Retrospective methods also include non-targeted and targeted medical record reviews. While non-targeted medical record reviews encompass a detailed look at all patient data, a targeted medical record review such as one using a trigger tool focuses on a review of a particular set of patients[18]. Alternatively a targeted medical record review can focus on a particular section of the chart such as the discharge summary[19]. Prospective methods frequently rely on automated systems using clinical decision support (CDS).

CDS systems improve treatment outcomes and patient care by providing clinicians with patient-specific information that is intelligently filtered and presented at relevant times[20]. CDS is defined as "computer software employing a knowledgebase designed for use by a clinician involved in patient care, as a direct aid to clinical decision-making"[21,22]. CDS is typically incorporated as part of a computerized prescriber order entry (CPOE) system and is used to facilitate prevention of ME and ADEs. This system is used to provide feedback to clinicians through alerts and reminders when triggered by certain information available in electronic format[23]. CDS is more effective than voluntary reporting at identifying ADEs with only 1% of those events identified with CDS provided as incident reports[24]. Although overlap between voluntary reporting and automated CDS for ADE detection is reported as high as 13%[25]. Jha *et al*[24] demonstrated that CDS is more efficient than non-targeted medical record review requiring one-fifth less time to complete ADE surveillance: 11 h/wk *vs* 55 h/wk, respectively. It was also noted that while CDS identified slightly fewer events, the ADEs identified were different between methods, asserting that CDS is a necessary adjunct to medical record review. Overall, CDS is faster, less expensive and can identify ADEs not typically detected by clinicians when compared with voluntary reporting[26-31].

Many hospital systems are moving towards adopting electronic health records with meaningful use guidelines and incentives provided by the Center for Medicare and Medicaid Services, and this is enhancing the incorporation of CDS in patient care[32]. A 2015 survey[33] indicated 94.1% of hospitals adopted an electronic health record. This is important because collecting patient data electronically and applying systems to screen these data for ADEs are the initial steps to develop effective safety surveillance[29]. The same survey reports 80.9% of hospitals employ an inpatient CPOE system with CDS, a remarkable 78.2% increase since 2003[33]. In this article, we discuss the effective use of CDS for detecting ME and ADEs, then we will propose ways to use CDS for the prevention of ADEs to further enhance the safety of patients.

Table 1	Definitions of drug related events

Term	Definition
Medication error[2]	"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. This may include errors in prescribing, distribution, administration and monitoring"
Adverse drug reaction[3]	"Any undesired, unexpected, or unintended outcome associated with drug use"
Drug-related hazardous condition[3,4]	"Is the antecedent to injury or the temporal gap between the identification of an adverse drug reaction and the drug induced injury". It occurs in the presence or absence of a medication error
ADE[5]	"Injury associated with the use of a drug"
Preventable ADEs[6]	"Injury associated with a medication error"
Potential ADEs[5]	"Medication errors with the potential to cause harm, but harm does not actually occur. Potential ADEs can be further described as intercepted and non-intercepted"
Trigger[6]	"Signals or clues used to identify adverse events"

ADE: Adverse drug event.

DETECTION OF ME AND ADES USING CDS

CDS systems are effective at detecting potential ME and alerting prescribers so that appropriate evaluation and action can be taken. Healthcare providers are inconsistent in the identification of ME because of personal knowledge, previous experience and timing of the medication order review; therefore, it is essential to have a reliable surveillance system to aid in identification[34]. Raschke *et al*[35] reported that 44% of ME would have been missed without the use of CDS. Further, a systematic review of studies evaluating CDS alerts generated in response to drug dose selection for patients with acute kidney injury (AKI) demonstrated that 17 out of 19 studies effectively detected ME allowing for intervention with the implementation of CDS[36]. The thought is that detection of ME with CDS due to scenarios such as inappropriate dosing based on age, weight, underlying condition and renal function will allow for intervention and prevention of potential ADEs.

An effective tool to assist with adverse event identification is the Institute for Healthcare Improvement Trigger Tool that contains a specific module focused on ADEs[6]. The trigger tool demonstrates utility as it was used to detect 230 ADEs in 1009 ICU patient days in 79 patients[14]. Interestingly in this study, only the three triggers were responsible for detecting 78% of ADEs. While the trigger tool was evaluated manually, the triggers can be used as the knowledge or signals for the development of automated alerts using CDS.

Classen *et al*[25] developed a clinical event monitor allowing for detection of ADEs using automated trigger or alert. An alert was sent to the physician when there was a potential for an ADE, upon confirmation of the ADE, the medication(s) were stopped, substituted or an antidote was given if needed. In this 18-mo study, 631 of 731 ADEs identified were detected using automated CDS with the majority of ADEs described as moderate or severe.

While research shows that automated CDS alerts are useful in the clinical setting, alerts for ADE detection can be ineffective at preventing harm because alerts are generated with minimal time for intervention or more often alerts are generated after the patient is already experiencing an ADE. This is apparent in the use of the alerts targeted at antidote administration designed for detection and not prevention since the event is already in the midst of treatment. Table 2[17,37-39] provides examples of alerts designed for event detection. Another type of alert geared to detection are abnormal laboratory value alerts with thresholds that exceed the recommended laboratory limit or higher. Alert thresholds with abnormal values higher than acceptable are often targeted at high specificity and low sensitivity, thus possibly reducing alert fatigue but limiting the value in ADE prevention[40]. Still antidote alerts and alerts set with a high abnormal laboratory value thresholds can be useful in understanding the environment, providing an opportunity to assess for causal factors and preventing future events through systematic changes[37]. It can even be beneficial to identify non-preventable ADEs using CDS systems to mitigate the intensity of the injury[9].

ADE PREVENTION CONSIDERATIONS FOR ALERT DEVELOPMENT

The next step in CDS advancement is predicting impending injury/end-organ damage and identifying events using pre-emptive triggers with ample time to intervene. This is the ideal application of a drug related hazardous condition (DRHC), which is the early identification of a drug-related event before the ADE occurs[3,4]. Ten drugs are responsible for over sixty percent of preventable ADEs, including anticoagulants, opiate agonists, and insulin[41]. This suggests that ADEs are not as random as one thinks and it is practical to use this information to build effective CDS. Also, these preventable events are triggered by the progressive decline in laboratory and physiologic markers allowing time for intervention and prevention of harm.

CDS that generates alerts to prevent ADEs utilizing patient laboratory values and drug information has great potential to improve patient outcomes. For example, Moore *et al*[42] suggests to create an alert to prevent a

Table 2 Examples of alerts designed to detect drug-related events

Ref.	Alert designed for detection
Stockwell *et al*[37]	Abnormal laboratory value exceeding recommended upper limit
	Examples
Harinstein *et al*[38]	ACE inhibitor/ARB and patient's serum potassium is > 6 mmol/L
	INR > 4 and on warfarin
	Blood glucose < 40 mg/dL and on antidiabetic agent
	Platelet count < 50000/mm^3 and on a drug that causes thrombocytopenia
Kane-Gill *et al*[39]	Unexpected discontinuation of drug
Kane-Gill *et al*[17,39]	Antidote evaluations such as flumazenil, naloxone, sodium polystyrene, protamine, dextrose 50%; lepirudin use; argatroban use

ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; INR: International normalized ratio.

severe hypoglycemic state by warning when the occurrence of three consecutive low glucose occurs in the presence of a new anti-diabetic medication. The alert should be generated as the glucose levels deteriorate, even before the patient reaches an unacceptable glucose level and experiences mental status changes. Another example of a prevention alert is a patient that does not have a bowel movement in 24 h following initiation of an opioid. In this scenario, there is no need to wait until the patient becomes impacted if a bowel stimulant is begun. Using CDS to generate alerts for ADE prevention have been tested with success[9,35,42-48]. More examples of preventative alerts are provided in Table 3.

MOVING TOWARDS BETTER ADE PREVENTION

Percent change in laboratory values instead of absolute cut points and trajectory analysis

Movement in the area of ADE prevention requires clinicians to change the mindset of specific cut points in the laboratory values and consider percent change and percent change over time when appropriate. An example of this is identifying drug induced AKI. Previous CDS alerts were built on an absolute serum creatinine value of $\geqslant$ 1.5 mg/dL or an absolute increase in serum creatinine of 0.5 mg/dL[49,50]. This approach does not account for the patient's baseline serum creatinine and is likely to miss important events in patients with low baselines (*e.g.*, young women, vegetarians) or result in false positives in patients with underlying chronic kidney disease. Others have applied knowledge to signal an alert at a 50% increase in serum creatinine from baseline; however, that may miss small changes in serum creatinine and miss opportunities for early intervention[51]. Recent alerts are designed on the Kidney Disease Improving Global Outcomes (KDIGO) criteria or the serum creatinine component of the KDIGO criteria when urine output is unavailable[52,53]. According to the

KDIGO guidelines, a patient is classified as AKI stage 1 if there is a 0.3 mg/dL increase in serum creatinine in 48 h or an increase in serum increase of 1.5-1.9 times baseline in 7 d. This abrupt change considers time and baseline values providing a more detailed assessment of kidney function and opportunities for early alert and interventions. If a baseline serum creatinine is unavailable, then there are methods of estimation to consider[54]. Stage 2 and Stage 3 AKI alerts per KDIGO may not provide opportunity for prevention but appropriate management at this point may mitigate severity and prevent permanent injury.

The concept of trajectory analysis applied to alerts would allow for a pre-emptive alert to be generated when there is a percent change in the laboratory value over a specified period. This would predict that the laboratory value would eventually be out of an acceptable range before it actually reaches the unacceptable range. Signals for alerts are set to a triglyceride of > 400 mg/dL (unacceptable range) when receiving propofol. There would be an advantage to scanning for a percent increase over a couple of days instead of waiting for the absolute number to be achieved. Importantly, this could be applied to abnormal international normalized ratio (INR) values for patient receiving warfarin. Waiting until an INR of 4 or 5 occurs before being alerted could waste valuable time in preventing an ADE, instead a 20% rise daily over 3 d could be a preventative trigger. This concept could also be applied to drug concentrations. The key to the successful use a trajectory analysis will be supporting the percent change as clinically meaningful by selecting percent changes relative to the occurrence of an ADE. Table 4 provides an example of using percent change for drug-induced thrombocytopenia instead of applying an absolute cut point[38].

Biomarkers

The use of DRHCs or biochemical, physiologic, or clinical status change caused by medications, portending further injury is sometimes difficult when our biomarkers lag behind the actual injury[3,4]. This is true in the case of AKI. Generating an alert after identifying a spike in serum creatinine may be too late as there is already significant damage and loss of kidney function[55].

Cystatin C, is a better detector of kidney injury when compared with serum creatinine and some research suggests that serum cystatin C can discriminate between patients that develop AKI and patients whose serum creatinine will return to baseline in 48 h[55]. This biomarker shows promise for early detection and earlier intervention. Additionally, a study by Frazee *et al*[56] shows that biomarkers can also improve drug dosing. This study showed that vancomycin dosing in the ICU can be improved 2.5 fold when using cystatin C and serum creatinine to estimate GFR as opposed to just serum creatinine alone[56]. Interestingly, some biomarkers can also identify the type of kidney injury and the location of damage. If these are included in the signals for alert generations, clinicians will be able to

Table 3	Examples of preventative alerts		
Ref.	Drug related hazardous condition for alert detection	Adverse drug event prevention	Criteria for prevention alert
Rommers *et al*[43]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Elderly patient who is not taking a PPI and is started on an NSAID
Moore *et al*[42]	Hypoglycemia	Mental status changes	Receiving a new antidiabetic agent and 3 consecutive low glucose results that are steadily declining over a period of time
Moore *et al*[42]	Hypokalemia	Dysrhythmia	Drug started causing hypokalemia + potassium level under 3.8 mEq/L
Moore *et al*[42]	Thrombocytopenia	Bleed	Drug started causing thrombocytopenia and platelets slowly decrease over 50000/mm^3 within 4 d
Moore *et al*[42]	Hyperkalemia	Dysrhythmia	Drug started causing hyperkalemia + potassium level over 5.5 mEq/L and increasing slowly over 72 h
Raschke *et al*[35]	C. difficile	Permanent gastrointestinal disorders (*i.e.*, irritable bowel syndrome, colectomy)	Antidiarrheal and recent aggressive antibiotic therapy OR history of Clostiridum difficile
Rommers *et al*[43] and Silverman *et al*[44]	Before DRHC occurs-eventually digoxin level elevated	Dysrhythmia, confusion	Patient with 3 consecutive increasing serum creatinine levels and also on digoxin therapy (or other renally cleared drugs would apply such as metformin, enoxaparin, vancomycin)
Rommers *et al*[43]	Constipation	Bowel obstruction	Narcotic started recently and patient has a history of constipation or narcotic started recently and patient has not had a bowel movement in over 24 h
Van Doormaal *et al*[45]	Constipation	Bowel obstruction	Opioid prescribed without a co-prescription of a stimulant laxative
Van Doormaal *et al*[45]	KDIGO stage 1 AKI-in the future biomarkers may be the early sign of AKI before SCr rise	KDIGO stage 3 AKI	Sulfonamide urea derivate is prescribed and the patient has a creatinine clearance of less than 10 mL/min
DiPoto *et al*[46]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Patient has epidural and started on an anticoagulant or antiplatelet
DiPoto *et al*[46]	Sedation	Mental status changes	Fentanyl patch and no documented history of long-acting opioid use
Silverman *et al*[44] and Jha *et al*[47]	ALT rising	Hepatic failure	Hepatotoxic drug and ALT increase by 20%
Silverman *et al*[44] and Jha *et al*[47]	Osmolarity increasing	Mental status changes, risk of death	Lorazepam use and osmolarity increasing

DRHC: Drug related hazardous condition; KDIGO: Kidney Disease Improving Global Outcomes; AKI: Acute kidney injury; ALT: Alanine aminotransferase.

make a quicker treatment decisions.

Another biomarker panel that is currently available in clinical practice is urinary tissue inhibitor of metalloproteinase (TIMP-2) and insulin-like growth factor-binding protein (IGFBP7). This combination of biomarkers available in Nephrocheck™ predict patients at risk for developing AKI within 12 to 24 h following sample collection[57]. This makes TIMP-2/IGFBP7 a valuable marker to consider when designing preventative alerts in the future as we learn about the impact of using these biomarkers on patient care.

Drug induced liver injury also continues to be problematic, and clinicians can benefit from early identification of this injury. Research continues to find biomarkers to indicate drug injury such as microRNAs and serum metabolites presenting as better indicators than ALT[58]. Biomarkers, such as the ones discussed above, can be employed in the future to guide clinicians in making early interventions with CDS alerts.

Drug combinations

The risk of an ADE may change when drugs are combined. Non-critically ill children receiving aminoglycosides or other nephrotoxins for more than 3 d in the hospital are at risk for drug induced AKI[59]. AKI can be prevented by using CDS to alert clinicians when patients receive 3 or more nephrotoxins followed by close monitoring of serum creatinine[59]. This CDS application resulted in improved patient outcomes including a 42% decrease in the observance of AKI intensity[60]. Future studies need to test this CDS in critically ill and non-critically ill adults. Constructing alerts based on thoughtful consideration of high-risk drug combinations has the potential to prevent ADEs.

Drug induced physiologic events

As noted, the majority of CDS for ADE prevention includes abnormal laboratory concentrations as the trigger for an alert. Less frequently, hospitals report surveillance of drug-induced physiologic events[17]. In general, we have created better CDS to identify patients undergoing clinical deterioration or at the first signs of sepsis by incorporating blood pressure, heart rate and respiratory rate into alerts[61,62]. Physiologic parameters such as blood pressure are drug induced and can be the next set of preventative ADE alerts we develop to improve patient care[3].

Predictive analytics and forecasting models

Using a holistic approach to predict the risk of disease

Table 4 Alerts to predict an impeding adverse drug event using percent changed in the laboratory value

Ref.	Drug related hazardous condition for alert detection	Adverse drug event preventing	Criteria for prevention alert
Harinstein *et al*[38]	Platelet drop	Bleed	≥ 50% decrease in platelets between most recent and second most recent platelet count
Harinstein *et al*[38]	Platelet drop	Bleed	2 consecutive decreases in platelets with ≥ 25% difference between the third most recent and the most recent platelet count

Table 5 Summary of proposed approaches to developing clinical decision support to prevent adverse drug events

Proposed approach	Description
Trajectory analysis	Identify laboratory values as they are on the incline or decline before they reach a critical value
Biomarkers	Use biomarkers that identify patients at risk for organ damage
Drug combinations	Generate alerts for drug combinations that place the patient at risk for drug-induced injury
Drug induced physiologic events	Add alerts for possible drug induced alterations in physiologic parameters to clinical decision support
Predictive analytics and forecasting models	Develop models that predict possible drug induced injury based on risk factors and use this information for advanced alerts using machine learning for adaptive response

may be the best way to prevent unfavorable health outcomes, such as ADEs. In the case of AKI, many predictive models have been developed, though not necessarily in the critical care setting where there is a need[63,64]. Variables included in predictive models are age, gender, race, co-morbidities and acute conditions. Combining known patient risk factors with laboratory data and biomarkers would make an ideal predictive model and aid in preventative ADE alert development. This model also could employ machine learning techniques and incorporate population/region specific data to better predict patient risk and outcomes to accommodate adaptive changes (Table 5).

CONCLUSION

The concern for harmful outcomes associated ADEs, especially preventable ADEs makes reliable and effective CDS systems a necessary addition for surveillance, especially for critically ill patients. CDS systems can be used to further improve patient outcomes when directed at preventing ADEs and moving beyond detection. CDS designed to generate alerts portending injury allows providers time for intervention. Studies designed to maximize the benefit of preventative alerts and

determine the impact on patient outcomes are needed.

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