Online Special Article

Clinical Practice Guideline: Safe Medication Use in the ICU

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Mr. Dasta received funding from Bayer Pharma (consultant: health economics pneumonia), the Medicines Company (consultant: pain management), and he disclosed that he owns stock in Merck, Pfizer, Abbvie, Abbott Labs, Bristol Myers Squibb, Eli Lilly, and Express Scripts. Dr. George participates in the American Association of Critical Care Nurses (journal article reviews for continuing education) and disclosed that she had a one-time contract with Medtronic for speaking engagement on capnography, presented at American Association of Critical Care Nurses National Training Institute May 2016. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000002533

Objective: To provide ICU clinicians with evidence-based guidance on safe medication use practices for the critically ill.

Data Sources: PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, Scopus, and ISI Web of Science for relevant material to December 2015.

Study Selection: Based on three key components: 1) environment and patients, 2) the medication use process, and 3) the patient safety surveillance system. The committee collectively developed Population, Intervention, Comparator, Outcome questions and quality of evidence statements pertaining to medication errors and adverse drug events addressing the key components. A total of 34 Population, Intervention, Comparator, Outcome questions, five quality of evidence statements, and one commentary on disclosure was developed.

Data Extraction: Subcommittee members were assigned selected Population, Intervention, Comparator, Outcome questions or quality of evidence statements. Subcommittee members completed their Grading of Recommendations Assessment, Development, and Evaluation of the question with his/her quality of evidence assessment and proposed strength of recommendation, then the draft was reviewed by the relevant subcommittee. The subcommittee collectively reviewed the evidence profiles for each question they developed. After the draft was discussed and approved by the entire committee, then the document was circulated among

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all members for voting on the quality of evidence and strength of recommendation.

Data Synthesis: The committee followed the principles of the Grading of Recommendations Assessment, Development, and Evaluation system to determine quality of evidence and strength of recommendations.

Conclusions: This guideline evaluates the ICU environment as a risk for medication-related events and the environmental changes that are possible to improve safe medication use. Prevention strategies for medication-related events are reviewed by medication use process node (prescribing, distribution, administration, monitoring). Detailed considerations to an active surveillance system that includes reporting, identification, and evaluation are discussed. Also, highlighted is the need for future research for safe medication practices that is specific to critically ill patients. (*Crit Care Med* 2017; 45:e877–e915)

Key Words: critical care intensive care unit; drug-related side effects and adverse reactions; medication errors; patient safety; safety management

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The landmark report "To Err Is Human" increased the awareness of unacceptably high rates of medical errors and sentinel events in U.S. hospitals with about 44,000–98,000 deaths annually attributed to these preventable mishaps (1). It is important to recognize preventing harm resulting from adverse drug events (ADEs) may be circumvented by averting medication errors (MEs) with appropriate medication use, planning, and monitoring (2). Frequency of MEs is estimated to occur in 19% of hospitalized patients (3). About one in every five medication doses administered to hospitalized patients are considered MEs (4).

MEs and ADEs are a common and significant concern in the ICU since they represent a leading cause of iatrogenic errors in the critically ill population (5–7). MEs occur at a higher frequency and with a greater likelihood of harm in ICU patients compared with non-ICU patients (8–11). The median frequency of MEs is 106 per 1,000 patient days in adult ICUs (9). Adult medical ICU (MICU) patients are one of the highest risk populations to experience a ME, compared with other critically ill adult populations (8, 10, 12, 13). Further, the pediatric critically ill patient is another population at high risk for MEs and ADEs (12).

MEs and ADEs are associated with deleterious outcomes. The increase in hospital length of stay (LOS) approaches 5 days as a result of preventable ADEs (14). Patients experiencing ADEs from IV administered medications in academic hospitals have longer hospital stays compared with those not experiencing an ADE (16.0 vs 11.3 d, respectively; $p = 0.0003$) (15); conversely, no increase in hospital LOS following an ADE is observed in nonteaching institutions (15). One study found a nonsignificant trend in increased the LOS following an ADE in ICU versus non-ICU patients (10). Vargas et al (16) reported the ICU LOS for patients with greater than or equal to two ADEs was significantly longer (10.7 d) than ICU patients without any ADEs (4.2 d) or only having one ADE (6.0 d). This translates into an additional 2.4 days for each ADE experienced by the patient (16). In a surgical ICU (SICU) population, the ICU LOS was increased by 2.3 days (17). ADEs may result in transient or permanent injury. High-risk medications with the potential for organ injury are commonly administered in the ICU (9). Errors with these high-risk medications may increase the risk of nonfatal, yet serious ADEs. Drug-induced complications may include bleeding diathesis, renal or hepatic failure, arrhythmias, and altered mentation (9).

The management of ADEs and associated complications, as well as the potential increase in hospital LOS as a result of preventable ADEs, incurs an enormous economic burden on the healthcare system. The mean attributable costs related to an ADE and for those considered serious ADEs were reported as $2,013 and $3,634 per event, respectively (18). Estimated hospital costs associated with each preventable ADE are $11,524, so the projected hospital expenditure is about $2.8 million annually (18). It should be noted these costs do not represent current value since these studies were published almost 2 decades ago, an estimate of current value is $4.1 million annually. Cullen et al (10) concluded total costs and charges accumulated after an ADE were not significantly higher in ICU compared with non-ICU patients. Also, the total costs and charges associated with an ADE were similar in a MICU and SICU setting (10).

Classen et al (14) observed a higher crude mortality rate of 3.5% in hospitalized (ICU and non-ICU) patients who had an ADE compared with 1.1% in those without ADEs ($p < 0.001$). Several ICU studies reported a relatively low frequency of death ranging from 0.03% to 4.2% possibly as a result of MEs and preventable ADEs (8, 12, 19, 20). However, establishing causality of death in an ICU patient as a direct result from a specific medication remains a challenge due to the presence of multiple confounding variables such as comorbid disease states, severity of illness, and treatment variability (9). One report estimated 106,000 hospitalized patients in the United States experienced a fatal adverse drug reaction (ADR) during 1994 (21). Comparing the fatal ADR rate to the overall recorded death rate (2,286,000) during that same year, these drug-induced fatalities ranked between the fourth and sixth leading causes of death in the United States (21). Therefore, drug-induced fatalities in the ICU are a pragmatic concern despite the paucity of data.

Patient safety is a priority for several government agencies, nonprofit organizations, and regulatory bodies considering the detrimental and financial consequences associated with MEs and ADEs. The Institute of Medicine (IOM) has recommended government agencies such as the Food and Drug Administration (FDA), Agency for Healthcare Research and Quality (AHRQ), Centers for Medicare & Medicaid Services (CMS), and the National Library of Medicine improve consumer-oriented drug information resources and medication self-management support (22). Overall, several government, as well as, nonprofit organizations have identified medication safety as a priority for healthcare in the United States (21–24). The Institute of Healthcare Improvement and Institute for Safe

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Medication Practices (ISMP) provide tools and resources to improve patient safety in healthcare systems (23, 24).

The implementation of CMS value-based purchasing programs has promoted a change in culture of adopting quality improvement strategies aimed at patient safety (23). This reimbursement model shifts the focus to the quality of care as opposed to the quantity of hospital services provided (23). This is especially true in the ICU given the variability, complexity, and high costs associated with care (23). The quality of care should be efficient, effective, accountable, and safe. Therefore, hospitals and ICUs must transform into high-reliability organizations (HROs) (2). HROs (e.g., aviation, nuclear power generation plants) are capable of maintaining a state of near failure-free operations in complex and hazardous environments (2). These HROs balance reliable processes with a capacity to learn from experience and adapt to changing circumstances by enacting five high-level values (24): 1) sensitivity to system operations and failures no matter how trivial; 2) avoiding overly simplistic explanations of failure; 3) learning from near misses to improve the system; 4) deference to expertise of each team member; and 5) resilience. Although the provision of healthcare is highly complex and different from other high-risk industries, HRO principles have been applied effectively (25, 26) to achieve significant and sustained reductions in preventable harm and mortality from healthcare-associated infections (27–31). Additional research is needed to evaluate if HRO principles can be applied to a broader set of interventions to reduce MEs.

An ideal patient safety culture in an ICU setting should incorporate multiple ME prevention strategies at all phases of the medication use process (prescribing, dispensing, administration, monitoring). Several strategies seem promising in circumventing MEs and improving patient outcomes. The use of technology including computerized prescriber order entry (CPOE), clinical decision support systems (CDSS), bar-coded medication administration (BCMA) systems, and smart IV infusion pumps is used to minimize the risk of error (32). Also, implementing new practices such as medication reconciliation and standardized IV medication concentration practices serve as a potential option to reduce MEs (2). An active patient safety surveillance system may identify possible drug-related events to either prevent injury in real time or prevent events in future patients (33). Other approaches include intensivist and clinical pharmacist participation in the care of ICU patients as well as ensuring adequate staffing levels for all healthcare professionals (2, 9).

MEs and ADEs in the ICU remain problematic despite increased awareness, regulatory mandates, and technological advances. Unfortunately, most hospitals face logistic, financial, and cultural challenges in implementing safe medication practices. Given the complexity of critically ill patients throughout the continuum of care and limited hospital resources, each institution must evaluate potential strategies to adopt in their respective ICUs. Patient safety is a priority for several government agencies, nonprofit organizations, and regulatory bodies considering the detrimental and financial consequences associated with MEs and ADEs. Despite the focus to improve safe medication use in the acute care setting, recommendations for safe medication practices are not specific to the ICU setting. Therefore, the goal of this clinical practice guideline is to recommend safe medication use practices with the supporting evidence, when available, specifically in the critically ill.

METHODS

Guideline Structure and Definitions

The American College of Critical Care Medicine appointed a 15-member interdisciplinary task force with expertise in medication safety. The committee met for an in-person meeting at the SCCM Congress in 2010 and decided to structure the guidelines on three key components: 1) environment and patient, 2) the medication use process, and 3) the patient safety surveillance system. The medication use process can be divided into four categories: prescription, dispensing, administration, and monitoring. As such, the committee collectively developed clinical questions pertaining to MEs and ADEs addressing the steps of the medication use process. To ensure that the committee used a consistent approach, a general consensus was reached on the definitions of these terms (**Table 1**). Another important concept of safe medication use is the ME and ADE surveillance to capture events, either retrospectively (after patient is discharged from hospital) or concurrently (while patient is still hospitalized). The concepts of surveillance that were considered include systems for reporting, methods of ME and ADE detection, and methods of evaluation. Population, Intervention, Comparator, Outcome (PICO) questions and quality of evidence statements were developed to consider these concepts of patient safety surveillance. The committee did undergo some changes during the process fluctuating between 15 and 17 members but always maintaining an interdisciplinary mix.

Question Development

Subcommittees were formed and assigned to one of nine topic areas: environment and patients, prescribing, dispensing, administration, monitoring, patient safety surveillance systems, methods of ME/ADE detection, suspicious clinical event evaluation, and methods of evaluating data. Each subcommittee refined clinical questions that were initially drafted by the committee at the in-person meeting. The clinical questions were categorized as either "descriptive" or "actionable" terms. They structured descriptive questions into quality of evidence statements and actionable questions in the PICO format. All refined questions and statements were then approved by the entire committee (40, 41). The subcommittees also identified, reviewed, and evaluated the literature, crafted recommendations, and drafted their section of the guidelines.

Literature Search Techniques

A total of 34 PICO questions, five quality of evidence statements, and one commentary on disclosure of drug-related events was developed. The committee determined appropriate keywords and medical subject heading (MeSH) terms that included at minimum: ME and/or ADEs crossed against the

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TABLE 1. Definitions of Terms Used to Describe Medication Related Events

Term	Definition
Medical error	The failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. Errors can include problems in practice, products, procedures, and systems (1).
ME	Any error in the medication process, whether or not there are adverse consequences (34).
Adverse drug reaction	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product (35).
ADE	Any injury related to use of drug. Not all ADEs are caused by medical errors. Also, not all MEs lead to ADEs (36, 37).
Preventable ADE	Injury associated with a ME (9, 38).
Near miss (potential ADE)	The occurrence of an error that did not result in harm. Potential ADEs can be intercepted or nonintercepted (9, 38).
Drug-related hazardous condition	Physiologic response to a drug with potential to cause injury; abnormal laboratory value before it results in ADE (39).

ADE = adverse drug event, ME = medication error.

general topic area and the specific question for each section of the guidelines. A professional librarian (C.K.) reviewed and developed appropriate search strategies for each section. Search results were stored in an electronic, Web-based, password-protected database using RefWorks software. Search strategies were then saved and used in the development of weekly alerts for each section providing access to any new published citations pertinent to each section. The seven databases that were included in all searches were PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, Scopus, ISI Web of Science, and the International Pharmaceutical Abstracts. Search terms included published English-only manuscripts on both pediatric and adult humans. Editorials, narrative reviews, case reports, animal or in vivo studies, and letters to the editor were excluded. Biweekly automated searches were continued up until March 2013 with identified relevant articles being incorporated into the guidelines. Available evidence was summarized in the form of tables.

In order to incorporate the most recent literature, a search was repeated inclusive of March 2013 to December 2015. A combination of keywords and MeSH terms used in the previous search was applied by a professional librarian (K.O.). The searches were conducted in the databases PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, Scopus, and ISI Web of Science. The results were limited to articles published in English.

Grading of Recommendations

The committee followed the principles of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to determine quality of evidence and strength of recommendations (42–44). The GRADE approach provides a framework for authors to perform a sequential assessment of the quality of evidence, followed by an evaluation of the balance between the benefits and risks, burden and cost, which leads to development and grading of recommendation. GRADE classifies quality of evidence as high (grade A), moderate (grade B), low (grade C), or very low (grade D), which have been described in previous guidelines (42–46). In general, randomized trials provide stronger evidence than observational trials for recommendations addressing two potential management strategies. Rigorous observational trials provide stronger evidence than uncontrolled case series. However, a randomized controlled trial (RCT) is not necessarily classified as high-quality evidence depending on the study design. A RCT can be downgraded due to major limitations, inconsistency or imprecision of results, indirectness of evidence, or possible publication bias. Evidence from observational trials without limitations is initially considered low quality. However, observational trials can be upgraded if there is a very large magnitude and consistent estimates in the treatment effect or clinically significant dose-response gradient. The clinical questions deemed descriptive and thus quality of evidence statements received a GRADE for quality of evidence but were not assigned a recommendation because they were not actionable.

After the quality of evidence is reviewed, then the strength of recommendations can be rated. GRADE classifies recommendations as either strong (grade 1) or weak (grade 2) and either for (+) or against (–) an intervention based on both quality of evidence and risks and benefits. A "no recommendation" (grade 0) could also be made due to either 1) a minimal level of evidence being insufficient to provide a recommendation or 2) no data published regarding the question with a corresponding quality evidence of "C", "D," or "no evidence." Thus, 0C, 0D or 0, no evidence is designated as appropriate. Questions with no evidence were included in these guidelines as the committee felt they were important questions that may generate future research. We also considered national organization recommendations and regulations in our assessment. National organization recommendations sometimes lack evidence for adoption but make intuitive sense for patient safety improvement. The committee did not use consensus statements based on expert opinion alone if no evidence supported

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a recommendation. Factors used to determine the strength of recommendation include balance between desirable and undesirable effects, quality of evidence, uncertainty of variability in values and preferences, and uncertainty about impact of intervention on resource allocations. The committee critically analyzed the desirable effects of adherence (e.g., desirable health outcomes, less burden on staff and patients, and potential cost savings) against the undesirable effects (e.g., patient harm due to adverse effects, increased burden on staff and patients, and greater costs). The strength of the recommendation is dependent on the committee's level of confidence regarding the analysis. The committee makes strong recommendations when they are confident the desirable effects of the intervention clearly outweigh the undesirable effects. On the basis of this information, the majority of patients and providers would favor this course of action if given the option. A strong recommendation is worded as "we recommend." Weak recommendations indicate that the desirable effects of adherence probably outweigh the undesirable effects, but the committee is less confident. Most people might pursue this course of action, but a significant number of patients and providers would consider alternative options. A weak recommendation is worded as "we suggest."

Subcommittee members were assigned selected PICO questions or quality of evidence statements. Once the subcommittee member completed their GRADE of the question with his/her quality of evidence assessment and proposed strength of recommendation, then the draft was reviewed by the relevant subcommittee. The subcommittee collectively reviewed the evidence profiles for each question they developed. They determined the overall quality of evidence, the strength of recommendations for actionable questions only, and drafted evidence summaries for review by other committee members. Upon subcommittee approval, the chair of the committee reviewed the draft and provided any comments and suggestions for revision. The comments from the discussion of the subcommittee and chair were incorporated into the next version of the recommendations and again discussed with the entire committee using electronic mail and regularly scheduled conference calls. After the draft was approved by the committee, the document was circulated among all members for voting on the quality of evidence and strength of recommendation.

Group consensus for all statements and recommendations was achieved using an anonymous voting scheme. Task force members reviewed the GRADE evidence summaries, statements, and recommendations. Then members voted as well as commented anonymously on each statement and recommendation using a web-based survey tool. To achieve consensus on strength of evidence for each question, the committee required a majority vote defined as greater than 50%. For strength of recommendations, consensus for a recommendation in favor of an intervention was defined as greater than 50% of the committee voting for a recommendation in favor; however, less than 20% of the committee had to vote for a recommendation against intervention in order for the voting to be accepted. If either of these consensus criteria was not met, then no recommendation was recorded for the statement. In order for a recommendation to be strong, at least 70% of the committee had to vote for a strong recommendation in favor of the intervention. Failure to meet this voting threshold resulted in a weak recommendation. This method for reaching consensus has been used in previous guidelines to ensure fairness, transparency, and anonymity in creation of the recommendations (45, 46). After voting was complete, the polling results were compiled and distributed to the committee for review and discussion. If a round of voting failed to achieve consensus among the committee members, then another round of voting commenced after additional discussion via e-mail and/or conference call. This approach was continued until the rate of agreement described above was reached. Polling for all questions was completed by August 2014. Revoting did occur when evidence was available that could alter the quality of evidence in the updated literature search (2013–2015). This voting was completed by June 2016. Distribution of the final voting tallies along with comments by task force members for each statement and recommendation is summarized in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C669). The article was edited for style and form by the writing committee (S.K.G., J.F.D., M.S.B., S.D., and H.C.) with final approval by the entire committee.

Conflict of Interest Policy

Task force members were required to complete annual conflict of interest statements. Any committee member who had a conflict of interest was asked to recuse from reviewing and grading evidence. All task force members voted anonymously on the final quality of evidence and strength of recommendations for each question. The task force did not receive any industry funding to develop any section of these guidelines.

A. ENVIRONMENT AND PATIENTS: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

1. Environment: ICU Versus Non-ICU

Statement: In adult ICU and PICU patients, the severity or harm associated with MEs/ADEs is greater compared to non-ICUs. (B)

Rationale: The ICU is a complex, high-acuity environment requiring specialized, skilled care. The risk associated with MEs and ADEs in the ICU is multifactorial including polypharmacy with a substantial number of IV medications and patients with organ dysfunction that alter the pharmacokinetics of drugs. Prospective and retrospective studies indicate the risk for harm from MEs and ADEs is more substantial in the ICU than non-ICU hospitalized patients (10). The risk for harm associated with MEs and ADEs is about 2–3 times greater in ICU patients than in non-ICU, whereas the probability of death is approximately a 2.5 times higher in the ICU (8, 11).

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2. Environment: Safety Culture–Part 1

Question: In adult ICU and PICU patients, do changes in the climate or culture of safety in the environment of the medication use process increase the frequency of reporting MEs or ADEs?

Answer: We suggest implementing changes in the culture of safety to increase the frequency of ME reporting. (2D)

Rationale: The IOM defines safety culture as "The product of individual and group values, attitudes, perceptions, competencies, and patterns of behavior that determine the commitment to, and the style and proficiency of, an organization's health and safety management." The term "safety climate" is used similarly. The nine included studies used a wide variety of definitions of changes to the hospital culture and equally wide variability in reported outcomes associated with these changes. Furthermore, the overall quality of evidence on the stated outcome is very low. Despite this quality of evidence and lack of uniform definitions of both culture change and stated outcomes, a weak recommendation in favor of implementing changes to the culture of safety in the organization was made. Although we recognize that many of these changes in culture will require considerable effort and increased staff time and are associated with significant costs of implementation, they are designed to have beneficial effects on medication safety. Increasing reporting allows for comprehensive analysis of events and systematic changes to avoid future occurrences. We also suggest future studies use uniform definitions of both culture change as well as outcomes and should evaluate rates of ME and ADE reporting in adult ICU and PICU settings.

The following studies evaluated either surrogate markers of changes in either culture or ME reporting rates. In a small exploratory study, Wakefield et al (47) surveyed nearly 300 nurses from ward and critical care units to assess correlations between culture of the organization and continuous quality improvement initiatives. The perceived rate of reporting MEs was associated with barriers to error reporting such as fear of blame on the individual and fear of being labeled as incompetent. Hence, the perceived rate of error reporting is influenced by these fears. The perceived rate of ME reporting was positively, but not statistically associated with either perceptions of the culture of patient safety or continuous quality improvement initiatives. These findings are limited since only nurse perceptions were reported and not actual number of MEs. McBride-Henry et al (48) conducted a survey to nurses using a Safety Climate Survey tool, which found those nurses involved with implementing a medication safety program at their hospital, stated that their involvement in this project raised their awareness of medication safety; thus, they were more likely to question physicians' prescribing. Zohar et al (49) studied the effect of a nursing climate on overall safety with a component involving medications. There were 955 nurses surveyed using a nursing climate scale (i.e., a survey covering key dimensions of nursing roles including patient orientation, professional development, and teamwork). The investigators compared these survey findings to a medication safety study using direct observation method, conducted 6 months after the survey. The percentage of nurses in the ICU was not provided. They reported both organization and unit climates of safety predict the degree of medication safety. Also, when the safety climate is low, the effect of unit climate has a more pronounced effect on medication safety. These results suggest hospitals should improve their safety climates at both the institutional level and in each ICU based on healthcare worker perception within an organization as a crude measure of patient safety change.

As in previous reports, two studies, Schuerer et al (50) and Ilan et al (51), implemented a similar change in their organization with the use of a new paper-based safety reporting form called "SAFE." Both studies were conducted in ICUs and were accompanied by educational programs on the appropriate use of SAFE. Ilan et al (51) used a broad definition of a patient safety event to include any situation or event that harmed, had the potential to harm a patient, resulted in a near miss, or created a risky situation. The authors used a rate ratio, consisting of the reporting rate during the use of the SAFE form, divided by the reporting rate before using the form. Data were presented as the rate/1,000 patient days. For both ICUs combined, the overall rate ratio was 2.45 and was driven by one ICU whose rate was 3.44. It was stated that the most common types of events were medication related, although they did not provide the percentage. Also, one third of the events reached the patient and about 25% were associated with patient harm. Schuerer et al (50) conducted a study using a before and after study design to evaluate the impact of the SAFE reporting tool on all error reports in a 24-bed SICU. Comparing the year before introducing the SAFE form to 9 months following the intervention, there were 19 and 51 reports per 1,000 patient days, respectively ($p < 0.001$). The most common type of patient safety report in the intervention period was medication related (39%) with 17% resulting in patient harm. This study did not provide the percent of medication-related reports associated with or without harm in the preintervention period. Both studies are limited by not providing the details of medication-related errors, in both the preintervention and postintervention periods; hence, comparisons cannot be made.

The remaining four studies implemented a broad range of patient safety initiatives at both hospital organization and nursing unit levels. They provide the strongest evidence to date that cultural change involving structure and process at the hospital organization and nursing unit levels can improve the rate of ME reporting. Cohen et al (52) initiated a series of interventions based on a perceived punitive safety culture to promote event reporting, encourage accountability, and create an atmosphere of understanding and eventually forgiving human error. Examples include forming a medication safety team, hiring a patient safety specialist, initiating education programs on safety, and developing an anonymous reporting system. Medical errors including MEs were collected from all reporting methods 6 months before the changes, during the transition phase, and for 1 year postintervention. The median rate of total MEs reported per 10,000 doses dispensed comparing the baseline, transition, and postintervention periods was

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4.16, 5.60, and 30.16, respectively. ($p < 0.001$). The median rate of total MEs resulting in harm reported per 10,000 doses dispensed comparing the baseline, transition, and postintervention periods was 0.06, 0.18, and 0.19, respectively ($p = 0.001$). These findings suggest a beneficial and long-lasting effect of changes in the culture of safety on rate of reporting of MEs. Odwazny et al (53) formed a patient safety committee in the department of medicine following concerns over patient safety at their institution. This committee required $300,000 annually to develop and implement safety initiatives. The committee implemented a series of hospital-wide safety initiatives such as an online adverse event reporting system, educational activities on safety, and protocols covering a variety of topics associated with a high risk for harm. There was no significant change in the distribution of ADE types. The authors only provided examples of before and after prescribing for a few of their projects. For example, the total dose of potassium milliequivalents prescribed decreased 73% and the number of patients receiving potassium decreased 68%. The conservative estimated cost savings were $68,000 per year. Also, total grams of magnesium fell 57% and the number of patients receiving magnesium fell 40%. Cost savings associated with magnesium were estimated to be $280,000 annually. Finally, there was a 75% reduction in orders for sliding scale insulin. Fewer orders for these agents may reduce ME and ADE reporting. However, this assumption limits the implications of their findings. Of note, this is one of the few studies reporting costs of program development and estimated cost of program impact. Marck et al (54) used principles of restoration science (i.e., optimizing limited resources to improve and sustain the environmental system) in an attempt to improve medication safety. Twenty-six nurses conducted the study on acute medical wards. After developing a list of medication safety problems from various surveys, they took photographs during the process to better understand the flow in the medication use process. They made numerous changes to the nursing wards such as new charting procedures, instituting near miss reports and enhancing the medication administration component of the nursing orientation program. Outcomes resulting from these interventions include an increase in medication incident reports from 26 in the 6 months before the changes to 59 in the 6 months following interventions. This study suggests changes in patient safety can increase the reporting of medication incidents. Finally, Abstoss et al (55) implemented seven interventions over 2.5 years to improve medication safety in both the overall hospital and a PICU. Initiatives include conducting safety awareness programs, developing focused educational programs, improved reporting forms, and implementing a CPOE system. The overall ME rate increased from 3.16 reports per 10,000 doses before change to 3.95 reports per 10,000 doses after the last change was implemented, a 25% increase ($p < 0.09$).

In summary, incident reporting may be reflective of the culture of the institution and possibly specific patient care unit. Perception of a punitive culture has been shown to be a significant barrier in reporting adverse events. Fortunately, several strategies have shown promise in changing the climate or culture regarding patient safety to improve the quantity of incident reports involving ME or ADEs. Educational efforts within an organization to promote accountability in an understanding, nonpunitive environment will increase incident reporting rates. Increased recognition and perception of a nonpunitive environment to improve reporting rates remains a pragmatic, feasible approach to develop change with the goal of increasing reporting rates. Also, improvements to the reporting system and the use of technology through the CPOE system may also improve ME and ADE reporting rates by making them anonymous and less time-consuming.

3. Environment: Safety Culture–Part 2

Question: In ICU patients, do changes in the climate or culture of safety in the environment of the medication use process reduce the frequency of MEs or ADEs?

Answer: We suggest implementing changes in the climate and culture of safety to reduce the frequency of MEs or ADEs. (2D)

Rationale: The literature documenting changes in the culture and climate of safety on reducing the frequency of MEs and ADEs is limited to three studies. Despite the IOM providing a definition for the culture of safety, these trials used various other definitions (1). The following summarizes the key findings of the studies on ME and ADE reductions, which provide the basis for our recommendation. This question differs from the prior question on "reporting frequency" and focuses on the actual frequency of MEs and ADEs. As such, several of the references that studied both aspects are also reviewed here.

Vogus and Sutcliffe (56) conducted a survey of 1,033 emergency department, internal medicine, ICU, and surgery unit nurses from 10 hospitals on the safety organizing process coupled with degrees of trusted leadership and use of care pathways. Safety organizing was defined as collecting, analyzing, and disseminating information from errors as well as proactive checks on the organization's processes vital for patient safety. The numbers of MEs were obtained from the incident reporting system for the 6 months after collecting data from the survey. Their findings revealed a correlation between safety organizing and extensive use of care pathways with reducing the number of reported MEs. The authors also suggest that the effects of a safety organizing process on MEs are augmented with high levels of trust in management and extensive use of care pathways.

Mark et al (57) conducted a large nursing survey of 278 medical-surgical units from 143 hospitals, as part of the Outcomes Research in Nursing Administration Project II. The survey consisted of information on hospital context and structure in addition to elements of the safety climate using the safety climate scale. The variable for effectiveness was the number of MEs per 1,000 inpatient days obtained from frequency reports for 6 consecutive months. The safety climate alone was not associated with MEs. Only the interaction between safety climate and unit capacity was statistically significant in their model. In particular, low levels of safety climate and higher

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unit capacity were associated with fewer MEs, whereas average and high levels of safety climate were not related to MEs. It should be noted that this model explains only 4.1% of the variance in reported MEs. The reduction in MEs observed with low levels of safety climate and higher unit capacity is likely due to one of two reasons: 1) there may be fewer MEs when the units are staffed with more nurses or 2) increased staffing may result in higher rate of reporting of errors, rather than actual number of errors. Either way, these data suggest that safety climate alone is insufficient in reducing the number of MEs.

Abstoss et al (55) implemented seven cultural and system-level changes over 2.5 years in an attempt to improve medication safety in a PICU. Examples of interventions include implementing a hospital-wide CPOE system in the PICU coupled with hiring a PICU medication manager, starting a series of quality improvement curricula, and commencement of ME e-mails summarizing recent MEs and near misses. In a before-after design, the reported number of MEs resulting in harm (also called "preventable ADEs") decreased from 0.56 per 10,000 doses to 0.16 per 10,000 doses, a 71% reduction. However, the overall institution's reporting rates fell, and there was no difference in ADEs. These findings suggest unit-based and institutional improvements in safety can result in lower number of MEs resulting in harm.

These data suggest that reductions in MEs and ADEs can occur when numerous improvements to the medication use system are implemented or when changes in safety climate are coupled with appropriate nurse staffing, high levels of trust from management, and extensive use of care pathways. We suggest future studies be conducted using similar types of changes in culture that the effect of these changes concentrate on the number of MEs and ADEs in both adult ICU and PICU.

4. Environment: Educational Efforts

Question: In adult ICU and PICU patients, do educational efforts reduce the frequency of MEs/ADEs?

Answer: We suggest including education as part of any comprehensive program to reduce MEs in the ICU. (2C)

Rationale: Six studies were evaluated relative to the impact of educational efforts on the frequency of MEs in the ICU (58, 59). Thomas et al (60) studied the impact of an audit tool and education on MEs in an adult ICU. MEs were identified by retrospective chart review. The investigators audited clinician prescribing then a pharmacist educated prescribers via tutorials, interactive ward-based training, and individual feedback on actual prescribing errors observed in the ICU. Investigators evaluated prescribing errors in a preintervention phase and two postintervention phases. Two postintervention phases were used to assess the durability of any changes in error rates over time after the educational intervention. The preintervention rate was 225.7 errors per 1,000 orders. Prescribing error rates per 1,000 orders decreased in postintervention phase one and two to 118 and 53.7, respectively, p value of less than 0.05 (60).

Campino et al (61) evaluated the impact of education on MEs in a neonatal ICU. Errors were identified by retrospective chart review. Pharmacists provided 15 educational sessions to all ICU healthcare professionals. Educational sessions focused on MEs and a nonpunitive culture. In addition, a multidisciplinary team including physicians, nurses, and pharmacists was formed to review MEs and implement preventative strategies. The educational interventions reduced the ME rate per 1,000 orders from 207.6 to 29.5, respectively, p value of less than 0.001 (61).

Chedoe et al (62) studied the impact of education on medication preparation and administration errors by nurses in a neonatal ICU. The educational program was developed by a multidisciplinary team and delivered by a pharmacist. Education activity consisted of multiple group and individual teaching sessions, and a tour of the pharmacy. MEs were detected using direct observation methodology, and clinical importance of each error was assessed by an independent review. Preparation and administration errors per 1,000 doses decreased from 221 to 85, respectively, p value of less than 0.001 (62).

Nguyen et al (58) assessed the impact of a clinical pharmacist-led training program on MEs during IV medication preparation and administration in a Vietnamese hospital. A controlled, prospective, before and after study was conducted in an ICU (intervention ward) and postsurgical unit (control ward) using a direct observation method. The intervention comprised didactic lectures, practical ward-based teaching activities, and provisions of posters/protocols/guidelines. This program was developed by a clinical pharmacist and the chief nurse and delivered by a clinical pharmacist. The prevalence of clinically relevant errors decreased significantly in the intervention ward (64–48.9%; $p < 0.001$) and unchanged in the control ward (57.9–64.1%; $p = 0.132$); yet, the overall rate of errors remained high. Furthermore, the intervention ward was 2.6 times less likely to have clinically relevant errors compared to the control ward ($p = 0.013$). However, one major limitation of this study was that clinical importance of each ME was not assessed by independent review, which may have confounded the results (58).

Niemann et al (59) evaluated the impact of a three-step intervention program on the prevalence of MEs in a 10-bed PICU in university hospital located in Germany. Errors were identified prospectively by clinical pharmacists ($n = 5$) who monitored and documented drug handling processes carried out by nurses in the regular morning hours of drug administration. The educational program was designed by a multidisciplinary team, and all were involved in rating the clinical relevance of each error using an independent survey. The three-step intervention program included a three-page handout for nurses, a 60-minute training course, and a comprehensive 76-page reference book. The prevalence of MEs decreased significantly from 83% to 63% after the intervention ($p < 0.001$) but still remained alarmingly high (59). All five of these studies demonstrated significant reductions in MEs using educational initiatives, use of multifaceted education programs beyond didactic lectures, and content development by multidisciplinary teams.

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Ford et al (63) evaluated the difference between simulation-based education and traditional didactic education on the rate of medication administration errors in MICU and cardiac ICU (CICU). MICU nurses received traditional didactic training on MEs, and CICU nurses attended a simulation-based session using a human-patient simulator. Medication administration errors were detected using a direct observation method, and all MEs were validated by blinded investigators. Medication administration errors in the preintervention phase were compared with two postintervention phases. Two postintervention phases were used to assess the durability of any changes in error rates over time after the educational intervention. Of interest, medication administration errors per 1,000 administered doses increased in the didactic education group from 207.5 preintervention to 226.7 and 367.3 in postintervention phase one and two, respectively, p value equals to 0.002. In the simulation training group, medication administration errors per 1,000 doses decreased from 307 preintervention to 40.3 in postintervention phase one and 61.9 in postintervention phase two, p value equals to 0.001. Blank et al (64) conducted a 3-mo educational intervention comparing pre- and postoutcomes of medication administration error rates for emergency medicine nurses. The educational approach provided was presentation slides and a "flip-chart" addressing specific errors previously identified in their emergency department with recommendations to avoid MEs in the future. Although nurses performed better on a knowledge-based examination in the postintervention compared with the preintervention period, this study failed to demonstrate a significant reduction in ME rates identified through chart review in the postintervention group. Therefore, these studies suggest different types of educational interventions, such as simulation training, may be more effective than other approaches (e.g., didactic).

Overall, the literature suggests educational efforts in the ICU can reduce MEs. No trials were identified evaluating the impact of educational efforts on ADEs. More studies are needed to determine what critical elements or approaches should be used in educational initiatives to ensure that the education results in desired changes in behavior and associated outcomes. Simulation training, multidisciplinary involvement, active engagement of staff, standardization of work, and regular process improvement are likely to be critical to successful educational interventions.

5. ICU Patients: Risk Factors for ADEs

Statement: Adult ICU and PICU patients have different risk factors for ADEs compared to general care patients (non-ICU). (C)

Rationale: It has been proposed that patients in an ICU may have greater risk for ADEs compared with non-ICU patients because of the intensity of the work environment, greater exposure to medications, including high-alert and IV medications, and the nature of the critical illness resulting in decreased physiologic reserve and organ dysfunction (9, 10).

Of the six studies found on risk factors for ADEs in the ICU (10, 19, 65–68), only one prospective study evaluated and compared the risk factors for ADEs between the critically ill and non-ICU patient populations (10). Five of the six studies examining the risk factors for ADEs in the ICU did not include a non-ICU patient control group. Also, the definitions of ADEs vary among studies, which makes comparing the rate of ADEs difficult. Therefore, these five studies (19, 65–68) will be discussed for the purpose of describing risk factors for ICU patients, but only the prospective study conducted by Cullen et al (10) will be included for consideration in the quality of evidence evaluation comparing risk factors for ICU to non-ICU patients.

Cullen et al (10) conducted a prospective cohort study in two tertiary hospitals over a 6-month period and compared risk factors for ADEs between the ICUs (two MICUs and three SICUs) and non-ICUs (four medical and two surgical general care units). The investigators found that ICU patients had longer hospital LOS (37 vs 17 d; $p < 0.001$) as well as increased acuity and severity of ADEs compared with those observed in non-ICUs. The rate of preventable and potential ADEs was nearly twice the rate of non-ICUs (19 vs 10 events per 1,000 patient days; $p < 0.01$); however, when adjusted for the number of drugs ordered since admission-to-event, no significant differences in ADE reporting was detected (0.61 vs 0.65 ADEs per 1,000 patient days; $p > 0.05$). ICU patients were prescribed and administered more medications 24 hours before the event than non-ICU (15 vs 9.3; $p < 0.001$). Cardiovascular medications contributed to majority of ADEs in ICU versus non-ICU patients (76% and 88% for MICU and SICU vs 26% and 30% for medical and surgical general care units; $p < 0.0001$). Therefore, the investigators concluded that the quantity of drugs may be a risk factor for ADEs in the ICUs compared with non-ICUs. However, when adjusted for the number of drugs ordered, there was no greater likelihood for preventable and potential ADEs to occur in ICUs than in non-ICUs.

However, there are several limitations of this study that may confound the comparisons of ADEs in ICUs and non-ICUs. Of note, Cullen et al (10) did not examine whether ICU patients had more acute and chronic comorbidities than non-ICU patients, or whether an appropriate indication was present for every medication that was ordered. Also, the authors did not compare the overall ADE rates since nonpreventable ADEs were excluded in the final analysis. The study partially relied on self-reporting by nurses and pharmacists, but the patient-to-nurse ratio is most likely smaller in ICUs than in non-ICUs (ratio not provided by the investigators), so ADEs may be more readily recognized in the ICUs providing another possible limitation to the study (10). These limitations may explain why there was no greater likelihood for preventable or potential ADEs in ICUs compared with non-ICUs despite the higher rates of ADEs observed in the ICUs.

Two other studies also demonstrated more medications (19, 67) as well as high usage of cardiovascular medications as risk factors for the development of ADEs in the ICU population (9, 65, 67). Compared with non-ICUs, ICU patients are often hemodynamically unstable and frequently require

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cardiovascular medications for hemodynamic support. Although it is unclear whether quantity of medications is a risk factor compared with non-ICU patients, a study that compared risk factors for ICU patients with ADEs to those with no-ADEs identified the number of drugs received as a risk factor in the ICU (67). Minimizing the use of unnecessary medications is a clinical intervention that can be done by any medical practitioner and is especially the role of the pharmacist as part of their daily practice. The cost of evaluating medication indications outweigh the risks associated with inappropriate polypharmacy and may be cost-beneficial. If minimizing the quantity of medications and use of cardiovascular medications is not feasible in the ICU, clinicians should be more vigilant for potential ADEs.

While one prospective study demonstrated a higher rate of preventable and potential ADEs in the ICUs compared with the non-ICUs, the study did not confirm if critically ill patients have unique risk factors compared with patients in the non-ICUs. It currently remains unclear whether patients in ICUs have additional or different risk factors for ADEs when compared with patients in non-ICUs due to limited data. More comparative studies are needed to determine if critically ill patients have unique risk factors for ADEs. However, studies have confirmed that ICU patients have established risk factors for ADEs that clinicians should monitor closely.

6. ICU Patients: Risk Factors for MEs

Statement: Adult and PICU patients have different risk factors for ADEs compared to general care (non-ICU) patients. (C)

Rationale: Of the 13 studies describing risk factors for MEs in ICU compared with non-ICU patients (6, 7, 10, 20, 68–76), only one prospective trial compared the risk factors for MEs between the two different patient populations within the same institution (10). Twelve studies examined risk factors for MEs either in the non-ICU setting or in the ICU population, but they did not directly compare risk factors between these two patient populations. The definitions of MEs vary between studies; only two studies (70, 71) used the National Coordinating Council for ME Reporting and Prevention's (NCC-MERP) taxonomy for MEs. Therefore, the 12 studies (7, 20, 68, 70–76) will be discussed for risk factors of MEs, but these will not be included for consideration in the quality of evidence for different risk factors for MEs between ICU and non-ICU patients.

The study by Cullen et al (10) did not specifically evaluate MEs, rather ADEs. However, they did assess whether there was a difference in error rates during the four different stages of the medication ordering and delivery process between the ICUs and non-ICUs. Although no statistical test was conducted, the error rates were similar throughout the stages between the ICUs and non-ICUs. Within the ICUs, more errors occurred during the medication administration phase followed by medication ordering phase, whereas in the non-ICUs, more errors occurred during the medication ordering phase followed by medication administration phase. Although not included for consideration in the quality of evidence, two studies (7, 75) also found the administration and ordering/dosing stages as either the first or second most common error processes. Stavroudis et al (70) found administration and transcribing to be common stages for MEs to occur. The difference in findings may have been attributed to the different study methods. The primary limitation of the Cullen et al (10) study was that it did not focus on MEs and did not assess specific risk factors contributing to MEs (e.g., types of medications, route of administration, and high-alert medications).

Risk factors for harmful MEs compared with MEs without harm that were identified in neonatal ICU across 163 facilities by Stavroudis et al (70) include the use of ISMP's high-alert medications such as potassium chloride, fentanyl, and fat emulsions, prescribing, and failure of nonsmart pump medication delivery devices. It remains unclear whether patients in ICUs have additional or different risk factors for MEs when compared with patients in non-ICUs due to the lack of comparative studies; however, established risk factors have been described for MEs in ICU patients that clinicians should consider to optimize patient outcomes.

7. Environment: Disclosure of MEs and ADEs to Patients and/or Family Members

The topic of disclosures could not be developed into a PICO question because there is not an ethically appropriate comparator group. There is no quality of evidence statement since we do not have any evidence regarding this topic. The committee agreed this was an important topic, and needed awareness, as such, should be included as a potential area of future research. Communication between healthcare providers and patients is critical when medical errors occur. Many ethical and professional guidelines clearly state that healthcare professionals have a responsibility to disclose medical errors and it is required by law in some States (77–79). Research shows that patients expect to be informed promptly when they are harmed by care and desire an apology, an explanation of what happened, and someone to take responsibility (80–85). However, this is not routinely performed in clinical practice today. Less than 30% of patients are informed about serious errors causing harm, and there is wide variation in the disclosed details (86–92). To address this issue, many organizations are developing standards, programs, and laws to encourage communication with patients after harmful errors have occurred (79, 93, 94). In the United States, the National Quality Forum recently updated standards in its list of safe practices to foster communication with patients in order to improve performance and reduce preventable harm (93).

Historically, clinicians have been conflicted about disclosure due to fear of litigation or embarrassment, or they were unsure of how to effectively communicate with patients about medical errors or if the hospital permitted them to do so. However, several studies have demonstrated patients are more likely to respond favorably to apologetic healthcare professionals who accept responsibility for their medical errors and provide full disclosure rather than those who do not (83, 95, 96). Full disclosure can result in greater trust and satisfaction with the healthcare provider. With full disclosure, no increased

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likelihood of seeking legal action has been reported. However, inadequate disclosure may increase the likelihood of a lawsuit regarding malpractice (97, 98). Research is needed to clarify key uncertainties about disclosure practices including effect on patient satisfaction, role of apology and acceptance of responsibility, and legal and financial consequences of disclosure. Until further research is conducted, the current regulation standards will likely remain advisory. Many organizations are continuing to work on a transformation in the disclosure process. Giving the providers the appropriate tools to disclose harmful medical errors to patients may encourage open communication and increase patients' level of trust in their medical care. The ultimate goal should be to establish policies for full disclosure of medical errors to patients and/or family members as a standard of clinical practice. Furthermore, institutions should evaluate the process for full disclosure to ensure that there is a positive impact on the patients and/or family members.

B. PRESCRIBING NODE: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

Leape et al (99) in their seminal study of adverse events in hospitalized patients identified prescription and transcription errors as responsible for over 50% of MEs. The majority of these errors were related to inaccurate dosing, lack of knowledge of the drug, lack of information about the patient, and illegible handwriting. Critically ill patients are particularly at risk for prescribing errors since they receive twice the number of medications compared with non-ICU patients (10). Over the past 2 decades, efforts have been made to address these prescribing and transcribing issues by introducing new standards and technologies designed to address these problems. These strategies include CPOE, CDSS, medication reconciliation, and protocol implementation. Additionally, a strategy commonly used for pediatric emergencies is the Broselow tape, which is an established dosing strategy. It is a color-coded tape measure that relates a child's height as measured by the tape to his/her weight to provide information needed for proper medication dosages, the size of the equipment used, and level of shock voltage needed for defibrillation. The Broselow tape has been reexamined for its reliability in determining patient weight in emergency situations with neonatal and pediatric patients.

1. Computer Provider Order Entry (CPOE)

Question: In adult ICU and PICU patients, does CPOE reduce MEs and preventable ADEs when compared with not having CPOE?

Answer: We suggest implementing CPOE to decrease MEs and preventable ADEs. (2B)

Rationale: A total of 14 studies compared the frequency of MEs and/or ADEs before and after the implementation of CPOE. Twelve of these studies were observational (100–111), and two used a prospective study design with random assignment (112, 113). Twelve of the 14 studies had MEs as the primary outcome evaluated (101, 103–113). The investigators in one study measured the occurrence of both MEs and ADEs (102), one evaluated only ADEs (104).

Eleven of the 14 studies reported significant decreases in MEs after the implementation of CPOE (100–103, 105–108, 111–113). One study found 100% prescription completeness following the implementation of CPOE in a cardiothoracic ICU (108). In the study evaluating both MEs and ADEs, the use of CPOE decreased both outcomes (102). Interestingly, the study by Maat et al (110) demonstrated a decrease in omission errors with CPOE (24%) compared with handwritten orders (66%) but observed the same number of dosing errors (21%) for both. An ME increase for duplicate orders was reported in the study evaluating only MEs (107). In the Holdsworth et al (104) study evaluating only ADEs, there was no significant overall decrease in these events following implementation of CPOE.

Although the primary outcome for the question evaluated was MEs and ADEs, assessing its effect on mortality is also important. A 4% absolute increase in mortality and a three times greater likelihood of mortality with CPOE compared to no CPOE has been described in the literature. Explanations for the negative mortality effects of CPOE were a delayed time to order entry, nurses spending time away from their patients at the computer, and a delay in the time to drug administration for essential drugs. Lessons can be learned from this study, and it is important to remember that implementation of technology does require thorough assessment and preparation both before and after implementation.

The cost of developing, implementing, and maintaining a CPOE system may be substantial; however, these costs may be offset by total savings over time (114). The Health Information Technology for Economic and Clinical Health Act allows CMS to offer incentives for the meaningful use of CPOE that may offset some of the costs (115). The clinical benefits are favorable for ME reduction, but the impact on ADEs requires further investigation. Clearly, CPOE provides the opportunity to reduce prescribing errors related to legibility problems, free text ordering, and abbreviations (105). However, CPOE does not reduce MEs occurring at other process nodes including distribution and administration. Also, it is possible that CPOE introduces new types of prescribing errors such as drug selection, wrong dose selection, wrong formulation, and wrong schedule (116). CPOE provides the opportunity to integrate computer systems and a platform for the integration of CDSS. CPOE does have negative attributes as well, including system downtimes, fragmented CPOE displays, inflexible ordering formats possibly resulting in errors, and potential for errors with wrong patient selection (117). This weak recommendation should not deter administrators, clinicians, and researchers from continuing to evaluate the effectiveness of CPOE in improving patient outcomes. Results from these evaluations will inform future recommendations by accreditation agencies and other groups committed to improving medication safety (118, 119).

2. CDSS

Question: In adult ICU and PICU patients, does CDSS (electronic or paper format) reduce ME/ADEs when compared with traditional medication decision-making?

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Answer: We suggest the use of CDSS (either electronic or paper format) to decrease the number of MEs/ADEs (2C).

Rationale: Eight observational studies, one feasibility study, and one prospective, controlled study were included in the review of this PICO question (110–112, 120–126). Interestingly, three of the eight observation studies were by the same investigators (120, 121, 124), who studied a variety of outcomes related to antibiotic prescribing from the same CDSS tool in the same hospital system. Data from these three studies were descriptive, epidemiological data, which supported the use of the decision-making tool to decrease the number of ADEs related to allergies, excessive dosing based on renal function, and inappropriate use. Four of the applicable observational studies (110, 111, 122, 123) were in the pediatric population. They were retrospective and showed that when compared with the preintervention phases, when the prescriber is alerted by the CDSS, there was a decreased rate of MEs related to renal function, resuscitation orders, a reduced rate of ADEs, and decreased inappropriate use (i.e., contraindications).

The feasibility study also investigated antibiotic selection (125). An alert was generated using CDSS in real time that mimicked clinical practice for critically ill patients receiving previous gram-negative antibiotics or positive culture with resistance. The nonalert group included patients without previous antibiotics or resistance. Alerted patients were more likely to receive inappropriate antibiotics than the nonalert group (7.1% vs 2.9%; $p < 0.001$). The use of an alert could have prevented use of inappropriate antibiotics in 40% of the patients.

Extending beyond antibiotics, a study conducted in a CICU that evaluated a variety of prescriptions errors before and after the implementation CPOE plus CDSS (112). A 40% reduction in prescribing errors including drug names, pharmaceutical form, route, and dose was noted with the use of this system ($p < 0.001$ for all types of errors).

A prospective, controlled study was conducted in the neonatal ICU to compare error rates in antibiotic orders before and after the implementation of CDSS. The antibiotic orders were independently reviewed by two pharmacists for errors and omissions. The overall error rate per order and potential error rate decreased from 1.7 to 0.8 ($p < 0.001$) and 1 to 0.06 ($p < 0.001$), respectively. However, the prescribing error rate increased from 0.4 to 0.7 ($p = 0.03$) due to incorrect patient weight entered ($p < 0.001$). In both the traditional medication decision-making and CDSS groups, renal dysfunction was significantly associated with an increased risk of prescribing errors (odds ratio [OR] = 3.7; $p = 0.01$) (126). The negative findings of this study could be attributed to limiting orders to antibiotic medications in a neonatal population at a single institution. Nonetheless, this study supports the need for a complete assessment when considering the implementation of CDSS.

The limited data on the use of CDSS indicate that when incorporated into clinical practice, CDSS will likely reduce MEs and ADEs. We acknowledge there are data outside of the ICU that suggests benefits and challenges to using CDSS (127, 128). The effect of CDSS has shown to have a modest effect on improvements in appropriate medication use. Since none of the studies were RCTs, the scientific rigor of future studies needs to be strengthened to improve our confidence in the estimate of the effect. The known utility of CDSS at many institutions relative to the lack of data indicates that either institutions are not performing rigorous evaluations of CDSS or publications on the impact of CDSS are sparse. An efficient and effective CDSS system requires implementation of quality alerts without generating significant alert fatigue (129). Performing quality assurance evaluations to assure meaningful alerts with positive clinical outcomes is necessary to appreciate the full benefit of CDSS.

In summary, we realize considerable effort and costs for time to implement, customize, train, and analyze the data generated from this technology are required to maintain CDSS in hospital systems. Many institutions do not have the resources available to support CDSS. A localized cost analysis evaluating the implementation of CDSS may assist decision makers. However, if an institution or system already has the infrastructure in place to add CDSS for specific medications or groups of medications, this extra layer of safety may be beneficial to reduce ADEs or MEs and improve appropriate medication use (130).

3. Drug Dosing Software

Question: In adult ICU and PICU patients, does computerized drug dosing software without CDSS reduce ME/ADEs compared to medication management without drug dosing software?

Answer: We suggest using computerized drug dosing software to decrease the number of MEs/ADEs for insulin prescribing. (2C)

Rationale: Thirteen studies were evaluated. All studies involved insulin guidelines/protocols for tight glycemic control. Eleven studies evaluated hypoglycemic episodes as the drug-related hazardous condition (DRHC) of interest (39). Three studies favored computerized guidelines/protocols compared with paper-based ones in reducing hypoglycemic events; one was a RCT, however this was a relatively small trial, the second one was a retrospective before and after study, and the third one was a low-quality observational study (131, 132). The remaining 10 trials showed no difference in hypoglycemic episodes (133–140). Limited data suggest a lower frequency of hyperglycemic episodes with computerized guidelines/protocols (131, 139). Also, a retrospective study conducted by Saur et al (141) compared glycemic metrics related to hyperglycemia, hypoglycemia, and glycemic variability between paper-based and software-based guidelines/protocols in a SICU using a blood glucose (BG) goal of 95–135 mg/dL. Patients treated with the software-based protocol had lower mean BG concentrations (117 vs 135 mg/dL; $p = 0.0008$), increased time in desired BG goal range (68% vs 52%; $p = 0.0001$), less frequency of hypoglycemia (0.51% vs 1.44%; $p = 0.04$), and less glycemic variability (± 29 vs ± 42 mg/dL; $p = 0.01$) (141).

All of the studies of computerized dosing software have been applied to insulin, and the DRHC evaluated was hypoglycemia.

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The emphasis on the high-risk medication, insulin, may be reasonable based on the recent negative findings from the post hoc analysis of the Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation trial indicating that patients with moderate hypoglycemia are more likely to have severe sepsis, trauma, diabetes, and cardiovascular failure (142). To date, the strategy of computerized dosing software has had a modest or neutral effect on avoidance of adverse events; however, the effect on mortality remains to be determined. In addition, the advantage of the computer dosing software needs to be explored for other drugs with complicated dosing strategies such as anticoagulants, pain management, sedation protocols, medication desensitization protocols, and renally cleared drugs.

In summary, computerized dosing software could address common problems associated with paper-based dosing guidelines/protocols or the absence of guidelines/protocols and improve clinical outcomes; however, more studies are warranted to clarify role of computer-based guidelines/protocols for medications other than insulin (e.g., anticoagulants, sedatives). Paper-based protocols for drug dosing in the ICU setting may be complex and confusing. There have been reports of MEs with complex dosing regimens, such as alteplase and acetylcysteine in the ICU (143, 144). Paper-based drug dosing protocols are labor-intensive, require manual calculations and interpretation, and are typically too broad to apply to diverse patient populations throughout the institution. One strategy to overcome these challenges is the use of computerized guidelines/protocols. Computerized guidelines/protocols minimize the complex calculations and remove practitioners' interpretation. In addition, they have the benefit of precision as they can interpret and integrate relevant specific patient information, thus providing a more individualized approach and potentially increasing compliance to the protocol.

4. Protocols

Question: In adult ICU and PICU patients, does the use of protocols/bundles prevent MEs/ADEs compared to not using protocols/bundles?

Answer: We suggest the use of protocols/bundles in the ICU to ensure ME/ADE reduction. (2B)

Rationale: For this question, a protocol was defined as an evidence-based tool designed to guide clinicians on appropriate medication use and safety in order to decrease variability among prescribers, promote safe practices, and potentially improve patient outcomes (145). An example of a safe medication use protocol developed for the ICU is the use of an insulin infusion protocol to decrease the risk of hypoglycemia. The Institute of Healthcare Improvement recommended the use of bundles to guide clinicians in providing optimal patient care undergoing particular treatments with inherent risks. A bundle consists of three to five evidence-based interventions that when implemented collectively and reliably have been shown to improve patient outcomes (146). An example of an evidence-based bundle is the use of a bundle to promote early goal-directed therapy in patients admitted with sepsis to reduce mortality (147). Evidence-based protocols have been widely adopted in the ICU (145). Healthcare professionals perceive protocols as a tool to improve patient outcomes and prevent patient harm (145). Protocol deviations result in MEs and preventable ADEs in the ICU per reports by numerous institutions (8, 11, 148). Protocol violations vary by hospital unit, the step in the care process, and circumstances of the violation (149). Due to this potential issue with protocol violations, it is uncertain if protocol implementation offers the benefit of safe medication use with the prevention of MEs and ADEs when compared with no protocol implementation.

There are limited data evaluating the impact of protocol adherence on ME reduction and none on ADE reduction (150, 151). Only one study evaluating the impact of a protocol on ME reduction in the ICU and one study evaluating an evidence-based bundle were identified (152). The study evaluating a protocol was completed in conjunction with a multifaceted education effort and included an updated prescription protocol that provided instructions on proper dosing based on patient's weight with the primary intent of reducing prescribing errors (151). The results of a protocol on prescribing errors will not be applicable to general protocols.

Romero et al (152) conducted a study to assess if a preventive interventions program (PIP) is associated with a significant reduction of MEs in a medical-surgical ICU in Chile. They designed a prospective before and after study and identified MEs using direct observation method of each medication use-related process by pharmacists at baseline and postintervention. The PIP was a bundle of interventions that was created by a multidisciplinary team and included the incorporation of a clinical pharmacist into the ICU, creation of standard operating procedures for medication preparation and administration, initiation of training on safety culture, and development of an anonymous, nonpunitive MEs reporting system. The PIP bundle led to a 31.7% decrease on the prevalence of patients with MEs (41.9–28.6%; $p < 0.05$). Main protocol variations occurred at the prescription and administration stage. However, this study did not evaluate the impact of general protocols used to guide clinicians on safe medication use (152).

We must realize that the safety benefits of protocols and bundles will depend on at least two principles. First, the protocol or bundle must be developed with safety in mind. Situations of excessive daily acetaminophen dosing, for example, have been associated with incorporating acetaminophen-containing opioid products in protocols without an appreciation for the maximum daily dose of acetaminophen. Compliance with this protocol resulted in identifying situations that exceeded the recommended daily dose of acetaminophen. Second, the clinical benefits of protocols or bundles are only observed with protocol adherence and not simply with the creation of a protocol or bundle (153).

We recognize a high rate of protocol or bundle adherence is associated with benefits in clinical outcomes (154). Protocol violation is provided as a reason for the occurrence of MEs (154). Importantly, there are data that suggest that violations may reflect a poor fit between protocols and clinical situations. In these instances, violations may actually improve safety rather than

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cause errors. The frequent implications of protocol or bundle violation as a cause of errors and the positive clinical outcomes of protocol adherence support their use. One study investigated a bundle approach and has demonstrated a significant improvement in MEs. Because of the substantial impact, it is reasonable to recommend the use of protocols and/or bundles to reduce MEs and ADEs in the ICU. The benefit of protocols on safe medication use and bundles for various treatments still needs to be further researched to determine the impact on MEs and ADEs.

5. Medication Reconciliation

Question: In adult ICU and PICU patients, does medication reconciliation reduce MEs/ADEs when compared with not having medication reconciliation?

Answer: We make no recommendation regarding the use of medication reconciliation to decrease MEs/ADEs, in ICU patients. (OD)

Rationale: The Joint Commission (TJC) defines medication reconciliation as "the process of comparing the medications a patient is taking (and should be taking) with newly ordered medications" (155). Medication reconciliation and medication review are interventions designed to prevent MEs at transition points. Medication reconciliation allows for identification and rectification of any discrepancies at each point-of-care (POC) transition before patient harm occurs. A systematic review conducted by Lehnbom et al (156) revealed that medication reconciliation identified unintentional medication discrepancies in 3.4–98.2% of patients depending on the clinical setting. Studies have demonstrated that patients' experience a lower frequency of MEs when medication reconciliation occurs compared with those receiving routine care (157, 158). However, there is limited evidence regarding the impact of medication reconciliation on clinical outcomes such as reduction in hospital admissions, decrease in LOS, and mortality. The medication reconciliation process in ICU patients has only been described in one publication (159). It is not expected that the impact of medication reconciliation upon hospital admission or discharge can be extrapolated to the ICU because of the different medications assessed during these transition nodes, so evaluations outside of the ICU were not considered.

An observational study in an adult SICU evaluated medication reconciliation for ICU patients by conducting a survey about current medications completed by the nurse prior to patient discharge from the ICU. The purpose of this survey was to identify prescribing errors. Researchers reported a decrease in errors (defined as the number of orders needing to be changed when the patient was discharged). No statistical analysis was reported; however, the authors reported a 94% frequency of errors prior to the implementation of the medication reconciliation process and a reduction to near zero following implementation (159).

While there has only been one study conducted in the ICU, it seems logical to consider implementing medication reconciliation processes at each POC transition including transfer from ICU to a step-down unit or general ward. There is a growing body of literature supporting the need to perform medication reconciliation upon ICU transfer to avoid continuation of unnecessary medication such as atypical antipsychotics being used for management of ICU delirium and proton pump inhibitors for stress ulcer prophylaxis. A retrospective cohort study conducted by Kram et al (160) investigated discharge prescribing patterns, monitoring, and attributable ADEs for patients receiving atypical antipsychotics in the ICU. For those who survived, atypical antipsychotics were continued for 84% of patients upon ICU transfer and for 29% of patients upon hospital discharge despite the majority having delirium resolution or baseline mental status (160). The inappropriate prolonged use of atypical antipsychotics is concerning since these medications have been associated with increased risk of falls and fractures and risk for mortality when treating elderly with dementia-related psychosis (161, 162).

In summary, the lack of rigorously conducted studies precludes us from making a recommendation in favor of using medication reconciliation. Research on optimal medication reconciliation methods in the ICU is needed. Nonetheless, we support taking every measure to ensure that appropriate medications are being administered at critical risk points such as during an ICU admission. Furthermore, medication reconciliation is required by TJC and addressed in the 2013 National Patient Safety Goals (NPSGs).

6. Broselow–Part 1

Statement: The Broselow tape is reliable in predicting patient weight for United States, European, Indian, New Zealand, Filipino, and Korean pediatric populations especially in younger (< 3 yr) and lower weight children (< 26 kg). (A)

Rationale: We found nine studies relevant to this question. In one study of U.S. children, the Broselow tape was statistically significantly accurate in children less than 25 kg (overall accuracy within 15% for 79% of children, within 10% for 60% of children) (163). In a second U.S. study, the overall accuracy for weight prediction was also within 10% for 55–60% of children depending on year 1998 tape versus year 2002 tape (164). In addition, Broselow tape estimations of weight were significantly more accurate than pediatric resident or nurse estimates of patient weight (163). In European children, the Broselow tape is accurate within 15% for 83% of children (slightly underestimates weight in children > 20 kg) (165). Two studies were conducted in Indian children: one found that the Broselow tape had high correlation ($R = 0.94$) although slightly decreased accuracy for older children. The other study found that in Indian children less than 18 kg, the weight was accurately predicted in 56–71% of children; however, in Indian children greater than 18 kg, the predicted weight was accurate in only 38%, and Broselow overestimated the weight by more than 10% (166, 167). A modified Broselow tape has been proposed for Indian children (168). For children living in New Zealand and under 143 cm, the Broselow tape accurately estimated weights within 10% of actual weight for 73.4% (169). The Broselow tape performed better than other weight estimate methods in Filipino children aged 1–9 (170). There are data to support the use of Broselow tape in Australia children less than 1 year old, but

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other methods may be more accurate in children greater than 1 year old (171). In Korean children, the Broselow tape is more accurate in those less than 26 kg and has an accuracy within 10% of actual weight in 58% of children (underestimates weight) (172).

Using the Broselow tape length measurement in pediatric emergency situations to estimate weight ranges is accurate in United States, European, Indian, New Zealand, Filipino, and Korean children given that proper education on the correct usage of the Broselow tape has been provided. Users should be aware that the Broselow tape seems to be more accurate in the lower weight (< 26 kg) and younger age (< 3 yr) ranges. Also, it should be noted that proper education on how to use the Broselow tape is necessary to improve overall accuracy (173).

7. Broselow–Part 2

Question: In critically ill neonatal and pediatric patients, does using the Broselow system/length-based weight drug dosing reduce MEs/ADEs when compared with not using the Broselow/length-based system in emergency situations?

Answer: We suggest using the Broselow tape in pediatric emergency situations, when patient weight is not available to determine the child's length and then the associated color-coded, weight-based dosing for emergency drug doses to reduce MEs and ADEs (2C).

Rationale: Pediatric and neonatal patients are unique because weight-based drug dosing is generally used (as opposed to standard drug dosing for many adult drugs). The Broselow tape is a tool that measures a patient's length to estimate a color-coded weight range. It is often used to estimate patient weight in pediatric emergency departments when patient weight is not readily available. For each color-coded weight range, the Broselow tape provides the appropriate dosing for emergency drugs and patient appropriate equipment sizes.

There were no studies examining this question of ME/ADE reduction in an actual clinical setting. However, there were four studies that evaluated the accuracy of Broselow to predict drug dosing in simulated scenarios or in theoretical settings. One study evaluated the accuracy of Broselow drug dosing versus drug dosing using length and body habitus adjustment and found that in children less than 3 years, epinephrine dosing was similar. However, in children greater than 3 years, there is a larger epinephrine dosing difference in obese patients (174). In two studies using simulated pediatric resuscitation scenarios, providing education on the correct usage of the Broselow tape and/or having the ability to use the Broselow tape helped decrease the median error of recommended drug dosing (173, 175). In contrast, one study found that a theoretical reformulation of pediatric drugs to standard drug concentrations compared to a standard volume-/weight-based dosing is faster and more accurate than using the Broselow tape (176).

Using the Broselow tape in emergency scenarios, in theory, should reduce medication dosing errors in pediatric patients compared with not using a Broselow tape for weight estimations. Therefore, we suggest using the Broselow tape in pediatric emergency situations, when patient weight is not available, to determine the child's length and then the associated color-coded weight-based dosing for emergency drug doses.

C. DISPENSING NODE: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

Dispensing medications is a complex process under the close supervision of the pharmacist. Flynn et al (177) conducted a study in 50 outpatient pharmacies (26 chain pharmacies, nine health-system pharmacies, and 15 independent pharmacies) across the United States where over three billion prescriptions per year were reviewed with a reported accuracy rate of 98.3%. However, with even a 1.7% error rate, over 51 million dispensing errors occur per year or four errors per day per 250 prescriptions filled (177). Regarding the frequency of dispensing errors in the hospital setting, various studies have reported both unprevented and prevented dispensing errors, which ranged from 0.01% to 81.8% and 0.11% to 2.7%, respectively. The wide range of rates reported for unprevented and prevented dispensing errors was likely due to differences in research methods, definitions for errors, and dispensing systems (178). The most common types of dispensing errors included incorrect medication, dosage strength, dosage form or quantity, dosage miscalculations, and mislabeling medication with incorrect directions (179). The most common causes associated with dispensing errors were high workload, interruptions, distractions, and inadequate lighting. Also, established factors that contribute to dispensing errors included look-alike, sound-alike drugs, low staffing levels, and unclear presentation of automated drug selection screens.

Traditionally, the dispensing process involved pharmacy staff manually selecting medications from shelves, counting the correct amount of medication, transferring this amount to a container, and labeling this product (180). However, because of the concern for dispensing errors, there has been a paradigm shift from this traditional process to the implementation of robotic automated dispensing systems and automated dispensing machines (ADMs) that use bar-code technology. This shift occurred to improve efficiency, maximize storage capacity, and minimize dispensing errors (181). To address other issues such as look-alike, sound-alike drugs and IV medication concentration errors, other strategies have been implemented, which include recent improved medication labeling practices (e.g., "tall man" lettering to differentiate look-alike, sound-alike medications like DOPamine and DOBUTamine), safer medication concentration practices (e.g., premixed IV preparations by pharmaceutical and sterile product compounding manufacturers), and the use of double checking in the dispensing process (i.e., pharmacy technicians check another pharmacy technician's work).

1. Automated Packaging of Medications

Question: In adult ICU and PICU patients, does the use of robotics versus human personnel for the packaging of medications to be dispensed impact outcomes such as MEs/ADEs?

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Answer: We suggest installing robotic dispensing systems as a component of the medication dispensing process of solid dosage forms to reduce MEs. (2C)

Rationale: Large volumes of medications are dispensed daily in institutional settings. MEs, even at low rates, can have serious consequences in terms of ADEs as well as morbidity and mortality (1, 182). Robotic dispensing systems are used to decrease errors in the medication distribution process before medications reach the patient (183–185). These systems are intended to reduce errors by proper selection, packaging, and dispensing of medications (183, 185). A common example of a robotic dispensing system is the unit-dose delivering robot (e.g., Pillpick Pharmacy Automation System, Swisslog, Maranello, Italy), where the robot prepares daily therapies in bags associated with a ring and sorted according to administration time. Each bag contains a single dose (tablet, capsule, vial, half/quarter-tablet, sachet) to be delivered to the patient and indicates medication name and dosage, batch, and expiration date. Robotic dispensing systems may also decrease costs by reducing MEs and potential consequences, minimize staffing requirements, and improving inventory management (186). Although there is supporting evidence on enhancing efficiency in delivery of medications, the impact of robotic dispensing systems on reduction of MEs is controversial.

The impact of unit-dose delivering robots on MEs has been evaluated in three studies using the direct observation method; one study was conducted in the nursing home and is not included in our evaluation (187). Two studies, conducted in an institutional setting, investigated robotic dispensing systems as a potential factor in reduction of MEs. In both studies, the investigators examined medication administration errors as the primary outcome and dispensing errors as a secondary outcome. While one study revealed an increase in MEs (188) in patients using enteral feeding tubes, the other study determined that the use of a unit-dose delivering robot significantly reduced MEs (64.5% vs 30.1%; OR, 0.33; 95% CI, 0.13–0.71) in general medicine patients (186). The conflicting results may partly be explained by the increased use of liquid formulations in patients with enteral feeding tubes in the first study (188). In that study, MEs associated with administration of liquid formulations were not prevented by the robotic dispensing system since these systems only packaged solid dosage forms. Further studies investigating the direct impact of robotic automated dispensing systems on dispensing or distribution errors are warranted.

To date, no studies have examined the frequency of robotic dispensing errors specifically in the ICU setting. Neither of the two included studies was conducted in the ICU setting; however, we believe that designing a study evaluating a robotic dispensing system specifically in an ICU setting may not be feasible since these systems are usually located in the central pharmacy serving an entire institution. Thus, the data regarding medications obtained from a robotic dispensing system may be transferable to any patient care unit in the institution, including the ICUs.

Like many of the other potential technological solutions, unit-dose delivering robots are simply tools that may or may not have an impact on MEs. Any organization committed to safety should evaluate the range of intended and unintended consequences prior to implementation of these robots. Introducing robots into the complex work system will affect the systems of care delivery, including all other system elements (i.e., workers and their tasks) and the outcomes of the system (either safe or unsafe care) (189, 190).

Robotic dispensing systems have been identified as a potential tool to reduce MEs. Intuitively, they are beneficial and merit serious consideration for implementation. However, there are case reports revealing the potential hazards of any automated medication technology. Wears and Perry (191) described a situation where a patient in the emergency department had a "near miss" due to an ADM failure. Also, hospitals in Indiana and California reported cases where neonates experienced harm and death due to stocking of incorrect heparin concentrations in ADMs (192). These errors reflect the failure of complex systems of care delivery that could have been made more vulnerable with the introduction of new automated technology. The reported errors in all three of these cases would not have occurred if the ADMs had not been implemented. However, this should not preclude the introduction of these automated technologies like robotic dispensing systems. Rather, because of these potential adverse consequences, implementation of automated technology should be performed cautiously with careful consideration of the potential benefits and risks.

Although considerable cost and effort is needed to install and maintain a robotic dispensing system, studies suggest a reduction in MEs while improving the efficiency of the medication dispensing process. However, systems of care delivery can vary due to the unique constellation of providers, tools/technology, tasks, environments, and organizations so institutions should carefully weigh the benefits, costs, and risk of implementing robotic dispensing systems against other potential opportunities (189, 190). We believe it is appropriate to evaluate the processes for filling and removing medications to ensure safe practices. We suggest the installation of robotic dispensing systems as a component of the medication dispensing process of solid dosage forms to reduce MEs.

2. Automated Dispensing of Medications

Question: In adult ICU and PICU patients, does the use of automated versus nonautomated (i.e., human personnel) methods for dispensing (ADM or ADM with bar-code technology) of medications impact outcomes such as MEs/ADEs?

Answer: We suggest that the implementation of automation strategies in the medication dispensing process may reduce MEs. (2C)

Rationale: Improving patient safety is a key focus in the hospital setting, and a variety of strategies and technologies have been explored to achieve this goal. One potential approach is the use of automated medication distribution systems accessible to nurses in the patient wards by providing computer-controlled storage, dispensing, and tracking of medications (193). Data suggest these systems improve efficiency and patient safety. Automated dispensing of medications is

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now widely used in many institutions to replace manual distribution systems (e.g., traditional floor stock and medication cart filling) (194–196). A common example of ADM is an automated dispensing cabinet (e.g., Pyxis Medstation Rx, San Diego, California), which electronically dispenses medications in a controlled fashion and track medication use. Although there is supporting evidence on enhancing efficiency of medication delivery, the impact of automation on reduction of MEs is controversial and depends on many factors, especially the design and implementation of automated dispensing systems. Several studies conducted in the institutional setting have demonstrated a reduction in medication dispensing errors and even a reduction in time to drug administration after the implementation of automated dispensing systems (194, 195, 197–203). However, two studies revealed no significant differences postimplementation (183, 185) and one study reported an increase in medication dispensing errors due to automation when compared with manual distribution systems (202). The impact on other types of MEs such as prescribing and administration errors is unclear. Like many of the other potential solutions evaluated as strategies for reduction in errors, ADMs are tools that may or may not be beneficial. Any organization committed to safety should evaluate both desired and potentially undesired outcomes before embarking on implementing ADMs (204). As with any process change, system elements (including workers and their tasks) and outcomes including safe or unsafe care may be impacted (190, 205). The strength of the available evidence is limited by inconsistent definitions of outcomes, lack of randomized study design, and potential confounders such as changes in workflow processes.

Intuitively, ADMs should be beneficial, and when viewed from the standpoint of evidence-based medicine, merit serious consideration. However, potential risks and benefits should be evaluated prior to implementation. Please refer to section on robotic dispensing systems in the dispensing node for additional details on potential ADM errors. The increased rate of ADM errors may be due to lack of use of bar-code technology when scanning medications to stock an ADM, lack of light-guided technology when nurses remove medications from ADM, and ability to override medications where nurses can remove them from ADM without pharmacist verification. Therefore, clinicians may consider the incorporation of other measures such as bar-code technology to prevent ADM errors.

Automated dispensing systems are costly and require significant time and effort to implement and maintain, although it may be worth the investment (206). The available evidence suggests improved efficiency and patient safety within the medication dispensing process. However, systems of care delivery vary due to the unique constellation of providers, tools/technology, tasks, environments, and organizations (190, 205), so organizations should thoughtfully weigh the benefits, costs, and risks of implementing ADMs against other strategies. We believe it is appropriate to evaluate effectively the processes for adding and removing medications to ensure safe practices. Hence, we suggest that the implementation of automation strategies in the medication dispensing process may reduce MEs, improve inventory management, and decrease staffing requirements.

3. Medication Labeling Practices–Sound-Alike Look-Alike Drugs (SALAD)

Question: In adult ICU and PICU patients, do medication labeling practices using tall man lettering for SALAD compared with medication labeling practices that do not use tall man lettering reduce the frequency of MEs/ADEs?

Answer: We suggest using medication labeling practices including tall man lettering for SALAD to reduce the number of MEs. (2B)

Rationale: Similar-looking commercial labeling and packaging are common causes of MEs, often because of nearly identical packaging for two separate items. Incidents most commonly reported to U.S. Pharmacopeia MEs Reporting Program between August 1991 and April 1993 involved problems with similar packaging or incomplete labeling (207). Although error rates caused by drug name confusion range from 9% to 25%, the impact of incorrect drug selection can be catastrophic (208, 209). Errors involving name confusion can occur because of similarities between names, whether proprietary (brand) or nonproprietary (generic). Strategies for reducing these errors must include avoidance of names of new drugs that may be confused with existing products and minimize confusion with existing name pairs (210). Examples to prevent confusion errors between existing names include use of nonalphabetical storage of drug products and changing appearance of names on product labels, computer screens, and shelf labels (211, 212). For example, ISMP suggests it may be easier to differentiate between "DOBUTamine" and "DOPamine" than between "dobutamine" and "dopamine" (213). This visually differentiates the names using tall man (uppercase) letters. The ISMP conducted a survey of practitioners on the use of tall man letters in 2008, which demonstrated an overwhelming support for using this technique. In fact, 87% indicated that the use of tall man lettering helped to reduce drug selection errors (213).

Six studies evaluated the use of tall man lettering system in a noninstitutional, simulated setting (209, 211, 214–217). These studies demonstrated a reduction, ranging from 1.3% to 6.1%, in the mean number of drug name confusion errors when compared with lower case lettering system (209, 211, 214, 217). Other strategies purported to reduce drug confusion errors included color differentiation and use of boldface or italics format, but these had no significant effect on error rates (211, 215). Since these simulated studies were conducted in a controlled, noninstitutional setting without distractions and interruptions, the generalizability for inpatient pharmacies and critical care settings is limited. However, the studies were well designed to analyze objectively drug name confusion errors as potential MEs in a controlled environment and should be considered supporting evidence despite the lack of real-world evaluation. Furthermore, one study investigated the impact of tall man lettering over several years on potential ME rates (218). These investigators pooled aggregate database information on 12 look-alike, sound-alike medications dispensed among 42

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children hospitals across the United States. This study failed to demonstrate a significant reduction in potential ME rates compared with preimplementation and postimplementation of this strategy. However, this may be explained by the method for identifying a potential ME. Any medication dispensed on a patient, which was subsequently changed to another look-a-like sound-a-like was considered a potential error. It should be noted no further investigation into these cases occurred to better determine if an error truly occurred. In certain clinical situations, performing logical prevention strategies despite lack of data in the ICU environment seems appropriate. Also, for the past several years, the FDA and ISMP have advocated and recommended the tall man letter approach in the institutional setting. This includes use in various pharmacy areas for distribution and dispensing and other aspects of the medication process like electronic prescription and order entry systems (213, 219). Furthermore, ISMP has developed a comprehensive list of tall man lettering for institutions to use.

4. Medication Concentration Practices

Question: In adult ICU and PICU patients, does the use of safe medication concentration practices versus not establishing safe medication concentration practices impact rates of MEs/ADEs?

Answer: We recommend compliance with safe medication concentration practices (i.e., use of premade IV preparations, requirement of pharmacists to prepare all IV medications) to reduce the number of MEs and potential ADEs. (1B)

Rationale: Parenteral MEs are recognized as a serious safety concern in ICUs, and many parenteral products have been identified as high-alert medications (6, 7, 67, 73). The risk of parenteral MEs may be higher in the ICU due to a higher proportion of IV medications administered than in the non-ICU patient populations (20). Also, the IV route of administration has been demonstrated as a risk factor for ADEs in the ICU (67). The medication use process from order entry to administration of an infusion is complex and involves several steps that can potentially result in a variety of MEs. In fact, Fraind et al (220) described 41 distinct steps in this process. About 10% of all IV infusions administered or prepared in the ICU are done in error (221). Common sources of parenteral MEs include numerous available concentrations and manual preparation of infusion solutions by nursing and medical staff (222–224). This practice may lead to incorrect calculations, erroneously prepared concentrations, wrong diluents, incompatible admixtures, contamination or insufficient mixing of solution, and improper labeling and expiration dates. Previous studies measuring drug concentrations confirmed that discrepancies existed between measured and ordered parenteral infusions manually prepared in ICU setting (223, 225). These discrepancies can potentially lead to subclinical response or life-threatening ADEs. In particular, variation in concentrations of high-risk medications has been previously reported to cause patient harm (226, 227). Changes in procedures or training programs for nurses and addition of a satellite pharmacy have been suggested; however, these interventions have not been implemented universally and data on outcomes are limited.

Ten studies have evaluated current medication concentration practices in an institutional setting, with seven studies occurring in an ICU setting (227–236). Two studies demonstrated a significant reduction in medication concentration and compounding error rates (16–59% reduction) when comparing manual preparation in the patient care unit to preparation in the pharmacy or use of commercially available premade IV solutions (227, 228). Other studies have implemented several process changes such as standardization of concentrations, developing a new protocol with detailed steps, changing to pharmacy preparation or use of commercially available premade solutions, integrating "smart" pump technology, and using titration charts (229, 231, 233–235). Three of these studies compared MEs before and after implementation of these changes. The investigators found a significant reduction in MEs, specifically averted overdoses, improper dose and concentration errors, and preparation errors by 13–73% (231, 233, 234). Another study focused on standardization of IV solutions also showed a reduction in MEs including calculation, exceeding maximum concentration, incomplete and illegible errors by 50% (236).

Many parenteral medications are commonly associated with patient harm; therefore, these agents are designated as high-alert medications to ensure increased awareness for the potential of a ME occurring (237). Parenteral MEs are nearly three times more likely to cause harm or death compared with any other type of errors (238). The IV route of administration was more likely to cause harmful or fatal errors (79%) compared with errors involving subcutaneous, epidural, or intrathecal routes (238). Taxis and Barber (239) determined an error rate of 49% in 430 IV drug preparations and administrations. These findings are higher than error rates reported for oral MEs, which has been reported between 3% and 8% (193, 202). A recent prospective observational study of 107 nurses preparing and administering 568 IV medications determined that approximately 70% of these administrations had at least one IV ME, and 26% of these were serious enough to cause patient harm (240). A retrospective study conducted in five ICUs over a 2-year period determined 397 ADEs involving IV administration, with 79% resulting in temporary physical injuries, 20% requiring interventions to sustain life, and 2% leading to in-hospital deaths. To determine if standardizing concentrations may reduce patient harm, two studies evaluated the severity of MEs and their potential for causing patient harm (227, 233). Barletta et al (227) revealed that 50% of the MEs were associated with significant patient harm (11% of these errors resulted in death) if IV solutions were manually prepared in the patient care unit. Maddox et al (233) developed a harm assessment tool with the following elements: 1) inherent risk of drug being infused, 2) risk associated with patient acuity, and 3) risk of an undetected infusion-related ADE. Over a 6-month period, after standardizing parenteral concentrations and implementing smart pump technology, the new system identified 328 high-risk overdoses that were prevented. Based

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on an estimated value of $6,000 per accidental drug overdose, the system resulted in estimated cost savings of $1,968,000 in 6 months (233). Although significant costs and effort are needed to ensure safe medication concentration practices, the studies demonstrate a significant reduction in ME rates and prevention of patient harm. Furthermore, the ISMP has stated a lack of standardized concentrations as "dangerous," and TJC has developed guidelines on limiting and standardizing concentrations of parenteral drugs (241, 242).

5. Pharmacist Participation in Medication Passes

Question: In adult ICU and PICU patients, does a pharmacist participating in medication passes versus no pharmacist involvement impact outcomes such as ME or ADE rates?

Answer: We make no recommendation regarding pharmacist involvement in medication passes to reduce the number of ME or ADE due to lack of evidence. (0, no evidence)

Rationale: Understanding the causes of MEs and their contributing factors are critical in order to make process changes for prevention. Several contributing factors have been associated with MEs including high workload, fatigue, knowledge deficit, poor communication, distractions, inexperienced staff, interruptions, and distractions (243–251). A medication pass is the delivery of medications from the nurse to the patient. Several studies have investigated the impact of medication pass time-out practices on ME rates (247, 252–254). Medication pass time-out is a period of protected time for the nurse during medication administration to not be distracted or interrupted (247, 252–254). Implementing medication pass time-out has resulted in a significant reduction in distractions by 81% and errors during medication administration by 2% (252). To be effective in reducing errors, medication pass time-out should include utilization of technology during medication administration. For example, nurses acquire medications from ADMs located on the patient unit, scan them with bar-code technology, and program smart infusion pumps for IV administration. However, there are opportunities for nurses to deviate from protocols (i.e., work arounds). Since pharmacists do not verify these work arounds prior to administration, these can lead to wrong administration of medications, wrong doses, wrong times, and wrong formulations (32, 255). In long-term care facilities, pharmacists are required by federal regulations to conduct medication administration observations (previously known as observing a medication pass), record nurse activities, and coach nurses on the safe technique to administer medications (256). Pharmacist collaboration with nurses during medication administration may prevent MEs. However, there are currently no studies that have investigated the outcome and feasibility of pharmacist participation during the medication pass in the acute care setting. Research evaluating the impact of pharmacist involvement in medication passes on MEs or ADEs in the ICU setting is needed.

6. Independent Double Check During Dispensing

Question: In adult ICU and PICU patients, do independent double checks versus no double checks during dispensing impact outcomes such as ME or ADE rates?

Answer: We suggest the use of independent double checks during the dispensing phase for high-risk medications or processes in the ICU to reduce the number of ME. (2C)

Rationale: Data were evaluated for settings both in and outside of the ICU. The results of applying double check could be extrapolated to the ICU setting and have a significant impact because of the high frequency of high-risk medication use. Double checking in the dispensing process is a procedure where two healthcare professionals check medications independently before they are dispensed from the pharmacy (i.e., pharmacist or pharmacy technician checking the accuracy of another pharmacy technician). In order for checking to be considered independent, the second person should follow a series of steps to confirm that he/she agrees with the first person without any prior knowledge to minimize potential bias (257). This double checking process is used in many institutional pharmacies where the check occurs in a location separate from where the technician fills the medication order prior to dispensing (258). Eleven studies were identified that investigated the use of pharmacy technicians to double-check other pharmacy technicians filling medication orders to allow pharmacists to focus on other responsibilities, including clinical activities (259–269). Ten studies were conducted in a hospital pharmacy setting using manual unit-dose systems (e.g., unit-dose cassettes, unit-dose carts, and patient-specific unit-dose envelopes) (259, 261–269). One study was performed in an outpatient dialysis pharmacy setting focusing on technician filling of IV syringes (260). Most studies compared the accuracy of technicians and pharmacists in checking the work of another technician before medications were dispensed from the pharmacy (259–261, 263, 264, 266–269). However, two studies only evaluated the accuracy of certified pharmacy technicians without comparison to pharmacists (262, 265). The accuracy rates between pharmacists and technicians were similar for most studies. Two studies demonstrated a significantly higher rate of detecting MEs when double checking was performed by a certified pharmacy technician compared with pharmacist (261, 268). The need for double checking was confirmed in one study where pharmacists observed 215 errors when checking the work of pharmacy technicians checking other technicians. Two studies evaluated severity of errors and showed no difference in serious errors when pharmacy technicians performed checking (261, 267). Limitations of these studies include lack of adequate statistical analyses, inconsistent definitions for severity of errors, use of controlled settings, and short duration. Also, many of these studies overestimated the frequency of dispensing errors.

The use of double checking as a process to reduce drug dispensing errors remains controversial due to variability and paucity of conclusive research evidence on its effectiveness. First, performing a true independent double check is a human endeavor and therefore subject to error. A second implication of double checks is interruption from the nurse's current task

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since for each double check, employees are required to stop what they are doing to perform this process. Third, implementation of a double check process creates a change to the systems of care delivery (189, 190). Any change to systems of care delivery will impact all components of the system and related outcomes. Thus, before adding double checks to high-risk medications in the ICU, both the intended and unintended consequences of this implementation should be carefully evaluated. These potential consequences are further described in the administration section (double check/double-signature section) where these consequences may have a greater impact.

Furthermore, it is unclear if the use of independent double checks would have a significant impact on MEs or ADEs in institutions already having medication dispensing process technology such as the use of bar coding and ADMs. These improvements may be adequate in providing positive outcomes in the systems of care delivery without the use of independent double checks. Further research is needed to clarify the role of independent checks in the dispensing process that uses one or more of these other strategies.

Because of these potential consequences, the use of independent double checks may not be the most cost-effective option. Alternatives such as single checking along with a method to reduce distractions should be explored. Advantages of a single check system include saving time and increasing responsibility on the checker leading to increased vigilance. Many studies revealed that double checking is a common process that is inconsistently performed, which may explain the variability in the reported outcomes. Evidence suggests a role for single and double checking depending on risk assessment (270). Recommendations have been stated in the literature to enforce double checking for high-risk medications and processes such as those requiring dosing calculations, chemotherapy, insulin administration, neuromuscular blockers, anticoagulants, and potassium chloride (258, 271).

In a report discussing the findings from the ISMP Medication Safety Self-Assessment for Hospitals 2000 survey, 45% of hospitals surveyed responded that high-alert medications (e.g., insulin, chemotherapy, opioids) were not double checked by a second practitioner when obtained from unit stock (272). Although errors may or may not be higher compared with other medications, these high-alert medications are associated with higher risk of serious patient harm if misused. Double checking by another health professional seems appropriate to reduce MEs; however, errors may still occur if a standardized procedure for double checking is not used. The ISMP currently recommends independent double checks should be performed for selected high-risk processes and high-alert medications like chemotherapy and patient-controlled analgesia administration (257, 273). We suggest developing a standardized and independent double checking system for high-risk medications and processes in the ICU may reduce MEs.

D. ADMINISTRATION NODE: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

Medication administration in the ICU is a multifaceted process requiring communication among nurses, pharmacists, and physicians. The complexity of the process of medication administration creates competing demands for caregivers with distractions and interruptions creating an opportunity for MEs. Reports estimate that 36–56% of MEs in ICUs occur during the medication administration phase (10, 274). The administration phase is the final step in the medication process, and this is the last chance for detection of an error before reaching the patient.

Medication administration errors can be the result of many issues such as deficient knowledge, protocol violations, inadequate patient information, interruptions, inadequate staffing, inaccurate dosing, or human error. Some of the most frequent types of medications errors relate to administration such as omission of medications and wrong time of administration (275, 276). New processes and technological advancements targeted to improve the medication administration phase include BCMA and smart infusion pump technology. To address additional aspects of medication administration, changes in systems of care delivery (i.e., double checks) and the use of subjective assessment tools to achieve therapeutic goals of medication titration have been implemented.

1. Bar Code Medication Administration

Question: In adult ICU and PICU patients, does the use of BCMA impact outcomes such as MEs/ADEs?

Answer: We suggest the use of BCMA to reduce MEs/ADEs in the ICU. (2C)

Rationale: A study by DeYoung et al (277) evaluated 1,465 medication administrations for MEs before and after implementation of BCMA in a MICU. Direct observation technique was used to detect MEs. The frequency of ME rate before and after implementation of BCMA was 19.7% and 8.7% ($p < 0.001$), respectively. However, significance was lost when wrong time errors were excluded (277). A study by Helmons et al (278) evaluated 2,353 medication administrations to determine the effect of BCMA on MEs in both ICU and non-ICU patient populations using a direct observation technique. Investigators observed a reduction in MEs after excluding "wrong time" errors from analysis in the general ward areas, but found no significant differences on MEs rates in the ICU (278). Despite the low frequency of MEs detected that were not wrong time errors, BCMA may improve patient safety during medication administration. In contrast, a study conducted in multiple units including the medical-surgical ICU demonstrated that there was an increase in MEs following the introduction of BCMA plus an electronic medication administration record for the ICU and a reduction for non-ICUs (279). This finding stresses the importance of evaluating technology for specialty care environments. Of note, none of these BCMA studies evaluated ADEs or their severity (277, 278).

A study by Morriss et al (280) conducted a retrospective chart review evaluating MEs, potential ADEs, and targeted

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preventable ADEs in a neonatal ICU. Total MEs increased from 69.5 to 79.7 errors per 1,000 doses after implementation of BCMA ($p < 0.001$). This result was attributed to BCMA increasing the detection of wrong time errors. Potential ADEs decreased from 15.1 to 4.4 events per 1,000 doses after implementation of BCMA ($p < 0.001$). In addition, targeted preventable ADEs decreased from 0.86 to 0.43 events per 1,000 doses after implementation of BCMA ($p = 0.008$) (280). Lastly, Poon et al (281) investigated the impact of BCMA on rates of errors during the transcription and administration stages among medical and surgical wards as well as ICUs. Direct observation methods were used to detect events. The investigators evaluated MEs not associated with wrong time administration and potential ADEs. After implementation of BCMA, there was a 41.4% relative reduction in MEs ($p < 0.001$). There was also a reduction in potential ADEs after implementation of BCMA from 3.1% to 1.6% ($p < 0.001$). Bar code medication administration technology reduced clinically significant, serious, and life-threatening potential ADEs (281). Overall, BCMA technology has been shown to be effective in reducing MEs and ADEs in the ICU.

BCMA has also been studied in combination with other ME reducing efforts such as provision of pharmacist services, quality process education, and nurse double-checks resulting in a reduction in ME rates (282, 283). For the purposes of this evaluation, we were interested in measuring the effects of BCMA and not the other ME reduction techniques.

It is important to note that the benefit of BCMA may be limited when nursing work-arounds are applied (284). The BCMA was not necessarily designed to accommodate all ICU medication administration scenarios, for example, managing stat orders often results in work-arounds with BCMA (285). Work-arounds are a key element to evaluate in real-world use, that is not always considered in controlled studies. Also, alarm burden is a concern in the ICU and BCMA may result in frequent alarms if programming does not allow for medication specific dosing requirements for this patient population. More well-designed BCMA evaluations specific to the ICU environment are needed to provide a conclusive determination as to the impact of BCMA on MEs and ADEs.

2. Smart Infusion Pumps

Question: In adult ICU and PICU patients, does the use of smart IV infusion pump technology reduce MEs/ADEs in ICU patients?

Answer: We suggest smart IV infusion pumps be used to reduce the rate of MEs/ADEs in the ICU. (2C)

Rationale: Unlike historical infusion pumps, smart pumps use dose error reduction software, commonly referred to as "drug libraries," in order to assist healthcare providers with selecting the appropriate programmed medications, and calculating both the dose and delivery rates (286). Nuckols et al (287) evaluated the impact of smart infusion pump technology on preventable ADEs in a variety of ICU settings (surgical, trauma/burn, and medical). Investigators conducted a retrospective chart review to identify ADEs (287). A total of 20,559 patient days were evaluated. The overall rate of preventable ADEs before and after implementation of smart infusion pumps did not significantly decrease (4.78 vs 4.95 ADEs per 1,000 patient days; $p = 0.96$). The investigators noted that only 4% of the observed IV ADEs in this study were capable of being prevented by smart pump technology; thus, statistical power was inadequate to determine if smart infusion pump impacts IV ADE rates. The frequency of errors occurred during the ordering and monitoring stages was 50% and 35%, respectively. Rothschild et al (288) performed a prospective, randomized time-series trial evaluating the impact of integrating decision support software on MEs and ADEs in a cardiac surgery ICU and a cardiac step-down unit. Actual and potential ADEs were identified by retrospective chart review and pump log events. Overall, 10,659 medication administrations and 8,145 pump days were evaluated. Smart pumps did not impact the rate of actual or potential ADEs as well as serious MEs. The lack of improved safety with this technology may be explained by the high rate of "bypassing the library" (i.e., drug administration outside of the specific concentration, dose or rate limits programmed in the pump) and alert overrides by the user. After adjusting the data for bypassing the library and overrides of alerts, investigators did show a reduction in nonintercepted preventable ADE per 100 pump days from 2.12 to 0.36 ($p = 0.001$) (288). It is important to note only "soft" limits (i.e., user has ability to override preset conditions such as maximum infusion rates) were used in this trial that may have contributed to the high rate of overrides. Another study evaluated the impact of smart pump infusion technology in 4,604 ICU patients at two hospitals (287). Patients receiving continuous infusion medications in the surgical, trauma/burn, and MICUs were evaluated by trained observers for retrospective, chart review on identifying ADEs. Overall, no significant difference was found comparing the rate of preventable MEs associated with conventional and smart pumps (4.78 vs 4.95 errors per 1,000 patient days; $p = 0.96$). The investigators determined only 4% of IV preventable ADEs among all study patients could have been intercepted by smart pump technology. Major limitations of this study included its retrospective design, excluding IV boluses administered (i.e., only evaluated continuous infusion), and possibly not optimizing drug library guardrails, which are set dosing limit precautions within the software for the infusion pump. Overall, two studies suggest smart infusion pumps may prevent select types of MEs and ADEs, whereas one study failed to show any impact on error rates in an ICU setting. Inappropriate use of this technology and excessive overriding safety alerts limit the effectiveness of smart pumps.

A prospective, observational study evaluated IV ME rates as well as severity before and after implementation of smart infusion pumps at a teaching hospital (289). Although this study included critically ill patients among all subjects, the investigators did report ICU-specific data. The overall ME rate was reduced by 47% between the preimplementation and postimplementation phases (18% vs 9.4%; $p = 0.003$). Interestingly, no significant difference was observed in the

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ME rates in either periods if drug guardrails were absent (preimplementation and postimplementation rates, 18% vs 19%; $p = 0.8$). The clinical significance of these errors (i.e., severity) was positively impacted by smart infusion pumps. The authors disclosed a potential shortcoming of this investigation was the limited observational period (weekdays only), which may have underestimated the number of errors. This study would have benefited from isolating the impact in the ICU and a comparison between ICU and non-ICU population. Nonetheless, this study provided insight on the importance of guardrails on reducing the number and more severe errors.

One study evaluated the impact of smart infusion pumps, drug concentration standardization, and pharmacy label reformatting on MEs in pediatric hospital. ME rates decreased from 3.1 to 0.8 per 1,000 doses for an absolute risk reduction of 2.3 errors per 1,000 doses (95% CI, 1.1–3.4; $p < 0.001$) after implementation of smart infusion pumps. In addition, pharmacy preparation errors decreased from 0.66 to 0.16 events per 1,000 doses (231). Fanikos et al (290) evaluated 863 anticoagulant-related smart pump medication alerts at an academic medical center. Smart infusion pump alerts led to 372 reprogramming events and 401 cancellations. Of these events, there were 90 overdose and 59 underdose potential errors that were intercepted. Comparing reported MEs before and after pump implementation, there was no difference in total reported anticoagulation errors, but a reduction in anticoagulant infusion rate errors was observed (290). Two studies (291, 292) demonstrated that smart infusion pumps alert feature led to reprogramming of incorrect infusion rates; thus, averting potential infusion errors. These studies further support the use of smart pumps in reducing the rates of certain type of errors, especially underdosing and overdosing errors at the time of pump programming.

A simulation study investigated IV administration MEs among traditional pumps, smart infusion pumps, and smart infusion pumps with bar-code technology (293). Comparing traditional pumps to smart infusion pumps, investigators demonstrated a higher rate of detection for errors related to wrong doses with hard limits and programming intermittent infusions. Wrong patient, wrong drug, soft limit dose errors, continuous infusion programming errors, and secondary infusion errors were not significantly different. Smart pumps with bar-code scanning were able to reduce wrong patient errors (293). Adachi and Lodolce (294) investigated total and IV pump-related errors before and after a failure mode and effects analysis (FMEA) was conducted on the use of smart infusion pumps at their institution. A lower number of total and IV pump-related errors were reported after the FMEA process, though rates of errors were not measured, and statistical analysis was not performed.

Overall, these results suggest smart infusion pump technology may reduce the rate of MEs and ADEs, specifically those related to incorrect infusion rates. Lack of compliance in using the smart pump technology or inappropriate overriding of alerts may limit the effectiveness of smart infusion pumps. To maximize the safety potential of smart infusion pump technology, it is suggested that multidisciplinary teams work together to establish the infusion pump library of alerts and maximum override limits for the highest impact on safe medication administration.

3. Double Checking During Medication Administration

Question: In adult ICU and PICU patients, does mandatory double checking versus no mandatory double checking during administration of high-risk medications impact outcomes such as ME/ADE rates?

Answer: We make no recommendation for the inclusion of mandatory double checking during administration of high-risk medications to prevent MEs/ADEs based on the lack of supporting evidence. (OD)

Rationale: Four studies evaluated double checking in the medication administration node (271, 295–297). When compared with single checking, double checking was shown to increase detection of MEs by 17–65% in one study (296). Another study demonstrated a decrease in the rate of MEs from 2.98 to 2.12 errors per 1,000 medications administered after implementing a double check system (295). However, two studies determined double checking resulted in similar rates of MEs compared with single checking (271, 297). Interestingly, one investigation observed an increase in errors with a double checking system compared with single checks (67% vs 30%, respectively) (258). Low reporting rates of MEs and a lack of statistical analysis might explain the discrepancies among the studies (258, 271, 297). One study determined an additional 17.1 hours per 1,000 medications administered was needed for double checking process to occur (295).

The use of double checking as a process improvement strategy to reduce MEs remains controversial due to the variability of results and lack of conclusive evidence on effectiveness. However, applying a systems perspective, there are potential unintentional consequences of implementing this procedure. First, performing a true independent double check is essentially a human endeavor and subject to error. A study of inspection (i.e., double check) revealed that the base error rate in which a "monitor or inspector fails to recognize the initial error by the operator" is 10% (298). So, a second person may miss or incorrectly identify a ME about one in every 10 medications that are double checked.

Another consequence of double checks is the impact it may have on healthcare providers' workflow. Most institutions have not accounted for additional resources including staff to implement these activities. In other words, the time required to perform double checking may interfere with other responsibilities. Some institutions may have substantial staffing resources, which can provide individuals to perform double checking without inadvertently impacting their workflow or potential opportunity costs. Unfortunately, the economic climate of healthcare makes this unlikely. To better illustrate the issue of opportunity cost, consider TJC's proposed 2005 National Safety Goal 2b, which mandates that a nurse should "perform an independent double check whenever programming or reprogramming

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infusion pumps." If a hospital's ICUs have 800 new infusions a month and 1,200 infusion changes, this equates to 2,000 changes. Assuming, it takes a practitioner 1 minute to find a second nurse, and then a minute to perform the double check, an additional 4,000 minutes or 66 hours of nursing time would be required simply to perform double checks. While this TJC proposal was not enacted, it illustrates the additional cost that double checks would add. Similarly, an organization can estimate the nursing time currently spent on existing double checks.

Double checking by another health professional seems logical to reduce MEs; however, improper use may result in errors. Institute of Safe Medication Practices currently recommends that independent double checks should be performed for selected high-risk processes and high-alert medications like chemotherapy and patient-controlled analgesia administration (257, 273). Unfortunately, minimal research has been conducted to measure the impact of this practice (299). Also, implementation is complicated by the lack of a clear definition of double checking and limited consensus on ideal procedures for double checking medications (296). While no recommendation can be suggested based on the lack of robust evidence, institutions should consider the practice of double checking medications prior to administration since it seems to be a logical safety procedure.

4. Use of Subjective Assessment Tools

Question: In adult ICU and PICU patients, does the use of subjective assessment tools (e.g., Richmond Agitation Sedation Scale, Ramsay Sedation Assessment Scale) to titrate medication administration impact outcomes such as ME/ADE rates?

Answer: We suggest using validated assessment tools to achieve therapeutic goals during administration/titration of medications in the ICU. (2B)

Rationale: Using validated assessment tools (e.g., sedation scales, pain instruments) is an integral component of patient focused medication administration. Previously published guidelines have commented on the value of protocols from a clinical outcomes perspective (46). From our perspective, we were interested in evaluating sedation and pain protocols for safety outcomes, specifically the value of protocols in titrating medication administration to achieve therapeutic goals. Safety is a significant concern in patients who are unresponsive or agitated when adequate sedation level goals are not achieved. In conjunction with various treatment algorithms, numerous randomized protocols have documented significant outcomes including reduced sedative and analgesic drug use, shorter duration of mechanical ventilation, and reduced time in the ICU and hospital by incorporating goal-directed interventions into bedside practice (grade 1B). Given the preponderance of data published, we recommend using validated assessment tools to achieve therapeutic goals during administration/titration of medications in the ICU.

E. MONITORING NODE: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

Medications with complex dosing strategies, narrow therapeutic indices, unique administration techniques may require intense monitoring to ensure safe and effective use (67). Inadequate monitoring is a contributing factor to MEs (8, 11, 12, 19). Clinical decision support that generates alerts as a reminder for monitoring drugs has the potential to be useful. If it is deemed important enough, then an alert can be bypassed and automatic ordering of laboratory values can occur. Rapid monitoring using POC testing offers a quicker response and possibly faster interventions. Monitoring patients requires effective communication between healthcare professionals to ensure follow-up is not missed and patient outcomes are optimized. Also, the engagement of family members/caregivers in patient care is becoming increasingly important and can be a useful tool to enhance the safe monitoring of patients.

1. Reflex Laboratory Monitoring

a. Question: In adult ICU and PICU patients, does reflex (automatic) versus clinician initiated laboratory orders impact outcomes such as reducing DHRC?

Answer: We suggest the use of reflex (automatic) ordering of laboratory values with the addition of a dosing suggestion for heparin orders since there is the potential of avoiding ADEs from this high-risk drug. (2C) It is unclear, if this benefit could also be achieved by providing recommendations for heparin dosing suggestions alone without the reflex laboratory monitoring.

b. Question: In adult ICU and PICU patients, do alerts suggesting laboratory ordering versus clinician initiated practice for laboratory ordering impact outcomes such as reducing DRHCs?

Answer: We suggest alerts prompting laboratory ordering during the drug prescribing process be used to reduce the rate of DRHCs. (2C)

Rationale: Reflex laboratory monitoring can include automatic ordering that requires no clinician initiation and an alert that will stimulate the clinician to monitor the drug response by ordering laboratory tests. We treated these as two separate questions since data were available to support each; however, the rationale supporting the recommendation was combined to minimize overlap. The IOM identified delay in diagnosis as a critical form of medical error in the To Err Is Human report (1, 300). Proactive laboratory monitoring of pharmacokinetic and pharmacodynamic effects of drugs provides a way to identify DRHCs before resultant injury, an ADE, occurs. Using health information technology to assist in the appropriate, proactive monitoring of drugs would provide standardization and convenience. Automated alerts for monitoring have been studied during two phases: 1) an automatic/reflex ordering of laboratory tests in response to a drug order and/or in response to a laboratory value after a dosing adjustment has been made or 2) in the drug ordering process, an alert is generated to remind clinicians to order laboratory tests. Obviously, using this type of health information technology does require the institution to have some type of electronic health record. The criteria (i.e., frequency, interval) for appropriate drug monitoring are at the discretion of the institution.

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There was one study identified that addressed automated ordering of laboratory values in response to a verified drug order (301). This study used automatic ordering of laboratory values (reflex ordering) in response to heparin orders for patients on a cardiovascular service, known as "HEPCARE." The focus was a safety evaluation of activated partial thromboplastin time (aPTT) monitoring for heparin orders. The study design was observational comparing patients receiving HEPCARE to those without HEPCARE or standard of care for aPTT monitoring for heparin orders. Important to note, HEPCARE included recommendations for dosing adjustments in response to aPTT concentrations and not simply reflex laboratory monitoring. The results indicated a significant increase in the number of aPTTs at goal range and decrease in the time to achieve the goal aPTT range. The limitations of this study were the lack of bleeding as a study endpoint and the use of cardiovascular patients as the treatment group compared with other patient populations for the control group. Indirectness of evidence was a concern for this study. In addition, we cannot delineate the effects of the reflex laboratory monitoring from the effects of the dosing recommendations provided.

Also, a before and after implementation study evaluated an automated request for laboratory value ordering as the prescriber entered the medication order. Investigators sent alerts to the prescriber during the ordering process of aminoglycosides inquiring about monitoring drug concentrations (302). The study endpoint was to reduce abnormal aminoglycoside serum concentrations. The results indicated no statistically significant change in the number of sub- or supratherapeutic concentrations obtained between the before and after period. A few limitations should be noted. First, laboratory monitoring was optional. Also, it was mentioned how many other alerts the physician received during the ordering process so the influence of alert burden was not known. The pharmacist rounding with the team intervened on the automated laboratory alerts and made recommendations after assessing for alert appropriateness. The pharmacist dissuading compliance was the primary reason for not monitoring. Although this evaluation was not specified as occurring in the ICU, it was implemented hospital-wide and included in this assessment because of the frequency of aminoglycoside use in critically ill patients. Automated prompting of laboratory values has shown to enhance monitoring outside of the ICU (303, 304).

Overall, automated or reflex ordering of laboratory values in response to a medication order may prevent errors of omission or monitoring. This additional laboratory ordering may need to be balanced with a clinician assessment for appropriateness when possible, since false positive alerts may occur (302, 303, 305). A potential problem of laboratory-related alerts is its contribution to alert fatigue. Also, inappropriate laboratory value ordering may result in additional institution expenses (306). In contrast, alerts have been used to aid in appropriate laboratory value ordering, reduce test turnaround time, and decrease costs (307, 308).

2. Handoff Communication

Question: In adult ICU and PICU patients, does handoff communication techniques used at shift change versus no handoff communication impact outcomes such as ME/ADE rates?

Answer: We make no recommendation for the use of handoff communication technique to prevent MEs/ADEs based on the lack of supporting evidence. (OD)

Rationale: The handoff between healthcare providers at shift change has been an important process in clinical nursing practice that allows for the exchange of patient information to facilitate safe care (309). This process has the potential to reduce MEs and ADEs in critically ill patients. No randomized studies assessing the benefits of handoffs have been published. However, the literature continues to highlight the effects of ineffective handoffs including adverse events and patient safety risks. One process improvement project showed pain medication availability increased from 12% to 88% in patients transferred from the hospital to a skilled nursing facility when a checklist and a "nurse-to-nurse" briefing was performed (310). A small presurvey and postsurvey ($n = 15$) of surgical nurses' perception of the impact from nurse-to-nurse handoff on one question stating "nurse-to-nurse shift report allows me to perform shift change medication reconciliation" increased significantly ($p = 0.003$) (309).

The Joint Commission NPSG of improved communication addresses the need for healthcare providers to communicate accurate patient medication information during shift handoffs. In addition, the U.S. Pharmacopeia identified handoff issues as a contributing factor to MEs within healthcare organizations (311). While there may be minimal agreement on the format or what content should be included in the shift handoff, patient medications can be part of that process. There is a need for research investigating the impact of handoff communication techniques on MEs and ADEs.

3. POC Testing

Question: In adult ICU and PICU patients, does POC testing versus not using POC testing impact outcomes such as ME/ADE rates?

Answer: We make no recommendation for the use of POC testing to prevent MEs/ADEs based on the lack of supporting evidence. (0D)

Rationale: Theoretically, POC testing may prevent ADEs in critically ill patients due to the benefits of instantaneous laboratory results. Although there were two studies that evaluated POC versus not using POC in regard to glycemic control in the ICU, ADE or ME rates were not evaluated (312, 313). Although the technology may be costly and present process challenges, there is the potential to improve the timeliness of laboratory results that may impact medication interventions, thus improve patient outcomes. However, with any technology, there is the chance for increasing MEs. Opportunities exist for MEs with POC testing due to inaccurate patient identification when results are available, incorrect specimen interpretation, and inaccurate transcribing of results in a nonintegrated computer system (314). These three factors should be taken

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into consideration when designing and monitoring a POC program. There is a need for systematic investigations to determine the impact of POC testing on MEs and ADEs.

4. Patient and Family Members Knowledge of Patient's Medication Regimen

Question: In adult ICU and PICU patients, does notification of medication regimens to the patient or family members versus no notification impact outcomes such as ME/ADE rates?

Answer: We make no recommendation regarding notification of medication regimens to the patient or family members to reduce the number of MEs/ADEs due to lack of evidence. (0, no evidence)

Rationale: The risk of MEs and ADEs (315) may be increased during hospitalization when multiple drug therapy changes occur without the provision of adequate patient education, follow-up, and continuity of care (316). Often, these problems lead to inappropriate prescribing practices, discrepancies between prescribed and actual regimens, and poor adherence and monitoring upon discharge (317). Data suggest that pharmacist-initiated counseling of patients prior to discharge reduces medication discrepancies and ADEs at 30 days postdischarge and improves medication compliance (318–322). Due to the increased complexity of care and vulnerability to rapid changes in pharmacotherapy in the ICU (9), it seems logical to notify patients and/or family caregivers regarding medication regimens (including initiation and any changes) to assist with surveillance and reduce the risk of MEs or ADEs. However, there are no studies to date that have investigated the impact of family involvement in the oversight of medication regimens in the ICU setting. Since previous studies have demonstrated the positive outcomes associated with medication counseling, we suggest that research should be conducted to determine if notification of medication regimens to patients and/or family members would aid in monitoring and reduce MEs or ADEs in the ICU setting.

F. PATIENT SAFETY SURVEILLANCE SYSTEMS REPORTING: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

There are several methods of detecting MEs and ADEs; however, most institutions are reliant upon voluntary reporting even for reporting events occurring in the ICU (323). There are several proposed barriers to voluntary reporting including the time it takes to report, a lack of knowledge on how to report, what should be reported and a fear of punitive action if an event is reported. Approaches to overcome these barriers should be applied to optimize the number of reported events. One approach is to make reporting as easy as possible, and there is a debate about which is easier, electronic, or analog reporting (324). The evidence surrounding this question will be reviewed.

1. Electronic Versus Analog Reporting Systems

Question: In adult ICU and PICU patients, does the use of electronic (web-based, handheld collection devices, electronic medical record) versus analog (paper-based) systems impact the quantity or quality of ADE reporting?

Answer: We make no recommendation on the use of electronic versus analog systems impacting the quantity or quality of ADE reporting in ICU patients based on the lack of supporting evidence. (0C)

Rationale: Logically, using electronic reporting methods may enhance the reporting process, the feedback loop, and data analysis. Tuttle et al (325) found the use of an electronic system that integrates an educational intervention increased the reporting by 54% compared with an analog approach. Foster et al (326) took electronic reporting further by prompting physicians to report during sign-out using an electronic format. Physician prompting resulted in an increase in reporting over previous methods, although the preintervention reporting methods were not fully elucidated. On the contrary, three completed studies with more rigorous methods indicate the analog system resulted in higher event reporting (50, 327). The conflicting data make it difficult to recommend one voluntary reporting mechanism over another. The overall lesson to learn is that the mechanism (electronic or analog) may not be as important for reporting. Instead, the interventions in place to encourage reporting are of more significance (324). Methods to encourage reporting that were used simultaneously with electronic and analog strategies included extensive education, feedback on reported events, optional anonymity, and establishing a culture of safety.

G. PATIENT SAFETY SURVEILLANCE SYSTEMS METHODS OF ME AND ADE DETECTION: QUESTIONS, STATEMENTS, AND RECOMMENDATIONS

Several methods of detection can be considered for an active patient safety surveillance system including family and patient involvement, nontargeted chart review, targeted chart review, and direct observation (33). The evidence evaluating the use of these methods of detection will be reviewed.

1. Family and Patient Involvement

Question: In adult ICU and PICU patients, how do patient/family interviews compared with other methods of reporting (voluntary reporting, medical chart review, etc) impact the quantity of ME/ADE reporting?

Answer: We suggest the application of a patient/family reported outcome interview at or after ICU discharge to improve ME/ADE reporting. (2C)

Rationale: Patient-reported outcomes are highly encouraged to better understand the impact of health services provided (328, 329). Although there are no studies regarding patient-reported events involving critically ill patients, there are data to support the benefit of patient reporting of MEs and ADEs compared with other detection methods in settings outside of the ICU (330–335). Two of these studies were conducted in hospitalized patients (330, 332). Kaboli et al (330) compared patient interviews to other methods of detecting

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MEs and ADEs. This was a prospective cohort study conducted in a general internal medicine inpatient ward. One hundred twenty-six patients were included with 76% being interviewed less than or equal to 2 days of discharge for potential medication misadventures. Overall, 63 patients experienced 106 medication misadventures as detected by the various methods with 11% detected through patient interviews. van den Bemt et al (332) conducted a comparison among three reporting groups (physicians, nurses, and patients) in four units (pediatric and internal medicine) over 2 months. Patients reported substantially more events than physicians or nurses with 269, 23, and 30 reports, respectively. Many of the reports provided by patients were considered serious. Also, patients were more apt to provide reports for newly started drugs. An intriguing observation in both of these studies was that the different detection methods found different medication misadventures. These studies corroborate the recommendations from other publications stating that a variety of ADE detection methods should be incorporated into patient safety surveillance systems (33, 335–337).

It should be noted the literature supporting this recommendation was not conducted in the ICU; however, the concept of interviewing patients/family about patient safety-related events is transferrable to the ICU and should be considered. The frequency of events reported by patients in non-ICUs may not be comparable to the ICU setting since some drugs administered (i.e., benzodiazepines with amnestic properties) may make patient interviews at ICU discharge challenging. This may also be an opportunity for family involvement in event reporting. Family involvement, specifically, parents, guardians, or caregivers involvement in safety issues is also crucial when advocating for their loved ones. Parent involvement has resulted in the detection of events in a neonatal ICU/PICU; however, family involvement has not been compared with other detection methods in the ICU (338). Based on the available evidence, we suggest including patient and/or family interviews as a method of ME and ADE detection in the ICU, when possible, to increase reporting and detect events not identified by other methods. Ideally, this model would include real-time reporting; however, other approaches may be useful such as scheduled reporting (i.e., daily, weekly, or at discharge). Future areas of study should include evaluating the potential benefits of conducting patient/family interviews during the ICU stay and at ICU discharge for detection of MEs and ADEs during ICU care.

2. Nontargeted Chart Review

Question: In adult ICU and PICU patients, does nontargeted chart review (manual or electronic) versus voluntary reporting strategies improve the rate of identifying MEs and ADEs?

Answer: We suggest performing chart reviews for detecting ADEs as part of a surveillance system. (2C)

Rationale: A total of eight studies have compared nontargeted (i.e., random) chart review to voluntary reporting strategies (179, 335, 337, 339–343). One study reported data specifically in a PICU and adult ICU (340). These investigators found facilitated incident reporting was more effective than retrospective chart reviews in identifying adverse events and providing more detailed information surrounding these incidents. However, these adverse events evaluated were not necessarily medication related or attributed to MEs. Seven observational studies reported ME and ADE rates comparing nontargeted chart review and voluntary reporting (179, 335, 337, 341–343). Five reports were either conducted in non-ICU patient populations ($n = 4$) or did not specify if ICU ($n = 1$) patients were included in their analysis (179, 335, 341–343). These studies were considered because of the probable applicability to the ICU population. Two investigations included ICU patients in their study population but did not report ICU-specific data on MEs and ADEs (337, 339).

Most studies found a nontargeted chart review method for identifying the quantity of MEs and/or ADEs to be better than voluntary reporting (179, 339, 341–343). However, two studies found inconsistent results on their performance at detecting MEs (335, 337). Jha et al (337) performed a prospective cohort study comparing three ADE and ME detection methods (computer-based ADE alerting system, nontargeted chart review, and voluntary reporting). The rate of ADEs identified was higher with a daily manual chart review approach (13.3 eventsper1,000 patient days) compared with both computerized alerting systems and voluntary reporting (9.6 vs 0.7 events per 1,000 patient days, respectively). However, chart review was less effective than voluntary reporting in identifying MEs. These investigators found both volunteer reporting and chart review to be very labor intensive. Another study identified more MEs with the voluntary reporting method, but more ADEs were found using chart review compared with voluntary reporting (1.96% vs 0.18% of all medication orders, respectively) (335). It should be noted the overall ME and ADE rates found in this study were significantly lower than other reports (335). The number of medication orders reviewed in this study for the chart review method was significantly lower than the voluntary reporting approach (5,466 and 73,117, respectively), so bias cannot be ruled out.

Nontargeted chart reviews resulted in higher rates of MEs and ADEs identified than relying on voluntary reporting. Although medical record review identifies more events when compared with voluntary reporting, other methods of detection (e.g., direct observation, computer alerts, voluntary reporting) find different types of events. Considerable effort, time, and resources are needed to perform the nontargeted chart review method to identify MEs and ADEs despite reports suggesting it may be more effective than relying on voluntary reporting. The feasibility of this approach may depend upon geographic location, hospital setting, and the hospital's financial position. Overall, the chart review process aids in the identification of ADEs more than voluntary reporting alone and should be performed as part of an active surveillance system.

3. Targeted Chart Review

Question: In adult ICU and PICU patients, does a targeted chart review (e.g., administrative coding, trigger alerts) versus

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voluntary reporting strategies improve the rate of identifying MEs and ADEs?

Answer: We suggest the use of trigger-initiated target chart review in addition to voluntary reports to improve the rate of identifying ADEs. (2B)

Rationale: Active surveillance of ADEs is essential for improving safety in medication use. One such method is targeted chart review, where the presence of a predefined component or characteristic (e.g., charting of an antidote, abnormal drug concentration) prompts an individual to conduct a thorough chart review to evaluate the possibility of an ADE occurring. A total of eight studies (336, 337, 345–347) have investigated a targeted chart review approach with three of these exclusively in the ICU population and have reported the rates of MEs or ADEs (336, 345). The targeting strategy used included trigger alerts (337, 346, 348), ICU transfer and hospital summary discharge papers (345), *International Classification of Diseases* (ICD)-10 codes (347), and a combination of triggers alerts with ICD-10 codes (336). Those studies using triggers alerts to prompt the medical chart review were notified by the use of antidotes as well as abnormal laboratory or drug serum concentrations (336, 337, 346, 348).

Four studies (336, 337, 346) found more ADEs reported with a trigger alert system compared with voluntary reporting, whereas one evaluation (348) found no significant difference in the rates of ADEs identified. These conflicting findings could have been attributed to the differences in both the existing and voluntary reporting systems among the various institutions. For example, Jha et al (337) submitted voluntary reports from confidential solicitation of events with nurses and pharmacists, whereas voluntary incident reports were collected through the institution's existing electronic system in two studies (336, 346). In contrast, the voluntary report system by Ferranti et al (348) was an internal web-based application where all hospital employees may report anonymously any safety incident including ADEs and nonmedication-related events (e.g., equipment issue). As a result, this allowed greater accessibility and willingness for ADEs to be reported. Of these studies only one evaluated an ICU-specific population (336). Anthes et al (345) found electronic notes on the day of ICU discharge resulted in more ADEs than voluntary reports (69 vs 25 events, respectively), whereas Brvar et al (347) found fewer ADEs with ICD-10 codes compared with chart documentation of ADE (1 vs 30 events, respectively). The use of ICU transfer summary is unique and specific to the ICU. Brvar et al (347) found fewer ADEs detected through ICD-10 codes to identify which chart to review. However, the study had significant limitations including not disclosing the type of Electronic Medical Record Adoption Model available at the studied institution as well as no interrater reliability or objective assessment on the ADE quality or severity provided. The study found a very low rate of ADEs (30 ADEs from 520 charts reviewed) detected over a 1-year period.

With the exception of Brvar et al (347) where the quality of ADEs was not assessed objectively nor reported, five studies assessed and/or reported on the quality of ADEs such as severity and causality, although the scale, method, and nomogram used were inconsistent and included the Harvard Medical Practice Scale (MPS), the Naranjo criteria, the Duke University Hospital (DUH) scoring system, and the NCC-MERP. The severity of ADEs varied depending on the study (347). For instance, Jha et al (337) found that targeted chart review reported ADEs with greater severity than voluntary reports (139 vs 11 events, respectively). In contrast, Ferranti et al (348) found greater severity with voluntary reports than with chart review although this was not statistically significant (1.6 vs 1.8 ADEs per 1,000 patient days, respectively; $p = 0.48$). The discordant results may be attributed to trigger-initiated chart review based on laboratory values, and these values may not corroborate with severity as it depends on each patient's clinical presentation (e.g., INR > 3 may be associated with no bleeding, minor bleeding, or clinically significant bleeding), whereas voluntary reports often required the reporter to recognize there is an event as a result of a medication. Another reason for the difference in results may be due to the difference in definition for a severe ADE; Jha et al (337) did not clearly define the term, whereas Ferranti et al (348) defined it via the DUH seven-point severity scoring system. Anthes et al (345) assessed the quality of the ADEs for the ICU transfer and hospital discharge summaries through the Harvard MPS and modified Leonard Assessment Scale.

The use of clinical event signals with high positive predictive values within an institution's ICU such as low sodium and elevated blood urea nitrogen and the use of CDSS for drug-induced thrombocytopenia may help identify additional ADEs that other triggers (e.g., antidote) may not be able to detect (349, 350). Further studies are warranted to better understand the role of triggers in ADE surveillance in different ICUs. We recommend the targeted chart reviews with triggers associated with high positive predictive values in addition to voluntary reporting to increase quantity of ADEs identified.

4. Trigger Systems–Severe ADEs

Question: In adult ICU and PICU patients, do trigger alert systems identify more severe ADEs compared with alternate detection methods?

Answer: We make no recommendation as to benefit of using trigger systems to identify more severe ADEs in critically ill patients compared with alternate detection methods. (0C)

Rationale: Four studies (337, 348, 351, 352) presented a severity comparison between the ADEs identified by automated triggers versus alternative method of detection (e.g., chart reviews and voluntary reports). Trigger systems resulted in identifying a higher rate of severe ADEs compared with alternative methods in two of these studies (351, 352), whereas the remaining two evaluations observed other detection methods to be superior to triggers (337, 348). The conflicting findings among these studies may have been attributed to large variations in interrater reliability for severity ratings between these studies, different methods as well as resources used for detection. Also, severity scales varied among these studies. One investigation evaluated differences

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in ADE preventability between triggers versus alternative methods (337). No differences in the frequency of preventable ADEs were found with chart reviews compared with triggers (27% vs 23%, respectively; $p = 0.16$) or voluntary reports compared with triggers (22%; $p = 0.07$). Chart review and voluntary reports were more effective than computer triggers for detecting symptoms, but inferior in regard to laboratory abnormality-related ADEs (e.g., toxic concentrations of antiepileptic medications).

Although some evidence suggest trigger alert systems may be more effective than alternative methods for detecting severe ADEs, this remains debatable. Also, the data supporting the utility of triggers may be more beneficial over other methods in regard to detecting preventable ADEs is lacking. Therefore, a recommendation cannot be made. Future investigations could focus on the advantages of triggers systems at identifying severe events, although maybe just knowing that trigger systems identify different types of ADEs than alternative surveillance methods is sufficient to justify its importance. Also, the potential advantage of prospective trigger system surveillance for preventing harm with early detection compared with usual care would be useful research and contribute to understanding the cost-benefit of the system.

5. Direct Observation

Question: In adult ICU and PICU patients, does direct observation compared with other reporting methods (voluntary reporting, chart review) impact the quantity of ME/ADE reporting?

Answer: We recommend including direct observation as a component of an active medication surveillance system since it provides the advantage of detecting more events and is likely to detect more administration errors than other surveillance methods. (1A)

Rationale: The administration phase of the medication use process is less likely to be identified with certain surveillance methods such as voluntary reporting or medical record review (33). Several studies have used the direct observation method developed by Barker et al (4, 353) to detect MEs, which includes directly observing a subject in their usual clinical environment and documenting the subjects activities so that it may be later evaluated for MEs (19, 63, 72). Studies that included direct observation were reviewed to determine whether a comparator to other surveillance methods was completed and those that were conducted in the ICU were considered for this recommendation. The direct observation method has been applied in the ICU (19, 63, 72), although comparisons to other detection methods are infrequent (354).

In fact, only two studies comparing direct observation to other methods of detection have been conducted (284, 354). Capuzzo et al (354) focused on all unintended events occurring in the ICU including MEs. The rate of MEs detected by direct observation was slightly higher than its comparator, voluntary reporting with three MEs versus five MEs, respectively. Unfortunately, the specifics of the direct observation method were not described, and the comparison between methods was sequential and not parallel time frames providing a very low quality of evidence. Hardmeier et al (284) conducted a prospective single-center study evaluating the quantity of medication administration errors between direct observation compared with voluntary reporting in multiple pediatric units including the neonatal ICU. Overall, direction observations found 15 medication administration errors compared with seven from the report. As with the study by Capuzzo et al (354), the quality of evidence is very low because the comparison between methods was sequential and not parallel, and the severity of the errors was not reported nor whether the error lead to an ADE (354).

Another well-designed study with explicit direct observation methods, conducted in high-volume units at 36 institutions by Flynn et al (179), was evaluated. This study was considered as part of our evaluation since ICUs could have been included as part of the high-volume unit consideration and the direct observation method should be transferrable to all patient care areas in the hospital. The study by Flynn et al (179) demonstrated an advantage of direct observation over medical record review and voluntary reporting for detection of MEs providing a high quality of evidence. Direct observation did identify more MEs compared with voluntary reporting and comprehensive medical record review (179). Of note, in this study, pharmacist surveillance detected more events overall and more clinically significant events than direct observation, although pharmacist surveillance was used as the determinant for true positives and not meant as a comparator.

We recommend including direct observation of medication administration practices as a component of an active medication surveillance system since it provides the advantage of detecting more events than other methods. Also, it is likely to detect more medication administration errors than other methods, simply based on the technique. It should be recognized direct observation is resource intensive with the training and time commitment of qualified evaluators, so a random, episodic approach to detection may be practical.

H. PATIENT SAFETY SURVEILLANCE SYSTEMS: EVALUATE A POSSIBLE EVENT AFTER SUSPICION

ADE determinations in the ICU can be a complex assessment, as it involves the evaluation of multiple potential contributing factors, in particular acute disease processes and complicated drug regimens. Importantly, a clinician's prior experience and knowledge impacts their assessment (355). These challenges may explain the inconsistencies in clinicians' determination of ADEs. Specifically, the rate of agreement between clinicians evaluating the same suspected ADE ranges between 17% and 50% (356, 357). Objective instruments for causality assessment are designed to standardize the ADE assessment process. This use of instruments for consistency in assessment is similar to the use of pain, sedation, and delirium scales. The use of ADE causality instruments improves clinician agreement (358).

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Many instruments for ADE causality assessment are currently available (359). There is no established gold standard, although the ADR Probability Scale is most frequently used in practice (323, 358).

1. Reliable and Valid ADE Causality Instrument

Statement: In adult ICU and PICU patients, a reliable and valid ADE causality assessment instrument can aid in the evaluation of suspected drug-induced events. (B)

Rationale: The ADR Probability Scale is the only ADE instrument tested for reliability and validity in the ICU (360). Although the ADR Probability Scale did demonstrate reliability and validity outside of the ICU, its testing was limited to a small sample size and lacked a description of the types of ADEs evaluated (358). In the ICU, the ADR Probability Scale performed marginally for interrater reliability ($\kappa = 0.14$–0.33) and the within-rater evaluation was good (weighted κ, 0.540-0.937) (360). The ADR Probability Scale should be modified for optimal performance in the ICU. Clinicians are still seeking a reliable and valid ADE causality instrument for use in the ICU to improve agreement for ADE determination. An approach that has been used in research, to improve the rigor of these assessments, is using three different instruments and concluding causality if at least two of the instruments suggest the event was drug-induced (349, 350). Until a reliable and valid ADE causality assessment tool is developed for the ICU, at minimum, it is reasonable to apply the overall concepts of rechallenge, dechallenge, temporal sequence between drug administration and adverse effect, consideration of other potential causes, and objective evidence in the evaluation of an ADE used in published instruments tested in non-ICU environments. The use of a reliable and valid ADE causality assessment instrument should be considered when one is available.

I. PATIENT SAFETY SURVEILLANCE SYSTEMS METHODS OF EVALUATING DATA

ADE surveillance specifically focused on ICU events seems to be lacking according to a survey of U.S. hospitals (323). The contributing factors, drug classes, and patient outcomes for events occurring in the ICU differ from general wards (8, 11). As such, ADE surveillance specific to the ICU is a consideration. After a surveillance system is employed, then detailed evaluations using FMEA, probabilistic risk assessments, six sigma, and lean process are a possible next step. An institution could also proceed with evaluation by benchmarking and compliance with existing safety standards. The evaluation methods for events identified in an active surveillance system will be reviewed.

1. Analyzing Reports by ICU and Non-ICU

Question: In adult ICU and PICU patients, does ICU differentiation (type of ICU or comparing ICU to general ward) versus not differentiating impact quantity or quality of ADE reporting?

Answer: We suggest performing ICU-specific ADE surveillance and evaluation but evaluation between types of ICU units seems unnecessary to improve the quantity and quality of reporting. (2C)

Rationale: The impact of differentiating ICU patients from non-ICU patients related to reporting ADEs has been evaluated in two observational studies and one survey of current practice (10, 11, 323). Specifically, differentiating the type of ICU (i.e., surgical vs medical) has been evaluated in only one of these three studies. In the study by Cullen et al (10), differentiation between ICU and general care units (non-ICU) was reported along with further differentiation between MICU and SICU. This study was prospectively conducted over 6 months in two hospitals including 11 patient care units of which three were SICU and two were MICU. The study demonstrated that the rate of preventable and potential ADEs was twice as high in ICUs (19 events per 1,000 patient days) compared with non-ICUs (10 events per 1,000 patient days) ($p < 0.01$). The MICU rate (25 events per 1,000 patient days) was significantly higher ($p < 0.05$) than the SICU rate (14 events per 1,000 patient days). ICU patients received significantly ($p < 0.001$) more drugs in the 24 hours before an ADE or from the time of admission to the time of the ADE than non-ICU patients. When adjusted for the number of drugs used in the previous 24 hours or drugs ordered since admission, there were no differences in rates between ICUs and non-ICUs. Additionally, acuity, LOS, and severity of the ADEs were greater in ICUs than non-ICUs, but there were no differences between MICU and SICU patients. The second observational study by Kane-Gill et al (11) was a retrospective study evaluating 3,252 MEs reported at a single institution over 4.5 years. The primary objective of this study was to compare the voluntarily reported ME data including type, cause, and outcomes for MEs occurring in the ICU with MEs occurring in non-ICUs. There were differences in ME data between ICU and non-ICUs with one of the major differences identified as significantly more MEs resulting in harm occurring in the ICU. This study confirmed the finding of the previous study that there is an increased severity associated with ADEs in the ICU. Kane-Gill and Devlin (323) reported results from a survey of current practices focusing on ADE reporting in ICU. The response rate to this survey was 22% and was predominantly from community hospitals (68%). Results showed that despite more ADEs occurring in ICU areas, ADE identification, reporting, and evaluation strategies did not differ between ICU and non-ICU areas. From this cohort of responders, only 22% of hospitals tracked ICU-specific data.

In summary, the rate of ADEs was twice as high in ICUs compared with non-ICUs. When adjusted for number of drugs ordered, the likelihood for ADE to occur in the critically ill was no greater than in non-ICUs or between different types of ICUs. Two of these studies confirm that outcomes from ADEs in the ICU resulted in more harm than when they occurred in non-ICU areas suggesting the ongoing need for ICU-specific surveillance. Factors contributing to this increased harm may include increased patient complexity, increased use of high-risk medications, and more frequent medication administration.

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2. Prospective Versus Retrospective Approaches

Question: In adult ICU and PICU patients, do prospective patient safety surveillance strategies (e.g., FMEA, Probabilistic Risk Assessments, six sigma, lean process) reduce MEs/ADEs compared with retrospective approaches (e.g., root-cause analysis)?

Answer: We make no recommendation on the effectiveness of prospective versus retrospective strategies at detecting MEs/ADEs in medication safety surveillance. (0D)

Rationale: Both prospective (FMEA) and retrospective (root-cause analysis) are quality improvement strategies used within the medication use process to identify and resolve potential MEs and ADEs (294, 361–364). Although several studies have evaluated prospective and retrospective patient safety surveillance strategies in a non-ICU setting, only one study evaluated the effects of FMEA in a PICU (230). However, the impact of this study cannot be clinically applied since ME rates or ADE rates were not reported. This study focused on the potential failure modes within the IV drug infusion process and their respective scores of three characteristics (severity, occurrence, and detection) to prioritize elements requiring immediate process improvement.

No evidence suggests either prospective or retrospective strategies have a more significant impact over the other on reducing the rates of MEs, ADEs, or mortality. However, it is important to note that prospective assessments using lean six sigma or FMEA tend to be proactive methods to minimize MEs irrespective of ME rates. Retrospective approaches are typically in response to sentinel events aimed at reducing events. Therefore, the impact on the frequency of MEs may not be feasible. Nonetheless, either or both of these strategies could be employed within healthcare institutions as a component of their patient safety surveillance programs since both have the potential to reduce MEs in the ICU.

3. Benchmarking

Question: In adult ICU and PICU patients, does benchmarking for patient safety surveillance strategies compared with no benchmarking impact outcomes such as ME/ADE rates?

Answer: We make no recommendation on the effectiveness of benchmarking for patient safety surveillance strategies on improving outcomes such as ME/ADE rate. (0, no evidence)

Rationale: The American Society of Health-System Pharmacists, AHRQ, and IOM recommend healthcare systems to develop and adapt an ongoing patient safety surveillance program involving ADE monitoring and reporting (344, 365, 366). A comprehensive program should involve ADE detection, monitoring, management, documentation, reporting, evaluation, and developing preventative strategies and programs (33, 365). Unfortunately, many institutions face challenges in implementing a comprehensive patient safety surveillance program. The various types of ADEs identified may be dependent on the method of ADE detection (chart review, triggers, direct observation, etc) used at the healthcare institution (33, 367), and limited resources may challenge healthcare centers in consistently identifying ADEs (367). Data from surveillance programs are necessary to identify trends in ADEs and measure success of any interventions to improve ADE rates.

No evidence exists regarding the impact of benchmarking for patient safety surveillance strategies on the rates of MEs, ADEs, or mortality in critically ill patients. One report described the implementation of a national ADE monitoring database among Department of Veterans Affairs (VA) institutions for improved medication safety (368). The purpose of the national database was to generate standardized summary reports, identify system changes needed, ADE surveillance, and benchmarking performance. ADE reporting facilitates benchmarking among VA systems at a national, regional, and facility level. Periodically, reports were generated on the 10 most common ADEs overall, 10 most common medications associated with ADEs, and ADE rates associated with new medications. Analysis of these reports may assist VA systems in evaluating their overall reporting performance. The Medicare Patient Safety Monitoring System (MPSMS) is a national surveillance system database, which tracks inpatient ADEs within the hospitalized fee-for-service Medicare population (369). Several "high-risk" medications are included in this database such as warfarin, heparin, low molecular weight heparin, insulin/oral hypoglycemic, digoxin, and systemic antibiotic exposure associated with *Clostridium difficile* infection. Comparing ADE rates associated with high-risk medications at individual hospitals with the MPSMS may serve as a benchmark to measure intervention effectiveness on improved patient safety. Unfortunately, no studies have evaluated the impact of benchmarking ADEs on patient outcomes. The above publications are more descriptive reports without assessing impact on outcomes (368, 369). Benchmarking ADEs at individual institutions against national or health-system databases may encourage institutions to increase ADE reporting if the rates are lower than the estimated benchmark, as well as measure impact of any medication safety intervention (368–370).

4. Compliance With Safety Standards

Question: In adult ICU and PICU patients, does strict compliance with patient safety standards set forth by regulatory bodies (e.g., TJC) versus no formal adherence policy impact outcomes such as ME/ADE rates?

Answer: We make no recommendation on the effectiveness of strict compliance with patient safety standards set forth by regulatory bodies on impacting outcomes such as ME/ADE rates. (0, no evidence)

Rationale: The Joint Commission accreditation and certification represents high-quality delivery of patient care by healthcare organizations (118). The NPSGs are regulatory standards established by TJC to address patient safety concerns within hospitals across the United States (118). Hospitals are expected to adhere to TJC recommendations and implement process improvement strategies to achieve these goals. A few of TJC NPSGs involve medication safety such as reduction of risk of ADEs associated with anticoagulants and preventing surgical site infections through appropriate antibiotic administration timing and management (118). However, several barriers may

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prevent many institutions from strictly complying with these regulatory standards (371). Differences among hospitals regarding organizational support, physician leadership, technology, education/training, and degree of awareness may hinder hospitals from achieving high compliance NPSG rates (371).

No evidence exists regarding the impact of strict compliance with regulatory standards involving medication on the rates of MEs or ADEs. Although several studies provide the evidence-based recommendations of TJC regarding medication safety, no studies have been conducted to demonstrate that institutions with high-compliance rates of the NPSGs involving medications significantly improve outcomes compared to those with high rates of noncompliance, particularly in an ICU patient population (371, 372). Several studies involving ICU patients have shown improved outcomes with increased protocol or guideline compliance. High compliance with sepsis and ventilator-associated pneumonia bundles in ICU patients have been associated with decreased mortality and infection rates (373, 374). Unfortunately, these strategies have not been mandated by TJC. Although we may assume increased compliance to established "best practices" may improve patient outcomes, no evidence exists to support that compliance with current TJC standards significantly improves patient outcomes.

SUMMARY

This guideline evaluates medication safety in the ICU environment since the critically ill is at a high risk of medication-related events and provides the environmental changes that are possible to improve safe medication use. Prevention strategies for medication-related events are recommended or suggested for each phase within the medication use process. Detailed components of an active surveillance system that includes reporting, identification, and evaluation are discussed. The goal of this guideline is to help clinicians and administrators consider the best practices to ensure safe medication use in an ICU setting. Also, highlighted in this document is the need for future research related to optimal safe medication practices in the critically ill.

ACKNOWLEDGMENTS

We would like to acknowledge Gilles Fraser (Board Liaison) and Sarah Kraus and Lori Harmon (SCCM Staff) for their support.

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