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Interventions to Reduce Medication Errors in Pediatric Intensive Care

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Abstract

Objective: To systematically examine the research literature to identify which interventions reduce medication errors in pediatric intensive care units. **Data Sources:** Databases were searched from inception to April 2014. **Study Selection and Data Extraction:** Studies were included if they involved the conduct of an intervention with the intent of reducing medication errors. **Data Synthesis:** In all, 34 relevant articles were identified. Apart from 1 study, all involved single-arm, before-and-after designs without a comparative, concurrent control group. A total of 6 types of interventions were utilized: computerized physician order entry (CPOE), intravenous systems (ISs), modes of education (MEs), protocols and guidelines (PGs), pharmacist involvement (PI), and support systems for clinical decision making (SSCDs). Statistically significant reductions in medication errors were achieved in 7/8 studies for CPOE, 2/5 studies for ISs, 9/11 studies for MEs, 1/2 studies for PGs, 2/3 studies for PI, and 3/5 studies for SSCDs. The test for subgroup differences showed that there was no statistically significant difference among the 6 subgroups of interventions, $\chi^2(5) = 1.88$, $P = 0.87$. The following risk ratio results for meta-analysis were obtained: CPOE: 0.47 (95% CI = 0.28, 0.79); IS: 0.37 (95% CI = 0.19, 0.73); ME: 0.36 (95% CI = 0.22, 0.58); PG: 0.82 (95% CI = 0.21, 3.25); PI: 0.39 (95% CI = 0.10, 1.51), and SSCD: 0.49 (95% CI = 0.23, 1.03). **Conclusions:** Available evidence suggests some aspects of CPOE with decision support, ME, and IS may help in reducing medication errors. Good quality, prospective, observational studies are needed for institutions to determine the most effective interventions.

Keywords

medication errors, pediatrics, critical care, clinical practice, medication safety

Medication management is an important component of the care of critically ill children. In these children, medications often carry significant risks of producing adverse events.[1] Children vary in weight, body surface area, and organ maturity, which can affect their ability to metabolize and excrete medications effectively. The lack of standardized dosage forms, the use of off-label formulations, and the need for precise dosage calculations also create additional risks.[2]

Between 2.5% and 5.7% of all pediatric patients experience a medication error while in hospital.[3,4] Children in intensive care settings are at even greater risk because of more frequent use of intravenous medications and medications with a narrow therapeutic range.[5,6] A 2-year prospective study identifying 441 medication errors in 682 pediatric patients showed that medication errors were 7 times more likely to occur in intensive care than other areas.[7] Past systematic reviews only considered the characteristics of incident reporting systems in neonatal intensive care units[8] or the effects of computerized physician order entry (CPOE) on prescription errors.[9] Previous reviews were narrative in their focus and were completed many years ago; but new information is now available.[10,11]

The aims of this article are as follows: to systematically examine the research literature to identify which interventions reduce medication errors in pediatric ICUs, to identify gaps in past research, and to suggest strategies for the reduction of medication errors. A medication error was defined as any preventable event that may cause inappropriate

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medication use or lead to patient harm.[12] Inappropriate medication use involves medications that should be entirely avoided, medications that should be avoided at excessive dosages, and medications that should not be used for excessive duration of treatment. Medication errors could occur at any stage of the medication management process, including prescription, transcription, preparation, and administration.

Methods

Data Sources

Databases searched included: The Cochrane Database of Systematic Reviews, Cumulative Index to Nursing & Allied Health Literature (CINAHL), EMBASE, Journals@Ovid, PsycINFO, PubMed, ScienceDirect, Scopus, and Web of Science. Various combinations of keywords and Medical Subject Headings (MeSH terms) were used, including: medication error, adverse drug event, neonate, infant, child, adolescent, pediatrics, intensive care, and critical care. Databases were searched from inception to April 2014.

Study Selection and Data Extraction

Studies were considered for inclusion if they involved the conduct of an intervention with the intent of reducing medication errors. Appropriate intensive care environments included pediatric cardiac care, pediatric intensive care, neonatal intensive care, or combined adult and pediatric ICUs as long as the pediatric results were readily identifiable. For children admitted to pediatric-specific units, no age specification was imposed because various units may have their own age requirements for admission. For patients admitted to combined ICUs, children were defined as individuals aged between 0 and 18 years. Only articles published in English were included. Articles were excluded if they involved case studies, epidemiological studies, reviews, editorials, or commentaries.

Two authors read identified abstracts following conduct of the search. Of those articles that were potentially relevant, full-text versions were read independently by the 2 authors to determine whether they met the inclusion criteria. If there was uncertainty or disagreement about whether certain studies met the inclusion criteria, the authors discussed and negotiated agreement on eligible studies.

Data were extracted using a standardized form. This form comprised the study design, country of study, setting type, sample size, intervention type, and outcomes obtained for medication errors, including severity of medication errors.[13] Two authors independently extracted data from the articles.

Level of Evidence and Quality Assessment

Level of evidence of included articles was assessed using the tool devised by the Oxford Centre for Evidence-Based Medicine.[14] The quality of included articles was calculated independently by 2 authors using the Downs and Black checklist, which assesses the quality of studies.[15] When inconsistencies occurred for scoring of items, the 2 authors achieved resolution by consensus.

Statistical Analysis

Statistical analysis was undertaken using Review Manager, version 5.1.4 (Cochrane Collaboration) software. The results were expressed as risk ratio (RR) meta-analysis and 95% CIs for the dichotomous primary outcome of medication errors and were calculated using the Mantel-Haenszel random effects model. Due to the presence of heterogeneity, a random effects model for RR was used.[16] This model assumes that separate studies represent a random sample from a population of studies, which has a mean intervention effect about which the individual study effects vary. Since statistical heterogeneity is present, RR meta-analysis has only been undertaken according to subgroups of the various intervention types identified.[16]

Results

An initial search of the databases and hand searching revealed a total of 639 articles. Articles were excluded because they were duplications, not interventions, not empirically based or not conducted in intensive care (n = 606). The full texts of 36 articles were retrieved for further review. Of these, 34 articles were considered relevant to the topic (Figure 1 and Appendix A).

Research Design and Participant Characteristics

Of the included articles, sample sizes ranged from 42 to 5975 patients for articles that had information about sample size (Table 1). In 24 articles, no information was given about the sample size of patients. In all studies, a pre-post, interventional design was used. Only 1 study involved the incorporation of an intervention group and concurrent control group.[17] In 24 studies, a prospective design was used,[5,17-39] and in 7 studies, a retrospective design was used.[40-46] In 3 studies, a retrospective approach was used for the preintervention phase and a prospective approach was used for the postintervention phase.[47-49] The studies were carried out in the following countries: United States (20), Spain (4), United Kingdom (3), Israel (2), Argentina (1), Egypt (1), Iran (1), Malaysia (1), and the Netherlands (1).

Level of Evidence and Quality of Studies

Appendix B shows the level of evidence and quality scores for studies included in the systematic review. One study was at level 3 for evidence, and the remaining 33 studies

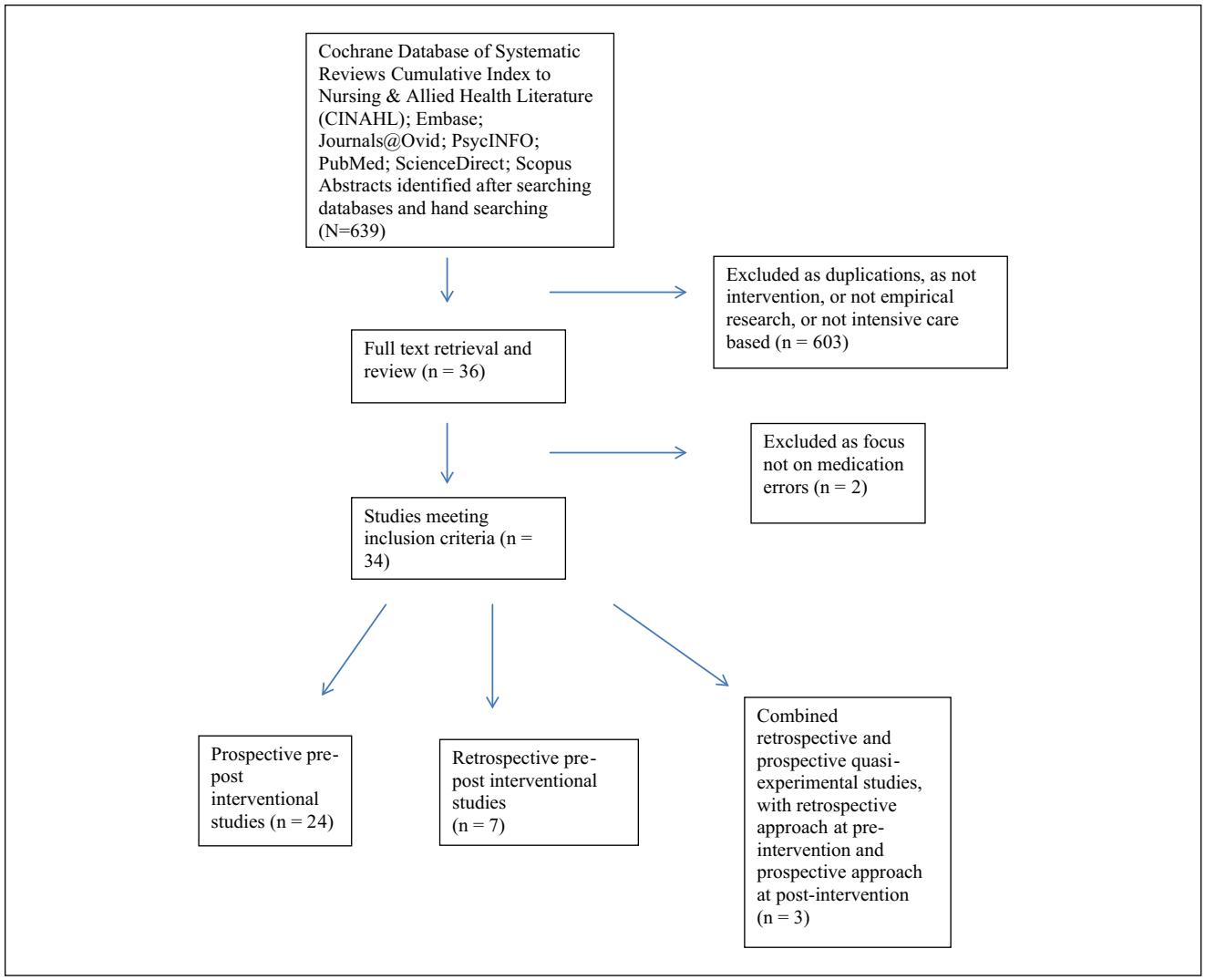

Figure 1. Flow chart of systematic review.

were at level 4 for evidence. Quality analysis showed reporting scores varied between 3 and 11 out of a possible total score of 11 (mean = 6.2), external validity scores varied between 1 and 3 out of 3 (mean = 1.6), internal validity for bias scores varied between 2 and 6 out of 7 (mean = 4.2), internal validity for confounding scores ranged between 1 and 3 out of 6 (mean = 1.9), and power analysis varied between 0 and 1 out of 1 (mean = 0.3).

Types of Interventions

There were 6 different types of interventions identified from the studies. These were (Table 1) CPOE, intravenous systems (ISs), modes of education (MEs), protocols and guidelines (PGs), pharmacist involvement (PI), and support systems for clinical decision making (SSCD). Previous comprehensive reviews have indicated that these are appropriate categorizations of strategies for preventing medication errors in ICUs.[50,51] Table 2 contains a summary of all included studies. Figure 2 shows the RR meta-analysis for subgroups relating to the 6 intervention types. RR meta-analysis could not be undertaken for 5 studies.[24,30,42,49] For 2 studies not included in the RR meta-analysis, no details were provided about the total opportunities for medication errors (denominator term).[24,49] In 1 study, the outcome variable was the number of days between intercepted errors, and no denominator term was included[30]; and in another study, medication errors were presented as triggers under or above particular limits and preintervention and postintervention data were not clearly identified.[42] In the remaining study, the outcome variables for preintervention and postintervention were different and could not be compared.[39] In examining the studies, considerable heterogeneity was apparent for the outcome variable—namely, medication errors. The test for subgroup differences showed that there was no statistically significant difference among the 6 subgroups of

Table 1. Overview of Studies Included in the Systematic Review.

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Computerized physician order entry (CPOE)							
Cordero et al (2004)[40]	Pre-post intervention retrospective study	United States; University medical center; neonatal intensive care unit (NICU)	253 In total; 136 preintervention; 117 postintervention	CPOE and clinical decision support system (CDSS)	Prescribed gentamicin dosing errors (dose >10% deviant from recommended dose)	Preintervention: 14 errors/105 patients (13%) Postintervention: 0 errors/100 patients (0%) No *P* value reported	Severity of harm of medication errors not addressed
Hilmas et al (2010)[18]	Prospective pre-post intervention audit study	United States; university medical center; 40-bed NICU (only post) and 24-bed pediatric intensive care unit (PICU) and pediatric intermediate care (pre and post)	Not stated	CPOE and CDSS	Continuous intravenous infusion prescription errors, 200 handwritten prescriptions reviewed at preintervention and postintervention	Preintervention: 13 calculation errors/200 prescriptions (3.5%), 2 errors exceeding maximum concentration/200 prescriptions (1%), 81 incomplete prescription errors/200 prescriptions (41%), 2 illegible errors/200 prescriptions (1%) Postintervention: 0 calculation errors/200 prescriptions (0%), 0 errors exceeding maximum concentration/200 prescriptions (0%), 0 incomplete prescription errors/200 prescriptions (0%), 0 illegible errors/200 prescriptions (0%). No *P* value reported	Severity of harm of medication errors not addressed
Kadmon et al (2009)[41]	Retrospective pre-post audit study	Israel; tertiary pediatric hospital; 12-bed PICU	Not stated	CPOE and CDSS: period 1, pre-CPOE; period 2, post-CPOE; period 3, CPOE and CDSS; period 4, CPOE and CDSS and prescription only by physician	Prescription errors out of 1250 orders for each period	Preintervention (period 1): 103 errors/1250 orders Postintervention (period 2): 97 errors/1250 orders (7.8%) *P* = 0.66 Postintervention (period 3): 55 errors/1250 orders (4.4%) *P* = 0.0004 Postintervention (period 4): 18 errors/1250 orders (1.4%) *P* < 0.0001	Severity of harm of medication errors: period 1, annual mortality rate = 2.79%; period 2, 3.87%; period 3, 3.30%; period 4, 2.37%
Kazemi et al (2011)[19]	Prospective pre-post intervention study	Iran; tertiary care referral teaching hospital; 17-bed neonatal ward with 2 NICU beds	Period 1: 96 patients; period 2: 83 patients; period 3: 79 patients	CPOE and CDSS: period 1, pre-CPOE; period 2, post-CPOE; period 3, CPOE and CDSS	Nonintercepted prescription and transcription errors	Preintervention (period 1): 891 errors/1688 medication days (53%) Postintervention (period 2): 765 errors/1489 medication-days (51%) *P* = 0.4 Postintervention (period 3): 457 errors/1331 medication-days (34%) *P* < 0.001	Severity of harm of medication errors not addressed
Myers et al (1998)[20]	Prospective pre-post audit study	United States; university children's hospital; academic tertiary 50-bed NICU	Not stated	CPOE and CDSS	All types of medication errors (transcription, dosage, formulation, preparation, and administration) assessed	Preintervention: 3.2 errors per 1000 patient-days (32 errors per 10 000 patient-days) Postintervention: 0.6 errors per 1000 patient-days (6 errors per 10 000 patient-days) No *P* value reported	Severity of harm of medication errors not addressed
Taylor et al (2008)[21]	Prospective pre-post observational study	United States; Army medical center; 30-bed NICU	Not stated	CPOE and CDSS	Medication administration errors (variances) relating to wrong time, omitted dose, wrong dose, and wrong route	Preintervention: 50 errors/253 total administrations (19.8%) Postintervention: 31 errors/268 total administrations (11.6%) *P* < 0.05	Severity of harm of medication errors not addressed

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Vardi et al (2007)[22]	Prospective cohort audit study	Israel; tertiary, university hospital; 18-bed pediatric critical care department	Not stated	CPOE and CDSS	Frequency of prescribing cardiopulmonary resuscitation medication errors	Preintervention: 3 errors/13 124 medication orders (0.02%), as reported by health professionals Postintervention: 0 errors/46 970 medication orders (0%), as identified by pharmacist, physician, and nurse examining orders No *P* value reported	Severity of harm: preintervention, all 3 errors did not reach the patient but would have caused harm as >maximal dose; postintervention: 0 errors and thus no harm
Warrick et al (2011)[23]	Prospective pre-post audit study	United Kingdom; National Health Service Trust hospital; PICU	Not stated	CPOE and CDSS: preintervention, paper charts; postintervention 1, 1 week after introduction of electronic prescribing; postintervention 2, 6 months after introduction	Chart audit of prescribing errors and dose omissions	Preintervention: 14 errors/159 prescriptions (8.8%), 43/528 omissions in scheduled doses (8.1%) Postintervention 1: 17 errors/208 prescriptions (8.1%), $P < 0.05$; 23 omissions/216 scheduled doses (10.6%), $P > 0.05$ Postintervention 2: 12 errors/257 prescriptions (4.6%), $P < 0.05$, 4 omissions/278 scheduled doses (1.4%), $P < 0.05$	Severity of harm of medication errors not addressed
Intravenous systems (ISs)							
Apkon et al (2004)[24]	Prospective pre-post study	United States; children's hospital of an academic medical center; 11-bed PICU	Not stated	Computerized decision support for IV drug delivery; prepackaged solutions used where possible	Failure mode effects analysis (FMEA) for severity, likelihood of occurrence, and likelihood that failures will escape detection (medication error rates not provided), RPNs (risk priority number) assigned\	Preintervention: 314 RPNs for preparation of IV, 269 RPNs for programming of pump, 234 RPNs for dosage calculation, 136 RPNs for infusion rate selection Postintervention: 88 RPNs for preparation of IV, 99 RPNs for programming of pump, 49 RPNs for dosage calculation, 26 RPNs for infusion rate selection No *P* value reported	Severity of harm of medication errors: preintervention ranged from 6.8 to 8.8 in FMEA, and postintervention ranged from 7.3 to 8.8 in FMEA
Bullock et al (2006)[26]	Retrospective preintervention and prospective postintervention study	United States; university children's hospital; PICU	Preintervention: 49 patients; postintervention: 51 patients	Development, dissemination, and implementation of standardized IV infusion concentration list; intensive education and one-on-one coaching and mentoring given	Parenteral IV administration concentration errors	Preintervention: improper dose, 26 errors/50 infusions (52%); improper concentration, 6 errors/26 infusions (23%); infusions with no standardized concentration, 31 errors/120 infusions (26%) Postintervention: improper dose, 7 errors/28 infusions (25%); improper concentration, 0 errors/7 infusions (0%); infusions with no standardized concentration, 17 errors/128 infusions (13%) $P < 0.05$ for all types of errors	Severity of harm of medication errors not addressed
Hennings et al (2010)[42]	Postretrospective study	United States; tertiary academic medical center; 16-bed PICU	Not stated	Automated infusion devices with programmed alerts	Programming errors of pediatric infusions	21 Errors/5268 infusions (0.4%) triggered 2.5× over limit; 15 errors/5268 infusions (0.3%) triggered 2.5× under limit; 42 overrides exceeded 10× predefined limits. No *P* value reported	Severity of harm: automated infusion devices reduced the number of serious adverse or sentinel events from 6 before to 3 after device implementation

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Larsen et al (2005)[43]	Pre-post retrospective study	United States; university-affiliated tertiary pediatric hospital; NICU, PICU	Not stated	Combining standard drug concentrations and smart pumps	Reported errors associated with continuous medication infusions	Preintervention (PICU): 21 errors/7527 infusions (0.28%) errors Postintervention (PICU): 5 errors/7520 infusions (0.07%) errors, $P < 0.001$ Preintervention (NICU): 12 errors/3431 infusions (0.12%) errors Postintervention (NICU): 5 errors/3620 infusions (0.14%), $P < 0.001$ Preintervention (PICU and NICU): no doses in either PICU or NICU made to standardized concentration Postintervention (PICU and NICU): PICU, >99% of doses standardized; NICU, 87% standardized concentrations	Severity of harm of medication errors not addressed
Manrique-Rodríguez et al (2013)[39]	Prospective observational intervention study	Spain; university maternal and children's hospital; 14-bed PICU	Not stated	Smart pump technology	Observation of medication administration errors at preintervention and programming errors prevented from detected alerts at postintervention	Preintervention: 26.5 errors per 100 doses administered Postintervention: 92 infusion-related programming errors intercepted out of 486 875 infusions No *P* value reported	Severity of harm: preintervention, not addressed; postintervention, 49% of intercepted errors were moderate to catastrophic, 51% were negligible or mild
Modes of education (MEs)							
Abstoss et al (2011)[48]	Retrospective pre-post prospective study	United States; university children's hospital; PICU	Not stated	Seven interventions: poster tracking, quality improvement channel, quality improvement curriculum, medication error e-mails, CPOE with treatment instructions to patients, medication manager program, report form revisions	Medication error reporting rates (process measure) and medication errors resulting in harm (outcome measure)	Preintervention: 3.16 errors per 10 000 doses overall reporting rate Preintervention: 0.056 events per 10 000 doses resulting in harm Postintervention: 3.95 errors per 10 000 doses overall reporting rate $P < 0.09$ Postintervention: 0.16 events per 10 000 doses resulting in harm $P < 0.01$ (one-sided tests)	Severity of harm of medication errors: Preintervention (to early part of interventions): NCC MERP Cat A, 6%; Cat B, 10%; Cat C, 42%; Cat D, 35%, Cat E, 8%. Postinterventions: Cat A, 7%; Cat B, 7%; Cat C, 47%, Cat D, 36%, Cat E, 4%
Alagha et al (2011)[25]	Pre-post prospective study	Egypt; university hospital; 12-bed PICU	Preintervention: 139 patients; postintervention: 101 patients	Dosing sheets, combined order and administration chart, orientation for new residents, residents' feedback	Prescribing errors rates	Preintervention: 1107 errors/1417 opportunities for error (78.1%) Postintervention: 391 errors/1097 opportunities for error (35.6%) $P < 0.001$	Severity of harm of medication errors: preintervention: potentially severe, 420/1417 (29.7%); potentially moderate, 564/1417 (39.8%); potentially minor, 123/1417 (8.6%). Postintervention: potentially severe, 77/1097 (7.0%); potentially moderate, 265/1097 (24.1%); potentially minor, 49/1097 (4.5%)
Burmester et al (2008)[26]	Prospective cohort intervention study	United States; tertiary academic hospital; 24-bed pediatric cardiac intensive care unit (CICU)	Not stated	Systematic physician education and post–cardiac surgery admission prescription forms	Prescription errors	Preintervention: 613 errors/3648 prescriptions (16.8%) Postintervention: 366 errors/8929 prescriptions (4.1%) $P < 0.001$	Severity of harm of medication errors not addressed

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Campino et al (2009)[5]	Prospective pre-post intervention study	Spain; university affiliated hospital; regional, 42-bed level III NICU	Not stated	Pharmacist led preventive information sessions and multidisciplinary group to implement strategies	Prescription errors (chart review)	Preintervention: 868 errors/4182 orders (20.7%) Postintervention: 47 errors/1512 orders (3.1%) $P < 0.001$	Severity of harm of medication errors not addressed
Chedoe et al (2012)[38]	Prospective pre-post study with direct observations	Netherlands; teaching hospital; 14-bed NICU	Preintervention: 20 patients; postintervention: 22 patients	One-hour theoretical teaching session to nurses, 1 individual practical teaching session of commonly used medications, short guided tour around pharmacy department	Preparation and administration errors observed	Preintervention: 151 medications with errors/311 observations (49%) Postintervention: 87 medications with errors/284 observations (31%) $P < 0.001$	Severity of harm of medication errors: Preintervention, 1% severe errors; 57% moderate errors; and 42% minor errors. Postintervention, 0% severe errors; 77% moderate errors, and 23% minor errors
Cimino et al (2004)[27]	Prospective pre-post study	United States; 9 tertiary care children's hospitals, with 6- to 24-bed PICUs	Not stated	Systematic education of physicians; availability of dosing guidelines	Prescribing errors	Preintervention: 3259 errors/12 026 orders (27.9%) Postintervention: 217 errors/9187 orders (23.7%) $P < 0.01$	Severity of harm: adverse drug events (ADEs) at preintervention, 16/12 026 (0.13%); postintervention, 3/9187 (0.03%)
Martinez-Anton et al (2012)[28]	Prospective before–after interventional study	Spain; tertiary, academic hospital; 16-bed PICU	Preintervention: 52 patients; postintervention: 67 patients	Standardization of prescription sources, pocket tables with dosing guidelines, an updated prescription protocol, and an educational program on correct prescribing	Prescribing errors	Preintervention: 761 errors/2228 prescriptions (34.2 %) Postintervention: 388 errors/1791 prescriptions (21.7 %) $P < 0.001$	Severity of harm: preintervention, 7 category C (errors occurred that reached the patient but did not cause patient harm) and 2 category D (errors occurred that reached the patient and required monitoring to confirm that it resulted in no harm and/or required intervention to preclude harm) errors; postintervention, 5 category C errors. No other errors reached patients
Otero et al (2008)[44]	Retrospective pre-post cross-sectional study	Argentina; tertiary care university hospital; 110-bed department of pediatrics with NICU and PICU	Preintervention: 95 patients; postintervention: 92 patients	Cultural change via multidisciplinary education and meetings	Medication errors relating to prescription and administration	Preintervention (NICU): 21 errors/181 prescriptions (22.5%) Postintervention (NICU): 34/324 prescriptions (10.5%) $P = 0.0006$ Preintervention (NICU): 31 errors /367 administrations (8.2%) Postintervention (NICU): 24 errors/801 administrations (2.9%) $P = 0.001$ Preintervention (PICU): 38 errors/169 prescriptions (11.6%) Postintervention (PICU): 29 errors/377 prescriptions (7.7%) $P = 0.1700$ Preintervention (PICU): 30 errors/364 administrations (8.2%) Postintervention (PICU): 29 errors/394 administrations (7.4%) $P = 0.7514$	Severity of harm of medication errors not addressed

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Pallás et al (2008)[37]	Before and after evaluation study	Spain; urban teaching hospital; neonatal unit (with intensive care facilities)	Not stated	Three informative talks to doctors about good prescribing practice and implementation of a pocket personal computer–based automatic calculation system	Prescription errors (violations of prescribing practice)	Preintervention: 2498/6320 (39.5%) of prescriptions Postintervention: 171/1435 (11.9%) of prescriptions No *P* value stated, prevalence ratio: 0.3 (0.26-0.34)	Severity of harm of medication errors not addressed
Raja Lope et al (2009)[29]	Prospective observational pre-post study	Malaysia; university hospital; 34-bed NICU	Not stated	Interactive reeducation program with nurses	Medication administration errors for the wrong time	Preintervention: 59 errors/188 doses (31.0%) Postintervention: 26 errors/169 doses (15.4%) $P \leq 0.001$	Severity of harm of medication errors not addressed
Sullivan et al (2013)[30]	Prospective observational pre-post study	United States; children's hospital; 75-bed NICU	Not stated	4-Stage approach: maximize error reporting, optimize data analysis, determine best feedback strategy, and ensure bidirectional communication between prescriber and feedback team	Prescribing errors (inability to determine denominator for medication errors)	Preintervention (number of days between narcotic intercepted errors): 3.94 days Postintervention (number of days between narcotic intercepted errors): 22.63 days (83% improvement) Preintervention (number of days between antibiotic intercepted errors): 2.14 days Postintervention (number of days between antibiotic intercepted errors): 2.14 days (no change noted) *P* values not reported	Severity of harm of medication errors not addressed
Protocols and guidelines (PGs)							
Brown et al (2007)[45]	Retrospective cross-sectional pre-post study	United States; women's and children's hospital NICU	Not stated	Computerized parenteral nutrition (PN) worksheet	PN prescribing error rates	Preintervention: 57 errors/204 orders (27.9%) Postintervention: 56 errors/480 orders (11.7%) *P* <0.001	Severity of harm of medication errors not addressed
Ross et al (2000)[46]	Retrospective interventional audit study	United Kingdom; children's hospital; 12-bed PICU, NICU	3373 NICU admissions; 2602 PICU admissions	Change in policy and error reporting system: double checking by pharmacists of all dispensed medications, development of less punitive reporting process, and introduction of fewer concentrations of certain medications; interventions introduced in staggered times	Reported medication errors	Preintervention (April 1994 to January 1997, 34 months: NICU, 3373 admissions/65 months = 1764 admissions in 34 months): 12 errors/1764 admissions (0.7%) Postintervention (February 1997 to August 1999, 31 months, NICU: 3373 admissions/65 months = 1609 admissions in 31 months): 21 errors/1609 admissions (1.3%) Preintervention (PICU: 2602 admissions/65 months = 1361 admissions in 34 months): 9 errors/1361 admissions (0.7%) Postintervention (February 1997 to August 1999, 31 months, PICU: 2602 admissions/65 months = 1241 admissions in 31 months): 11 errors/1241 admissions (0.9%) *P* values not reported	Severity of harm overall: 96% minor, 3% medium, 1% serious but no long-term morbidity or mortality

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Pharmacist involvement (PI)							
Kaushal et al (2008)[17]	Prospective cohort, pre-post study, control and intervention units involved	United States; academic medical center; PICU, NICU	1249 Patients; preintervention PICU intervention group, 209 patients; postintervention PICU intervention group, 401 patients; preintervention cardiac ICU control group, 280 patients; postintervention cardiac ICU control group, 359 patients	Full-time pharmacist participation on consultant ward rounds, nurse support, continuous quality improvement team; preintervention, dispensing pharmacists sent ready-to-administer doses to units but participated only intermittently in rounds	Serious medication errors in ordering, transcribing, dispensing, administering, or monitoring	Preintervention (PICU: intervention group): 29 errors/1000 patient-days (2.9%) Postintervention (PICU: intervention group): 6 errors/1000 patient-days (0.6%) $P < 0.01$ Preintervention (cardiac ICU: control group): 20 errors/1000 patient-days (2.0%) Postintervention (cardiac ICU: control group): 30 errors/1000 patient-days (3.0%) $P < 0.01$	Severity of harm of medication errors: only serious medication errors examined
Morriss et al (2009)[31]	Prospective, observational, cohort study	United States; university children's hospital; 36-bed NICU	475, No bar-coded medication administration (BCMA) and 483 with BCMA = 958 patients (including 865 unique patients)	Pharmacist dispensed bar-coded medications, BCMA	Medication errors in ordering, transcribing, dispensing, administering, or monitoring identified in audit of preceding 24 hours by nurse practitioners; preventable ADEs (harm to a patient resulting from medication errors); potential ADEs (medication errors could have caused harm but were intercepted)	Medication errors from audit Preintervention: 69.5 medication errors/1000 doses Postintervention: 79.7 medication errors/1000 doses P <0.001 Preventable ADEs Preintervention: 0.86 ADEs/1000 doses (0.086%) Postintervention: 0.43 ADEs/1000 doses (0.043%) $P = 0.008$ Potential ADEs Preintervention: 15.1 ADEs/1000 doses (1.51%) Postintervention: 4.4 ADEs/1000 doses (0.44%) $P < 0.001$	Severity of harm of medication errors addressed through ADEs
Simpson et al (2004)[32]	Prospective pre-post study	United Kingdom; tertiary maternity hospital; NICU	Not stated	Pharmacist-led education program and medication order review	Prescription and administration errors (critical incident reporting)	Preintervention: 24.1 errors/1000 neonatal activity days (2.41%) Postintervention: 5.1 errors/1000 neonatal activity days (0.51%) $P = 0.037$	Severity of harm of medication errors: 105 medication errors identified, 4 serious, 45 potentially serious, and 56 minor; 3 serious errors at preintervention, 1 serious error at postintervention
Support systems for clinical decision making (SSCD)							
Costello et al (2007)[49]	Pre-post study, with retrospective data collection at pre-intervention and prospective data collection at two post-intervention phases	United States Children's hospital 19-bed pediatric critical care centre (PCCC)	Not stated	Phase 1: retrospective collection of medication-error reports Phase 2: pediatrics clinical pharmacist Phase 3: pharmacist-led pediatrics medication safety team (with critical care nurse and intensivist), a new reporting form, and educational forums	Medication errors reported	Total of 109 medication errors reported overall. Pre-intervention (Phase 1): 11 errors Post-intervention (Phase 2): 22 errors Post-intervention (Phase 3): 76 errors P-value not reported	Severity of harm of medication errors - Category D or E: Phase 1: 46%, Phase 2: 8%, Phase 3: 0% (Category D: patient required monitoring or intervention to preclude harm, Category E: error may have resulted in temporary harm and required intervention). Near-miss errors: 9% in phase 1, 38% in phase 2, 51% in phase 3

(continued)

Table 1. (continued)

Reference	Study Design, Patient Enrolment	Country and Settings	Number of Patients (n)	Intervention Type	Type of Medication Error Analyzed	Effect of Intervention on Medication Error Rate	Severity of Harm of Medication Errors
Lehmann et al (2004)[33]	Prospective pre-post study	United States; university hospital NICU	Not stated	Pharmacist-led design, implement online total parenteral nutrition (TPN) calculator: preintervention; postintervention period 1: immediately after intervention; postintervention period 2: 2 years after intervention	Medication prescription errors	Preintervention: 60 errors/557 TPN orders (10.8%) Postintervention period 1: 20 errors/471 TPN orders (4.2%) $P < 0.01$ Postintervention period 2: 8 errors/656 TPN orders (1.2%) $P < 0.001$	Severity of harm of medication errors not addressed
Menke et al (2001)[34]	Prospective one group pre-post cohort study	United States; children's hospital 16-bed PICU	Not stated	Computerized clinical documentation system; two 3-month preintervention periods (paper chart at time of preinterventions) and 1 postintervention period 3 months after intervention	Medication delivery delay in minutes (difference between scheduled and actual medication delivery)	Preintervention (period 1): average delay of 8.5 minutes out of 601 events Preintervention (period 2): average delay of 12.8 minutes out of 513 events Postintervention: average delay of 16.9 minutes out of 856 events $P < 0.01$	Severity of harm of medication errors not addressed
Mullett et al (2001)[35]	Prospective pre-post study	United States; university children's hospital; 26-bed PICU	1758 Patients; preintervention, 809 patients; postintervention, 949 patients	Design and implement anti-infective management decision support tool	Dose adjustments	Preintervention: 36/1000 anti-infective orders Postintervention: 15/1000 anti-infective orders $P < 0.01$ Anti-infective therapeutic dosing targets (subtherapeutic and excessive doses) and total risk days for prescription errors Preintervention: 15.80 total risk days/100 days (15.8%) Postintervention: 10.77 total risk days/100 days (10.8%) $P < 0.0001$ Preintervention: 7.35 subtherapeutic days/100 days (7.35%) Postintervention: 4.72 subtherapeutic days/100 days (4.72%) $P < 0.001$ Preintervention: 8.45 excessive dose risk days/100 days (8.5%) Postintervention: 6.06 excessive dose risk days/100 days (6.1%) $P < 0.001$	Severity of harm of medication errors: preintervention, 12 adverse drug reactions relating to anti-infectives; postintervention, 12 adverse drug reactions relating to anti-infectives, no difference in severity, only 1 in each group was preventable
White et al (2005)[36]	Prospective pre-post cohort study	United States; university teaching hospital; 16-bed tertiary care academic PICU	Not stated	Mandatory drug (potassium chloride) request form	Postinfusion elevation of serum potassium level >4.5 mmol/L	Preintervention: 103 elevations/1341 administration events (7.7%) Postintervention: 0 elevations/150 administration events (0%) $P < 0.001$	Severity of harm of medication errors: no clinical morbidity or mortality relating to potassium levels identified after intervention, no mention of morbidity or mortality preintervention

Table 2. Summary of All Included Studies.

Intervention Type	Number of Studies	Total Number of Patients	Countries Involved	Results Found	Severity of Harm Addressed in Studies
Computerized physician order entry	8	511	United States (4); Israel (2); Iran (1); UK (1)	7 Studies showed significant reductions in medication errors	2 Studies
Intravenous systems	5	100	United States (4); Spain (1)	2 Studies showed significant reductions in medication errors	3 Studies
Modes of education	11	588	United States (4); Spain (3); Argentina (1); Egypt (1); Malaysia (1); Netherlands (1)	9 Studies showed significant reductions in medication errors	5 Studies
Protocols and guidelines	2	5975	United States (1); UK (1)	1 Study showed significant reductions in medication errors	1 Study
Pharmacist involvement	3	2207	United States (2); UK (1)	2 Studies showed significant reductions in medication errors	3 Studies
Support systems for clinical decision making	5	1758	United States (5)	3 Studies showed significant reductions in medication errors	3 Studies

interventions: $\chi^2(5) = 1.88$; $P = 0.87$. The following RR results for meta-analysis were obtained: CPOE = 0.47 (95% CI = 0.28, 0.79), IS = 0.37 (95% CI = 0.19, 0.73), ME = 0.36 (95% CI = 0.22, 0.58), PG = 0.82 (95% CI = 0.21, 3.25), PI = 0.39 (95% CI = 0.10, 1.51), and SSCD = 0.49 (95% CI = 0.23, 1.03).

Computerized Physician Order Entry. The efficacy of CPOE in reducing medication errors was examined in 8 studies; 7 studies showed significant reductions in medication error rates when CPOE was combined with clinical decision support (Table 1).[18-22,40,41] Clinical decision support involves the use of tools to help health professionals make informed judgments about medications. In 2 studies where the postintervention periods included comparisons with and without clinical decision support systems,[19,41] no significant changes in error rates were observed when no clinical decision support was used. Conversely, in these same studies, when clinical decision support was added to CPOE, significant reductions in error rates were observed.

Cordero et al[40] examined prescribed gentamicin dosing errors that deviated by more than 10% of the recommended dose and found that 14 errors occurred in 105 patients before the intervention, whereas no errors occurred in 100 patients following the intervention. Hilmas et al[18] investigated intravenous infusion prescription errors associated with miscalculations, exceeding the maximum concentration, incompleteness, or illegibility before and after implementing CPOE and clinical decision support. These error types reduced to zero postintervention. Medication administration errors have also been found to reduce following CPOE and clinical decision support. Taylor et al[21] examined medication administration errors associated with wrong time, omitted doses, wrong doses, and wrong routes of administration. They found the number of administration errors to be significantly reduced at postintervention (31/268 administrations, 11.6%) compared with preintervention (50/253 administrations, 19.8%); $P < 0.05$. In a prospective cohort study conducted by Vardi et al,[22] cardiopulmonary prescription errors were examined. During the preintervention phase, health professionals reported medication errors, whereas following conduct of the intervention, a pharmacist, a nurse and a physician scrutinized large numbers of medication orders. Three errors were detected before the intervention (n = 13 124 medication orders), whereas no errors were found after the intervention (n = 46 970 medication orders). Myers et al[20] found reduced medication error rates of different types of errors (transcription, dosage, formulation, preparation, and administration) following their CPOE and clinical decision support intervention (3.2 errors/1000 patient-days versus 0.6 errors/1000 patient-days). However, the investigators conducted no inferential analysis to test for possible relationships relating to error rates obtained. Warrick et al[23] showed no significant changes in prescription errors at 1 week postintervention and at 6 months postintervention. They interpreted this lack of change as resulting from new types of prescription errors created by the computerized system. On the other hand, by 6 months, omitted errors had significantly reduced compared with the number present at preintervention (1.4% vs 8.1%, respectively; $P < 0.05$).

Intravenous Systems. Five studies were identified that used IS to decrease medication errors, and 2 of these studies

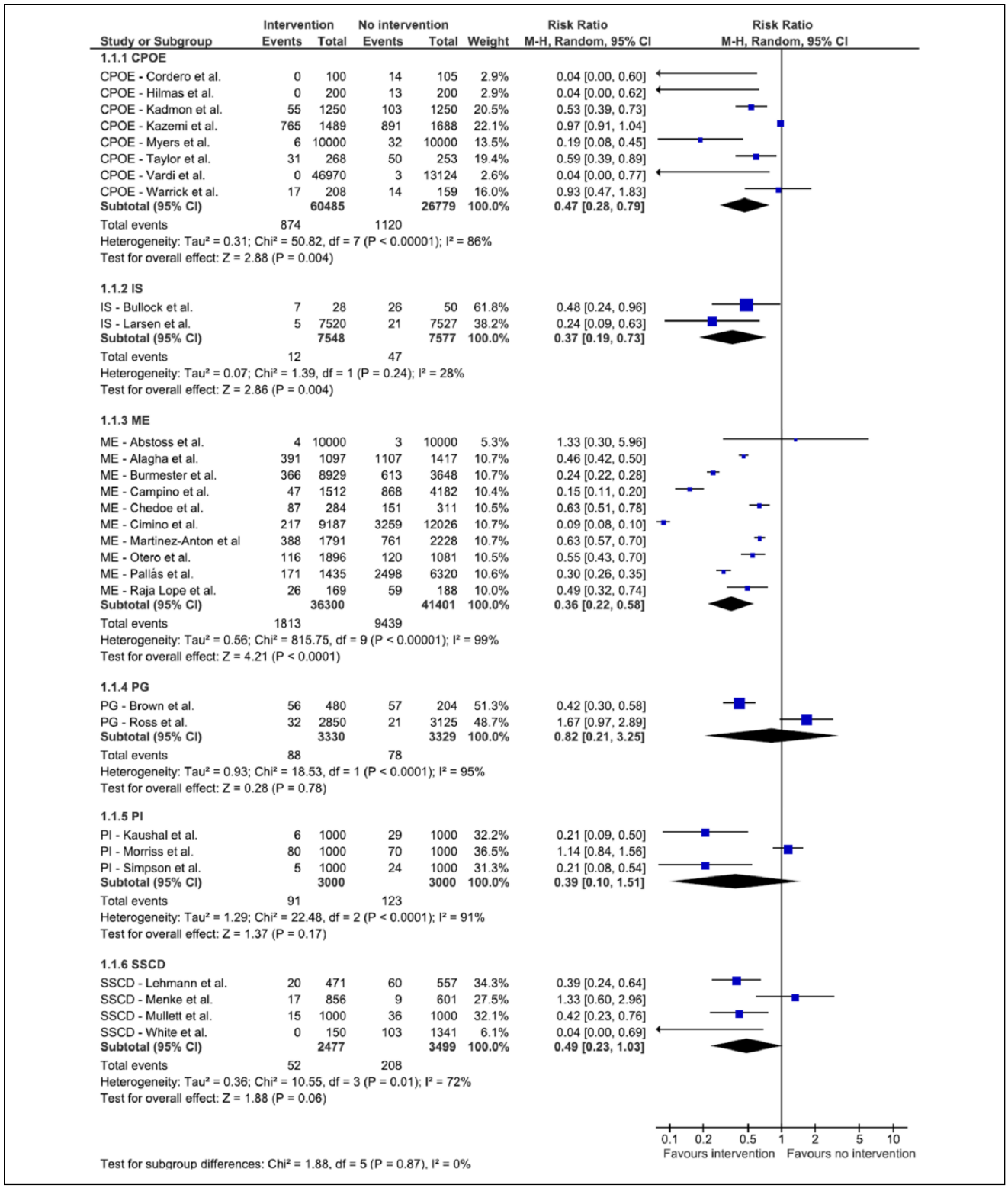

Figure 2. Risk ratio meta-analysis of subgroups of intervention types.[a]

Abbreviations: CPOE, computerized physician order entry; IS, intravenous systems; ME, modes of education; PG. protocols and guidelines; PI, pharmacist involvement; SSCD, support systems for clinical decision making.

[a]For Kadmon et al[41] and Kazemi et al,[19] the postintervention results used were errors associated with use of CPOE and clinical decision support rather than CPOE without clinical decision support. For Myers et al,[20] the figures for preintervention and postintervention were 3.2 errors per 1000 patient-days and 0.6 errors per 1000 patient-days, respectively. To enable whole numbers to be included as events in the risk ratio calculations, data have been converted to events per 10 000 patient-days.

showed significant improvements (Table 1).[43,47] It was not possible to determine the efficacy of IS in 3 studies because no denominator term was given in 1 study[24]; in another study, no preintervention data were given[42]; and in the last study, different outcome variables were used for preintervention and postintervention.[39] Types of IS implemented included the use of computerized decision support,[24] infusion devices with programmed alerts,[39,42,43] and the use of standardized infusion concentrations.[43,47]

Apkon et al[24] used failure mode effects analysis to determine risk priority numbers for preparation programming, dosage calculation, and infusion rate selection. Risk priority numbers obtained following introduction of computerized decision support were fewer than those obtained before the intervention (n = 262 vs n = 953, respectively). However, no information was given on the total number of infusions examined. Two studies involving the use of standardized infusion concentration lists both demonstrated significant reductions in medication errors following the intervention.[43,47] In the study conducted by Larsen et al,[43] where standardized infusion concentrations were combined with smart pumps, a large number of infusions were assessed, and few errors were identified. At preintervention, 10 958 infusions were assessed, with 33 errors identified, whereas at postintervention, 11 140 infusions were assessed, with 10 errors identified. Hennings et al[42] only provided medication data for programming errors following the introduction of automated infusion devices. They demonstrated that 21 errors were triggered at 2.5 times over the limit and 15 errors were triggered at 2.5 times under the limit for a total of 5268 infusions. Manrique-Rodríguez et al[39] found that 92 programming infusion pump errors were intercepted by the alert system of smart pump technology over a 17-month testing period. Preintervention data were based on a 2-week observational pilot study, which identified an error rate of 26.5 medication errors per 100 doses administered. Because of the disparity in the types of outcome variables used at preintervention and postintervention, it is difficult to determine the efficacy of the intervention.

Modes of Education. In total, 11 studies were identified that used ME to reduce medication errors, and 9 demonstrated significant reductions in medication errors (Table 1).[5,25-29,37,38,44] Two studies showed unclear or no changes in medication error rates.[30,48] All educational interventions were multimodal in nature, which included strategies such as the conduct of meetings, the use of revised prescription forms, and orientation programs. Whereas 2 interventions were multidisciplinary, 7 were directed at doctors, and 1 was directed at nurses.

The study by Abstoss et al,[48] which showed no statistical reductions in medication errors, incorporated the use of different educational approaches. These approaches focused on the safety culture and teamwork around medications and on the structural means of facilitating safe medication management and error reporting. At preintervention, 3.16 errors per 10 000 doses overall were reported, whereas at postintervention, 3.95 errors per 10 000 doses overall were reported ($P > 0.05$). Sullivan et al[30] examined prescribing errors occurring in narcotic and antibiotic medications. Errors were reported as the number of days between intercepted errors rather than as actual errors. For narcotic medications, the number of days between intercepted errors was 3.94 days at preintervention and 2.63 days at postintervention, indicating an 83% improvement. With respect to antibiotic intercepted errors, the number of days was unchanged at 2.14 days for preintervention and postintervention. Pallás et al,[37] who conducted training in good prescribing practice and implemented a pocket dosage calculation system, showed that prescription errors decreased from 39.5% before the intervention to 11.9% after the intervention, and the most common error involving incorrect dose calculations reduced by 80%. Chedoe et al[38] used a multifaceted education program with nurses, leading to a reduction in preparation and administration errors from 49% to 31%.

Protocols and Guidelines. Two studies were identified that examined the testing of PG, with one of these studies demonstrating a significant reduction in medication errors (Table 1).[45] One study involved examining a computerized parenteral nutrition worksheet,[45] and in the second study, the investigators evaluated changes in policy for checking dispensed medications, introducing fewer concentrations of medications, and developing less-punitive reporting mechanisms.[46] In the study by Brown et al,[45] the implementation of a parenteral nutrition worksheet was associated with a reduction in prescribing errors (57 errors/204 orders [27.9%] vs 56 errors/480 orders [11.7%], respectively). Ross et al[46] conducted a retrospective audit study over several months in pediatric ICU and neonatal ICU settings to determine the efficacy of comprehensive changes to policy on reported medication errors. Error rates remained relatively low across the preintervention (12 errors/1764 admissions [0.7%] in neonatal ICUs and 9 errors/1361 admissions [0.7%] in pediatric ICUs) and postintervention periods (21 errors/1609 admissions [1.3%] in neonatal ICUs and 11 errors/1241 admissions [0.9%] in pediatric ICUs.

Pharmacist Involvement. Three studies were identified that tested PI to reduce medication errors (Table 1). Of these studies, 2 showed significant reductions in medication errors following the intervention,[17,32] whereas the third showed mixed effects.[31] The study by Kaushal et al[17] comprised a multifaceted and comprehensive approach involving full-time pharmacist participation on ward rounds and quality improvement teams. This is the only study identified in the review that had a parallel control ward as well as an intervention ward. The investigators found 29 errors per 1000 patient-days (2.9%) at preintervention and 6 errors per 1000 patient-days (0.6%) at postintervention in

the intervention ward ($P < 0.01$). Morriss et al[31] examined barcoded medications that were dispensed by pharmacists. They found that following medical record audits conducted by nurse practitioners in the preceding 24 hours, medication errors increased from preintervention (69.5 errors/1000 doses) to postintervention (79.7 errors/1000 doses), $P < 0.001$. Conversely, preventable adverse drug events reduced from preintervention (0.86 errors/1000 doses) to postintervention (0.43 errors/1000 doses); $P = 0.008$. Through critical incident reporting, Simpson et al[32] showed that following the introduction of a pharmacist-led education program and medication order review, medication errors reduced from 24.1 errors/1000 neonatal activity days at preintervention, to 5.1 errors/1000 neonatal activity days at postintervention; $P = 0.037$.

Support Systems for Clinical Decision Making. There were 5 studies that involved SSCDs to reduce medication errors (Table 1). Of these, 3 studies demonstrated statistical reductions in medication errors.[33,36] In 1 study, it was not possible to determine the efficacy of SSCD because no denominator term was provided for medication errors,[49] and in another study, insignificant changes were found for medication errors in RR analysis.[34] Support systems involved the development of new reporting forms and educational forums[49] and the design of an online total parenteral nutrition (TPN) calculator,[33] an anti-infective management tool,[35] a computerized clinical documentation system,[34] and a potassium chloride request form.[36]

Costello et al[49] conducted their pre-post study in 3 phases. Phase 1 comprised retrospective collection of medication error reports before any interventions; phase 2 introduced a pediatric clinical pharmacist to the unit; and phase 3 involved the introduction of a new reporting form and support provided by a pediatrics medication safety team. The investigators hypothesized that these measures would provide support for clinical decision making and nonpunitive reporting, thereby leading to an increase in medication error reporting and a reduction in the severity of errors reported. The number of errors increased progressively for each of the 3 phases: 11, 22, and 76 errors, respectively. Conversely, the percentage of severe errors reduced progressively in each of the 3 phases: 46%, 8%, and 0% respectively. No denominator term was used in the results. Lehmann et al[33] developed and tested an online TPN calculator and found 60 errors/557 TPN orders (10.8%) at preintervention and 20 errors/471 TPN orders (4.2%) at postintervention. The reduction in errors extended to 2 years following the intervention. In introducing a computerized clinical documentation system, Menke et al[34] examined the difference between scheduled and actual medication delivery delay. This intervention did not comprise a physician order entry component. The investigators found an average delay of 8.5 minutes out of 601 medication events at preintervention and an average delay of 16.9 minutes out of 856 medication events at postintervention ($P < 0.01$). In interpreting these unexpected results, the investigators found that when using the paper system, nurses commonly charted a medication that was delivered within 30 minutes of a scheduled time as being given on time. Conversely, the exact time of delivery of medications when using the clinical documentation system was logged automatically during the charting process. Following the introduction of an anti-infective management decision support tool, Mullett et al[35] found reductions in the number of dosing adjustments needed. At preintervention, there were 36 dose adjustments/1000 anti-infective orders and 15 dose adjustments/1000 anti-infective orders at postintervention. In testing a potassium chloride request form, White et al[36] showed 103 elevations in 1341 administration events at preintervention and 0 elevations in 150 administration events at postintervention.

Discussion

This systematic review examined the efficacy of different interventions in reducing medication errors in pediatric intensive care. Apart from 1 study,[17] all studies involved single-arm, before-and-after designs without a comparative, concurrent control group. No study involved the conduct of a randomized controlled trial. Quality assessments showed that particular aspects were not sufficiently addressed. External validity or generalizability to other pediatric populations was compromised by a lack of demographic information provided about the pediatric samples. Possible bias was present in studies where assessors were not blinded to the analysis of medication errors, and insufficient information was provided about whether health professionals in pediatric ICUs complied with interventions. Internal validity was affected by confounding caused by the predominant use of before-and-after designs. Patients in different intervention groups were not recruited over the same time period, and there was lack of concealing patient assignment after recruitment was complete. Quality assessment also identified the general absence of power calculations to determine sample size. There was also lack of statistical consideration of the clustering effect involving children experiencing the medication error or health professionals committing the error; and lack of subgroup and adjusted statistical analyses. Many studies had no information about severity of harm associated with identified medication errors. A further concern is possible publication bias of included studies because most studies were positive in nature and of limited research design. Although the majority of studies favored the intervention, these methodological limitations make it difficult to fully develop comprehensive understandings of the clinical impact of interventions. RR subgroup meta-analysis shows that there is no statistically significant difference among the 6 subgroups of interventions. Available evidence suggests that

some aspects of CPOE with decision support, MEs, and ISs may help in reducing medication errors.

RR subgroup meta-analysis of MEs shows that multifaceted interventions may have been helpful in reducing medication errors. These interventions incorporated opportunities for interactional communication and feedback and were multidisciplinary in their approach. Different educational strategies were adopted depending on the cultural needs of the intensive care environment. There was a concern about how medication errors were measured in the ME study conducted by Abstoss et al.[48] They showed an increase in the rate of reported medication errors after conducting an ME intervention. It must be emphasized that reporting of medication errors is an inaccurate method of capturing actual medication events.[52] Different medication types can also affect the efficacy of ME interventions. In the study by Sullivan et al,[30] after the ME intervention, an 83% improvement was observed in the number of days between intercepted narcotic errors, whereas no effect was found in the number of days between antibiotic prescribing errors during the same period. These results show that antibiotic prescribing seems to involve a more complex ordering process than narcotic prescribing.[30]

In considering the results of RR subgroup meta-analysis, the use of CPOE with the incorporation of a clinical decision support system was generally associated with a reduction in medication errors compared with interventions that lacked use of this system. Nevertheless, complexities exist in interpreting results, which can be illustrated by considering the study undertaken by Warrick et al.[23] The investigators identified new types of errors after the intervention, such as infusions being prescribed without a base solution or without a daily rate noted. Further studies need to take into account the potential for these new types of errors.

Of the 5 studies examining ISs, 2 demonstrated significant reductions in medication errors according to RR subgroup meta-analysis.[43,47] In the case of research involving efficacy of smart pumps and automatic infusion devices, extensive bypasses of medication libraries and overriding of alerts could affect the potential benefits obtained from these systems.[53,54] In implementing novel ISs in clinical practice, intensive education and one-on-one coaching and mentoring can greatly assist in maximizing potential benefits and minimizing problems associated with bypasses and overriding of alerts.

Interventions involving PGs need further work to demonstrate their impact. According to RR subgroup analysis, one study demonstrated significant reductions in error rates,[45] whereas in the other study, mixed results were achieved.[46] Differences in data collection methods could have affected results. In the study by Brown et al,[45] in determining the efficacy of using an electronic parenteral nutrition worksheet, pharmacists proactively checked orders for medication errors relating to component amounts exceeding limits and solubility data. They also relayed options for correction to prescribers. It was, therefore, possible to refine the worksheet over time to address prescribing patterns and barriers to completing the worksheet. In the study by Ross et al,[46] data were collected through documenting medication errors on a standardized reporting form. Nurses reported more than half (59%) of medication errors, and it is therefore possible that errors committed by other health professional disciplines may have been missed. In the early stages of data collection, the study hospital had a mandatory requirement for all staff to complete the forms, and failure to report an error could be considered a disciplinary matter. The punitive nature of the reporting policy may have affected reporting trends.

Interventions using PI also demonstrated mixed results according to RR subgroup meta-analysis. Of the 3 studies, 2 showed reduced medication errors,[17,32] whereas in the study undertaken by Morriss et al,[31] an increase in medication errors occurred following the intervention. In the study by Morriss et al,[31] pharmacists assessed medication orders and dispensed barcoded medications. They discussed any orders of concern with prescribing practitioners and then entered orders into the pharmacy information system. In implementing the intervention, it appears that pharmacists were absent from clinical settings because they were not able to intercept bedside medication administration errors.

According to RR subgroup analysis for studies using SSCD, 3 out of the 5 studies demonstrated significant reductions in medication errors.[33,35,36] It was difficult to determine the impact of the study by Costello et al[49] because information about the total opportunities for medication errors was not provided. Surprising results were found in the study by Menke et al,[34] where following the introduction of a clinical documentation system, an increase resulted in medication delivery time by nurses compared with their use of a paper-based system. In using the paper-based charts, nurses often documented that medications were administered on time even though they may have been up to 30 minutes late.

There were limitations related to the systematic review. Only articles published in English were considered. Efficacy of reducing medication errors was classified in terms of intervention types to provide some structure and meaning to the possible benefits of these types. Although this classification was based on past interpretations of interventions, there was the possibility of overlap between intervention types. For instance, some studies associated with PI had components of MEs and SSCDs, and some studies involving SSCDs had components of PI. In these cases, arbitrary decisions had to be made about the predominant aspect of the intervention in classifying the type. The Downs and Black tool used to assess quality was helpful in comprehensively evaluating constructs associated with reporting, internal and external validity, and power considerations. Nevertheless, the tool was cumbersome to complete, and none of the items addressed the ability of interventions to affect patient safety and reduce the severity of harm.

Conclusions

The systematic review demonstrates that data are limited and are inconsistently gathered without standard denominators. Most interventions are without a comparative group, and efficacy of any intervention remains unknown. Available evidence suggests that some aspects of CPOE with decision support, MEs, and ISs may help in reducing medication errors. The conduct of good quality, prospective, observational designs is needed for institutions to determine the most effective interventions. Future observational studies should include a comparative, concurrent control group, with clear measurement effects and with comprehensive reporting of research processes that address internal and external validity. Clinicians and policy makers would, therefore, be in a better position to make justifiable decisions about interventions to be adopted in clinical practice.

Appendix A

Database Searching Results

Database	Search Terms and Refinement	Results
Cochrane Database of Systematic Reviews	'(medication error OR adverse drug event) AND (neonate OR infant OR child OR adolescent OR pediatric OR paediatric) AND (intensive care OR critical care) in Title, Abstract, Keywords in Cochrane Reviews'	8
Cumulative Index to Nursing & Allied Health Literature (CINAHL)	((“medication error” OR “adverse drug event”) AND (neonate OR infant OR child OR adolescent OR pediatric) AND (“intensive care” OR “critical care”))	47
	Limiters: Published Date: 19000101-20141231; English Language; Research Article; Human	25
	Search modes: Boolean/Phrase	
EMBASE	((“medication error” or “adverse drug event”) and (neonate or infant or child or adolescent or pediatric) and (“intensive care” or “critical care”)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	207
	limit 1 to (human and English language and yr=“1900- April 2014”)	167
	Refined by topic intervention	25
Journals@Ovid	(“medication error” or “adverse drug event”) and (neonate or infant or child or adolescent or pediatric) and (“intensive care” or “critical care”)).mp. [mp=title, abstract, full text, caption text]	574
	limit 1 to (yr=“1860 – April 2014” and original articles)	332
	Refined by topic intervention	153
PsycINFO	(“medication error” or “adverse drug event”) and (neonate or infant or child or adolescent or pediatric) and (“intensive care” or “critical care”))	2
	Limiters: Publication Year: 1900-2014; Published Date: 19000101-20140431; English; Age Groups: Childhood (birth-12 yrs), Neonatal (birth-1 mo), Infant, Adolescent; Population Group: Human	
PubMed	MeSH Terms, all fields, Medication errors OR Drug-Related Side Effects and Adverse Reactions AND Infant OR Newborn OR Child OR Adolescent OR Paediatrics OR pediatrics AND Intensive care OR Critical care	554
	Include only human	542
	English only	477
	Dates: (“1900/01/01”[PDAT] : “2014/04/31”[PDAT]))	477
	Clinical trial OR observational study OR pragmatic clinical trial OR randomized controlled trial	36
ScienceDirect	pub-date from 1822 to April 2014 and ((“medication error” OR “adverse drug event”) AND (neonate OR infant OR child OR adolescent OR pediatric) AND (“intensive care” OR “critical care”)) [All Sources(- All Sciences -,Medicine and Dentistry, Nursing and Health Professions, Pharmacology, Toxicology and Pharmaceutical Science)]	1407
	AND LIMIT-TO(topics, “patient safety,medication error,health care,intensive care,adverse event,critical care,icu,cpoe system,medical error,adverse drug,decision support,medication safety”)	383
	LIMIT-TO intervention	292
Scopus	((“medication error” OR “adverse drug event”) AND (neonate OR infant OR child OR adolescent OR pediatric) AND (“intensive care” OR “critical care”)) AND pub year 1960-April 2014	347
	Limit to English language only, research article or conference paper	214
	Refined by topic intervention	77
Web of Science	((“medication error” OR “adverse drug event”) AND (neonate OR infant OR child OR adolescent OR pediatric) AND (“intensive care” OR “critical care”))	79
	Timespan: 1900-2014	
	Document Types: (Article Or Proceedings Paper)	63
	English only	58
	Refined by topic intervention	21

Appendix B

Level of Evidence and Quality Analysis of Data Based on the Downs and Black Checklist (n = 31)[a]

	Items 1-10, Reporting										Items 11-13, External Validity			Items 14-20, Internal Validity: Bias							Items 21-27, Internal Validity: Confounding and Power						
Study and Level of Evidence	1, Aim (1)	2, Otc (1)	3, Pts (1)	4, Int (1)	5, Dis (2)	6, Fin (1)	7, Ran (1)	8, Adv (1)	9, Cha (1)	10, Pro (1)	11, Rep (1)	12, Rec (1)	13, Maj (1)	14, Blp (1)	15, Blm (1)	16, Outs (1)	17, Foll (1)	18, App (1)	19, Com (1)	20, Acc (1)	21, Sam (1)	22, Per (1)	23, Ing (1)	24, Con (1)	25, Ad (1)	26, Lo (1)	27, Po (1)
Cordero et al (2004)[40] (CPOE), level 4	1	1	1	1	2	1	1	0	1	0	0	0	1	1	0	0	0	1	1	1	1	0	0	0	0	1	0
Hilmas et al (2010)[18] (CPOE), level 4	1	0	0	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	0	1	1	0	0	0	0	1	0
Kadmon et al (2009)[41] (CPOE), level 4	1	1	0	1	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	0	0	0	0	1	0
Kazemi et al (2011)[19] (CPOE), level 4	1	1	0	1	0	1	0	0	1	0	1	0	1	1	0	0	0	1	0	1	1	0	0	0	0	1	0
Myers et al (1998)[20] (CPOE), level 4	0	0	0	1	0	1	0	0	1	0	1	0	1	1	0	1	1	0	0	1	1	0	0	0	0	1	0
Taylor et al (2008)[21] (CPOE), level 4	1	1	0	1	0	1	1	0	1	1	1	0	1	1	0	1	0	1	0	1	1	0	0	0	0	1	0
Vardi et al (2007)[22] (CPOE), level 4	1	1	0	1	0	1	0	1	1	0	1	0	1	1	0	1	0	0	0	1	1	0	0	0	0	1	0
Warrick et al (2011)[23] (CPOE), level 4	1	1	0	1	0	1	1	0	1	0	1	0	1	1	0	1	0	1	0	1	1	0	0	0	0	1	0
Apkon et al (2004)[24] (IS), level 4	0	0	0	1	0	0	0	1	1	0	1	0	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0
Bullock et al (2006)[26] (IS), level 4	1	1	1	1	0	1	0	0	1	0	0	0	1	1	0	1	0	0	0	1	1	0	0	0	0	1	0
Hennings et al (2010)[42] (IS), level 4	1	1	0	1	0	1	1	1	1	0	0	0	1	1	0	1	0	0	0	1	1	0	0	0	0	0	1
Larsen et al (2005)[43] (IS), level 4	1	1	0	1	0	1	1	0	1	0	0	0	1	1	0	1	1	1	0	1	1	0	0	0	0	1	1
Manrique-Rodríguez et al (2013)[39] (IS), level 4	1	0	0	1	0	0	0	1	1	0	0	0	1	1	0	1	0	0	1	0	1	0	0	0	0	1	0
Abstoss et al (2011)[48] (ME), level 4	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	1	0	0	1	1	0	0	0	0	1	1
Alagha et al (2011)[25] (ME), level 4	1	1	1	1	0	1	0	1	1	0	1	0	1	1	0	1	1	1	0	1	1	0	0	0	0	1	0
Burmester et al (2008)[26] (ME), level 4	1	1	0	0	0	1	1	0	1	0	1	0	1	1	1	1	0	1	0	1	1	0	0	0	0	1	0
Campino et al (2009)[5] (ME), level 4	1	1	0	0	0	1	0	0	1	1	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	1	0
Chedoe et al (2012)[38] (ME), level 4	1	1	1	1	2	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	0	0	1	1	1
Cimino et al (2004)[27] (ME), level 4	1	1	0	1	0	1	0	1	1	0	0	0	1	1	0	1	1	1	0	1	1	0	0	0	0	1	1
Martinez-Anton et al (2012)[28] (ME), level 4	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0	1	0
Otero et al (2008)[44] (ME), level 4	1	1	1	1	0	1	1	0	1	1	1	0	1	1	0	1	0	1	0	1	1	0	0	0	0	1	0
Pallás et al (2008)[37] (ME), level 4	1	1	0	1	2	1	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1	0	0	0	1	1	0
Raja Lope et al (2009)[29] (ME), level 4	1	1	0	0	0	1	0	0	1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	1	0
Sullivan et al (2013)[30] (ME), level 4	1	1	0	1	0	0	0	0	1	0	0	0	1	1	0	1	0	0	0	0	1	0	0	0	0	1	0
Brown et al (2007)[45] (PG), level 4	1	1	0	1	0	1	0	0	1	1	0	0	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1
Ross et al (2000)[46] (MR), level 4	1	1	0	0	0	1	0	1	1	0	0	0	1	1	0	1	1	0	0	1	1	0	0	0	0	1	0
Kaushal et al (2008)[17] (PI), level 3	1	1	1	1	0	1	0	1	1	0	1	0	1	1	0	1	1	1	0	1	1	1	0	0	0	1	0
Morriss et al (2009)[31] (PI), level 4	1	1	1	1	2	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	0	0	0	1	1	1
Simpson et al (2004)[32] (PI), level 4	1	1	0	1	1	1	0	1	1	1	1	0	1	1	0	1	1	1	0	1	1	0	0	0	1	1	1
Costello et al (2007)[49] (SSCD), level 4	1	1	0	1	0	0	0	1	1	0	0	0	1	1	0	1	0	0	0	1	1	0	0	0	0	1	0
Lehmann et al (2004)[33] (SSCD), level 4	1	1	0	1	1	1	0	0	1	0/1	1	0	1	1	0	1	0	1	1	1	1	0	0	0	0	1	0
Menke et al (2001)[34] (SSCD), level 4	1	1	1	1	0	0	1	0	1	0	0	0	1	0	0	1	1	1	0	1	1	0	0	0	0	1	0
Mullett et al (2001)[35] (SSCD), level 4	1	1	1	1	2	1	1	1	1	0	1	0	1	0	0	1	1	1	1	1	1	0	0	0	1	1	0
White et al (2005)[36] (SSCD), level 4	1	1	0	1	0	1	0	0	1	0	1	0	1	0	0	1	0	1	1	1	1	0	0	0	0	1	1

Abbreviations: CPOE, computerized physician order entry; IS, intravenous systems; ME, modes of education; PG, protocols and guidelines; PI, pharmacist involvement; SSCD, support systems for clinical decision making; Aim, Aim clearly described; Otc, main outcomes measured clearly; Pts, characteristics of patients clearly described; Int, intervention clearly described; Dis, distributions of key confounders in each patient group clearly described; Fin, main findings clearly described; Ran, random variability estimates given; Adv, adverse effects reported; Cha, characteristics of patients lost to follow-up described; Pro, actual probability values reported; Rep, patients asked to participate representative of population; Rec, distribution of factors were the same in the sample and source population; Maj, clinicians and facilities were representative of that used in source population; Blp, attempt to blind patients; Blm, attempt to blind those measuring outcomes; Outs, analyses planned from outset; Foll, analyses adjusted for different periods between intervention and outcome; App, statistical tests appropriate; Com, compliance with intervention reliable; Acc, outcome measures accurate; Sam, patients in different intervention groups from same hospital; Per, patients in different interventions recruited from same period; Ing, patients randomized to intervention groups; Con, randomized assignment concealed from patients and clinicians until recruitment complete; Ad, adequate adjustment for confounding; Lo, loss of patients taken into account; Po, study showed power analysis to detect clinically important effect.

a Numbers in brackets at the tops of columns indicate total possible score for a particular item. Level 3 evidence refers to nonrandomized controlled cohort or follow-up studies. Level 4 evidence refers to case-series, case-control studies, or historically controlled studies.

Declaration of Conflicting Interests

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