Optimization of electronic prescribing in pediatric patients

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Optimization of electronic prescribing in pediatric patients

Optimalisatie van elektronisch voorschrijven voor kinderen
(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
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door

Barbara Maat

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Copromotoren:	Dr. C.M.A. Rademaker
	Dr. C.W. Bollen

Voor mijn ouders

Een dag niet gelachen, is een dag niet geleefd

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Chapter 1

General introduction

Background

Medication prescribing errors

The US Institute of Medicines' 1999 report, *To Err is Human: Building a Safer Health System*, refueled medical errors to worldwide attention, both because of the huge numbers of avoidable disabilities and deaths that it presented, as well as because of the associated costs. The report describes that in the US annually at least 44,000 people die as a result of medical errors and estimates that preventable medical errors result in total costs of between 17 and 19 billion US dollars a year.[1]

Medication-related errors constitute an important part of the described medical errors. The report[1] refers to a study from 1997 by Bates et al.[2] exposing that about 2% of admitted patients experienced a preventable adverse drug event (ADE) caused by a medication error. This resulted in extrapolated annual US hospital costs of about 2 billion dollars. More recent reports from the US, UK and other EU countries still show impressive figures and conclusions concerning medication errors.[3-10] For example, the British report 'Building a Safer NHS for Patients: Improving Medication Safety' describes that 10% of patients in two London hospitals experienced an adverse event, of which half were preventable, and that medication errors accounted for 10 – 20% of all adverse events.[3] In the Netherlands, the Dutch Institute for Health Services Research concluded that 2.3% of all hospitalized patients in 2004 suffered from a harmful adverse event that could have been prevented and that more than 15% of these events was related to medication.[4] In 2006 the large Dutch HARM study showed that 2.4% of all admissions and 5.6% of acute admissions was related to medication and almost half of these were potentially preventable.[10]

In short: medication errors in hospitalized patients are common, often lead to patient harm that could have been prevented and contribute to high health care expenditure. Medication errors occur during all the stages of the medication process in a hospital: during prescribing, transcribing, dispensing (compounding and distributing), preparing and administering drugs and during monitoring and evaluating drug therapy (figure 1). This thesis focuses on prescribing errors for several reasons. Prescribing errors are those occurring in the stages of selecting and prescribing a drug or in the stages of monitoring and evaluating drug therapy.[11] An error in any of these stages of the medication process can cause harm if it reaches the patient, but prescribing errors are common and potentially cause serious harm as, unless detected, they may be repeated systematically for a prolonged period (i.e. the dashed line in figure 1 is followed repeatedly).[12-15] Above that, even if prescribing errors do not lead to harm, they influence the medication process as a whole, e.g. because they may lead to confusion for the dispensing pharmacy or because they may disrupt nurse workflow when administering drugs.

In hospital settings, prescribing errors can be classified into three main groups: 1. administrative and procedural errors, 2. dosing errors and 3. therapeutic errors. Each of these groups can be subdivided into more specific error types, as shown in table 1, including examples.[11,16]

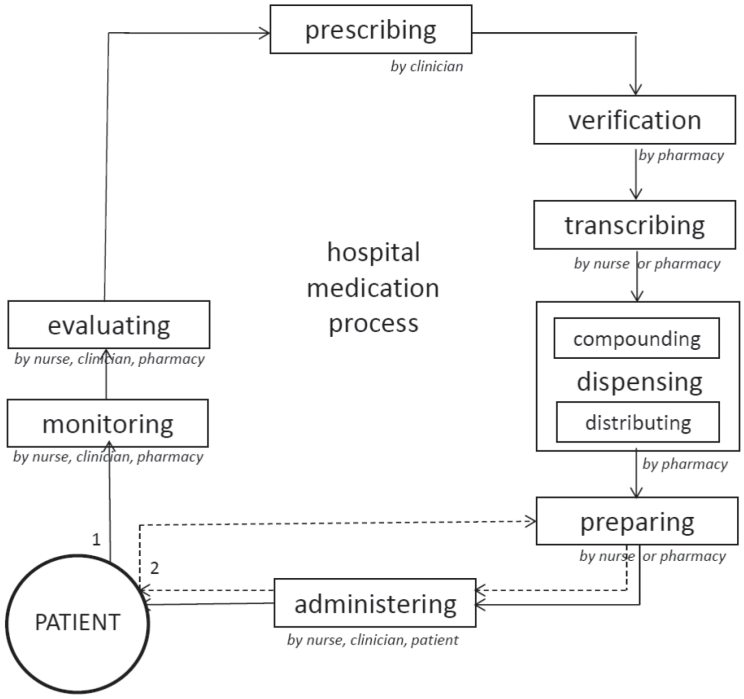


Figure 1 Hospital medication process.

A physician orders medication for a patient by prescribing a drug. The order is verified by the clinical pharmacy. Then, nursing or pharmacy personnel may have to transcribe the physician's order, e.g. onto a medication administration sheet or into the pharmacy system, respectively. Consequently, the order is dispensed by the pharmacy: checking, compounding and/or distribution to the patient's ward takes place. If the drug has not been prepared for administration yet by the pharmacy, a nurse or physician may do so and consequently administer the medication to the patient. Two subsequent scenarios are possible. 1. Administration is followed by patient monitoring, e.g. patient's response to the drug, blood pressure monitoring and blood glucose measurements, resulting in therapy evaluation and, if necessary, medication order adjustment whereto the physician prescribes a new order. This is depicted by the solid line. 2. Administration is followed by preparation and administration of the next dose that is to be administered according to the prescribed dosing regimen. This is depicted by the dashed line.

Table 1 Examples of prescribing errors.

Type of error	Example
Administrative and procedural errors	
Patient or ward data wrong, unclear or absent	'levothyroxine 50 mcg tablet qd oral' is ordered for Damian Johnson on the NICU instead of Brian Johnson on the PICU (patient and ward mix-up)
Prescriber data wrong, unclear or absent	'levothyroxine 50 mcg tablet qd oral' is written in patient's chart without mention of name or initials of prescriber
Legibility	parts of 'levothyroxine 50 mcg tablet qd oral' are illegible due to messy handwriting of prescriber that wrote it in patient's chart
Use of unauthorized abbreviations	'ltx 50 mcg tablet qd oral' is written in patient's chart instead of 'levothyroxine 50 mcg tablet qd oral'
Drug name wrong, unclear or absent	'levofloxacine' is ordered instead of 'levothyroxine' (drug name mix-up)
Route of administration wrong, unclear or absent	'levothyroxine 50 mcg tablet qd i.v.' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Dosage form wrong, unclear or absent	'levothyroxine 50 mcg qd oral' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Dosing errors	
Strength/concentration wrong, unclear or absent	'levothyroxine tablet qd oral' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Frequency wrong, unclear or absent	'levothyroxine 50 mcg tablet qid oral' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Dose wrong, unclear or absent	'levothyroxine 500 mcg tablet qd oral' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Maximum use on demand medication absent	'morphine 5 mg tablet oral as needed for pain' is ordered instead of 'morphine 5 mg tablet oral as needed for pain, maximally 6 times per 24 hours'
Length of therapy wrong, unclear or absent	'levofloxacine 500 mg tablet bid oral' instead of 'levofloxacine 500 mg tablet bid oral for 14 days'
Unit(s) wrong, unclear or absent	'levothyroxine 50 mg tablet qd oral' is ordered instead of 'levothyroxine 50 mcg tablet qd oral'
Therapeutic errors	
Indication	propylthiouracil instead of levothyroxine is ordered for a patient with hypothyroidism
Contra-indication	morphine is prescribed for patient with paralytic ileus
Allergy	levofloxacine is prescribed for patient with chinolone allergy
Monitoring	response to levothyroxine therapy not monitored by checking TSH and T4
Drug-drug interaction	levothyroxine and antacid are taken concurrently, although dosages should be separated by at least two hours as antacid reduces levothyroxine uptake
Incorrect mono-therapy/ therapy missing	opioid is prescribed without concurrent laxative therapy, NSAID is prescribed without proton pump inhibitor for gastric protection
Duplicate therapy	two drugs from the same therapeutic category are prescribed for one patient, e.g. two laxatives lactulose and magnesium hydroxide

mcg = microgram NICU = neonatal intensive care unit PICU = pediatric intensive care unit qd = once daily bid = twice daily qid = three times a day i.v.= intravenously mg = milligram TSH = thyroid stimulating hormone T4 = thyroxine

The different types of prescribing errors can have different types of clinical consequences. An administrative error for example, may not affect the patient at all, while a dosing error may lead to permanent patient harm. The US National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) has developed a standardized categorization of medication errors according to the severity of the outcome.[17] The index considers factors such as whether the error reached the patient and, if the patient was harmed, to what degree. See figure 2.

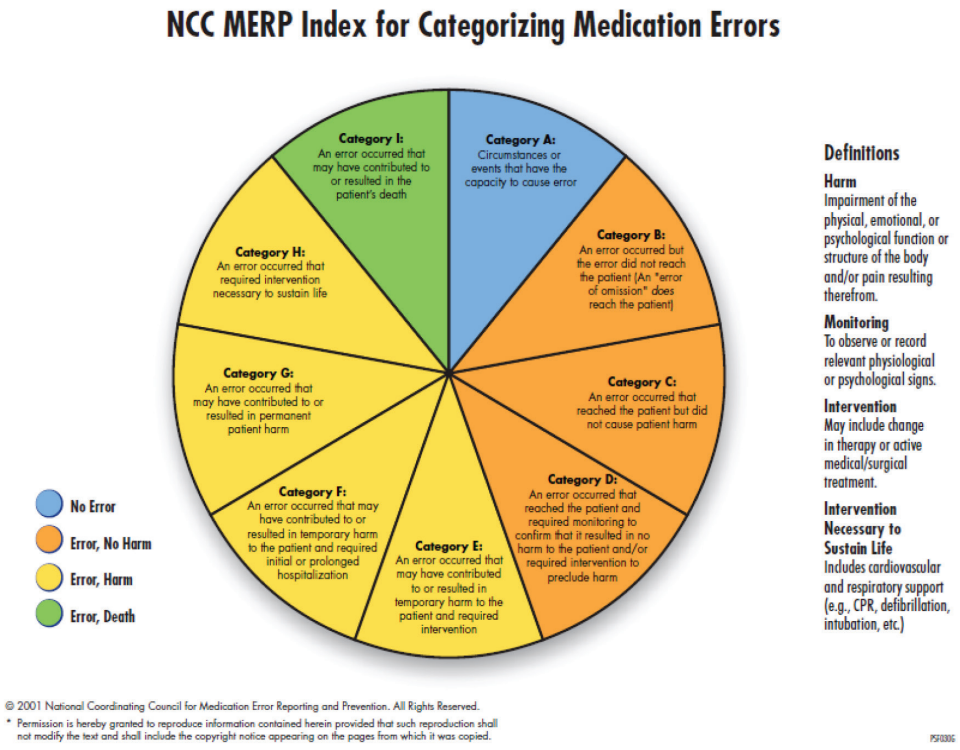


Figure 2 NCC MERP classification of medication error consequences for the patient.
Adapted from National Coordinating Council for Medication Error Reporting and Prevention index for categorizing medication errors.[17]

Medication prescribing errors in pediatric patients

As described above, medication prescribing errors frequently occur in hospitalized patients. This thesis focuses on medication prescribing errors in hospitalized children and neonates, because they constitute a special group among hospitalized patients: Kaushal et al. reported that potential ADEs due to medication errors occurred significantly more often in pediatric than in adult hospital settings.[18] Children, and especially neonates, are more vulnerable than adults. When a prescribing error reaches them, the chance of the error causing actual damage is greater as they may have less internal reserves to physically cope with the error compared to adults. Also, when a prescribing error reaches a child, it may not be able to communicate about the adverse effect that it is experiencing. Second, prescribing in pediatrics and neonatology is more complex than in adult medicine. When prescribing drugs for a neonate, infant, child or adolescent, many varying factors have to be taken into account: gestational age, postnatal age, birth weight, body weight, body surface area and developmental physiology, which affects pharmacokinetics and pharmacodynamics.[19] Above that, because of the weight-based dosing in this population, calculations are needed more often than in adults enhancing prescribing complexity. Third, as a result of a well-known lack of clinical trials in the pediatric population, pediatric pharmacotherapeutic evidence and -knowledge are scarce, leading to the extensive use of off-label and unlicensed drugs.[20-23] Together with the also well-known paucity of drug formulations suitably adapted for children, this causes pediatric prescribing to be difficult and error-prone.

Among pediatric inpatients, the intensive care population is a special group. This thesis pays extra attention to this group because it offers an extra challenge in the field of medication errors: in intensive care units (ICUs) the rate of preventable and potential ADEs is almost twice as high as in other wards.[24] Patients in an ICU often have several complex health problems and are treated with numerous and high-risk drugs, which increases the risk of a medication error and consequent harm. Also, they are mostly unconscious or sedated and not able to call attention to potential errors.

In pediatrics and neonatology, reported medication error rates in general, and prescribing error rates in particular, vary between studies. For example, in 2006 Ghaleb et al. reviewed the literature on the incidence of medication errors in pediatric patients in the UK and published a range of 0.15 – 17.2 *per 100 admissions*.[25] In 2007, Chedoe et al. did the same for neonatal intensive care and concluded with a range up to 5.5 medication errors *per 100 orders*.[26] Miller et al. systematically reviewed medication errors in pediatric care and reported the identified medication error rates per stage of the medication process. Focussing on prescribing errors, Miller at al. reported an estimated prescribing error rate of 4 – 30 *in 100 medication orders* and an estimated prescribing error rate of 0.4 – 40 *per 100 patients*.[27] The variety in reported rates seems to depend on the definitions and study methods used, and the setting studied.[25-27] Additionally, because most studies did not assess the potential clinical impact of the errors, it is difficult to determine the actual size of the problem.

Prevention of pediatric medication prescribing errors by electronic prescribing

Medication prescribing errors in hospitals are caused by individuals, by system factors, organizational factors, environmental factors, or by combinations of these. Tully et al.[28] reviewed the several studies on this subject. Inadequate knowledge of the drug or the patient, calculation errors, drug name confusion and communication problems are only a few of the identified reasons for prescribing errors. Other factors such as fatigue, stress, workload and distraction also play a role.[28]

Clinical risk management is concerned with improving the quality and safety of healthcare services by identifying the circumstances and opportunities that put patients at risk of harm and then acting to prevent or control those risks. The following five-step process is commonly used to manage clinical risks: 1. establish the context (strategic, organizational, etc.), 2. identify the risks, 3. analyze the risks (qualitatively and quantitatively), 4. evaluate the risks (which risks are acceptable and which are not), 5. treat the risks (control, reduce or eliminate the risk). The risk treatments have to be monitored and reviewed.

Because many factors contribute to prescribing error rates, many measures can be taken as clinical risk management strategies to prevent them and their consequences. These include interventions in the fields of education, patient and drug data availability, pharmacy involvement in the medication process, communication between health care providers, double-checking of calculations and last but not least information technology (IT).[3,29-31] In general, in the past decades healthcare IT has rapidly developed, resulting in a simultaneously growing availability of IT systems that support

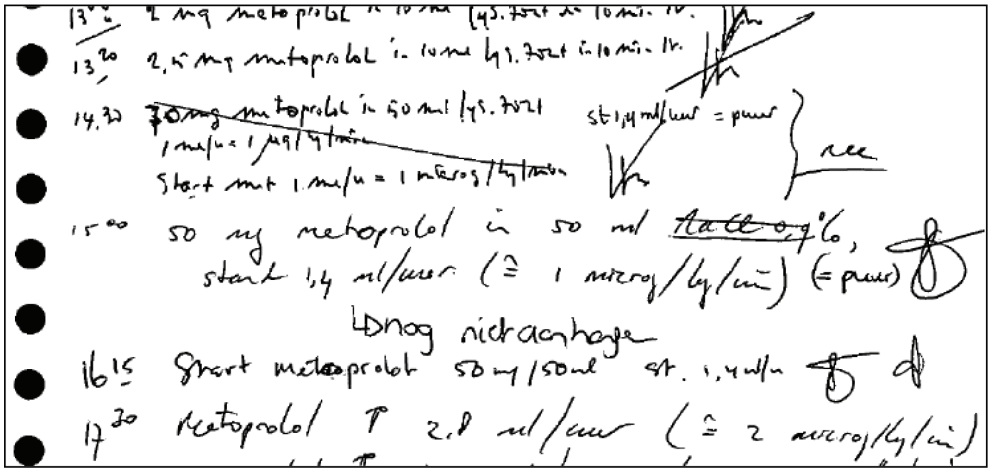


Figure 3A Handwritten medication order list for a PICU patient.

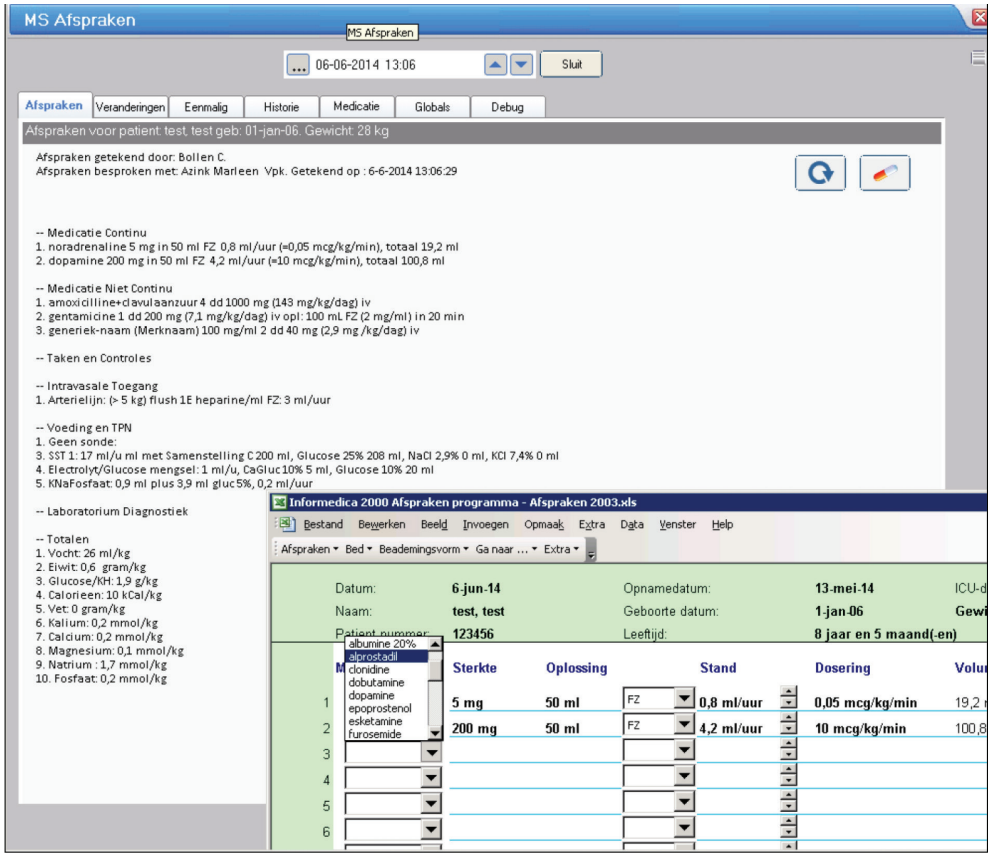


Figure 3B CPOE medication order list for a PICU patient, including a CPOE screen for ordering intravenous infusions (right lower corner).

the prescribing of medication in hospitals: computerized physician order entry (CPOE) systems and clinical decision support (CDS) systems.[32]

CPOE systems are electronic systems that allow physicians to enter medication orders per patient in a structured way. Using CPOE systems for prescribing medication is meant to have several advantages over paper-based prescribing. To begin with CPOE enhances the legibility of prescriptions: medication is ordered electronically using a computer system instead of handwritten in patient's charts. When the system additionally forces prescribers to enter data such as dose and route of administration in each medication order, then the completeness of the prescriptions is also enhanced. Above that, the standardized format of electronic prescriptions should lead to clear, structured and unambiguous lists of prescribed medication per patient. Figure 3 shows an example

Table 2 Pediatric requirements for safe and effective electronic prescribing.

Adapted from Johnson et al. [37]

Category	Pediatric requirements
Patient information	Date of birth or age in units more specific than years Weight in kg Height in cm Any history of intolerable adverse effects or allergy to medications
Medication information	Indication-based dosing and individual and daily dose alerts, using mg/kg per day or mg/m^2 per day formula, unless inappropriate Weight-based dosing calculations All available formulations, including liquid formulations that may be specific brands Common formulations requiring extemporaneous compounding or combinations of active ingredients
Cognitive support	Dose range checking (minimum and maximum amount per dose, amount per day based on weight, surface area, and total dose) Automatic strength to volume conversions for liquid medications Adverse-effect warnings specific to pediatric populations Alternative therapies based on ameliorable adverse effects Tall-man lettering to reduce medication selection errors Medication-specific indications to reduce ordering of sound-alike drugs
Pharmacy information	Pharmacies that will create extemporaneous compounds
Data transmission	Use of messaging standards for data transmission to pharmacies that include the patient's weight and notes pertaining to weight-based calculations Transmission of strength, concentration, and dose volume labeled in metric units for liquid medications

of what handwritten medication orders look like versus an electronic medication order list. CPOE can also improve the availability of pharmacotherapeutic information about a patient: electronic data do not get lost like paper sheets do and are more readily available at any time or place in the hospital, provided computers are present. Overall, CPOE systems should improve the safety and efficiency of the medication prescribing process in a hospital.[32]

CPOE systems can include or be combined with CDS systems, meant to offer support to physicians during the prescribing of medication. This form of automated support is needed because of the increasing number of available drugs, the growing complexity of therapeutic regimens and the rapidly expanding insights into indications, adverse effects, drug-drug interactions (DDIs) etc.[33] CPOE systems can be linked with databases containing background information and deliver alerts concerning doses, DDIs and contraindications. So-called clinical rules can be implemented in a CPOE system as well. Clinical rules are computerized algorithms that combine patient characteristics, laboratory results and pharmacotherapy in order to generate patient specific alerts concerning dosage with renal or liver failure for example.[34] Above that, especially in pediatric and

neonatal care, CDS systems may be used to carry out calculations that play a role in prescribing medication.[35]

In conclusion, CPOE en CDS are widely used and promising methods to prevent medication prescribing errors in inpatient settings.[32] Hence, in the Netherlands, electronic prescribing has become mandatory for all health care providers per January 1st 2014.[36] However, in order to be able to use these tools to reduce medication prescribing error rates in a specific population such as children and neonates, the exact nature of the current errors, their causes and their consequences should be characterized. Although the American Academy of Pediatrics has published a list of general pediatric requirements for safe and effective electronic prescribing (see table 2)[37], relatively little is known on this topic in this population and even less is known about the most vulnerable subgroup, pediatric and neonatal ICU patients. Consequently, worldwide governmental and non-governmental bodies and international literature emphasise time and time again that more research is needed on the nature, frequency and determinants of prescribing errors in these populations.[3,18,25,26,38,39]

Objectives

The objectives of this thesis are to determine the nature, frequency and determinants of medication prescribing errors in pediatric patients and to study the effect of computerized physician order entry and clinical decision support on these errors.

Outline

Therefore, in **Part I** of this thesis pediatric prescribing errors, identified in the Wilhelmina Children's Hospital in Utrecht, The Netherlands, are described. In 2003 CPOE and CDS were implemented hospital-wide in the Wilhelmina Children's Hospital, excluding the pediatric and neonatal intensive care units that already used a CPOE system since 2001. **Chapter 2** focuses on prescribing errors in both handwritten and electronically ordered prescriptions on the pediatric intensive care unit (PICU). **Chapter 3** addresses a subgroup of these prescribing errors, namely DDIs: a retrospective cohort study on DDIs in the PICU is presented. In **chapter 4** hospital pharmacy interventions as a result of prescribing errors in all pediatric wards using a custom CPOE system with basic CDS are studied.

The influence of the implementation of CPOE and CDS systems on medication prescribing errors and ADEs in hospitals has been studied, mostly in adult settings[40-44], but also in pediatric wards and -hospitals.[44,45] Most studies conclude that CPOE and CDS systems lead to a decline in prescribing error- and ADE rates. However, CPOE and CDS systems have unintended consequences: they can introduce new kinds of prescribing errors, such as wrong patient or drug selection and skipping of important alerts because of desensitisation to them.[46-48]

Because prescribing for children is different from adults, it may be expected that CPOE and CDS systems require specific features for pediatric prescribing and that custom CPOE/CDS systems introduce different errors in a pediatric than in an adult setting.[49] This is underlined by the earlier mentioned report 'Building a Safer NHS for Patients: Improving Medication Safety' that designates children as a specifically challenging patient group and that appoints supplemental measures to reduce the risks in pediatrics.[3] Identifying the current problems with CPOE systems in pediatric prescribing helps to specify the features needed to develop more advanced evidence based CPOE/CDS systems tailored to children.[50-54] As mentioned before, the need for tailored systems is particularly prominent for the most vulnerable and complex patients among hospitalized children: the PICU and NICU patients.[24,55]

Therefore, in **Part II** of this thesis the effect of CPOE and CDS on prescribing problems in pediatric and neonatal intensive care is described, as studied in the Wilhelmina Children's Hospital in Utrecht, The Netherlands. **Chapter 5** is a literature study focusing on the effect of CPOE on prescribing errors and clinical outcome in pediatric and neonatal intensive care. **Chapter 6** addresses the effect of a computerized prescribing and calculating CDS tool especially developed for glucose prescribing in the NICU. In **chapter 7** system requirements and system design of a CPOE system aiming to solve several of the main problems related to the medication process in PICUs and NICUs are described and tested.

In the final chapter, **chapter 8**, the results presented in thesis are put in a broader perspective and concludes with implications and recommendations for future patient care and research.

References

1 Kohn LT. To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.

2 Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA 1997;277:307-11.

3 Smith J. Building a safer NHS for patients: improving medication safety. A report by the Chief Pharmaceutical Officer. Department of Health of the UK government, 2004.

4 de Bruijne MC, Zegers M, Hoonhout LH, et al. Accidental harm in Dutch hospitals [in Dutch]. EMGO Institute/VUmc and NIVEL Dutch Institute for research in health care, 2007. Available at: http://www.onderzoekpatientveiligheid.nl/rapport.pdf [Accessed 12 May 2014].

5 Aspden P, Wolcott J, Bootman J, et al. Preventing medication errors: quality chasm series. Institute of Medicine of the National Academies. Washington, DC, National Academies Press, 2007. Available at: http://www.iom.edu/Reports/2006/Preventing-Medication-Errors-Quality-Chasm-Series.aspx [Accessed 12 May 2014].

6 The 2010 Commonwealth Fund survey: Results from a comparative population survey in 11 countries. Available at: http://www.commonwealthfund.org/Publications.aspx [Accessed 12 May 2014].

7 Classen DC, Resar R, Griffin F, et al. 'Global trigger tool' shows that adverse events in hospitals may be ten times greater than previously measured. Health Aff (Millwood) 2011;30:581-9.

8 European Commission Patient Safety Policy. Available at: http://ec.europa.eu/health/patient_safety/policy/index_en.htm [Accessed 12 May 2014].

9 A spoonful of sugar. Medicines management in NHS hospitals. The Audit Commission, London. Available at: http://archive.audit-commission.gov.uk/auditcommission/sitecollectiondocuments/AuditCommissionReports/NationalStudies/nrspoonfulsugar.pdf [Accessed 12 May 2014].

10 van den Bemt PM, Egberts AC, Leendertse A. Hospital Admissions Related to Medication (HARM). A prospective, multicenter study on medication related hospital admissions [In Dutch]. Division of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, 2006. Available at: http://www.knmp.nl/downloads/medicijnen-zorgverlening/medicatieveiligheid/harm-rapport.pdf [Accessed 12 May 2014].

11 van den Bemt PM, Egberts AC. Drug-related problems: definitions and classification. EJHP Practice 2007;13:62-4.

12 Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA 1995;274:35-43.

13 Bates DW. Frequency, consequences and prevention of adverse drug events. J Qual Clin Pract 1999;19:13-7.

14 Barber N, Rawlins M, Dean Franklin B. Reducing prescribing error: competence, control, and culture. Qual Saf Health Care 2003;12 Suppl 1:i29-32.

15 Lisby M, Nielsen LP, Mainz J. Errors in the medication process: frequency, type, and potential clinical consequences. Int J Qual Health Care 2005;17:15-22.

16 Fijn R, Van den Bemt PM, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors.Br J Clin Pharmacol 2002;53:326-31.

17 National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. Available at: http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf [Accessed 12 May 2014].

18 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114-20.

19 Bartelink IH, Rademaker CM, Schobben AF, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006;45:1077-97.

20 Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. Drug Saf 2002;25:1-5.

21 Lindell-Osuagwu L, Korhonen MJ, Saano S, et al. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 2009;34:277-87.

22 Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005;164:552-8.

23 Shah SS, Hall M, Goodman DM, et al. Off-label use in hospitalized children. Arch Pediatr Adolesc Med 2007;161:282-90.

24 Colpaert K, Decruyenaere J. Computerized physician order entry in critical care. Best Pract Res Clin Anaesthesiol 2009;23:27-38.

25 Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. Ann Pharmacother 2006;40:1766-76.

26 Chedoe I, Molendijk HA, Dittrich ST, et al. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety: a review of the current literature. Drug Saf. 2007;30:503-513.

27 Miller MR, Robinson KA, Lubomski LH, et al. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. Qual Saf Health Care 2007;16:116-26.

28 Tully MP, Ashcroft DM, Dornan T, et al. The causes of and factors associated with prescribing errors in hospital inpatients: a systematic review. Drug Saf 2009;32:819-36.

29 Barber N, Rawlins M, Dean Franklin B. Reducing prescribing error: competence, control, and culture. Qual Saf Health Care 2003;12 Suppl 1:i29-32.

30 Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care: a systematic review. Arch Intern Med 2006;166:955-64.

31 Agrawal A. Medication errors: prevention using information technology systems. Br J Clin Pharmacol 2009;67:681-6.

32 Bates DW. Using information technology to reduce rates of medication errors in hospitals. BMJ 2000;320:788-91.

33 Schiff GD, Rucker TD. Computerized prescribing: building the electronic infrastructure for better medication usage. JAMA 1998;279:1024-9.

34 Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf 2007;16:1129-35.

35 Lehmann CU, Kim GR, Gujral R, et al. Decreasing errors in pediatric continuous intravenous infusions. Pediatr Crit Care Med 2006;7:225-30.

36 Guidelines on electronic prescribing [in Dutch]. Royal Dutch Medical Association, 2013. Available at: http://knmg.artsennet.nl/Publicaties/KNMGpublicatie/136411/Richtlijn-elektronisch-voorschrijven-2013.htm [Accessed 7 May 2014].

37 Johnson KB, Lee CK, Spooner SA, et al. Automated dose-rounding recommendations for pediatric medications. Pediatrics 2011;128:e422-8.

38 The Joint Commission. Sentinel event alert, issue 39: preventing pediatric mediation errors. Available at: http://www.jointcommission.org/sentinel_event_alert_issue_39_preventing_pediatric_medication_errors/ [Accessed 12 May 2014].

39 World Health Organization. Promoting safety of medicines for children, 2007. Available at: http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childrens.pdf [Accessed 12 May 2014].

40 Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003;163:1409-16.

41 Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerized physician medication order entry in hospitalized patients—a systematic review. Int J Med Inform 2008;77:365-76.

42 Ammenwerth E, Schnell-Inderst P, Machan C, et al. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. J Am Med Inform Assoc 2008;15:585-600.

43 Wolfstadt JI, Gurwitz JH, Field TS, et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. J Gen Intern Med 2008;23:451-8.

44 Reckmann MH, Westbrook JI, Koh Y, et al. Does computerized provider order entry reduce prescribing errors for hospital inpatients? A systematic review. J Am Med Inform Assoc 2009;16:613-23.

45 Conroy S, Sweis D, Planner C, et al. Interventions to reduce dosing errors in children: a systematic review of the literature. Drug Saf 2007;30:1111-25.

46 van der Sijs H, van Gelder T, Vulto A, et al. Understanding handling of drug safety alerts: a simulation study. Int J Med Inform 2010;79:361-9.

47 Ash JS, Sittig DF, Poon EG, et al. The extent and importance of unintended consequences related to computerized provider order entry. J Am Med Inform Assoc 2007;14:415-23.

48 Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293:1197-203.

49 Kim GR, Lehmann CU and the Council on Clinical Information Technology. Pediatric aspects of inpatient health information technology systems. Pediatrics 2008;122:e1287-96.

50 Sard BE, Walsh KE, Doros G, et al. Retrospective evaluation of a computerized physician order entry adaptation to prevent prescribing errors in a pediatric emergency department. Pediatrics 2008;122:782-7.

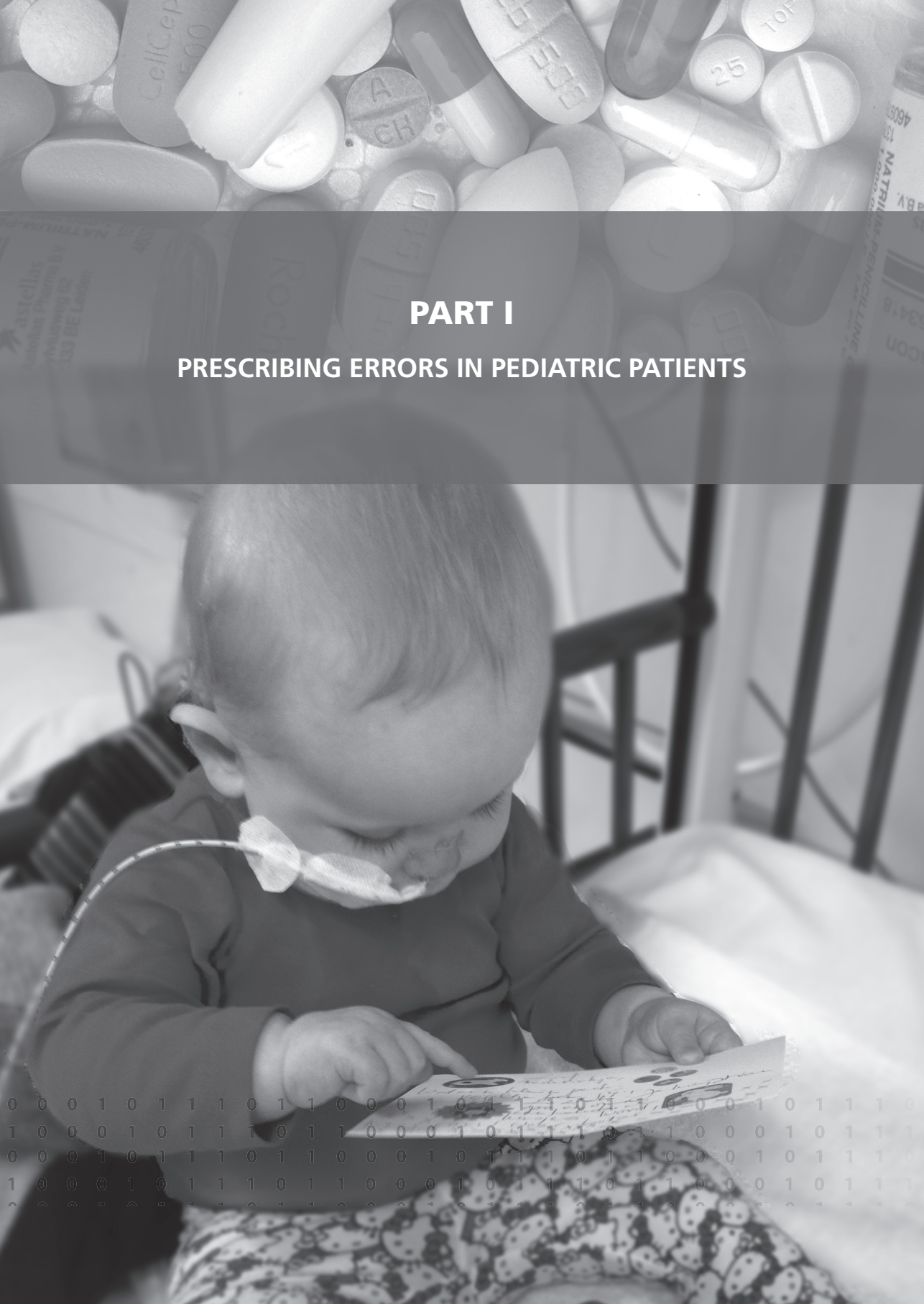
51 Kaushal R. Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? Arch Pediatr Adolesc Med 2001;155:1002-07.

52 Spooner SA, Council on Clinical Information Technology. Special requirements of electronic health record systems in pediatrics. Pediatrics 2007;119:631-7.

53 Caldwell NA, Power B. The pros and cons of electronic prescribing for children. Arch Dis Child 2012;97:124-8.

54 Ferranti JM, Horvath MM, Jansen J, et al. Using a computerized provider order entry system to meet the unique prescribing needs of children: description of an advanced dosing model. BMC Med Inform Decis Mak 2011;11:14.

55 Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a PICU. Pediatrics 2009;124:935-40.



PART I

PRESCRIBING ERRORS IN PEDIATRIC PATIENTS

Chapter 2

Prescribing errors in pediatric intensive care patients

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Abstract

Purpose Prescribing errors frequently occur in pediatric intensive care units (PICUs). This study examined frequency, types and risk factors of PICU prescribing errors and the relation to the use of a computerized physician order entry (CPOE) system.

Methods Prospective cohort with risk factor analysis at a tertiary children's hospital's PICU, The Netherlands. PICU patients 0-18 years with at least one medication order hospitalized between February 2008 and December 2010 were included. Medication orders with errors were compared with orders without errors. Frequency and types of prescribing errors, and risk factors thereof (patient-, medication order- and drug related) were assessed.

Results 718 patients with 22,280 medication orders were included. Per 1,000 medication orders, 180 administrative errors, 525 omissions and 121 dosing errors were identified. Most important risk factors for omissions were handwritten orders and intermittently dosed medication (OR = 7.95 [7.42, 8.53] and OR = 2.15 [1.99, 2.32] resp.). Most important risk factors for dosing errors were alterations in medication orders (OR = 3.28 [2.13, 5.05]) and intermittent dosing (OR = 5.59 [3.20, 9.76]).

Conclusions PICU prescribing errors frequently occur. CPOE was associated with minimizing omissions but not with reduction of dosing errors. To prevent dosing errors electronic clinical decision support (CDS) should focus on alterations in medication orders and on intermittently dosed medication. Furthermore, free-text entry should be minimised, fast and easy alteration of infusion pump flow rates facilitated and dose checking integrated using a suitable PICU drug formulary including off label drugs.

Introduction

Medication errors constitute a substantial part of medical errors. Estimates of medication error rates vary greatly among studies, partly due to the lack of a uniform definition and classification of medication errors and variability in the settings and populations studied.[1]

Medication errors can occur in all stages of the medication process, i.e. prescribing, transcribing, dispensing, administering and monitoring drugs. Prescribing errors are potentially one of the most serious type of medication errors as they may be repeated systematically for a prolonged period if not detected.[2] Prescribing errors may lead to adverse drug events (ADEs), prolonged hospital admissions and even deaths: 1–2% of patients in US and UK hospitals is thought to be harmed by medication errors, mostly arising from prescribing rather than the later phases of the process.[3,4] Patients in an intensive care unit (ICU) are at increased risk for prescribing errors and consequent harm. They are severely ill and have several complex health problems for which they are treated with numerous, often potent, drugs. Additionally, capacity to cope with physiological disturbances is diminished due to poor general condition. Also, they are mostly unconscious or sedated and not able to call attention to potential errors. In adult ICUs the rate of preventable and potential ADEs is almost twice as high as in non-ICUs[5] and more harmful medication errors are reported in ICU than in non-ICU settings.[6] The same, or even worse, may be expected for pediatric ICUs (PICUs), as prescribing drugs for children is considered more complex than for adults and because children may be at higher risk for complications of ADEs.[7-9]

A few studies have shown that computerized physician order entry (CPOE) systems, including clinical decision support (CDS), offer the potential to reduce prescribing error rates in PICU patients, but only if well-designed and -implemented.[10-12] None of these studies though, has identified patient-, medication order- and drug related risks that a CPOE/CDS system should focus on to prevent prescribing errors in such a specific setting. Therefore, the objective of this study was to examine the frequency, types and risk factors of PICU prescribing errors and the relation to the use of a CPOE system.

Materials and Methods

Setting

This study was conducted at the 14 bed PICU of the 220 bed Wilhelmina Children's Hospital, which is part of the University Medical Center Utrecht, The Netherlands. In January 2001 a homegrown CPOE system was introduced on the PICU. Every clinician is trained how to use the system in a face to face introduction by a medical staff member before permitted to prescribe. To prescribe drugs, the clinician enters standard fields, e.g. drug, dose, dosing regimen and route of administration, using dropdown menus. Suitable dosing ranges are visible during prescribing. If a drug is not commonly used, the clinician has to enter details, such as drug name and concentration,

and dosing ranges are not shown. In both cases though, the system calculates the prescribed dose per kg body weight in order to support the clinician in dosing correctly. The CPOE system does not include CDS such as checking of drug allergy, duplicate therapy or drug-drug interactions.
The clinician enters all new medication orders into the CPOE system once daily, every morning after the bedside report round, and then prints an up-to-date medication record per patient. Contemporaneously, handwritten medication orders were in use during the study period, because new medication orders and alterations in existing medication orders were written down on the medication record during the day. As described above, these new and changed orders were entered into the CPOE system and printed the next morning.

Study population and study design

The study population consisted of patients between 0 and 18 years with at least one medication order, admitted to the PICU between 1 February 2008 and 1 December 2010. If a patient was admitted more than once during the study period, he or she was considered a new patient at every admission.
Frequency and types of prescribing errors were determined using a prospective cohort design. Within this cohort a risk factor analysis was performed. The measures of outcome were the frequency of prescribing errors, expressed as number of errors per 1,000 medication orders and per admitted patient, and the risk factors thereof.
The study was approved by the Institutional Review Board.

Data collection

Medication orders of all included patients were collected from the medication records. A medication order was defined as a direction for a pharmacological active substance, i.e. a therapeutic or corrective agent, written or electronically ordered by a clinician (pediatric intensivist or resident). Orders for (par)enteral feeding, standard glucose/saline electrolyte solutions and heparin/saline flushes for clearing out intravenous lines were excluded.
From February 2008 – December 2009 medication orders were collected every day. For efficiency reasons, this was reduced to two alternate days a week from December 2009 – December 2010.
Supplementary data concerning the patient (length of PICU stay, type and urgency of admission, severity of illness scores, ventilated or not and if so duration of ventilation, deceased or not) were extracted from the Pediatric Intensive Care Evaluation (PICE) database. The PICE database is a Dutch national data registration project that contains patient data from all Dutch PICUs to evaluate and compare quality of care.[13] Patients that were not found in the PICE database were excluded from the study.
Data were collected by a clinical pharmacist in training (BM) and by trained researchers (master's degree students of the Utrecht University Faculty of Pharmaceutical Sciences).

Prescribing errors

Each medication order was independently reviewed for prescribing errors by both one of the trained researchers and BM. Based on the definition for medication error by the US National Coordinating Council for Medication Error Reporting and Prevention[14] and literature on hospital prescribing errors[15-17], four types of prescribing errors were distinguished: 1. administrative errors, 2. omissions, 3. dosing errors and 4. therapeutic errors. Each of these groups was subdivided into more specific error types (Appendix 1). In this study therapeutic errors were not taken into account because the studied CPOE system does not include CDS for this purpose.

Primary sources for dose checking were the Dutch National Children's Formulary[18] and the Wilhelmina Children's Hospital drug formulary for homegrown preparations.[19] Local dosing rules and treatment protocols of the PICU were also taken into account, e.g. minimum and maximum infusion pump flow rates. If the guidelines mentioned above did not contain a dosing advice for a certain drug, then the UK's British National Formulary for Children[20] and the US' Pediatric Dosage Handbook were consulted.[21]

Risk factors

In order to examine risk factors for prescribing errors medication orders *with* a prescribing error were compared with orders *without* an error from the study cohort. The studied potential risk factors included patient characteristics (gender, age, body weight, length of PICU stay, type and urgency of admission, severity of illness scores (PIM2 and PRISMII at admission)[22,23], ventilated or not), medication order characteristics (new order or altered existing order, handwritten or electronically ordered, day of the week, season) and drug related characteristics (drug class, route of administration, continuous or intermittent, on demand use, in dosing guidelines or not).

Risk factors for administrative errors were not analyzed because of their low potential for harm. Risk factors for omissions were studied separately from those for dosing errors. Risk factor analysis of dosing errors focused on evident dosing errors, i.e. dose factor 5 or more *higher* than guidelines' *maximum* and dose factor 5 or more *lower* than guidelines' *minimum*.

Statistical analysis

Data were processed with MS Excel 2003 and statistically analyzed using SPSS version 20.0. Logistic regression analysis was used to estimate the strengths of the associations between patient-, medication order- and drug related characteristics and prescribing errors, expressed as odds ratios (OR), both crude and adjusted, with 95% confidence intervals (95% CI). The covariates used for adjustment were determined using forward selection.

Results

During the 34 months study period 718 admitted patients with 22,280 medication orders were included (mean 31 orders per patient, range 1 – 421). Table 1 shows the patient characteristics and figure 1 the medication order characteristics. Considering drug classes, drugs concerning the nervous system (e.g. morphine and midazolam) and the cardiovascular system (e.g. furosemide and dopamine) were prescribed most often (9,266 (42%) and 5,860 (26%), respectively).

Table 1 Patient characteristics (February 2008 – December 2010).

Patient characteristics n = 718[a]	
Female – n (%)	288 (40.1)
Age – median (range) in years	0.74 (0 – 18.4)
Weight – median (range) in kg	8.0 (1.8 – 90.0)
Length of PICU stay – median (range) in days	6.0 (1 – 294)
Type of admission – n (%)	
– Medical	426 (59.3)
– surgical	292 (40.7)
Urgency of admission – n (%)	
– elective	314 (43.7)
– emergency	404 (56.3)
Severity of illness scores	
– PIM2 at admission – median (range)	-3.71 (-6.93 – 3.65)
– PRISMII at admission – median (range)	11 (0 – 44)
Ventilation	
– no. of ventilated patients – n (%)	620 (86.4)
– duration – median (range) in days	5.0 (0 – 294)
Deceased – n (%)	37 (5.2)

[a]n = 718 admissions of n = 617 individual patients. If a patient was re-admitted during the study period, he or she was considered a new patient. During the study period 22,424 medication orders of 722 admissions were collected. Four of these admissions were not found in the PICE database[13] and therefore the 144 medication orders belonging to these admissions were discarded.
PIM 2 pediatric index of mortality 2 score
PRISM II pediatric risk of mortality II score

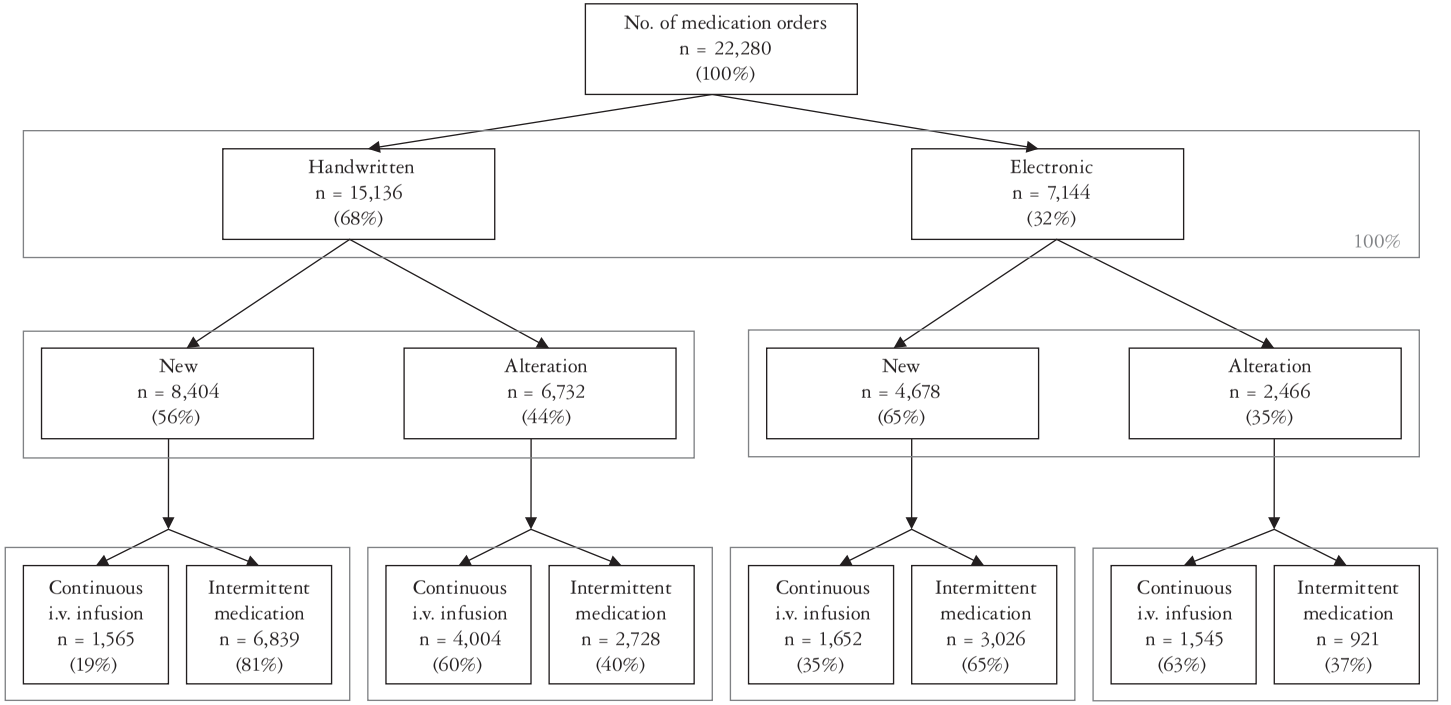

Figure 1 Medication order characteristics (February 2008 – December 2010).
Almost 70% of medication orders was handwritten. Both handwritten and electronic medication orders mainly consisted of new orders rather than alterations (56% and 65%, respectively). A new order was defined as a medication order prescribed for a patient for the first time. An alteration, i.e. an altered existing order, was defined as a change of strength/concentration, dosing regimen, rate of administration and/or route of administration in an existing medication order. If an order was new, it often concerned intermittently dosed medication. On the contrary, if an order was altered, it mainly concerned alteration of continuous intravenous medication. These alterations of continuous intravenous medication were handwritten 2.5 times as often as electronically ordered ($n_{handwritten}$ = 4,004 versus $n_{electronic}$ = 1,545 respectively).

Frequency and types of prescribing errors

Overall, 18% (4,021) of the 22,280 medication orders contained an administrative error, 53% (11,697) an omission and 12% (2,703) a dosing error. Per 1,000 orders, that is 180 administrative errors, 525 omissions and 121 dosing errors. Or, per admitted patient, that is 5.6 administrative errors, 16.3 omissions and 3.8 dosing errors.

Table 2 gives an overview of the identified types of prescribing errors and their frequencies. Most often dosage form (24.1%), time of administration (17.4%) or dose (16.8%) was unclear or missing. Dosing errors most frequently concerned doses > 10% below or above therapeutic range. Figure 2 shows that most of these deviations are > 10% *below* rather than *above* guidelines' therapeutic range. In total, 95 medication orders (0.7%) for 75 patients were more than a factor 5 or 10 outside guidelines' therapeutic range.

All medication orders were reviewed for administrative errors and omissions, but not all for dosing errors. To be able to review orders for dosing errors, they had to be legible and contain all components relevant to dose checking, e.g. route of administration and drug strength/concentration. This led to exclusion of 9,401 (42%) medication orders for dosing error review. The remaining 12,879 (58%) medication orders could be fully reviewed. Figure 3 depicts the distribution of all error types among the fully and partially reviewed medication orders.

Table 2 Types and frequencies of prescribing errors.

	Number of orders with administrative error	% of reviewed orders n=22,280
Administrative errors		
Prescriber data unclear/absent	3,485	15.6
(Partly) illegible	869	3.9
Total number of orders with administrative error[a]	4,021	18.0
	Number of orders with omission	**% of reviewed orders n=22,280**
Omissions, drug-related		
Drug name unclear/absent	325	1.5
Strength/concentration unclear/absent	531	2.4
Dosage form unclear/absent	5,370	24.1
Unauthorized drug name abbreviations	753	3.4
Omissions, dosing regimen-related		
Frequency unclear/absent	2,316	10.4
Dose unclear/absent[b]	3,748	16.8
Route of administration unclear/absent	3,128	14.0
Time(s) of administration unclear/absent	3,882	17.4
Unit(s) unclear/absent	558	2.5
Total number of orders with omission[c]	11,697	52.5

Table 2 Continued.

	Number of orders with dosing error	% of orders reviewed n=12,879
Dosing error		
Frequency *below* therapeutic range in guidelines[d]	153	1.2
Frequency *above* therapeutic range in guidelines[d]	132	1.0
Dose > 10% *below* therapeutic range in guidelines[d]	1,409	10.9
Dose > 10% *above* therapeutic range in guidelines[d]	1,007	7.8
Of the doses > 10% outside therapeutic range:		
Dose ≥ factor 2 outside therapeutic range	551	4.3
Dose ≥ factor 5 outside therapeutic range	63	0.5
Dose ≥ factor 10 outside therapeutic range	32	0.2
Drug name incorrect	5	<0.1
Strength/concentration incorrect	1	<0.1
Route of administration inconsistent with dosage form	10	0.1
Units incorrect	166	1.3
Total number of orders with dosing error[e]	2,703	21.0

[a] One medication order can contain more than one type of administrative error. That is why the total number of orders with an administrative error is not equal to the sum of the separate numbers of orders with an administrative error.

[b] Rate of administration or infusion pump flow rate of continuous intravenous medication, dose of intermittent medication or maximum dose of on demand medication unclear/absent

[c] One medication order can contain more than one type of omission. That is why the total number of orders with an omission is not equal to the sum of the separate numbers of orders with an omission.

[d] Dutch National Children's Formulary[18], Wilhelmina Children's Hospital drug formulary[19] and local PICU dosing rules and treatment protocols

[e] One medication order can contain more than one type of dosing error. That is why the total number of orders with a dosing error is not equal to the sum of the separate numbers of orders with a dosing error.

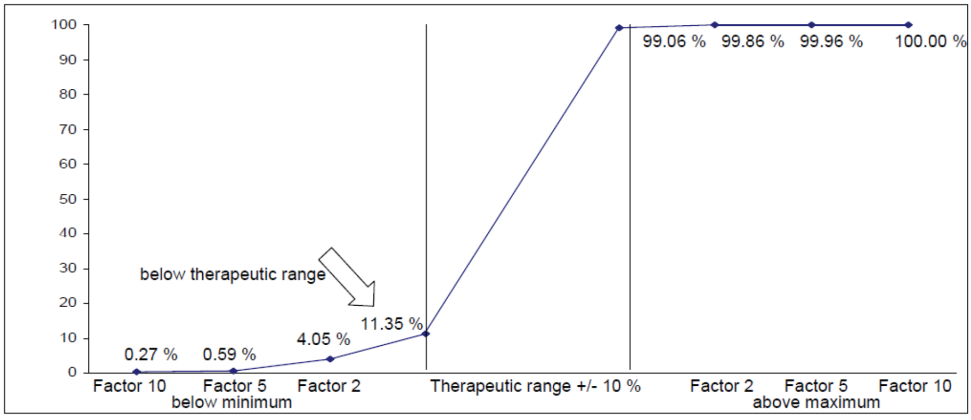

Figure 2 Cumulative percentage of medication orders in- and outside the guidelines' therapeutic dosing range.

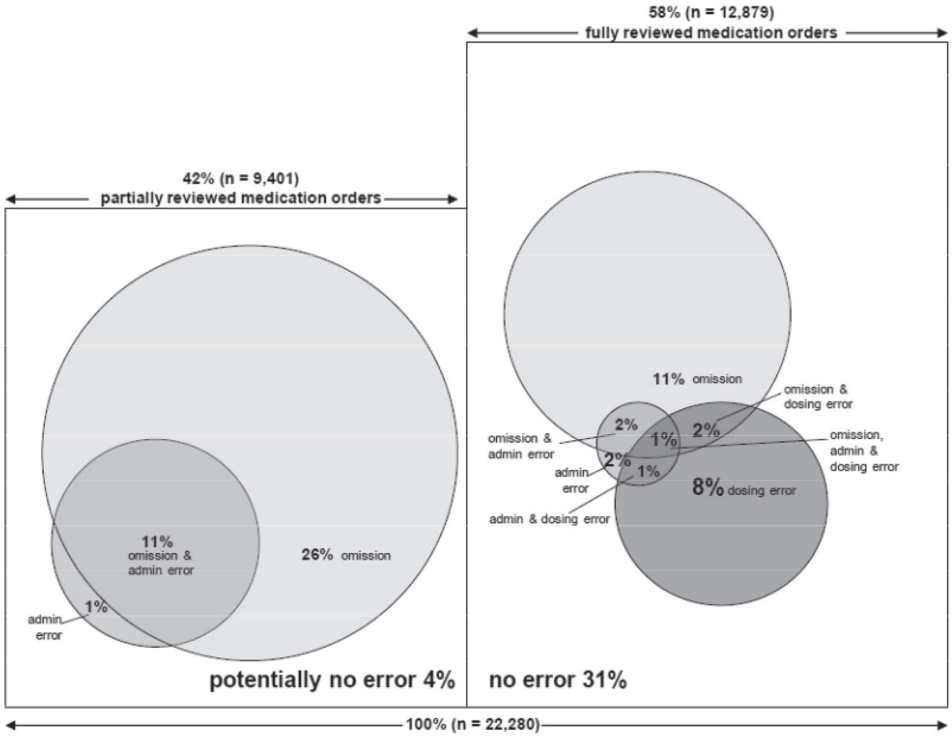

Figure 3 Distribution of prescribing errors among partially and fully reviewed medication orders.
Circles depict medication orders with administrative errors, omissions or dosing errors. Overlapping areas concern orders with more than one type of error. Right panel depicts the 58% of the 22,280 medication orders that could be fully reviewed for all types of prescribing errors. Left panel shows the remaining 42% that could only be reviewed for administrative errors and omissions, and not for dosing errors due to illegibility or incompleteness. Of all medication orders, 31% was clear, complete and properly dosed (white area surrounding circles in right panel) and 4% was clear, complete and potentially properly dosed (white area surrounding circles in left panel). Appendix 2 shows how medication orders were determined to be reviewed for dosing errors in detail.

Risk factors

To identify risk factors for omissions and dosing errors, 11,697 medication orders *with* an omission were compared with 9,677 orders *without* an omission and 95 medication orders *with* a dosing error factor ≥ 5 were compared with 10,176 orders *without* a dosing error, respectively. Table 3 shows the identified risk factors.

Table 3 Risk factors for omissions and dosing errors ≥ factor 5.

Omissions	Medication orders with omission n = 11,697 (100%)	Medication orders without omission n = 9,677 (100%)	OR_{crude} [95% CI]	$OR_{adjusted}$ [95% CI]
Handwritten/CPOE				
Handwritten	9,969 (85.2)	4,261 (44.0)	**7.33 [6.87, 7.82]**	**7.95 [7.42, 8.53]**
CPOE	1,728 (14.8)	5,416 (56.0)	ref	ref
New/alteration				
Alteration	4,901 (41.9)	3,867 (40.0)	**1.08 [1.03, 1.15]**	**1.26 [1.18, 1.36]**
New	6,796 (58.1)	5,810 (60.0)	ref	ref
Continuous/ intermittent				
Intermittent	8,077 (69.1)	4,918 (50.8)	**2.16 [2.04, 2.28]**	**2.15 [1.99, 2.32]**
Continuous	3,620 (30.9)	4,759 (49.2)	ref	ref
In dosing guidelines[a]				
No	199 (1.7)	95 (1.0)	**1.75 [1.37, 2.23]**	1.31 [0.99, 1.74]
Yes	11,498 (98.3)	9,582 (99.0)	ref	ref
On demand use				
On demand	329 (2.8)	141 (1.5)	**1.96 [1.60, 2.39]**	**1.83 [1.46, 2.30]**
Set dosing regimen	11,368 (97.2)	9,536 (98.5)	ref	ref
Dosing errors ≥ factor 5	**Medication orders with dosing error n = 95 (100%)**	**Medication orders without dosing error n = 10,176 (100%)**	**OR_{crude} [95% CI]**	**$OR_{adjusted}$ [95% CI]**
Handwritten/CPOE				
Handwritten	63 (66.3)	5,305 (52.1)	**1.81 [1.18, 2.77]**	1.39 [0.88, 2.19]
CPOE	32 (33.7)	4,871 (47.9)	ref	ref
New/alteration				
Alteration	49 (51.6)	3,718 (36.5)	**1.85 [1.24, 2.77]**	**3.28 [2.13, 5.05]**
New	46 (48.4)	6,458 (63.5)	ref	ref
Continuous/ intermittent				
Intermittent	75 (78.9)	5,413 (53.2)	**3.30 [2.01, 5.41]**	**5.59 [3.20, 9.76]**
Continuous	20 (21.1)	4,763 (46.8)	ref	ref

[a] Dutch National Children's Formulary 18, Wilhelmina Children's Hospital drug formulary 19 and local PICU dosing rules and treatment protocols.
OR odds ratio
95% CI 95% confidence interval
ref reference for odds ratio

Writing by hand was the strongest risk factor for omissions: risk of an omission was almost 8 times higher when the order was handwritten versus electronically ordered ($OR_{adjusted}$ = 7.95 [95% CI 7.42, 8.53]). Accordingly, *all* administrative errors concerned handwritten orders. On the contrary, writing by hand was not a significant risk factor for dosing errors ($OR_{adjusted}$ = 1.39 [95% CI 0.88, 2.19]).

An intermittent dosing regimen appeared to be the strongest risk factor for dosing errors: odds of a dosing error in intermittent dosing regimens were more than five times the odds in continuously dosed medication ($OR_{adjusted}$ = 5.59 [95% CI 3.20, 9.76]). An intermittent dosing regimen had higher odds for omissions too ($OR_{adjusted}$ = 2.15 [95% CI 1.99, 2.32]).

Another important risk factor was whether it concerned a new or altered medication order. This particularly applied to dosing errors: the risk of a dosing error was a factor 3 higher in alterations in existing orders than in newly prescribed medication ($OR_{adjusted}$ = 3.28 [2.13, 5.05]).

Finally, 'on demand use' was a risk factor for omissions, because maximum dose per day was often missing ($OR_{adjusted}$ = 1.83 [95% CI 1.46, 2.30]).

None of the patient characteristics proved to be a prominent risk factor for omissions or dosing errors.

Discussion

This study examined the frequency and types of PICU prescribing errors and found 18% administrative errors, 53% omissions and 12% dosing errors. Other PICU studies report rates of about 10% up to about 80%.[11,12,24-26] None of these studies though, examined risk factors for these errors. This study identified writing by hand, alterations in prescribed medication, intermittent dosing and 'on demand use' as most important risk factors. Based on these results, several recommendations can be made on what CPOE/CDS systems should focus on to prevent PICU prescribing errors.

First, all medication should be electronically ordered, as writing by hand was the strongest risk factor by far. Several previous studies in PICUs have shown that implementing a CPOE system helps to enhance legibility and completeness of medication orders.[10-12,27]

Nonetheless, even if medication is electronically ordered, omissions occur: in this study more than 25% of the electronic orders was incomplete (data not shown). This is due to the possibility to enter free text into the CPOE system. Free text entry should be minimized to prevent omissions for two reasons. First, an unclear or incomplete medication order may lead to drug name confusion, misunderstanding of abbreviations etc., which in turn may lead to errors in the execution of the order by pharmacy or nurse, potentially leading to patient harm.[28, 29] In the second place, an order has to be complete for the purpose of dose checking, or at least contain those elements relevant to dose checking. In other words, CDS regarding dose checking can only function if free text

entry is minimized. Minimization of free text entry has been recommended previously for general pediatric units[30], and this recommendation is repeated here specifically for the PICU.

Also, CPOE for PICUs should be designed such that fast and easy alteration of intravenous infusion pump flow rates is possible. This study showed that alterations in existing medication orders led to errors rather than new orders did. These alterations mainly concerned handwritten adjustments of infusion pump flow rates. Clinicians tended to write these adjustments down because, at the time of this study, the CPOE system did not easily facilitate this. In a critical care environment though, patients are mainly treated with intravenous drugs and flow rates are often adjusted. CPOE systems are challenged to support the complexity of ordering such infusions while attaining easy order entry.[31,32] In this context, CPOE/CDS tailored to a specific pediatric critical care process has already been shown to be useful in resuscitation medication orders: Vardi et al. reported a 100% error reduction and a significant profit in prescribing time by computerizing the ordering of resuscitation medications.[27]

Next, specific decision support for intermittent dosing regimens, corresponding routes of administration and dosage forms should be provided, as intermittent medication was identified as risk factor for omissions and dosing errors. This is underlined by the finding that all routes of administration related to intermittent dosing, e.g. oral, rectal and pulmonary, were risk factors for omissions and dosing errors compared to the parenteral route (data not shown). Additionally, this study showed that almost 25% of the omissions concerned an unclear/absent dosage form. Dosage form is important to pay attention to in a PICU setting, because children have specific needs (e.g. oral liquids versus solids as suitable dosage form), because medication is often administered through nasogastric tubes and because dosing regimens may differ per dosage form.

Finally, CDS regarding dosing should include both drugs from existing pediatric formularies/handbooks *and* off label drugs. In this study, if a prescribed drug was not mentioned in the used dosing guidelines, the risk of an incomplete order was elevated. Also, 1.4% of the medication orders could not be reviewed because the prescribed drug was not mentioned in the used dosing guidelines. The importance of using suitable dosing guidelines for designing CDS regarding dosing has already been noted for adult and pediatric health care[30,33] and this study emphasizes the need to include dosing information on off-label drugs as well.

Other studies have also made recommendations on preventing prescribing errors in PICUs, using technical or non-technical interventions. For example, Kadmon et al. also concluded that CPOE in a PICU has to be accompanied by CDS that checks medication dosages to significantly reduce prescribing error rates.[12] Kadmon's study though was limited to overdosing and this study adds that prevention of underdosing also has to be incorporated in CDS as the number of dosages below guideline recommendations was significant. Both Alagha et al. and Cunningham recently showed that non-technical interventions such as clinical pharmacist's activities, improving physician-nurse communication, physician drug knowledge and awareness of errors, were effective in reducing PICU prescribing errors, underlining the importance of human factor in the medication process.[26,34]

In order to study prescribing errors, they have to be defined and classified. Many different definitions and classifications have been used.[35] A reason for this may be that the objective of the study influences the definition and classification: prescribing errors may be examined from the perspective of outcome of the patient (e.g. mortality, morbidity) or from the perspective of the process of prescribing (e.g. composing the prescription, decision making).[35] But the setting of the study should also be taken into account; the setting determines both the composition of the prescription and the decision making of its therapeutic content. In the setting of the studied PICU three types of prescriptions were recognized, each comprising of different elements: prescriptions for continuous intravenous medication, for an alteration in infusion pump flow rate and for intermittently dosed medication (appendix 3). Thus, determination whether a prescription contains an omission, depends on the type of prescription.

Even more challenging is to evaluate decision making of the therapeutic content, i.e. determine dosing and therapeutic errors. In the first place, the therapeutic content of a prescription may be correct in a PICU setting, but erroneous in a non-PICU setting, e.g. dosage of anaesthetics. In the second place, a prescription has to be complete, or at least contain certain essential elements, to be able to be reviewed for these kind of errors. In this study only 58% of the prescriptions could be reviewed for dosing errors because the remainder lacked information. To our knowledge, this is the first study that addresses this important distinction between prescriptions that can and cannot be reviewed. Thus, CDS for dosing requires that all prescriptions are properly composed and complete.

This study has its limitations. First, it has limited generalizability as the studied CPOE system is used in the PICU of the Wilhelmina Children's Hospital only. Second, inter-rater variability may have influenced the results, because prescribing error identification rates vary depending on the kind of health care provider that identifies them.[36] Because medication order review was performed strictly according to protocol, inter-rater variability is considered to be minimal. Another limitation could be that *actual* consequences of the prescribing errors were not studied. But, as mentioned by Tully, knowledge about *potential* for harm, can be used to improve health care systems in the same way as can knowledge about *actual* harm.[35] Above that, several studies have shown that, even if errors do not have potential for harm, they still can influence efficiency and workflow.[37,38]

Development of pediatric-specific CPOE and CDS systems tailored to meet the specific needs of pediatric settings is critical to the success of these systems.[39] Above that, intensive care has unique requirements leading to the need for research to inform the design and management of CPOE and CDS systems in such a setting.[40] This study can help to specify requirements to build such a system.

Conclusions

PICU prescribing errors frequently occur. CPOE systems minimize administrative errors and omissions, but do not adequately prevent dosing errors if the system does not include extensive CDS. To prevent dosing errors CDS should focus on alterations in medication orders and on intermittently dosed medication, the corresponding routes of administration and dosage forms. Furthermore, free-text entry should be minimised, fast and easy alteration of infusion pump flow rates facilitated and dose checking for both under- and overdosing integrated using a suitable PICU drug formulary including off label drugs. Future research should focus on electronic CDS development, taking into account that CDS can only be designed if CPOE warrants properly composed and complete medication orders.

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References

1 Lisby M, Nielsen LP, Brock B, et al. How are medication errors defined? A systematic literature review of definitions and characteristics. Int J Qual Health Care 2010;22:507-18.

2 Barber N, Rawlins M, Dean Franklin B. Reducing prescribing error: competence, control, and culture. Qual Saf Health Care 2003;12 Suppl 1:i29-32.

3 Routledge PA. Safe prescribing: a titanic challenge. Br J Clin Pharmacol 2012;74:676-84.

4 Schachter M. The epidemiology of medication errors: how many, how serious? Br J Clin Pharmacol 2009;67:621-23.

5 Colpaert K, Decruyenaere J. Computerized physician order entry in critical care. Best Pract Res Clin Anaesthesiol 2009;23:27-38.

6 Latif A, Rawat N, Pustavoitau A, et al. National study on the distribution, causes and consequences of voluntarily reported medication errors between the ICU and non-ICU settings. Crit Care Med 2013;41:389-98.

7 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114-20.

8 Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:85-90.

9 McDonnell C, Hum S, Frndova H, et al. Pharmacotherapy in pediatric critical illness: a prospective observational study. Paediatr Drugs 2009;11:323-31.

10 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

11 Warrick C, Naik H, Avis S, et al. A clinical information system reduces medication errors in paediatric intensive care. Intensive Care Med 2011;37:691-4.

12 Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a PICU. Pediatrics 2009;124:935-40.

13 Pediatric Intensive Care Evaluation. Available at: http://www.pice.nl [Accessed 1 October 2013].

14 National Coordinating Council for Medication Error Reporting and Prevention. About Medication Errors. Available at: http://www.nccmerp.org [Accessed 1 October 2013].

15 van den Bemt PM, Egberts AC. Drug-related problems: definitions and classification. EJHP Practice 2007;13:62-4.

16 Fijn R, Van den Bemt PM, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol 2002;53:326-331.

17 Dean B, Barber N, Schachter M. What is a prescribing error? Qual Health Care 2000;9:232-7.

18 Nederlands Kenniscentrum Farmacotherapie bij Kinderen. Available at: http://www.kinderformularium.nl [Accessed 1 October 2013].

19 Rademaker CMA: Geneesmiddelformularium voor kinderen. Wilhelmina Kinderziekenhuis Utrecht, Universitair Medisch Centrum Utrecht; 2008.

20 BMJ Group: British National Formulary for Children 2010-2011. Pharmaceutical Press, London; 2010.
21 American Pharmacists Association: Pediatric Dosage Handbook 15th edition. Lexi-Comp, Hudson; 2008.
22 Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29:278-85.
23 Pollack M, Ruttimann U, Getson P. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110-6.
24 Cimino MA, Kirschbaum MS, Brodsky L, et al. Assessing medication presribing errors in pediatric intensive care units. Pediatr Crit Care Med 2004;5:124-132.
25 Buckley MS, Erstad BL, Kopp BJ, et al. Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. Pediatr Crit Care Med 2007;8:145-52.
26 Alagha HZ, Badary OA, Ibrahim HM, et al. Reducing prescribing errors in the paediatric intensive care unit: an experience from Egypt. Acta Paediatr 2011;100:e169-74.
27 Vardi A, Efrati O, Levin I, et al. Prevention of potential errors in resuscitation medications orders by means of a computerised physician order entry in paediatric critical care. Resuscitation 2007;73:400-6.
28 Aronson JK. Confusion over similar drugnames. Problems and solutions. Drug Saf 1995;12:155-60.
29 Dooley MJ, Wiseman M, Gu G. Prevalence of error-prone abbreviations used in medication prescribing for hospitalised patients: multi-hospital evaluation. Intern Med J 2012;42:e19-22.
30 Maat B, Au YS, Bollen CW, et al. Clinical pharmacy interventions in paediatric electronic prescriptions. Arch Dis Child 2013;98:222-7.
31 Vaidya V. CPOE revisited: a computerized calculator for continuous medication infusions. Pediatr Crit Care Med 2006;7:282-3.
32 Lehmann CU, Kim GR, Gujral R, et al. Decreasing errors in pediatric continuous intravenous infusions. Pediatr Crit Care Med 2006;7:225-30.
33 Coleman JJ, Nwulu U, Ferner RE. Decision support for sensible dosing in electronic prescribing systems. J Clin Pharm Ther 2012;37:415-9.
34 Cunningham KJ. Analysis of clinical interventions and the impact of pediatric pharmacists on medication error prevention in a teaching hospital. J Pediatr Pharmacol Ther 2012;17:365-73.
35 Tully MP. Prescribing errors in hospital practice. Br J Clin Pharmacol 2012;74:668-75.
36 van Doormaal JE, Mol PG, van den Bemt PM, et al. Reliability of the assessment of preventable adverse drug events in daily clinical practice. Pharmacoepidemiol Drug Saf 2008;17:645-54.
37 Ali NA, Mekhjian HS, Kuehn PL, et al. Specificity of computerized physician order entry has a significant effect on the efficiency of workflow for critically ill patients. Crit Care Med 2005;33:110-4.
38 Chapman AK, Lehmann CU, Donohue PK, et al. Implementation of computerized provider order entry in a neonatal intensive care unit: impact on admission workflow. Int J Med Inform 2012;81:291-5.
39 Kim GR, Lehmann CU and the Council on Clinical Information Technology. Pediatric aspects of inpatient health information technology systems. Pediatrics 2008;122:e1287-96.

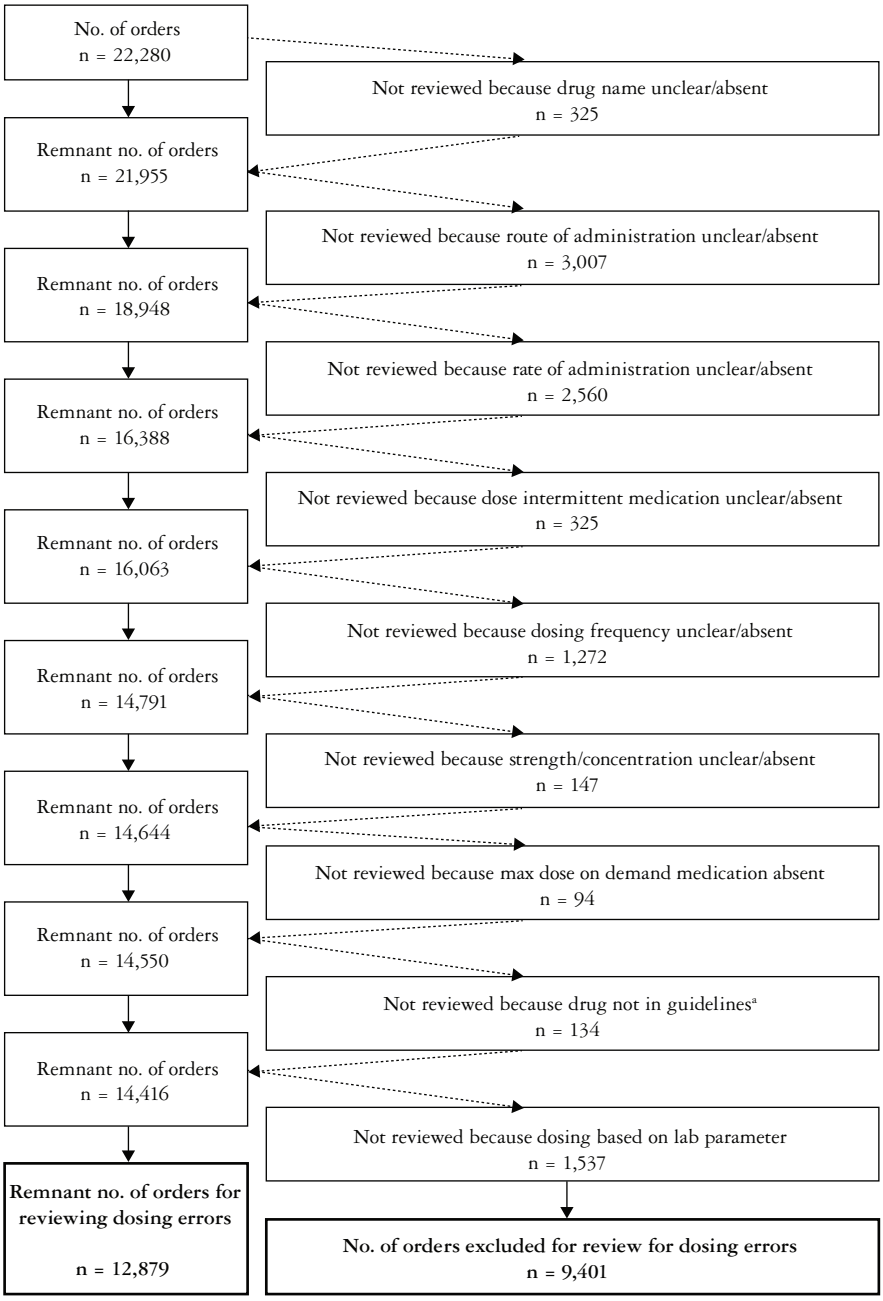
40 Maslove DM, Rizk N, Lowe HJ. Computerized physician order entry in the critical care environment: a review of the current literature. J Intensive Care Med 2011;26:165-71.

Appendix 1 Definition and classification of prescribing errors.

Definition		
Prescribing error	An incomplete or incorrect medication order that may have the potential to result in adverse clinical consequences if executed as prescribed	
Classification		**Sub classification**
Administrative error	Mandatory administrative component unclear or absent from medication order	Prescriber data unclear/absent (Partly) illegible
Omission[a]		
Drug-related	Mandatory component of prescribed drug unclear or absent from medication order	Drug name unclear/absent Strength/concentration unclear/absent Dosage form unclear/absent Unauthorized drug name abbreviations
Dosing regimen-related	Mandatory component of prescribed dosing regimen unclear or absent from medication order	Frequency unclear/absent Dose unclear/absent Route of administration unclear/absent Time(s) of administration unclear/absent Unit(s) unclear/absent
Dosing error	Drug- or dosing regimen-related component of medication order incorrect	Frequency below or above therapeutic range Dose > 10% below or above therapeutic range Drug name incorrect Strength/concentration incorrect Route of administration inconsistent with dosage form Units incorrect
Therapeutic error		Indication Contra-indication Allergy Monitoring Drug-drug interaction Incorrect mono-therapy/therapy missing Duplicate therapy

[a] To be able to review the collected medication orders for omissions, three types of PICU medication orders were distinguished: orders for continuous intravenous (i.v.) medication, for an alteration in infusion pump flow rate of continuous i.v. medication and for intermittent medication. Depending on the type of medication order, each order had to be composed of certain components to be considered complete and clear. Electronic supplement 1B gives an overview of these three types of medication orders and their mandatory components.

Appendix 2 Determination of medication orders reviewed for dosing errors.



[a] Dutch National Children's Formulary, Wilhelmina Children's Hospital drug formulary, local PICU dosing rules and treatment protocols, British National Formulary for Children or US' Pediatric Dosage Handbook

Appendix 3 Types of PICU prescriptions and their mandatory components.

Prescription type	Mandatory components	Examples
continuous i.v. medication	– drug – amount of drug – volume and type of solvent to dissolve the amount of drug in – infusion pump flow rate (in mL/hr) – rate of administration (in dose/kg bodyweight/time unit) – prescriber's initials or signature – units	morphine 4 mg in 50 mL NaCl 0.9% 0.3 mL/hr (= 0.16 mg/kg/day) milrinone 5 mg in 50 mL dextrose 10% 1 mL/hr (= 0.57 mcg/kg/min)
alteration in infusion pump flow rate	– time of change in infusion pump flow rate – drug – new infusion pump flow rate (in mL/hr) – new rate of administration (in dose/kg bodyweight/time unit) – prescriber's initials or signature – units	15:25 morphine 0.4 mL/hr (= 0.21 mg/kg/day) 01:50 milrinone 2 mL/hr (= 1.14 mcg/kg/min)
intermittent medication	– drug – strength/concentration – dose – administration route – administration frequency – administration time(s) – prescriber's initials or signature – if relevant, dose run time and solvent – maximum use of on demand medication – units	frusemide 2mg/capsule 2 dd 6 mg p.o. at 10:00 and 22:00 dexamethasone 4 mg/mL 4 dd 1 mg i.v. at 06:00, 12:00, 18:00 and 24:00

Chapter 3

Drug-drug interactions in pediatric intensive care patients

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Submitted

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Abstract

Purpose Data on the occurrence, potential consequences and advised risk management of potential drug-drug interactions in pediatric intensive care units are very limited. This study examined frequency and types of pDDIs in a PICU.

Methods Retrospective observational study at a Dutch tertiary children's hospital. PICU patients 0-18 years with at least two medication orders hospitalized between February 2011 and October 2013 were included. Per patient overlapping drug treatment episodes were checked for pDDIs using the national DDI management guideline. Frequency and types of pDDIs were assessed, including potential consequences and advised management strategies. If the latter implied monitoring, it was verified whether this was actually performed. Using Lexi-Interact™ and Micromedex® additional pDDIs involving PICU-specific high-risk drugs were assessed.

Results 1,996 patients accounting for 8,502 PICU-days and 17,141 drug treatment episodes were included. For 19.4% of patients at least one pDDI was identified (0.54 (95% CI 0.46-0.62) pDDIs per patient). One or more pDDIs were present during 3,346 (40%) of PICU-days. 72% potentially resulted in side effects/toxicity, 27% potentially in decreased therapy efficacy. Guidelines stated that 95% should be managed by monitoring (75%) and/or therapy adjustment (82%). Identified pDDIs should have led to 1,131 monitoring values: 72% was actually measured. The Dutch guideline identified 1,078 pDDIs; Lexi-Interact™ and Micromedex® an additional 2,557 pDDIs involving PICU-specific high-risk drugs.

Conclusions pDDIs frequently occur in PICU patients and often include high-risk drugs. Most DDIs potentially result in toxicity and can be managed by monitoring. However, required monitoring is often not performed, unless part of routine. Advanced clinical decision support may improve this and should be focus of future studies.

Introduction

Drug-drug interactions (DDIs) may result in decreased or increased effects of drugs leading to therapy failure or toxicity. In hospitalized patients it is estimated that 17% of all adverse drug events (ADEs) are caused by a DDI and that approximately 1% of patients experiences an ADE due to a DDI.[1]

Pediatric intensive care unit (PICU) patients are even more likely to experience a DDI and consequent harm for two main reasons. First, they are mostly severely ill, often have multiple complex health problems and their capacity to cope with physiological disturbances is diminished. Second, they are treated with numerous, often high-risk, drugs,[2,3] which is important because polypharmacy and drugs with a narrow therapeutic range are well-known risk factors for DDIs and consequent ADEs.[4] Additionally, prescribing, and especially dosing drugs for children is considered more complex than for adults and children may be at higher risk for complications of ADEs.[5] On the other hand, the PICU environment may partly protect patients from harm by DDIs as a result of continuous monitoring and bedside biomarker testing.

ADEs due to DDIs in the PICU may be predicted and prevented by detecting potential DDIs (pDDIs) at the stage of ordering. However, data on the occurrence, potential consequences and advised risk management of pDDIs in PICUs are very limited. Therefore, the objective of this study was to examine the frequency and types of pDDIs, their potential clinical consequences and management strategies, in a PICU.

Materials and Methods

Setting

This study was conducted at the 14 bed PICU of the 220 bed Wilhelmina Children's Hospital, which is part of the University Medical Center Utrecht, a tertiary care teaching hospital in The Netherlands. In January 2001 a homegrown computerized physician order entry (CPOE) system was introduced on the PICU. Every clinician is trained how to use the system in a face to face introduction by a medical staff member before being permitted to prescribe. To prescribe drugs, the clinician enters standard fields, e.g. drug, dose, dosing regimen and route of administration, using dropdown menus. Suitable dosing ranges are visible during prescribing. The CPOE system does not include clinical decision support (CDS) that enables automated checking for e.g. drug allergy, duplicate therapy or DDIs.

Study population and study design

The study population consisted of patients between 0 and 18 years for whom at least two medication orders were prescribed during PICU stay, admitted to the PICU between 1 February 2011 and

1 October 2013. If a patient was admitted more than once during the study period, he or she was considered a new patient at every admission.
Frequency and types of pDDIs were determined using a retrospective cohort design. The study was in accordance with the Institutional Review Board guidelines.

Data collection

Medication orders of all included patients were extracted from the medication administration record of the PICUs electronic Patient Data Management System (ePDMS; Metavision; iMDsoft, Sassenheim, The Netherlands). A medication order was defined as a direction for a pharmacological active substance, i.e. a therapeutic or corrective agent, electronically ordered by a clinician (pediatric intensivist or resident). Orders for (par)enteral feeding, standard glucose/saline electrolyte solutions and heparin/saline flushes for clearing out intravenous lines were excluded.
Length of PICU stay, type and urgency of admission, severity of illness scores, ventilated or not and if so duration of ventilation and PICU survival were extracted from the Pediatric Intensive Care Evaluation (PICE) database. The PICE database is a Dutch national data registration project that contains patient data from all Dutch PICUs to evaluate and compare quality of care.[6] Patients that were not found in the PICE database were excluded from the study (n = 24).

pDDIs – Dutch guideline

A pDDI was defined as an overlapping drug treatment episode of two interacting drugs. Based on start- and stop dates and -times of each drug, overlapping drug treatment episodes per patient were constructed. These overlapping drug treatment episodes were electronically checked for pDDIs using the Dutch national guideline for DDI management ('G-Standaard' November 2013). This guideline provides evidence based DDI management including an indication of clinical importance and quality of evidence per DDI and is described in detail elsewhere.[7] Potential clinical consequences, e.g. increased toxicity or decreased efficacy, and by the guideline advised risk management strategies, e.g. laboratory monitoring or dose adjustment, were registered for every pDDI. Only pharmacokinetic and pharmacodynamic DDIs that potentially led to relevant clinical effects and/or potentially required alteration in therapy were included. Intravenous drug incompatibilities (interactions between intraveanous drug fluids) were excluded. For all pDDIs, it was assessed which drugs and drug classes were involved. It was also registered whether the involved drugs were on the list of high-alert medications of the Institute for Safe Medication Practices (ISMP)[8] and/or on a PICU-specific high-alert medications list.[3]

pDDIs – international guidelines

Because the Dutch national guideline for DDI management may not include certain DDIs relevant to the PICU setting and because it is well known that generally used DDI databases lack congruence,[9] overlapping drug treatment episodes were also checked for PICU-specific pDDIs

mentioned in Lexi-Interact™ and Micromedex® but missing in the Dutch guideline.[10,11] For this purpose a list of high-risk PICU-specific drugs was composed using the list of high-alert medications of the ISMP[8] and a PICU-specific high-alert medications list[3]: alprostadil, alteplase, atracurium, clonidine, dopamine, dobutamine, epinephrine, (es)ketamine, fentanyl, milrinone, nitroprusside, norepinephrine, phenylephrine, propofol, rocuronium and sufentanyl. Each of the selected drugs constituted at least 1% of all medication orders. Lexi-Interact™ and Micromedex® were checked for DDIs involving these drugs but missing in the Dutch guideline. Consequently, the number of patients that had these DDIs among their overlapping drug treatment episodes was determined. Again, only DDIs that potentially led to relevant clinical effects and/or potentially required alteration in therapy were included: i.e. Lexi-Interact™ risk ratings C (monitor therapy), D (consider therapy modification) and X (avoid combination), Micromedex® severity scores moderate, major and contraindicated.

Monitoring

If the recommended management strategy for a pDDI concerned laboratory monitoring, recording an electrocardiogram (ECG) and/or measuring blood pressure, it was verified whether this was actually performed during the overlapping drug treatment episode or thereafter until discharge. Laboratory monitoring data were extracted from the Utrecht Patient Oriented Database (UPOD), a large University Medical Center Utrecht database that links administrative, laboratory and medical patient data.[12] Data on ECG recordings and blood pressure measurements were extracted from ePDMS.

Data analysis

The measure of outcome was the frequency of pDDIs, expressed as (i) number of patients with at least one pDDI, (ii) number of pDDIs per patient and (iii) number of PICU-days with at least one pDDI.

The types of pDDIs were described by listing the occurring pDDIs, the drug classes and drugs involved, their potential clinical consequences and advised risk management strategies. pDDIs that should be avoided entirely according to the guidelines' advised risk management strategies were listed seperately.

Data were processed with MS Excel 2003 and statistically analyzed using SPSS version 20.0.

Results

During the 32 months study period 1,996 admitted patients accounting for 8,502 PICU-days and 17,141 drug treatment episodes were included. Table 1 shows the patient characteristics. The study population included more males (56%) than females and largely consisted of surgical patients (63%). Most admissions concerned elective hospitalizations (59%).

Table 1 Patient characteristics (February 2011 – October 2013).

Patient characteristics, n = 1,996[a]	
Female – n (%)	870 (43.6)
Age – median (range) in years	1.8 (0 – 18.7)
Length of PICU stay – median (range) in days	1.4 (1 – 203)
Type of admission – n (%)	
– medical	746 (37.4)
– surgical	1,250 (62.6)
Urgency of admission – n (%)	
– elective	1,169 (58.6)
– emergency	827 (41.4)
Severity of illness scores	
– PIM2 at admission – median (range)	-4.28 (-8.41 – 4.66)
– PRISMII at admission – median (range)	7 (0 – 50)
Ventilation	
– no. of ventilated patients – n (%)	1,326 (66.4)
– duration – median (range) in days	2.0 (1 – 158)
Deceased – n (%)	57 (2.9)

[a]n = 1,996 admissions of n = 1,581 individual patients.
PIM 2 pediatric index of mortality 2 score
PRISM II pediatric risk of mortality II score

pDDI frequency

At least one pDDI was identified in 387 patients (19.4%) with a mean number of 2.8 (95% CI 2.5-3.1) pDDIs per patient (range 1 – 24). The mean number of pDDIs per all admitted patients was 0.54 (95% CI 0.46-0.62). One or more pDDIs were present during 3,346 (40%) of all PICU-days. In total 1,078 pDDIs (6.3% of drug treatment episodes) were identified. Table 2 shows the 20 most often identified pDDIs ranked according to number of patients with a pDDI in the left panel and ranked according to number of PICU-days with a pDDI in the right panel.

pDDI types

Of the 358 pDDI types in the Dutch national guideline for DDI management 64 (18%) occurred on the studied PICU. The five most frequent were: potassium salt + potassium sparing diuretic (170 (15.8%)), renin angiotensin system (RAS) inhibitor + potassium salt/potassium-sparing agent (127 (11.8%)), RAS inhibitor + diuretic (101 (9.4%)), QT drug + QT drug (90 (8.3%)) and diuretic + NSAID (74 (6.9%)). Most commonly involved drug classes concerned diuretics (23%), agents acting on RAS (11%), mineral supplements (10%), antibacterials for systemic use (10%), antithrombotic agents (8%), antiepileptics (7%), psycholeptics (7%), drugs for functional gastrointestinal disorders (4%), corticosteroids for systemic use (4%) and cardiac therapy (3%). Of

Table 2 Frequencies and types of pDDIs – top 20 ranked according to number of patients (left) versus number of PICU-days (right).

pDDI top 20, ranked according to no. of patients with pDDI	No. of patients (%)	pDDI top 20, ranked according to no. of PICU-days with pDDI	No. of PICU-days (%)
Potassium salt + potassium sparing diuretic	161 (8.1)	Potassium salt + potassium sparing diuretic	1,534 (18.0)
RAS inhibitor + potassium salt or potassium-sparing agent	83 (4.2)	QT drug + QT drug	1,488 (17.5)
RAS inhibitor + diuretic	82 (4.1)	Midazolam/alprazolam + CYP3A4 inhibitor	959 (11.3)
QT drug + QT drug	53 (2.7)	RAS inhibitor + potassium salt or potassium-sparing agent	921 (10.8)
Midazolam/alprazolam + enzyme inducer	46 (2.3)	Coumarin + antibiotic*	820 (9.6)
Midazolam/alprazolam + CYP3A4 inhibitor	43 (2.2)	RAS inhibitor + diuretic	745 (8.8)
Diuretic + NSAID	37 (1.9)	Trimethoprim + RAS inhibitor/spironolactone	672 (7.9)
Corticosteroid + enzyme inducer	29 (1.5)	Midazolam/alprazolam + enzyme inducer	653 (7.7)
Dopaminergic drug + antiemetic drug (antidopaminergic)	28 (1.4)	Acetazolamide + diuretic (potassium depleting)	633 (7.4)
NSAID + corticosteroid	26 (1.3)	Diuretic + NSAID	539 (6.3)
Coumarin + antibiotic*	24 (1.2)	Dopaminergic drug + antiemetic drug (antidopaminergic)	463 (5.4)
Acetazolamide + diuretic (potassium depleting)	23 (1.2)	Corticosteroid + enzyme inducer	435 (5.1)
Trimethoprim + RAS inhibitor/spironolactone	23 (1.2)	NSAID + corticosteroid	203 (2.4)
Epinephrine + beta blocker (non)selective	11 (0.6)	Dopaminergic drug + antipsychotic drug	190 (2.2)
Ciclosporin + CYP3A4 inhibitor	11 (0.6)	Sildenafil + CYP3A4 inhibitor/ciprofloxacin	182 (2.1)
Coumarin + (es)omeprazole	11 (0.6)	Coumarin + (es)omeprazole	149 (1.8)
Dopaminergic drug + antipsychotic drug	10 (0.5)	Ciclosporin + CYP3A4 inhibitor	142 (1.7)
Ciclosporin + nephrotoxic drug	9 (0.5)	Ciclosporin + nephrotoxic drug	118 (1.4)
Beta blocker + NSAID	8 (0.4)	Coumarin + carbamazepine/barbiturate	97 (1.1)
RAS inhibitor + NSAID	8 (0.4)	Topiramate + enzyme inducer	78 (0.9)

*excl. cotrimoxazole, metronidazole, cefamandole
RAS = renin angiotensin system
NSAID = non-steroidal anti-inflammatory drug
CYP = cytochrome P 450

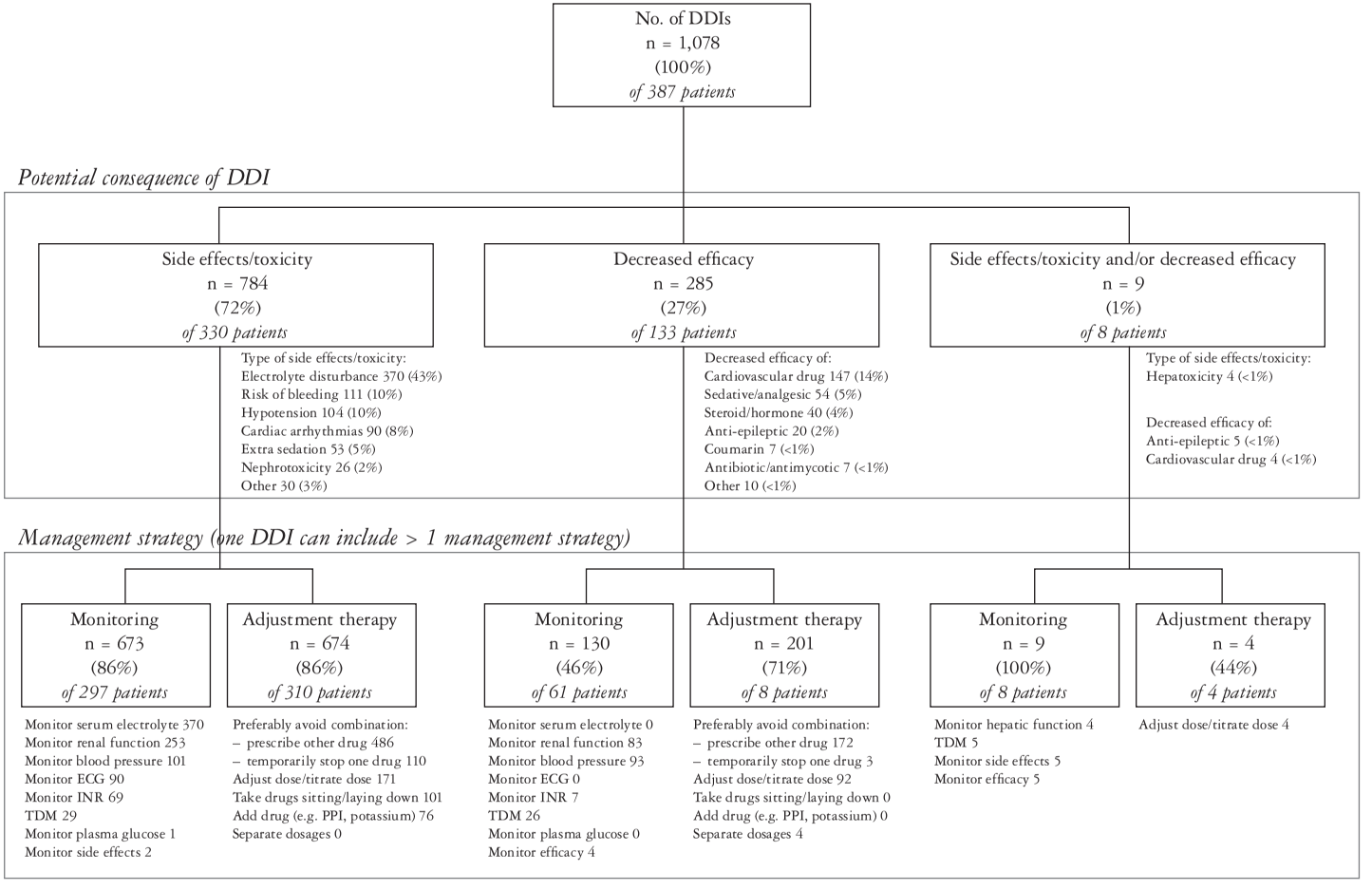

Figure 1 Potential consequences and management strategies of the identified DDIs.

the 105 different drugs involved in the identified pDDIs 36 (34%) were on the list of high-alert medications of the ISMP[8] and/or on a PICU-specific high-alert medications list[3].
As shown in figure 1, of the 1,078 pDDIs in this study, the largest part potentially resulted in side effects/toxicity (72%) rather than decreased therapy efficacy (27%), most frequent potential consequences being electrolyte disturbances (34%), decreased efficacy of cardiovascular drugs (14%) and risk of bleeding (10%). According to the Dutch guidelines' advised risk management strategies, most pDDIs concerned drug combinations that should preferably be avoided, but can be managed by monitoring (75%) and/or therapy adjustment (82%) (see figure 1). Nonetheless, 53 (5%) pDDIs should have been avoided entirely (see table 3). For an overview of all observed pDDIs, their frequency, potential consequences and advised management strategies, see appendix 1.

DDIs from international guidelines

Lexi-Interact™ and Micromedex® were checked for pDDIs involving high-risk PICU-specific drugs but missing in the Dutch guideline: 288 additional pDDI types were found (147 in Lexi-Interact™ and 141 in Micromedex®, respectively). Of these, 85 (30%) types actually occurred at least once in the study cohort: 55 were from Lexi-Interact™, 19 from Micromedex® and 11 from both. Appendix 2 shows the number of patients per pDDI type, including sources, severity scores and potential consequences. In total, 2,557 additional pDDIs were counted among the studied patients. Almost 90% of these were rated as moderate by Micromedex® and/or C (monitor therapy) by Lexi-Interact™. One pDDI was contraindicated (fentanyl + CYP3A4 inhibitor), see table 3. Clonidine dominates the list (39%), followed by fentanyl (11%), rocuronium (10%) and norepinephrine (8%), respectively.

Monitoring

According to the Dutch guidelines, 39 (61%) of the 64 different pDDI types in this study should be monitored by measuring one or more laboratory value, recording an ECG and/or measuring blood pressure. In total, the 1,078 DDIs should have led to 1,131 observations of which 817 (72%) were actually measured. Table 4 shows the types and frequencies of monitoring management strategies potentially and actually performed. Least performed were monitoring of renal function (27%) and drug level determination (35%).
Additionally, 7 (11%) of the pDDI types included a management strategy that advised risk factor monitoring for potential clinical consequence of the pDDI: laboratory values and/or blood pressure can be measured. In total, the 1,078 pDDIs should have led to 1,060 risk factor monitoring values of which 542 (51%) were actually measured.

Table 3 Frequencies and types of determined pDDIs that should be avoided entirely according to guidelines' advised risk management strategy.

pDDI (from Dutch guideline)	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%)*
Dopaminergic drug + antiemetic drug (antidopaminergic)	Decreased efficacy drugs	Avoid combination, prescribe other drug	30 (2.8)	28 (1.4)
Epinephrine + beta blocker (non)selective	Decreased efficacy epinephrine	Avoid combination, prescribe other drug Preferably avoid combination, prescribe other drug	13 (1.2)	11 (0.6)
Nitrate + phosphodiesterase inhibitor	Hypotension	Avoid combination, prescribe other drug	3 (0.3)	3 (0.2)
Coumarin + miconazole enteral/vaginal/cutaneous	Risk of bleeding (incl. GI ulcer)	Avoid combination, prescribe other drug	2 (0.2)	1 (<0.1)
Valproic acid + carbapenem	Decreased efficacy valproic acid	Avoid combination, prescribe other drug	2 (0.2)	2 (0.1)
Clopidogrel + (es)omeprazole	Decreased efficacy clopidogrel	Avoid combination, prescribe other drug	2 (0.2)	2 (0.1)
Betalactam antibiotic + tetracycline	Decreased efficacy betalactam/tetracycline	Avoid combination in serious infection such as meningitis, sepsis, endocarditis or in neutropenic patients, prescribe other drug	1 (<0.1)	1 (<0.1)
pDDI (from Micromedex®)	**Potential consequence**	**Management strategy**	**No. of pDDIs (%)**	**No. of patients (%)***
Fentanyl + CYP3A4 inhibitor	Increased risk of fentanyl toxicity	Contraindicated	NA	32 (1.6)

*a patient could experience a DDI type more than once
GI = gastrointestinal
CYP = cytochrome P 450
NA = not available

Table 4 Frequencies and types of monitoring management strategies potentially and actually performed.

Monitoring management strategy for potential clinical consequence of pDDI	pDDI (n)	No of measurements *potentially* performed	No of measurements *actually* performed (%)
ECG	QT drug + QT drug (90)	90	90 (100)
Blood pressure	RAS inhibitor + diuretic (101), Diuretic + NSAID (74), Beta blocker + NSAID (10), RAS inhibitor + NSAID (9)	194	194 (100)
Blood clotting time (INR)	Coumarin + antibiotic*(53), Coumarin + (es)omeprazole (13), Coumarin + carbamazepine/barbiturate (5), Coumarin + fluconazole/voriconazole (2), Coumarin + thyroid supplement (1), Coumarin + rifampicin/rifabutin (1), Coumarin + bosentan (1)	76	60 (79)
Serum potassium	Potassium salt + potassium sparing diuretic (170), RAS inhibitor + potassium salt or potassium-sparing agent (127), Acetazolamide + diuretic (potassium depleting) (36), Trimethoprim + RAS inhibitor/spironolactone (35)	368	357 (97)
Serum sodium	(Ox)carbamazepine + diuretic (2)	2	1 (50)
Plasma glucose	Beta blocker nonselective + insulin (1)	1	1 (100)
Renal function	RAS inhibitor + potassium salt or potassium-sparing agent (127), RAS inhibitor + diuretic (101), Diuretic + NSAID (74), Ciclosporin + CYP3A4 inhibitor (13), Ciclosporin + nephrotoxic drug (10), RAS inhibitor + NSAID (9), Ciclosporin + cotrimoxazole/trimethoprim (2)	336	90 (27)
Hepatic function	Bosentan + sildenafil (4)	4	3 (75)
Drug level (TDM)	Ciclosporin + CYP3A4 inhibitor (13), Lamotrigine + enzyme inducer**(8), Topiramate + enzyme inducer (8), Haloperidol + enzyme inducer (7), Phenytoin + enzyme inhibitor (6), Clobazam/valproic acid + stiripentol (3), Phenobarbital + valproic acid (2), Phenytoin + cotrimoxazole/trimethoprim/sulphonamide (2), Quetiapine + CYP3A4 inhibitor (2), Digoxin + amiodarone (1), Ciclosporin + enzyme inducer (1), Phenytoin + valproic acid (1), Tacrolimus + CYP3A4 inhibitor (1), Lamotrigine + valproic acid (1), Phenytoin + chemotherapeutic agent (1), Phenytoin + folic acid (1), Carbamazepine/phenobarbital/phenytoin + stiripentol (1), Zonisamide + enzyme inducer (1)	60	21 (35)
Total		1,131	817 (72)

Table 4 Continued.

Monitoring management strategy for *risk factor* for potential clinical consequence of pDDI	pDDI (n)	No of measurements *potentially* performed	No of measurements *actually* performed (%)
Blood pressure	RAS inhibitor + diuretic (101)	101	101 (100)
Serum potassium	QT drug + QT drug (90)	90	85 (94)
Serum sodium	Diuretic + NSAID (74), RAS inhibitor + NSAID (9)	83	83 (100)
Serum calcium	QT drug + QT drug (90)	90	90 (100)
Serum magnesium	QT drug + QT drug (90)	90	59 (66)
Renal function	Potassium salt + potassium sparing diuretic (170), RAS inhibitor + potassium salt or potassium-sparing agent (127), RAS inhibitor + diuretic (101), QT drug + QT drug (90), Diuretic + NSAID (74), Trimethoprim + RAS inhibitor/spironolactone (35), RAS inhibitor + NSAID (9)	606	124 (20)
Total		1,060	542 (51)

INR = International Normalized Ratio TDM = therapeutic drug monitoring CYP = cytochrome P450 RAS = renin angiotensin system NSAID = non-steroidal anti-inflammatory drug

*excl. cotrimoxazole, metronidazole, cefamandole **excl. anticonceptives

Discussion

This study examined frequency and types of pDDIs in a PICU. In almost 20% of patients at least one pDDI was identified during admission and on 40% of all PICU-days at least one pDDI was present. The Dutch DDI guideline resulted in identification of 64 pDDI types in the study population. Searching for additional high-risk PICU-specific pDDIs from Lexi-Interact™ and Micromedex® led to an extra 85 pDDI types. Most pDDIs potentially caused toxicity rather than decreased therapy efficacy and could be managed by monitoring. However, only 72% of these monitoring measurements were actually performed.

Several earlier studies focused on DDIs in adult ICUs[10,13-23] and in pediatric settings[24-29] respectively, but none concentrated on PICUs. At a national level, the identified percentage of PICU patients with at least one pDDI (19%) was low in comparison to recently assessed percentages in adult ICU patients: 54% and 40%, respectively.[22,23] On the other hand, the percentage of PICU-days with at least one DDI was relatively high: 40% versus 27% and 34% of ICU-days, respectively.[22,23] Compared to the largest recent Dutch study on pediatric wards, this PICU study found a higher percentage of patients with one or more pDDIs: 19% versus 11%[26], as may be expected in a critical care setting that requires relatively many drugs per patient.

The most commonly involved drug classes largely corresponded to those in adult ICU studies[10,17,19-22] and pediatric studies.[25] Interestingly, one third of the drugs involved in the identified pDDIs were on the list of high-alert medications of the ISMP[8] and/or on a PICU-specific high-alert medications list.[3] This confirms that PICU patients are not only exposed to numerous, but also high-risk drugs and underlines the importance of insight into PICU-specific pDDIs to prevent consequent ADEs due to these high-risk drugs.

This study used the Dutch national guideline for DDI management as it is common practice in The Netherlands[7,22,23,26]. However, the pDDI frequencies reported above would have been higher if the identified pDDIs from widely used international guidelines, Lexi-Interact™ and Micromedex®, would have been included. Indeed, the number of *additional* pDDIs found using these databases (n = 2,557) was higher than the *total* number of pDDIs using the Dutch guideline (n = 1,078). This lack of congruence is an important finding as all these additional pDDIs involved high-risk PICU-specific drugs and may have serious consequences for the patient. Smithburger et al. compared Lexi-Interact™ to Micromedex® in the ICU setting and observed that each reference identified different numbers of pDDIs and disagreed on DDI severity ratings in almost 80% of the pDDIs.[10] It was concluded that the assessment of pDDIs in patient care should include more than one reference in order not to miss a potentially significant DDI.[10] This conclusion may be repeated here specifically for PICUs, as the frequency of pDDIs determined using the Dutch national guideline seems an underestimation.

On the other hand, the determined frequency may be an overestimation of DDIs that are actually relevant: only 8 out of 149 identified pDDI types from Dutch and international guidelines

should have been avoided entirely according to the advised risk management strategies. All other pDDI types would preferably have been avoided, but were probably accepted due to the need for treatment. The determined pDDI frequency may also be an overestimation of relevant DDIs, given the continuous intensive patient monitoring on a PICU. In the studied PICU population, blood pressure, ECG, serum potassium, serum sodium and plasma glucose were routinely monitored. If these parameters fluctuated, whether due to a DDI or not, this was detected and, if necessary, corrected. Important is to focus on those parameters that are not routinely monitored but should be monitored in case of certain pDDIs. For example, in this study, monitoring of renal function was performed in only 27% of drug combinations that required such, whilst impaired renal function may be a significant cause of drug- and metabolite accumulation or electrolyte disturbances and subsequent ADEs.[30] Other such parameters not monitored routinely but important for DDI management included INR, hepatic function, serum magnesium, serum calcium and drug levels. To prevent ADEs due to DDIs, CPOE systems often include CDS software that checks prescribed medication for pDDIs. However, electronic screening for DDIs is often not effective, due to generation of too many nonspecific and irrelevant alerts, lacking important clinical information.[4,25,31-34] Nonetheless, these systems are an important tool in mitigating medication errors. In relation to DDI risk management, electronic CDS should generate safety alerts, that fire in case of a DDI that may result in clinical consequences for the individual patient. The alert should warn the prescriber why and to what level the patient is at risk and advise a management strategy to reduce this risk to an acceptable level for that individual patient. To achieve this, DDI knowledgebases, that form the backbone of CDS for DDI risk management, need to take into account more patient-specific information.[33]

This study provides PICU patient-specific information and adds that setting-specific information should also be included for optimal DDI risk management. For example, CDS should take into account that required monitoring is performed, depending on whether the required monitoring is part of routine procedures or not, e.g. by employing (reminders for) corollary orders.[35] Two other setting-specifics that advanced CDS on a PICU should be able to manage are interactions between more than two drugs and between intravenous drug fluids. The former because of the numerous drugs prescribed on a PICU, for example important when several QT prolonging drugs are used. The latter because of the relatively many intravenously administered drugs leading to intravenous drug incompatibilities.[24,36]

This study may have its limitations. First, the Dutch national DDI guideline was primarily developed for adult medicine and for use in community pharmacies thus may not be suitable for use in a PICU. This was however accounted for by also using Lexi-Interact™ and Micromedex® for DDI assessment. Second, it was not studied whether the assessed pDDIs actually resulted in ADEs, as it is practically impossible to attribute clinical outcomes to pDDIs in complex and severely ill patients.

Nonetheless, this is the first study to give insight into PICU-specific DDIs, potential consequences and management thereof. It also provides information on what CDS for DDI management may enclose. Studies on the effect of CPOE/CDS on prescribing errors and consequent ADEs in PICUs have shown positive results.[37-39] Next step would be to study advanced CDS for DDI management in PICUs to achieve further evidence-based optimization of DDI risk management resulting in minimization of consequent ADEs in this vulnerable population.

Conclusions

pDDIs frequently occur in PICU patients and often include high-risk drugs. Most pDDIs potentially cause toxicity rather than decreased therapy efficacy and should preferably be avoided. If not avoidable, most pDDIs can be managed by monitoring and/or therapy adjustment. However, required monitoring is often not performed, unless part of routine. Sophisticated electronic CDS, linking laboratory data to prescribing data and automatically generating corollary orders for example, may improve this and should be the focus of future PICU DDI studies.

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References

1 Krähenbühl-Melcher A, Schlienger R, Lampert M, et al. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 2007;30:379-407.

2 McDonnell C, Hum S, Frndova H, et al. Pharmacotherapy in pediatric critical illness: a prospective observational study. Paediatr Drugs 2009;11:323-31.

3 Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:85-90.

4 Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin Drug Saf 2012;11:83-94.

5 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114-20.

6 Pediatric Intensive Care Evaluation. Available at: http://www.pice.nl [Accessed 17 October 2013].

7 van Roon EN, Flikweert S, le Comte M, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005;28:1131-39.

8 Institute for Safe Medication Practices ISMP's List of High-Alert Medications. Available at: https://www.ismp.org/tools/highalertmedications.pdf [Accessed 19 March 2014].

9 Smithburger PL, Kane-Gill SL, Seybert AL. Drug-drug interactions in cardiac and cardiothoracic intensive care units: an analysis of patients in an academic medical centre in the US. Drug Saf 2010;33:879-88.

10 Micromedex healthcare series. Interactions. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Updated periodically. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [Accessed 7 January 2014].

11 Up-to-Date. Lexi-Interact Online. Available at: http://www.uptodate.com/crlsql/interact/frameset.jsp [Accessed 7 January 2014].

12 ten Berg MJ, Huisman A, van den Bemt PM, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.

13 Romac DR, Albertson TE. Drug interactions in the intensive care unit. Clin Chest Med 1999;20:385-99,ix.

14 Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. Clin Pharmacokinet 2001;40:833-68.

15 Kopp BJ, Erstad BL, Allen ME, et al. Medication errors and adverse drug events in an intensive care unit: direct observation approach for detection. Crit Care Med 2006;34:415-25.

16 Nazari MA, Moqhadam NK. Evaluation of pharmacokinetic drug interactions in prescriptions of intensive care unit (ICU) in a teaching hospital. Iranian Journal of Pharmaceutical Research 2006;3:215-8.

17 Hammes JA, Pfuetzenreiter F, da Silveira F, et al. Potential drug interactions prevalence in intensive care units. Rev Bras Ter Intensiva 2008;20:349-54.

18 Spriet I, Meersseman W, de Hoon J, et al. Mini-series: II. clinical aspects. clinically relevant CYP450-mediated drug interactions in the ICU. Intensive Care Med 2009;35:603-12.
19 Lima RE, De Bortoli Cassiani SH. Potential drug interactions in intensive care patients at a teaching hospital. Rev Lat Am Enfermagem 2009;17:222-7.
20 Reis AM, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo) 2011;66:9-15.
21 Smithburger PL, Kane-Gill SL, Seybert AL. Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. Int J Pharm Pract 2012;20:402-8.
22 Askari M, Eslami S, Louws M, et al. Frequency and nature of drug-drug interactions in the intensive care unit. Pharmacoepidemiol Drug Saf 2013;22:430-7.
23 Uijtendaal EV, van Harssel LL, Hugenholtz GW, et al. Analysis of potential drug-drug interactions in medical intensive care unit patients. Pharmacotherapy 2014;34:213-9.
24 Baird-Lambert J, MacKintosh D. Clinically important drug interactions in pediatric practice. Indian J Pediatr 1986;53:19-23.
25 Martinbiancho J, Zuckermann J, Dos Santos L, et al. Profile of drug interactions in hospitalized children. Pharmacy Practice 2007;5:157-61.
26 Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, et al. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009;68:187-93.
27 Ruggiero A, Rizzo D, Mastrangelo S, et al. Interactions between antiepileptic and chemotherapeutic drugs in children with brain tumors: is it time to change treatment? Pediatr Blood Cancer 2010;54:193-8.
28 Qorraj-Bytyqi H, Hoxha R, Krasniqi S, et al. The incidence and clinical relevance of drug interactions in paediatrics. J Pharmacol Pharmacother 2012;3:304-7.
29 Manias E, Kinney S, Cranswick N, et al. Medication errors in hospitalized children. J Paediatr Child Health 2014;50:71-7.
30 Daschner M. Drug dosage in children with reduced renal function. Pediatr Nephrol 2005;20:1675-86.
31 Bottiger Y, Laine K, Andersson ML, et al. SFINX - A drug-drug interaction database designed for clinical decision support systems. Eur J Clin Pharmacol 2009;65:627-33.
32 Classen DC, Phansalkar S, Bates DW. Critical drug-drug interactions for use in electronic health records systems with computerized physician order entry: review of leading approaches. J Patient Saf 2011;7:61-5.
33 Smithburger PL, Buckley MS, Bejian S, et al. A critical evaluation of clinical decision support for the detection of drug-drug interactions. Expert Opin Drug Saf 2011;10:871-82.
34 Mille F, Schwartz C, Brion F, et al. Analysis of overridden alerts in a drug-drug interaction detection system. Int J Qual Health Care 2008;20:400-5.
35 Colpaert K, Decruyenaere J. Computerized physician order entry in critical care. Best Pract Res Clin Anaesthesiol 2009;23:27-38.

36 Bertsche T, Mayer Y, Stahl R, et al. Prevention of intravenous drug incompatibilities in an intensive care unit. Am J Health Syst Pharm 2008;65:1834-40.

37 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

38 Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a PICU. Pediatrics 2009;124:935-40.

39 Warrick C, Naik H, Avis S, et al. A clinical information system reduces medication errors in paediatric intensive care. Intensive Care Med 2011;37:691-4.

Appendix 1 Frequency and types of pDDIs identified using Dutch national guideline (February 2011 – October 2013).

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Potassium salt + potassium sparing diuretic	Electrolyte disturbance	Preferably avoid combination, prescribe other drug Monitor serum potassium – Risk factor management strategy: monitor renal function	170 (15.8)	161 (8.1)	1,534 (18.0)
RAS inhibitor + potassium salt or potassium-sparing agent	Electrolyte disturbance	Preferably avoid combination, prescribe other drug Monitor serum potassium Monitor renal function (serum creatinine) – Risk factor management strategy: monitor renal function	127 (11.8)	83 (4.2)	921 (10.8)
RAS inhibitor + diuretic	Hypotension	Preferably avoid combination, temporarily stop drug Monitor blood pressure Monitor renal function (serum creatinine) Adjust dose/titrate dose RAS inhibitor Take drugs sitting/laying down – Risk factor management strategy: monitor blood pressure – Risk factor management strategy: monitor renal function	101 (9.4)	82 (4.1)	745 (8.8)
QT drug + QT drug	Cardiac arrhythmias (incl. QT prolongation)	Preferably avoid combination, prescribe other drug Monitor ECG – Risk factor management strategy: monitor serum potassium, serum calcium and serum magnesium – Risk factor management strategy: monitor renal function	90 (8.3)	53 (2.7)	1,488 (17.5)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Diuretic + NSAID	Decreased efficacy diuretic	Preferably avoid combination, prescribe other drug Monitor blood pressure Monitor renal function (serum creatinine) – Risk factor management strategy: monitor renal function – Risk factor management strategy: monitor serum sodium	74 (6.9)	37 (1.9)	539 (6.3)
Midazolam/alprazolam + CYP3A4 inhibitor	Extra sedation	Preferably avoid combination, prescribe other drug Adjust dose/titrate dose midazolam/alprazolam	53 (4.9)	43 (2.2)	959 (11.3)
Coumarin + antibiotic*	Risk of bleeding (incl. GI ulcer)	Monitor blood clotting time (INR)	53 (4.9)	24 (1.2)	820 (9.6)
Midazolam/alprazolam + enzyme inducer	Decreased efficacy benzodiazepine	Preferably avoid combination, prescribe other drug Adjust dose/titrate dose midazolam/alprazolam	50 (4.6)	46 (2.3)	653 (7.7)
Corticosteroid + enzyme inducer	Decreased efficacy corticosteroid	Adjust dose/titrate dose corticosteroid	39 (3.6)	29 (1.5)	435 (5.1)
Acetazolamide + diuretic (potassium depleting)	Electrolyte disturbance	Monitor serum potassium Add potassium or potassium sparing therapy	36 (3.3)	23 (1.2)	633 (7.4)
Trimethoprim + RAS inhibitor/spironolactone	Electrolyte disturbance	Monitor serum potassium – Risk factor management strategy: monitor renal function	35 (3.2)	23 (1.2)	672 (7.9)
NSAID + corticosteroid	Risk of bleeding (incl. GI ulcer)	Add gastric protection (PPI)	34 (3.2)	26 (1.3)	203 (2.4)
Dopaminergic drug + antiemetic drug (antidopaminergic)	Decreased efficacy drugs	Avoid combination, prescribe other drug	30 (2.8)	28 (1.4)	463 (5.4)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Epinephrine + beta blocker nonselective Epinephrine + beta blocker selective	Decreased efficacy epinephrine	Avoid combination, prescribe other drug Preferably avoid combination, prescribe other drug	13 (1.2)	11 (0.6)	72 (0.8)
Ciclosporin + CYP3A4 inhibitor	Nephrotoxicity and side effects/toxicity ciclosporin	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) ciclosporin Monitor renal function (serum creatinine)	13 (1.2)	11 (0.6)	142 (1.7)
Coumarin + (es)omeprazole	Risk of bleeding (incl. GI ulcer)	Monitor blood clotting time (INR)	13 (1.2)	11 (0.6)	149 (1.8)
Dopaminergic drug + antipsychotic drug	Decreased efficacy drugs	Preferably avoid combination, prescribe other drug	11 (1.0)	10 (0.5)	190 (2.2)
Beta blocker + NSAID	Decreased efficacy beta blocker	Monitor blood pressure	10 (0.9)	8 (0.4)	27 (0.3)
Ciclosporin + nephrotoxic drug	Nephrotoxicity	Preferably avoid combination, prescribe other drug Monitor renal function (serum creatinine)	10 (0.9)	9 (0.5)	118 (1.4)
RAS inhibitor + NSAID	Decreased efficacy RAS inhibitor	Preferably avoid combination, prescribe other drug Monitor blood pressure Monitor renal function (serum creatinine) – Risk factor management strategy: monitor renal function – Risk factor management strategy: monitor serum sodium	9 (0.8)	8 (0.4)	52 (0.6)
Sildenafil + CYP3A4 inhibitor/ciprofloxacin	Side effects/toxicity sildenafil	Preferably avoid combination, temporarily stop drug Adjust dose/titrate dose sildenafil	9 (0.8)	8 (0.4)	182 (2.1)
Lamotrigine + enzyme inducer**	Decreased efficacy lamotrigine	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) lamotrigine	8 (0.7)	5 (0.3)	21 (0.2)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Topiramate + enzyme inducer	Decreased efficacy topiramate	Monitor drug level (TDM) topiramate	8 (0.7)	6 (0.3)	78 (0.9)
Haloperidol + enzyme inducer	Decreased efficacy haloperidol	Monitor drug level (TDM) haloperidol	7 (0.6)	6 (0.3)	55 (0.6)
Phenytoin + enzyme inhibitor	Side effects/toxicity phenytoin	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) phenytoin	6 (0.6)	5 (0.3)	29 (0.3)
Coumarin + carbamazepine/barbiturate	Decreased efficacy coumarin	Monitor blood clotting time (INR)	5 (0.5)	4 (0.2)	97 (1.1)
Dihydropyridine + CYP3A4 inhibitor/cimetidine/fluoxetine	Side effects/toxicity dihydropyridine	Adjust dose/titrate dose dihydropyridine	4 (0.4)	3 (0.2)	26 (0.3)
Bosentan + sildenafil	Hepatotoxicity and side effects/toxicity bosentan and decreased efficacy sildenafil	Monitor hepatic function Monitor side effects/toxicity bosentan Monitor effectiveness sildenafil	4 (0.4)	3 (0.2)	30 (0.4)
Salicylate antithrombotic (≤ 100 mg) + NSAID	Risk of bleeding (incl. GI ulcer)	Preferably avoid combination, prescribe other drug Add gastric protection (PPI)	4 (0.4)	4 (0.2)	5 (<0.1)
Nitrate + phosphodiesterase inhibitor	Hypotension	Avoid combination, prescribe other drug	3 (0.3)	3 (0.2)	27 (0.3)
Caspofungin + enzyme inducer	Decreased efficacy caspofungine	Adjust dose/titrate dose caspofungin	3 (0.3)	2 (0.1)	52 (0.6)
Clobazam/valproic acid + stiripentol	Side effects/toxicity clobazam/valproic acid and decreased efficacy stiripentol	Monitor drug level (TDM) clobazam/valproic acid/stiripentol Adjust dose/titrate dose clobazam/valproic acid	3 (0.3)	3 (0.2)	26 (0.3)
Ciclosporin + cotrimoxazole/trimethoprim	Nephrotoxicity	Preferably avoid combination, prescribe other drug Monitor renal function (serum creatinine)	2 (0.2)	2 (0.1)	12 (0.1)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Coumarin + miconazole enteral/vaginal/cutaneous	Risk of bleeding (incl. GI ulcer)	Avoid combination, prescribe other drug	2 (0.2)	1 (<0.1)	13 (0.2)
Methadone + enzyme inducer	Decreased efficacy methadone	Monitor effectiveness methadone	2 (0.2)	2 (0.1)	71 (0.8)
Opioid agonist + mixed opioid agonist-antagonist	Decreased efficacy opioid agonist	Preferably avoid combination, prescribe other drug Monitor effectiveness opioid agonist	2 (0.2)	1 (<0.1)	2 (<0.1)
Phenobarbital + valproic acid	Side effects/toxicity phenobarbital	Monitor drug level (TDM) phenobarbital Adjust dose/titrate dose phenobarbital	2 (0.2)	2 (0.1)	38 (0.4)
Phenytoin + cotrimoxazole/trimethoprim/sulphonamide	Side effects/toxicity phenytoin	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) phenytoin	2 (0.2)	2 (0.1)	12 (0.1)
Coumarin + fluconazole/voriconazole	Risk of bleeding (incl. GI ulcer)	Preferably avoid combination, prescribe other drug Monitor blood clotting time (INR)	2 (0.2)	1 (<0.1)	12 (0.1)
Valproic acid + carbapenem	Decreased efficacy valproic acid	Avoid combination, prescribe other drug	2 (0.2)	2 (0.1)	24 (0.3)
Quetiapine + CYP3A4 inhibitor	Side effects/toxicity quetiapine	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) quetiapine	2 (0.2)	1 (<0.1)	5 (<0.1)
(Ox)carbamazepine + diuretic	Electrolyte disturbance	Monitor serum sodium	2 (0.2)	2 (0.1)	2 (<0.1)
Clopidogrel + (es)omeprazole	Decreased efficacy clopidogrel	Avoid combination, prescribe other drug	2 (0.2)	2 (0.1)	9 (0.1)
Acetazolamide + salicylate analgetic (> 100 mg)	Side effects/toxicity acetazolamide/salicylate	Preferably avoid combination, prescribe other drug Monitor side effects/toxicity acetazolamide/salicylate	1 (<0.1)	1 (<0.1)	4 (<0.1)
Digoxin + amiodarone	Side effects/toxicity digoxin	Monitor drug level (TDM) digoxin Adjust dose/titrate dose digoxin	1 (<0.1)	1 (<0.1)	9 (0.1)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Betalactam antibiotic + tetracycline	Decreased efficacy betalactam/tetracycline	Avoid combination in serious infection such as meningitis, sepsis, endocarditis or in neutropenic patients, prescribe other drug	1 (<0.1)	1 (<0.1)	13 (0.2)
Beta blocker nonselective + insulin	Masking of hypoglycemia	Preferably avoid combination, prescribe other drug Monitor plasma glucose Monitor side effects/toxicity insulin	1 (<0.1)	1 (<0.1)	3 (<0.1)
Ciclosporin + enzyme inducer	Decreased efficacy ciclosporin	Preferably avoid combination, prescribe other drug Monitor drug level (TDM) ciclosporin	1 (<0.1)	1 (<0.1)	8 (<0.1)
Coumarin + NSAID	Risk of bleeding (incl. GI ulcer)	Preferably avoid combination, prescribe other drug Add gastric protection (PPI)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Phenytoin + valproic acid	Decreased efficacy valproic acid and side effects/toxicity or decreased efficacy phenytoin	Monitor effectiveness phenytoin/valproic acid Monitor side effects/toxicity phenytoin Monitor drug level (TDM) phenytoin and valproic acid	1 (<0.1)	1 (<0.1)	3 (<0.1)
Quinolone + calcium/bismuth oxide	Decreased efficacy quinolone	Preferably avoid combination, prescribe other drug Preferably avoid combination, temporarily stop drug Separate dosages	1 (<0.1)	1 (<0.1)	10 (0.1)
Quinolone + iron	Decreased efficacy quinolone	Preferably avoid combination, prescribe other drug Preferably avoid combination, temporarily stop drug Separate dosages	1 (<0.1)	1 (<0.1)	42 (0.5)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Quinolone + magnesium/zinc	Decreased efficacy quinolone	Preferably avoid combination, prescribe other drug Preferably avoid combination, temporarily stop drug Separate dosages	1 (<0.1)	1 (<0.1)	2 (<0.1)
Tacrolimus + CYP3A4 inhibitor	Nephrotoxicity and side effects/toxicity tacrolimus	Preferably avoid combination, prescribe other drug Preferably avoid combination, temporarily stop drug Monitor drug level (TDM)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Coumarin + thyroid supplement	Risk of bleeding (incl. GI ulcer)	Monitor blood clotting time (INR)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Lamotrigine + valproic acid	Side effects/toxicity lamotrigine	Monitor drug level (TDM) lamotrigine Adjust dose/titrate dose lamotrigine	1 (<0.1)	1 (<0.1)	3 (<0.1)
Coumarin + rifampicin/rifabutin	Decreased efficacy coumarin	Monitor blood clotting time (INR)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Coumarin + salicylate antithrombotic (≤ 100 mg)	Risk of bleeding (incl. GI ulcer)	Preferably avoid combination, prescribe other drug Add gastric protection (PPI)	1 (<0.1)	1 (<0.1)	33 (0.4)
Thyroid supplement + antacid/calcium	Decreased efficacy thyroid supplement	Preferably avoid combination, prescribe other drug Separate dosages	1 (<0.1)	1 (<0.1)	2 (<0.1)
Coumarin + bosentan	Decreased efficacy coumarin	Monitor blood clotting time (INR)	1 (<0.1)	1 (<0.1)	5 (<0.1)
Phenytoin + chemotherapeutic agent	Decreased efficacy phenytoin	Monitor drug level (TDM) phenytoin	1 (<0.1)	1 (<0.1)	1 (<0.1)

Appendix 1 Continued.

pDDI	Potential consequence	Management strategy	No. of pDDIs (%)	No. of patients (%) ***	No. of PICU-days (%)
Phenytoin + folic acid	Decreased efficacy phenytoin	Monitor drug level (TDM) phenytoin	1 (<0.1)	1 (<0.1)	1 (<0.1)
Carbamazepine/phenobarbital/phenytoin + stiripentol	Side effects/toxicity carbamazepine/phenobarbital/phenytoin	Monitor drug level (TDM) carbamazepine/phenobarbital/phenytoin/stiripentol	1 (<0.1)	1 (<0.1)	19 (0.2)
Zonisamide + enzyme inducer	Decreased efficacy zonisamide and side effects/toxicity or decreased efficacy carbamazepine/phenytoin	Monitor drug level (TDM) zonisamide/carbamazepine/phenytoin Adjust dose/titrate dose zonisamide	1 (<0.1)	1 (<0.1)	1 (<0.1)
Total number of DDIs			1,078 (100)		

*excl. cotrimoxazole, metronidazole, cefamandole
**excl. anticonceptives
***a patient could experience a DDI type more than once
RAS = renin angiotensin system
INR = international normalized ratio
GI = gastrointestinal
NSAID = non-steroidal anti-inflammatory drug
TDM = therapeutic drug monitoring
PPI = proton pump inhibitor
ECG = electrocardiogram

Appendix 2 Frequency and types of additional pDDIs involving high-risk PICU-specific drugs* identified using Lexi-Interact™ and Micromedex®.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Clonidine + CNS depressant	Lexi [C]	CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants.	The concomitant use of two or more drugs that have the potential to depress CNS function (either as a therapeutic intention or a side effect) is often clinically appropriate. However, it is important to recognize that the risk of unwanted effects may increase with such use. Consider the duration of CNS depressant use and each patient's response (particularly tolerance to CNS depressant effects) when selecting additional agents and their doses. Monitor for additive CNS-depressant effects whenever two or more CNS depressants are concomitantly used. Advise patients to avoid any unprescribed, illicit, or recreational use of other CNS depressants.	203 (10.2)
Clonidine + SSRI	Lexi [C]	CNS Depressants may enhance the adverse/toxic effect of Selective Serotonin Reuptake Inhibitors. Specifically, the risk of psychomotor impairment may be enhanced.	Monitor for increased psychomotor impairment in patients who initiate SSRIs during treatment with CNS depressants.	203 (10.2)
Dopamine + sympathicomimetic	Lexi [C]	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics.	Monitor for increased effects of sympathomimetics (eg, blood pressure, heart rate) during concomitant use. Risk would seem less with locally applied dosage forms (eg, ophthalmic drops, or as a vasoconstrictor in a combination local anesthetic). However, higher doses of these products could yield high enough systemic concentrations of the sympathomimetic to cause problems.	174 (8.7)
Clonidine + antihypertensive	Lexi [C]	Antihypertensives may enhance the hypotensive effect of other Antihypertensives.	Monitor hemodynamic status closely when using multiple blood pressure-lowering agents in combination. Depending on the specific mechanism of action of the specific drugs being used, heart rate and/or electrolytes may also require additional monitoring.	163 (8.2)
Clonidine + hypotensive agent	Lexi [C]	Hypotensive Agents may enhance the adverse/toxic effect of other Hypotensive Agents.	Monitor blood pressure closely and advise patients regarding signs/symptoms of hypotension when two or more of these agents are used in combination.	163 (8.2)
Clonidine + prostacyclin analogue	Lexi [C]	Prostacyclin Analogues may enhance the hypotensive effect of Antihypertensives.	Monitor response to antihypertensive therapy closely (e.g., blood pressure, heart rate).	163 (8.2)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Propofol + midazolam	Lexi [C]	Midazolam may increase the serum concentration of Propofol. Propofol may increase the serum concentration of Midazolam.	Increase monitoring of clinical response to both midazolam and propofol when these agents are used together.	140 (7.0)
Norepinephrine + sympathicomimetic	Lexi [C]	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics.	Monitor for increased effects of sympathomimetics (eg, blood pressure, heart rate) during concomitant use. Risk would seem less with locally applied dosage forms (eg, ophthalmic drops, or as a vasoconstrictor in a combination local anesthetic). However, higher doses of these products could yield high enough systemic concentrations of the sympathomimetic to cause problems.	96 (4.8)
Epinephrine + spironolactone	Lexi [C]	Spironolactone may diminish the vasoconstricting effect of Alpha-/Beta-Agonists.	Use extra caution in the clinical care of patients who do or who may require treatment with norepinephrine or other vasoactive amines when such patients are also receiving spironolactone.	96 (4.8)
Fentanyl + CNS depressant	Lexi [C]	CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants.	The concomitant use of two or more drugs that have the potential to depress CNS function (either as a therapeutic intention or a side effect) is often clinically appropriate. However, it is important to recognize that the risk of unwanted effects may increase with such use. Consider the duration of CNS depressant use and each patient's response (particularly tolerance to CNS depressant effects) when selecting additional agents and their doses. Monitor for additive CNS-depressant effects whenever two or more CNS depressants are concomitantly used. Advise patients to avoid any unprescribed, illicit, or recreational use of other CNS depressants.	78 (3.9)
	MM (major)	Increased risk of CNS depression	NA	
Rocuronium + loop diuretic	Lexi [C]	Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.	Be aware that the therapeutic effects of neuromuscular blockers may be altered by coadministration of loop diuretics. Low doses of the diuretic appear to enhance blockade, whereas higher doses may diminish blockade.	74 (3.7)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Norepinephrine + spironolactone	Lexi [C]	Spironolactone may diminish the vasoconstricting effect of Alpha-/Beta-Agonists.	Use extra caution in the clinical care of patients who do or who may require treatment with norepinephrine or other vasoactive amines when such patients are also receiving spironolactone.	73 (3.7)
Nitroprusside + antihypertensive	Lexi [C]	Antihypertensives may enhance the hypotensive effect of other Antihypertensives.	Monitor hemodynamic status closely when using multiple blood pressure-lowering agents in combination. Depending on the specific mechanism of action of the specific drugs being used, heart rate and/or electrolytes may also require additional monitoring.	65 (3.3)
Nitroprusside + hypotensive agent	Lexi [C]	Hypotensive Agents may enhance the adverse/toxic effect of other Hypotensive Agents.	Monitor blood pressure closely and advise patients regarding signs/symptoms of hypotension when two or more of these agents are used in combination. Additive or synergistic hypotensive effects may result from concomitant use of these agents.	65 (3.3)
Fentanyl + diuretic	Lexi [C]	Analgesics (Opioid) may enhance the adverse/toxic effect of Diuretics.	Patients should be monitored for reduced efficacy of diuretics, urinary retention, and symptoms of orthostasis when treated with both a diuretic and an opioid analgesic. Consider increased clinical monitoring of blood pressure (both sitting and standing) in these patients.	62 (3.1)
Rocuronium + corticosteroid	Lexi [D]	Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur.	Monitor closely for new onset or worsening muscle weakness, reduction or loss of deep tendon reflexes and/or peripheral sensory decriments. Although concomitant neuromuscular blockade and corticosteroid therapy may be therapeutically necessary, critical care guidelines[1] recommend using a neuromuscular blocking drug only when absolutely necessary, employing the lowest doses possible and limiting the duration of either agent to limit the risk of developing myopathy or neuropathy.	57 (2.9)
	MM (moderate)	Decreased rocuronium effectiveness; prolonged muscle weakness and myopathy	NA	
Rocuronium + spironolactone	Lexi [C]	Spironolactone may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing).	Monitor for increased response to nondepolarizing neuromuscular blockers in patients who are also receiving spironolactone.	57 (2.9)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Fentanyl + anticholinergic	Lexi [C]	Anticholinergics may enhance the adverse/toxic effect of Analgesics (Opioid). Specifically, the risk for constipation and urinary retention may be increased with this combination.	Increase the monitoring for evidence of constipation and/or urinary retention in patients using this combination. Advise patients to promptly report signs or symptoms suggestive of such adverse effects. Consider means of preventing or treating these effects if or when they occur.	55 (2.8)
Epinephrine + sympathicomimetic	Lexi [C]	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics.	Monitor for increased effects of sympathomimetics (eg, blood pressure, heart rate) during concomitant use. Risk would seem less with locally applied dosage forms (eg, ophthalmic drops, or as a vasoconstrictor in a combination local anesthetic). However, higher doses of these products could yield high enough systemic concentrations of the sympathomimetic to cause problems.	42 (2.1)
Fentanyl + CYP3A4 inhibitor	Lexi [D]	CYP3A4 Inhibitors may increase the serum concentration of FentaNYL.	Concurrent use of fentanyl with any CYP3A4 inhibitor may result in increased fentanyl concentrations and could increase or prolong adverse effects, including potentially fatal respiratory depression. Patients receiving fentanyl and any CYP3A4 inhibitor should be closely monitored for several days following initiation of the combination, and fentanyl dosage reductions should be made as appropriate.	32 (1.6)
	MM (contraindicated)	Increased risk of fentanyl toxicity	NA	
Alprostadil + heparin	MM (major)	Increased risk of bleeding	NA	31 (1.6)
(Es)ketamine + CYP2C9 inhibitor	Lexi [C]	CYP2C9 Inhibitors may decrease the metabolism of CYP2C9 Substrates.	Consider an alternative for one of the interacting drugs in order to avoid toxicity of the substrate. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for increased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased.	30 (1.5)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Phenylephrine + sympathicomimetic	Lexi [C]	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics.	Monitor for increased effects of sympathomimetics (eg, blood pressure, heart rate) during concomitant use. Risk would seem less with locally applied dosage forms (eg, ophthalmic drops, or as a vasoconstrictor in a combination local anesthetic). However, higher doses of these products could yield high enough systemic concentrations of the sympathomimetic to cause problems.	26 (1.3)
Rocuronium + vancomycin	Lexi [C]	Vancomycin may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.	Monitor for increased therapeutic effects of neuromuscular-blocking agents (NMB), specifically respiratory depression, if vancomycin is initiated/dose increased, or decreased effects if vancomycin is discontinued/dose decreased.	25 (1.3)
Rocuronium + aminoglycosides	Lexi [C]	Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents.	Monitor for increased therapeutic effects of neuromuscular-blocking agents (NMB), specifically respiratory depression, if an aminoglycoside is initiated/dose increased, or decreased effects if an aminoglycoside is discontinued/dose decreased.	23 (1.2)
	MM (major)	Enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis	NA	
Clonidine + haloperidol	MM (moderate)	Induction or exacerbation of orthostatic regulation disturbances and increased arrhythmogenic potential	NA	20 (1.0)
Propofol + fentanyl	MM (major)	Increased risk of CNS depression	NA	18 (0.9)
Clonidine + insulin	MM (moderate)	Hypoglycemia or hyperglycemia	NA	17 (0.9)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Clonidine + beta blocker	Lexi [D]	Alpha2-Agonists may enhance the AV-blocking effect of Beta-Blockers. Sinus node dysfunction may also be enhanced. Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha2-agonist is abruptly withdrawn.	Closely monitor heart rate in patients receiving clonidine in combination with beta blockers. Withdraw the beta blocker several days before clonidine is gradually withdrawn if possible, and monitor blood pressure closely. Specific recommendations for other alpha2-agonists are not available. Ophthalmic beta-blockers likely pose a reduced risk.	16 (0.8)
	MM (major)	Increased risk of sinus bradycardia; exaggerated clonidine withdrawal response (acute hypertension)	NA	
(Es)ketamine + CYP3A4 inhibitor	Lexi [C/D]	CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates.	Consider an alternative for one of the interacting drugs in order to avoid toxicity of the substrate. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for increased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased.	16 (0.8)
Propofol + bupivacaine	MM (major)	Increased hypnotic effect of propofol	NA	15 (0.8)
Clonidine + phosphodiesterase 5 inhibitor	Lexi [C]	Phosphodiesterase 5 Inhibitors may enhance the antihypertensive effect of Antihypertensives.	Monitor blood pressure response to phosphodiesterase 5 (PDE5) inhibitors in patients receiving concurrent antihypertensive therapy. PDE5 inhibitors can cause additional mild-moderate blood pressure reductions (and related adverse effects, such as dizziness, lightheadedness, and/or fainting), and the magnitude of this effect may vary somewhat depending on the particular antihypertensive therapy.	14 (0.7)
Norepinephrine + antacid	Lexi [C]	Antacids may decrease the excretion of Alpha-/Beta-Agonists.	Monitor for increased therapeutic effects of alpha-/beta-agonists if an antacid is initiated/dose increased, or decreased effects if an antacid is discontinued/dose decreased. The use of epinephrine in combination local anesthetics should not be affected.	14 (0.7)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Norepinephrine + beta blocker	Lexi [D]	Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems.	Monitor for increases in pressor effects of alpha-/beta-agonists if used in patients receiving beta-blocker therapy (including ophthalmic products). Beta1-selective (i.e., "cardioselective") agents may confer a more limited risk if used in low enough doses to allow them to retain their selectivity. The amount of epinephrine used in dental procedures as part of local anesthetic administration is not likely to be of clinical concern. Infiltrating larger volumes of local anesthetics for other surgical procedures (e.g., more than 0.06mg epinephrine) may cause clinically-relevant problems. Patients with allergies that require carrying and periodically using subcutaneous epinephrine (e.g., bee sting kits) should probably avoid the use of beta blockers.	14 (0.7)
Clonidine + calcium channel blocker	Lexi [C]	CloNIDine may enhance the AV-blocking effect of Calcium Channel Blockers (Nondihydropyridine). Sinus node dysfunction may also be enhanced.	Closely monitor heart rate in patients receiving clonidine in combination with nondihydropyridine calcium channel blockers.	10 (0.5)
Clonidine + cyclosporine	MM (moderate)	Increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)	NA	10 (0.5)
Epinephrine + CAI	Lexi [C]	CAIs may decrease the excretion of Alpha-/Beta-Agonists.	Monitor for increased therapeutic effects of alpha/beta agonists if a CAI is initiated/dose increased, or decreased effects if a CAI is discontinued/dose decreased. The use of epinephrine in combination local anesthetics should pose no clinical concern.	10 (0.5)
Sufentanyl + CYP3A4 inhibitor	Lexi [C/D]	CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates.	Consider an alternative for one of the interacting drugs in order to avoid toxicity of the substrate. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for increased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased.	10 (0.5)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
(Es)ketamine + CYP2C9 inducer	Lexi [D]	CYP2C9 Inducers may increase the metabolism of CYP2C9 Substrates.	Consider an alternative for one of the interacting drugs in order to avoid therapeutic failure of the substrate. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for decreased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and increased effects if a CYP inhibitor is discontinued/dose decreased.	9 (0.5)
Fentanyl + azithromycin	MM (moderate)	Increased or prolonged opioid effects (CNS depression, respiratory depression)	NA	9 (0.5)
Sufentanyl + CNS depressant	Lexi [C]	CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants.	The concomitant use of two or more drugs that have the potential to depress CNS function (either as a therapeutic intention or a side effect) is often clinically appropriate. However, it is important to recognize that the risk of unwanted effects may increase with such use. Consider the duration of CNS depressant use and each patient's response (particularly tolerance to CNS depressant effects) when selecting additional agents and their doses. Monitor for additive CNS-depressant effects whenever two or more CNS depressants are concomitantly used. Advise patients to avoid any unprescribed, illicit, or recreational use of other CNS depressants.	9 (0.5)
Norepinephrine + CAI	Lexi [C]	CAIs may decrease the excretion of Alpha-/Beta-Agonists.	Monitor for increased therapeutic effects of alpha/beta agonists if a CAI is initiated/dose increased, or decreased effects if a CAI is discontinued/dose decreased. The use of epinephrine in combination local anesthetics should pose no clinical concern.	9 (0.5)
Sufentanyl + SSRI	Lexi [C]	Analgesics (Opioid) may enhance the serotonergic effect of SSRIs. This may cause serotonin syndrome.	Monitor for evidence of serotonin syndrome during concomitant use of narcotic analgesics and SSRIs.	9 (0.5)
Sufentanyl + benzodiazepine	MM (major)	Additive respiratory depression	NA	9 (0.5)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Fentanyl + alpha-/beta-agonist	Lexi [C]	Alpha-/Beta-Agonists (Indirect-Acting) may decrease the serum concentration of FentaNYL. Specifically, fentanyl nasal spray serum concentrations may decrease and onset of effect may be delayed.	Monitor for delayed onset of action, and decreased systemic effects, of intranasally administered fentanyl in patients receiving vasoconstrictive nasal decongestant medications. Avoid dose titration of intranasal fentanyl during treatment with such medications.	8 (0.4)
Sufentanyl + anticholinergic	Lexi [C]	Anticholinergics may enhance the adverse/toxic effect of Analgesics (Opioid). Specifically, the risk for constipation and urinary retention may be increased with this combination.	Increase the monitoring for evidence of constipation and/or urinary retention in patients using this combination. Advise patients to promptly report signs or symptoms suggestive of such adverse effects. Consider means of preventing or treating these effects if or when they occur.	8 (0.4)
Sufentanyl + diuretic	Lexi [C]	Analgesics (Opioid) may enhance the adverse/toxic effect of Diuretics.	Patients should be monitored for reduced efficacy of diuretics, urinary retention, and symptoms of orthostasis when treated with both a diuretic and an opioid analgesic. Consider increased clinical monitoring of blood pressure (both sitting and standing) in these patients.	8 (0.4)
Phenylephrine + propranolol	MM (moderate)	Increased blood pressure	NA	7 (0.4)
Rocuronium + magnesium salt	Lexi [C]	Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.	Monitor for enhanced or prolonged effects of neuromuscular blocking agents in patients receiving magnesium supplementation. High-risk patients include those with elevated serum magnesium concentrations or renal impairment and those receiving parenteral magnesium.	6 (0.3)
	MM (moderate)	Increased risk of rocuronium toxicity (neuromuscular block prolongation, respiratory depression, apnea)	NA	

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Dopamine + phenytoin	Lexi [C]	DOPamine may enhance the hypotensive effect of Phenytoin.	Monitor for decreased blood pressure in patients receiving intravenous phenytoin. Hemodynamically unstable patients, including those requiring dopamine to maintain adequate blood pressure, are at elevated risk.	5 (0.3)
	MM (major)	Hypotension and/or cardiac arrest	NA	
Dobutamine + sympathicomimetic	Lexi [C]	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics.	Monitor for increased effects of sympathomimetics (eg, blood pressure, heart rate) during concomitant use. Risk would seem less with locally applied dosage forms (eg, ophthalmic drops, or as a vasoconstrictor in a combination local anesthetic). However, higher doses of these products could yield high enough systemic concentrations of the sympathomimetic to cause problems.	5 (0.3)
Fentanyl + CYP3A4 inducer barbiturate	MM (major)	Decreased clearance of opioid with possible decreased efficacy and development of withdrawal syndrome or increased risk of additive CNS depression	NA	5 (0.3)
Rocuronium + calcium channel blocker	Lexi [C]	Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing).	Monitor for enhanced or prolonged effects of nondepolarizing neuromuscular blockers in patients receiving calcium channel blockers.	5 (0.3)
Epinephrine + antacid	Lexi [C]	Antacids may decrease the excretion of Alpha-/Beta-Agonists.	Monitor for increased therapeutic effects of alpha-/beta-agonists if an antacid is initiated/dose increased, or decreased effects if an antacid is discontinued/dose decreased. The use of epinephrine in combination local anesthetics should not be affected.	4 (0.2)
Epinephrine + haloperidol	MM (moderate)	Decreased or reversal of epinephrine pressor response	NA	4 (0.2)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Propofol + CYP2B6 inhibitor	Lexi [C]	CYP2B6 Inhibitors may decrease the metabolism of CYP2B6 Substrates.	Consider an alternative for one of the interacting drugs in order to avoid toxicity of the substrate. Some combinations are specifically contraindicated by manufacturers. Suggested dosage adjustments are also offered by some manufacturers. Please review applicable package inserts. Monitor for increased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased.	4 (0.2)
Sufentanyl + calcium channel blocker	Lexi [C]	Anilidopiperidine Opioids may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine).	Monitor blood pressure, heart rate, and overall cardiovascular status closely when administering an anilidopiperidine opioid (e.g., sufentanil, alfentanil, etc.) to a patient who is also receiving a nondihydropyridine calcium channel blocker (i.e., verapamil, diltiazem).	4 (0.2)
Alteplase + anticoagulant	Lexi [C]	Thrombolytic Agents may enhance the anticoagulant effect of Anticoagulants.	Carefully monitor for signs and symptoms of bleeding if thrombolytic agents are to be used with other drugs that alter coagulation, inhibit platelet function, or are thrombolytic. Use of such combinations may further increase the potential for bleeding complications. See full drug monograph for guidelines for the use of alteplase for acute ischemic stroke during treatment with oral anticoagulants.	3 (0.2)
	MM (major)	Increased risk of bleeding	NA	
Atracurium + loop diuretic	Lexi [C]	Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.	Be aware that the therapeutic effects of neuromuscular blockers may be altered by coadministration of loop diuretics. Low doses of the diuretic appear to enhance blockade, whereas higher doses may diminish blockade.	3 (0.2)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Atracurium + spironolactone	Lexi [C]	Spironolactone may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing).	Monitor for increased response to nondepolarizing neuromuscular blockers in patients who are also receiving spironolactone.	3 (0.2)
Clonidine + cardiac glycoside	Lexi [C]	Clonidine may enhance the AV-blocking effect of Cardiac Glycosides. Sinus node dysfunction may also be enhanced.	Closely monitor heart rate in patients receiving clonidine in combination with cardiac glycosides.	3 (0.2)
Clonidine + magnesium sulfate	Lexi [C]	Magnesium Sulfate may enhance the CNS depressant effect of CNS Depressants.	Monitor patients closely for evidence of enhanced CNS depression when using higher dose and/or injectable magnesium sulfate together with a CNS depressant. Dose adjustments of the CNS depressant may be necessary.	3 (0.2)
Fentanyl + beta blocker	Lexi [C]	Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers.	Monitor blood pressure, heart rate, and overall cardiovascular status closely when administering an anilidopiperidine opioid (e.g., sufentanil, alfentanil, etc.) to a patient who is also receiving a beta-blocker.	3 (0.2)
Nitroprusside + calcium channel blocker	Lexi [C]	Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside.	Caution should be used when initiating nitroprusside therapy in a patient who is also receiving a calcium channel blocker, as a significantly reduced dose of nitroprusside might be adequate to produce the desired blood pressure-lowering effects.	3 (0.2)
Propofol + rifampin	Lexi [D]	Rifampin may enhance the hypotensive effect of Propofol.	Note that use of propofol in a patient who has been taking rifampin may result in clinically significant hypotension. If possible, avoid use of this combination.	3 (0.2)
Sufentanyl + voriconazole	MM (moderate)	Increased sufentanyl exposure and an increased risk of sufentanyl adverse events	NA	3 (0.2)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Atracurium + aminoglycoside	Lexi [C]	Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents.	Monitor for increased therapeutic effects of neuromuscular-blocking agents (NMB), specifically respiratory depression, if an aminoglycoside is initiated/dose increased, or decreased effects if an aminoglycoside is discontinued/dose decreased.	2 (0.1)
	MM (major)	Enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis	NA	
Atracurium + corticosteroid	Lexi [D]	Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur.	Monitor closely for new onset or worsening muscle weakness, reduction or loss of deep tendon reflexes and/or peripheral sensory decriments. Although concomitant neuromuscular blockade and corticosteroid therapy may be therapeutically necessary, critical care guidelines[1] recommend using a neuromuscular blocking drug only when absolutely necessary, employing the lowest doses possible and limiting the duration of either agent to limit the risk of developing myopathy or neuropathy.	2 (0.1)
	MM (moderate)	Decreased atracurium effectiveness; prolonged muscle weakness and myopathy	NA	
Dopamine + digoxin	MM (major)	Increased risk of cardiotoxicity (arrhythmias)	NA	2 (0.1)
Dobutamine + carvedilol	MM (moderate)	Decreased dobutamine efficacy	NA	2 (0.1)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Alteplase + agent with antiplatelet properties	Lexi [C]	Agents with Antiplatelet Properties may enhance the anticoagulant effect of Thrombolytic Agents.	Carefully monitor for signs and symptoms of bleeding if thrombolytic agents are to be used with other drugs that alter coagulation, inhibit platelet function, or are thrombolytic. Use of such combinations may further increase the potential for bleeding complications. Antiplatelet agents should be discontinued, and enough time should elapse for their effects to subside, before initiation of long-term streptokinase treatment.	1 (<0.1)
Alteplase + salicylate	Lexi [C]	Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur.	Carefully monitor for signs and symptoms of bleeding if thrombolytic agents are to be used with other drugs that alter coagulation, inhibit platelet function, or are thrombolytic. Use of such combinations may further increase the potential for bleeding complications. Antiplatelet agents should be discontinued, and enough time should elapse for their effects to subside, before initiation of long-term streptokinase treatment (new or continued aspirin use can still be considered).	1 (<0.1)
Alteplase + ACE inhibitor	MM (major)	Increased risk of orolingual angioedema	NA	1 (<0.1)
Atracurium + calcium channel blocker	Lexi [C]	Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing).	Monitor for enhanced or prolonged effects of nondepolarizing neuromuscular blockers in patients receiving calcium channel blockers.	1 (<0.1)
Atracurium + vancomycin	Lexi [C]	Vancomycin may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents.	Monitor for increased therapeutic effects of neuromuscular-blocking agents (NMB), specifically respiratory depression, if vancomycin is initiated/dose increased, or decreased effects if vancomycin is discontinued/dose decreased.	1 (<0.1)
Clonidine + olanzapine	MM (moderate)	Induction or exacerbation of orthostatic regulation disturbances	NA	1 (<0.1)
Clonidine + risperidone	MM (moderate)	Induction or exacerbation of orthostatic regulation disturbances	NA	1 (<0.1)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Fentanyl + mixed agonist/antagonist opioid	Lexi [D]	Mixed Agonist / Antagonist Opioids may diminish the analgesic effect of Analgesics (Opioid).	Seek alternatives to mixed agonist/antagonist opioids in patients receiving pure opioid agonists, and monitor for symptoms of therapeutic failure/high dose requirements (or withdrawal in opioid-dependent patients) if patients receive these combinations.	1 (<0.1)
Fentanyl + octreotide	Lexi [C]	Octreotide may enhance the analgesic effect of Analgesics (Opioid).	Monitor for possible decreased dose requirements if octreotide is added/dose increased or increased requirements if octreotide is discontinued/dose decreased.	1 (<0.1)
Fentanyl + nifedipine	MM (major)	Severe hypotension	NA	1 (<0.1)
Fentanyl + infliximab	MM (moderate)	Decreased fentanyl plasma concentrations	NA	1 (<0.1)
Phenylephrine + fentanyl	Lexi [C]	Alpha1-Agonists may decrease the serum concentration of FentaNYL. Specifically, fentanyl nasal spray serum concentrations may decrease and onset of effect may be delayed.	Monitor for delayed onset of action, and decreased systemic effects, of intranasally administered fentanyl in patients receiving vasoconstrictive nasal decongestant medications. Avoid dose titration of intranasal fentanyl during treatment with such medications.	1 (<0.1)
Rocuronium + lincosamide antibiotic	Lexi [C] MM (moderate)	Lincosamide Antibiotics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Enhanced and prolonged neuromuscular blockade	Monitor for prolonged/enhanced neuromuscular blockade during concomitant use of these agents. NA	1 (<0.1)
Rocuronium + carbamazepine	MM (moderate)	Decreased duration of rocuronium-induced neuromuscular blockade	NA	1 (<0.1)

Appendix 2 Continued.

pDDI	Source and severity score	Potential consequence	Management strategy	No. of patients (%)
Sufentanyl + beta blocker	Lexi [C]	Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers.	Monitor blood pressure, heart rate, and overall cardiovascular status closely when administering an anilidopiperidine opioid (e.g., sufentanil, alfentanil, etc.) to a patient who is also receiving a beta-blocker.	1 (<0.1)

* Lexi-Interact™ and Micromedex® were checked for DDIs involving alprostadil, alteplase, atracurium, clonidine, dopamine, dobutamine, epinephrine, (es)ketamine, fentanyl, milrinone, nitroprusside, norepinephrine, phenylephrine, propofol, rocuronium and sufentanyl
CNS = central nervous system
SSRI = selective serotonin reuptake inhibitor
ACE = angiotensin converting enzyme
Lexi = Lexi-Interact™, risk rating C (monitor therapy), D (consider therapy modification)
MM = Micromedex®, severity score moderate, major and contraindicated
NA = not available
CAI = carbonic anhydrase inhibitor, e.g. acetazolamide
CYP = cytochrome P 450

Chapter 4

Clinical pharmacy interventions in pediatric electronic prescriptions

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Abstract

Purpose Identifying the current problems in pediatric electronic prescribing helps to specify the features needed to develop evidence based electronic prescribing systems tailored for children.This study examined the frequency, nature and determinants of clinical pharmacy interventions in pediatric electronic prescriptions.

Methods Prospective cohort with nested case-control study at a tertiary children's hospital, The Netherlands. Patients 0-18 years with at least one medication prescription hospitalized from 01/03/2004-01/01/2008 were included. Intensive care patients were excluded. Electronic medication prescriptions for pediatric inpatients were verified and if necessary intervened by the pediatric clinical pharmacy. Intervened prescriptions (cases) were compared to non-intervened prescriptions (controls). Frequency of clinical pharmacy interventions, per 10,000 pediatric electronic prescriptions, and the determinants thereof were the main outcome measures.

Results 1,577 (1.1%) of 138,449 prescriptions were intervened. 81% of the interventions concerned correction of a prescription that could potentially have adverse clinical consequences. Prescriptions for antibacterials for systemic use were intervened most often. Most corrections concerned wrong doses (45%). 1,577 cases were compared to 1,983 controls. Children of 1 month-2 years were at higher risk for interventions than 12-18 year olds (OR 1.97 [1.63-2.38]). 'Free-text' prescriptions had a five times higher risk than 'standardized structured template' prescriptions. No differences were found between day-, evening- and nightshifts. The oral dosage form (OR 1.63 [1.41-1.88]) and -administration route (OR 1.80 [1.55-2.09]) were significantly more intervened than others.

Conclusions Pediatric prescribing errors occur frequently. Electronic prescribing systems do not fully prevent them. This study provides information for improvements in electronic prescribing for pediatric patients. Incorporating tailored solutions, such as minimised free-text entry, certain obligatory fields and integrated dose checking and indications, can improve the quality and efficiency of electronic prescribing in pediatrics.

Introduction

Improving patient safety by preventing medical errors that result in adverse events is a worldwide challenge to healthcare.[1-3] Because a substantial part of these medical errors in hospitalized patients has been reported to be attributable to medication, clinical medication errors receive a lot of attention.[4-6] Medication errors occur during prescribing, transcribing, dispensing, administering and monitoring drugs. Errors occurring in the prescribing stage are common, multifactorial and potentially have the most serious clinical consequences since, unless detected, they may be repeated systematically for a prolonged period.[7-9] A prescribing error is defined as an incomplete or incorrect medication order that may result in adverse clinical consequences if given as prescribed.[10] In pediatrics prescribing error rates vary, with one of the most recent reports identifying a prescribing error rate of 13% of medication orders.[11,12]

Computerized physician order entry (CPOE) systems, including clinical decision support (CDS), help to reduce prescribing error rates and even death rate in pediatric inpatients, if well-designed and well-implemented.[11-13] However, CPOE with CDS has unintended consequences which may introduce new kinds of challenges and prescribing errors.[14-18]

In the Netherlands, clinical pharmacy is a rapidly developing specialty in both adult and pediatric healthcare. Dutch clinical pharmacy focuses on individual patient treatment – for instance, by developing automated CDS and rules tailored to specific patients.[19,20]

Because prescribing for children is different than for adults, it may be expected that CPOE and CDS systems require specific features for pediatric prescribing and that custom systems introduce different errors in a pediatric than in an adult setting.[21] Identifying problems with CPOE systems in pediatric prescribing helps to specify the features needed to develop evidence-based CPOE/CDS systems tailored for children.[22] The objective of this study was to examine the frequency, nature and determinants of clinical pharmacy interventions in electronic medication prescriptions for pediatric inpatients.

Methods

Setting, design, study population and outcome

This study was conducted at the 220 bed Wilhelmina Children's Hospital, which is part of the University Medical Center Utrecht, The Netherlands. In February 2003 a CPOE system (Mirador V5 Medicator by iSOFT) was gradually implemented in all pediatric wards. The physicians order all medication electronically in a standardized way using structured templates, drop-down menus and/or free-text entry. The system includes basic CDS: automated checking of drug allergy, duplicate treatment and drug-drug interactions, and a number of medication treatment protocols are incorporated to facilitate prescribing. The system does not include dose checking. Physicians receive a mandatory individual training on site before using the CPOE system. Each day all

electronic medication prescriptions are verified according to protocol and, if necessary, interventions are made by the clinical pharmacists and technicians of the children's hospital, directly supervised by one of two clinical pharmacists, specialized in pediatric clinical pharmacy.

The frequency and nature of the clinical pharmacy interventions were determined using a prospective cohort design. The determinants of these interventions were assessed using a case-control design.

The study cohort consisted of all patients aged between 0 and 18 years with at least one medication prescription admitted to hospital between 1 March 2004 and 1 January 2008. Patients in both medical and surgical wards were included. The pediatric and neonatal intensive care units were excluded, because the CPOE system used in these units differs from the studied system. Informed consent was waived by the hospital's medical ethics committee.

The measures of outcome were the frequency of clinical pharmacy interventions, expressed as number of occurrences per 10,000 electronic prescriptions, and the determinants thereof.

Definitions

Table 1 shows definitions and examples of the clinical pharmacy interventions and their nature. The definitions were based on the definition for medication error by the US National Coordinating Council for Medication Error Reporting and Prevention.[10] The nature of the interventions was classified into two groups: completions and corrections. One prescription could lead to more than one intervention – for example, if the route of administration was missing (completion) *and* the prescribed dose was too high (correction). Whether or not an intervention led to a modification of the prescription in the CPOE system by the prescriber was recorded.

Cases, controls and determinants

To examine the determinants of the interventions, patient-, prescription- and medication-related characteristics of all prescriptions requiring intervention (cases) were compared with prescriptions requiring no intervention (controls). The controls were randomly selected from the same population as the cases, using the Utrecht Patient Oriented Database (UPOD). All the hospital's CPOE prescriptions are saved in the UPOD, a large database that links administrative, laboratory and medical patient data.[23] The cases and controls were not matched in order to be able to examine as many variables as possible.

Statistical analysis

Data were processed with MS Excel 2003 and statistically analyzed using SPSS V.15.0. Logistic regression analysis was used to estimate the strengths of the associations between the patient, prescription and medication characteristics and clinical pharmacy intervention, expressed as OR with 95% CI.

Table 1 Definition and classification of interventions.

Definition	Description	
Intervention	Any action taken by a member of the pediatric clinical pharmacy staff towards the prescribing physician with the intention of correcting or completing the electronic medication prescription entered by the physician.	
Complete prescription	Prescription with the following components: patient name and hospital identification number, gender, date of birth, prescription date, body weight, medicine and strength/concentration, dose, dosage form, route of administration, -requency and time and, if relevant, body surface area, dose run time and solvent, maximum use of on-demand medication and units.	
Classification		**Examples**
Completion	Essential administrative feature missing in the electronic medication prescription.	Body weight absent Route of administration absent 'See protocol' on prescription
Correction	Potentially adverse clinical consequences if the medication were to be given as prescribed.	(Tenfold) overdose/underdose Wrong drug Non-corresponding dosage form and route of administration – for example, oral use of suppository Wrong drug formulation[a] Drug-drug interaction Miscalculation
Modification	Modification of the prescription in the CPOE system by the prescribing physician, in order to realize a completion/correction.	Pharmacy calls prescriber because the dose is too high, prescriber subsequently adjusts dose in CPOE system. Pharmacy calls prescriber because the antibiotic dose is potentially too low, but prescriber clarifies that dose is meant to be prophylactic and thus does not modify the prescription. Other reasons for not modifying a prescription were that the patient had already been discharged or transferred to another ward or the patient had already received the once-only medication that the intervention concerned.

[a] The category 'wrong drug formulation'. This refers to infeasible prescriptions that cannot or can scarcely be carried out – for example, clopidogrel 75 mg tablet, 9 mg once daily orally. This prescription suggests that 0.12 of a tablet is to be given to the patient, but such a proportion is practically impossible to dispense.
CPOE computerized physician order entry.

Results

Frequency and nature

During the 46 months study period 138,449 electronic prescriptions were ordered for 9,992 pediatric patients. Interventions were made in 1,577 (1.1%) of these prescriptions, as shown in figure 1. For 950/9,992 (9.5%) patients, interventions were made in at least one prescription. These patients, during their stay in hospital, had a total of 64,144 prescriptions (46% of the total number of prescriptions). This suggests that these patients were in hospital for longer, received more drugs and also, possibly, were more seriously ill.

This study identified a total number of 2,282 interventions in 1,577 prescriptions: 165 per 10,000 electronic prescriptions. The frequency of interventions did not change significantly during the study (data not shown). One thousand eight hundred and fifty-one (81.1%) of the interventions concerned a correction and 431 (18.9%) a completion (figure 1). Most corrections concerned a wrong dose (45.4%) (table 2). Amongst these, 96 (11.4%) were more than 10 times outside the guideline's therapeutic dosing range. Although less outstanding than the wrong doses, wrong drug formulations (9.4%) were another main reason for corrections. Most completions concerned an absent body weight (55.7%), followed by absent dosage form (17.9%) and absent strength/concentration (16.2%).

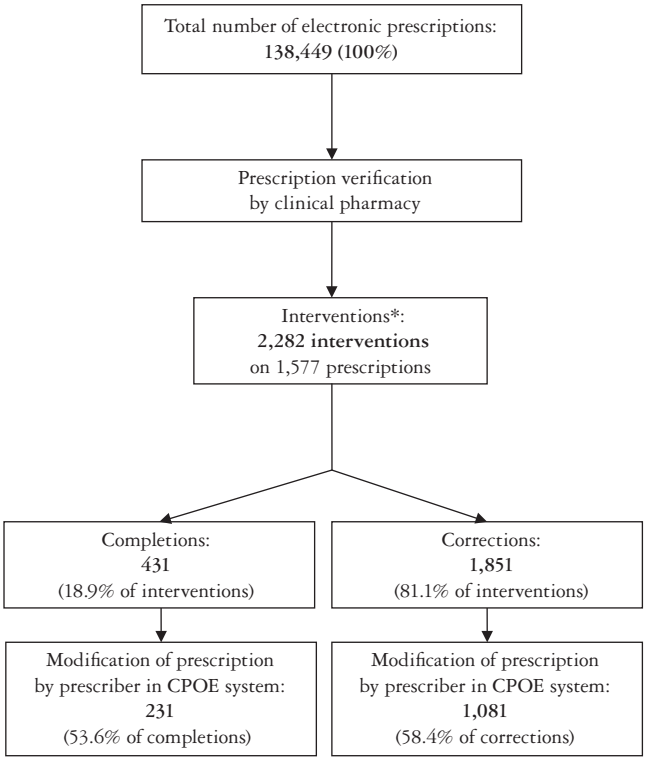
Interventions were most frequently conducted in the immunology/haematology unit: 31.1%, followed by the neurology unit and the internal medicine unit with 20.3% and 17.5% of the interventions, respectively. Interventions were made most often in prescriptions for antibacterial agents for systemic use (15.6%), followed by alimentary tract and metabolism drugs (13.9%) and nervous system drugs (13.4%).

Overall, 1,312 (57.5%) interventions led to a modification of the electronic prescription by the prescriber. Main reasons for prescribers not modifying a prescription were that the patient had already been discharged or transferred to another ward, the patient had already received the once-only medication or that the prescriber did not have the time.

Determinants

The 1,577 electronic prescriptions where interventions had occurred (cases) were compared with 1,983 electronic prescriptions where no intervention had taken place (controls). The strongest determinant was free-text entry: when the prescriber typed the prescription rather than using standardized structured templates the risk of an intervention was almost five times higher (OR = 4.71 (95% CI 3.61 to 6.13)).

A less strong, but nonetheless important determinant was age. The risk of intervention in prescriptions for the youngest of age children – that is, 0 – 2 years, was higher than for 12 – 18-year olds (age 0 – 1 month OR = 1.77 (95% CI 1.19 to 2.64) and age 1 month – 2 years OR = 1.97 (95% CI 1.63 to 2.38)).



* Interventions could be made in one prescription for more than one reason, adding up to 2,282 interventions
CPOE computerized physician order entry

Figure 1 Frequency and nature of interventions by the pediatric clinical pharmacy staff in electronic medication prescriptions for pediatric inpatients (March 2004 – January 2008).

Interestingly, no differences were found between the evening and night shifts versus the day shifts. A few significant differences were found among the days of the weekand seasons of the year, but the differences were small.

When the medication-related characteristics were considered, it was found that the oral dosage form and oral route of administration were methods with a relatively high risk for intervention (OR = 1.63 (95% CI 1.41 to 1.88) and OR = 1.80 (95% CI 1.55 to 2.09), respectively). Conversely, the rectal dosage form and route of administration had a relatively low risk for intervention (OR = 0.50 (95% CI 0.38 to 0.67) and 0.56 (95% CI 0.43 to 0.73), respectively).

For a more detailed overview of the results of the studied determinants, see appendix 1.

Table 2 Frequency and nature of corrections by the pediatric clinical pharmacy staff in electronic medication prescriptions for pediatric inpatients (March 2004 – January 2008).

	Corrections (n=1,851), n(%)	Modifications (n=1,081)	Percentage of corrections that led to modification
Reasons for corrections			
Wrong dose[a]	840 (45.4)	407	48.5
Dose higher than guideline[b] maximum[a]	515	218	42.3
Dose lower than guideline[b] minimum[a]	223	100	44.8
Dose ≥ 10x higher than guideline[b] maximum[a]	42	35	83.3
Dose ≥ 10x lower than guideline[b] minimum[a]	54	48	90.7
Wrong dose – miscellaneous[a]	6	5	83.3
Wrong drug formulation	174 (9.4)	137	78.7
Non-adherence to anticancer treatment protocol	120 (6.5)	81	67.5
Free-text entry instead of standard line selection	119 (6.4)	96	80.7
Dosage form and route of administration do not correspond	112 (6.1)	85	75.9
Wrong frequency	82 (4.4)	35	42.7
Miscellaneous	72 (3.9)	29	40.3
Wrong drug	58 (3.1)	51	87.9
Wrong unit(s)	46 (2.5)	38	82.6
Drug-drug interaction	43 (2.3)	8	18.6
Drug not in hospital assortment	41 (2.2)	28	68.3
Wrong route of administration	34 (1.8)	20	58.8
Wrong body weight	32 (1.7)	7	21.9
Wrong strength/concentration	24 (1.3)	20	83.3
Wrong dosage form	16 (0.9)	13	81.3
Drug not on market	9 (0.5)	9	100.0
Wrong duration of therapy	9 (0.5)	7	77.8
(Pseudo) double medication	9 (0.5)	2	22.2
Wrong patient	6 (0.3)	5	83.3
Wrong body surface area	5 (0.3)	3	60.0

[a] Wrong doses were separately studied for doses higher/lower than guideline maximum/minimum and for doses ≥ 10 times higher and lower than guideline maximum/minimum.
[b] Primary source Wilhelmina Children's Hospital drug formulary.

Discussion

Frequency and nature

To our knowledge this is the first study on clinical pharmacy interventions in electronic prescribing in pediatrics. Most of the interventions in this study concerned corrections, rather than completions, whilst Ghaleb et al.[12] recently identified incomplete, rather than incorrect, pediatric prescriptions as accounting for most of the errors. However, Ghaleb et al. studied *handwritten*, not *electronic* prescriptions, causing incompleteness to be of minor importance as it has been shown that CPOE systems enhance legibility and completeness of prescriptions.[24-26] Nonetheless, this study shows that the studied custom CPOE system, not originally designed for use in children, does not secure 100% completeness. Thus, as a result of this study, the CPOE system was adjusted: body weight is now an obligatory field because most completions concerned an absent body weight.

The incomplete prescriptions were considered to be clinically irrelevant, as opposed to the corrected prescriptions which were considered to have had potentially adverse clinical consequences. In this study more than 80% of the interventions concerned a correction of a prescription that might have had adverse clinical consequences. Most of these corrections concerned a wrong dose. It is well known that dosing errors are the most common type of error in pediatric patients.[27] In this study, dose discrepancies constituted 36% of all interventions. Ghaleb et al.[12] recently found a similar percentage of dosing errors in handwritten prescriptions in a hospitalized pediatric population, demonstrating that the studied custom CPOE system with basic CDS does not necessarily solve the problem of dosing complexity in children. As a result of this study the CDS was adjusted: dose checking is now integrated and an alert is generated when prescribing a dose outside the limits for children. Another form of CDS, electronic drug-drug interaction checking, had already been adjusted to the pediatric setting of the hospital before this study, because it had been shown that the scope of drug-drug interactions in a children's hospital is different from that in adults.[28]

The physician acceptance rates in pediatric hospital pharmacy intervention studies varied from 60% to 98%.[29,30] Almost 50% of the interventions in this study did not lead to a modification of the prescription by the prescriber. This may be explained by suboptimal CDS design in two ways. On the one hand, the system does not show the reason for prescribing a certain drug. As many drug doses are dependent on the indication for which they are prescribed, this information would be useful. On the other hand, the system does not support treatment decisions for unlicensed drugs and off-label use, both common in pediatrics.[31,32] By adding visible indications to drugs in the standardized structured templates, the CDS system could help physicians prescribing both inside and outside product licenses.

A unique reason for intervention was wrong drug formulations. This is probably owing to the well-known lack of suitably adapted medicines for children, resulting in the need for extemporaneous dispensing.[33] Almost 80% of these interventions led to a modification of the prescription,

indicating that pediatric clinical pharmacy expertise is needed, that the CDS cannot yet overcome the difficulties with formulations for children and that further research is required in this field.
Tailored CPOE and CDS systems as described above, are not the sole solution to preventing prescribing errors. CPOE and CDS do not prevent all kinds of errors, especially not the more complex errors specific to pediatrics. Other non-technical solutions are also needed: education for prescribers in the fields of pharmacotherapy, prescribing skills and error prevention for example, and medication reconciliation at admission and discharge, have been shown to play an important role in preventing prescribing errors.[7,8,34,35]

Determinants

In this study the strongest determinant for clinical pharmacy intervention was free-text entry. Free-text entry in CPOE systems has been shown to result in many typing and spelling errors, a great diversity in the vocabulary used and inconsistent communication, leading to significant safety risks. [36,37] It may be concluded that standardized structured templates and drop-down menus are an essential tool for prescribing accurately and efficiently and that free-text entry should be limited to a minimum.
Of the patient-related determinants an age of 0-2 years was associated with clinical pharmacy intervention. This finding supports the earlier mentioned recommendations: CDS that supports prescribing both inside and outside product licenses and that supports drug formulation choices should be developed.
Unlike a recent pediatric study that associated evening and night shifts with higher medication error rates,[38] in this study evening and night shifts did not appear to be determinants.
The oral dosage form and oral route of administration were methods with a relatively high risk for intervention. This may indicate that dosing knowledge and oral dosage forms are not appropriate for children, especially because gastric tubes are extensively used in hospital.[39,40]
Summarizing, this study leads to several recommendations which should be focused on in the development of CPOE with CDS appropriate for use in children (table 3).

Limitations

This study has several limitations. The prescribers' physician class – for example, staff versus resident, was not studied because this could not be extracted from the data. In view of prior publications on differences in prescribing skills, this information would have been interesting.[41-43]
Another limitation is the potential variability in the way in which prescriptions were verified and interventions carried out under direct supervision of the two involved clinical pharmacists. This variability is expected to be minimal because the process followed a strict protocol and the two clinical pharmacists were highly specialized in pediatric clinical pharmacy. Overall, generalization of specific study results may be difficult and limited, because of the different CPOE and CDS

Table 3 Interpretation of the study: aspects that should be focused on in the development of CPOE systems with CDS appropriate for use in children.

1. Free-text entry should be minimized to prevent typing and spelling errors, diversity in vocabulary used and inconsistent communication leading to medication errors.
2. Certain fields should be obligatory, for example body weight and indication/reason for prescribing, to optimize CDS.
3. Dose checking should be integrated to prevent dosing errors.
4. Drug formularies, (off-label) treatment protocols and indications should be integrated to minimize free-text entry, give insight into the use of drugs outside the product license and make clinical pharmacy interventions more efficient.
5. CDS for prescribing correct and suitable drug formulations for children should be developed.
6. Efficiency could be enhanced by authorising hospital pharmacy staff to complete missing administrative prescription features without having to consult the prescriber.
7. Attention should be paid to CDS for prescriptions for children up to 2 years of age and prescriptions for oral drug use.

CPOE computerized physician order entry; CDS clinical decision support

systems used in other hospitals. Nonetheless, this kind of research, seeking potential ways of reducing error, is required for evidence-based development and optimization of CPOE systems and CDS tools for hospitalized patients and hospitalized children, in particular.[11,22]

Conclusion

In pediatric settings prescribing errors often occur and the use of CPOE and CDS systems does not fully prevent these errors. This study provides suggestions for improvements by incorporating tailored solutions in CPOE/CDS systems, such as minimised free-text entry, integrated dose checking and certain obligatory fields – for example, body weight and (off-label) indications. Future research to improve the quality and efficiency of electronic prescribing in pediatrics should focus on further CDS developments – for example, for the youngest of age, use of products outside the product license and drug formulation choice. Besides developing CPOE and CDS, non-technical solutions such as prescriber education and medication reconciliation should continue to recieve attention to reduce pediatric prescribing error rates as far as possible.

References

1 Topic: Quality and Patient Safety. Institute of Medicine of the National Academies. Available at: http://www.iom.edu/Reports.aspx [Accessed 1 August 2012].

2 Patient Safety, Department of Health of the UK government. Available at: http://www.dh.gov.uk/en/Healthcare/Patientsafety/index.htm [Accessed 1 August 2012].

3 European Commission Public Health Patient Safety Policy. Available at: http://ec.europa.eu/health/patient_safety/policy/index_en.htm [Accessed 1 August 2012].

4 Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 1991;324:377-84.

5 Aspden P, Wolcott J, Bootman J, et al. Preventing medication errors: quality chasm series. Institute of Medicine of the National Academies. Washington, DC, National Academies Press, 2007. Available at: http://www.iom.edu/Reports/2006/Preventing-Medication-Errors-Quality-Chasm-Series.aspx [Accessed 1 August 2012].

6 Smith J. Building a safer NHS for patients: improving medication safety. A report by the Chief Pharmaceutical Officer. Department of Health of the UK government 2004. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4071443 [Accessed 1 August 2012].

7 Lewis PJ, Dornan T, Taylor D, et al. Prevalence, incidence and nature of prescribing errors in hospital inpatients: a systematic review. Drug Saf 2009;32:379-89.

8 Tully MP, Ashcroft DM, Dornan T, et al. The causes of and factors associated with prescribing errors in hospital inpatients: a systematic review. Drug Saf 2009;32:819-36.

9 Barber N, Rawlins M, Dean Franklin B. Reducing prescribing error: competence, control, and culture. Qual Saf Health Care 2003;12 Suppl 1:i29-32.

10 National Coordinating Council for Medication Error Reporting and Prevention. About Medication Errors. Available at: http://www.nccmerp.org [Accessed 1 August 2012].

11 Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. Ann Pharmacother 2006;40:1766-76.

12 Ghaleb MA, Barber N, Franklin BD, et al. The incidence and nature of prescribing and medication administration errors in paediatric inpatients. Arch Dis Child 2010;95:113-8.

13 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

14 Kim GR, Chen AR, Arceci RJ, et al. Error reduction in pediatric chemotherapy: computerized order entry and failure modes and effects analysis. Arch Pediatr Adolesc Med 2006;160:495-8.

15 Longhurst CA, Parast L, Sandborg CI, et al. Decrease in hospital-wide mortality rate after implementation of a commercially sold computerized physician order entry system. Pediatrics 2010;126:14-21.

16 Ash JS, Sittig DF, Poon EG, et al. The extent and importance of unintended consequences related to computerized provider order entry. J Am Med Inform Assoc 2007;14:415-23.
17 Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293:1197-203.
18 Maslove DM, Rizk N, Lowe HJ. Computerized physician order entry in the critical care environment: a review of current literature. J Intensive Care Med 2011;26:165-71.
19 Helmons PJ, Grouls RJ, Roos AN, et al. Using a clinical decision support system to determine the quality of antimicrobial dosing in intensive care patients with renal insufficiency. Qual Saf Health Care 2010;19:22-6.
20 Maat B, Rademaker CM, Oostveen MI, et al. The effect of a computerized prescribing and calculating system on hypo- and hyperglycemias and on prescribing time efficiency in neonatal intensive care patients. JPEN J Parenter Enteral Nutr 2013;37:85-91.
21 Kim GR, Lehmann CU and the Council on Clinical Information Technology. Pediatric aspects of inpatient health information technology systems. Pediatrics 2008;122:e1287-96.
22 Caldwell NA, Power B. The pros and cons of electronic prescribing for children. Arch Dis Child 2012;97:124-8.
23 ten Berg MJ, Huisman A, van den Bemt PM, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.
24 van Doormaal JE, van den Bemt PM, Zaal RJ, et al. The influence that electronic prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. J Am Med Inform Assoc 2009;16:816-25.
25 Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280:1311-6.
26 Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerized physician medication order entry in hospitalized patients--a systematic review. Int J Med Inform 2008;77:365-76.
27 Wong IC, Ghaleb MA, Franklin BD, et al. Incidence and nature of dosing errors in paediatric medications: a systematic review. Drug Saf 2004;27:661-70.
28 Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, et al. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009;68:187-93.
29 Virani A, Crown N. The impact of a clinical pharmacist on patient and economic outcomes in a child and adolescent mental health unit. Can J Hosp Pharm 2003;56:158-62.
30 Condren ME, Haase MR, Luedtke SA, et al. Clinical activities of an academic pediatric pharmacy team. Ann Pharmacother 2004;38:574-8.
31 Lindell-Osuagwu L, Korhonen MJ, Saano S, et al. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 2009;34:277-87.
32 Shah SS, Hall M, Goodman DM, et al. Off-label use in hospitalized children. Arch Pediatr Adolesc Med 2007;161:282-90.

33 Tuleu C. Paediatric formulations in practice. In: Florence AT, Moffat AC, eds. Paediatric Drug Handling. London: Pharmaceutical Press 2007:43-74.

34 Dornan T, Ashcroft D, Heathfield H, et al. An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. EQUIP study. Available at: http://www.gmc-uk.org/about/research/research_commissioned_4.asp [Accessed 3 October 2012].

35 Mueller SK, Sponsler KC, Kripalani S, et al. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med 2012;172:1057-69.

36 Seidling HM, Paterno MD, Haefeli WE, et al. Coded entry versus free-text and alert overrides: What you get depends on how you ask. Int J Med Inform 2010;79:792-6.

37 Singh H, Mani S, Espadas D, et al. Prescription errors and outcomes related to inconsistent information transmitted through computerized order entry: a prospective study. Arch Intern Med 2009;169:982-9.

38 Miller AD, Piro CC, Rudisill CN, et al. Nighttime and weekend medication error rates in an inpatient pediatric population (November). Ann Pharmacother 2010;44:1739-46.

39 Chua SS, Chua HM, Omar A. Drug administration errors in paediatric wards: a direct observation approach. Eur J Pediatr 2010;169:603-11.

40 van den Bemt PM, Fijn R, van der Voort PH, et al. Frequency and determinants of drug administration errors in the intensive care unit. Crit Care Med 2002;30:846-50.

41 Glover ML, Sussmane JB. Assessing pediatrics residents' mathematical skills for prescribing medication: a need for improved training. Acad Med 2002;77:1007-10.

42 Taylor BL, Selbst SM, Shah AE. Prescription writing errors in the pediatric emergency department. Pediatr Emerg Care 2005;21:822-7.

43 Coombes ID, Stowasser DA, Coombes JA, et al. Why do interns make prescribing errors? A qualitative study. Med J Aust 2008;188:89-94.

Appendix 1 Determinants of interventions by the pediatric clinical pharmacy staff in electronic medication prescriptions for pediatric inpatients.

	Intervened prescriptions n=1,577 (100%)	Non-intervened prescriptions n=1,983 (100%)	OR_{crude} [95% CI]
Patient characteristics			
Gender			
Female	720 (45.7)	819 (41.3)	1.19 [1.05, 1.37]
Male	857 (54.3)	1,164 (58.7)	ref
Age			
0-1 month	55 (3.5)	56 (2.8)	1.77 [1.19, 2.64]
1 month-2 years	493 (31.3)	452 (22.8)	1.97 [1.63, 2.38]
2-6 years	390 (24.7)	454 (22.9)	1.55 [1.28, 1.89]
6-12 years	338 (21.4)	479 (24.2)	1.28 [1.05, 1.55]
12-18 years	300 (19.0)	542 (27.3)	ref
Prescription characteristics			
Way of prescribing			
Free-text entry	252 (16.0)	77 (3.9)	4.71 [3.61, 6.13]
Standardized structured templates	1,325 (84.0)	1,906 (96.1)	ref
Medical discipline			
Day care internal medicine	91 (5.8)	281 (14.2)	0.38 [0.29, 0.50]
Surgery	247 (15.7)	367 (18.5)	0.79 [0.65, 0.97]
Neurology	320 (20.3)	292 (14.7)	1.29 [1.06, 1.58]
Cardiology	147 (9.3)	158 (8.0)	1.10 [0.85, 1.42]
Internal medicine	276 (17.5)	305 (15.4)	1.07 [0.87, 1.31]
Immunology/haematology	491 (31.1)	579 (29.2)	ref
Shift			
Night shift (23:00-08:00)	52 (3.3)	64 (3.2)	0.99 [0.68, 1.44]
Evening shift (18:00-23:00)	140 (8.9)	167 (8.4)	1.02 [0.80, 1.29]
Day shift (08:00-18:00)	1,045 (66.3)	1,270 (64.0)	ref
Day of the week			
Monday	371 (23.5)	354 (17.9)	1.48 [1.20, 1.82]
Tuesday	329 (20.9)	356 (18.0)	1.30 [1.05, 1.61]
Thursday	226 (14.3)	334 (16.8)	0.95 [0.76, 1.20]
Friday	202 (12.8)	326 (16.4)	0.87 [0.69, 1.10]
Saturday	65 (4.1)	120 (6.1)	0.76 [0.55, 1.10]
Sunday	95 (6.0)	87 (4.4)	1.54 [1.11, 2.14]
Wednesday	288 (18.3)	406 (20.5)	ref
Season			
Summer (21/6-20/9)	500 (31.7)	479 (24.2)	1.34 [1.12, 1.61]
Autumn (21/9-20/12)	377 (23.9)	547 (27.6)	0.89 [0.74, 1.07]
Winter (21/12-20/3)	310 (19.7)	456 (23.0)	0.87 [0.72, 1.06]
Spring (21/3-20/6)	390 (24.7)	501 (25.3)	ref

OR odds ratio; CI confidence interval.

Appendix 1 Continued.

	Intervened prescriptions n=1,577 (100%)	Non-intervened prescriptions n=1,983 (100%)	OR_{crude} [95% CI]
Medication characteristics			
Dosage form			
Oral dosage forms	783 (49.7)	697 (35.1)	1.63 [1.41, 1.88]
Powders & liquids for inhalation	41 (2.6)	62 (3.1)	0.96 [0.64, 1.44]
Eye drops & eye ointments	12 (0.8)	10 (0.5)	1.74 [0.75, 4.05]
Dermatics	14 (0.9)	17 (0.9)	1.19 [0.58, 2.44]
Suppositories	74 (4.7)	214 (10.8)	0.50 [0.38, 0.67]
Miscellaneous	33 (2.0)	58 (3.1)	0.83 [0.53, 1.28]
Injections/infusions	611 (38.8)	886 (44.7)	ref
Route of administration			
Oral	840 (53.3)	742 (37.4)	1.80 [1.55, 2.09]
Rectal	88 (5.6)	251 (12.7)	0.56 [0.43, 0.73]
Miscellaneous	133 (8.4)	175 (8.8)	1.21 [0.94, 1.55]
Parenteral	512 (32.4)	814 (41.1)	ref
Drug class			
Antimycotics for systemic use	22 (1.4)	13 (0.7)	2.14 [1.08, 4.27]
Antibacterials for systemic use	245 (15.6)	273 (13.8)	1.16 [0.96, 1.40]
Alimentary tract and metabolism	219 (13.9)	297 (15.0)	0.92 [0.76, 1.11]
Nervous system	212 (13.4)	206 (10.4)	1.33 [1.09, 1.63]
Cardiovascular system	158 (10.0)	132 (6.7)	1.56 [1.23, 1.99]
Anti cancer drugs	154 (9.8)	155 (7.8)	1.28 [1.01, 1.16]
Painkillers (acetaminophen and NSAIDs)	104 (6.6)	284 (14.3)	0.42 [0.33, 0.53]
Respiratory system	79 (5.0)	178 (9.0)	0.53 [0.41, 0.70]
Miscellaneous	375 (23.8)	464 (23.4)	1.02 [0.87, 1.20]

OR odds ratio; CI confidence interval; NSAID non-steroidal anti-inflammatory drug.

PART II

EFFECTS OF ELECTRONIC SUPPORT ON PRESCRIBING ERRORS IN PEDIATRIC PATIENTS

Chapter 5

The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review

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Abstract

Purpose Pediatric and intensive care patients are particularly at risk for medication errors. Computerized physician order entry systems could be effective in reducing medication errors and improving outcome. Effectiveness of computerized physician order entry systems has been shown in adult medical care. However, in critically ill patients and/or children, medication prescribing is a more complex process, and usefulness of computerized physician order entry systems has yet to be established. This study evaluated the effects of computerized physician order entry systems on medication prescription errors, adverse drug events, and mortality in inpatient pediatric care and neonatal, pediatric or adult intensive care settings.

Methods PubMed, the Cochrane library, and Embase up to November 2007 were used as our data sources. Inclusion criteria were studies of (1) children 0 to 18 years old and/or ICU patients (including adults), (2) computerized physician order entry versus no computerized physician order entry as intervention, and (3) randomized trial or observational study design. All studies were validated, and data were analyzed.

Results Twelve studies, all observational, met our inclusion criteria. Eight studies took place at an ICU: 4 were adult ICUs, and 4 were PICUs and/or NICUs. Four studies were pediatric inpatient studies. Meta-analysis showed a significant decreased risk of medication prescription errors with use of computerized physician order entry. However, there was no significant reduction in adverse drug events or mortality rates. A qualitative assessment of studies revealed the implementation process of computerized physician order entry software as a critical factor for outcome.

Conclusions Introduction of computerized physician order entry systems clearly reduces medication prescription errors; however, clinical benefit of computerized physician order entry systems in pediatric or ICU settings has not yet been demonstrated. The quality of the implementation process could be a decisive factor determining overall success or failure.

Introduction

According to the Institute of Medicine, medical errors lead to 44.000 to 98.000 deaths in the United States annually.[1] Currently, prevention of medical errors receives a large amount of attention and presents a major challenge to health care. In particular, critically ill patients are vulnerable and at risk for medication prescription errors (MPEs). Within this population, neonatal and pediatric patients present an even more vulnerable group. A study by Kaushal et al[2,3] underlined this by showing that potentially harmful errors occurred 3 times more frequently in pediatric than in adult patients. Moreover, an increasing number of drugs, regimen complexity, and the continuously growing knowledge base of drug indications and adverse effects create the need for automated systems to deliver clinical support.[4] Use of computerized physician order entry (CPOE) systems could possibly address these problems. For example, it has been shown that computer support in drug dosing has resulted in more patients with drug concentrations in the therapeutic range, reduced time to achieve therapeutic benefits, and resulted in fewer adverse effects of treatment in adults.[5] Computer systems, therefore, may support doctors in tailoring drug doses more closely to the needs of individual patients.

CPOE can also improve patient safety in several ways. First, CPOEs are obviously more legible than handwritten ones. Furthermore, CPOE can force physicians to include dose, route of administration, and frequency in the order before authorizing the prescription, thus resulting in better structured and more complete medication prescriptions. CPOE systems can be linked to databases with background information and deliver decision support by warning for drug-dosage errors, interactions, or contraindications.[6] However, although it is generally assumed that CPOE systems decrease medication error rates and improve clinical outcome, unfavorable findings associated with CPOE have been reported as well.[7] In a study by Han et al,[8] the mortality rate in a pediatric population increased after CPOE implementation. Therefore, specific settings such as pediatric or neonatal care or complex environments such as ICUs could determine the eventual clinical effect of CPOE systems.

We performed a systematic review of the use of CPOE systems in the most demanding and complex situations, that is, adult ICUs, PICUs, and NICUs, and in general pediatric and neonatal care. Meta-analysis was performed to estimate effects on MPEs, adverse drug events (ADEs), and mortality rate. Factors associated with success or failure of CPOE systems were identified.

Methods

This systematic review was conducted according to the criteria as defined in the Quality of Reporting of Metaanalyses (QUORUM) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) statements.[9,10]

Literature research

Studies were identified by searching PubMed, the Cochrane library, and Embase up to November 2007. The literature search strategy was performed by using the following search terms: (child*[tiab] or paediatr*[tiab] or pediatr*[tiab] or infant*[tiab] or toddler*[tiab] or "pre school"[tiab] or preschool[tiab] or adolescent*[tiab] or pediatrics[Medical Subject Headings (MeSH)] or child[MeSH] or infant[MeSH] or adolescent[MeSH] or intensive care units[MeSH] or intensive care units, neonatal[MeSH] or intensive care, neonatal[MeSH] or intensive care[tiab]) and (CPOE[tiab] or "computerized physician order entry"[tiab] or "computerized provider order entry"[tiab] or "computerized prescribing"[tiab] or "electronic prescribing systems"[tiab] or "computerized order entry"[tiab] or "computer order entry"[tiab] or "medical order entry systems"[MeSH]).

Study selection

After title screening, we examined abstracts and selected articles that met all of the following inclusion criteria: (1) hospitalized children 0 to 18 years old and/or ICU patients (including adults); (2) intervention CPOE compared with no CPOE; and (3) randomized trial or observational cohort study design. Exclusion criteria were descriptive studies (ie, case reports, narrative reviews, comments, etc) and CPOE research in populations targeted at specific diseases. Literature lists of included articles were searched for possible additional studies.

Definitions

A CPOE system was defined as a computer-based system that automates the medication-ordering process to ensure standardized, legible, and complete orders. A clinical decision-support system consists of at least basic dosing guidance for medication, formulary decision support, and drug allergy, duplicate therapy, and drug-drug interaction checking.[11] Clinical decision-support systems are built into most CPOE systems.[3] An MPE was defined as any error in prescription of medication irrespective of outcome. Potential ADEs were defined as medication errors with significant potential to harm a patient without reaching a patient, and ADEs were defined as actual harm that resulted from a medication error.[2]

Data extraction

The following data were extracted: year of study, study design, study period, whether the study was performed in an academic hospital, patient population (adult ICU, PICU, NICU, or pediatric ward), software manufacturer, presence of decision regarding support. With respect to the implementation process, use of classroom training and individual training and on-site support present after CPOE implementation was assessed.

Validity assessment

Observational studies were evaluated by applying criteria from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[12] We determined validity by assessing whether control and intervention groups were defined, whether possible sources of confounding, selection bias, or misclassification were identified and/or adjusted for, whether outcome measures were clearly defined, whether the exact study period was mentioned, whether the implementation process was described, and whether original outcome data were available in the publication. Validity of randomized trials was assessed by using the criteria published by Jadad et al.[13]

Data analysis

All data were analyzed on an intention-to-treat basis. Risk rates for MPEs were calculated by dividing the number of errors by the total number of prescriptions in the intervention and control groups, respectively. Risk rates for ADEs and mortality were calculated by the number of incidents divided by the population at risk in the 2 groups: CPOE and no CPOE. Using the risk rates in both groups, relative risk (RR) estimates were calculated along with 95% confidence intervals (CI). Pooled RR estimates were calculated by using a random-effects model. Heterogeneity was assessed by the I[r]^2 statistic.[14] I^2 describes the percentage of total variation across studies resulting from heterogeneity rather than chance. I^2 ranges from 0% to 100%; a value of 0% indicates no heterogeneity, and larger values indicate increasing heterogeneity. All analyses were conducted by using Excel 2007 (Microsoft, Redmond, WA).

Results

Search

Our literature search yielded 122 citations that were screened for relevance, which left 12 articles that were included in the systematic review (Fig 1). We also cross-referenced the results of our literature search with lists of studies published in another systematic review.[15] This did not yield any additional studies that were not already found in our search. Although the studies of Han et al[8] and Upperman et al[16] took place in the same hospital, the outcomes were different and both, therefore, were included.

Included studies

Among the 12 included studies, which are summarized in Table 1, there were no randomized trials. There was 1 controlled cross-sectional trial.[17] Eight studies were retrospective,[8,16,18–23] and 3 studies were prospective cohort studies.[7,24,25] Of the included studies, 4 were performed with adult ICU patients,[7,17,22,23] and 8 were performed with pediatric patients.[8,16,18–21,24,25] Of those 8 pediatric studies, 4 were performed on a PICU and/or NICU,[18–20,25] 1 on a ward with a PICU,[24] and 3 on a pediatric ward.[8,16,21]

Table 1 Included studies.

Study (Year)	Study design	Academic	Patient set	Setting	Software	Decision support	Comparison	Outcome	Implementation process	Conclusion
Thompson et al[22] (2004)	Retrospective cohort	Yes	Adult	ICU	Eclipsys	No	No CPOE	Ordering times	Classroom training, personal training, on-site support	Improved timeliness of urgent tests
Shulman et al[7] (2005)	Prospective cohort	Yes	Adult	ICU	Cis	No	Handwritten orders	MPEs and/or ADEs	Not described	Small decrease in MEs and timeliness of service
Colpaert et al[17] (2006)	Controlled cross-sectional trial	Yes	Adult	ICU	Not described	Yes, Moderate level	Paper-based unit	MPEs	Not described	Decrease in MPEs
Weant et al[23] (2007)	Retrospective cohort	No	Adult	ICU	Not described	Not described	No CPOE	MPEs and/or ADEs	Training (kind of training not mentioned)	Increase in medication errors during initial period after CPOE implementation
Cordero et al[18] (2004)	Retrospective cohort	Yes	Neonatal	NICU	Siemens	Yes	No CPOE	MPEs, medication turnaround time	Classroom training, personal training, on-site support	Significant reduction in medication turnaround times and MPEs
Keene et al[20] (2007)	Retrospective cohort	No	Neonatal/pediatric	NICU/PICU	PHAMIS	Not described	No CPOE	Mortality rate	Classroom training, personal training, on-site support	Mortality rate did not increase during CPOE implementation
King et al[21] (2003)	Retrospective cohort	Yes	Pediatric	Ward	Eclipsys	No	No CPOE	MPEs and/or ADEs	Not described	Decrease in MPEs, not in ADEs
Potts et al[25] (2004)	Prospective cohort	Yes	Pediatric	PICU	WizOrder	Yes	No CPOE	MPEs and/or ADEs	Training (kind of training not mentioned)	Decrease in MPEs, and potential ADEs

Table 1 Continued.

Study (Year)	Study design	Academic	Patient set	Setting	Software	Decision support	Comparison	Outcome	Implementation process	Conclusion
Upperman et al[16] (2005)	Retrospective cohort	No	Pediatric	Ward	Cerner	Yes	No CPOE	Number-needed-to-treat analogue	Classroom training, extra training on request	CPOE would prevent 1 ADE every 64 patient-days
Han et al[8] (2005)	Retrospective cohort	No	Pediatric	Ward	Cerner	Yes	No CPOE	Mortality rate	Classroom training	Increase in mortality rate
Del Beccaro et al[19] (2006)	Retrospective cohort	Yes	Pediatric	PICU	Cerner	Yes	No CPOE	Mortality rate	Classroom training, personal training, on-site support	No increase in mortality rate, even shortly after CPOE implementation
Holdsworth et al[24] (2007)	Prospective cohort	Yes	Pediatric	PICU/ward	Eclipsys	Yes, substantial	No CPOE	ADEs	Not described	CPOE associated with reduction in ADEs and potential ADEs

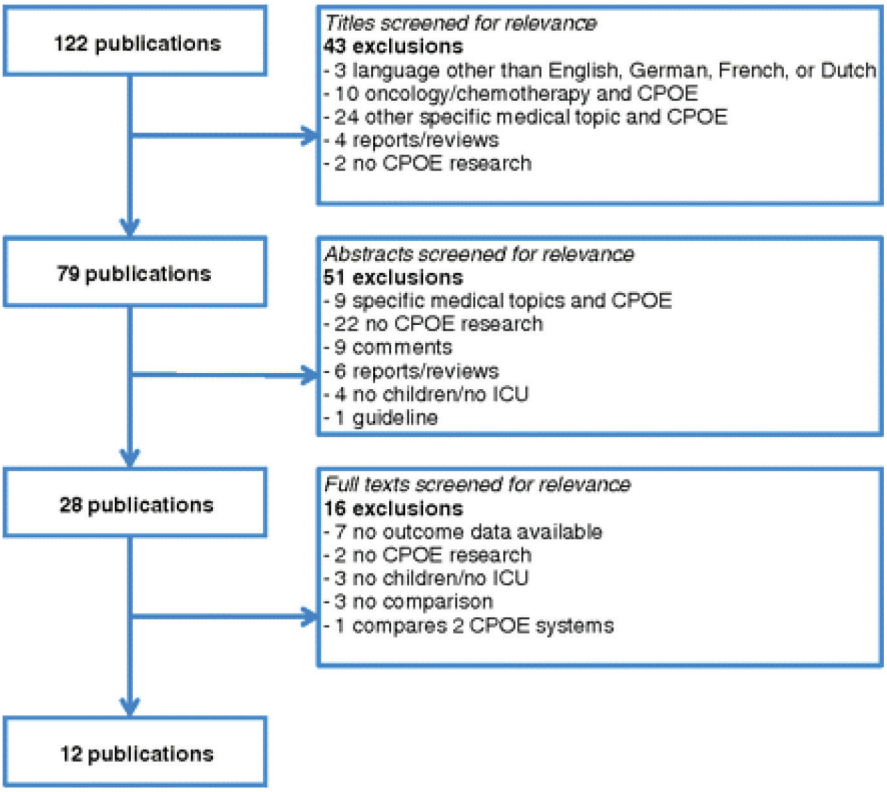

Figure 1 Study selection.

Three of the 12 studies reported mortality as outcome,[8,19,20] 1 analyzed workflow,[22] 7 of them studied MPEs and/or ADEs,[7,16,17,21,23–25] and 1 study[18] reported 3 outcomes: medication turnaround times, radiology procedure completion time, and MPEs (only gentamicin dosages). The definitions of MPEs and ADEs varied considerably among studies.

Different kinds of CPOE software systems were used: Siemens (Munich, Germany), Eclipsys (Atlanta, GA), Cerner (Kansas City, KS), PHAMIS (Seattle, WA), Wiz-Order (Nashville, TN), and homegrown systems. Because of a lack of consistency among studies, quantitative data analysis across vendors was not possible.

In 7 studies, implementation of decision support was explicitly mentioned,[8,16–19,24,25] in 3 studies there was no decision support,[7,21,22] and 2 studies did not describe whether decision support was available.[20,23] A quantitative data analysis on decision support also was not possible, either because the studies poorly described the decision-support systems or because of the different levels of decision support among studies.

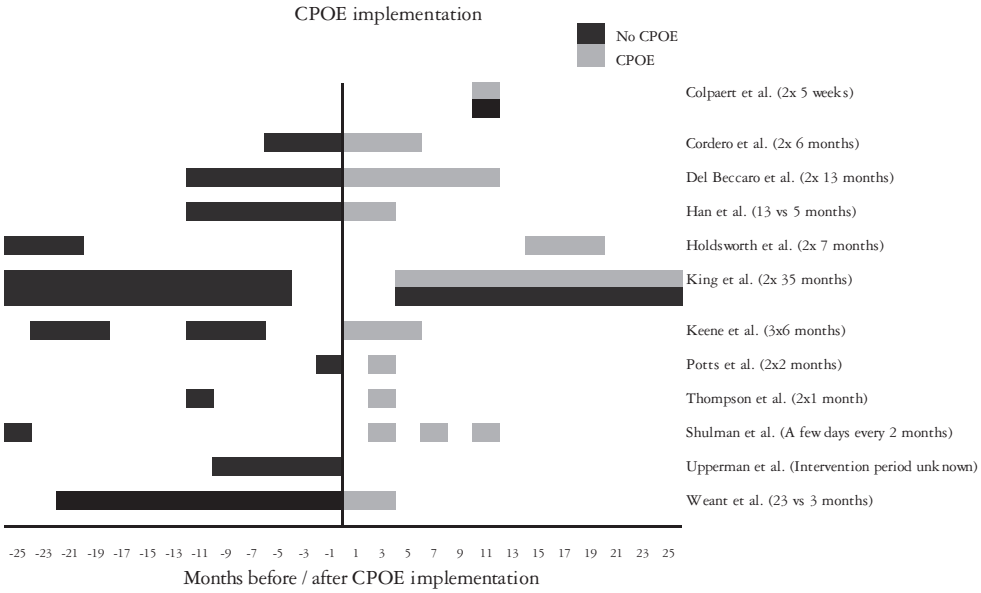

Figure 2 Distribution of the study periods.

There was considerable variation in timing and length of the periods in which outcome was measured without or before CPOE and with CPOE among studies (Fig 2). Five of the studies started their intervention period right after CPOE implementation.[8,18–20,23] Therefore, a socalled learning-curve in these studies was included in the measurements. The other 7 studies did not include the period right after CPOE implementation in the measurement period.

Adult ICU studies

All 4 adult ICU studies described an intervention and a control group, assessed potential confounding, and mentioned quantitative outcome data on number of MPEs, ADEs, and/or mortalities. Study periods varied among the ICU studies (Fig 2). For 2 of the studies, the implementation process was not described,[7,17] for 1 study it was mentioned only briefly,[23] and for only 1 study was it described extensively.[22] An increase in MPEs was observed by Weant et al[23] during the initial period after CPOE implementation. Three studies showed a clinical beneficial effect.[7,17,22] In the study by Colpaert et al,[17] CPOE only had a beneficial effect when potential ADEs were taken into account.

Pediatric, PICU, and NICU studies

In all 8 studies the intervention and/or control group were clearly defined. All studies reported patient and clinical characteristics that implied comparability between the intervention and control groups. The original outcome data could be extracted from all studies except that of

Upperman et al.[16] In this study, only aggregate outcome estimates were reported. Again, study periods varied considerably (Fig 2). King et al[21] did not describe their implementation process, Potts et al[25] and Holdsworth et al[24] mentioned it briefly, and the other 5 authors[8,16,18–20] described their implementation process more extensively.

Of 5 studies with MPEs and/or ADEs as outcome measures, CPOE conferred a significant beneficial effect in 3 studies,[18,24,25] and in 1 study a nonsignificant beneficial effect was reported.[16] In the study by King et al,[21] the overall result was beneficial: MPEs decreased, as did ADEs, but potential ADEs increased. In the 3 studies with mortality rate as main outcome,[8,19,20] results varied; in the study by Han et al[8] the mortality rate increased, whereas Del Beccaro et al[19] reported a nonsignificant decrease in mortality rate, and Keene et al[20] reported a significant decrease in mortality rate.

Implementation process

Four studies described classroom training before implementation, extensive individualized instruction, and onsite support during and after CPOE implementation.[18–20,22] Two of those studies showed a significant beneficial effect of CPOE.[18,22] In the other 2 studies, mortality rates did not increase after CPOE implementation.[19,20] Han et al[8] and Upperman et al reported 3 hours of classroom computer practice 3 months before CPOE implementation. In the Upperman et al[16] study, CPOE had a positive effect on ADEs, but in the Han et al[8] study, introduction of a CPOE system increased mortality rates.

Meta-analysis

A meta-analysis was conducted to pool the outcome measures: MPEs, ADEs (potential and actual ADEs taken together), and mortality rate (Table 2). MPEs were pooled, taking all studies together. ADEs and mortality rates were pooled for pediatric and neonatal studies only. There was a significant reduction in MPEs (RR: 0.08 [95% CI: 0.01–0.77]), uniformly observed in all studies. The number of potential and actual ADEs showed a nonsignificant decrease with the use of CPOE (RR: 0.65 [95% CI 0.40–1.08]). However, there was significant heterogeneity (I^2 = 65%) among the studies. Quantitative analysis to explore the causes for this heterogeneity was not possible because of the limited number of studies available. Mortality rates were not significantly influenced by CPOE (RR: 1.02 [95% CI: 0.52–1.94]). This was observed in all studies except for the study by Han et al.8 In that study, an RR of 2.35 (95% CI: 1.51–3.65) was observed. Even after adjustment for possible confounders, the mortality risk associated with CPOE remained elevated (odds ratio: 3.28 [95% CI: 1.94–5.55]).

Table 2 Meta-analyses.

	With CPOE			No CPOE				
	n	**Errors/ADEs/ Mortalities, *n***	**%**	***n***	**Errors/ADEs/ Mortalities, *n***	**%**	**RR**	**95% CI**
Errors								
Potts et al (2004)	7025	12[a]	0	6803	2049[a]	30	0.01	0.00-0.01
Shulman et al (2005)	2429	117[a]	5	1036	71[a]	7	0.70	0.53-0.94
Colpaert et al (2006)	1286	44[a]	3	1224	330[a]	27	0.13	0.09-0.17
Pooled (I^2 = 34%)							0.08	0.01-0.76
ADEs								
King et al (2003)	5786	7[b]	0.12	11699	5[b]	0.04	2.83	0.89-10.33
Potts et al (2004)	246	88[b]	36	268	147[b]	55	0.65	0.58-0.73
Holdsworth et al (2007)	1210	72[b]	6	1197	170[b]	14	0.42	0.33-0.55
Pooled (I^2 = 65%)							0.65	0.40-1.08
Mortalities								
Cordero et al (2004)	100	9[c]	9	111	16[c]	14	0.62	0.29-1.35
Han et al (2005)	548	36[c]	7	1394	39[c]	3	2.35	1.51-3.65
Del Beccaro et al (2006)	1301	45[c]	3	1232	52[c]	4	0.82	0.55-1.21
Keene et al (2007)	374	9[c]	2	917	29[c]	3	0.76	0.36-1.59
Pooled (I^2 = 0%)							1.02	0.52-1.94

[a] Errors
[b] ADEs
[c] Mortalities

Discussion

In this systematic review we affirmed the important potential of CPOE systems to reduce MPEs. However, to what extent the application of CPOE systems actually results in clinical benefit remains to be established. Our meta-analysis showed a nonsignificant and heterogeneously distributed reduction in ADEs. Overall, mortality did not seem to be affected by the use of CPOE. The implementation process without individual practice and in-house support after CPOE-implementation could be related with unfavorable clinical outcome.

This is the first systematic review that concentrates on the effects of CPOE on pediatric care and critical care in general. It is necessary to specifically focus on these groups because of their high vulnerability and the complexity of their treatments. We pooled results on MPEs, taking pediatric non-ICU, PICU, NICU, and adult ICU studies together, because of the involved complexity of the prescription process mentioned above. We assumed that the effect of CPOE systems on MPEs would be mainly influenced by the level of demand posed by the setting in which the CPOE system was used and the complexity of the patients. These patients probably demand a nonordinary CPOE system to improve MPEs and patient outcome, including ADEs. Obviously though, pediatric non-ICU, PICU, NICU, and adult ICU patients are quite different, and it would be interesting to distinguish between these groups and study them in more detail with regard to clinical outcome. Unfortunately, only a limited set of clinical outcome data restricted to pediatric and neonatal patients was available.

It is evident that CPOE gives rise to better structured and more clearly legible prescriptions. The dramatic decrease in MPEs experienced after CPOE implementation in different studies clearly illustrates this aspect. Moreover, improvement in communication between physicians, nurses, and pharmacists has been shown as well.[22] Ordering and prescribing by CPOE have been found to be more efficient than handwritten prescribing. Although it might be expected that CPOE systems can introduce new errors, in the present study this was not demonstrated. However, reductions in MPEs did not directly result in reduction in clinically relevant ADEs or improvement of clinical outcome.

The increase in mortality rates associated with the introduction of a CPOE system as reported by Han et al,[8] has been discussed extensively in the literature.[19,20,26] Del Beccaro et al[19] studied the exact same CPOE system as Han et al but did not find a significant change in mortality rates. Ammenwerth et al[26] compared these 2 studies and stated that there were important differences in design and implementation of these studies. Han et al studied CPOE use in a more critically ill and much younger patient population compared with Del Beccaro et al. Furthermore, Han et al only studied[5] months after CPOE implementation, whereas Del Beccaro et al extended their postimplementation study period to 13 months. The longer study period of Del Beccaro et al may have averaged out a potentially higher error rate in the first few months after CPOE implementation (learning curve). Besides Del Beccaro et al and Han et al, Keene et al[20] also studied the effect of

CPOE introduction in a critically ill pediatric population with comparable results to those of Del Beccaro et al. Potential causes of the increase in mortality rate in the study by Han et al have been hypothesized as slowing down of adequate patient treatment resulting from (1) the inability to register patients during transport to the hospital (medication could only be ordered when the patient had arrived in the hospital), (2) an increase in time needed to enter orders, (3) a reduction in verbal communication, (4) drug relocation from ward to central pharmacy, and (5) technical problems with network connections.[8,19,20,26] Most of these causes cannot be attributed to the CPOE system itself but resulted from the implementation process.

As can be concluded from the previous paragraph, the implementation of a CPOE system could be critical. We argue that 3 hours of training 3 months before the implementation day (Del Beccaro et al[19] and Han et al[8]) is far from sufficient. House staff cannot learn enough in just 3 hours, and 3 months later they probably will have forgotten most of what they did learn.

Seven systematic reviews about CPOE have been published as yet,[3,11,15,27–30] but none of them concentrated on CPOE in a pediatric and ICU population, which represent the most demanding and complex situations. For 1 study the effect of CPOE on medication safety in general was described,[3] for 1 clinical decision support and clinicians' behavior were described,[29] for 1 the effect on time records in clinical staff was studied,[30] 1 focused on the effect on pathology services,[28] 1 studied costs, adherence, and safety in a noncritical adult population,[27] and 1 focused on decision support and examined costeffectiveness.[11] Only 1 of these 7 reviews examined the use of CPOE in a pediatric and/or critically ill population.[15] However, this review did not assess the exclusive effects of CPOE systems on enhancing medication safety but, rather, investigated other interventions as well. In addition, this review applied other inclusion criteria and so included studies that differed from ours.

Ideally, a large randomized trial would provide valid evidence for the effect of CPOE systems on patient safety and clinical outcome. However, because of the nature of the intervention, a randomized trial would be practically nearly impossible to conduct. Therefore, most studies were based on a before/after design; however, this design permits limited conclusions about the causative nature of observed associations between CPOE introduction and change in outcome. More valid effect estimates could be obtained by using a "controlled before/after" design in a multicenter setting. An intervention setting with and a control setting without the intervention are both followed in time. Observed differences before and after the intervention, thus, can be adjusted for general changes in time in the control setting. Furthermore, in future studies, strict criteria should be used to define MPEs and ADEs, and methods of detecting and evaluating should be clearly described. We found definitions of detection and evaluation of MPEs and ADEs to vary widely among studies, which possibly led to variable results and making comparison between studies difficult (Table 3). Finally, intervention data should preferably be collected directly after CPOE implementation to make assessment of a potential learning curve possible.

Table 3 Definitions of medication prescription errors and adverse drug events.

	Study	Definition of MPE
1	Shulman R et al. 2005	Medication error = an error that occurred when a prescribing decision or prescription writing process resulted in either an unintentional significant reduction in the probability of treatment being timely and effective or an unintentional significant increase in the risk of harm when compared with generally accepted practice. – Minor error = causing no harm or an increase in patient monitoring with no change in vital signs and no harm noted – Moderate error = causing an increase in patient monitoring, a change in vital signs but without associated harm or a need for treatment or increased length of stay – Major error = causing permanent harm or death (according to an adapted scale) Intercepted errors (where the patient did not receive the drug) were separated from non-intercepted errors (where the patient received the drug)
2	Colpaert K et al. 2006	Medication prescription error = an error in the prescribing or monitoring of a drug – Minor MPE = no potential to cause harm – Intercepted MPE = potential to cause harm but intercepted on time – Serious MPE = non-intercepted potential adverse drug event or adverse drug event (adverse drug event being MPE with potential to cause, or actually causing, patient harm) (use of adjusted version of National Coordinating Council for Medication Error Reporting and Prevention guidelines)
3	Weant KA et al. 2007	Medication error not defined. Medication errors were classified as ordering, transcription, dispensing or administration errors. Medication errors were also classified as capacity for error (category A), error but no harm to patient (category B), error resulting in patient harm (category C). And medication errors were also classified in wrong patient, wrong dose, wrong time, wrong medication, omission, wrong i.v. rate, unauthorized dose, wrong diluent and other. All of these classifications without further explanation.
4	King WJ et al. 2003	Medication error = any event involving medication prescription, dispensing, administration, or monitoring of medications irrespective of outcome.
5	Cordero L et al. 2004	Prescription dosage error = prescribed dose > 10% deviation from recommended dose Only gentamicin prescribing taken into account. No other MPEs or MEs taken into account. Medication turn-around times of caffeine citrate included.
6	Potts AL et al. 2004	An error = an order found to be incomplete, incorrect, or inappropriate at the time of physician ordering. Errors were classified as: – Potential ADE = any error that, if allowed to reach the patient, could result in patient injury (the ordering physician provided incorrect or inappropriate information, or failed to account for patient-specific information e.g. allergy) – MPE = error in which inadequate information was provided or further interpretation (e.g. illegibility) was required for the order to be processed – Rule violation = error that was not compliant with standard hospital policies (e.g. abbreviations)

Table 3 Continued.

	Study	Definition of ADE
1	Colpaert K et al. 2006	Adverse drug event = an MPE with potential to cause, or actually causing, patient harm (appropriateness of drug choice was not considered)
2	King WJ et al. 2003	Adverse drug event = a medication error resulting in an injury to the patient – Potential ADE = a medication error with the potential for patient injury where no actual harm occurred.
3	Potts AL et al. 2004	An error = an order found to be incomplete, incorrect, or inappropriate at the time of physician ordering. Errors were classified as: – Potential ADE = any error that, if allowed to reach the patient, could result in patient injury (the ordering physician provided incorrect or inappropriate information, or failed to account for patient-specific information e.g. allergy) – MPE = error in which inadequate information was provided or further interpretation (e.g. illegibility) was required for the order to be processed – Rule violation = error that was not compliant with standard hospital policies (e.g. abbreviations)
4	Holdsworth MT et al. 2007	Adverse drug event = an injury from a medicine or lack of an intended medicine – Potential ADE = an error that had the potential to result in at least a significant injury (including errors detected before drug administration, as well as errors that were administered without causing significant adverse consequences) – Preventable ADE = all of the ADEs that were associated with a medication error

Conclusions

CPOE systems indisputably reduce MPEs effectively. However, as to what extent this results in improved patient safety and better clinical outcome remains to be established. The implementation process of CPOE systems requires specific attention, because this may be associated with adverse outcome. Multicenter studies, preferably designed as controlled before/after studies, are needed to ascertain the role and requirements of CPOE systems in improving hospital care for pediatric and critically ill patients.

References

1 Kohn LT. To Err is Human: Building a Safer Health System. Washington, DC: National Academy Press; 1999.

2 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114–20.

3 Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003;163:1409–16.

4 Schiff GD, Rucker TD. Computerized prescribing: building the electronic infrastructure for better medication usage. JAMA 1998;279:1024–9.

5 Walton R, Dovey S, Harvey E, et al. Computer support for determining drug dose: systematic review and metaanalysis. BMJ 1999;318:984–90.

6 Bates DW. Using information technology to reduce rates of medication errors in hospitals. BMJ 2000;320:788–91.

7 Shulman R, Singer M, Goldstone J, et al. Medication errors: a prospective cohort study of hand-written and computerized physician order entry in the intensive care unit. Crit Care 2005;9:R516–21.

8 Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system [published correction appeared in Pediatrics 2006;117:594]. Pediatrics 2005;116:1506–12.

9 Clarke M. The QUORUM statement. Lancet 2000;355:756–7.

10 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

11 Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007;14:29–40.

12 von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [published correction appeared in Ann Intern Med 2008;148:168]. Ann Intern Med 2007;147:573–7.

13 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.

14 Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

15 Conroy S, Sweis D, Planner C, et al. Interventions to reduce dosing errors in children: a systematic review of the literature. Drug Saf 2007;30:1111–25.

16 Upperman JS, Staley P, Friend K, et al. The impact of hospitalwide computerized physician order entry on medical errors in a pediatric hospital. J Pediatr Surg 2005;40:57–9.

17 Colpaert K, Claus B, Somers A, et al. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. Crit Care 2006;10:R21.

18 Cordero L, Kuehn L, Kumar RR, et al. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. J Perinatol 2004;24:88–93.
19 Del Beccaro MA, Jeffries HE, Eisenberg MA, et al. Computerized provider order entry implementation: no association with increased mortality rates in an intensive care unit. Pediatrics 2006;118:290–5.
20 Keene A, Ashton L, Shure D, et al. Mortality before and after initiation of a computerized physician order entry system in a critically ill pediatric population. Pediatr Crit Care Med 2007;8:268–71.
21 King WJ, Paice N, Rangrej J, et al. The effect of computerized physician order entry on medication errors and adverse drug events in pediatric inpatients. Pediatrics 2003;112:506–9.
22 Thompson W, Dodek PM, Norena M, et al. Computerized physician order entry of diagnostic tests in an intensive care unit is associated with improved timeliness of service. Crit Care Med 2004;32:1306–9.
23 Weant KA, Cook AM, Armitstead JA. Medication-error reporting and pharmacy resident experience during implementation of computerized prescriber order entry. Am J Health Syst Pharm 2007;64:526–30.
24 Holdsworth MT, Fichtl RE, Raisch DW, et al. Impact of computerized prescriber order entry on the incidence of adverse drug events in pediatric inpatients. Pediatrics 2007;120:1058–66.
25 Potts AL, Barr FE, Gregory DF, et al. Computerized physician order entry and medication errors in a pediatric critical care unit. Pediatrics 2004;113:59–63.
26 Ammenwerth E, Talmon J, Ash JS, et al. Impact of CPOE on mortality rates: contradictory findings, important messages. Methods Inf Med 2006;45:586–93.
27 Eslami S, bu-Hanna A, de Keizer NF. Evaluation of outpatient computerized physician medication order entry systems: a systematic review. J Am Med Inform Assoc 2007;14:400–6.
28 Georgiou A, Williamson M, Westbrook JI, et al. The impact of computerised physician order entry systems on pathology services: a systematic review. Int J Med Inform 2007;76:514–29.
29 Kawamoto K, Lobach DF. Clinical decision support provided within physician order entry systems: a systematic review of features effective for changing clinician behavior. AMIA Annu Symp Proc 2003:361–5.
30 Poissant L, Pereira J, Tamblyn R, et al. The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. J Am Med Inform Assoc 2005;12:505–16.

Chapter 6

The effect of a computerized prescribing and calculating system on hypo- and hyperglycemias and on prescribing time efficiency in neonatal intensive care patients

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Abstract

Purpose Prescribing glucose requires complex calculations because glucose is present in parenteral and enteral nutrition and drug vehicles, making it error prone and contributing to the burden of prescribing errors. This study evaluated the impact of a computerized physician order entry (CPOE) system with clinical decision support (CDS) for glucose control in neonatal intensive care patients (NICU) focusing on hypo- and hyperglycemic episodes and prescribing time efficiency.

Methods An interrupted time-series design to examine the effect of CPOE on hypo- and hyperglycemias and a crossover simulation study to examine the influence of CPOE on prescribing time efficiency. NICU patients at risk for glucose imbalance hospitalized at the University Medical Center Utrecht during 2001–2007 were selected. The risks of hypo- and hyperglycemias were expressed as incidences per 100 patient days in consecutive 3-month intervals during 3 years before and after CPOE implementation. To assess prescribing time efficiency, time needed to calculate glucose intake with and without CPOE was measured.

Results No significant difference was found between pre- and post-CPOE mean incidences of hypo- and hyperglycemias per 100 hospital days of neonates at risk in every 3-month period (hypoglycemias, 4.0 [95% confidence interval, 3.2–4.8] pre-CPOE and 3.1 [2.7–3.5] post-CPOE, P =.88; hyperglycemias, 6.0 [4.3–7.7] pre-CPOE and 5.0 [3.7–6.3] post-CPOE, P =.75). CPOE led to a significant time reduction of 16% (1.3 [0.3–2.3] minutes) for simple and 60% (8.6 [5.1–12.1] minutes) for complex calculations.

Conclusions CPOE including a special CDS tool preserved accuracy for calculation and control of glucose intake and increased prescribing time efficiency.

Introduction

Maintaining optimal glycemic control in critically ill children is difficult but important. Multiple episodes of hypoglycemia can lead to severe brain damage, whereas recurrent episodes of hyperglycemia may cause osmotic diuresis, dehydration, and weight loss. Both hypoglycemia and hyperglycemia are associated with increased mortality in critically ill children and neonates.[1-9] Accurate glucose prescribing can help achieve and maintain optimal glycemic control in critically ill children. But the prescribing process may involve complex calculations to take all variables that affect glycemia into account. The use of glucose solution as a vehicle or infusate to deliver medications, for example, is an independent risk factor in causing glycemic variability. Information technology interventions may provide support in prescribing drugs and nutrition support regimens to optimize glycemic provision, thereby reducing the incidence of errors and unintended adverse events.[10-18]

Computerized physician order entry (CPOE) systems with basic clinical decision support (CDS) include drug-allergy checking, basic dosing guidance, formulary decision support, duplicate order verification, and drug-drug interaction checking.[19] Systems that assist in the ordering of parenteral nutrition (PN) have been studied.[20-22] However, systems that combine CPOE and PN and enteral nutrition (EN) ordering by calculating the projected daily total glucose intake as a consequence of both prescriptions of drugs and PN and EN have not been described before. Such a system could facilitate the determination of the total glucose intake over a period of time.

In the Wilhelmina Children's Hospital, a CPOE system with additional CDS for glucose calculations has been developed. This study evaluated the impact of CPOE with CDS as a calculation tool for glucose prescribing in a neonatal intensive care unit (NICU), focusing on hypo- and hyperglycemic episodes and prescribing time efficiency.

Methods

Setting and study population

The study was conducted at the 28-bed level III NICU of the Wilhelmina Children's Hospital. The Wilhelmina Children's Hospital is part of the University Medical Center Utrecht in the Netherlands and treats an average of 540 neonates per year.

All neonates hospitalized for at least 1 day during 2001–2007 with 1 or more risk factors for hypo- or hyperglycemias were included. Risk factors for glucose imbalance were prematurity (<37 weeks gestational age), small for gestational age (SGA; birth weight <2.5th percentile for gestational age), maternal diabetes, or macrosomy (birth weight >97.7th percentile for gestational age).[9,23-25] Patients with an insulinoma were excluded. Informed consent was waived by the hospital's medical ethics committee.

Table 1 Neonatal intensive care unit glucose policy.

Plasma glucose concentrations		
Normal plasma glucose concentration	2.6–7.0 mmol/L	47–126 mg/dL
Hypoglycemia	<2.5 mmol/L	<45 mg/dL
Hyperglycemia	>10 mmol/L	>180 mg/dL
Glucose intake		
Minimal glucose intake	4–6 mg/kg/min	
Plasma glucose concentration measurements		
Enteral nutrition: neonate with enteral feeding within 3 hours after birth: plasma glucose concentration measurement 1 and 2 hours after birth and before first feeding, subsequently at least twice a day until plasma glucose concentration is stable and normal		
Parenteral nutrition: neonate with parenteral glucose: plasma glucose concentration measurement before starting intravenous glucose, subsequently every 3–4 hours and then at least once a day		
Hypoglycemia		
Plasma glucose concentration <2.5 mmol/L (<45 mg/dL): adjustment of glucose intake		
Symptomatic hypoglycemia: slow (in 5–10 minutes) injection of 0.2 g glucose/kg (2 mL glucose 10%/kg) intravenously		
Hyperglycemia		
Plasma glucose concentration >10 mmol/L (>180 mg/dL): adjustment of glucose concentration		
In exceptional cases, continuous intravenous insulin infusion (0.01 IU/kg/h, max 0.1 IU/kg/h, titrated to plasma glucose concentrations)		

All included neonates were prescribed glucose (either solely or as a component of their PN). In all these neonates, plasma glucose concentrations were routinely measured to conform to local protocol (Table 1). During the 6-year study period, the NICU policy concerning plasma glucose concentration measurements, cutoff points for hypo- and hyperglycemia, and associated treatment consequences remained unchanged.

Design

Hypo- and hyperglycemic episodes were used as a measure for the accuracy of daily total glucose intake prescribing. An interrupted time-series (ITS) design was used to examine the effect of CPOE on these hypo- and hyperglycemic episodes.[26,27] A simulation study was performed to examine the influence of CPOE on prescribing time. Prescribing time was defined as the time (in minutes) needed to calculate glucose intake for NICU patients, taking both nutrition and medication into account. To determine the time that prescribers needed to calculate glucose intake, 7 randomly selected neonatologists, fellows, and residents were asked to calculate glucose intake (mg/kg/min) for 3 different clinical scenarios similar to real-life situations, both manually and with CPOE, in a crossover design. The 3 simulation cases are described in Table 2. Differences in calculation times between the different levels of prescribers were not studied.

Table 2 Description of the 3 simulation cases.

Case 1
3000 g, 40 weeks old, born March 5, 2008. Solely IV nutrition: PN, glucose intake 7.3 mg/kg/min. Plasma glucose concentration is a bit low (eg, 2.5 mmol/l), so 1 mg/kg/min should be added to the parenteral glucose intake. Calculate how to compose a PN infusion, needed for a higher glucose intake (1 mg/kg/min higher).
Case 2
1500 g, 32 weeks old. Total enteral nutrition ("Friso Premature" baby food, 8 g of carbohydrates per 100 mL): 10 mL, 24 times a day. Collapses because of neonatal necrotizing enterocolitis. Has to be put on PN (nil per os). Neonate is mechanically ventilated, for which morphine is given (about 0.25 mg/kg/d in glucose 10% IV). Neonate tends to have hypotension, for which it receives dopamine (about 5 µg/kg/ min in glucose 10% IV). Has an arterial line. Calculate how to compose a PN infusion (160 mL/kg/d), needed for a lower glucose intake (2 mg/kg/min lower) because of hyperglycemia.
Case 3
Neonate 27 weeks, 650 g. Step-up enteral feeding. Received breast milk: 2 mL, 24 times a day. Now receives breast milk: 3 mL, 24 times a day. Calculate the glucose intake of the former and latter regimen. Breast milk: 7 g of carbohydrate per 100 mL.

IV, intravenous; PN, parenteral nutrition.

Intervention

On April 26, 2004, a homegrown CPOE system was introduced, designed to perform physician order entry and basic CDS. Also, it provides calculations to assist prescribing of glucose, taking the amount of glucose present in PN and EN and medication into account. The CPOE system interfaces with hospital-wide systems, for example, with regard to laboratory test results. An additional connection between the CPOE system and the hospital's PN compounding pump has not been realized yet.

Before CPOE implementation, glucose intake was manually calculated on a paper order sheet. The interface of the CPOE system (Figure 1) was designed to look similar to this sheet to enhance acceptance of the system.

Outcomes

The primary outcomes were the pre- and post-CPOE incidences of hypo- and hyperglycemic episodes of patients at risk. Hypo- and hyperglycemic episodes were defined as plasma glucose concentrations <2.5 mmol/L and >10 mmol/L (or <45 mg/dL and >180 mg/dL), respectively, in accordance with the local NICU glucose policy (Table 1).

Also, the general pre-CPOE fluctuation of plasma glucose concentrations of patients at risk was compared with the general post-CPOE fluctuation. The 6-year study period was divided into consecutive 3-month intervals, resulting in 12 pre- and 12 post-CPOE intervals.

To adjust for the length of stay of the patients, the incidences of hypo- and hyperglycemic episodes *per 100 hospital days* of patients at risk were determined for each 3-month period. To adjust for

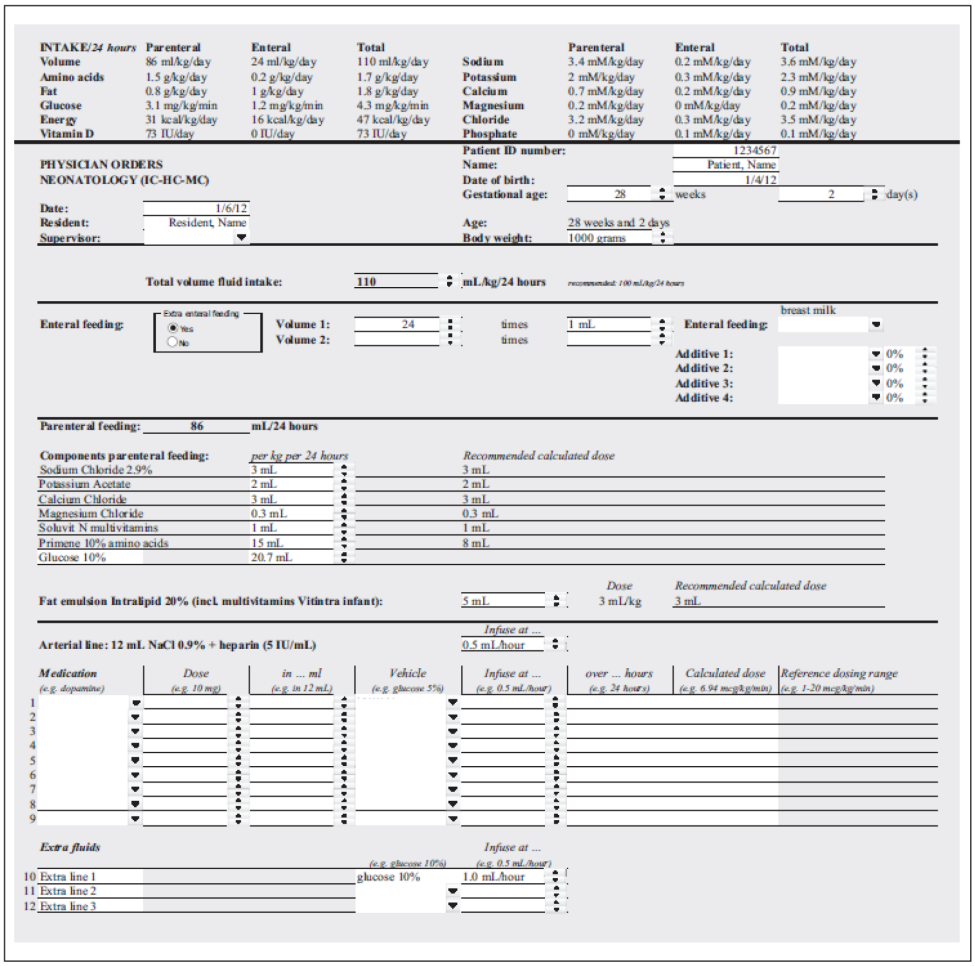

Figure 1 Interface of the computerized physician order entry system: total intake, patient characteristics, enteral nutrition, parenteral nutrition, and intravenous medication.

differences in the frequency of glucose checks per neonate in our population, the numbers of hypo- and hyperglycemias *per 100 glucose measurements* of patients at risk were also established for each 3-month period.

Outcome for prescribing time efficiency was the prescribing time: the time (in minutes, rounded up) needed to calculate glucose intake with and without the use of CPOE. A significant decrease in prescribing time was considered an increase in prescribing time efficiency.

Data collection

Patient characteristics, such as birth weight, gender, gestational age (weeks), and diagnoses, were selected from the Nationwide Neonatal Registry system, a nationwide database where all neonates in the Netherlands are registered.

Glucose measurement results were extracted from the Utrecht Patient Oriented Database (UPOD) in which routine clinical laboratory results are linked to administrative data (eg, patient characteristics) and clinical data (eg, medication, diagnoses, procedures).[28] Plasma glucose concentrations were determined at least once daily; samples were taken from an arterial catheter and measured in the hospital's central lab. During the 6-year study period, the NICU policy concerning plasma glucose concentration measurements remained unchanged (Table 1).

Statistical analysis

A $\chi 2$ analysis and unpaired Student *t* test were used to compare the pre-CPOE and post-CPOE patient groups ($\alpha = 0.05$). Regression analysis, with inverse variance-weighted ratios per 3-month period, was used to estimate and compare trends of numbers of hyper- and hypoglycemias pre- and post-CPOE implementation. To assess whether CPOE implementation had a different effect in SGAs than in neonates appropriate for gestational age, a stratified analysis was performed as well. To compare the fluctuation of plasma glucose concentrations of patients at risk pre- and post-CPOE, median and mean plasma glucose concentrations were calculated. SPSS Version 15.0.1 for Windows (SPSS, Inc, an IBM Company, Chicago, Illinois) was used for all analyses.

The study design met the generally recommended criteria for an ITS study – that is, among others, at least 3 data points before and 3 data points after the intervention – to conduct regression analysis and protect against secular variation.[27,29] The desirable number of at least 100 observations per data point to achieve an acceptable level of variability of the estimate at each time point was also achieved.[27,29]

Results

Patients

This study included 2040 patients (Table 3). Mean (SD) birth weight was significantly lower before CPOE implementation (1659 [769] *g* pre-CPOE vs 1735 [823] *g* post-CPOE, $P = .03$). Concurrently, the mean number of SGAs was significantly higher before CPOE implementation (102 pre-CPOE vs 57 post-CPOE, $P < .01$).

Effect of CPOE on hypo- and hyperglycemias

There was no significant difference between the pre- and post-CPOE mean numbers of hypo- and hyperglycemias per 100 hospital days of patients at risk in every 3-month period (hypoglycemias,

Table 3 Comparison of patient characteristics before and after computerized physician order entry (CPOE) system implementation.

	Pre-CPOE[a] (n = 1070)	Post-CPOE[a] (n = 970)	*P* Value
Male, No. (%)	608 (56.8)	566 (58.4)	.49
Length of admission, d, mean (SD)	19.4 (20.1)	20.4 (22.5)	.31
Weeks of pregnancy, mean (SD)	31.8 (3.3)	31.9 (3.4)	.36
Grams birth weight, mean (SD)	1659 (769)	1735 (823)	.03
Premature infants[b], No. (%)	1010 (94.4)	905 (93.3)	.30
SGA[c], No. (%)	102 (9.5)	57 (5.9)	<.01
Maternal Diabetes, No. (%)	51 (4.8)	50 (5.1)	.69
Macrosomy[d], No. (%)	28 (2.6)	37 (3.8)	.12

[a] Pre-CPOE: April 2001 – March 2004 (3 years), post-CPOE: April 2004 – March 2007 (3 years).
[b] Premature infants: < 37 weeks of gestational age.
[c] SGA = small for gestational age: birth weight < 2.5th percentile for gestational age.
[d] Macrosomy: birth weight > 97.7th percentile for gestational age.

4.0 [95% confidence interval (CI), 3.2–4.8] pre-CPOE and 3.1 [2.7–3.5] post-CPOE, P = .88; hyperglycemias, 6.0 [4.3–7.7] pre-CPOE and 5.0 [3.7–6.3] post-CPOE, P = .75) (Figure 2).

Stratification for SGA showed no effect: hypo- and hyperglycemia incidences per 100 hospital days of patients at risk in every 3-month period in SGAs were 6.3 (95% CI, 3.9–8.7) and 9.6 (5.5–13.7) pre-CPOE vs 6.9 (4.6–9.2) and 7.6 (2.6–12.6) post-CPOE. Hypo- and hyperglycemia incidences per 100 hospital days of patients at risk in every 3-month period in neonates appropriate for gestational age were 3.7 (95% CI, 2.9–4.5) and 5.5 (3.9–7.1) pre-CPOE vs 2.9 (2.5–3.4) and 5.1 (3.7–6.5) post-CPOE.

There was no significant difference between the pre- and post-CPOE mean numbers of hypo- and hyperglycemias per 100 glucose measurements of patients at risk in every 3-month period (hypoglycemias, 2.1 [95% CI, 1.7–2.5] pre-CPOE and 1.7 [1.4–2.0] post-CPOE, P = .91; hyperglycemias, 3.1 [2.4–3.8] pre-CPOE and 2.6 [1.9–3.3] post-CPOE, P = .74).

There was no difference in the fluctuation of plasma glucose concentrations of patients at risk pre- and post-CPOE: pre-CPOE, the median plasma glucose concentration was 4.8 (interquartile range [IQR], 4.0–5.8) mmol/L, and the mean (SD) plasma glucose concentration was 5.2 (0.01) mmol/L. Post-CPOE, the median plasma glucose concentration was 4.7 (IQR, 4.0–5.6) mmol/L, and the mean (SD) plasma glucose concentration was 5.0 (0.01) mmol/L.

Efficiency

All physicians completed the simulation cases correctly, both manually and with CPOE (Figure 3). Comparing CPOE with manual calculation showed a significant time reduction of 1.3 (95% CI, 0.3–2.3) minutes (16%) for simple and 8.6 (5.1–12.1) minutes (60%) for complex cases.

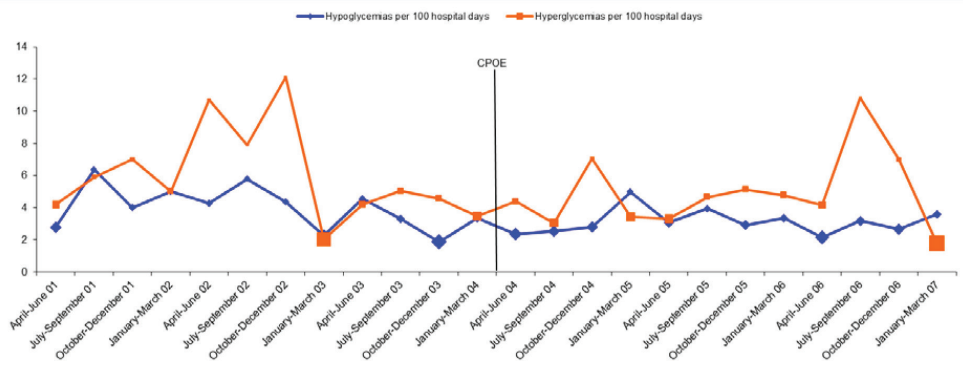

Figure 2 Number of hypo- and hyperglycemias per 100 hospital days of patients at risk in every 3-month period. CPOE computerized physician order entry. Dark grey line graph: hypoglycemias per 100 hospital days. Light grey line graph: hyperglycemias per 100 hospital days.

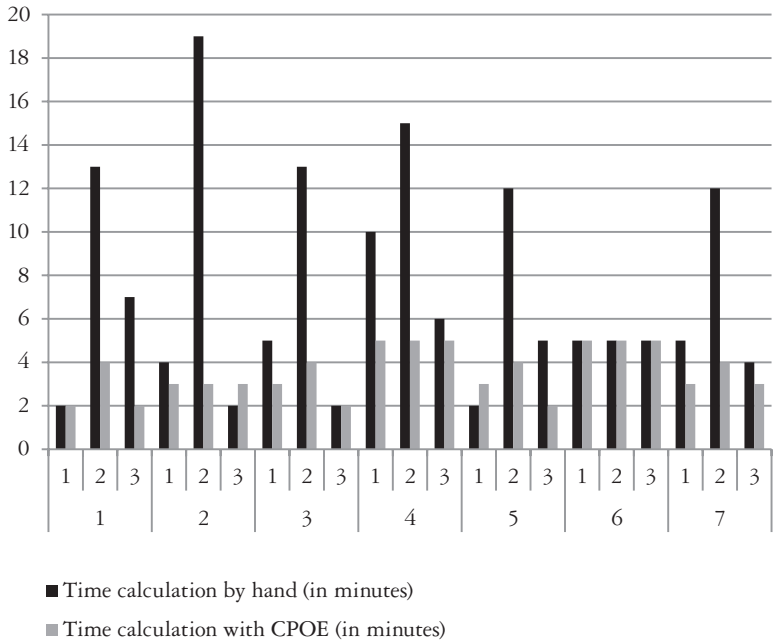

Figure 3 Time needed to calculate simulation cases 1, 2, and 3 per physicians 1–7 (in minutes), both manually and with the computerized physician order entry (CPOE) system. Left bar: calculation by hand. Right bar: calculation with CPOE.

Discussion

Principal findings

This study demonstrates that after implementation of a CPOE system in the NICU, a high level of accuracy for calculation and control of glucose intake was maintained. There was no difference between the incidences of hypo- and hyperglycemias per hospital day or in the fluctuation of plasma glucose concentrations of patients at risk before and after CPOE/CDS implementation. However, comparing CPOE with manual calculation did show a significant time reduction, particularly for complex calculations.

Implications

The results indicate that prescription of glucose intake was accurate both with CPOE and with manual calculation. It is expected that the time-saving impact positively affects the quality of patient care, as more time can be spent at the bedside. Conversely, Han et al[30] found that with CPOE, more time was spent at the computer and less at the bedside, which resulted in a higher mortality after CPOE implementation. However, a recent systematic review on the effect of CPOE on medication prescription errors and clinical outcome in intensive care unit (ICU) settings showed that mortality was generally not influenced.[31] A recent ITS study also showed similar results: a CPOE system with basic CDS reduced the incidence of medication errors but did not affect actual patient harm (measured as preventable adverse drug events) in an inpatient population.[32] In neonates specifically, Kazemi et al[33] studied the effect of CPOE and CDS with a medication dosing calculation tool and noted a significant reduction in dosing errors. None of these studies, though, focused on a specific CDS item for calculation and control of glucose intake via both PN and EN and medication. In adult and pediatric ICU settings, electronical support of glucose control has been studied before, but focusing on insulin treatment protocols, not on glucose intake.[34-41]

Comparison to other studies

To our knowledge, this is the first evaluation of the effects of a CPOE system, including calculations to assist prescribing of glucose, on glycemic control in an NICU population. The rates of glucose imbalance in the study population were comparable to rates found in other studies among infants with 1 or more risk factors for glucose imbalance. This study found at least 1 episode of hypoglycemia in 32% and hyperglycemia in 27% of neonatal patients, consistent with the percentages others found: an incidence of hypo- and hyperglycemias of 35% and 24%, respectively, although slightly different definitions were used in their studies (<2.2 mmol/L and >12 mmol/L, respectively).[9,42]

Limitations

Potential confounding in ITS studies is limited to factors that are related to the outcome, and that changed at the time of the intervention, such as cointerventions, seasonal changes, changes in measurement of the outcome, and changes of the study population during the time of intervention.[27] As mentioned before, this study's time span was long enough to rule out seasonal changes, and NICU policy concerning plasma glucose concentration measurements, cutoff points for hypo- and hyperglycemia, and associated treatment consequences remained unchanged. One limitation that may have affected the results is the lower mean body weight in the pre-CPOE population. This may be due to the higher number of SGAs in the pre-CPOE population. Stratifying for SGA, though, showed similar results. Another limitation of this study is that comparing the studied CPOE system with others may be complicated as the system was developed locally and is used in the pediatric ICU and NICU of the Wilhelmina Children's Hospital only. Nonetheless, as recently described by Caldwell et al,[43] this kind of research is required for evidence-based development and optimization of CPOE systems and CDS tools. Commercially available CPOE systems are currently not tailored to pediatrics and do not necessarily improve error rates and clinical effectiveness of pediatric prescribing.[43] Accordingly, CPOE systems need further evolution by the development of CDS specific for pediatric and neonatal settings. The calculation tool for glucose prescribing in this study is an example of such a development.

Conclusions

In conclusion, the introduction of a basic CPOE system that provides support for complex calculations preserved the accuracy and improved the efficiency in prescribing glucose intake in NICU patients. Future studies, preferably multicenter and designed as controlled before/after studies, are warranted to elucidate the role of CPOE in the improvement of patient care and safety in neonatal and pediatric intensive care settings.

References

1 NICE-SUGAR Study Investigators, Finfer S, Chittok DR, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.

2 Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised, controlled study. Lancet 2009;373:547-56.

3 Ulate KP. A critical appraisal of Vlasselaers D, Milants I, Desmet L, et al: intensive insulin therapy for patients in paediatric intensive care: a prospective, randomized controlled study. Lancet 2009;373:547-556. Pediatr Crit Care Med 2011;12:455-8.

4 Rake AJ, Srinivasan V, Nadkarni V, et al. Glucose variability and survival in critically ill children: allostasis or harm? Pediatr Crit Care Med 2010;11:707-12.

5 Faustino EV, Bogue CW. Relationship between hypoglycemia and mortality in critically ill children. Pediatr Crit Care Med 2010;11:690-8.

6 Yung M, Wilkins B, Norton L, et al; Paediatric Study Group; Australian and New Zealand Intensive Care Society. Glucose control, organ failure, and mortality in pediatric intensive care. Pediatr Crit Care Med 2008;9:147-52.

7 Wintergerst KA, Buckingham B, Gandrud L, et al. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. Pediatrics 2006;118:173-9.

8 Hume R, Burchell A, Williams FL, et al. Glucose homeostasis in the newborn. Early Hum Dev 2005;81:95-101.

9 Zanardo V, Cagdas S, Golin R, et al. Risk factors of hypoglycemia in premature infants. Fetal Diagn The. 1999;14:63-7.

10. Bankhead R, Boullata J, Brantley S, et al. Enteral nutrition practice recommendations. JPEN J Parenter Enteral Nutr 2009;33:122-67.

11 Taylor JA, Loan LA, Kamara J, et al. Medication administration variances before and after implementation of computerized physician order entry in a neonatal intensive care unit. Pediatrics 2008;121:123-8.

12 Walsh KE, Landrigan CP, Adams WG, et al. Effect of computer order entry on prevention of serious medication errors in hospitalized children. Pediatrics 2008;121:e421-7.

13 Chedoe I, Molendijk HA, Dittrich ST, et al. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety: a review of the current literature. Drug Saf 2007;30:503-13.

14 Larsen GY, Parker HB, Cash J, et al. Standard drug concentrations and smart-pump technology reduce continuous-medication infusion errors in pediatric patients. Pediatrics 2005;116:e21-5.

15 Seres D, Sacks GS, Pedersen CA, et al. Parenteral nutrition safe practices: results of the 2003 American Society for Parenteral and Enteral Nutrition survey. JPEN J Parenter Enteral Nutr 2006;30:259-65.

16 Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39-70.

17 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114-20.

18 Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's health care? Arch Pediatr Adolesc Med 2001;155:1002-7.

19 Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007;14:29-40.

20 Lehmann CU, Conner KG, Cox JM. Provider error prevention: online total parenteral nutrition calculator. Proc AMAI Symp 2002:435-9.

21 Lehmann CU, Conner KG, Cox JM. Preventing provider errors: online total parenteral nutrition calculator. Pediatrics 2004;113:748-53.

22 Lehmann CU, Kim GR, Gujral R, et al. Decreasing errors in pediatric continuous intravenous infusions. Pediatr Crit Care Med 2006;7:225-30.

23 Ferrara A, Weiss NS, Hedderson MM, et al. Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycaemia and hyperbilirubinaemia. Diabetologia 2007;50:298-306.

24 Kao LS, Morris BH, Lally KP, et al. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol 2006;26:730-6.

25 Hey E. Hyperglycaemia and the very preterm baby. Semin Fetal Neonatal Med 2005;10:377-87.

26 Mol PG, Wieringa JE, Nannanpanday PV, et al. Improving compliance with hospital antibiotic guidelines: a time-series intervention analysis. J Antimicrob Chemother 2005;55:550-7.

27 Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27:299-309.

28 ten Berg MJ, Huisman A, van den Bemt PM, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.

29 The Cochrane Effective Practice and Organisation of Care Group (EPOC). Available at: http://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/inttime.Pdf [Accessed 2 November 2011].

30 Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system [published correction appeared in Pediatrics 2006;117:594]. Pediatrics 2005;116:1506–12.

31 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

32 van Doormaal JE, van den Bemt PM, Zaal RJ, et al. The influence that electronic prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. J Am Med Inform Assoc 2009;16:816-25.

33 Kazemi A, Ellenius J, Pourasghar F, et al. The effect of computerized physician order entry and decision support system in medication errors in the neonatal ward: experiences from an Iranian teaching hospital. J Med Syst 2011;35:25-37.

34 Branco RG, Xavier L, Garcia PC, et al. Prospective operationalization and feasibility of a glycemic control protocol in critically ill children. Pediatr Crit Care Med 2011;12:265-70.

35 Faraon-Pogaceanu C, Banasiak KJ, Hirshberg EL, et al. Comparison of the effectiveness and safety of two insulin infusion protocols in the management of hyperglycemia in critically ill children. Pediatr Crit Care Med 2010;11:741-9.

36 Verhoeven JJ, Brand JB, van de Polder MM, et al. Management of hyperglycemia in the pediatric intensive care unit: implementation of a glucose control protocol. Pediatr Crit Care Med 2009;10:648-52.

37 Dossett LA, Collier B, Donahue R, et al. Intensive insulin therapy in practice: can we do it? JPEN J Parenter Enteral Nutr 2009;33:14-20.

38 Dortch MJ, Mowery NT, Ozdas A, et al. A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. JPEN J Parenter Enteral Nutr 2008;32:18-27.

39 Vogelzang M, Loef BG, Regtien JG, et al. Computer-assisted glucose control in critically ill patients. Intensive Care Med 2008;34:1421-7.

40 Preissig CM, Hansen I, Roerig PL, et al. A protocolized approach to identify and manage hyperglycemia in a pediatric critical care unit. Pediatr Crit Care Med 2008;9:581-8.

41 Boord JB, Sharifi M, Greevy RA, et al. Computer-based insulin infusion protocol improves glycemia control over manual protocol. J Am Med Inform Assoc 2007;14:278-87.

42 Manzoni P, Castagnola E, Mostert M, et al. Hyperglycaemia as a possible marker of invasive fungal infection in preterm neonates. Acta Paediatr 2006;95:486-93.

43 Caldwell NA, Power B. The pros and cons of electronic prescribing for children. Arch Dis Child 2012;97:124-8.

Chapter 7

System requirements for a safe and efficient integrated computerized physician order entry system for PICU and NICU patients

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Abstract

Purpose The objective of this study was to define requirements, design and test a computerized physician order entry (CPOE) system that provides safe and efficient integrated support for the pediatric and neonatal intensive care unit (PICU and NICU) medication process.

System requirements A set of PICU- and NICU-specific elements that a CPOE system should support was constructed, based on theoretical data from literature and local data from statistical analysis of PICU and NICU prescribing errors. A CPOE system should offer integrate support for all stages of the medication process, all stakeholders in the medication process (e.g. pharmacist, physician, nurse) and all categories of patient and pharmacotherapeutic complexity. A CPOE system should also be safe and efficient by default.

System design Based on the described system requirements, an electronic system was developed integrating and supporting the different stakeholders, sub-processes and all categories of patient and pharmacotherapeutic complexity in the medication process. The developed system consists of a decision support system and a CPOE system, of which the backbone consists of a model that is based on patient-, product and rule-related information.

System test A software verification methodology was developed to be able to test the developed system. The backbone of the system was tested to make sure that import and application of database information, rules and calculations are correct: for a number of order types, it was tested whether the system performed as predicted. All obtained results were as predicted.

Conclusions This study demonstrates a proof of concept of an innovative, integrated, efficient and safe by default CPOE system that can be used in NICU and PICU populations, and is generalizable to other settings. Further studies are necessary to further develop and clinically validate the system for actual use in practice.

Introduction

Medication errors in neonatal and pediatric intensive care unit (PICU and NICU) patients often occur: reported rates vary up to about 15% of medication orders.[1-3] These errors may result in adverse drug events (ADEs). In adult intensive care units (ICUs) the rate of preventable and potential ADEs is almost twice as high as in non-ICUs,[4] and more harmful medication errors are reported in ICU than in non-ICU settings.[5] Additionally, Kaushal et al. reported that potential ADEs due to medication errors occurred significantly more often in pediatric than in adult hospital settings.[6] Medication errors can occur in all stages of the medication process on PICUs and NICUs: prescribing, transcribing, dispensing, preparing, administering drugs, and monitoring and evaluating drug therapy. Especially in PICUs and NICUs, the medication process is error-prone due to patient diversity, multi-drug use, frequent dosing adjustments,[7] required dosing- and preparation-related calculations,[1,8,9] extensive preparation and administration of high risk medication[10] and problems with availability of suitable drug formulations.[7]

In pediatrics, the prescribing phase is one of the most important risk factors for the occurrence of harmful medication errors and among the error types made in this phase dosing errors prevail.[11] To prevent medication prescribing errors and consequent ADEs in PICUs and NICUs, computerized physician order entry (CPOE) and clinical decision support (CDS) systems have shown positive effects on error- and ADE-rates.[3,12,13] Caution is warranted though, because such systems may also introduce new kinds of errors, for example human-machine interface problems, particularly surrounding the selection and dosing of pediatric medications.[14] Therefore, it is important that CPOE/CDS is tailored to both the workflow of the setting it is used in and the needs of the healthcare professionals it is used by. For PICUs/NICUs this implies, for example, ensuring easy and efficient order entry in acute situations and support for complex calculations.[15,16]

A CPOE/CDS system that combines all abovementioned aspects to support the medication process for PICU and NICU patients, has not been described yet. The objective of this study was to define requirements, design and test a CPOE system that provides safe and efficient integrated support for the PICU and NICU medication process.

System requirements

As mentioned in the introduction, the PICU/NICU medication process is error-prone, errors made may lead to ADEs, and CPOE/CDS systems have the potential to prevent this. A set of PICU- and NICU-specific elements that such a system should support was constructed, based on theoretical data from literature[12] and local data from statistical analysis of PICU and NICU prescribing errors.[7,8,17] These requirements were categorized as patient-related, product-related

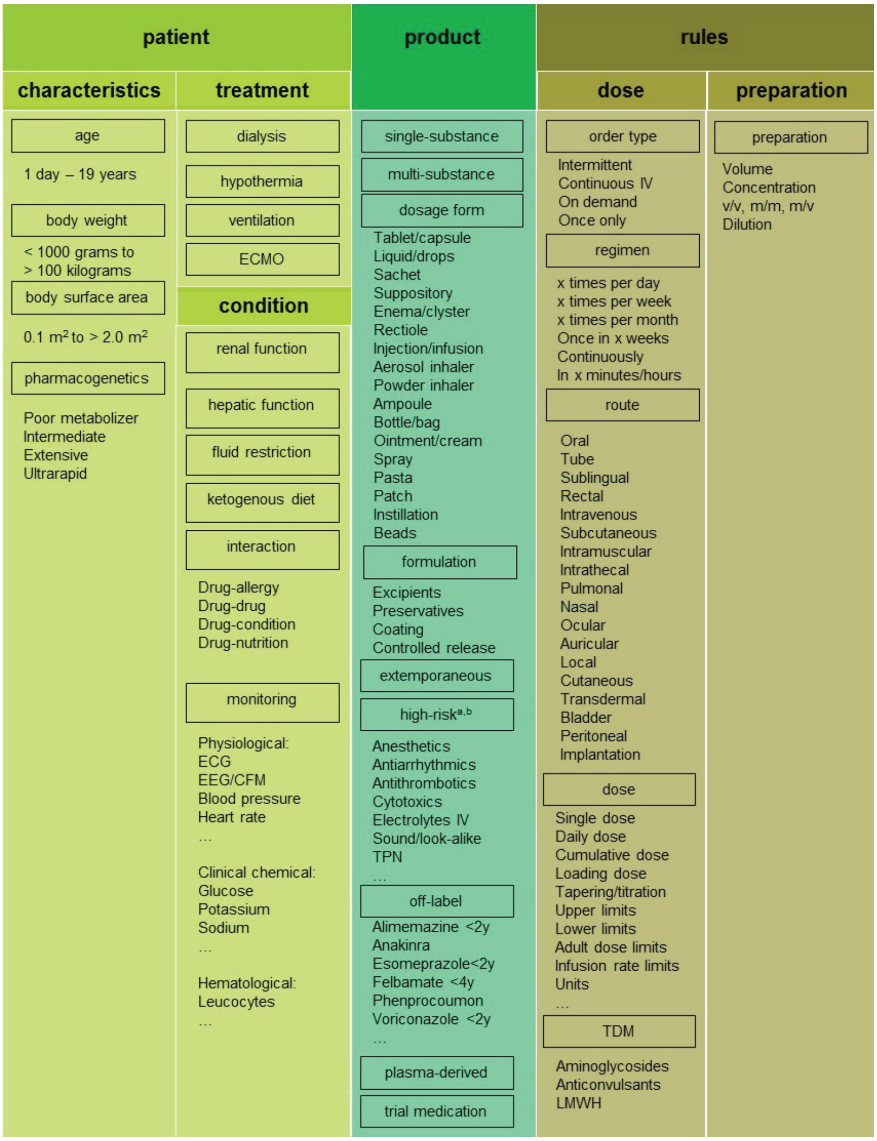

Figure 1 Overview of CPOE and CDS requirements.

References in relation to high risk medication: a Institute for Safe Medication Practices ISMP's List of High-Alert Medications. Available from https://www.ismp.org/tools/highalertmedications.pdf Accessed 19 March 2014. b Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:85-90. ECMO = extracorporeal membrane oxygenation ECG = electrocardiogram EEG/CFM = electroencephalography/cerebral function monitor TPN = total parenteral nutrition TDM = therapeutic drug monitoring

and rule-related and are shown in Figure 1. Patient-related requirements include patient characteristics and treatment- and condition details that may influence medication prescribing. Rules include dosing rules, e.g. from a formulary, and preparation rules, e.g. form local medication preparation protocols. Although this is not an exhaustive sub-classification of all categories, it offers a useful overview of the diversity and complexity of factors that influence the design of a system appropriate for PICU and NICU.

CPOE alone does not fully prevent medication prescribing errors: it eliminates administrative errors, but omissions and dosing errors still frequently occur.[7,12,17] CDS is essential to further reduce clinically relevant prescribing error rates. Based on a combination of scientific evidence[3,8,13,16,18-26] and experiences from local PICU/NICU practice, CDS requires at least:

1) Medication dosing support:
   a) Medication dose calculation, including cumulative dose calculations per day/lifetime, including calculations for complex administrations and preparations.
   b) Formulary checking.
   c) Single dose range checking, maximum daily dose checking, including lower and upper limits, including adult limits.
   d) Maximum lifetime dose checking.
   e) Providing common doses and indication-based dosing, including off-label drugs and drugs used outside product license.
   f) Medication dose adjustment support, including fast and easy alteration of intravenous infusion pump flow rates.
2) Point of care alerts/reminders:
   a) Drug-drug interaction checking (including between two or more drugs and incompatibilities between intravenous fluids), drug-condition interaction checking, drug-allergy interaction checking, duplicate order checking, look-alike/sound-alike medication warnings.
3) Order integration:
   a) Medication order sentences, order sets and treatment protocols, including complex condition-specific treatment protocols, automated drug-protocol linkage and possibility to add new or experimental drugs.
   b) Subsequent and corollary orders: physiological parameter monitoring, laboratory monitoring, therapeutic drug monitoring (TDM).
4) Drug formulation, preparation and administration support:
   a) Simultaneous support for continuous infusions and intermittent dosing schemes.
   b) Specific support for intermittent dosing regimens, corresponding routes of administration and dosage forms suitable for children (with/without nasogastric tube).

c) Dose rounding such that dose can be measured accurately from available drug formulation.
d) Preparation information.
e) Administration information, e.g. when and how to administer.

At present, several CDS tools tailored to the PICU and NICU medication process have been developed and combined with existing CPOE systems.[3,8,13,16,18-26] These advanced CDS tools however, provide fragmented support, focusing either on prescribing / ordering[3,16,18,19], dosing[13,20,21], calculating[8,16,20,22], dispensing / preparing[23,24], administering[25,26] or monitoring[16], rather than on an integrated approach of all (Figure 2 Panel A). In other words, current CDS tools either assist physicians, pharmacy personnel or nurses. Additionally, CPOE/CDS systems typically enable either prescribing for 'ordinary' patients, or prescribing for more complex patients/treatment categories. This is of particular interest in relation to the PICU and NICU population as these populations cover the entire spectrum of very simple to very complex pharmacotherapy. The current fragmented approach results in undesirable side-effects, such as difficulties in connecting of and digital communication between the various systems, inability to view all active medication orders of a patient concurrently, or extensive free-text order entry if standardized order entry does not provide suitable options.

Integrated

A CPOE system should offer integrate support for all stages of the medication process, all stakeholders in the medication process, all categories of patient and pharmacotherapeutic complexity.

Figure 2 depicts the shift that should be made from a fragmented approach (panel A) to an integrated approach (panel B) of the hospital medication process. This shift includes the advantage of reduction of the number of steps in the process: pharmacy verification and transcribing become redundant and can be eliminated, dispensing becomes part of order entry and monitoring becomes part of evaluation. Planning of administrations should be added as a separate sub-process, because experiences in practice pointed out that planning is time-consuming and error-prone due to multi-drug use and frequent dosing adjustments in PICU and NICU patients. Moreover, a distinction should be made between setting prescription frequency and determining the exact time upon which medication orders are to be administered.

Figure 2, panel B, also clearly delineates that a medication order is viewed and used by different stakeholders, each with its own perspective, in different phases of the medication process. The different views of the different stakeholders on what a medication order is, has been exemplified in table 1. Hence, system requirements can be separated according to stakeholder and phase in the medication process.

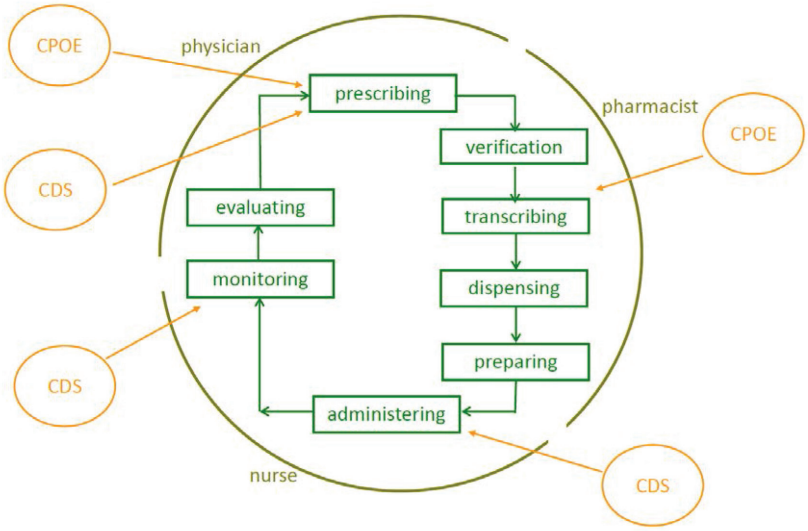

Figure 2 panel A The medication process and stakeholders, fragmented approach.

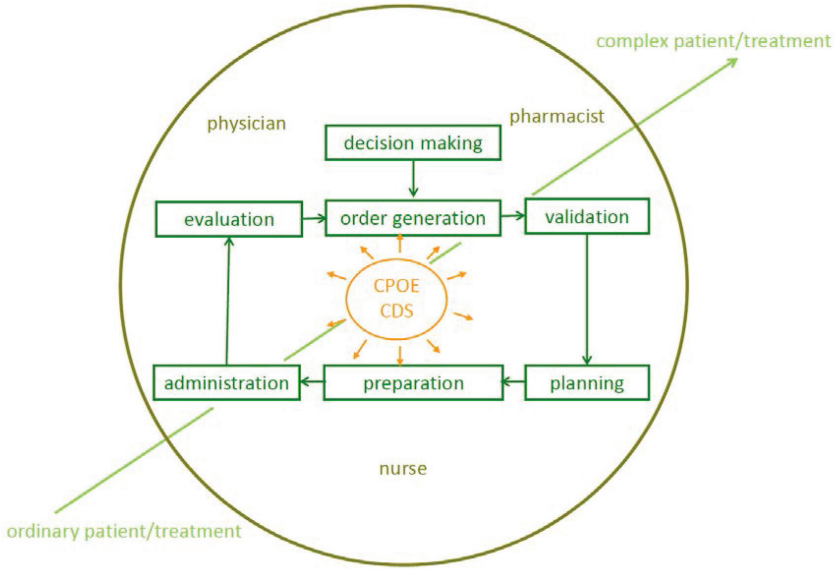

Figure 2 panel B The medication process and stakeholders, integrated approach.

Table 1 Three examples of different views of pharmacist, physician and nurse on medication orders.

Pharmacist	Physician	Nurse
patients 6 months to 18 years: per rectum: 1-3 mg/kg/day in 2-4 times maximum dose: 200 mg/day	patient weight: 28 kg.	patient in bed 2.1 with hospital number 123456 and daily schedule …
diclofenac 12.5 mg supp Voltaren® diclofenac 25 mg supp Voltaren® diclofenac 50 mg supp Voltaren® diclofenac 100 mg supp	diclofenac suppository per rectum 2.68 mg/kg/day in 3 times per day	08:00: diclofenac 25 mg supp 12:00: diclofenac 25 mg supp 20:00: diclofenac 25 mg supp

Pharmacist	Physician	Nurse
patients 1 month to 18 years: intravenously: 6-7 mg/kg/day frequency: 1 times per day max concentration: 2.0 mg/mL	patient weight: 28 kg.	patient in bed 2.1 with hospital number 123456 and daily schedule …
gentamicin injection fluid 10 mg/mL gentamicin injection fluid 40 mg/mL sodiumchloride injection fluid 9 mg/mL	gentamicin injection fluid intravenously 7 mg/kg/day in 1 time per day	09:00 gentamicin 1.96 mg/mL (= 4.9 mL of 40 mg/mL injection fluid with normal saline 95.1 mL) 1 dd 100 mL infuse iv in 20 min

Pharmacist	Physician	Nurse
patients 0 months to 18 years: 0-20 mcg/kg/min	patient weight: 28 kg.	patient in bed 2.1 with hospital number 123456 and daily schedule …
dopamine injection fluid 200 mg/5 mL ampoule and sodiumchloride injection fluid 9 mg/mL	dopamine injection fluid intravenously 5 mcg/kg/min	start: dopamine 4 mg/mL (5 mL concentrate for infusion in normal saline 45 mL) pump 2.1 mL/hour

Pharmacist requirements

To the pharmacist medication orders are relevant to know what drug to dispense per patient and/or ward and to maintain an inventory. Furthermore, pharmacists have a role in making available an accurate medication list per patient and medication verification, such as dose checking and drug-drug interaction checking. Additionally, pharmacists supply pharmacotherapeutic information, i.e. decision support for the physician, that includes, for example, dosing schemes and therapeutic drug monitoring. The pharmacist also provides decision support for nurses, for example by taking care of medication preparation and administration rules. Therefore, the system should be able to keep a product inventory and be able to provide an accurate medication list per patient, and specific drug information related to dosing, preparation, interactions etc.

Physician requirements

Physicians want to treat patients based on indications. Therefore, the system should provide for indication driven generation of treatment. To prescribe treatment, treatment can be viewed as an 'orderable', i.e. anything that can be ordered. In case of medication prescribing, the relevant factors that an orderable should comprise of are: a) therapeutic substance(s) and b) dosage form. Prescription details come along with the 'orderable', e.g. the route of administration, the drug dose, frequency and/or rate of administration.

Secondly, prescribing should be related to already existing orders. Not only because of checking for drug-drug interactions and duplicate orders, but also, for example, because of total fluid intake calculation, that is governed by the cumulative sum of prescribed medications that are fluids. Also, on substance level, cumulative quantities are relevant as is the case for glucose intake, caloric intake etc.

Therefore, the process of generating a prescription entails the following steps: 1) Selection of the appropriate treatment according to indication, interaction, contra-indications and other relevant patient factors, 2) Determination of the proper route and dose (i.e. calculation taking into account specific patient factors), 3) Product selection that is appropriate for the calculated dose and individual patient and 4) Calculation of the cumulative effects of the entire medication order list of a patient including identification of potential drug-drug interactions, duplicate orders, etc..

Nurse requirements

Nursing staff should know when and how orders should be prepared for and administered to which patient. Therefore, the system should facilitate translation of a prescribed frequency to planning of administrations to specific time slots. For each administration of an order, the specific preparation and administration guidelines should be available. For complex orders in a wide range of patients, such as on PICU and NICU, this poses a challenge as many drug formulations have to be specifically prepared to meet the desired prescribed dose. While a physician views a medication order as for example: dopamine 5 mcg/kg/min in a 28 kg patient, nursing staff has to administer this as 2.1 mL/hour (given a concentration of 4 mg/mL). Calculations of orders have to take into account and translate specific drug products to 'preparable' and 'administerable' compositions.

Patient and treatment requirements

Different patients and different dosing regimens require different types of medication orders. This can be as simple as prescribing diclofenac three times daily to an adult patient, to as complex as prescribing total parenteral nutrition tailored to meet the demands of a neonate along with concomitant intravenous solutions. Furthermore, medication orders have to be related to the entire

treatment regime. For example, in neonates prescribing a drug in glucose as base solution will influence total daily glucose intake next to the total volume of maintenance fluids.

In short: physicians want the system to generate medication orders including execution of all required calculations related to specific patient characteristics and concomitant (pharmacotherapeutic) treatment, pharmacists want the system to ensure correct pharmacotherapy, an accurate medication order list, correct preparation and administration and to know which product to dispense, nursing staff requires the system to present all relevant information for preparation and administration, including calculations related to specific drug and patient characteristics.

Safe and efficient (by default)

A CPOE system should be safe and efficient by default. Obviously, a CPOE system should be safe because medication errors can result in patient harm. However, a CPOE system should also be efficient, as time to treatment and treatment delay can be of great consequence to overall patient outcome. Efficiency can be defined and measured in different ways. In relation to CPOE, an abstract definition of efficiency is proposed. Efficiency can be achieved by assessing the steps of the medication process that the system can eliminate or for which the system can provide support. This is outlined below in more detail.

Current electronic prescribing typically consists of the following steps: 1.) Selection of drug (preceded by selection of diagnosed indication), 2) Selection of route of administration, 3) Searching for and application of dosing information including calculations, 4) Presentation of alerts by the system warning for incorrect dose, interactions, etc., 5) Either repetition of steps 3 and 4 until dose is correct or ignoring the alert, 6) Alerts from clinical pharmacy or nursing staff that prescribed dosage form, concentration or else is not available, or that preparation of the order is not possible, 7) Repetition of steps 1 to 6 until medication order contains correct and available dose and dosage form and preparation is possible.

CPOE should prevent this unsafe and inefficient sequence by: 1) Pre-calculating and presenting only those calculated dosing options that are possible and allowed (taking into account, product, treatment and patient information), 2) Performing calculations needed for preparations, taking specific preparation rules into account (for example maximum concentration) and 3) Selecting and presenting to the physician only those products and dosage forms that are available and allowed. Thus, the medication order becomes 'safe by default', i.e. the physician can only select correct dose and /or other options generated by the system. 'Default' is any information (e.g. database) that is integrated into the system to deliver the decision support. This principle is demonstrated in the following sections.

System design

Based on the system requirements described above, an electronic system was developed integrating and supporting the different stakeholders, sub-processes and all categories of patient and pharmacotherapeutic complexity in the medication process. As shown in figure 3, the developed system consists of a decision support system and a CPOE system, that will be part of and provide input for the development of additional system components for medication order validation, order planning, preparation, a medication administration record and assessment and evaluation of effects of administered medication.

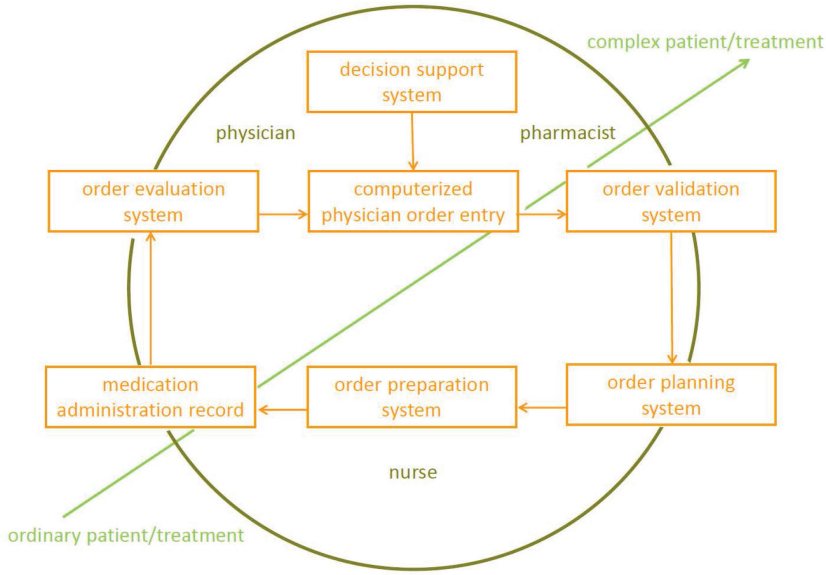

Figure 3 System components.

The backbone of the developed CPOE system consists of a model that is based on the required decision support as shown in Figure 1: patient-, product and rule-related information. The model is depicted in figure 4, panel A. Three types of information are integrated in the system: 1) Patient information (e.g. body weight, renal function, imported from the hospital's health information system (HIS)), 2. Product information (imported from a medication database of uniquely identifiable drugs), 3. Rules (dosing rules and medication preparation rules, imported from a pediatric/neonatal pharmacotherapeutic database and from medication preparation protocols for example)). In short, the system functions as follows: first, the physician selects a patient, a so-called

'orderable' and prescription details (dashed box), then, the system calculates and selects available medication order options suitable for the patient, finally a medication order is generated. This is explained by the following example (Figure 4, panel B):

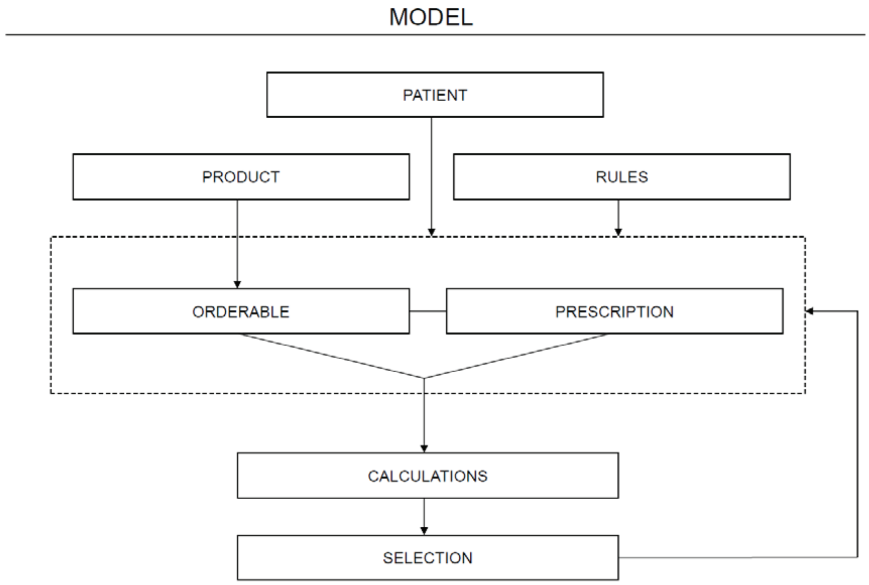

Figure 4 panel A System model.

PATIENT = patient information e.g. body weight, renal function
(imported from the hospital's health information system)

PRODUCT = the actual medicinal or non-medicinal physical entity that can be used for treatment
(product information imported from a medication database of uniquely identifiable drugs)

RULES = dosing rules and medication preparation rules
(e.g. imported from a pharmacotherapeutic database and from medication preparation protocols)

ORDERABLE = a descriptive abstract entity that defines what can be ordered; for a medicinal product, an 'orderable' is a combination of medicinal substance(s) and dosage form. Content of an orderable is defined by available products that apply to the patient.

PRESCRIPTION = result of application of dosing- and preparation rules to an orderable. Content of a prescription is defined by dosing rules that apply to the patient and preparation- and administration rules that apply to the product.

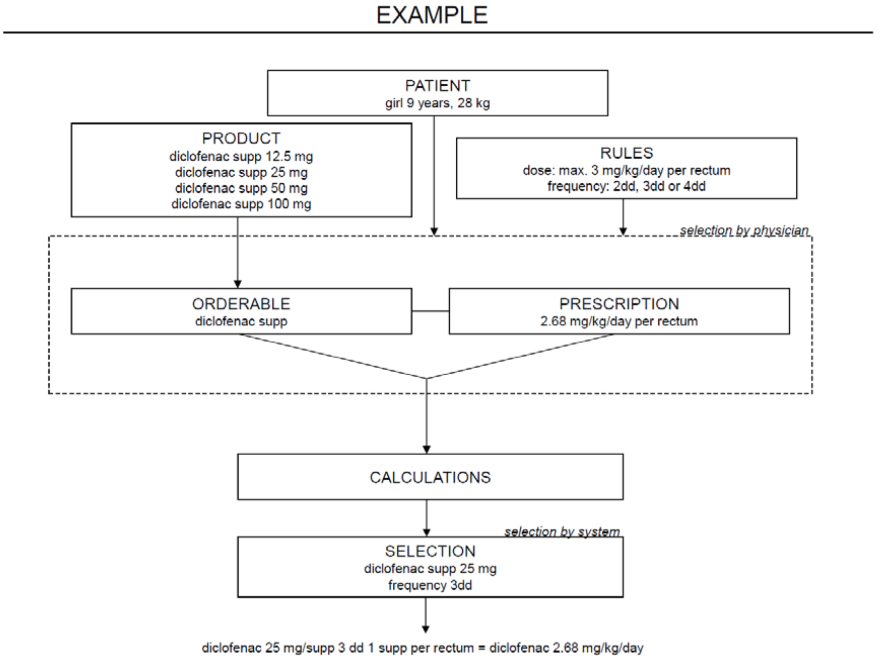

Figure 4 panel B System example.

Once the physician has selected a patient the system 'knows' the weight of the patient. The physician then selects the 'orderable', i.e. diclofenac suppository, as shown as an example in Figure 4, Panel B. The orderable is generated by the system and represents the different drug products that can be used to treat the patient with diclofenac suppositories. By selecting the orderable, the system also 'knows' that the maximum allowed daily dose is 3 mg/kg/day per rectum and that the frequency should be two, three or four times daily. Thus, given the patient weight (28 kg), the available product strengths (12.5, 25, 50 and 100 mg) and the abovementioned dose rules, the system calculates and presents possible doses to the physician: 0.89, 1.34, 1.78 and 2.68 mg/kg/day along with the frequency options of 2, 3 or 4 times/day. When the physician selects, for example, the 2.68 mg/kg/day dose, the system automatically defines the only remaining possible frequency and product: the system automatically selects 3 times/day and the 25 mg suppository and a medication order is generated. Figure 5 shows the resulting screenshot of the actual system.

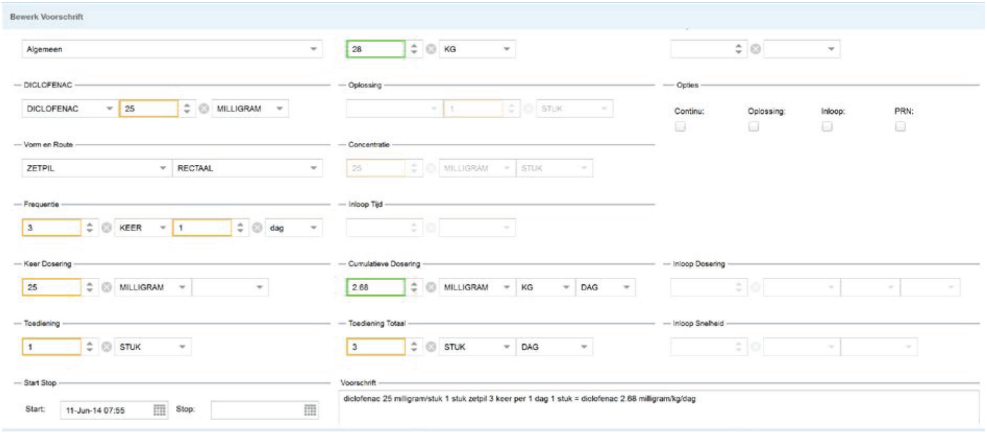

Figure 5 System screen shot.

This exemplifies the concept of efficient and safe by default. The system is safe because the physician is basically only allowed to select from options that are configured as default for a specific patient-treatment combination (along with concomitant treatment as shown in Figure 1). Defaults are determined by available products, patient information and configured rules such as dosing and preparation rules. And the system is efficient as it eliminates all unnecessary steps of finding specific drug products, performing calculations and looking up specific dosing, preparation and administration rules. Also, calculations and selections are performed by the system as soon as the physician enters additional information. This concept applies to every possible medication order. This has been elaborated in appendix 1 and 2.

System test

According to the US 'General Principles of Software Validation', a guidance for pharmaceutical industry and FDA staff, consecutive activities in a typical software life cycle model are: 1) Quality planning, 2) System requirements definition, 3) Detailed software requirements specification, 4) Software design specification, 5) Construction or coding, 6) testing, 7) installation, 8) operation and support, 9) maintenance and 10) retirement.[27] Thus, after the system requirements are composed, the system is designed and the software is developed, software verification tests (step 6) have to be performed. According to the guidelines mentioned above, software verification tests should provide objective evidence that the design outputs of a particular phase of the software development life cycle meet all of the specified requirements for that phase.[27] However, further explanation in relation to CPOE systems is not available. Therefore, a software verification methodology was developed to be able to test the developed system.

The used medication database for product information was the Dutch national drug database, the 'G-standaard'. The 'G-standaard' also includes a dosing guidelines with adult and pediatric dosing rules that were used as rules to test the system. The test patient was extracted from the hospital's health information system (HIS). Software testing is one of many verification activities intended to confirm that software development output meets its input requirements. Other verification activities include various static and dynamic analyses, code and document inspections, walkthroughs, etc.,[27] but those activities are excluded from this chapter.

The first step of software verification was to test the backbone of the system (Figure 4, panel A) to make sure that import and application of database information, rules and calculations are correct. The second step is to validate the system as a whole by testing whether it meets all of the specified requirements (Figure 3). In this chapter, only step 1 is presented as 'proof of concept' of the developed system. The following elements had to be tested to make sure that import and application of database information, rules and calculations are correct:

1. Translation of product information into 'orderables'
    1.1. Import of product information from the medication database
    1.2. Application of automatic configuration, e.g. if an order for suppositories is composed, the fields for frequency and single dose should be calculated and the fields for concentration and pump flow rate should be blocked by default.
2. Translation of patients details, orderable, prescription details and rules into selection options and final medication order:
    2.1. Import of patient information from HIS.
    2.2. Import of rules from the dosing guidelines/preparation protocols.
    2.3. Calculations per order, e.g. multiplication of dose per kilogram multiplied by body weight should render the correct dose.
    2.4. Calculations per order type, e.g. for continuous intravenous medication orders the correct infusion rate should be calculated from prescribed dose and concentration.

Thereto, per order type it was tested whether:

1. The right patient information was imported and applied to compose orderable and prescription
2. The right product information was imported and applied to compose orderable
3. The right rules were imported and applied to compose orderable and prescription
4. The right default settings were applied per order type to compose orderable and prescription
5. The right calculations were performed to compose selection options
6. Calculations rendered the right answers

A cross table was constructed per order type to predict the result of orderable, prescription and final medication order. Consequently, it was tested whether the system performed as predicted.

Table 2 Calculation of predicted results for diclofenac suppository for rectal use.

Patient: 28 kg
Products: 12.5 mg, 25 mg, 50 mg and 100 mg suppositories
Rules: Dose = max. 3 mg/kg/day, Frequency: 2, 3 or 4 times/day
Total daily dose in mg/day (rule: max. 3 mg/kg/day * 28 kg = max. 84 mg/day)

	2dd	3dd	4dd
12.5 mg supp	2 * 12.5 = 25 mg/day	3 * 12.5 = 37.5 mg/day	4 * 12.5 = 50 mg/day
25 mg supp	2 * 25 = 50 mg/day	3 * 25 = 75 mg/day	4 * 25 = 100 mg/day
50 mg supp	2 * 50 = 100 mg/day	3 * 50 = 150 mg/day	4 * 50 = 200 mg/day
100 mg supp	2 * 100 = 200 mg/day	3 * 100 = 300 mg/day	4 * 100 = 400 mg/day

White = dose ≤ 84 mg/day = option for patient, Grey = dose > 84 mg/day = not an option for patient

Total daily dose in mg/kg/day (rule: max. 3 mg/kg/day)

	2dd	3dd	4dd
12.5 mg supp	25 mg/day : 28 kg = 0.89 mg/kg/day	37,5 mg/day : 28 kg = 1.34 mg/kg/day	50 mg/day : 28 kg = 1.78 mg/kg/day
25 mg supp	50 mg/day : 28 kg = 1.78 mg/kg/day	75 mg/day : 28 kg = 2.68 mg/kg/day	100 mg/day : 28 kg = 3.57 mg/kg/day
50 mg supp	100 mg/day : 28 kg = 3.57 mg/kg/day	150 mg/day : 28 kg = 5.36 mg/kg/day	200 mg/day : 28 kg = 7.14 mg/kg/day
100 mg supp	200 mg/day : 28 kg = 7.14 mg/kg/day	300 mg/day : 28 kg = 10.71 mg/kg/day	400 mg/day : 28 kg = 14.29 mg/kg/day

White = dose ≤ 3 mg/kg/day = option for patient, Grey = dose > 3 mg/kg/day = not an option for patientt

Frequency (rule: 2 – 4 dd)

	0.89 mg/kg/day	1.34 mg/kg/day	1.78 mg/kg/day	2.68 mg/kg/day
12.5 mg supp	(0.89 * 28 kg) ÷ 12.5 = 2 dd	(1.34 * 28 kg) ÷ 12.5 = 3 dd	(1.78 * 28 kg) ÷ 12.5 = 4 dd	(2.68 * 28 kg) ÷ 12.5 = 6 dd
25 mg supp	(0.89 * 28 kg) ÷ 25 = 1 dd	(1.34 * 28 kg) ÷ 25 = 11/2dd	(1.78 * 28 kg) ÷ 25 = 2 dd	(2.68 * 28 kg) ÷ 25 = 3 dd
50 mg supp	(0.89 * 28 kg) ÷ 50 = 1/2dd	(1.34 * 28 kg) ÷ 50 = 3/4dd	(1.78 * 28 kg) ÷ 50 = 1 dd	(2.68 * 28 kg) ÷ 50 = 11/2dd
100 mg supp	(0.89 * 28 kg) ÷ 100 = 1/4dd	(1.34 * 28 kg) ÷ 100 = 3/8dd	(1.78 * 28 kg) ÷ 100 = 1/2dd	(2.68 * 28 kg) ÷ 100 = 3/4dd

White = frequency 2 – 4 dd = option for patient, Grey = frequency < 2 dd or > 4 dd = not an option

Table 3 Predicted and obtained results for diclofenac suppository for rectal use.

Predicted result	Obtained result	Conclusion
Screen field: Indication (selected) General painkilling	Screen field: Indication General painkilling	obtained = predicted
Screen field: Product (calculated) 2 options: diclofenac 12.5 mg and diclofenac 25 mg	Screen field: Product 2 options: diclofenac 12.5 mg and diclofenac 25 mg	obtained = predicted
Screen field: Dosage form and route of administration (selected) suppository rectal	Screen field: Dosage form and route of administration suppository rectal	obtained = predicted
Screen field: Frequency (calculated) 3 options: 2dd, 3dd, 4dd	Screen field: Frequency 3 options: 2dd, 3dd, 4dd	obtained = predicted
Screen field: Single dose (calculated) 2 options: 12.5 mg per dose or 25 mg per dose	Screen field: Single dose 2 options: 12.5 mg per dose or 25 mg per dose	obtained = predicted
Screen field: Dose unit (calculated) 1 option: 1 suppository per dose	Screen field: Dose unit 1 option: 1 piece per dose	obtained = predicted
Screen fields: Solution, Concentration, Runtime, Dose rate, Infusion rate Blocked by default	Screen fields: Solution, Concentration, Runtime, Dose rate, Infusion rate Blocked	obtained = predicted
Screen field: Total daily dose in mg/kg/day (calculated) 4 options: 0.89, 1.34, 1.78 and 2.68	Screen field: Total daily dose in mg/kg/day 4 options: 0.89, 1.34, 1.78 and 2.68	obtained = predicted
Screen field: Total daily dose in dose units (calculated) 3 options: 2, 3 or 4 suppositories	Screen field: Total daily dose in dose units 3 options: 2, 3 or 4 suppositories	obtained = predicted

Predicted results

Using the same example as presented in figure 4, according to the used medication database, the available diclofenac suppositories were those containing 12.5 mg, 25 mg, 50 mg and 100 mg diclofenac (orderables). According to the used formulary, in children aged 6 months up to 18 years, diclofenac suppositories for general pain killing, should be dosed 2 to 4 times daily with a maximum of 3 mg/kg/day rectally (dosing rules). A test patient was used to test the dose calculations: girl, 9 years, body weight 28 kg. The predicted selection options for the test patient were determined using the cross table shown in Table 2. Consequently, it was predicted which calculated or default information should be shown as option per screen field when ordering this medication for the test patient. This is shown in Table 3, left column.

Obtained results

The test patient was selected. Then, diclofenac suppositories were selected as orderable and 'general painkilling' was selected as indication. Thereafter, the system was commanded to 'get selection options'. The obtained results are shown in Table 3, right column. All obtained results were as predicted, see table 3.

The test results of two other order types are presented as appendix 1 and 2: gentamicin intravenous infusion and dopamine continuous infusion. Both tests led to the conclusion that the obtained results were as predicted.

Discussion

The current study of system requirements and subsequent system design, development and tests demonstrates a proof of concept of an integrated safe by default and efficient CPOE that can be used in the diverse and complex NICU and PICU population. This study described the development of such a system, based on system requirements abstracted from literature and local error analyses. The system was tested according to a tailored software verification methodology and proved to provide safe and efficient support for PICU and NICU prescribing for a number of test scenarios.

CPOE/CDS has become essential for medication prescribing. According to the most recent US survey, in 2012, 44% of general care hospitals in the US had at least basic electronic health record (EHR) systems including CPOE/CDS for medications.[28] In the UK, a national survey of inpatient medication systems pointed out a much lower adoption rate: 13% of hospitals had an electronic prescribing system in 2011.[29] In the Netherlands, a 2011 survey determined that 60% of Dutch hospitals had adopted CPOE/CDS systems. Per January 1st 2014 electronic prescribing has become mandatory for all health care providers in the Netherlands and per January 1st 2015 all prescribers must prescribe electronically.[30] Thus, CPOE/CDS use is becoming widespread and obligatory.

However, sufficient support, particularly for specific patient and treatment categories, seems to be lacking or is fragmented available. A 2014 systematic review and meta-analysis studied the effect of CPOE, whether including CDS or not, in hospital care on its primary outcome of interest: reducing preventable adverse drug events (pADEs) caused by medication errors.[31] CPOE was associated with about half as many pADEs as paper-order entry (pooled RR = 0.47, 95% CI 0.31-0.71, study heterogeneity I^2 = 69%). CPOE was also associated with about half as many medication errors (pooled RR = 0.46, 95% CI 0.35-0.60, I^2 = 99%), in accordance with another recent systematic review that concluded that CPOE decreased the likelihood of a medication error by 48% (95% CI 41-55%).[32] Secondary objective of the meta-analysis was to identify factors contributing to variability in effectiveness at reducing medication errors. Five intervention design and implementation factors were examined among which 'CDS present versus absent' and 'CDS basic versus moderate or advanced', but none reached statistical significance.[31] In the abovementioned surveys and studies, the types of CPOE systems and their included level of CDS varied largely. Wright et al. performed a survey among nine US commercial vendors and health care institutions and concluded that a diverse range of CDS tools exists in both vendor and internally developed systems. Additionally, certain classes of CDS tools proved to be more commonly available than others: the more complex, the more investment (financial, time, expertise) needed, the less available.[33]

CPOE/CDS systems prevent errors and consequent patient harm, but have unintended effects as well.[34,35] Besides unintended effects such as workflow issues, communication issues and overdependence on technology, new kinds of medication errors are introduced.[36] Two main medication error types are distinguished: information errors, generated by fragmentation of data and failure to integrate the hospital's several computer and information systems, and human-machine interface flaws, reflecting machine rules that do not correspond to work organization or usual behavior.[36] Westbrook et al. recently demonstrated that errors using CPOE/CDS were most frequent when prescribers selected information from drop-down menus (43%), edited information in predefined order sentences (21%), and performed new tasks as workaround in response to systems limitations, i.e. errors in recording/changing times for administration and discontinuation, and errors associated with ancillary free-text information.[37] Thus, CPOE system can lead to errors that may result in patient harm, possibly related to non-compliance of the system to existing workflows and/or to introducing inefficiency. This should be taken into account when designing and developing CPOE/CDS systems.

Additionally, besides preventing the abovementioned selection errors, editing errors and errors due to workarounds, another challenge is posed by determining what alerts should be presented to the prescriber. It is well known that high burdens of reminders and clinically irrelevant alerts lead to so-called 'alert fatigue', causing clinicians to override both important and unimportant alerts. Low specificity, high sensitivity, unclear information content of alerting systems and unnecessary

workflow disruptions by alerting systems lead to unsafe and inefficient handling.[38] This may be improved by developing more intelligent CPOE/CDS that that combines patient data (e.g. degree of renal impairment, hyperkalemia, lack of potassium level measurements) and therapeutic information (e.g. dose ranges per degree of renal failure, DDIs that potentially lead to hyperkalemia) from different databases, and only fires if specific rules are violated for an individual patient.[39] If CDS is to contribute to preventing errors, it needs to be advanced and avoid nonsensical alerts.

Designing CPOE/CDS systems for pediatric, PICU and NICU populations poses an extra challenge due to patient and treatment diversity and complexity. A 2013 report by the US Council on Clinical Information Technology discussed the advances in electronic prescribing systems in pediatrics and acknowledged there are positive pediatric data supporting the role of electronic prescribing in mitigating medication errors. On the basis of this report, the American Academy of Pediatrics recommends and provides guidelines for the adoption of CPOE/CDS in pediatric settings.[40] CPOE/CDS systems for pediatrics have greater information requirements than for adults due a number of pediatric-specific issues in the medication process. Main identified pediatric-specific problems that require CPOE/CDS assistance are: 1. dosing and required calculations for (cumulative) dosing, taking patient variables such as weight, age, renal function etc. into account,[8,41] 2. matching and rounding of calculated doses to available products, product strengths/concentrations and formulations,[7,17,42,43,44] 3. preparing and required calculations for preparing to be able to administer a drug that is suitable for a child.[23,45] As may be expected, dosing support is the most extensive studied CDS tool in pediatrics. Main themes in these studies are poor appropriateness and suboptimal accuracy of dosing support and the need for customization to pediatrics, including support for off-label indications and drug use outside its product license.[46-51]

The effect of CPOE/CDS systems in PICUs and NICUs in particular, has been studied: in general, CPOE/CDS systems offer the potential to reduce prescribing error rates in PICU/NICU patients, if well-designed and -implemented, yet clinical benefit remains to be established.[3,12,13] Two NICU studies focused on the effects of customized CPOE/CDS systems on workflow and efficiency and showed positive results in medication turn-around time, radiology response time and time to pharmacy verification.[19,20] One study found a significant profit in PICU prescribing time by computerizing the ordering of resuscitation medications.[18] Implementation of CPOE in a NICU was associated with a significant decrease in the rate of discrepancies between ordered and administered medication.[25] On the other hand, the introduction of a CPOE system in another NICU did not significantly improve antibiotic administration times.[19] Additionally, a PICU study by Han et al. showed an unexpected increased mortality potentially due to delays in therapies and diagnostic testing after CPOE implementation.[15]

Only few studies focused on effects of specific CDS tools in PICUs/NICUs. The majority concerned evaluations of calculation tools and are summarized here. In a PICU study evaluating the effect of a web-based calculator and decision support system on continuous infusion ordering errors, a significant reduction of errors was achieved.[22] A second PICU study also focused on continuous infusions: it evaluated the effect of a CPOE/CDS tool in combination with standardized concentrations and determined near-elimination of pharmacy processing and preparation errors.[23] A Cochrane review on CDS systems for neonatal care included a study that examined CDS for calculation of neonatal drug dosages. It was found that the time taken for calculation was significantly reduced and there was a significant reduction in the number of calculation errors.[16] Other published studies on NICU dose calculation tools also showed significant reductions in dosing-, rounding- and calculation errors, e.g. for gentamicin[20] and antibiotics and anticonvulsants.[21] An advanced CDS calculating tool supporting the complex calculations for glucose control in NICU patients, taking cumulative glucose doses in (par)enteral nutrition, maintenance fluids and drug base solutions into account, proved to preserve accuracy for calculation and control of glucose and increased prescribing time efficiency.[8]

The above leads to the assumption that CPOE/CDS should be integrated to match the practical workflows and stakeholders in the medication process. Therefore, the presented CPOE system allows different views of the same process. In this paper, stakeholders in the medication process were presented as physicians performing medication ordering, pharmacists performing medication verification and dispensing, and nurses performing preparation and administration. This distribution of tasks by professionals is only an example to explain the different possible views on the medication process. In practice, the exact task differentiation per professional can be otherwise.

A carefully designed CDS should support safety and efficiency in the medication process. Basically, this is accomplished by letting the system create the necessary selection options to generate a medication order, in which the selection by the user limits additional options, until all order details are set. This approach is radically different from letting the user set an option upon which the system later on prompts the problem with that setting. Thus, the resulting system allows for an integrated approach of the medication process, facilitating safety and efficiency by default. This approach was demonstrated to be feasible in the very diverse and complex PICU/NICU setting, and is claimed to be generalizable to other, less diverse and less complex, settings.

However, although the demonstrated system is advanced, it needs to be further developed, refined and validated. As mentioned, the presented system consists of a decision support system and a CPOE system, that will be part of and provide input for the development of additional system components for medication order validation, order planning, preparation, a medication administration record and assessment and evaluation of effects of administered medication.

Additionally, ideally, the system would be intelligent and be able to learn from data, i.e. would be able to copy human intelligence, for example by proposing a dopamine continuous infusion dose adjustment when it registers a period of hypotension for an individual patient.

Conclusions

Although becoming widespread and even legally required in some countries, a clinically practical and safe CPOE system for integrated use in the entire medication process does not exist. This study demonstrates a proof of concept of an innovative, integrated, efficient and safe by default CPOE system that can be used in NICU and PICU populations, and is generalizable to other settings. Further studies are necessary to further develop and clinically validate the system for actual use in practice.

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References

1 Chedoe I, Molendijk HA, Dittrich ST, et al. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety: a review of the current literature. Drug Saf 2007;30:503-13.

2 Buckley MS, Erstad BL, Kopp BJ, et al. Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. Pediatr Crit Care Med 2007;8:145-52.

3 Warrick C, Naik H, Avis S, et al. A clinical information system reduces medication errors in paediatric intensive care. Intensive Care Med 2011;37:691-4.

4 Colpaert K, Decruyenaere J. Computerized physician order entry in critical care. Best Pract Res Clin Anaesthesiol 2009;23:27-38.

5 Latif A, Rawat N, Pustavoitau A, et al. National study on the distribution, causes and consequences of voluntarily reported medication errors between the ICU and non-ICU settings. Crit Care Med 2013;41:389-98.

6 Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285:2114-20.

7 Maat B, Bollen CW, van Vught AJ, et al. Prescribing errors in pediatric intensive care patients. Intensive Care Med 2014;40:458-9.

8 Maat B, Rademaker CM, Oostveen MI, et al. The effect of a computerized prescribing and calculating system on hypo- and hyperglycemias and on prescribing time efficiency in neonatal intensive care patients. JPEN J Parenter Enteral Nutr 2013;37:85-91.

9 Bartelink IH, Rademaker CM, Schobben AF, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006;45:1077-97.

10 Franke HA, Woods DM, Holl JL. High-alert medications in the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:85-90.

11 Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. Ann Pharmacother 2006;40:1766-76.

12 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

13 Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a PICU. Pediatrics 2009;124:935-940.

14 Walsh KE, Landrigan CP, Adams WG, et al. Effect of computer order entry on prevention of serious medication orders in hospitalized children. Pediatrics 2008;121:e421-7.

15 Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system [published correction appeared in Pediatrics 2006;117:594]. Pediatrics 2005;116:1506–12.

16 Tan K, Dear PR, Newell SJ. Clinical decision support systems for neonatal care. Cochrane Database Syst Rev 2005;18:CD004211.

17 Maat B, Au YS, Bollen CW, et al. Clinical pharmacy interventions in paediatric electronic prescriptions. Arch Dis Child 2013;98:222-7.

18 Vardi A, Efrati O, Levin I, et al. Prevention of potential errors in resuscitation medications orders by means of a computerised physician order entry in paediatric critical care. Resuscitation 2007;73:400-6.

19 Chapman AK, Lehmann CU, Donohue PK, et al. Implementation of computerized provider order entry in a neonatal intensive care unit: Impact on admission workflow. Int J Med Inform 2012;81:291-5.

20 Cordero L, Kuehn L, Kumar RR, et al. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. J Perinatol 2004;24:88-93.

21 Kazemi A, Ellenius J, Pourasghar F, et al. The effect of computerized physician order entry and decision support system in medication errors in the neonatal ward: experiences from an Iranian teaching hospital. J Med Syst. 2011;35:25-37.

22 Lehmann CU, Kim GR, Gujral R, et al. Decreasing errors in pediatric continuous intravenous infusions. Pediatr Crit Care Med 2006;7:225-30.

23 Sowan AK, Vaidya VU, Soeken KL, et al. Computerized orders with standardized concentrations decrease dispensing errors of continuous infusion medications for pediatrics. J Pediatr Pharmacol Ther 2010;15:189-202.

24 Sauberan JB, Dean LM, Fiedelak J, et al. Origins of and solutions for neonatal medication-dispensing errors. Am J Health Syst Pharm 2010;67:49-57.

25 Taylor JA, Loan LA, Kamara J, et al. Medication administration variances before and after implementation of computerized physician order entry in a neonatal intensive care unit. Pediatrics 2008;121:123-8.

26 Morriss FH Jr, Abramowitz PW, Nelson SP, et al. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study. J Pediatr 2009;154:363-8.

27 US Department Of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research. General Principles of Software Validation; Final Guidance for Industry and FDA Staff. 2002.

28 DesRoches CM, Charles D, Furukawa MF, et al. Adoption of electronic health records grows rapidly, but fewer than half of US hospitals had at least a basic system in 2012. Health Aff (Millwood) 2013;32:1478-85.

29 McLeod M, Ahmed Z, Barber N, et al. A national survey of inpatient systems in English NHS hospitals. BMC Health Serv Res 2014;14:93.

30 M&I Report Adoption electronic prescribing systems in Dutch hospitals, 2011. Available at: http://mxi.nl/upload/documenten/i1103_jerge-jacjg_ziekenhuizenkiezenvoorgeleidelijkinvoeren_pharmaceutischweekblad-20110701.pdf [Accessed 9 June 2014].

31 Nuckols TK, Smith-Spangler C, Morton SC, et al. The effectiveness of computerized order entry at reducing preventable adverse drug events and medication errors in hospital settings: a systematic review and meta-analysis. Syst Rev 2014;3:56.

32 Radley DC, Wasserman MR, Olsho LE, et al. Reduction in medication errors in hospitals due to adoption of computerized provider order entry systems. J Am Med Inform Assoc 2013;20:470-6.

33 Wright A, Sittig DF, Ash JS, et al. Development and evaluation of a comprehensive clinical decision support taxonomy: comparison of front-end tools in commercial and internally developed electronic health record systems. J Am Med Inform Assoc 2011;18:232-42.

34 Ash JS, Sittig DF, Dykstra R, et al. The unintended consequences of computerized provider order entry: findings from a mixed methods exploration. Int J Med Inform 2009;78 Suppl 1:S69-76.

35 Reckmann MH, Westbrook JI, Koh Y, et al. Does computerized provider order entry reduce prescribing errors for hospital inpatients? A systematic review. J Am Med Inform Assoc 2009;16:613-23.

36 Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293:1197-203.

37 Westbrook JI, Baysari MT, Li L, et al. The safety of electronic prescribing: manifestations, mechanisms, and rates of system-related errors associated with two commercial systems in hospitals. J Am Med Inform Assoc 2013;20:1159-67.

38 van der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138-47.

39 Eppenga WL, Derijks HJ, Conemans JM, et al. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. J Am Med Inform Assoc 2012;19:66-71.

40 American Academy of Pediatrics Council on Clinical Information Technology Executive Committee, 2011–2012. Electronic prescribing in pediatrics: toward safer and more effective medication management. Pediatrics 2013;131:824-6.

41 Johnson KB, Lehmann CU; Council on Clinical Information Technology of the American Academy of Pediatrics. Electronic prescribing in pediatrics: toward safer and more effective medication management. Pediatrics 2013;131:e1350-6.

42 van Riet-Nales, DA, de Jager KE, Schobben AF, et al. The availability and age-appropriateness of medicines authorized for children in The Netherlands. Br J Clin Pharmacol 2011;72:465-73.

43 van Riet-Nales DA, de Neef BJ, Schobben AF, et al. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013;98:725-31.

44 Johnson KB, Lee CK, Spooner SA, et al. Automated dose-rounding recommendations for pediatric medications. Pediatrics 2011;128:e422-8.

45 van Riet-Nales DA, Doeve ME, Nicia AE, et al. The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife. Int J Pharm 2014;466:44-51.

46 Kirkendall ES, Spooner SA, Logan JR. Evaluating the accuracy of electronic pediatric drug dosing rules. J Am Med Inform Assoc 2014;21:e43-9.

47 Stultz JS, Porter K, Nahata MC. Sensitivity and specificity of dosing alerts for dosing errors among hospitalized pediatric patients. J Am Med Inform Assoc 2014 Feb 4. [Epub ahead of print]

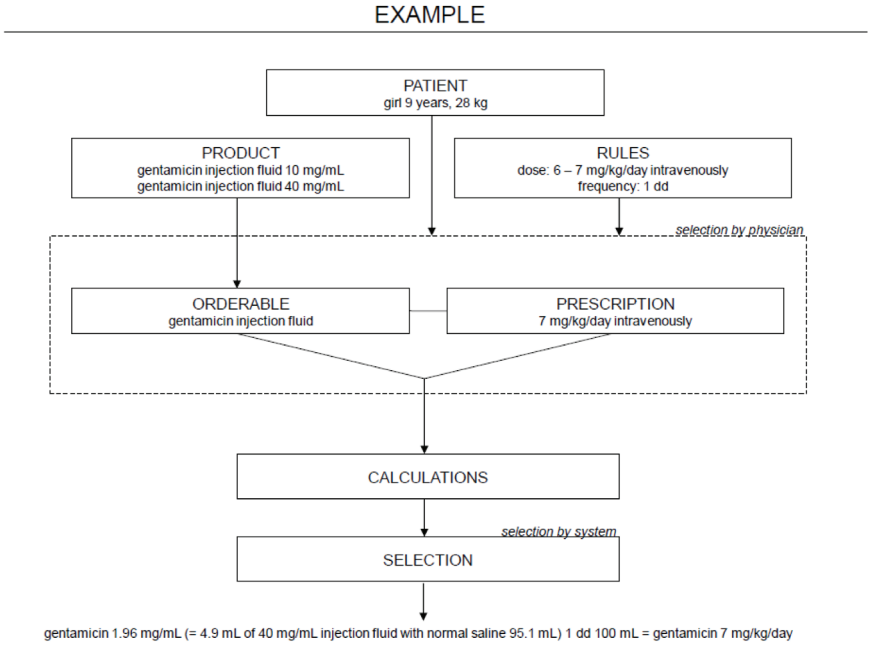
48 Stultz JS, Nahata MC. Appropriateness of commercially available and partially customized medication dosing alerts among pediatric patients. J Am Med Inform Assoc 2014;21:e35-42.

49 Scharnweber C, Lau BD, Mollenkopf N, et al. Evaluation of medication dose alerts in pediatric inpatients. Int J Med Inform 2014;82:676-83.

50 Ferranti JM, Horvath MM, Jansen J, et al. Using a computerized provider order entry system to meet the unique prescribing needs of children: description of an advanced dosing model. BMC Med Inform Decis Mak 2011;11:14.

51 Perlman SL, Fabrizio L, Shaha SH, et al. Response to medication dosing alerts for pediatric inpatients using a computerized provider order entry system. Appl Clin Inform 2011;2:522-33.

Appendix 1 Test gentamicin intravenous infusion.



Appendix 1 Continued.

Patient: 28 kg
Product: 10 mg/mL or 40 mg/mL injection fluid, dosing per 0.1 mL (minimum measurable volume)
Rules: - dose: 6-7 mg/kg/day - frequency: 1dd
Total daily dose in mg/day = 6-7 mg/kg/day * 28 kg = 168-196 mg/day
Total daily dose in mL/day = 168-196 mg/day ÷ 10 mg/mL = 16.8-19.6 mL/day, dosing per 0.1 mL
Total daily dose in mL/day = 168-196 mg/day ÷ 40 mg/mL = 4.2-4.9 mL/day, dosing per 0.1 mL
Calculation of predicted results for gentamicin intravenous infusion

Total daily dose in mg/day		Total daily dose in mg/kg/day	
10 mg/mL	**1 dd**		**1 dd**
< 16.8 mL/day	< 16.8 mL * 10 mg/mL = < 168 mg/day	< 168 mg/day	< 168 mg/day ÷ 28 kg = < 6.00 mg/kg/day
16.8 mL/day	16.8 mL * 10 mg/mL = 168 mg/day	168 mg/day	168 mg/day ÷ 28 kg = 6.00 mg/kg/day
16.9 mL/day	16.9 mL * 10 mg/mL = 169 mg/day	169 mg/day	169 mg/day ÷ 28 kg = 6.04 mg/kg/day
17.0 mL/day	17.0 mL * 10 mg/mL = 170 mg/day	170 mg/day	170 mg/day ÷ 28 kg = 6.07 mg/kg/day
17.1 mL/day	17.1 mL * 10 mg/mL = 171 mg/day	171 mg/day	171 mg/day ÷ 28 kg = 6.11 mg/kg/day
17.2 mL/day	17.2 mL * 10 mg/mL = 172 mg/day	172 mg/day	172 mg/day ÷ 28 kg = 6.14 mg/kg/day
17.3 mL/day	17.3 mL * 10 mg/mL = 173 mg/day	173 mg/day	173 mg/day ÷ 28 kg = 6.18 mg/kg/day
17.4 mL/day	17.4 mL * 10 mg/mL = 174 mg/day	174 mg/day	174 mg/day ÷ 28 kg = 6.21 mg/kg/day
17.5 mL/day	17.5 mL * 10 mg/mL = 175 mg/day	175 mg/day	175 mg/day ÷ 28 kg = 6.25 mg/kg/day
17.6 mL/day	17.6 mL * 10 mg/mL = 176 mg/day	176 mg/day	176 mg/day ÷ 28 kg = 6.29 mg/kg/day
17.7 mL/day	17.7 mL * 10 mg/mL = 177 mg/day	177 mg/day	177 mg/day ÷ 28 kg = 6.32 mg/kg/day
17.8 mL/day	17.8 mL * 10 mg/mL = 178 mg/day	178 mg/day	178 mg/day ÷ 28 kg = 6.36 mg/kg/day
17.9 mL/day	17.9 mL * 10 mg/mL = 179 mg/day	179 mg/day	179 mg/day ÷ 28 kg = 6.39 mg/kg/day
18.0 mL/day	18.0 mL * 10 mg/mL = 180 mg/day	180 mg/day	180 mg/day ÷ 28 kg = 6.43 mg/kg/day
18.1 mL/day	18.1 mL * 10 mg/mL = 181 mg/day	181 mg/day	181 mg/day ÷ 28 kg = 6.46 mg/kg/day
18.2 mL/day	18.2 mL * 10 mg/mL = 182 mg/day	182 mg/day	182 mg/day ÷ 28 kg = 6.50 mg/kg/day
18.3 mL/day	18.3 mL * 10 mg/mL = 183 mg/day	183 mg/day	183 mg/day ÷ 28 kg = 6.54 mg/kg/day
18.4 mL/day	18.4 mL * 10 mg/mL = 184 mg/day	184 mg/day	184 mg/day ÷ 28 kg = 6.57 mg/kg/day
18.5 mL/day	18.5 mL * 10 mg/mL = 185 mg/day	185 mg/day	185 mg/day ÷ 28 kg = 6.61 mg/kg/day

Appendix 1 Continued.

10 mg/mL	1 dd		1 dd	
18.6 mL/day	18.6 mL * 10 mg/mL =	186 mg/day	186 mg/day	186 mg/day ÷ 28 kg = 6.64 mg/kg/day
18.7 mL/day	18.7 mL * 10 mg/mL =	187 mg/day	187 mg/day	187 mg/day ÷ 28 kg = 6.68 mg/kg/day
18.8 mL/day	18.8 mL * 10 mg/mL =	188 mg/day	188 mg/day	188 mg/day ÷ 28 kg = 6.71 mg/kg/day
18.9 mL/day	18.9 mL * 10 mg/mL =	189 mg/day	189 mg/day	189 mg/day ÷ 28 kg = 6.75 mg/kg/day
19.0 mL/day	19.0 mL * 10 mg/mL =	190 mg/day	190 mg/day	190 mg/day ÷ 28 kg = 6.79 mg/kg/day
19.1 mL/day	19.1 mL * 10 mg/mL =	191 mg/day	191 mg/day	191 mg/day ÷ 28 kg = 6.82 mg/kg/day
19.2 mL/day	19.2 mL * 10 mg/mL =	192 mg/day	192 mg/day	192 mg/day ÷ 28 kg = 6.86 mg/kg/day
19.3 mL/day	19.3 mL * 10 mg/mL =	193 mg/day	193 mg/day	193 mg/day ÷ 28 kg = 6.89 mg/kg/day
19.4 mL/day	19.4 mL * 10 mg/mL =	194 mg/day	194 mg/day	194 mg/day ÷ 28 kg = 6.93 mg/kg/day
19.5 mL/day	19.5 mL * 10 mg/mL =	195 mg/day	195 mg/day	195 mg/day ÷ 28 kg = 6.96 mg/kg/day
19.6 mL/day	19.6 mL * 10 mg/mL =	196 mg/day	196 mg/day	196 mg/day ÷ 28 kg = 7.00 mg/kg/day
> 19.6 mL/day	> 19.6 mL * 10 mg/mL =	> 196 mg/day	> 196 mg/day	> 196 mg/day ÷ 28 kg = > 7.00 mg/kg/day

White = dose ≥ 168 mg/day and ≤ 196 mg/day = option for patient
Grey = dose < 168 mg/day or > 196 mg/day = not an option for patient

White = dose ≥ 6 mg/kg/day and ≤ 7 mg/kg/day = option for patient
Grey = dose < 6 mg/kg/day or > 7 mg/kg/day = not an option for patient

Appendix 1 Continued.

Total daily dose in mg/day		Total daily dose in mg/kg/day	
40 mg/mL	**1dd**		**1 dd**
< 4.2 mL/day	< 4.2 mL * 40 mg/mL = < 168 mg/day	< 168 mg/day	< 168 mg/day ÷ 28 kg = < 6.00 mg/kg/day
4.2 mL/day	4.2 mL * 40 mg/mL = 168 mg/day	168 mg/day	168 mg/day ÷ 28 kg = 6.00 mg/kg/day
4.3 mL/day	4.3 mL * 40 mg/mL = 172 mg/day	172 mg/day	172 mg/day ÷ 28 kg = 6.14 mg/kg/day
4.4 mL/day	4.4 mL * 40 mg/mL = 176 mg/day	176 mg/day	176 mg/day ÷ 28 kg = 6.29 mg/kg/day
4.5 mL/day	4.5 mL * 40 mg/mL = 180 mg/day	180 mg/day	180 mg/day ÷ 28 kg = 6.43 mg/kg/day
4.6 mL/day	4.6 mL * 40 mg/mL = 184 mg/day	184 mg/day	184 mg/day ÷ 28 kg = 6.57 mg/kg/day
4.7 mL/day	4.7 mL * 40 mg/mL = 188 mg/day	188 mg/day	188 mg/day ÷ 28 kg = 6.71 mg/kg/day
4.8 mL/day	4.8 mL * 40 mg/mL = 192 mg/day	192mg/day	192 mg/day ÷ 28 kg = 6.86 mg/kg/day
4.9 mL/day	4.9 mL * 40 mg/mL = 196 mg/day	196 mg/day	196 mg/day ÷ 28 kg = 7.00 mg/kg/day
> 4.9 mL/day	> 4.9 mL * 40 mg/mL = > 196 mg/day	> 196 mg/day	> 196 mg/day ÷ 28 kg = > 7.00 mg/kg/day

White = dose ≥ 168 mg/day and ≤ 196 mg/day = option for patient
Grey = dose < 168 mg/day or > 196 mg/day = not an option for patient

White = dose ≥ 6 mg/kg/day and ≤ 7 mg/kg/day = option for patient
Grey = dose < 6 mg/kg/day or > 7 mg/kg/day = not an option for patient

Appendix 1 Continued.

Predicted and obtained results for gentamicin intravenous infusion

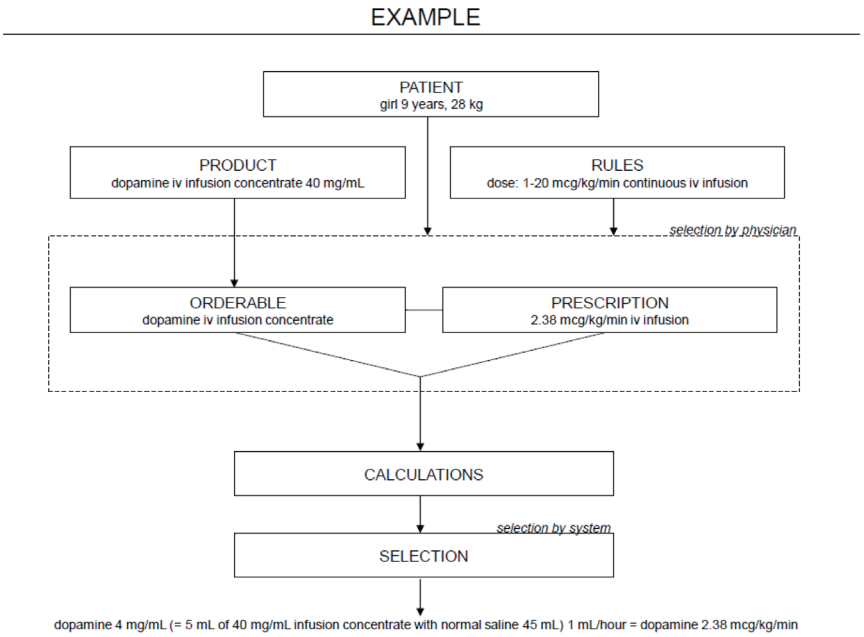
Predicted result	Obtained result	Conclusion
Screen field: Indication (selected) General	Screen field: Indication General	obtained = predicted
Screen field: Product (calculated) 2 options: gentamicin 10 mg/mL and gentamicin 40 mg/mL	Screen field: Product 2 options: gentamicin 10 mg/mL and gentamicin 40 mg/mL	obtained = predicted
Screen field: Total daily dose gentamicin (calculated) 29 options: 168, 169, 170, 171, 172, 173, 174, 175,176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195 and 196 mg	Screen field: Total daily dose gentamicin 29 options: 168, 169, 170, 171, 172, 173, 174, 175,176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195 and 196 mg	obtained = predicted
Screen field: Dosage form and route of administration (selected) Injection fluid intravenous	Screen field: Dosage form and route of administration Injection fluid intravenous	obtained = predicted
Screen field: Frequency (calculated) 1 option: 1dd	Screen field: Frequency 1 option: 1 dd	obtained = predicted
Screen field: Single dose (calculated) 29 options: 168, 169, 170, 171, 172, 173, 174, 175,176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195 and 196 mg	Screen field: Single dose 29 options: 168, 169, 170, 171, 172, 173, 174, 175,176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195 and 196 mg	obtained = predicted
Screen fields: Solution (selected) Normal saline in 100 mL	Screen fields: Solution (selected) Normal saline in 100 mL	obtained = predicted
Screen field: Dose unit (calculated) 1 option: 100 mL	Screen field: Dose unit 1 option: 100 mL	obtained = predicted
Screen field: Concentration in mg/mL (calculated) 29 options: 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75,1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, 1.90, 1.91, 1.92, 1.93, 1.94, 1.95 and 1.96 mg/mL	Screen field: Concentration in mg/mL 29 options: 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75,1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, 1.90, 1.91, 1.92, 1.93, 1.94, 1.95 and 1.96 mg/mL	obtained = predicted

Appendix 1 Continued.

Screen field: Total daily dose in mg/kg/day (calculated) 29 options: 6.00, 6.04, 6.07, 6.11, 6.14, 6.18, 6.21, 6.25, 6.29, 6.32, 6.36, 6.39, 6.43, 6.46, 6.50, 6.54, 6.57, 6.61, 6.64, 6.68, 6.71, 6.75, 6.79, 6.82, 6.86, 6.89, 6.93, 6.96, 7.00 mg/kg/day	Screen field: Total daily dose in mg/kg/day 29 options: 6.00, 6.04, 6.07, 6.11, 6.14, 6.18, 6.21, 6.25, 6.29, 6.32, 6.36, 6.39, 6.43, 6.46, 6.50, 6.54, 6.57, 6.61, 6.64, 6.68, 6.71, 6.75, 6.79, 6.82, 6.86, 6.89, 6.93, 6.96, 7.00 mg/kg/day	obtained = predicted
Screen field: Total daily dose in dose units (calculated) 1 option: 100 mL/day	Screen field: Total daily dose in dose units 1 option: 100 mL/day	obtained = predicted
Screen fields: Dose rate, Run time, Infusion rate Blocked by default	Screen fields: Dose rate, Run time, Infusion rate Blocked	obtained = predicted

Appendix 2 Test dopamine continuous intravenous infusion.

Dopamine continuous intravenous infusion standard syringe A, 50 mL



Appendix 2 Test dopamine continuous intravenous infusion standard syringe A, 50 mL.

Patient: 28 kg
Product: 40 mg/mL intravenous infusion concentrate
Rules:
- dose: 1-20 mcg/kg/min
- preparation: standard syringe A 200 mg dopamine = 5 mL with 45 mL normal saline = 4 mg/mL, 50 mL
- administration: pump flow rate maximum 5 mL/hour, minimum pump flow rate adjustment 0.1 mL/hour
- rounding to 3 decimal places < 1, 2 decimal places 1-10, 1 decimal place 10-100

Calculation of predicted results for dopamine continuous intravenous infusion standard syringe A, 50 mL
Dose in mcg/kg/min

4 mg/mL	1-20 mcg/kg/min
0.1 mL/hour	0.1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 0.238 mcg/kg/min
0.2 mL/hour	0.2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 0.476 mcg/kg/min
0.3 mL/hour	0.3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 0.714 mcg/kg/min
0.4 mL/hour	0.4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 0.952 mcg/kg/min
0.5 mL/hour	0.5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 1.19 mcg/kg/min
0.6 mL/hour	0.6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 1.43 mcg/kg/min
0.7 mL/hour	0.7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 1.67 mcg/kg/min
0.8 mL/hour	0.8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 1.90 mcg/kg/min
0.9 mL/hour	0.9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 2.14 mcg/kg/min
1.0 mL/hour	1.0 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 2.38 mcg/kg/min
1.1 mL/hour	1.1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 2.62 mcg/kg/min
1.2 mL/hour	1.2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 2.86 mcg/kg/min
1.3 mL/hour	1.3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 3.10 mcg/kg/min
1.4 mL/hour	1.4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 3.33 mcg/kg/min
1.5 mL/hour	1.5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 3.57 mcg/kg/min
1.6 mL/hour	1.6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 3.81 mcg/kg/min
1.7 mL/hour	1.7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 4.05 mcg/kg/min
1.8 mL/hour	1.8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 4.29 mcg/kg/min
1.9 mL/hour	1.9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 4.52 mcg/kg/min
2.0 mL/hour	2.0 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 4.76 mcg/kg/min
2.1 mL/hour	2.1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 5.00 mcg/kg/min
2.2 mL/hour	2.2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 5.24 mcg/kg/min
2.3 mL/hour	2.3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 5.48 mcg/kg/min
2.4 mL/hour	2.4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 5.71 mcg/kg/min
2.5 mL/hour	2.5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 5.95 mcg/kg/min
2.6 mL/hour	2.6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 6.19 mcg/kg/min
2.7 mL/hour	2.7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 6.43 mcg/kg/min
2.8 mL/hour	2.8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 6.67 mcg/kg/min
2.9 mL/hour	2.9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 6.90 mcg/kg/min
3.0 mL/hour	3.0 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 7.14 mcg/kg/min
3.1 mL/hour	3.1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 7.38 mcg/kg/min
3.2 mL/hour	3.2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 7.62 mcg/kg/min
3.3 mL/hour	3.3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 7.86 mcg/kg/min

Appendix 2 Continued.

3.4 mL/hour	3.4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 8.10 mcg/kg/min
3.5 mL/hour	3.5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 8.33 mcg/kg/min
3.6 mL/hour	3.6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 8.57 mcg/kg/min
3.7 mL/hour	3.7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 8.81 mcg/kg/min
3.8 mL/hour	3.8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 9.05 mcg/kg/min
3.9 mL/hour	3.9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 9.29 mcg/kg/min
4.0 mL/hour	4.0 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 9.52 mcg/kg/min
4.1 mL/hour	4.1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 9.76 mcg/kg/min
4.2 mL/hour	4.2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 10.0 mcg/kg/min
4.3 mL/hour	4.3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 10.2 mcg/kg/min
4.4 mL/hour	4.4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 10.5 mcg/kg/min
4.5 mL/hour	4.5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 10.7 mcg/kg/min
4.6 mL/hour	4.6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.0 mcg/kg/min
4.7 mL/hour	4.7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.2 mcg/kg/min
4.8 mL/hour	4.8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.4 mcg/kg/min
4.9 mL/hour	4.9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.7 mcg/kg/min
5.0 mL/hour	5.0 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.9 mcg/kg/min
> 5.0 mL/hour	> maximum pump flow rate

White = dose ≥ 1 mcg/kg/min and ≤ 20 mcg/kg/min = option for patient
Grey = dose < 1 mcg/kg/min or pump flow rate > 5.0 mL/hour = not an option for patient

Appendix 2 Continued.

Predicted and obtained results for dopamine continuous intravenous infusion standard syringe A, 50 mL

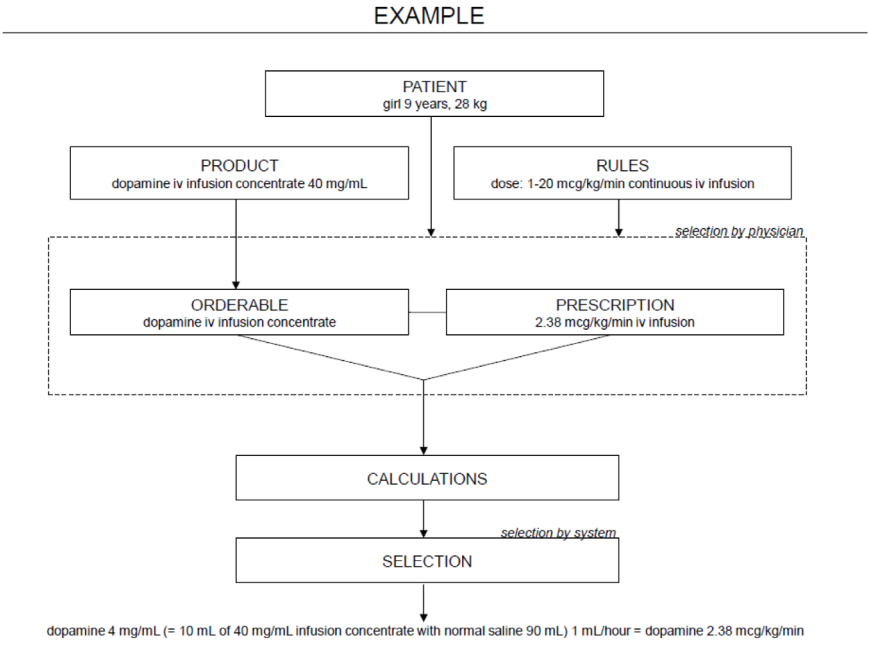
Predicted result	Obtained result	Conclusion
Screen field: Indication (selected) General	Screen field: Indication General	obtained = predicted
Screen field: Total daily dose dopamine (calculated) Standard quantity for standard concentration 200 mg by default	Screen field: Total daily dose dopamine 200 mg	obtained = predicted
Screen field: Dosage form and route of administration (selected) Infusion concentrate intravenous	Screen field: Dosage form and route of administration Infusion concentrate intravenous	obtained = predicted
Screen field: Frequency Blocked by default	Screen field: Frequency Blocked	obtained = predicted
Screen field: Single dose Blocked by default	Screen field: Single dose Blocked	obtained = predicted
Screen fields: Solution (calculated) Standard volume for standard concentration 50 mL by default	Screen fields: Solution 50 mL	obtained = predicted
Screen field: Dose unit (mL/day) Blocked by default	Screen field: Dose unit Blocked	obtained = predicted
Screen field: Concentration in mg/mL (calculated) Standard concentration 4 mg/mL by default	Screen field: Concentration in mg/mL 4 mg/mL	obtained = predicted
Screen fields: Run time Blocked by default	Screen fields: Run time Blocked	obtained = predicted
Screen field: Total daily dose in mg/kg/day Blocked by default	Screen field: Total daily dose in mg/kg/day Blocked	obtained = predicted
Screen field: Total daily dose in dose units (mL/day) Blocked by default	Screen field: Total daily dose in dose units Blocked	obtained = predicted

Appendix 2 Continued.

Screen fields: Dose rate (calculated)	Screen fields: Dose rate	obtained = predicted
46 options: 1.19, 1.43, 1.67, 1.90, 2.14, 2.38, 2.62, 2.86, 3.10, 3.33, 3.57, 3.81, 4.05, 4.29, 4.52, 4.76, 5.00, 5.24, 5.48, 5.71, 5.95, 6.19, 6.43, 6.67, 6.90, 7.14, 7.38, 7.62, 7.86, 8.10, 8.33, 8.57, 8.81, 9.05, 9.29, 9.52, 9.76, 10.0, 10.2, 10.5, 10.7, 11.0, 11.2, 11.4, 11.7, 11.9 mcg/kg/min	46 options: 1.19, 1.43, 1.67, 1.90, 2.14, 2.38, 2.62, 2.86, 3.10, 3.33, 3.57, 3.81, 4.05, 4.29, 4.52, 4.76, 5.00, 5.24, 5.48, 5.71, 5.95, 6.19, 6.43, 6.67, 6.90, 7.14, 7.38, 7.62, 7.86, 8.10, 8.33, 8.57, 8.81, 9.05, 9.29, 9.52, 9.76, 10.0, 10.2, 10.5, 10.7, 11.0, 11.2, 11.4, 11.7, 11.9 mcg/kg/min	

Screen fields: Pump flow rate (calculated)	Screen fields: Pump flow rate	obtained = predicted
46 options: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0 mL/hour	46 options: 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0 mL/hour	

Appendix 2 Continued.



Appendix 2 Continued.

Patient: 28 kg
Product: 40 mg/mL intravenous infusion concentrate
Rules:
- dose: 1-20 mcg/kg/min
- preparation: standard syringe B 400 mg dopamine = 10 mL with 90 mL normal saline = 4 mg/mL, 100 mL
- administration: pump flow rate maximum 10 mL/hour, minimum pump flow rate adjustment 1 mL/hour
- rounding to 2 decimal places 1-10, 1 decimal place 10-100

Calculation of predicted results for dopamine continuous intravenous infusion standard syringe B, 100 mL
Dose in mcg/kg/min

4 mg/mL	1-20 mcg/kg/min
1 mL/hour	1 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 2.38 mcg/kg/min
2 mL/hour	2 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 4.76 mcg/kg/min
3 mL/hour	3 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 7.14 mcg/kg/min
4 mL/hour	4 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 9.52 mcg/kg/min
5 mL/hour	5 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 11.9 mcg/kg/min
6 mL/hour	6 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 14.3 mcg/kg/min
7 mL/hour	7 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 16.7 mcg/kg/min
8 mL/hour	8 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 19.1 mcg/kg/min
9 mL/hour	9 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 21.4 mcg/kg/min
10 mL/hour	10 mL/hour * 4 mg/mL * 1000/60 ÷ 28 kg = 23.8 mcg/kg/min
> 10 mL/hour	> maximum pump flow rate

White = dose ≥ 1 mcg/kg/min and ≤ 20 mcg/kg/min = option for patient
Grey = dose > 1 mcg/kg/min and/or pump flow rate > 10 mL/hour = not an option for patient

Predicted and obtained results for dopamine continuous intravenous infusion standard syringe B, 100 mL.

Predicted result	Obtained result	Conclusion
Screen field: Indication (selected) General	Screen field: Indication General	obtained = predicted
Screen field: Total daily dose dopamine (calculated) Standard quantity for standard concentration 400 mg by default	Screen field: Total daily dose dopamine 400 mg	obtained = predicted
Screen field: Dosage form and route of administration (selected) Infusion concentrate intravenous	Screen field: Dosage form and route of administration Infusion concentrate intravenous	obtained = predicted
Screen field: Frequency Blocked by default	Screen field: Frequency Blocked	obtained = predicted

Appendix 2 Continued.

Screen field: Single dose Blocked by default	Screen field: Single dose Blocked	obtained = predicted
Screen fields: Solution (calculated) Standard volume for standard concentration 100 mL by default	Screen fields: Solution 100 mL	obtained = predicted
Screen field: Dose unit (mL/day) Blocked by default	Screen field: Dose unit Blocked	obtained = predicted
Screen field: Concentration in mg/mL (calculated) Standard concentration 4 mg/mL by default	Screen field: Concentration in mg/mL 4 mg/mL	obtained = predicted
Screen fields: Run time Blocked by default	Screen fields: Run time Blocked	obtained = predicted
Screen field: Total daily dose in mg/kg/day Blocked by default	Screen field: Total daily dose in mg/kg/day Blocked	obtained = predicted
Screen field: Total daily dose in dose units (mL/day) Blocked by default	Screen field: Total daily dose in dose units Blocked	obtained = predicted
Screen fields: Dose rate (calculated) 8 options: 2.38, 4.76, 7.14, 9.52, 11.9, 14.3, 16.7, 19.1 mcg/kg/min	Screen fields: Dose rate 8 options: 2.38, 4.76, 7.14, 9.52, 11.9, 14.3, 16.7, 19.1 mcg/kg/min	obtained = predicted
Screen fields: Pump flow rate (calculated) 8 options: 1, 2, 3, 4, 5, 6, 7, 8 mL/hour	Screen fields: Pump flow rate 8 options: 1, 2, 3, 4, 5, 6, 7, 8 mL/hour	obtained = predicted

Chapter 8

General discussion

Introduction

Medication prescribing errors frequently occur and potentially lead to patient harm. CPOE/CDS systems have shown to prevent part of these errors and enhance safety and efficiency in the medication prescribing process. In order to be able to use these tools to reduce medication prescribing error rates in a specific population such as children and neonates, part I of this theses aimed to describe nature, frequency and determinants of medication prescribing errors with and without the use of CPOE/CDS in hospitalized children. Extra attention was paid to the PICU population as these patients offer extra challenges due to their several complex health problems and multi-drug treatments.

In **Chapter 2** frequency and types of prescribing errors in both handwritten and CPOE medication orders for PICU patients were examined: 18% contained administrative errors, 53% omissions and 12% dosing errors. This study identified writing by hand, alterations in existing medication orders, intermittent dosing and 'on demand use' as most important risk factors for prescribing errors. Additionally, in **Chapter 3**, frequency and types of potential drug-drug interactions (pDDIs) were examined in the same PICU. pDDIs frequently occurred and often concerned high-risk drugs: in almost 20% of patients at least one pDDI was identified during admission, on 40% of all PICU-days at least one pDDI was present and more than one third of pDDIs included high-risk medication. **Chapter 4** concluded that prescribing errors also frequently occur in pediatric non-ICU patients. Approximately 1% of electronic medication orders in the children's hospital had to be intervened by the clinical pharmacy: about 80% concerned a correction and about 20% a completion. The majority of the corrections concerned a wrong dose or a wrong drug formulation. The majority of the completions concerned absent body weight, dosage form or strength/concentration of the prescribed drug.

To optimally prevent prescribing errors using CPOE/CDS in children, the systems need to be more advanced and better tailored to pediatric care, preferably based on clinical experience and scientific evidence. The lack of data evaluating the effects of more advanced CPOE/CDS on prescribing problems in pediatric and neonatal intensive care, led to the content of part II of this thesis.

In **Chapter 5** the effects of CPOE systems on medication prescribing errors, ADEs, and mortality in inpatient pediatric care and neonatal and pediatric intensive care settings were reviewed. Overall, CPOE systems clearly reduced medication prescribing errors. However, effect on clinically relevant outcomes could not be demonstrated, possibly due to a limited set of outcome data restricted to pediatric and neonatal data. In an attempt to contribute to the evidence base, **chapter 6** described the effects of advanced CPOE/CDS for glucose control in NICU patients focusing on hypo- and hyperglycemic episodes (a clinically relevant outcome for this population) and prescribing time efficiency. The studied computerized prescribing and calculating CDS tool proved to preserve accuracy for calculation and control of glucose intake and decrease time needed to prescribe. Finally, in **chapter 7**, system requirements and design of an electronic prescribing system for

PICU and NICU is presented, including testing of the underlying model. The developed system aims to be integrated, safe by default and efficient and has the potential to solve several of the main problems related to the medication process in such specific patients.
In this general discussion the results and implications of the previous chapters are put in a broader perspective. They are discussed in relation to the main objective of this thesis: to determine the nature, frequency and determinants of medication prescribing errors in pediatrics and to study the effect of CPOE and CDS on these errors.

Defining and classifying medication prescribing errors in pediatric patients

When studying medication prescribing errors, the first question to be answered is: 'What is the definition of a medication prescribing error?'. This seemingly easy question turned out to be a serious brainteaser. To design studies aiming to examine medication error rates it is very important to have an extremely clear definition thereof, because the assessed error rates ought to be compared to those found in other studies to be able to place the results in a broader perspective and to identify areas of high priority for intervention. Medication errors can only be compared if they are clearly defined, as comparing apples and oranges may hamper valid conclusions. There are two ways to obtain a useful definition: from an (inter)national official body and/or from literature.
Several official bodies provide definitions for medication errors. A few examples:

- US Food and Drug Administration (FDA): Within the Center for Drug Evaluation and Research (CDER), the Division of Medication Error Prevention and Analysis (DMEPA) reviews medication error reports on marketed human drugs including prescription drugs, generic drugs, and over-the-counter drugs.[1] The DMEPA uses the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) definition of a medication error: "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."[2]
- US Institute of Medicine (IOM): IOM is an institution that aims to secure quality of health care in the US. In 2007 IOM published a large report on preventing medication errors.[3] An error was defined as "the failure of a planned action to be completed as intended (error of execution) or the use of a wrong plan to achieve an aim (error of planning); an error may be an act of commission or an act of omission". A medication error was defined as "any error occurring in the medication-use process", based on a publication by Bates et al.[4]

- UK National Health Service (NHS): NHS England and the Medicines and Healthcare products Regulatory Agency (MHRA) have developed a National Reporting and Learning System (NRLS) to function as an integrated reporting route for medication error incidents. Medication incident reports are defined as "those which actually caused harm or had the potential to cause harm involving an error in the process of prescribing, dispensing, preparing, administering, monitoring or providing medicines advice".[5]
- EU European Medicines Agency (EMA): Since July 2012, the new EU pharmacovigilance legislation has required all adverse drug reactions resulting from medication errors at the EU level to be reported in EudraVigilance, the EU database of adverse drug reactions. "Medication errors are unintentional errors in the prescribing, dispensing, or administration of a medicine while under the control of a healthcare professional, patient or consumer."[6]
- International Pharmaceutical Federation (FIP) is the global federation representing three million pharmacists and pharmaceutical scientists worldwide: In 1998, FIP published a Statement of Professional Standards on Medication Errors Associated with Prescribed Medication which aimed to define the term "medication error" and to suggest a standard nomenclature to categorize such errors and their severity. For this statement FIP adopted the NCC MERP definition of a medication error as mentioned above.[7]
- American Society of Hospital Pharmacists (ASHP): The ASHP published a standard definition of medication error in 1982. "A medication error is broadly defined as a dose of medication that deviates from the physician's order as written in the patient's chart or from standard hospital policy and procedures. Except for errors of omission, the medication dose must actually reach the patient; a wrong dose that is detected and corrected before administration to the patient is not a medication error. Prescribing errors (e.g., therapeutically inappropriate drugs or dosages) are excluded from this definition." Additionally, the ASHP published guidelines on preventing medication errors in hospitals in 1993.[8,9]
- European Association of Hospital Pharmacists (EAHP): EAHP is an association of national organizations representing hospital pharmacists at European and international levels. In the EAHP statements on hospital pharmacy 2014[10] it is clearly stated that hospital pharmacists should decrease the risk of medication errors, but an exact definition is not mentioned.
- Dutch Association of Hospital Pharmacists (NVZA) and Dutch Association of Hospitals (NVZ): In 2006, the NVZA and NZA initiated the national 'Central Registration of Medication Errors' (CMR) to centrally collect and analyze hospital medication errors. An error is defined as "an unintended event during the medication process (from prescribing to administration), that resulted or potentially resulted in patient harm". The errors are classified according to a uniform classification based on type, cause and harm.[11]
- Dutch Health Care Inspectorate, part of Government Oversight of public health (IGZ): Due to the growing pool of information and studies on patient safety, IGZ called attention to standardization of patient safety terms and published a list of patient safety definitions

in 2005. In this list medication error is defined as "any error in the process of prescribing, dispensing, or administering a drug, whether there are adverse consequences or not".[12]

Table 1 summarizes the essential elements per definition of these official bodies and clearly demonstrates diversity. This diversity led to several difficulties trying to use these definitions during the design of the studies in this thesis. To begin with, one of the definitions focuses on errors that actually reach the patient, whilst errors that do not reach a patient, so-called 'near misses', need to be included in research as well because these are very instructive. Also, not all official bodies clearly define and classify medication error subtypes, such as prescribing or administration errors. Above that, if categorized, distinction has not always been made between the stages of the medication process particular to a hospital: prescribing, transcribing, dispensing (compounding and distributing), preparing and administering drugs and monitoring and evaluating drug therapy. Additionally, these categorizations are developed for adult health care. However, some issues in relation to medication prescribing errors are relatively unique to children, such as weight-based dose calculations and extensive use of drugs outside their product license. Last but not least, the categorizations are constructed from merely one point of view: they solely classify errors based on the potential harm to the patient for example. When examining medication prescribing errors though, several (combinations of) perspectives are possible: prescribing errors may indeed be examined from the perspective of outcome of the patient (e.g. mortality, morbidity, harm), but also from the perspective of the process of prescribing (e.g. composing the medication order, decision making) and/or from the perspective of causes of the error (e.g. miscommunication, fatigue).
Summarizing, the definitions and classifications for medication errors provided by (inter)national official bodies are not detailed enough because they don't take differences between studied settings, patient populations and potential research perspectives into account. As mentioned earlier, a second way to obtain a useful definition is from literature. Several reports have been published in an effort to develop a definition and classification for drug-related problems and errors for use in studies.[13-15] Although this has led to better insight into useful definitions and classifications for hospital settings, published studies on prescribing errors, especially in pediatric and neonatal settings, still employ many different definitions and classifications.[16-23] For example, Ghaleb et al. reviewed studies on medication errors in pediatrics and came across 6 different definitions for prescribing error and, even worse, found that 10 out of 32 studies (31%) entirely lacked a definition.[19] Chapter 5 of this thesis resulted in a comparable conclusion when reviewing studies on prescribing errors in pediatric and neonatal intensive care settings: the definitions of medication prescribing errors and ADEs varied considerably among studies (see table 3 in chapter 5).

The above may radiate negativity and must be placed in perspective: it is important to realize that structured registration of and scientific research on medical and medication errors is relatively new in health care. Not until 1999, when 'To err is human: building a safer health system' was published

Table 1 Contents of definition and classification of medication error per (inter)national official body.

Author	Definition: In definition it is mentioned that medication error							Classification	
	Is pre-ventable	Is unin-tented	Is part of medication process	Leads to actual/ potential harm	Reaches patient	Takes place under control of person	Details	Present	Based on hospital process
NCCMERP FDA FIP	Yes	No	No	Both	No	Yes	Certain person subdivided into: health care profes-sional, patient or consumer.	Yes	No
NHS	No	No	Yes	Both	No	No	Medication process sub-divided into: prescribing, dispensing, preparing, ad-ministering, monitoring or providing medicines advice.	Yes	No
EMA	No	Yes	Yes	No	No	Yes	Certain person subdivided into: health care profes-sional, patient or consumer. Medication process subdi-vided into: prescribing, dis-pensing or administration.	Yes	No
ASHP	No	No	Yes	No	Yes	No	A wrong dose that is de-tected and corrected before administration is not a medication error. Prescribing errors are excluded.	Yes	Yes
NVZA NVZ	No	Yes	Yes	Both	No	No	Medication process sub-divided into: 'from pre-scribing to administration'. Errors are classified according to type, cause and harm.	Yes	Yes
IGZ	No	No	Yes	Both	No	No	Medication process sub-divided into: prescribing, dispensing, administering	No	No

by the US Institute of Medicine, did errors in health care attract great attention. Since then, policy and research in this field have rapidly evolved, and are still moving fast. Concurrently, it is important to realize that definitions and classifications are always subject to changes throughout time; think of the evolution of the Diagnostic and Statistical Manual for Mental Disorders (DSM) I (1952) to DSM 5 (2013) in psychiatry for example. Professionals, policy makers and researchers in health care will always be challenged to define and classify terms as well as possible according to that moment's knowledge. Additionally, when comparing data, they should always be aware of the differences between published results. Because studied setting, patient population and research perspectives are of influence, it seems impossible to create a universal definition and classification of medication errors. Instead, it may be useful to develop definitions and classifications per setting, population and research perspective, as was done in chapter 6, for example. During the design of the studies in this thesis, focused on prescribing errors in pediatrics, it appeared that a stepwise approach was useful: define study perspective and setting, define and select medication process steps and medication order details, classify errors based on defined and selected medication process steps and medication order details. These steps are shown in more detail in figure 1. Examples of definition and classification are depicted in figure 2 and 3 respectively. It is recommended to use this approach in studies on prescribing errors in pediatrics (see chapter 2 for PICU prescribing errors), but it may also be useful in designing studies on other errors/in other settings.

Preventing medication prescribing errors using CPOE/CDS systems in pediatric patients

Research on medication prescribing errors is important to identify areas for intervention with the intention of error prevention. Worldwide, medication error prevention is an element of clinical risk management programs that promote safe and effective patient care practices. Information and communication technology (ICT) systems are considered essential tools to support clinical risk management. Among these, CPOE/CDS systems are essential tools for medication error prevention, because of the rapidly expanding number and growing complexity of pharmacotherapeutic treatment options. CPOE systems are electronic systems that allow physicians to enter medication orders per patient in a structured way and have several advantages compared with paper-based prescribing, see table 2. CPOE can include or be combined with CDS systems, designed to improve clinician decision making at the point of care. Pediatric departments, PICUs and NICUs are particularly complex settings and demand extra attention to accomplish effective CPOE and CDS. CPOE systems have been shown to prevent medication prescribing errors and consequent harm in these settings.[19-21,23-33] However, as shown in chapter 2, 4 and 5 of this thesis, CPOE alone does not fully prevent medication prescribing errors: it eliminates administrative errors, but omissions and dosing errors still frequently occur. CDS is essential to further reduce pediatric prescribing error rates. In the paragraphs below, CDS tools useful for pediatrics are described. The paragraphs

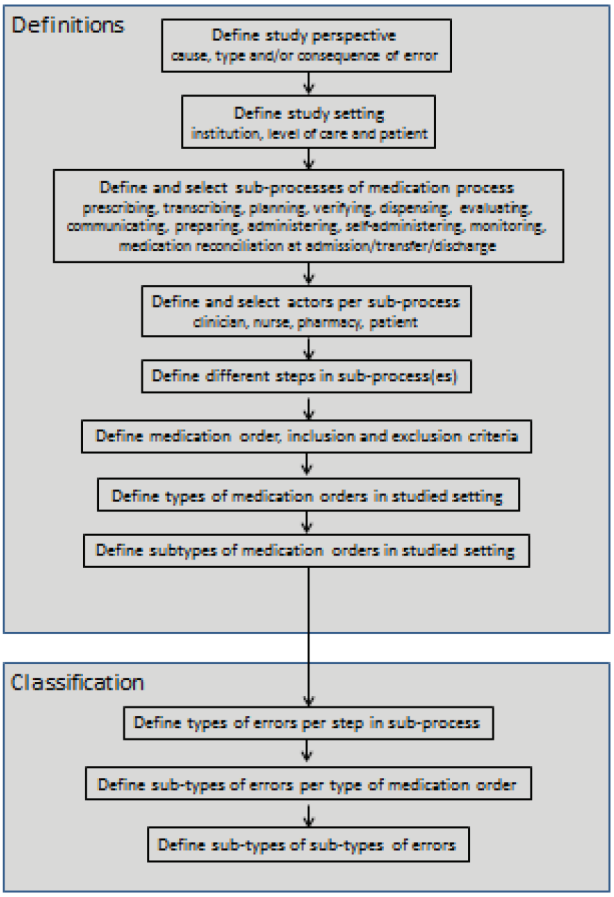


Figure 1 Stepwise approach to defining and classifying prescribing errors.

are titled according to the CDS taxonomy developed by Wright et al.[34] This CDS taxonomy distinguishes six tools of which three are related to medication: medication dosing support, point-of-care alerts/reminders and order facilitators. Per tool, it is described how the tool is or can used in current pediatric practice and which studies have been performed. The recommendations made throughout the paragraphs are summarized in table 3.

Medication dosing support

Dosing errors are the most commonly occurring prescribing errors in general pediatrics, PICUs and NICUs. Additionally, a survey among physicians, nurses and hospital pharmacists to assess attitudes regarding medication dosing to children showed that dosing guidance tools were strongly

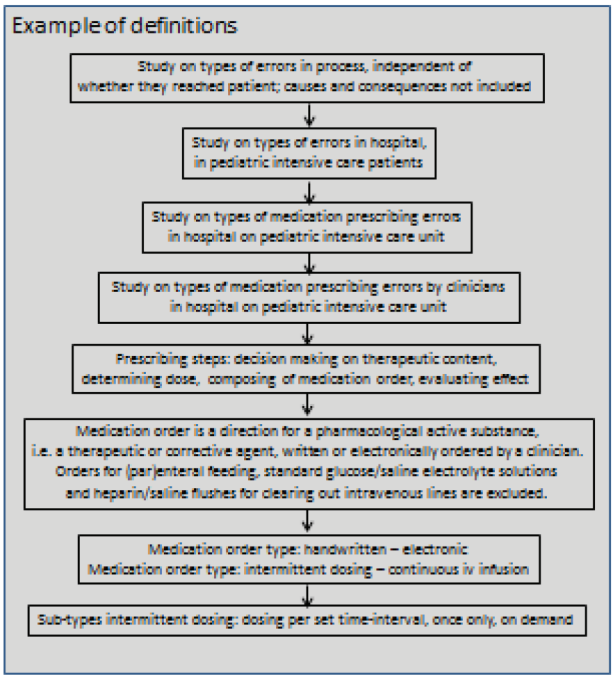


Figure 2 Example of definition.

endorsed by the questionnaire response with over 70% stating these would be desirable.[35] Not surprisingly, medication dosing support is the most extensive studied CDS tool in pediatrics: CDS performs flawlessly compared to human and is therefore considered essential for dosing error prevention. According to the taxonomy by Wright et al.[34] medication dosing support is subdivided in assistance with: a. medication dose calculation and -adjustment, b. formulary checking, c. single dose range and maximum daily dose checking, d. maximum lifetime dose checking, e. providing common doses and indication-based dosing.

a. <u>Medication dose calculation and -adjustment</u>

When prescribing drugs for a neonate, infant, child or adolescent, many varying factors have to be taken into account that may influence the required single- or daily drug dose: gestational age, postnatal age, birth weight, body weight, body surface area and developmental changes in physiology that affect pharmacokinetics and -dynamics.[36] Because prescribed dosages depend on these factors, calculations are needed to determine the correct dose and compose a correct medication order. When ordering medication for a child in a general pediatric ward, these calculations usually 'merely' involve multiplications of doses per kilogram body

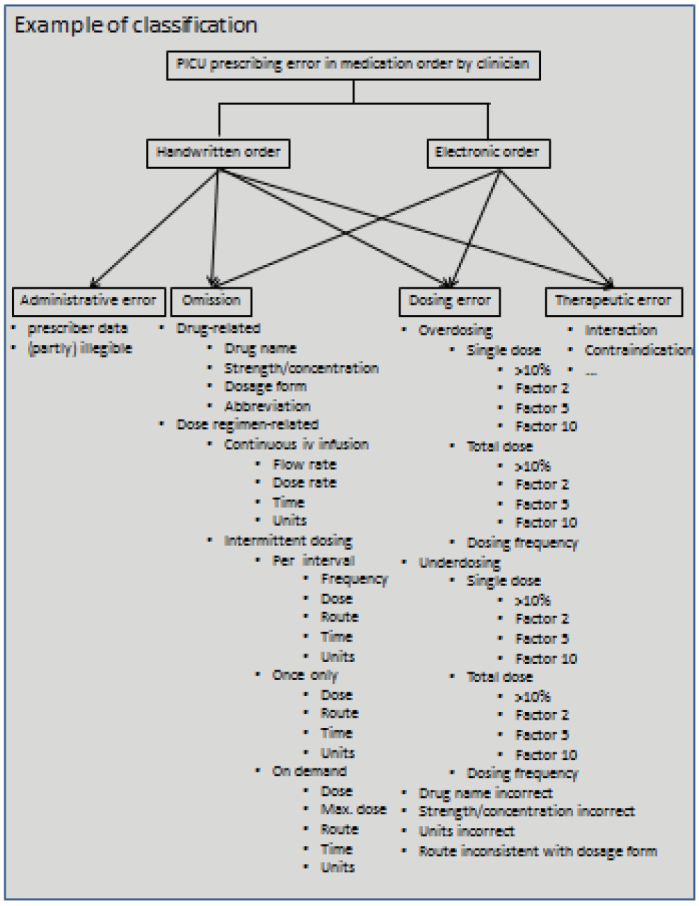


Figure 3 Example of classification

weight by actual body weight. But when ordering for PICU or NICU patients, more complex calculations are needed. For example, on admission to a NICU gentamicin may be dosed according to birth weight at 5 mg/kg, but later, especially in very-low-birth-weight neonates where there are significant daily weight changes, dose must be adjusted to actual weight and to postconceptional age. Cordero et al. studied a CDS calculation tool supporting this: upon selection of gentamicin, CPOE presented the prescribing physician with a weight verification screen, the recommended dose per kilogram of body weight, frequency of administration and dose calculations. Pre-CPOE there were 14 dosing errors, 1/3 being overdosages and 2/3 underdosages, due to errors in dose calculations and dose rounding, post-CPOE there were

Table 2 Advantages of CPOE systems compared with paper-based systems.

Adapted from Koppel et al.[95]

Free of handwriting identification problems
Faster to reach the pharmacy
Less subject to error associated with similar drug names
More easily integrated into medical records and decision-support systems
Less subject to errors caused by use of apothecary measures
Easily linked to drug-drug interaction warnings
More likely to identify the prescribing physician
Able to link to ADE reporting systems
Able to avoid specification errors, such as trailing zeros
Available and appropriate for training and education
Available for immediate data analysis, including postmarketing reporting
Claimed to generate significant economic savings
With online prompts, CPOE systems can link to algorithms to emphasize cost-effective medications
With online prompts, CPOE systems can reduce underprescribing and overprescribing
With online prompts, CPOE systems reduce incorrect drug choices

none.[37] Another study in neonates evaluated the effect of a medication dosing calculation tool for antibiotics and anticonvulsants and noted a significant reduction in dosing errors too.[38]

CDS for medication dose calculation and -adjustment needs to be tailored even further than this. For example in glycemic control in pediatric and neonatal critical care. This is a complex issue of ongoing debate in literature[39-43], not only because hypo- and hyperglycemias may cause patient harm, but also because hyperglycemias require the use of insulin, which is considered a high-risk drug that demands very accurate dosing. Advanced CDS dose calculation and -adjustment tools may help refine glycemic control in various ways, e.g. by supporting blood glucose monitoring, glucose dosing and insulin dosing. Regarding blood glucose monitoring, Meyfroidt et al. showed that a computer-generated blood glucose pop-up alert was able to significantly improve the quality of glucose control in an adult ICU. At five different blood glucose thresholds nurses received an alert at the bedside computer. Each pop-up contained a suggestion for the timing of a next blood glucose measurement, an instruction to double-check caloric intake and the current insulin infusion rate – and, when relevant, an advice for extra glucose infusion. The alert was repeated in case no control blood glucose result was entered into the system within the suggested time frame.[44] Regarding glucose dosing, CDS dose calculation tools are not only useful in supporting single- and daily dose calculations, but also in cumulative dose calculations. In chapter 6 of this thesis a homegrown advanced CDS dose calculation tool tailored to the neonatal critical care setting is described: a computerized prescribing and calculating system that provides calculations to assist prescribing of glucose,

Table 3 Recommendations for optimization of CPOE/CDS systems in pediatric and PICU/NICU patients.

CPOE/CDS for pediatric patient	CDS tools
In general	
Patient data needed for calculations are available and up-to-date, e.g. body weight and indications	Obligatory fields, point-of-care alerts/reminders
Minimization of fee-text entry	Order facilitators, appropriate selection menus, formulary checking
Extra attention for medication orders for children up to 2 years of age and orders for oral drug use	Point-of-care alerts/reminders
Clinical pharmacy staff completes omissions, with or without consulting prescriber depending on issue	Not applicable
Drug dosing	
Patient parameters (gestational/postnatal age, birth/body weight, body surface area etc.) are incorporated	Dose calculation and –adjustment
Dose checking includes cumulative dose calculations per day/lifetime	Dose calculation and –adjustment
Inclusion of adult limits	Single dose range and maximum daily dose checking
Clear references and guidelines for dosing limits	Single dose range and maximum daily dose checking
Clear definitions of dosing limits (warning limits and disallow limits)	Single dose range and maximum daily dose checking
Drug formularies including indication-specific dose ranges	Common dose and indication-based dosing support
Off-label drug use and drug use outside product license support	Common dose and indication-based dosing support
Treatment protocols, automated drug-protocol linkage and possibility to add new or experimental drugs	Order facilitators
Physiologic parameter monitoring, laboratory monitoring, therapeutic drug monitoring (TDM) support	Point-of-care alerts/reminders linked with dosing tools and order facilitators
Drug and drug formulation choice	
Availability of correct drug formulations suitable for children	Appropriate selection menus, formulary checking, order facilitators
DDI management	
DDI assessment includes more than one reference	Not applicable
Patient-specific and setting-specific information is taken into account	Point-of-care alerts/reminders linked with dosing tools and order facilitators

Table 3 Continued.

CPOE/CDS for PICU/NICU patient	CDS tool
Drug dosing	
Inclusion of lower and upper limits	Single dose range and max (daily) dose checking
Fast and easy alteration of intravenous infusion pump flow rates	Dose calculation and –adjustment
Calculations for complex administrations and preparations	Dose calculation and –adjustment
Condition-specific treatment protocols	Order facilitators linked with dosing tools and point-of-care alerts/reminders
Drug and drug formulation	
Simultaneous support for continuous infusions and intermittent dosing schemes	Obligatory fields, blocking fields by default
Specific support for Intermittent dosing regimens, corresponding administration routes and dosage forms	Appropriate selection menus, formulary checking, order facilitators
Dose rounding such that dose can be measured accurately from available drug formulation	Dose calculation and –adjustment
DDI management	
Support of PICU-specific DDIs involving high-risk drugs	Point-of-care alerts/reminders linked with dosing tools and order facilitators
Focus on those parameters that are not routinely monitored (laboratory and physiologic parameters)	Order facilitators
Support for DDIs between more than two drugs	Point-of-care alerts/reminders
Support for incompatibilities between intravenous drug fluids	Point-of-care alerts/reminders
Timing tuned to practice	Point-of-care alerts/reminders

taking the amount of glucose present in parenteral and enteral nutrition *and* medication into account. Regarding insulin dosing, several studies, in adult and pediatric ICU settings, have focused on computerized insulin treatment support, the most recent one by Fogel et al.[45] In an adult ICU setting a CDS tool was implemented designed specifically to customize the insulin dosing to the individual patient. The CDS tool analyzed trends of glucose using mathematical modeling and assessed a patient-specific physiologic insulin-dosing curve. The system automatically generated a bolus dose, an infusion rate and a time to next blood glucose measurement. Patients whose blood glucose was managed using this tool were statistically significantly more likely to have a glucose reading under control and to avoid serious hypoglycemia.[45] Additionally, although not tested in ICU patients yet, an interesting new development concerns the use of mobile systems that provide decision support in glycemic control: Spat et al. described a mobile decision support system for insulin dosing using Google Android.[46] CDS tools as mentioned above should be combined and further developed to optimize efficiency and safety in glycemic control in pediatric and neonatal critical care. And these advanced tools, analyzing trends and mathematically modelling data, should also function as an example for development and application in other pharmacotherapeutic areas that require precise dosing, e.g. drugs with narrow therapeutic ranges that are dosed based on therapeutic drug monitoring (measurement of drug concentration in blood, TDM).

CDS dose calculation tools are also useful in supporting calculations for complex administrations, such as continuous intravenous infusions, especially in critical care environments such as PICUs and NICUs, where patients are mainly treated with intravenous drugs and flow rates are often adjusted. As underlined in chapter 2, 6 and 7 of this thesis, CPOE systems are challenged to support the complexity of ordering such infusions while attaining easy order entry. In a study evaluating the effect of a web-based calculator and decision support system on continuous pediatric infusion ordering errors, a significant reduction of errors and elimination of high-risk errors in the prescribing process was achieved.[47] Besides reducing prescribing errors, CPOE/CDS that supports continuous pediatric infusion ordering may also prevent preparation errors. Sowan et al. evaluated the effect of CPOE/CDS for continuous pediatric infusions with standardized concentrations on the frequency of pharmacy processing errors. The use of standardized drug concentrations eliminates the need to prepare a large number of individualized concentrations. The CPOE-generated order sheet with standardized concentrations had safety features for pharmacists to process and compound infusion orders. These included legible and complete orders, a dosing-infusion rate reference table that helped quickly identify the correct dose-infusion rate relationship without the need for calculation, and a mnemonic for each drug that helped the pharmacist process the order, also without the need for calculation, using the computerized pharmacy system. This tool eliminated almost all pharmacy processing and preparation errors.[48]

As described above, automated support for medication dose calculation and -adjustment and accessory alerts are useful tools. But further refining is needed, because new problems arise. For example, Walsh et al. described that although the studied CPOE/CDS system contained automated pediatric weight-based dosage calculation and -checking, the rate of dosing errors did not change in a time-series analysis, partly because alerts were overridden by the ordering physician without a change in the order.[25]

CDS that provides weight-based dose calculations leads to another problem, very typical for pediatrics, where children, and especially hospitalized children with gastric tubes, often use liquid medications. The doses generated by calculating systems are often difficult for caregivers to measure and administer accurately. Johnson et al. studied this and provided evidence-based and expert-validated rounding recommendations to improve the rounding capabilities of electronic CDS systems for a set of commonly prescribed drugs.[49] More of these pediatric-specific initiatives should be worked out, studied, combined and implemented.

b. Formulary checking

Formulary checking is described as checking medication orders against hospital formularies and suggesting alternatives if necessary. Fundamental problem for pediatrics, is that most CPOE/CDS systems employ a formulary with a pharmacy assortment that consists primarily of registered, adult medications and that does not take preparation and drug manipulation activities into account that are needed for administration to children. A pediatric-specific problem to take into account, concerns the availability and choice of drug formulations suitable for children. Both chapter 2 and 4 of this thesis describe the relevance hereof: almost 25% of the omissions in PICU medication orders concerned an unclear or absent dosage form and an ubiquitous reason for clinical pharmacy intervention and consequent medication order adjustment were wrong drug formulations. Dosage form is important to pay attention to in a pediatric settings, because children have specific needs (e.g. oral liquids or minitablets versus larger solids or injectables as suitable dosage form)[50], because medication is often administered through nasogastric tubes and because dosing regimens may differ per dosage form. Additionally, there is a well-known lack of suitably adapted medicines for children,[51] resulting in the need for use of drugs outside their product license and extemporaneous dispensing.[52]

c. Single dose range checking, maximum daily dose checking

CPOE in pediatric, PICU and NICU care has to be accompanied by CDS that checks medication dosages to significantly reduce prescribing error rates.[24] Of main importance is that dose checking is grounded on evidence based and/or experience based dosing limits. Scharnweber et al. recently studied medication dose alerts in pediatric inpatients, including both over- and underdosing alerts and taking into account single doses and daily doses. Although the dose range alerts were created by a team of pediatric pharmacists based on literature, experience and established guidelines, 92% of the alerts generated through the study period were disregarded by prescribers. Particularly alerts concerning underdosing seemed to

be perceived as not useful, although they had been built only for those therapeutic groups that pose a risk for the patient if dosed below lower limit (chemotherapeutics, antimicrobials and atropine injection).[53] Apparently, alerts are not the best CDS tool to direct attention to underdosing. Future studies will have to point out what the best way is, because, as stressed in chapter 2 of this thesis, prevention of dosing below lower limit has to be incorporated in CDS because the number of dosages below guideline recommendations was alarming.

Another aspect that needs attention in dose checking support development is the heterogeneity in used references/guidelines for and definitions of dosing limits. In chapter 2 of this thesis dosing errors concerned doses > 10% below or above therapeutic range from Wilhelmina Children's Hospital drug formulary or local dosing rules/treatment protocols. If the guidelines mentioned above did not contain a dosing advice for a certain drug, then the UK's British National Formulary for Children and the US' Pediatric Dosage Handbook were consulted. Evident dosing errors were defined as doses a factor 5 or more higher than guidelines' maximum or lower than guidelines' minimum. Kadmon et al. also defined a normal limit as >10% deviation from the recommended dosage according to accepted drug databases.[24] Besides, a legal limit was defined as a dose that was highly unlikely to be prescribed intentionally in any medical circumstance, usually 2 to 3 times the normal limit.[24] Scharnweber et al. handled other limits again: the maximum total daily dose values selected were the upper daily dose limits for the indication that required the largest dose plus 20% to prevent clinically irrelevant alerts. The maximum single dose limit chosen was the total daily dose maximum, divided by the least number of doses per day typically used.[53] These are only a few examples to underline the variety seen in used formularies for and definitions of pediatric dosing limits. The importance of using suitable input when designing CDS regarding dosing has recently led to a dose range checking algorithm to construct more effective decision support.[54] This algorithm was primarily developed for adult health care but is a useful guide to develop a similar algorithm taking the crucial aspects of pediatrics, such as different dosing regimens per dosage form, into account. In 2008, in the Netherlands, a by the government subsidized initiative of multidisciplinary health care providers, led to a web-based national pediatric drug formulary to tackle the problem of pediatric dose limit ignorance and heterogeneity (www.kinderformularium.nl). Per drug, dose ranges grounded on evidence based and/or experience based dosing limits are summed up, including those for off-label use and including those for different available dosage forms. This formulary proved to be a great success and has been adopted nationwide by health care providers in both ambulatory and hospital care. Next step should be to incorporate it in CPOE/CDS as base for dose checking.

Besides well-defined pediatric limits, adult dosing limits should be taken into account in developing pediatric single dose range checking and maximum daily dose checking too. This is important because weight-based calculations in larger, mostly older or obese, children, may lead to doses that exceed adult maximum doses with subsequent potential patient harm.

Interestingly, the study by Scharnweber et al. indirectly proved this: the highest prescriber compliance rates were determined with dose range alerts for single and daily adult dose overdosing (17%).[53]

d. Maximum lifetime dose checking

Maximum lifetime dose checking refers to checking whether the combined lifetime dose of a drug exceeds a specified maximum lifetime dose, mainly important in chemotherapy dosing. An example of CDS for maximum lifetime dose checking would be an alert if the total cumulative dose of doxorubicin over a patient's lifetime exceeded 550 mg/m2. This form of CDS requires cumulative dose calculations over a prolonged period and an advanced alerting system triggering alarm at the right moment. An extra challenge is posed by the fact that a patient may receive drug dosages in different hospital departments or even in different hospitals altogether. Ideally, healthcare technology systems would automatically communicate with each other or would automatically update a patient dossier 'in the cloud' for example, to enable such cumulative dose calculations. However, for the time being medication reconciliation, which is described as a tool for preventing prescribing errors further on, may help overcome this issue. Kim et al. studied the effect of CPOE/CDS on errors in pediatric chemotherapy, including (cumulative) dose calculations and found that chemotherapy orders were less likely to have improper dosing, incorrect dose calculations, missing cumulative dose calculations and incomplete nursing checklists postintervention. On the other hand, Kim et al. also found a statistically significant decrease in the matching of chemotherapy orders to specific protocols.[55] There were several reasons for this (i.e. no automated drug-protocol linkage, no possibility to add new or experimental drugs to predefined menus and human transcription failures) and it may be concluded that for complex medication processes such as pediatric chemotherapy, combinations of advanced CDS tools should be deployed to further decrease error rates.

In relation to maximum cumulative *lifetime* dose checking, maximum cumulative *daily* dose checking also forms an important tool in pediatric prescribing, especially in critical care settings. An example is described in chapter 6 of this thesis, that describes advanced CDS that adds up the amount of glucose present in parenteral and enteral nutrition *and* medication in NICU patients. Similar tools may be helpful in calculating and monitoring patient fluid balance including (par)enteral nutrition and drug infusions, or may be helpful in calculating carbohydrate load from nutrition and medication in patients with ketogenic diet as treatment for refractory status epilepticus and the like.

e. Providing common doses and indication-based dosing

Provision of common doses by CDS in pediatrics is difficult due to heterogeneity in used references/guidelines for and definitions of dosing limits, as mentioned above. Off-label prescribing and prescribing outside product license is another pediatric-specific aspect that influences the way medication dosing support ought to be arranged. Off-label refers to use

of a drug for an indication or in a patient population that it is not registered for, outside product license refers to use of a drug in another pharmaceutical form than it is registered as, e.g. crushed tablet added to liquid so that infant is able to swallow the drug. The need for support for treatment decisions when using off-label and unlicensed drugs use was appointed in chapter 2 and 4 of this thesis. CDS may help by checking dose limits, but only if off-label and unlicensed drugs are actually included in the formulary that forms the backbone of the dose checking tool of the system: in a study on sensitivity (a measure of the extent to which doses that are *unreasonable* generate warnings) and specificity (a measure of the extent to which doses that are *reasonable* do not generate warnings) of alerts for dosing errors in hospitalized children, the lack of indication-specific dose ranges was the most common reason why an alert did not occur for a dosing error.[56] CDS could also help physicians prescribing both in- and outside product licenses by adding visible indications to drugs in drop-down menus. A CDS tool such as indication-based dosing may also help solve this problem: CDS may adjust default medication doses based on indications in the patient problem list entered by the ordering physician. Another way CDS could assist is by generating alerts when a drug is ordered without an approved indication in the patient problem list. A trial of inpatient indication-based prescribing with medications commonly used off-label in adults studied this last option. The alerts prompted clinicians to enter either a labelled or off-label indication for the order, but did not lead to accurate indication information, unfortunately.[57] Part of the solution could be to set dosing limits for off-label therapies using expert opinion and to refine those using statistical analysis of historical medication order data by determining dosing alert sensitivity and specificity.[58]

Point of care alerts/reminders

According to the taxonomy by Wright et al. point of care alerts/reminders are subdivided in 14 subtypes of which the following are directly related to medication: drug-drug interaction checking, drug-condition interaction checking, drug-allergy interaction checking, duplicate order checking, look-alike/sound-alike medication warnings, intravenous/per os conversion and polypharmacy alerts.[34] This is a questionable subclassification, as drug-allergy checking may be considered an element of drug-condition checking and duplicate order checking may be regarded as a form of drug-drug interaction checking. Additionally, these subtypes may be considered insufficiently elaborated for the scope of current health care, e.g. drug-genotype checking may be added. Regardless, compared to CDS for medication dosing, point of care alerts and reminders have hardly been studied in pediatric, PICU and NICU settings. An important reason for this may be that basic knowledge on these topics in such specific settings is limited. That is why chapter 3 of this thesis focused on assessing frequencies and types of PICU drug-drug interactions (DDIs) as such, as a first step towards developing PICU-specific drug-drug interaction checking.

Interestingly, in chapter 3, most DDIs proved to be of a pharmacokinetic nature (one drug affects the other's absorption, distribution, metabolism, or excretion) rather than of a pharmacodynamic nature (two drugs act at the same or interrelated receptor sites, resulting in additive, synergistic, or antagonistic effects of each drug at the target receptor). Consequently, most advised management strategies concerned dose adjustments and/or laboratory/physiologic biomarker monitoring. This leads to the assumption that advanced CDS for DDI checking should be linked with CDS tools for medication dosing and with order facilitators, which are described more extensively in below. Additionally, it is crucial that DDI alerts, and any other point of care alerts or reminders, are customized to pediatric settings as properly as possible, because it is well known that high burdens of reminders and clinically irrelevant alerts lead to so-called 'alert fatigue', causing clinicians to override both important and unimportant alerts. Low specificity, high sensitivity, unclear information content of alerting systems and unnecessary workflow disruptions by alerting systems lead to unsafe and inefficient handling.[59] Few pediatric studies have focused on alert handling during pediatric prescribing. A UK pediatric study found 89% of visible alerts were overridden at point of prescribing, despite many alerts being permanently suppressed. Drug-allergy conflict alerts were the most accepted, and drug duplication alerts the least.[60] Mille et al. analysed overridden DDI alerts in a pediatric hospital and defined three categories of overridden alerts: informational errors, system errors and accurate alerts. Two reasons accounted for 40% of false-positive alerts: 1. inability of the system to recognize real conflicts between drug treatments and 2. guidelines stating that the two drugs can be used together, because the benefit outweighs the risk of side effects due to the DDI.[61] A third pediatric study determined rates of physician acceptance of computerized dosing and frequency suggestions: only 32% were accepted exactly.[62] Apparently, it is insufficient to customize alerts to pediatric settings; part of the alerts need to be individualized, i.e. customized to individual patient level. This matches current trend in health care: 'precision medicine' or 'personalized medicine', that aims to couple established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements.

Point of care alerts or reminders, can be customized to (pediatric) settings or individual (pediatric) patients, by changing the 'classic' order of mediation surveillance. According to the most recent medication safety guidelines of the Royal Dutch Pharmaceutical Society (KNMP) point of care alerts for drug-drug, drug-condition, drug-allergy interaction and duplicate order checking, operate in the following order: 1. alert generation during prescribing medication for patient, 2. evaluation whether alert applies to patient after collecting all relevant patient information, 3. decision whether action is needed and if so, execution of required management strategy, 4. documentation of the (reasons for the) decision and executed management strategy, if applicable.[63] To overcome the above-mentioned problems, this order of surveillance should be changed so that step 2 (evaluation whether alert applies to patient after collecting all relevant patient information) becomes step 1 as much as possible. This can be achieved by developing intelligent CDS that automates the different

steps and that increases alert specificity by handling data from different databases, e.g. clinical chemistry and pharmacy databases. By combining patient data (e.g. degree of renal impairment, hyperkalemia, lack of potassium level measurements) and therapeutic information (e.g. dose ranges per degree of renal failure, DDIs that potentially lead to hyperkalemia) from these databases, CDS can be programmed to merely fire if specific rules are violated for an individual patient.[64]

Caution is warranted though. If fired point of care alerts are too compelling, unintended effects may occur. This was observed in a randomized controlled trial evaluating a nearly hard-stop alert intended to reduce concomitant orders for warfarin and trimethoprim-sulfamethoxazole, a DDI that may lead to substantially increased anticoagulant effects and consequent bleedings. Although the hard-stop alert seemed extremely effective in changing prescribing, it led to clinically important treatment delays in 4 patients who needed immediate warfarin or antibiotic therapy. This necessitated early termination of the study for ethical reasons because of potential harm in the intervention arm patients.[65] Another important issue for effective point of care alerts is timing: at what moment should the alert pop-up? In the field of DDI checking for example, DDI alerts typically fire when a drug is first prescribed or when an existing order is modified, while the effects may occur days later. Or, in the field of drug-condition interaction checking for example, refined alerts for drug dosage in children with reduced renal function are important and useful, but should not only fire when renal function reduces but also when it improves.[66,67] Again, combinations of CDS tools are desirable as proved by Kazemi et al. in neonates: an antibiotic and antiepileptic dosing decision support tool taking renal function into account, was studied. The CDS system comprised of an alert tool that fired if the prescribed dose was out of range, an automated calculation tool for glomerular filtration rate (GFR), a calculation tool for dose calculation and a knowledge base containing relevant dose and frequency ranges. This advanced form of CDS resulted in a significant reduction of dosing errors.[38]

Among point of care alerts/reminders the so-called 'care reminders' are not directly related to medication but nonetheless very important for pediatric prescribing. Care reminders are reminders to order a diagnostic or therapeutic procedure based on patient parameters/biomarkers., e.g. 'order an HbA1c every six months for patient with diabetes'.[34] As pediatric doses are usually based on body weight or body surface area and as these parameters can change rapidly, certainly in younger age groups, an up-to-date value is required for correct dose calculation. In chapter 4 of this thesis a commercially available CPOE system without tailored CDS was studied in a pediatric hospital and led to the conclusion that a large part of the interventions in medication orders by hospital pharmacy staff concerned absent up-to-date body weight. Consequently the system was adjusted: body weight became an obligatory field. More advanced CDS in this area was studied by Jani et al.: the system 1. alerted the prescriber if the height or weight entered was outside the expected 96th centile range based on the child's age, 2. prompted for the patient weight to be updated if the date of the previous entry exceeded the specified time period for the age of the child, for example, for older children, the weight needed to be revalidated on a monthly basis, and 3. alerted for weight

change of ±10% compared with the previous weight entry. A 1% absolute reduction in dose error rates was achieved, proving the benefit of tailored CDS once and again.[68]

Order facilitators

Order facilitators include medication order sentences, subsequent or corollary orders, indication-based ordering, condition-specific treatment protocols, transfer order sets, service-, condition-, and procedure specific order sets, and non-medication order sentences.[34] The importance of indication-based dosing and ordering in pediatrics has already been described above. Here, a. medication order sentences and b. subsequent/corollary orders will be discussed.

a. Medication order sentences, order sets and treatment protocols

Order sentences are predefined medication orders and order sets are groups of orders used to manage a disease state or procedure. Pre-specified standardized medication orders facilitate prescribing. Particularly in relation to the prescribing errors determined in chapter 2 and 4, order sentences offer the opportunity to avert omission errors, selection of wrong drug formulations/strengths/concentrations and selection of inconsistent combinations of dosage form and route of administration.

Leu et al. studied the development and use of CPOE order sets in a tertiary pediatric teaching hospital.[69] Analysis of the order set development and use revealed several issues: 1. 'order sets lacked clinical owners' resulting in rework or delays in customizing order sets to practice, 2. 'lack of leadership support to maintain standards' resulting in poor internal and external consistency of order sets, 3. 'ad hoc multidisciplinary review' instead of a formal review process resulting in order sets that did not reflect or respect current practice, 4. 'order sets not maintained' resulting in outdated and inappropriate orders because changes to formulary, clinical guidelines or hospital policies would occur without order set updates, 5. 'requested order sets not sufficiently specified for building' resulting in development delays of months to even years.[69] Consequently, a new order set development and update process was created, taking into account the abovementioned issues and the US' Institute for Safe Medication Practices Guidelines for Standard Order Sets. Updating the order sets through the new process led to correction of a wide range of errors, e.g. suboptimal or incorrect dosing, dosing duration or dosing time, incorrect laboratory orders and build errors resulting in duplicate orders and incorrect nursing orders.[69] This study clearly demonstrated that CDS tools for medication order sentences and order sets should be subject to rigorous development and updating processes to ensure both clinical appropriateness and correctness.

A special challenge in developing order facilitators is posed by condition-specific treatment protocols. These are treatment protocols for a specific condition, characterized by complex or temporal logic, in comparison to order sets which are usually simpler. This particularly applies to pediatric and neonatal condition-specific treatment protocols. Such treatment protocols do not only include the 'general' complexities of pediatric prescribing such as dosing influenced

by body weight and gestational age, but also include more complex physiological, diagnostic and drug treatment components. For example, in neuroprotective treatment in asphyxiated neonates a combination of hypothermia and antiepileptics may be used. Hypothermia has been proved to affect pharmacokinetic and pharmacodynamic drug profiles resulting in adjusted drug dosing strategies as compared to normothermia.[70,71] To incorporate such a treatment protocol in CDS combining all relevant condition-specific parameters and tailored dosing information is difficult but may help prevent errors and optimize such specialized therapy.

b. Subsequent and corollary orders

Subsequent and corollary orders are suggested or automatically generated orders, based on or in response to another order. Providing these kinds of corollary actions has been mentioned as determinant of success for CPOE/CDS.[72] Physicians often fail to order tests or treatments needed to monitor the effects of other tests or treatments. Overhage et al. hypothesized that automated, guideline-based reminders to physicians, provided as they wrote orders, could reduce these omissions and demonstrated a greater than 25% improvement in the rates of corollary orders with implementation of computerized reminders. Examples of trigger orders were orders for opioid prescriptions, NSAIDs and potassium supplements. Examples of consequent response orders were laxative, creatinine monitoring and electrolyte monitoring orders, respectively.[73]

In relation to pediatric care, only few studies comment on use of corollary orders. Abboud et al. studied workflow-integrated corollary orders on aminoglycoside monitoring in children. A reminder to order blood levels was presented to the clinician during each aminoglycoside ordering session. Interestingly, this did not significantly improve laboratory monitoring rates, nor did it result in a reduction in the rate of either toxic or subtherapeutic levels. However, it was concluded that aminoglycoside corollary orders may have an important role in institutions where pharmacists are not actively involved in monitoring therapy.[74] In chapter 3 of this thesis (reminders for) corollary orders are mentioned as potentially useful element of advanced CDS for DDI risk management, as it is determined that laboratory monitoring and physiologic biomarker monitoring are important in DDI risk management in pediatric intensive care settings. Automatically generating (suggestions for) corollary orders during prescribing may help prevent omissions in subsequent monitoring orders when DDIs occur. In chapter 6 of this thesis the importance of blood glucose monitoring in glucose dosing and insulin dosing, is described. Corollary orders, prompting the user to order glucose checks after ordering insulin for example, may be useful as well.

In conclusion, CPOE/CDS offers great potential to reduce prescribing errors in pediatrics but current tools have to be refined and combined to acquire optimal effects. See table 3 for an overview of the mentioned recommendations for optimization of CPOE/CDS in pediatrics and PICUs/NICUs.

Other uses and effects of CPOE/CDS systems in pediatric patients

Prevention of other medication errors using CPOE/CDS systems in pediatric patients

Prescribing errors are not the only kind of medication errors that CPOE/CDS systems may prevent. The medication process in a hospital comprises of several stages, each of which may be electronically supported: prescribing, transcribing, dispensing, preparing and administering drugs and monitoring and evaluating drug therapy.

a. Transcribing errors

Transcribing errors occur when transcribing or interpreting a medication order of the physician, mostly by nurses or pharmacy staff. In literature no subclassification of these errors can be found: an order is either transcribed correctly or not.[14] Transcribing errors have not been studied as such in pediatrics, but in hospital care in general CPOE leads to great reductions or total elimination if CPOE is accurately embedded in clinical workflow.[75,76]

b. Dispensing errors

Next, dispensing errors include wrong drugs, dosage forms or strengths prepared or dispensed by the pharmacy or correct drugs but dispensed for the wrong patient or ward, for example.[14] A CPOE system may help prevent these errors by providing clear, complete and legible prints or interfaces of medication orders to the pharmacy. If CPOE is electronically linked to or internally includes an electronic pharmacy drug dispensing- and/or preparing system, dispensing and preparing errors are even less likely. Medication order tracking, bar-code technology and automated dispensing machines/robotic dispensing may help reduce these error rates even further.[77] Holdsworth et al. studied the impact of CPOE in pediatric inpatients and found a large reduction in dispensing errors. This was mainly due to automation of discontinuation orders that prevented the dispensing of discontinued medication.[78] However, a study by Sauberan et al. revealed neonatal medication dispensing errors despite the use of CPOE, partly due to mix-up between neonatal and adult or pediatric products.[79] In pediatrics, dispensing of the correct product and suitable dosage form is essential, for example because children need liquid dosage forms if too young to swallow solids. By dispensing suitable drugs and dosage forms, difficulties and errors in the next step of the medication process are prevented. [52]

c. Preparing errors

Preparing medication may be executed by the pharmacy or by a nurse or doctor and relates to crushing a tablet for administration through a gastric tube, adding water to a powder for suspension or preparing an intravenous infusion by adding the content of an ampoule to a sodium chloride infusion bag and the like. There is a lot of room for improvement of CPOE/CDS development in this step of the medication process, because most CPOE/CDS systems do not support preparing. However, in pediatrics, preparing is a crucial step in the medication process. Preparing drugs for children typically involves several steps and complex calculations

as compared with for adults. For example, a tablet has to be split in four before crushing, or the content of an ampoule has to be diluted first before adding to a base solution, because of the small dose needed. CPOE/CDS may help to prevent consequent preparation errors: a study by Sowan et al., described in more detail earlier in this chapter, evaluated the effect of CPOE/CDS for continuous pediatric infusions on the frequency of pharmacy processing and preparation errors and proved near total elimination of them.[48] In chapter 7 of this thesis the design of a CPOE system is described that offers the potential to eliminate preparation errors as well.

d. Administration errors

The next step of the medication process is administration of the drug to the patient by nurse or doctor, or, in case of hospitalized children, by parents for example. Errors in administering drugs can be classified as omissions, wrong drug, wrong dosage form, wrong route of administration, wrong administration technique, wrong dose and wrong time.[14] Interventions to reduce administration errors receive a lot of attention because it is the last step of the drug delivery process and errors made cannot be reversed. Information technology can help prevent these errors by including electronic prescribing, automated dispensing and bar-coding.[80] Implementation of CPOE in a NICU was associated with a significant decrease in the rate of discrepancies between ordered and administered medication. However, even then, discrepancies were noted for more than 10% of all medication administrations, suggesting that additional methods are needed.[81] Systems supporting drug administration with bar-code tools, so-called bar-code assisted medication administration (BCMA) systems were developed to improve compliance with checking the 5 rights of medication administration: right patient, right route, right drug, right dose and right time. Studies on the impact of BCMA on medication administration errors were recently reviewed: BCMA mostly shows reduction of error rates, although the effect on patient outcome is limited.[82] Among the reviewed studies, one took place in a NICU.[83] Before the implementation of the BCMA system, nurses maintained a paper medication administration record (MAR) to which medication orders were transcribed and on which administered doses were recorded. After BCMA system implementation, all medication orders were transmitted to an electronic MAR. A nurse or respiratory therapist signed on to the BCMA system, scanned the patient's wristband barcode to select the patient, scanned the unit dose medication barcode and administered the medication item if the system software signaled that the drug, dose, route, time, frequency, and patient were correct. Unexpectedly, total number of medication errors was higher after BCMA system implementation, primarily because more wrong-time errors were detected, which may reflect the precision of the recorded time of administration by the BCMA system. Other medication error types were reduced, e.g. omitted doses and transcription errors.[83]

Besides checking the 5 rights of administration, other elements of the administration stage should be electronically supported as well. Incompatibilities between intravenous drug

infusions for example, cannot be prevented by BCMA systems. An integrated CPOE system as described in chapter 7, does have this potential, as it includes an administration planning tool.

e. Monitoring/evaluating errors

Once a drug has been administered, patient monitoring takes place: a patient's response to the drug is assessed, reported and documented. This information can be used to adjust medication dose, type, frequency, etc. physiological biomarker testing (e.g. blood pressure, ECG, peak flow) and laboratory testing (e.g. blood glucose, INR, therapeutic drug monitoring (TDM)) by using point-of-care testing devices or by sending samples of patient material to a laboratory can support patient monitoring. However, several studies have shown gaps between optimal and actual monitoring practice.[84] For example, in a study designed to assess the appropriateness of antiepileptic drug monitoring, only 27% of antiepileptic drug levels had an appropriate indication and, among these, half were drawn at an inappropriate time.[85] Of clinical laboratory tests, 28% were ordered too early to be clinically useful.[86] In chapter 3 of this thesis the identified DDIs should have led to 1,131 monitoring values: 756 (67%) were actually measured. Inappropriate testing may lead to adverse clinical events, for example in case of omitted TDM, and to increased treatment costs, for example in the case of overuse of diagnostic laboratory tests. CPOE/CDS can improve this: Levick et al. recently showed a reduction of unnecessary testing including a positive financial impact,[87] and Mahoney et al. showed an improvement in TDM in patients with renal insufficiency[88] through CDS alerting tools. These are examples of the earlier mentioned care reminders, that may fire either if monitoring is required or if required monitoring is not ordered, and lead to subsequent/corollary orders. The use of CPOE/CDS in relation to clinical laboratory testing has recently been reviewed by Baron et al. and it is concluded that the role of CPOE/CDS in this field will probably expand in scope and importance.[89,90]

f. Across setting errors

An additional type of error related to the medication process are 'across setting medication errors' that are due to miscommunication regarding children's transfer across different (clinical) settings. A recent study appointed this as the most important key contributing factor to medication errors in hospitalised children.[91] Huynh et al. reviewed literature on medication discrepancies at transitions in pediatrics.[92] Only few studies were identified that observed medication discrepancies in children under 18 years of age upon hospital admission, transfer and discharge, or had reported medication reconciliation interventions. Most studies related to admissions and reported consistently high rates of discrepancies.[92] No studies have been published evaluating CPOE/CDS to prevent across setting medication errors in pediatrics.

Other effects of using CPOE/CDS systems in pediatric patients

This thesis concentrates on CPOE/CDS to prevent prescribing errors and consequent patient harm, but CPOE/CDS may have unintended effects, as summarized in table 4.[24,25,30,33,93-96]

Crucial to prevent many of these unintended effect is implementation of the system and extensive ongoing end-user training. On the other hand, designing the CPOE/CDS system such that they appropriately fit into end-user prescribing practice also mitigates unintended effects. Bates et al. published ten experience-based commandments for system developers to achieve effective system development: 1. speed is everything, 2. anticipate needs and deliver in real time, 3. fit into the user's workflow, 4. little things can make a big difference, 5. recognize that physicians will strongly resist stopping, 6. changing direction is easier than stopping, 7. simple interventions work best, 8. ask for additional information only when you really need it, 9. monitor impact, get feedback, and respond, 10. manage and maintain your knowledge-based systems.[84] Although these commandments are very generic, it is clear that they are a call for the development and continuous improvement of advanced CPOE/CDS tailored to the setting it is used in. This thesis may be considered an elaboration thereof for pediatric patients.

Besides these unintended effects, CPOE/CDS influences other factors as well. Studies may also focus on the impact of CPOE/CDS on workflow, efficiency, health care costs, etc. Concerning workflow for example, effects of CPOE/CDS are crucial to study in complex settings such as PICU and NICU, where children are critically ill and often need acute care. Cordero et al. and Chapman et al. studied the effects of customized CPOE/CDS systems on workflow and efficiency in a NICU and showed positive results in medication turn-around time, radiology response time and time to pharmacy verification.[37,97] In chapter 6 of this thesis comparing CPOE with manual calculations of glucose intake in neonates also showed a significant time reduction, particularly for complex calculations. And Vardi et al. found a significant profit in prescribing time by computerizing the ordering of resuscitation medications for PICU patients.[98] On the contrary, in the same study by Chapman et al., the introduction of a CPOE system in the NICU did not significantly improve antibiotic administration times.[97] Also, the earlier mentioned PICU study by Han et al. showed an unexpected increased mortality potentially due to delays in therapies and diagnostic testing after CPOE implementation.[33] These contradictory results imply the need for more studies evaluating how CPOE/CDS systems affect workflow and overall patient care. Concerning health care costs, return on investment studies publish contradictory results as well: some show positive, some negative return.[99-101] Implementing CPOE/CDS systems include specific financial investments: hardware, software, implementation and support. Potential benefits that may lead to cost reductions are: medical error reduction, improved compliance with formularies and dosing guidelines, improved charge capture, improved workflows and productivity, standardization of the ordering process and decreased redundancy, etc.[101] In pediatric inpatients, only two studies have been performed evaluating cost-effectiveness of electronic medical record (EMR) use in general and CPOE use in particular: EMR was associated with an average 7% greater cost per case and hospitals with CPOE that treat children did not have significantly lower cost per case, respectively.[102,103] This emphasizes the importance of future studies and financial incentives to tailor CPOE/CDS to these settings in order to improve return on investment.

Table 4 Unintended consequences of CPOE/CDS.

In general [93,94]
More/new work issues Physicians find that CPOE adds to their workload by forcing them to enter required information, respond to alerts, deal with multiple passwords, and expend extra time.
Workflow issues include process issues, policy/procedure issues, human computer interaction issues, clinical personnel issues, and situation awareness issues.
Never-ending demands Because there is a continuous need for new hardware, more space for hardware, more space on the screen to display information, maintenance of the knowledge base and training demands.
Paper persistence CPOE should reduce the amount of paper used to communicate and store information, but this is not necessarily the case since it is useful as a temporary display interface.
Communication issues CPOE changes communication patterns among care providers, creating that people think that because information went into the computer the right person will see and act on it.
Emotions These systems cause intense emotions in users. Unfortunately, many of these emotions are negative and often result in reduced efficacy of system use, at least in the beginning.
New kinds of errors such as juxtaposition errors (clinicians click on adjacent patient or drug from a list), duplicate orders and failure to discontinue drugs (due to inability to view all active medication concurrently).
Overdependence on technology As hospitals become more dependent on these systems, system failures can wreak havoc when paper backup systems are not readily available.
Changes in the power structure Mandatory data entry fields often reduce power/autonomy of physicians in an effort to standardize, while power of nursing staff, IT specialists, and administration is increased.
In relation to prescribing errors [95]
Information errors are generated by fragmentation of data and failure to integrate the hospital's several computer and information systems: - assumed dose information, - medication discontinuation failures, - procedure-linked medication discontinuation faults, - immediate orders and give-as-needed medication discontinuation faults, - antibiotic renewal failure, - diluent options and errors, - allergy information delay, - conflicting or duplicative medications.
Human-machine interface flaws reflect machine rules that do not correspond to work organization or usual behaviors: - patient selection errors, - wrong medication selection, - unclear Log on/Log off, - failure to provide medications after surgery, - postsurgery "suspended" medications, - loss of data, time, and focus when CPOE is nonfunctional, - sending medications to wrong rooms when the computer system has shut down, - late-in-day orders lost for 24 hours, - role of charting difficulties in inaccurate/delayed medication administration, - inflexible ordering screens, incorrect medications.
From pediatric studies
System errors On a PICU nurse electronic signature was linked to medication order instead of physician electronic signature due to flaw in system [24]
Selection errors particularly surrounding selection and dosing of pediatric medications.[25] Incorrect infusion rates were selected or no base solution was prescribed, incorrect selection occurred from the multiple dosage options available for some drugs, particularly acyclovir.[30] A NICU study showed that CPOE led to selection of incorrect strengths when multiple strengths of medication were available[96]
Mortality unexpectedly increased after implementation of a commercially sold CPOE system in a PICU. It was clearly demonstrated that unintended effects occur if CPOE is not tailored to such a complex setting: delays in therapies and diagnostic testing, significant amounts of time spent at a separate computer terminal and away from the bedside and diminished opportunities for face-to-face physician–nurse communication.[33]

Non-technical interventions for preventing medication prescribing errors in pediatric patients

The causes of and factors associated with prescribing errors in hospital inpatients were recently systematically reviewed by Tully et al.[104] Causes of prescribing errors were categorized according to Reason's commonly used model for human error.[105] According to Reason, two approaches to the problem of human error exist: the person and the system approaches. The person approach focuses on the errors of individuals, blaming them for forgetfulness, inattention, poor motivation, carelessness, negligence and recklessness. The associated countermeasures are directed mainly at reducing unwanted variability in human behavior, e.g. campaigns that appeal to people's sense of fear, (re-)writing procedures, disciplinary measures, (re-)training, naming, blaming and shaming. The system approach concentrates on the conditions under which individuals work and tries to build defenses to avert errors or mitigate their effects. Errors are seen as consequences rather than causes, having their origins in the workplace and the organizational processes rather than in the imperfect human nature. Countermeasures are based on the assumption that the human condition cannot be changed, but the conditions under which humans work can. A central idea is that of system defenses: when an adverse event occurs, the important issue is not who blundered, but how and why defenses, barriers and safeguards failed. Defenses fail for a combination of three reasons: active failures, error-provoking conditions and latent conditions.[105]

The causes of prescribing errors in hospitalized patients determined by the 16 studies included in the review by Tully et al. are summarized according to this categorization in table 5.[104] As shown in table 5, Tully et al. identified that individual, environmental and organizational factors play a role in the occurrence of medication prescribing errors. Hence, merely using technical interventions such as CPOE and CDS to prevent these errors is insufficient. Moreover, as proven in chapter 4 of this thesis, even if CPOE/CDS is in place, non-technical intervention such as clinical pharmacy involvement is needed in the prescribing process. Other non-technical interventions may be related to health care provider education, patient and drug data availability, communication between health care providers, double-checking of calculations etc. The influence of several (combinations) of these non-technical interventions on medication prescribing error rates has been studied, mainly in adult but also in pediatric settings.

Education

Education is noted as key factor in reducing (pediatric) prescribing errors.[23] Education can concentrate on several fields, e.g. pharmacotherapeutic decision making, prescribing skills and error prevention. Additionally, calculations play a very important role in pediatric prescribing education. Conroy et al. reviewed educational interventions to reduce prescribing errors in pediatrics.[106] Several educational methods were observed. Most frequently used was a presentation by a pediatric pharmacist, usually at doctor's induction. In these presentations the following information was

Table 5 Causes of prescribing errors, grouped by stages of Reason's model of accident causation. Adapted from Tully et al.[104]

Active failures (individual unsafe acts)	Error-provoking conditions (task and environment)		Latent conditions (organizational processes and culture)
Knowledge-based mistakes:	Prescriber:	Patient:	Attitude:
Lack of drug knowledge	Hungry, thirsty	Complex problem	Low importance attached to re-prescribing
Lack of drug interaction knowledge	Tired	Acute problem	Perception of prescribing as a chore
Lack of dosing knowledge	Unwell	Unhelpful	Prescribing not considered important
Absence of knowledge of a relevant rule	Low morale	Language difficulties	Transcription is not prescribing
Application of the wrong rule	Distracted	Communication difficulties	Low self-awareness about making errors
Lack of patient information	Inadequate knowledge		Do not learn about drug doses at med' school
	Inadequate skill	Workload:	
Violations:	Inadequate experience	High/heavy workload	Culture within team:
Inadequate monitoring	Inadequate training	Long hours	Lack of questioning
Not following chemotherapy policy	Inadequate calculations	Pressure	Lack of feedback systems
		Physical environment	Poor conflict resolution
Slips:	Working environment:		Reluctance to question people with greater authority
Busy or interrupted during routine tasks	Staffing level inadequate	Prescribing task:	
Skill-based	Unfamiliar with patient	Medical chart layout or location	Organization:
	Inadequate new or locum staff	Ambiguous or unavailable guidelines	Simultaneous multiple-prescribing tasks
Lapses:	Dealing with another doctor's patient	Not routine	Lack of training in drug knowledge
Busy or interrupted during routine tasks	Poor staff and work assignment	Protocols	Lack of training in prescribing skills
Skill-based	Lack of access to drug information	Lack of standardization of doses	Long hours scheduled
Memory lapses	Lack of access to patient information	Lack of standardization of frequencies	Staffing numbers

Table 5 Continued.

Active failures (individual unsafe acts)	Error-provoking conditions (task and environment)		Latent conditions (organizational processes and culture)
	Patient-related knowledge not delivered efficiently	Lack of standardization of procedures	Need to admit specialist patients out of hours
	Slow access to information		Pharmacy systems separate from clinical services
	Lack of access to workstations to find information		Logistical problems with knowledge transfer in prescribing
	Communication negatively influenced by medium used		Poor allergy defence systems
			Difficulties in storing data
	Healthcare team:		Difficult to access specialized expertize (at weekend)
	Inability to read handwriting	Communication problems	
	Absence of documentation	Remote, unclear or lack of supervision	
	Faulty interaction with other services	Trust or assume that senior checks	
	Failure to communicate intents/plans behind orders	Decision by senior	
	Unwarranted shifts in planning at staff changeover	Detail by junior	
	Not rechecking after query 'are you sure?'	Weighing risks and benefits	
	Responsibility for patient care ambiguously distributed	Responsibility too great	

Active failures: unsafe acts by humans, such as errors due to slips, lapses, mistakes and violations [slips: errors in performing an intended action, such as intending to prescribe carbamazepine but instead choosing chlorpromazine, lapses: errors resulting from a memory failure, such as prescribing a medication to which a patient is allergic, despite this being known, mistakes: rule-based errors (misapplying a good rule or choosing a poor one) or knowledge-based errors (such as lacking or overlooking relevant information), violations: the act of doing something that is not allowed by a law or rule]. Error-provoking conditions: environmental or individual factors that affect performance at the time of the error, such as time pressure, understaffing, fatigue and inexperience. Latent conditions: weaknesses in the defences of organization processes, such as untrustworthy alarms and indicators, unworkable procedures, design and construction deficiencies

included: why is prescribing important, common errors, effects of errors, examples of errors, how to prescribe correctly, unit conversion, dosages, routes of administration, example calculations, pharmacokinetics and sources of information. Workbooks, computer based trainings and practice questions were other ways of educating doctors in pediatrics, the questions mainly being related to unit conversions and drug dose calculations. Finally, the review concludes that prescribing competency is assessed in only a minority of centers and that no validated assessment tool exists but is desirable.[106] Two recent before-after studies showed reduction in PICU prescribing errors due to a combination of interventions. The interventions included prescriber education, standardization of dosing information sources, provision of drug dosing sheets and -pocket tables, and structured order- and/or administration charts.[107,108] Interestingly, in one of the studies, education did not only include classical lectures on good prescribing, prescription writing and medication errors, but also included individualized reports about resident's own errors to create awareness of and learning from one's own errors.[107]

An important issue related to education is whether there is a difference in needs between juniors (e.g. residents) and seniors (e.g. medical staff). Studies in adult medicine found that resident physicians wrote more errant medication orders than other physician classes and that prescription errors doubled when new doctors joined the rotation.[109,110] On the contrary, studies in pediatric medicine found that there was no correlation between the length of training (0 to 4 years) and likelihood of making a mistake and that error rates were not associated with new residents.[111-113] A large UK report on the prevalence and causes of prescribing errors did not find such differences either and concluded that "prescribing errors are not simply an issue for undergraduate education. If education is to be the solution, it must also include postgraduate and continuing education."[114]

Clinical pharmacy involvement in the medication process

Clinical pharmacist services can be involved in the inpatient medication process in several ways: medication profile and patient review, presentation of drug-related recommendations to care team or physician, drug monitoring and recommendation follow-up, drug therapy and -dosing management, interacting with the health care team on patient rounds, interviewing patients, reconciling medications, and providing patient discharge counseling and follow-up. This involvement generally results in improved care, with no evidence of harm.[115]

Recently a large study in eight Spanish hospitals treating pediatric patients examined the profile of prescribing errors in both handwritten and electronic medication orders detected by pediatric clinical pharmacists.[116] Dosing errors were the most common reason for clinical pharmacist intervention, followed by inappropriate or unavailable dosage form, just like in the Dutch study presented in chapter 4 of this thesis. The physician acceptance rates in pediatric hospital pharmacy intervention studies vary from 60% - 98%.[116-119] In chapter 4 the acceptance rate was at the lower end of this spectrum (57.5%), explained by suboptimal CPOE/CDS design: indication for prescribing a drug is not visible to the pharmacy or not entered into the system at all, while

dosing, and thus dose verification by the pharmacy, often depends on indication. In relation to intensive care, a recent multi-center study evaluated clinical pharmacist interventions in both handwritten and electronic medication orders in four pediatric cardiac and intensive care units in France, Quebec, Switzerland and Belgium, respectively. The pharmacist's interventions mainly concerned optimizing mode of administration, dose and therapeutic monitoring and were accepted in 98% of cases.[120] This is congruent with the prescribing errors detected in the PICU in chapter 2: most often dose, dosage form and/or time of administration were unclear, missing or incorrect. Not shown in chapter 2 but among the results, was that therapeutic drug monitoring was often not performed when indicated.

Important to note: in all these studies, clinical pharmacy involvement proved useful, even though CPOE/CDS was in place. Apparently CPOE/CDS alone is not sufficient to prevent prescribing problems. This particular issue was studied in an adult setting and led to the conclusion that less than 10% of drug-related problems identified by a clinical pharmacist triggered a CPOE/CDS alert. 56% of the interventions proposed by the clinical pharmacy were accepted underlining the importance of clinical pharmacy involvement in the hospital medication process.[121] It is likely, that this involvement is even more important in pediatrics given the mostly higher acceptance rates in pediatrics mentioned above (60-98%) and given pediatric specific difficulties concerning drug dosing, drug formulations, drug preparing issues, off-label and unlicensed drug use.

Communication and medication reconciliation

Communication, whether face to face or via ICT, takes place between all health care providers within and in between all stages of the hospital medication process. Additionally, communication is essential when a patient is moved from one care setting to another, i.e. at admission and discharge and also from one department to another within a hospital. It is well known that many medication errors occur due to miscommunications within health care teams and at patient transfer points.[104,122,123] Medication reconciliation is the process of creating the most accurate overview possible of all medicines a patient is taking and comparing that overview against the physician's admission, transfer, and/or discharge orders, with the goal of providing correct medication to the patient at all transition points within the hospital.[124]

Within a hospital clear communication of medication orders between physicians, pharmacy and nurses should be ensured, but is difficult to achieve. Think of verbal medication orders from doctor to nurse in acute situations in emergency departments or intensive care units, for example. Structuring and automating the medication ordering process from prescribing to administration using CPOE systems including pharmacy systems and nurse administration registration systems supports clear and correct communication. But non-technical interventions may positively influence communication as well. Starmer et al. found a decrease in rates of medical errors and preventable adverse events among hospitalized children following implementation of a resident handoff bundle, for example. Preintervention there was no team-based approach, standardized structure or dedicated

physical environment for handoffs. Handoffs were verbal and included exchange of a printed handoff document created using a word-processing program not integrated within the electronic medical record. The intervention consisted of implementation of a resident handoff bundle that consisted of several elements to improve communication in two pediatric units: 1. communication training regarding best practices for verbal and written handoffs, 2. introduction of a commonly used structured handoff mnemonic to standardize verbal handoff, 3. restructuring handoffs to include all health care providers involved in the rotation of shifts, 4. relocation to a private and quiet space, 5. introduction of periodic handoff oversight by a chief resident or attending physician, 6. introduction of a computerized handoff tool integrated into the electronic medical record, that automatically imported relevant patient data and contained structured fields to prompt entry of key handoff information (in one of two pediatric units). Postintervention the total number of medical errors and adverse events, of which the majority were related to medication, significantly decreased in both units while resident workflow was not adversely affected.[125]

Besides communication *within* teams, communication *between* teams of healthcare providers, whether in- or outside the hospital, also needs attention: it is estimated that 46% of all medication errors occur during the patient's admission or discharge from a clinical unit.[126] Poor communication and documentation of medical information has been cited as the main cause for these medication errors.[126-128] Across settings, ideally communications should be electronic, transferring information between hospital prescribing systems and general practitioner and community pharmacy systems, for example.[122] But when electronic systems differ between settings they are often not able to electronically exchange patient data and, additionally, mere exchange of most recent medication lists is often insufficient, emphasizing the need for structured non-technical communication. Mueller et al. recently systematically reviewed hospital-based medication reconciliation practices and concluded that studies comparing different inpatient medication reconciliation practices and their effects on clinical outcomes are scarce, stressing the need for more research on interventions that aim to improve communication at transfer points in health care.[129]

In pediatrics communication at transfer points is of particular importance, because parents often have a role in children's care, e.g. administering drugs to their child in hospital and/or at home. Communication should include doctors, pharmacists, the child *and* the child's carers.[122] Also, typical for pediatrics is that problems can occur after discharge with drugs that can only be prescribed by hospitals, drugs that are manufactured as 'specials', extemporaneously prepared products and drugs that are prescribed outside the manufacturer's product license.[122] Manias et al. determined communication relating to children's transfer across different clinical settings as key contributing factor to medication errors in pediatrics.[91] Huynh et al. reviewed literature on medication reconciliation in pediatrics.[92] The primary objective was to identify studies reporting the rate and clinical significance of medication discrepancies at transition points and the secondary objective was to ascertain whether any specific interventions had been used for medication reconciliation in pediatric settings. A mere 10 studies could be included in the review and these were

heterogeneous in definitions, methods and patient populations. Most studies consistently reported high rates of discrepancies ranging from about 20% to 70%. A variation of methods was used to identify the discrepancies, e.g. involvement of clinical pharmacy at transfer points, contact with the patient's community pharmacist, review of the medication list in the patient's chart etc. Two of the mentioned methods may be considered specific for pediatrics: 1. interview of the caregiver at admission about medications being taken at home and 2. obtaining mother's medication history at admission for breast-fed children. The review concludes that little information on medication reconciliation in children is available, that medication reconciliation tools and interventions used in adults may not be appropriate for use in children, and that future research is required to fully understand how medication reconciliation can reduce medication discrepancies in pediatrics.[92]

Organization and culture

A manuscript by three medication safety opinion leaders suggests interventions at three levels to improve prescribing: 1. the individual, 2. the individual's immediate surroundings and 3. the organizational culture. The interventions needed are: 1. improved training and competence testing of the individual prescriber, 2. control and standardization of the environment in which prescribers perform, control of high-risk drugs and use of technology to provide decision support, and 3. change of organizational cultures in order to support the belief that prescribing is complex and important to get right, respectively.[130] The first two interventions have been discussed extensively above. The third, organizational culture, is discussed here as an important part of non-technical interventions for prevention of medication prescribing errors in pediatric patients. In table 5 many cultural and organizational factors are mentioned as causes of prescribing errors: lack of knowledge and training, lack of standardization of prescribing, lack of inter-colleague questioning and feedback, lack of acknowledgement of importance, lack of systematic prescribing and prescribing error analysis, suboptimal working environment, distraction, high workload, time-pressure, and so on.[104] Preferably, the earlier mentioned systems approach, that focuses on the conditions under which individuals work and how those conditions can predispose to errors, is used to understand the conditions that may predispose to error and to enable system defenses to be developed such that the errors are avoided. Booth et al. successfully used this approach to reduce prescribing errors on a PICU.[131] Interventions aimed at facilitating safe and accurate prescribing were discussed in a multi-disciplinary team of medical, nursing and pharmacy staff. Interventions that could rapidly be introduced, were low-cost and low-technology were selected, specifically targeting distraction and time-pressure. The interventions were a combination of provision of a dedicated well-equipped area for prescribing, no prescribing permitted outside of this area, a formal set of rules to which all prescriptions had to comply, nursing staff explicitly supported in not administering inadequate prescriptions and daily feedback of prescribing errors at morning ward rounds. These combined organizational interventions led to a significant reduction in prescribing errors in the PICU.[131]

An important aspect to enable use of the systems approach to develop defenses that prevent prescribing errors, is a safe error reporting culture.[105] Although voluntary error- and incident reporting tends to underestimate error rates,[132] it contributes to an open culture in which errors and near-misses can be discussed and learned from. Other important aspects are the presence of a just culture (a collective understanding of where the line should be drawn between blameless and blameworthy actions)[105] and a non-punitive approach to increase disclosure of errors.[133-135] In 2007, Snijders et al. reviewed incident- and error reporting systems in neonatal intensive care and concluded that multi-institutional, voluntary, non-punitive, system based incident reporting is likely to generate valuable information on type, aetiology, outcome and preventability of incidents in the NICU. However, the beneficial effects of incident reporting systems and consecutive system changes on patient safety were difficult to assess from the available evidence and therefore remained to be investigated.[136] Consequently, Snijders et al. introduced voluntary, non-punitive incident reporting in eight Dutch level III NICUs and one pediatric surgical ICU and found more incidents than had previously been observed.[137] It was studied which aspects of safety culture predicted incident reporting behavior in the NICU and concluded that a non-punitive approach to error, hospital management support for patient safety, and overall perceptions of safety predict incident reporting behavior in the NICU.[138]

Recapitulating, non-technical solutions should be combined with technical solutions and should keep receiving attention to maximally reduce pediatric prescribing error rates.

Implications and recommendations for future patient care and research

Implications and recommendations for future patient care

The main objective of this thesis was to determine the nature, frequency and determinants of medication prescribing errors in pediatrics and to study the effect of CPOE and CDS on these errors.

The thesis leads to the following implications and recommendations for future patient care.

a. Distinction should be made between ill children and critically ill children

   To prevent prescribing errors in the pediatric population, distinction should be made between ill children and critically ill children as types of prescribing errors differ in these populations. For example, chapter 2 identified support for the complexity of intravenous drug infusion ordering as important in PICU patients, whereas chapter 4 in general pediatric settings makes no mention of intravenous infusions at all. Likewise, chapter 3 showed that drug-drug interactions in critically ill children differ from those in general pediatrics.

b. CPOE should be combined with CDS

   In pediatrics, CPOE is an essential tool for prevention of medication prescribing errors but CPOE alone is insufficient to eliminate all types of prescribing errors: chapter 2 and 4 conclude that CPOE was associated with elimination of administrative errors, but that

omissions, dosing errors and therapeutic errors remain frequent in PICU/NICU and pediatric patients, respectively. CPOE should be combined, or rather integrated with CDS, see the next recommendation.

c. CPOE/CDS should be integrated

It is crucial that CPOE/CDS systems are representative for daily clinical practice and workflow. Current combinations of CPOE with separate CDS tools, lead to fragmented support of the medication process. For optimal support, the distinction between CPOE and CDS should be abolished. CPOE/CDS should integrate support for 1. all stages of the medication process, 2. all professionals engaged in the medication process, 3. all levels of patient diversity and 4. all levels of pharmacotherapy complexity. Integrated CPOE/CDS, as described in chapter 7, is promising and should be further developed and validated in practice.

d. CPOE/CDS should be tailored to pediatric, PICU and NICU patients

Table 3 in this chapter gives an overview of specific recommendations to tailor CPOE/CDS to pediatric and PICU/NICU patients, respectively. Main identified pediatric problems that should be tackled by integrated CPOE/CDS are: 1. dosing and required calculations for (cumulative) dosing, taking patient variables such as weight, age, renal function etc. into account, 2. matching and rounding of calculated doses to available products, product strengths/concentrations and formulations, 3. preparing and required calculations for preparing to be able to administer a drug that is suitable for a child. For Dutch pediatrics, linking integrated CPOE/CDS systems with the earlier mentioned web-based Dutch national pediatric drug formulary may be a very useful step to overcome these problems and should be explored.

e. CPOE/CDS should be individualized

By handling data from different databases, e.g. pharmacotherapy, clinical chemistry, pharmacy, genotype databases, CPOE/CDS specificity can be increased, for example programmed such that alerts are merely fired if specific rules for an individual patient are violated (precision medicine).

f. CPOE/CDS should be continuously maintained and updated

Because of ongoing development of ICT in health care and because of never ending new insights into pharmacotherapy and patient treatment, CPOE/CDS systems and their content, e.g. databases, require permanent maintenance and updates to ensure both clinical appropriateness and correctness. Current CPOE/CDS systems often compose of several applications linked to a main system, resulting in maintenance difficulties, and consequent time and money investments. Integrated CPOE/CDS systems, linked to national drug databases that are centrally maintained and updated, would improve this.

g. CPOE/CDS user education should be a never ending process

Accurate CPOE/CDS implementation, including thorough training of all users, preferably on-site, is of utmost importance for optimal error prevention. Moreover, after implementation, ongoing education and training is critical to ensure that new errors are not introduced,

especially after system or application updates. Application managers should be appointed and made responsible for the availability of user education and training. On the other hand end-users are responsible for maintaining their individual level of competence.

h. CPOE/CDS should be combined with non-technical interventions
Essential for optimal error prevention is that CPOE/CDS is combined with non-technical, human, interventions, such as education, clinical pharmacy involvement in the medication process, accurate communication and medication reconciliation in an organization that promotes and supports safe prescribing in combination with a non-punitive error reporting culture.

i. CPOE/CDS is a shared responsibility
Health care providers, e.g. clinicians, nurses and pharmacists, official bodies, policy makers and software developers should *all* demonstrate leadership in preventing medication errors and collaborate to develop CPOE/CDS systems thereto. Health care providers are responsible for calling attention to prescribing problems and errors they come across in daily practice, software developers should be responsive for these experiences from daily practice and policy makers and official bodies should provide a network and funding for continuous knowledge sharing and CPOE/CDS development. Additionally, government should dictate the framework in which health care providers and system developers may operate and clearly appoint the responsibilities mentioned above to solve current problems such as escalating proliferation of poorly interoperating systems and budget overrun.

Implications and recommendations for future research

A 2011 report prepared for the Agency for Healthcare Research and Quality of the US Department of Health and Human Services reviewed the evidence on the impact of health information technology (IT) on all phases of the medication management process (prescribing and ordering, order communication, dispensing, administration and monitoring as well as education and reconciliation), to identify the gaps in literature and to make recommendations for future research. Among the identified gaps the report mentioned the special needs of children as not adequately pursued. Among the recommendations it was mentioned that more study of IT in pediatric patients would be beneficial.[139] This thesis fills part of the identified gap and underlines the need for further IT research in pediatrics. More specifically, this thesis leads to the following implications and recommendations for future research.

a. Defining and classifying medication errors needs ongoing attention in scientific literature
In chapter 2, 4 and 5 attention was called to difficulties in defining and classifying medication errors. As described above, clinical research is ideally based on uniform definitions and classifications. A stepwise approach for developing more detailed definitions and classifications per research perspective and clinical setting is proposed. Present and future researchers in

the field of medication error prevention should test this approach and keep trying to clearly and accurately define and classify medication errors so that determined error rates can be compared and learned from. Also important is to include used definitions and classifications in publications and to be aware of the differences when comparing study results.

b. CPOE/CDS development should be based on medication error research

A crucial aspect for optimal error prevention is that CPOE/CDS design is based on system requirements obtained from a combination of theoretical data from literature and historical data from statistical analysis of prescribing errors from daily practice to ensure that CPOE/CDS effectively prevents errors and fits into daily workflow. To achieve this, continuous structured registration and evaluation is needed, see the next recommendation.

c. Medication error input for research should be structured and come from pediatric practice

Continuous structured registration, evaluation and periodic statistical analysis of medication errors, including near misses, in the medication process should be implemented on all pediatric departments and in all children's hospitals. To be able to perform properly powered error subtype analyses, this should also be done at a national level, conform the Dutch Central Registration of Medication Errors (CMR)[11] but then focused on pediatrics. Registration, evaluation and statistical analysis of medication errors should carefully distinguish causes of errors, errors as such and consequences of errors to give direction to error prevention programs.

d. Research data on medication errors should be evaluated multidisciplinary, including IT-specialists

Evaluation of medication errors requires a multidisciplinary approach, involving clinicians, nurses and pharmacy staff, to enable integrated solutions. The registered errors, their causes and consequences, derived from these evaluations, should be statistically analyzed periodically at a local and at a national level, as mentioned above. To optimally profit from the data, the results should be evaluated multidisciplinary, not only involving clinicians, nurses and pharmacy staff, but also health-IT specialists, preferably CPOE/CDS-experts. By involving health-IT specialists in research data evaluation, software developers have up-to-date information from practice at their disposal to continuously optimize CPOE/CDS systems.

e. Effects of CPOE/CDS in pediatrics should be studied at a national level

Research on CPOE/CDS systems in pediatrics, should be part of a greater (national) pediatric research project. By doing so, problems such as underpowered studies not able to prove clinical benefit or harm because of small numbers, may be solved. These projects should include studies on effects of CPOE/CDS on 1. patient outcome (ADEs, morbidity, mortality), 2. medication errors in all stages of the mediation process, 3. workflow, efficiency and costs and 4. combinations with non-technical interventions such as education and clinical pharmacy involvement in the medication process. The studies should preferably be designed as prospective multicenter before-after analyses.

f. Effects of CPOE/CDS on pediatric prescribing errors in outpatient setting should be studied too

In this thesis CPOE/CDS is studied in pediatric wards, PICU and NICU, but medication prescribing for children in other settings needs to be studied as well. Emergency departments for example pose other challenges than inpatient departments do.[140] Several studies have been performed to establish types and frequencies of pediatric prescribing errors and factors associated with those errors in emergency departments (EDs),[141-145] but little is known about potentially useful CPOE/CDS tools to prevent these errors. One study retrospectively evaluated addition of a pediatric medication quicklist as drug dosing support tool to a CPOE system in a pediatric ED. A significant reduction in medication prescribing errors followed implementation of this quicklist.[146] Another study evaluated the effect of a patient-centered health information technology tool designed to enhance communication between parents and emergency clinicians during emergency care. Parents used the tool to enter data on symptoms and medication-related history; a printout provided recommendations to clinicians. This resulted in minimal non-significant impact on prescribing errors during ED care.[147] Kirk et al. showed that computer calculated dosing significantly reduced pediatric acetaminophen and promethazine prescribing error rates at an outpatient clinic, emergency department and at discharge.[148] All of these studies emphasize the need for more extensive investigation of CPOE/CDS to prevent prescribing errors in children, whether hospitalized or not.

g. Order entry by others than physicians should be studied

Current focus is on *physician* order entry, while nurses and pharmacy staff play a crucial role in the pediatric medication process as well. It has been shown that nurse order entry (NOE) can increase physicians' compliance with warnings and recommended dose and frequency and reduce non-intercepted medication dosing errors in a neonatal ward as effectively as physician order entry (POE) or even better.[149] In chapter 2 of this thesis it is mentioned that efficiency could be enhanced by authorising hospital pharmacy staff to complete missing prescription features in electronic medication orders without having to consult the prescriber. Future research should elucidate further potential of order entry by others than merely physicians.

Conclusions

In conclusion, medication prescribing errors frequently occur in pediatrics, their causes are multi-factorial and an integrated combination of pediatric-specific CPOE/CDS systems with non-technical interventions can positively affect pediatric medication prescribing error rates. Several recommendations have been made throughout this thesis for future practice and research to further improve this. In 2013, a report by the US Council on Clinical Information Technology discussed the advances in electronic prescribing systems in pediatrics and acknowledged there are positive pediatric data supporting the role of electronic prescribing in mitigating medication

errors. On the basis of this report, the American Academy of Pediatrics recommends and provides guidelines for the adoption of CPOE/CDS in pediatric settings.[150] In the Netherlands, electronic prescribing has become mandatory for all health care providers per January 1st 2014, as stated in the Royal Dutch Medical Association's Guidelines on electronic prescribing.[151] To ensure compliance, the Dutch Health Care Inspectorate, a part of Government Oversight of public health, assesses whether Dutch health care providers have actually adopted electronic prescribing. A few compulsory functionalities are mentioned in the guidelines: prescribing from a medication database of uniquely identifiable drugs, interoperability with other electronic systems, support for medication reconciliation and CDS for dose checking, DDI checking, drug-condition interaction checking, drug-allergy interaction checking, duplicate order checking. However, concrete, more elaborated national guidelines for IT implementation in healthcare are still lacking, let alone national guidelines for IT implementation in pediatrics. To optimize electronic prescribing in pediatric patients, CPOE/CDS tailored to Dutch pediatric health care is needed. This requires collaboration between pediatric health care providers and software developers in combination with governmental guidance to anchor that experiences from pediatric practice and findings from pediatric research fuel the development of CPOE/CDS systems to ensure pediatric patient safety.

References

1 US Food and Drug Administration. Available at: http://www.fda.gov/drugs/drugsafety/medicationerrors/default.htm [Accessed 15 April 2014].

2 National Coordinating Council for Medication Error Reporting and Prevention. Available at: http://www.nccmerp.org/aboutMedErrors.html [Accessed 15 April 2014].

3 US Institute of Medicine. Available at: http://www.iom.edu/Reports/2006/Preventing-Medication-Errors-Quality-Chasm-Series.aspx [Accessed 15 April 2014].

4 Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. Journal of General Internal Medicine 1995;10:100–205.

5 UK National Health Service National Patient Safety Agency. Available at: http://www.nrls.npsa.nhs.uk/resources/patient-safety-topics/medication-safety/ [Accessed 15 April 2014].

6 EU European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000570.jsp [Accessed 15 April 2014].

7 International Pharmaceutical Federation. Available at: https://www.fip.org/www/uploads/database_file.php?id=229&table_id [Accessed 15 April 2014].

8 ASHP Standard definition of a medication error. Am J Hosp Pharm 1982;39:321.

9 ASHP guidelines on preventing medication errors in hospitals. Am J Hosp Pharm 1993;50:305–14.

10 EAHP Statements on hospital pharmacy 2014. European Association of Hospital Pharmacists, 2014. Available at: http://www.eahp.eu/ [Accessed 3 June 2014].

11 Central registration of medication errors. Available at: http://www.medicatieveiligheid.info/ [Accessed 3 June 2014].

12 List of patient safety definitions. Dutch Health Care Inspectorate, 2005. Available at: http://www.medischcontact.artsennet.nl/ [Accessed 3 June 2014].

13 Dean B, Barber N, Schachter M. What is a prescribing error? Qual Health Care 2000;9:232-7.

14 van den Bemt PM, Egberts AC. Drug-related problems: definitions and classification. EJHP Practice 2007;13:62-4.

15 Bürkle T, Müller F, Patapovas A, et al. A new approach to identify, classify and count drug-related events. Br J Clin Pharmacol 2013;76 Suppl 1:56-68.

16 Fijn R, Van den Bemt PM, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol 2002;53:326-31.

17 Lisby M, Nielsen LP, Brock B, et al. How are medication errors defined? A systematic literature review of definitions and characteristics. Int J Qual Health Care 2010;22:507-18.

18 Tully MP. Prescribing errors in hospital practice. Br J Clin Pharmacol 2012;74:668-75.

19 Ghaleb MA, Barber N, Franklin BD, et al. Systematic review of medication errors in pediatric patients. Ann Pharmacother 2006;40:1766-76.

20 Chedoe I, Molendijk HA, Dittrich ST, et al. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety: a review of the current literature. Drug Saf 2007;30:503-13.

21 Ghaleb MA, Barber N, Franklin BD, et al. The incidence and nature of prescribing and medication administration errors in paediatric inpatients. Arch Dis Child 2010;95:113-8.

22 Bobb A, Gleason K, Husch M, et al. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med 2004;164:785-92.

23 Burridge AM, Wilson K, Terry D. Support tools for paediatric inpatient prescribers: a review. Eur J Hosp Pharm 2014;21:113-7.

24 Kadmon G, Bron-Harlev E, Nahum E, et al. Computerized order entry with limited decision support to prevent prescription errors in a PICU. Pediatrics 2009;124:935-40.

25 Walsh KE, Landrigan CP, Adams WG, et al. Effect of computer order entry on prevention of serious medication orders in hospitalized children. Pediatrics 2008;121:e421-7.

26 Kaushal R, Barker KN, Bates DW. How can information technology improve patient safety and reduce medication errors in children's healthcare? Arch Pediatr Adolesc Med 2001;155:1002-7.

27 Kuperman GJ, Bobb A, Payne TH, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007;14:29-40.

28 Caldwell NA, Power B. The pros and cons of electronic prescribing for children. Arch Dis Child 2012;97:124-8.

29 van Rosse F, Maat B, Rademaker CM, et al. The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review. Pediatrics 2009;123:1184-90.

30 Warrick C, Naik H, Avis S, et al. A clinical information system reduces medication errors in paediatric intensive care. Intensive Care Med 2011;37:691-4.

31 Maslove DM, Rizk N, Lowe HJ. Computerized physician order entry in the critical care environment: a review of current literature. J Intensive Care Med 2011;26:165-71.

32 Longhurst CA, Parast L, Sandborg CI, et al. Decrease in hospital-wide mortality rate after implementation of a commercially sold computerized physician order entry system. Pediatrics 2010;126:14-21.

33 Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system [published correction appeared in Pediatrics 2006;117:594]. Pediatrics 2005;116:1506–12.

34 Wright A, Sittig DF, Ash JS, et al. Development and evaluation of a comprehensive clinical decision support taxonomy: comparison of front-end tools in commercial and internally developed electronic health record systems. J Am Med Inform Assoc 2011;18:232-42.

35 Barrett JS, Narayan M, Patel D, et al. Prescribing habits and caregiver satisfaction with resources for dosing children: rationale for more informative dosing guidance. BMC Pediatr 2011;11:25.

36 Bartelink IH, Rademaker CM, Schobben AF, et al. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006;45:1077-97.
37 Cordero L, Kuehn L, Kumar RR, et al. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. J Perinatol 2004;24:88-93.
38 Kazemi A, Ellenius J, Pourasghar F, et al. The effect of computerized physician order entry and decision support system in medication errors in the neonatal ward: experiences from an Iranian teaching hospital. J Med Syst 2011;35:25-37.
39 Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547-56.
40 Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA 2012;308:1641-50.
41 Agus MS, Steil GM, Wypij D, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med 2012;367:1208-19.
42 Tasker RC. Pediatric critical care, glycemic control, and hypoglycemia: what is the real target? JAMA 2012;308:1687-8.
43 Macrae D, Tasker RC, Elbourne D. A trial of hyperglycemic control in pediatric intensive care. N Engl J Med 2014;370:1355-6.
44 Meyfroidt G, Wouters P, De Becker W, et al. Impact of a computer-generated alert system on the quality of tight glycemic control. Intensive Care Med 2011;37:1151-7.
45 Fogel SL, Baker CC. Effects of computerized decision support systems on blood glucose regulation in critically ill surgical patients. J Am Coll Surg 2013;216:828-35.
46 Spat S, Höll B, Petritsch G, et al. Automatic system testing of a decision support system for insulin dosing using Google Android. Stud Health Technol Inform 2013;186:187-91.
47 Lehmann CU, Kim GR, Gujral R, et al. Decreasing errors in pediatric continuous intravenous infusions. Pediatr Crit Care Med 2006;7:225-30.
48 Sowan AK, Vaidya VU, Soeken KL, et al. Computerized orders with standardized concentrations decrease dispensing errors of continuous infusion medications for pediatrics. J Pediatr Pharmacol Ther 2010;15:189-202.
49 Johnson KB, Lee CK, Spooner SA, et al. Automated dose-rounding recommendations for pediatric medications. Pediatrics 2011;128:e422-8.
50 van Riet-Nales DA, de Neef BJ, Schobben AF, et al. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013;98:725-31.
51 van Riet-Nales, DA, de Jager KE, Schobben AF, et al. The availability and age-appropriateness of medicines authorized for children in The Netherlands. Br J Clin Pharmacol 2011;72:465-73.
52 van Riet-Nales DA, Doeve ME, Nicia AE, et al. The accuracy, precision and sustainability of different techniques for tablet subdivision: breaking by hand and the use of tablet splitters or a kitchen knife. Int J Pharm 2014;466:44-51.

53 Scharnweber C, Lau BD, Mollenkopf N, et al. Evaluation of medication dose alerts in pediatric inpatients. Int J Med Inform 2013;82:676-83.
54 Coleman JJ, Nwulu U, Ferner RE. Decision support for sensible dosing in electronic prescribing systems. J Clin Pharm Ther 2012;37:415-9.
55 Kim GR, Chen AR, Arceci RJ, et al. Error reduction in pediatric chemotherapy: computerized order entry and failure modes and effects analysis. Arch Pediatr Adolesc Med 2006;160:495-8.
56 Stultz JS, Porter K, Nahata MC. Sensitivity and specificity of dosing alerts for dosing errors among hospitalized pediatric patients. J Am Med Inform Assoc 2014 Feb 4. [Epub ahead of print]
57 Walton SM, Galanter WL, Rosencranz H, et al. A trial of inpatient indication based prescribing during computerized order entry with medications commonly used off-label. Appl Clin Inform 2011;2:94-103.
58 Coleman JJ, Hodson J, Ferner RE. Deriving dose limits for warnings in electronic prescribing systems: statistical analysis of prescription data at University Hospital Birmingham, UK. Drug Saf 2012;35:291-8.
59 van der Sijs H, Aarts J, Vulto A, et al. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138-47.
60 Jani YH, Barber N, Wong IC. Characteristics of clinical decision support alert overrides in an electronic prescribing system at a tertiary care paediatric hospital. Int J Pharm Pract 2011;19:363-6.
61 Mille F, Schwartz C, Brion F, et al. Analysis of overridden alerts in a drug-drug interaction detection system. Int J Qual Health Care 2008;20:400-5.
62 Killelea BK, Kaushal R, Cooper M, et al. To what extent do paediatricians accept computer-based dosing suggestions? Pediatrics 2007;119:e69-75.
63 Guidelines on medication surveillance [in Dutch]. Royal Dutch Medical Association, 2013.
64 Eppenga WL, Derijks HJ, Conemans JM, et al. Comparison of a basic and an advanced pharmacotherapy-related clinical decision support system in a hospital care setting in the Netherlands. J Am Med Inform Assoc 2012;19:66-71.
65 Strom BL, Schinnar R, Aberra F, et al. Unintended effects of a computerized physician order entry nearly hard-stop alert to prevent a drug interaction: a randomized controlled trial. Arch Intern Med 2010;170:1578-83.
66 Daschner M. Drug dosage in children with reduced renal function. Pediatr Nephrol 2005;20:1675-86.
67 Boussadi A, Caruba T, Zapletal E, et al. A clinical data warehouse-based process for refining medication orders alerts. J Am Med Inform Assoc 2012;19:782-5.
68 Jani YH, Barber N, Wong IC. Paediatric dosing errors before and after electronic prescribing. Qual Saf Health Care 2010;19:337-40.
69 Leu MG, Morelli SA, Chung OY, et al. Systematic update of computerized physician order entry order sets to improve quality of care: a case study. Pediatrics 2013;131 Suppl 1:S60-7.

70 van den Broek MP, Groenendaal F, Toet MC, et al. Pharmacokinetics and clinical efficacy of phenobarbital in asphyxiated newborns treated with hypothermia: a thermopharmacological approach. Clin Pharmacokinet 2012;51:671-9.

71 van den Broek MP, Rademaker CM, van Straaten HL, et al. Anticonvulsant treatment of asphyxiated newborns under hypothermia with lidocaine: efficacy, safety and dosing. Arch Dis Child Fetal Neonatal Ed 2013;98:F341-5.

72 Niès J, Colombet I, Degoulet P, et al. Determinants of success for computerized clinical decision support systems integrated in CPOE systems: a systematic review. AMIA Annu Symp Proc 2006:594-8.

73 Overhage JM, Tierney WM, Zhou XH et al. A randomized trial of "corollary orders" to prevent errors of omission. J Am Med Inform Assoc 1997;4:364-75.

74 Abboud PA, Ancheta R, McKibben M, et al. Impact of workflow-integrated corollary orders on aminoglycoside monitoring in children. Health Informatics J 2006;12:187-98.

75 van Doormaal JE, van den Bemt PM, Zaal RJ, et al. The influence that electronic prescribing has on medication errors and preventable adverse drug events: an interrupted time-series study. J Am Med Inform Assoc 2009;16:816-25.

76 Mirco A, Campos L, Falcão F, et al. Medication errors in an internal medicine department. Evaluation of a computerized prescription system. Pharm World Sci 2005;27:351-2.

77 Helmons PJ, Dalton AJ, Daniels CE. Redesigning the automated dispensing cabinet refill process decreases medication refill errors. Am J Health Syst Pharm 2012;69:1659-64.

78 Holdsworth MT, Fichtl RE, Raisch DW, et al. Impact of computerized prescriber order entry on the incidence of adverse drug events in pediatric inpatients. Pediatrics 2007;120:1058-66.

79 Sauberan JB, Dean LM, Fiedelak J, et al. Origins of and solutions for neonatal medication-dispensing errors. Am J Health Syst Pharm 2010;67:49-57.

80 Keers RN, Williams SD, Cooke J, et al. Impact of interventions designed to reduce medication administration errors in hospitals: a systematic review. Drug Saf 2014;37:317-32.

81 Taylor JA, Loan LA, Kamara J, et al. Medication administration variances before and after implementation of computerized physician order entry in a neonatal intensive care unit. Pediatrics 2008;121:123-8.

82 Hassink JJ, Jansen MM, Helmons PJ. Effects of bar-code assisted medication administration (BCMA) on frequency, type and severity of medication administration errors: a review of the literature. Eur J Hosp Pharm Sci Pract 2012;19:489-94.

83 Morriss FH Jr, Abramowitz PW, Nelson SP, et al. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study. J Pediatr 2009;154:363-8.

84 Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. J Am Med Inform Assoc 2003;10:523-30.

85 Schoenenberger RA, Tanasijevic MJ, Jha A, et al. Appropriateness of antiepileptic drug level monitoring. JAMA 1995;274(:1622–6.

86 Bates DW, Boyle DL, Rittenberg E, et al. What proportion of common diagnostic tests appear redundant? Am J Med 1998;104:361–8.

87 Levick DL, Stern G, Meyerhoefer CD, et al. "Reducing unnecessary testing in a CPOE system through implementation of a targeted CDS intervention." BMC Med Inform Decis Mak 2013;13:43.

88 Mahoney CD, Berard-Collins CM, Coleman R, et al. Effects of clinical information system on medication safety in a multi-hospital setting. Am J Health Syst Pharm 2007;64:1969-77.

89 Baron JM, Dighe AS. Computerized order entry in the clinical laboratory. J Pathol Inform 2011;2:35.

90 Baron JM, Dighe AS. The role of informatics and decision support in utilization management. Clin Chim Acta 2014;427:196-201.

91 Manias E, Kinney S, Cranswick N, et al. Medication errors in hospitalised children. J Paediatr Child Health 2014;50:71-7.

92 Huynh C, Wong IC, Tomlin S, et al. Medication discrepancies at transitions in pediatrics: a review of the literature. Paediatr Drugs 2013;15:203-15.

93 Ash JS, Sittig DF, Dykstra R, et al. The unintended consequences of computerized provider order entry: findings from a mixed methods exploration. Int J Med Inform 2009;78 Suppl 1:S69-76.

94 Reckmann MH, Westbrook JI, Koh Y, Lo C, Day RO. Does computerized provider order entry reduce prescribing errors for hospital inpatients? A systematic review. J Am Med Inform Assoc 2009;16:613-23.

95 Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293:1197-203.

96 Lucas AJ. Improving medication safety in a neonatal intensive care unit. Am J Health Syst Pharm 2004;61:33-7.

97 Chapman AK, Lehmann CU, Donohue PK, et al. Implementation of computerized provider order entry in a neonatal intensive care unit: Impact on admission workflow. Int J Med Inform 2012;81:291-5.

98 Vardi A, Efrati O, Levin I, et al. Prevention of potential errors in resuscitation medications orders by means of a computerised physician order entry in paediatric critical care. Resuscitation 2007;73:400-6.

99 Zimlichman E, Keohane C, Franz C, et al. Return on investment for vendor computerized physician order entry in four community hospitals: the importance of decision support. Jt Comm J Qual Patient Saf 2013;39:312-8.

100 Kaushal R, Jha AK, Franz C, et al. Return on investment for a computerized physician order entry system. J Am Med Inform Assoc. 2006;13:261-6.

101 Menachemi N, Brooks RG. Reviewing the benefits and costs of electronic health records and associated patient safety technologies. J Med Syst 2006;30:159-68.

102 Teufel RJ 2nd, Kazley AS, Ebeling MD, et al. Hospital electronic medical record use and cost of inpatient pediatric care. Acad Pediatr 2012;12:429-35.

103 Teufel RJ, Kazley AS, Basco WT Jr. Is computerized physician order entry use associated with a decrease in hospital resource utilization in hospitals that care for children? J Med Syst 2012;36:2411-20.
104 Tully MP, Ashcroft DM, Dornan T, et al. The causes of and factors associated with prescribing errors in hospital inpatients: a systematic review. Drug Saf 2009;32:819-36.
105 Reason J. Human error: models and management. BMJ 2000;320:768-70.
106 Conroy S, North C, Fox T, et al. Educational interventions to reduce prescribing errors. Arch Dis Child 2008;93:313-5.
107 Alagha HZ, Badary OA, Ibrahim HM, et al. Reducing prescribing errors in the paediatric intensive care unit: an experience from Egypt. Acta Paediatr 2011;100:e169-e74.
108 Martinez-Anton A, Sanchez JI, Casanueva L. Impact of an intervention to reduce prescribing errors in a pediatric intensive care unit. Intensive Care Med 2012;38:1532-8.
109 Ho L, Brown GR, Millin B. Characterization of errors detected during central order review. Can J Hosp Pharm 1992;45:193-7.
110 Wilson DG, McArtney RG, Newcombe RG, et al. Medication errors in paediatric practice: insights from a continuous quality improvement approach. Eur J of Pediatr 1998;157:769-74.
111 Pacheco GS, Viscusi C, Hays DP, et al. The effects of resident level of training on the rate of pediatric prescription errors in an academic emergency department. J Emerg Med 2012;43:e343-8.
112 Rowe C, Koren T, Koren G. Errors by paediatric residents in calculating drug doses. Arch Dis Child 1998;79:56-8.
113 Honey BL, Bray WM, Gomez MR, et al. Frequency of prescribing errors by medical residents in various training programs. J Patient Saf 2014 Apr 8. [Epub ahead of print]
114 Dornan T, Ashcroft D, Heathfield H, et al. An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education. EQUIP study. Available at: http://www.gmc-uk.org/about/research/research_commissioned_4.asp [Accessed 10 May 2014].
115 Kaboli PJ, Hoth AB, McClimon BJ, et al. Clinical pharmacists and inpatient medical care: a systematic review. Arch Intern Med 2006;166:955-64.
116 Fernández-Llamazares CM, Pozas M, Feal B, et al. Profile of prescribing errors detected by clinical pharmacists in paediatric hospitals in Spain. Int J Clin Pharm 2013;35:638-46.
117 Cunningham KJ. Analysis of clinical interventions and the impact of pediatric pharmacists on medication error prevention in a teaching hospital. J Pediatr Pharmacol Ther 2012;17:365-73.
118 Virani A, Crown N. The impact of a clinical pharmacist on patient and economic outcomes in a child and adolescent mental health unit. Can J Hosp Pharm 2003;56:158-62.
119 Condren ME, Haase MR, Luedtke SA, et al. Clinical activities of an academic pediatric pharmacy team. Ann Pharmacother 2004;38:574-8.
120 Prot-Labarthe S, Di Paolo ER, Lavoie A, et al. Pediatric drug-related problems: a multicenter study in four French-speaking countries. Int J Clin Pharm 2013;35:251-9.

121 Zaal RJ, Jansen MM, Duisenberg-van Essenberg M, et al. Identification of drug-related problems by a clinical pharmacist in addition to computerized alerts. Int J Clin Pharm 2013;35:753-62.
122 Smith J. Building a safer NHS for patients: improving medication safety. A report by the Chief Pharmaceutical Officer. Department of Health of the UK government, 2004.
123 Wagner C, Smits M, Van Wagtendonk I, et al. Oorzaken van incidenten en onbedoelde schade in ziekenhuizen. [Causes of incidents and unintentional harm in hospitals]. Amsterdam: EMGO Institute and NIVEL; 2008.
124 Institute for Healthcare Improvement. 5 million lives campaign. Getting started kit: prevent adverse drug events (medication reconciliation) how-to guide. Cambridge: Institute for Healthcare Improvement; 2008. Available at: http://www.ihi.org [Accessed 10 May 2014].
125 Starmer AJ, Sectish TC, Simon DW, et al. Rates of medical errors and preventable adverse events among hospitalized children following implementation of a resident handoff bundle. JAMA 2013;310:2262-70.
126 Santell JP. Reconciliation failures lead to medication errors. Jt Comm J Qual Patient Saf 2006;32:225-9.
127 Kripalani S, Jackson AT, Schnipper JL, et al. Promoting effective transitions of care at hospital discharge: a review of key issues for hospitalists. J Hosp Med 2007;2:314-23.
128 Paparella S. Medication reconciliation: doing what's right for safe patient care. J Emerg Nurs 2006;32:516-20.
129 Mueller SK, Sponsler KC, Kripalani S, et al. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med 2012;172:1057-69.
130 Barber N, Rawlins M, Dean Franklin B. Reducing prescribing error: competence, control, and culture. Qual Saf Health Care 2003;12 Suppl 1:i29-32.
131 Booth R, Sturgess E, Taberner-Stokes A, et al. Zero tolerance prescribing: a strategy to reduce prescribing errors on the paediatric intensive care unit. Intensive Care Med 2012;38:1858-67.
132 Montesi G, Lechi A. Prevention of medication errors: detection and audit. Br J Clin Pharmacol 2009;67:651-5.
133 Aronson JK. Medication errors: what they are, how they happen and how to avoid them. QJM 2009;102:513-21.
134 Leape LL. Errors in medicine. Clin Chim Acta 2009;404:2-5.
135 Holdsworth M, Wittstrom K, Yeitrakis T. Current approaches to punitive action for medication errors by boards of pharmacy. Ann Pharmacother 2013;47:475-81.
136 Snijders C, van Lingen RA, Molendijk A, et al. Incidents and errors in neonatal intensive care: a review of the literature. Arch Dis Child 2007;92:F391-8.
137 Snijders C, van Lingen RA, Klip H, et al. Specialty-based, voluntary incident reporting in neonatal intensive care: description of 4846 incident report. Arch Dis Child Fetal Neonatal Ed 2009;94:F210-5.
138 Snijders C, Kollen BJ, van Lingen RA, et al. Which aspects of safety culture predict incident reporting behaviour in neonatal intensive care units? A multilevel analysis. Crit Care Med 2009;37:61-7.

139 McKibbon KA, Lokker C, Handler SM, et al. Enabling medication management through health information technology (Health IT). Evid Rep Technol Assess (Full Rep) 2011;201:1-951. Available at: http://www.ahrq.gov/research/findings/evidence-based-reports/medmgt-evidence-report.pdf [Accessed 7 May 2014].

140 Handler JA, Feied CF, Coonan K, et al. Computerized physician order entry and online decision support. Acad Emerg Med 2004;11:1135-41.

141 Vilà-de-Muga M, Colom-Ferrer L, Gonzàlez-Herrero M, et al. Factors associated with medication errors in the pediatric emergency department. Pediatr Emerg Care 2011;27:290-4.

142 Hixson R, Gandhi M, Holton F. A randomised trial to evaluate prescribing accuracy when using the Paediatric Analgesia Wheel. Arch Dis Child 2009;94:268-72.

143 Rinke ML, Moon M, Clark JS, et al. Prescribing errors in a pediatric emergency department. Pediatr Emerg Care 2008;24:1-8.

144 Larose G, Bailey B, Lebel D. Quality of orders for medication in the resuscitation room of a pediatric emergency department. Pediatr Emerg Care 2008;24:609-14.

145 Taylor BL, Selbst SM, Shah AE. Prescription writing errors in the pediatric emergency department. Pediatr Emerg Care 2005;21:822-7.

146 Sard BE, Walsh KE, Doros G, et al. Retrospective evaluation of a computerized physician order entry adaptation to prevent prescribing errors in a pediatric emergency department. Pediatrics 2008;122:782-7.

147 Porter SC, Kaushal R, Forbes PW, et al. Impact of a patient-centered technology on medication errors during pediatric emergency care. Ambul Pediatr 2008;8:329-35.

148 Kirk RC, Li-Meng Goh D, Packia J, et al. Computer calculated dose in paediatric prescribing. Drug Saf 2005;28:817-24.

149 Kazemi A, Fors UG, Tofighi S, et al. Physician order entry or nurse order entry? Comparison of two implementation strategies for a computerized order entry system aimed at reducing dosing medication errors. J Med Internet Res 2010;12:e5.

150 Johnson KB, Lehmann CU; Council on Clinical Information Technology of the American Academy of Pediatrics. Electronic prescribing in pediatrics: toward safer and more effective medication management. Pediatrics 2013;131:e1350-6.

151 Guidelines on electronic prescribing [in Dutch]. Royal Dutch Medical Association, 2013. Available at: http://knmg.artsennet.nl/Publicaties/KNMGpublicatie/136411/Richtlijn-elektronisch-voorschrijven-2013.htm [Accessed 7 May 2014].

Abbreviations

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Abbreviations

ACE	angiotensin converting enzyme
ADE	adverse drug event
ASHP	American Society of Hospital Pharmacists
BCMA	bar-code assisted medication administration
bid	twice daily
CAI	carbonic anhydrase inhibitor
CDER	Center for Drug Evaluation and Research
CDS	clinical decision support
CFM	cerebral function monitor
CI	confidence interval
CMR	Central Registration of Medication Errors
CNS	central nervous system
CPOE	computerized physician order entry
CYP	cytochrome P 450
DDI	drug-drug interaction
DMEPA	Division of Medication Error Prevention and Analysis
DSM	Diagnostic and Statistical Manual for Mental Disorders
EAHP	European Association of Hospital Pharmacists
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EEG	electroencephalography
e.g.	for example (*exempli gratia*)
EMA	European Medicines Agency
EMR	electronic medical record
EN	enteral nutrition
ePDMS	electronic Patient Data Management System
et al.	and others
etc.	etcetera
EU	European Union
excl.	excluding
FDA	Food and Drug Administration
FIP	International Pharmaceutical Federation
GFR	glomerular filtration rate
GI	gastrointestinal
HIS	health information system

ICT	information and communication technology
ICU	intensive care unit
i.e.	in other words (*id est*)
IGZ	Dutch Health Care Inspectorate
INR	International Normalized Ratio
IOM	Institute of Medicine
IQR	interquartile range
ISMP	Institute for Safe Medication Practices
IT	information technology
ITS	interrupted time-series
IU	international unit
IV	intravenous
i.v.	intravenous
KNMP	Royal Dutch Pharmaceutical Society
Lexi	Lexi-Interact™
MAR	medication administration record
ME	medication error
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Micromedex©
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MPE	medication prescription error
n	number
NA	not available
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
NHS	National Health Service
NICU	neonatal intensive care unit
NMB	neuromuscular-blocking
NOE	nurse order entry
NRLS	National Reporting and Learning System
NSAID	non-steroidal anti-inflammatory drug
NVZ	Dutch Association of Hospitals
NVZA	Dutch Association of Hospital Pharmacists
OR	odds ratio
pADE	preventable adverse drug event
pDDI	potential drug-drug interaction
PDE5	phosphodiesterase 5
PICE	Pediatric Intensive Care Evaluation
PICU	pediatric intensive care unit

PIM2	pediatric index of mortality 2 score
PN	parenteral nutrition
POE	physician order entry
PPI	proton pump inhibitor
PRISMII	pediatric risk of mortality II score
qd	once daily
qid	three times a day
QUORUM	Quality of Reporting of Metaanalyses
RAS	renin angiotensin system
ref	reference
resp.	respectively
RR	relative risk
SD	standard deviation
SGA	small for gestational age
SSRI	selective serotonin reuptake inhibitor
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T4	thyroxine
TDM	therapeutic drug monitoring
TSH	thyroid stimulating hormone
UK	United Kingdom
UPOD	Utrecht Patient Oriented Database
US	United States

Summary

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Summary

Medication errors in hospitalized patients are common, may lead to patient harm and contribute to high health care expenditure. In the Netherlands, it is estimated that about 2.5% of hospitalized patients suffer from a harmful adverse event that could have been prevented and that more than 15% of these events are related to medication. Medication errors may occur during all stages of the medication process in a hospital: during prescribing, transcribing, dispensing, preparing and administering drugs and during monitoring and evaluating drug therapy. This thesis concentrates on prescribing errors. Prescribing errors are common, may cause harm and may influence the medication process as a whole, e.g. because they may lead to confusion for the dispensing pharmacy or because they may disrupt nurse workflow when administering drugs. This thesis focuses on prescribing errors particularly in hospitalized children and neonates, because they constitute a special group among hospitalized patients. They are more vulnerable than adults as they have less internal reserves and may not be able to communicate about an adverse effect. Additionally, pediatric prescribing is complex and error-prone due to the many variable factors between and within patients that have to be taken into account (e.g. body weight and gestational age), due to calculations that are often needed, and due to paucity of pediatric pharmacotherapeutic evidence and -knowledge and suitable drug formulations. In pediatrics and neonatology, reported prescribing error rates vary from about 4 to 30 prescribing errors per 100 medication orders and from about 0.4 to 40 per 100 patients, depending on the definitions and study methods used, and the setting studied.

To prevent pediatric prescribing errors and their consequences, many measures can be taken as clinical risk management strategy, one of the most rapidly developing being information technology (IT) support. Computerized physician order entry (CPOE) systems allow physicians to enter medication orders per patient in a structured way, thereby improving safety and efficiency of the medication prescribing process. CPOE systems can include or be combined with clinical decision support (CDS) systems, meant to offer support to physicians during the prescribing of medication. In the Netherlands, electronic prescribing has become mandatory for all health care providers per January 1st 2014. However, in order to be able to use these systems for the reduction of medication prescribing error rates in a specific population such as children and neonates, the exact nature of the current errors, their causes and their consequences should be characterized. Therefore, the studies in this thesis aim to determine the nature, frequency and determinants of medication prescribing errors in pediatric patients (part I) and to study the effect of CPOE and CDS on these errors (part II).

Part I of this thesis describes nature, frequency and determinants of medication prescribing errors with and without the use of CPOE/CDS in hospitalized children admitted to the Wilhelmina Children's Hospital, Utrecht. Extra attention is paid to the pediatric and neonatal intensive care

(PICU resp. NICU) populations as these patients offer extra challenges due to their multiple and complex health problems, multi-drug use and high-risk drug treatments.

In **Chapter 2** frequency and types of prescribing errors in both handwritten and electronic medication orders for PICU patients are examined: 18% contains administrative errors, 53% omissions and 12% dosing errors. This study identifies writing by hand, alterations in existing medication orders, intermittent dosing and 'on demand use' as most important risk factors for prescribing errors. The study concludes that CPOE systems minimize administrative errors and omissions, but do not adequately prevent dosing errors if the system does not include extensive CDS. To prevent dosing errors CDS should focus on alterations in medication orders and on intermittently dosed medication, the corresponding routes of administration and dosage forms. Furthermore, free-text entry should be minimized, fast and easy alteration of infusion pump flow rates facilitated and dose checking for both under- and overdosing integrated using a suitable PICU drug formulary including off label drugs.

Additionally, in **Chapter 3**, frequency and types of potential drug-drug interactions (pDDIs) are examined in the same PICU. pDDIs frequently occur and often concern high-risk drugs: in almost 20% of patients at least one pDDI is identified during admission, on 40% of all PICU-days at least one pDDI is present and more than one third of pDDIs include high-risk medication. Most pDDIs potentially cause toxicity rather than decreased therapy efficacy and should preferably be avoided. If not avoidable, most pDDIs can be managed by monitoring and/or therapy adjustment. However, required monitoring is often not performed, unless part of routine. The study suggests that sophisticated electronic CDS, linking laboratory data to prescribing data and automatically generating corollary orders for example, may improve this and should be the focus of future PICU DDI studies.

Chapter 4 studies clinical pharmacy interventions in electronic medication orders in non-ICU pediatric wards. Approximately 1% of electronic medication orders in the children's hospital have to be intervened by the clinical pharmacy: about 80% of interventions concerns a correction and about 20% a completion. The majority of the corrections concern a wrong dose or a wrong drug formulation. The majority of the completions concern absent body weight, dosage form or strength/concentration of the prescribed drug. Free-text entry, the youngest of age and the oral dosage form and -route of administration are associated with prescribing errors. This study demonstrates that the use of a CPOE/CDS system does not fully prevent prescribing errors in a pediatric setting and provides information for improvements by incorporating tailored solutions in CPOE/CDS systems, such as minimized free-text entry, integrated dose checking and certain obligatory fields, e.g. body weight and (off-label) indications.

The lack of data evaluating the effects of more advanced CPOE/CDS on prescribing problems in pediatric and neonatal intensive care, led to the content of **part II** of this thesis.

In **Chapter 5** the effects of CPOE systems on medication prescribing errors, adverse drug events (ADEs), and mortality in inpatient pediatric care and neonatal and pediatric intensive care settings

are reviewed. Overall, CPOE systems clearly reduce medication prescribing errors, if well-designed and -implemented. However, effect on clinically relevant outcomes cannot be demonstrated, possibly due to a limited set of outcome data.
In an attempt to contribute to the evidence base, **chapter 6** describes the effects of advanced CPOE/CDS for glucose control in NICU patients of the Wilhelmina Children's Hospital, Utrecht, focusing on hypo- and hyperglycemic episodes (clinically relevant outcomes for this population) and prescribing time efficiency. This study demonstrates that after implementation of a computerized prescribing and calculating CDS tool in the NICU, a high level of accuracy for calculation and control of glucose intake is maintained. There is no difference between the incidences of hypo- and hyperglycemias per hospital day or in the fluctuation of plasma glucose concentrations of patients at risk before and after implementation. However, comparing the computerized calculating tool with manual calculation did show a significant time reduction, particularly for complex calculations. The tailored computerized prescribing and calculating CDS tool proves to preserve accuracy for calculation and control of glucose intake and to decrease time needed to prescribe.

In **chapter 7**, system requirements and the design of an electronic prescribing system for PICU and NICU are presented, including testing of the underlying model. The system requirements and design are based on system requirements abstracted from literature and from the studies described above. The developed system aims to be integrated, safe by default, and efficient and has the potential to solve several of the main problems related to the medication process in these specific patients: 1. dosing and required calculations for (cumulative) dosing, taking patient variables such as body weight, age, renal function etc. into account, 2. matching and rounding of calculated doses to available products, product strengths/concentrations and formulations, 3. preparing a formulation that is suitable for administration to a child, including required calculations, e.g. calculations for dilutions. The developed system is tested according to a tailored software verification methodology and proves to provide safe and efficient support for PICU and NICU prescribing for a number of test scenarios. Additional studies are necessary to further develop and clinically validate the system for actual use in practice.

In the general discussion (**chapter 8**) the results of the individual studies presented in this thesis are placed in a broader perspective. Specific attention is paid to defining and classifying medication prescribing errors in pediatric patients and to available scientific evidence for preventing medication errors using CPOE/CDS systems and non-technical interventions in pediatric patients. The general discussion ends with implications and recommendations for future patient care and research.

In conclusion, medication prescribing errors frequently occur in pediatrics, their causes are multi-factorial and an integrated combination of pediatric-specific CPOE/CDS systems with non-technical interventions can positively affect pediatric medication prescribing error rates. For future

patient care it is recommended that 1. CPOE/CDS is integrated and tailored to pediatric, PICU and NICU patients respectively, 2. CPOE/CDS systems are continuously maintained and updated, including user education, and 3. CPOE/CDS development becomes a shared responsibility for clinicians, nurses and pharmacists, and official bodies, policy makers and software developers involved in health care. Considering future research, most important recommendations are that 1. defining and classifying of medication errors needs ongoing attention in scientific literature, 2. CPOE/CDS development should be structured and based on medication error research at a national level with input from pediatric practice, and 3. research data on medication errors should be evaluated multidisciplinary, including IT-specialists. This is needed to anchor that experiences from pediatric practice and findings from pediatric research fuel the development of CPOE/CDS systems to ensure pediatric patient safety.

Samenvatting

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Samenvatting

Medicatiefouten komen veelvuldig voor in het ziekenhuis. Ze kunnen leiden tot schade bij de patiënt en dragen bij aan de hoge kosten van de gezondheidszorg. In Nederland ondervindt naar schatting 2,5% van de opgenomen patiënten onbedoelde vermijdbare schade, waarvan meer dan 15% gerelateerd is aan medicatiefouten. Zulke fouten kunnen plaatsvinden in elk stadium van het medicatieproces in een ziekenhuis: tijdens voorschrijven, distribueren, voor toediening gereed maken en toedienen van medicatie, en ook tijdens monitoren en evalueren van medicamenteuze therapie. Dit proefschrift is gericht op fouten in het stadium van voorschrijven van medicatie. Voorschrijffouten komen veel voor en kunnen de patiënt schade berokkenen bijvoorbeeld in geval van over- of onderdosering. Ze beïnvloeden bovendien het medicatieproces, bijvoorbeeld door verwarring en inefficiëntie te veroorzaken voor apotheekmedewerkers en verpleegkundigen, die de voorgeschreven medicatie moeten beoordelen, leveren en toedienen. Dit proefschrift richt zich specifiek op voorschrijffouten bij kinderen en neonaten omdat zij in het ziekenhuis een speciale populatie vormen. Kinderen en neonaten zijn kwetsbaarder dan volwassenen daar zij minder interne reserves hebben en zij, afhankelijk van leeftijd en ontwikkeling, niet altijd in staat zijn te communiceren over nadelige effecten, die zij ondervinden. Daar komt bij dat het voorschrijven van medicatie voor kinderen en neonaten complex en foutgevoelig is als gevolg van de vele variërende patiëntkenmerken waarmee rekening gehouden moet worden (bijvoorbeeld lichaamsgewicht en postconceptuele leeftijd). Ook de berekeningen, die vaak nodig zijn, en het gebrek aan zowel wetenschappelijk onderbouwde farmacotherapeutische kennis, als voor kinderen geschikte toedieningsvormen, spelen een rol bij deze complexiteit en foutgevoeligheid. In de kindergeneeskunde en neonatologie variëren de in de literatuur vermelde prevalenties van voorschrijffouten van ongeveer 4 tot 30 per 100 medicatieopdrachten en van 0,4 tot 40 per 100 patiënten, afhankelijk van de gebruikte definities, studie-opzet en bestudeerde setting.

Om voorschrijffouten en de gevolgen ervan te voorkomen, kunnen allerlei maatregelen genomen worden, waaronder die op het gebied van informatie technologie (IT), een zich snel ontwikkelende '*clinical risk management*' strategie. Een elektronisch voorschrijfsysteem (EVS) biedt de voorschrijver de mogelijkheid om medicatieopdrachten gestructureerd per patiënt in te voeren en bevordert daarmee de veiligheid en efficiëntie van het proces van voorschrijven. Een EVS kan gecombineerd worden met een zogenaamd '*clinical decision support*' systeem (CDSS), dat de voorschrijver inhoudelijk ondersteunt tijdens het voorschrijven van medicatie. In Nederland is het gebruik van een EVS per 1 januari 2014 verplicht gesteld voor alle zorgverleners en -instellingen. Echter, om een EVS zodanig in te kunnen zetten dat het daadwerkelijk leidt tot minder voorschrijffouten in specifieke patiëntenpopulaties als kinderen en neonaten, moet eerst vastgesteld worden wat de huidige voorschrijffouten inhouden en wat de oorzaken en gevolgen van deze fouten zijn. Om die reden is het doel van dit proefschrift om de aard van de voorschrijffouten in deze populaties te onderzoeken,

vast te stellen hoe vaak ze voorkomen en wat de determinanten ervoor zijn (deel I). Daarna wordt onderzocht wat het effect van gebruik van een EVS en CDSS op deze voorschrijffouten is (deel II).
Deel I van dit proefschrift beschrijft de soorten voorschrijffouten bij kinderen en neonaten opgenomen in het Wilhelmina Kinderziekenhuis (WKZ) te Utrecht, de frequenties ervan en de determinanten ervoor, zowel met als zonder gebruik van EVS/CDSS. Extra aandacht gaat uit naar de kinder- en neonatale intensive care units (respectievelijk PICUs en NICUs), omdat de kinderen in die setting een extra uitdaging vormen door hun meervoudige en complexe gezondheidsproblemen en door de vele geneesmiddelen die zij nodig hebben, waaronder bovendien veel risicogeneesmiddelen.
In de studie in **hoofdstuk 2** worden voorschrijffouten in zowel handgeschreven als elektronisch voorgeschreven medicatieopdrachten op de PICU onderzocht: 18% bevat een administratieve fout, 53% is farmacotherapeutisch onvolledig en 12% bevat een doseringsfout. Deze studie identificeert als meest belangrijke risicofactoren voor deze voorschrijffouten: handgeschreven medicatieopdrachten, wijzigingen in bestaande medicatieopdrachten, intermitterende doseerregimes en 'zo nodig' gebruik. De studie concludeert dat een EVS weliswaar administratieve fouten en farmacotherapeutische onvolledigheden tot een minimum beperkt, maar dat een EVS doseringsfouten niet adequaat tegengaat tenzij gecombineerd met een uitgebreid CDSS. Om doseringsfouten op de PICU te voorkomen moet een CDSS zich volgens deze studie richten op het ondersteunen van wijzigingen in bestaande medicatieopdrachten en van intermitterende doseerregimes, bijbehorende toedieningsroutes en toedieningsvormen. Bovendien moet het invoeren van vrije tekst tot een minimum beperkt kunnen worden, moet het mogelijk zijn om makkelijk en snel infuusstanden aan te passen en moet geautomatiseerde doseringscontrole ter preventie van zowel over- als onderdosering geïntegreerd worden, gebruik makend van een voor de PICU geschikt geneesmiddelformularium inclusief adviezen voor *off label* en *unlicensed* geneesmiddelgebruik.
Aanvullend worden in **hoofdstuk 3** interacties tussen geneesmiddelen op de PICU onderzocht. Het blijkt dat geneesmiddelinteracties veel voorkomen en vaak risicogeneesmiddelen betreffen: bij bijna 20% van de patiënten en op 40% van alle ligdagen is ten minste één geneesmiddelinteractie vastgesteld, waarbij bij meer dan een derde van de interacties een risicogeneesmiddel een rol speelt. De vastgestelde geneesmiddelinteracties kunnen over het algemeen eerder tot toxiciteit dan tot verminderd therapeutisch effect leiden en moeten bij voorkeur worden vermeden. Als een geneesmiddelcombinatie niettemin wordt voorgeschreven, dan zijn nadelige gevolgen ervan meestal te voorkomen door een vorm van monitoring toe te passen en/of door de farmacotherapie, bijvoorbeeld de dosering, aan te passen. Echter, deze studie toont aan dat de benodigde monitoring vaak niet plaatsvindt, tenzij deze toevallig onderdeel is van routinematige monitoring op de PICU. De studie suggereert dat een geavanceerd CDSS, dat laboratoriumuitslagen en voorschrijfgegevens combineert en dat bijvoorbeeld automatisch laboratoriumaanvragen genereert, de inzet van benodigde monitoring bij geneesmiddelinteracties kan verbeteren en de focus moet zijn voor vervolgonderzoek met betrekking tot geneesmiddelinteracties op de PICU.

Hoofdstuk 4 beschrijft soorten en aantallen interventies uitgevoerd door WKZ apotheekmedewerkers richting de WKZ voorschrijver (met uitzondering van de PICU en NICU) met de bedoeling om een elektronische medicatieopdracht administratief compleet te maken en/of farmacotherapeutisch dan wel farmaceutisch te verbeteren. De klinische farmacie intervenieert in ongeveer 1% van de elektronische medicatieopdrachten in het kinderziekenhuis: ongeveer 80% van de interventies betreft een farmacotherapeutische/farmaceutische correctie en ongeveer 20% een administratieve verbetering. Foutieve doseringen of formuleringen vormen het merendeel van de farmacotherapeutische/farmaceutische correcties; het ontbreken van lichaamsgewicht, toedieningsvorm en/of sterkte/concentratie vormt het merendeel van de administratieve interventies. Het invoeren van vrije tekst in het EVS, de jongste leeftijdscategorieën en orale toedieningsroute en -vormen zijn geassocieerd met het optreden van deze voorschrijffouten. Deze studie toont aan dat het gebruik van een EVS en CDSS voorschrijffouten niet geheel voorkomt in een pediatrische setting en pleit ter verbetering van het voorschrijfsysteem voor op maat gemaakte, passende oplossingen in de elektronische systemen, zoals minimalisatie van vrije tekst invoer, geïntegreerde doseringsbewaking en bepaalde verplichte velden voor bijvoorbeeld lichaamsgewicht en (*off label*) indicaties.

Het gebrek aan beschikbare data ter evaluatie van het effect van meer geavanceerde, op de pediatrie toegesneden elektronische systemen op voorschrijfproblemen in de PICU en NICU populaties, heeft geleid tot de inhoud van **deel II** van dit proefschrift.

Hoofdstuk 5 is een systematische literatuurreview, inclusief meta-analyse, van de effecten van EVS op voorschrijffouten, bijwerkingen en mortaliteit bij kinderen die opgenomen zijn op kinderafdelingen, PICUs en NICUs. Over het geheel genomen reduceert gebruik van een EVS het aantal voorschrijffouten, mits het systeem zorgvuldig ontworpen en geïmplementeerd wordt. Effect op klinisch relevante uitkomsten is echter niet aangetoond, mogelijk als gevolg van een beperkte hoeveelheid beschikbare data op dat gebied.

In een poging deze data aan te vullen, gaat **hoofdstuk 6** in op het effect van een geavanceerd EVS/CDSS ter regulatie van de glucose intake bij NICU patiënten in het WKZ op hypo- en hyperglykemie (klinisch relevante uitkomsten voor deze populatie) enerzijds, en de tijd nodig voor het voorschrijven anderzijds. Deze studie demonstreert dat na implementatie van een applicatie, die voor een specifiek voorschrijfproces op de NICU elektronisch voorschrijven combineert met automatische (cumulatieve) berekeningen, een hoge mate van juistheid van berekeningen en een adequate glucoseregulatie behouden blijft. Zowel de incidenties van hypo- en hyperglykemieën per ligdag, als de mate van fluctuatie in plasma glucose concentraties, verschillen niet significant voor en na implementatie van de applicatie. Vergeleken met handmatige berekeningen geeft het geautomatiseerde systeem een significante afname van de tijd nodig voor voorschrijven, met name bij meer complexe berekeningen. Deze voor de NICU op maat gemaakte applicatie blijkt dus correcte berekeningen en adequate glucoseregulatie te genereren en de voorschrijftijd te verminderen.

Hoofdstuk 7 presenteert een overzicht van systeem specificaties en een systeem ontwerp voor een EVS voor PICU en NICU, evenals testen van het onderliggende model. De systeem specificaties en het ontwerp zijn gebaseerd op literatuurstudies en de hierboven beschreven onderzoeken. Het ontwikkelde systeem heeft tot doel geïntegreerd, veilig en efficiënt voorschrijven te garanderen en heeft de potentie om een aantal kernproblemen van het PICU en NICU medicatieproces op te lossen: 1. doseren met in acht name van patiëntvariabelen als lichaamsgewicht, leeftijd, nierfunctie etc. en de daarbij behorende berekeningen voor (cumulatieve) dosering, 2. afronden van de benodigde dosering en koppelen aan een bestaand, geschikt product, met geschikte sterkte/concentratie en toedieningsvorm, 3. bereiden/voor toediening gereed maken, inclusief de benodigde berekeningen, om een geneesmiddel geschikt te maken voor toediening bij een kind. Het ontworpen systeem is getest met behulp van een aangepaste bestaande software verificatie methodologie, en blijkt veilig en efficiënt voorschrijven voor PICU en NICU patiënten mogelijk te maken voor een aantal testscenario's. Additionele studies zijn nodig om het systeem verder te ontwikkelen en klinisch te valideren om gebruik in de dagelijkse praktijk mogelijk te maken.

In het laatste hoofdstuk (**hoofdstuk 8**) worden de resultaten van bovengenoemde studies in een breder perspectief geplaatst. Specifieke aandacht wordt besteed aan het definiëren en classificeren van voorschrijffouten in de pediatrie en aan het beschikbare wetenschappelijke bewijs voor het voorkómen van medicatiefouten in de pediatrie met behulp van een EVS/CDSS enerzijds en met behulp van niet-technische interventies anderzijds. De discussie eindigt met een overzicht van implicaties en aanbevelingen voor toekomstige patiëntenzorg en wetenschappelijk onderzoek.

Concluderend komen voorschrijffouten frequent voor bij opgenomen kinderen en neonaten. Een combinatie van EVS/CDSS en niet-technische interventies kan het aantal voorschrijffouten positief beïnvloeden. Voor de toekomstige patiëntenzorg wordt aanbevolen om een geïntegreerd EVS/CDSS te ontwikkelen dat 1. op maat gemaakt is voor respectievelijk de algemene pediatrie, PICUs en NICUs, 2. continu onderhouden en ge-update wordt, inclusief gebruikersinstructies, en 3. onder de verantwoordelijkheid valt van zowel artsen, verpleegkundigen en apothekers, als officiële instanties, beleidsmakers en software ontwikkelaars in de zorg. Met betrekking tot toekomstig onderzoek op dit gebied wordt aanbevolen om 1. aandacht te blijven besteden aan het definiëren en classificeren van voorschrijffouten in de pediatrie, 2. het onderzoek naar medicatiefouten in de pediatrie op een nationaal niveau te structureren met input vanuit de klinische praktijk en EVS/CDSS ontwikkeling daarop te baseren, en 3. de wetenschappelijke data multidisciplinair te evalueren, inclusief IT-specialisten. Dit is nodig om te kunnen borgen dat de ontwikkeling van EVS/CDSS voortvloeit uit praktijkervaringen enerzijds en bevindingen uit wetenschappelijk onderzoek anderzijds, met als doel medicatieveiligheid voor kinderen en neonaten in het ziekenhuis te garanderen.

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List of publications related to this thesis

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List of publications related to this thesis

Impact of computerized physician order entry (CPOE) on PICU prescribing errors
B. Maat, C.W. Bollen, A.J. van Vught, A.C.G. Egberts and C.M.A. Rademaker
Intensive Care Med 2014;40(3):458-9.

Clinical pharmacy interventions in paediatric electronic prescriptions
B. Maat, YS. Au, C.W. Bollen, A.J. van Vught, A.C.G. Egberts and C.M.A. Rademaker
Arch Dis Child 2013;98(3):222-7.

The effect of a computerized prescribing and calculating system on hypo- and hyperglycemias and on prescribing time efficiency in neonatal intensive care patients
B. Maat, C.M.A. Rademaker, M.I. Oostveen, T.G. Krediet, A.C.G. Egberts and C.W. Bollen
JPEN J Parenter Enteral Nutr 2013;37(1):85-91.

The effect of computerized physician order entry on medication prescription errors and clinical outcome in pediatric and intensive care: a systematic review
F. van Rosse, B. Maat, C.M.A. Rademaker, A.J. van Vught, A.C.G. Egberts and C.W. Bollen
Pediatrics 2009;123(4):1184-90.

Dankwoord

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Dankwoord

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Curriculum vitae

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Curriculum vitae

Barbara Maat was born on April 26th 1980 in Gouda, The Netherlands. She graduated at the 'Stedelijk Gymnasium' in Leiden in 1998 and subsequently started her studies Pharmaceutical Sciences at Utrecht University. During her studies she completed a research project at the Faculty of Pharmacy of Sydney University, Australia in 2004/2005 (supervisors prof.dr. J. van der Gugten and associate professor dr. I. Ramzan) and performed several projects at the Health Access Network in Ghana in 2007 (supervisors P. J. N. Lamberts and C. Allotey). During her studies she was a member of the sorority 'Utrechtse Vrouwelijke Studenten Vereeniging/Nieuwe Vereniging van Vrouwelijke Studenten te Utrecht' and participated in the sorority board a full year as treasurer in 2002/2003. She obtained her Master's degree in 2007.

In September 2007 she started her professional career at the Department of Clinical Pharmacy of the University Medical Center Utrecht, combining her training to become a clinical pharmacist (supervisor Dr. C. M. A. Rademaker) with a PhD research project, performed in close collaboration with the department of Pediatric Intensive Care of the University Medical Center Utrecht. During her training to become a clinical pharmacist she was a member of the association of clinical pharmacists in training ('VAZA') and participated in the association's board as president in 2009 and 2010. She received her degree as clinical pharmacist in 2012.

As of September 2014 she holds a position as clinical pharmacist at the Department of Clinical Pharmacy of the Elisabeth-TweeSteden Hospital in Tilburg.

Barbara is engaged to Diederik. They are proud parents of two daughters, Stephanie (2011) and Frederique (2013).