Medication safety in pediatric care
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Chapter 10

Summary and general discussion
SUMMARY

Medication safety in pediatric hospital care is not yet fully understood. With the research presented in this thesis, we aimed to contribute to the knowledge, ultimately to improve medication safety and prevent medication-related harm in pediatric patients in hospital. Specific objectives were:

1. to gain knowledge on the prevalence, nature and impact of medication errors, and factors that contribute to medication errors;
2. to attribute to the existing evidence on interventions to improve medication safety;
3. to explore measurement tools to monitor medication safety.

In chapter 2, we describe a cross-sectional study that explored the prevalence and type of medication errors (MEs) and the severity of patient harm due to MEs in hospitalized children from birth to 18 years. We identified MEs by reviewing patients’ clinical records, making direct observations, monitoring pharmacy logs and reviewing voluntary incident reports. Subsequently, the MEs were classified according to type of error, type of medication and stage of the medication process. Pediatricians rated the severity of the observed harm. We collected data from 426 hospitalized children during 3 months. A total of 322 MEs were identified, of which 39 caused patient harm. Harmful events were mainly due to wrong time of administration (41%). Pediatricians rated the observed harm as minor in 77% and significant in 23% of the incidents. None of the harmful MEs resulted in permanent harm or was considered life-threatening or fatal. Patients admitted for a surgical procedure were at higher risk for a harmful event compared to patients admitted for non-surgical reasons (adjusted OR 2.79, 95% CI 1.35-5.80). Non-opioid analgesics and anti-emetic drugs accounted for 67% of the harmful MEs. Harmful MEs occurred most frequently during medication prescription (28%) and administration (62%). We concluded that MEs increase the burden for hospitalized children, especially for surgical patients. Although the harm was considered minor in most cases, it still caused discomfort for the patients, and the high prevalence is a source of concern.

In chapter 3 we present a qualitative study that contributes to a further understanding of the contributory factors that may lead to medication errors as experienced by the key professionals: doctors, nurses and pharmacists. We collected our data from focus group discussions. The transcripts of these discussions were coded by three researchers, who read the transcripts independently, keeping the research question in mind. After completing the initial coding, the researchers sorted the resulting codes into similar contextual categories. Finally, the categories were developed further into interpretative main themes. Four main themes emerged: “lack of coherent teamwork”, “suboptimal work process”, “inability to work safely” and “culture”. Culture appeared to be a central element, linking the three themes. The participants concluded that particularly
organizational issues contribute to unsafe patient care. They expressed feelings of frustration, confusion and uncertainty, as well as resignation. Our results highlight the need for interventions on the organizational level, with a focus on interdisciplinary teamwork and re-design of the medication process. An essential aspect is to create an organizational culture that gives priority to medication safety and is supported by both healthcare management and healthcare professionals.

In chapter 4 we describe an international modified Delphi study that aimed to generate a list of high-alert medications for a pediatric inpatient population from birth to 18 years. Based on the literature, a list of potential high-alert medications and medication classes was compiled and given to experts to rate. They were also asked to add other medications or medication classes to the list that they considered as high-alert. We validated the results with reports on medication incidents in children based on national data. The rating panel consisted of 34 experts from 13 countries. In total, 14 medications and 4 medication classes were included with the predefined level of consensus of 75%. The high-alert medications were: amiodarone, digoxin, dopamine, epinephrine, fentanyl, gentamycin, heparine, insulin, morphine, norepinephrine, phenytoin, potassium, propofol and tacrolimus. The high-alert medication classes included in the final list were: chemotherapeutic drugs, immunosuppressive medications, lipid/total parenteral nutrition and opioids.

In chapter 5 we present a systematic review of the existing evidence to determine the effectiveness of interventions to reduce MEs in hospitalized children. We searched the following databases: CENTRAL, Cinahl, Dissertations and Theses Database, Embase, EPOC Group Specialized Register, Medline, Nursing & Allied Health, PsycInfo and Web of Science. Furthermore, we searched the Cochrane Database of Systematic Reviews and the DARE, the grey literature, as well as trial registries for ongoing studies. We also hand searched reference lists of all included studies and relevant systematic reviews. We included randomized controlled trials, controlled before-after studies and interrupted time series investigating interventions applied to hospitalized children (≤ 18 years) to improve medication safety. The outcome measures included MEs, (potential) patient harm, resource utilization and unintended consequences of the interventions. Two reviewers independently selected studies and assessed study quality using the EPOC checklist. The risk of bias was estimated using the GRADE approach. The selection process revealed seven studies describing five different interventions: clinical pharmacist (two studies), computerized physician order entry (two studies), barcode medication administration, a structured prescribing form, and a check & control checklist in combination with feedback. Most studies resulted in a reduction in MEs, but the benefits for the patients in terms of less harm were not conclusive. Clinical and methodological heterogeneity between the studies precluded meta-analyses.
Although all hospitalized pediatric patients are vulnerable, children admitted to the Pediatric Intensive Care Unit (PICU) are even more at risk to be exposed to harm. In chapter 6 we describe the results of an interrupted time series study that examined the effectiveness of a multi-faceted intervention by a clinical pharmacist, on MEs in critically ill children. We expanded the multidisciplinary team with a clinical pharmacist, who was available on the PICU for approximately 3 hours on workdays. The clinical pharmacist performed structured medication reviews and provided feedback to the prescribing pediatrician-intensivists and nurses during the ward rounds on the same day. Primary endpoint was the prevalence of MEs per 100 prescriptions. We explored the patients’ clinical records and the incident reporting system for MEs. If a ME was suspected, a pediatrician-intensivist and a clinical pharmacist determined causality and preventability. They classified the ME as harmful according to the National Coordinating Council for Medication Error Reporting and Prevention categories. We included 254 patients in the pre-intervention and 230 patients in the post-intervention period. We identified 153 MEs in the pre-intervention period, corresponding with 2.27 per 100 prescriptions, and 90 MEs in the post-intervention period, corresponding with 1.71 per 100 prescriptions. ARIMA analyses revealed a significant change in slopes between the pre-intervention and post-intervention period (β -0.21, 95% CI -0.30 to -0.04, p = 0.02). We did not observe a significant decrease immediately after the start of the intervention (β -0.61, 95% CI -1.31 to 0.08, p = 0.07). We concluded that the implementation of structured medication review, followed by feedback by a clinical pharmacist as part of the multidisciplinary team, resulted in a significant reduction of MEs in a tertiary PICU.

To monitor the medication safety and patient harm, we need valid and reliable measurement instruments. It is suggested that a trigger tool may be an effective and time-saving strategy to measure MEs, but its measurement performance is unclear. Therefore, we studied the diagnostic accuracy of an existing pediatric medication-focused trigger tool in detecting harmful MEs. This study is described in chapter 7. Firstly, we established a multi-faceted method as a reference comparison. Secondly, we compared the pediatric medication-focused trigger tool with the multi-faceted method in a new cohort of patients. All patients admitted in February and March 2013 were screened using the trigger tool and the multi-faceted method to obtain full verification. Data collection was performed in separate teams to guarantee blinding of the test results. Review of the patients’ clinical records and the voluntary incident reports were most effective in detecting harmful MEs, so this approach was chosen as reference comparison. In the second part of the study 369 patients were included. The multi-faceted method identified 33 harmful MEs. In contrast, the trigger tool did not identify any harm. When the two symptoms “pain” and “nausea/vomiting” were added to the trigger tool, 19 harmful MEs were identified. This extended trigger tool
resulted in a sensitivity of 21.2 and a positive predictive value of 36.8. The original pediatric medication-focused trigger tool yielded only false positive scores and left unsafe situations undiscovered. We concluded that a multi-faceted method remain the preferred method to detect harmful MEs.

The COMFORT scale is a well-known measurement tool to assess distress, sedation and pain in nonverbal pediatric patients. A number of studies describe the COMFORT scale in children of different ages, with different health conditions and in different clinical contexts, but no formal assessment of the methodological quality has been undertaken. Therefore, we performed a systematic review to study the clinimetric properties of the original COMFORT scale or any of the modified versions: chapter 8. We searched CENTRAL, Cinahl, Embase, Medline, PsycInfo and Web of Science. The selection, data extraction and quality assessment were performed independently by 2 reviewers. Quality of the included studies was appraised using the COSMIN checklist. We found 30 studies that met the inclusion criteria. Most participants were ventilated children up to 4 years without neurological disorders. The results on internal consistency and interrater reliability showed values of >0.70 in most studies, indicating an adequate reliability. Construct validity resulted in correlations between 0.68 and 0.84 for distress, between 0.42 and 0.94 for sedation and between 0.31 and 0.96 for pain. The responsiveness of the (modified) COMFORT scale seems to be adequate. The quality of the included studies ranged from poor to excellent. The COMFORT scale shows overall an adequate reliability in providing information on distress, sedation and pain. Construct validity varies from good to excellent for distress, from moderate to excellent for sedation, and from poor to excellent for pain. The included studies were clinically and methodologically heterogeneous, hampering firm conclusions.

In chapter 9 we describe a longitudinal study in which we investigated whether the safety culture changed during a five years period of active safety management in our pediatric hospital. During the last decade, awareness has grown about the added value of safety culture to increase the safety for patients, but evidence on the effectiveness of interventions to improve safety culture is limited and not conclusive. The aim of this five-year study was twofold: to determine the effect of multi-faceted safety interventions on the patient safety culture and to establish priorities for future safety activities. Between 2009 and 2014 a two stages safety program was implemented. In the first-stage intervention, a ward-based patient safety program was initiated that focused on (a) incident reporting, (b) blame-free response to error and (c) collaboration in multidisciplinary safety teams. In the second-stage intervention, patient safety became a top strategic priority when the hospital started the Joint Commission International accreditation process. During this period we studied the patient safety culture by means of the Hospital Survey on Patient Safety Culture (HSoPSC). All nurses, pediatricians and
allied healthcare professionals, employed on four non-Intensive Care Units (non-ICUs) and two Intensive Care Units (ICUs), were invited to participate. Differences in mean scores between the time points were analyzed using regression techniques and multi-level modeling was performed to account for clustering of respondents’ scores within wards. We collected a total of 811 questionnaires in 2009, 2011 and 2013. On the non-ICUs 6 of the 11 dimensions of the HSoPSC improved. The greatest improvement was found after the first intervention period. The accreditation process in the second period did not lead to statistical significant positive changes in the safety culture. The two ICUs showed smaller changes in the HSoPSC scores, probably due their longer history in safety management compared to the non-ICU wards. The dimensions “teamwork across hospital units”, “handovers and transitions” and “hospital management support for safety” were considered areas for future improvement. We concluded that multi-faceted safety interventions, including ward-based safety teams, an incident reporting system and a blame free environment, are associated with improvements on most patient safety dimensions.

**GENERAL DISCUSSION**

The field of medication safety has progressed in recent years. Nonetheless, the work must continue to increase medication safety in general and for children specifically.

**Special consideration for pediatric patients**

Medication safety differs in several ways for children compared with adults. It is important to understand these differences as they may affect the recommended safety interventions and the way in which healthcare is provided [1]. Child-specific characteristics play an important role: age-based variability and necessary adaptation to physiological development and growth [2-4]. These specific characteristics hamper standardization in all stages of the medication process, while standardization is believed to decrease the risk of error and patient harm [5,6]. In addition, the absence of medications in formulations and dosages appropriate for children makes it necessary to manipulate the medications before administration, which increases the complexity and the risk of error and patient harm. Finally, children cannot communicate (side) effects and are dependent on the observations of their caregivers. The latter is even more important as many medications are described off-label and the awareness on off-label prescribing in children is low [7-9]. Although there may be other factors that contribute to medication safety problems, such as equipment failures, workload, or confusing medication packaging and names, child-specific characteristics are believed to contribute up to half of the pediatric patient safety problems [4].
All studies presented in this thesis are executed in a pediatric academic hospital. The constant need of dosing adjustments might explain the high prevalence of MEs related to dosages (chapter 2 and 6). Specific characteristics of pediatric care, like feeding and sleeping schedules, might explain the deviation in the time the medications are administered (chapter 2). Limited knowledge on medication specific in pediatric care was mentioned as a contributory factor to medication safety (chapter 3). Still, we did not identified specific pediatric medication safety issues as much as we expected beforehand. The participants in our studies were pediatricians and pediatric nurses, and all were familiar with pediatric daily practice; dealing with the specific pediatric characteristics of the medication process is “business as usual”. The interventions described in our systematic review were performed on pediatric wards, but none of them addressed interventions targeting the specific pediatric situations described above (chapter 5).

Evidence-based interventions that increase medication safety must include specific pediatric characteristics. For example, technology such as CPOE and bar-code technology has proven to improve medication safety, but pediatric safety features incorporated in the CPOE are scarce. We strongly advise CPOE systems with decision support based on the best available pediatric pharmacological knowledge. Also specific features such as integrated dose checking and obligatory fields (weight, age) must be considered. Nurses must be supported in the administering process with bar-code technology, again adapted to the specific pediatric context. Calculation aids and alerts to prevent dosing errors are essential. Clinical pharmacists appear to be a key role professional in medication safety. We plead to acknowledge their clinical role, and also underpin the necessity for a pediatric trained clinical pharmacist. This specialized pediatric clinical pharmacist might play an important role in the prevention of MEs by clinical activities, but is also essential in spreading available knowledge on medication efficacy and safety for children.

**Interdisciplinary teamwork**

Interdisciplinary teamwork is considered a pivotal condition for patient safety [10-12]. Recent evidence suggests that improvement in interdisciplinary teamwork results in a significant decrease in complications and mortality [13]. Effective interdisciplinary teamwork entails communication, coordination and cooperation amongst all disciplines and departments [10,12]. Communication includes sharing information that is relevant, accurate and timely. Coordination is related to logistics such as daily schedules and routines, and might be influenced by the geographical location of the various departments. Cooperation includes the acknowledgement of the expertise, tasks and responsibilities of other healthcare professionals, and a team orientation characterized
by “mutual trust, supportive behaviour and shared goals” [12]. Those elements for interdisciplinary teamwork are highly relevant for the medication process with doctors, nurses and pharmacists as the key role players. Unfortunately, healthcare professionals tend to disregard the capabilities of those not part of their own profession. Medication advice-seeking and information sharing across doctors, nurses and pharmacists are limited and they tend to work alongside one another rather than with each other [14-17].

The lack of interdisciplinary teamwork was identified as a main theme in our qualitative study; the healthcare professionals appeared to work mainly within their own discipline and on their own ward (chapter 3). Also, the survey on patient safety culture shows low scores on teamwork between hospital units (chapter 9). Moving forward towards improvements, we found two high quality studies that show the valuable contribution of a clinical pharmacist when part of an interdisciplinary team (chapter 5). These results were confirmed in our research at the PICU, where we expanded the multidisciplinary team with a clinical pharmacist, resulting in a significant reduction of MEs (chapter 6).

Interdisciplinary teamwork must be encouraged, organized and facilitated in order to increase medication safety. In the medication safety process, the members of the interprofessional team are the doctor, the nurse and the pharmacist. Those professionals must meet not only to discuss the medication regimes of individual patients, but also to combine expertise in the development of protocols and policies. The working processes of the different professionals and departments must be synchronized to prevent unsafe and inefficient situations. Interprofessional education and training must be considered as this might increase mutual understanding and support. The challenge is to change a team of experts into an expert team.

Patient safety culture
Medication safety does not occur in isolation, but is affected by the context [18]. Nowadays, it is generally believed that an important element of this context is the patient safety culture. Patient safety culture can be defined as “the values shared among organization members about what is important, their beliefs about how things operate in the organization, and the interaction of these with work unit and organizational structures and systems, which together produce behavioral norms in the organization that promote safety” [19]. The idea is that a more positive culture is related to better clinical performance. Although the evidence for this relationship is limited [20], several studies show that hospitals that score higher on patient safety culture surveys tend to have fewer reported adverse events [19,21,22]. These results have initiated interventions to improve a safety culture [23-25]. The best evidence seems to include multi-faceted interventions that include team training, improvement of team communication and executive safety walk rounds [23,25].
Several healthcare organizations take an example on the so called High Reliability Organizations (HROs) [26,27]. HROs are complex and dynamic organizations with a constant risk of catastrophic failure, e.g. aviation and nuclear power plants. For those organizations the prevention of errors is top priority. Therefore, strong leadership and robust process improvement are emphasized. But the most appealing feature of HROs is their safety culture. The HRO safety culture is reflected in five shared characteristics: preoccupation with failure, reluctance to simplification, sensitivity to operations, commitment to resilience and deferent to expertise. In practice this means that every employee is responsible for safety, incident reporting is rewarded, errors are thoroughly analyzed and used for shared learning, education and team training are daily practice, and the additional value of all employees is recognized and acknowledged [27,28]. Although healthcare organizations differ from other industries, they can be considered HRO and its principles might help hospitals to develop and sustain a comprehensive approach to patient safety [26,27,29].

Patient safety culture emerged as one of the main themes in relation to the contributory factors leading to MEs (chapter 3). This research shows that a shared attitude toward medication safety, the reaction towards unsafe behavior and the ability to learn from errors need further improvement. These results are complementary to the survey on patient safety culture (chapter 9).

A positive patient safety culture must be aimed for in all healthcare organizations, as they are obliged to guarantee their patients safe. Therefore, strong leaders are essential. They must be unanimous and clear on the safety principles and desirable behavior, and act accordingly. A good start is to discussed safety issues and behavior openly, e.g. during executive safety rounds.

Future perspectives
The aforementioned child-specific characteristics show the need for effective and safe medications for children. Still, it is estimated that over half of the children receives an unlicensed or off label drug prescription during hospitalization [8,9]. To ensure that children are treated with drugs that are fully tested, ongoing research is needed to determine the most appropriate formulations, dose, frequency, and routes of administration in children of different ages. Children are viewed as a vulnerable population that historically is underserved in research. An important reason is the ethical principle of “scientific necessity”: children should only be enrolled in clinical trials to obtain knowledge that attributes to the health and welfare of children [30]. As many medications work differently in children, clinical trials in pediatric populations are scientific necessary and should therefore be executed. Recent developments in the legislation (Better Pharmaceuticals for Children Act 2002 and Regulation on Medicinal Products for Paediatric Use 2007) and the start of research networks (European Network
of Paediatric Research and the Medicines for Children Research Network) are promising. The costs of research for the relatively small pediatric population may not hamper research programs as it is a moral duty to guarantee children are treated with drugs that are effective and safe. Furthermore, we must be prepared for the increased number of children with complex care needs, that often includes medication dependency [31]. In addition, patients spend less time in hospital and care is provided in home settings more frequently [32]. Consequently, the research agenda within the field of medication safety changes: medication reconciliation, family education, interventions to improve compliance and medication safety at home will become more and more important.

Given the limited high quality evidence on interventions to improve medication safety in pediatric care, more methodologically sound research is obviously needed. Researchers should use the most robust design possible, e.g. cluster-randomized trials, stepped wedge trial designs, controlled before-after studies or interrupted time series [33]. There has been debate on the outcome measures, but nowadays it is recommended that evaluation of complex interventions include both process and patient relevant outcomes [34]. Future studies in the field of medication safety should include MEs, potentially harmful MEs and patient harm as main outcome measures. Efforts must be made by international safety institutes to ensure an uniform nomenclature to be used in medication safety research. A multi-faceted method is the preferred method to detect MEs, but is time-consuming [35,36]. New possibilities might arise from patient records, that become more and more electronically. By combining patient information it might become feasible to detect MEs and related harm in a more effective and efficient way. Reporting systems need further development from simple registrations to systems that support the healthcare professionals in decision making and error prevention. Future research is needed to discover the possibilities of electronically patient records in the identification of (harmful) MEs, and the effectiveness of real-time correction measures.

And last but not least, we must pay attention to the implementation of the available evidence in clinical practice [37]. It must be recognized that the generalizability of improvement interventions to different settings is low [38]. Therefore, hospitals should analyze the specific context, choose implementation strategies tailored to this specific context and pay attention to barriers and facilitators to change [39]. Evaluation in a pilot seems sensible to prevent an organization to start with interventions that might not work well or introduce new safety problems [40]. As the key role players in the medication process are doctors, nurses and pharmacists, these disciplines should participate in implementation projects. Clearly, healthcare professionals must become familiar with implementation knowledge and competencies in order to integrate evidence and clinical practice successfully, ultimately to improve medication safety for children [41,42].
CONCLUSION

Knowledge of medication safety for children has grown in recent years; the epidemiology of medication errors and contributory factors are better understood. Nonetheless, the work must continue as evidence-based interventions are still limited. Information technology and interdisciplinary teamwork look promising and these interventions should be implemented, taking into account the specific pediatric characteristics. Special attention should be paid to the safety culture within an organization. Comprehensive and sustained medication safety for children can only be achieved in an organization with shared values among all disciplines, and processes with a focus on patient safety.
REFERENCES


