Medication safety in pediatric care
Maaskant, Jolanda

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Chapter 6

Medication review and feedback by a clinical pharmacist decrease medication errors at the PICU: an interrupted time series analysis

Jolanda Maaskant
Marieke Tio
Reinier van Hest
Hester Vermeulen
Vincent Geukers

Submitted.
ABSTRACT

Introduction
Medication errors (MEs) are one of the most frequently occurring types of adverse events in hospitalized patients and potentially more harmful in children than in adults. In order to increase the medication safety, we studied the effect of structured medication review, followed by feedback performed by a clinical pharmacist as part of the multidisciplinary team, on MEs in critically ill children admitted at a tertiary PICU.

Methods
We performed an Interrupted Time Series with six pre-intervention and six post-intervention data collection points. The multidisciplinary team was expanded 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 pediatrician-intensivists and nurses during the ward rounds. We measured the prevalence of MEs per 100 prescriptions by exploring the clinical records of the patients and the incident reporting system for MEs. If a ME was suspected, a pediatrician-intensivist and a clinical pharmacist determined causality and preventability.

Results
In the pre-intervention period we included 254 patients and identified 2.27 MEs per 100 prescriptions. In the post-intervention period we included 230 patients and identified 1.71 MEs 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, \( p = 0.07 \)). Harmful MEs decreased from 0.34 to 0.11 per 100 prescriptions.

Conclusion
Structured medication review, followed by feedback by a clinical pharmacist as part of the multidisciplinary team, resulted in a significant decrease of the MEs at a tertiary PICU.
INTRODUCTION

Medication errors (MEs) are one of the most frequently occurring types of adverse events in hospitalized patients, and 3% to 10% of MEs result in patient harm [1-3]. MEs are also associated with additional costs up to $8,500 per patient, as estimated for hospitals in the United States of America [4]. The reported prevalence of MEs varies from 5 to 24 per 100 prescriptions in pediatric patients [5-8]. A previous study has suggested that MEs are potentially more harmful in children than in adults [6]. Children admitted to the Pediatric Intensive Care Unit (PICU) are especially vulnerable to harmful MEs due to their dependence on multiple and life supporting medications [9].

Due to growing awareness of the complexity of the medication process and medication safety issues, it has been suggested that active involvement of a clinical pharmacist on pediatric wards might be of additional value. Three systematic reviews reported a reduction of MEs after a pharmacist was employed on clinical wards, but the included studies did not provide a clear description of the interventions by the clinical pharmacist and were generally of poor quality [10-12]. A recent published Cochrane systematic review [13] included only one high quality, controlled before-after study that showed a significant reduction of serious MEs after the implementation of a multifaceted intervention by a full time clinical pharmacist on a PICU [14].

Due to the scarce existing evidence, we decided to study the effect of a structured review of prescribed medication, followed by feedback to the prescribing pediatrician-intensivist and bedside nurse, by a clinical pharmacist as part of the multidisciplinary team. We formulated the following research questions:

- Do MEs and medication-related patient harm decrease after the implementation of a structured medication review, followed by feedback from a clinical pharmacist as part of a multidisciplinary team?
- What types of recommendations are made by the clinical pharmacist, and to what extent are they accepted by the medical and nursing staff?

METHODS

The study design was based on the recommendations for Interrupted Time Series Designs [15]. The Institutional Review Board of the Academic Medical Center in Amsterdam ascertained that medical ethical approval was not required according to Dutch Medical Ethics Law. In accordance with the study protocol, all data were analyzed and reported anonymously.
Setting and study population
We performed our study in the tertiary PICU of Emma Children’s Hospital/Academic Medical Center, Amsterdam, the Netherlands. This mixed PICU has an operational capacity of 12 beds and provides care to approximately 600 intensive care patients and 300 additional high care patients annually, ranging in age from newborns to 18 years.

As a daily routine, medication is prescribed or altered during the morning round, using a stand-alone Patient Data Management System (PDMS). This PDMS is a generic ordering system and is not equipped with a medication safety monitoring or decision support system. At the start of every nursing shift an electronically generated sign-off medication list is printed for all patients separately, and the prints are kept bedside. Electronic alterations can be made to the medication list by the attending resident, fellow or pediatrician-intensivist. If extensive alterations have been made, a new sign-off list is printed. Minor changes to the electronic list are hand copied to a separate bedside log, without printing a new sign-off list. After a mandatory double-check, the prescribed medications are administered to the patient, and both nurses sign off the medications on the list. Continuous intravenous medications are prepared into ready-to-administer doses by a decentralized pharmacy adjacent to the PICU. Additionally, limited stocks of commonly used intermittent medications are kept on the ward for immediate preparation by the bedside nurses. The decentralized pharmacy prepares the continuous medication during daytime for the next 24 hours, seven days a week. During evening and night hours all medication preparations are performed by the nurses. Guidelines of all medications are available on the ward in a hospital formulary.

We included all patients with at least one medication prescription and with an expected length of stay (LOS) in the PICU of >24 hrs.

Study design and endpoints
We performed an Interrupted Time Series (ITS) with six pre-intervention data collection points and six post-intervention data collection points. We considered one-month interval between data collection points adequate to identify trends in MEs. For accurate comparison of the pre- and post-intervention data, the reviews took place during the same calendar months during two consecutive years to rule out seasonal effect that might influence the characteristics and medication profiles of patient groups. Primary endpoint was the prevalence of MEs per 100 prescriptions. Secondary outcomes were medication-related patient harm per 100 prescriptions, and the types and acceptance of the recommendations by the clinical pharmacist.

We used the definitions and categories for error and harm as described by the National Coordinating Council for Medication Error Reporting and Prevention [16] (Appendix 1). High-alert medications were recorded according to the list for pediatric patients [17].
Interventions by the clinical pharmacist

We expanded the PICU team with a clinical pharmacist who rotated within a group of eight pharmacists. The clinical pharmacists received a two-days mandatory training before the implementation period on the PICU started. During this training they familiarized themselves with prevailing medication protocols and guidelines, and they learned how to collect relevant information from the electronic hospital systems, including the PDMS. In addition, the clinical pharmacists were trained in their proactive role within the multidisciplinary PICU team by an external trainer.

The clinical pharmacist was present on the PICU for a maximum of three hours every morning from Monday through Friday. At the beginning of the workday, patients considered most at risk for MEs were selected by the attending pediatrician-intensivists together with the clinical pharmacist for the medication review using the following criteria: (a) patients with reduced renal and/or hepatic clearance, (b) patients with high-alert medication prescriptions, (c) patients with more than 5 medications and (d) medication prescriptions with which the PICU professionals were unfamiliar. The clinical pharmacist performed a structured review of the prescribed medication for the selected patients, followed by feedback and recommendations to the attending pediatrician-intensivist and nurse during the ward round later during the same morning. Administration of medication was discussed with the bedside nurse, e.g. compatibility of medication administration, and infusion pump rates. If appropriate, the clinical pharmacist provided bedside instruction on pharmacological issues. A structured form was used for the medication review and bedside evaluation.

Data collection

Data on MEs and patient harm were collected for all included patients, i.e. the patients who were reviewed by the clinical pharmacist and the non-reviewed patients. To establish the incidence of MEs and patient harm, we used a three-step approach that was validated in a previous study [18]. During the first step, the clinical records of discharged patients were retrospectively reviewed by one of the investigators (JM or MT). Potential MEs were identified by reviewing all medication overviews, check-off lists, medical and nursing daily notes, symptom registration (e.g. Comfort scores) and postoperative notes. We systematically compared the potential MEs with the local protocols, the Dutch pediatric formulary [19] or international publications. In addition, the hospital incident reporting system, in which caregivers themselves report incidents, was reviewed for reported MEs during the study period. During the second step of the identification process, we presented the identified potential MEs to a blinded pediatrician-intensivist and pharmacist. They determined causality, preventability and the patient harm of the identified MEs. In the third step, they classified the MEs as harmful according to the NCC MERP categories. The process of data collection is visualized in Figure 1.
Every day during the post-intervention period, the clinical pharmacists registered information on the recommendations and the acceptance on the structured medication review form. Acceptance was scored positively when a recommendation was followed-up within 24 hours. The data collection on MEs and potential patient harm was performed by two researchers (JM and MT). Data collection of the demographic data (gender, age, severity of illness, diagnosis category, length of stay) and medication profiles (number of prescriptions, number of administrations, high-alert medications) was supported by instructed research assistants. Data were collected on paper on self-designed structured forms that were kept in locked cupboards. One researcher (JM) then entered this data electronically. During the collection of data on all MEs (harmful and otherwise) in the post-intervention period, the researchers (JM and MT) and the experts (VG and RvH) were blinded for the patients selected for medication reviews.

Two researchers (JM and MT) collected the data in parallel from the first month of the pre-intervention period independently, and discrepancies were discussed until consensus was reached. During the other study data collection periods the investigators performed double checks on the patients files that were considered complex by discretion of the researchers.

Analysis

We estimated a prevalence of 10 MEs per 100 prescriptions in the pre-intervention group and 5 MEs per 100 prescriptions in the post-intervention group. With a type 1 error of 0.05 and a power of 0.80, we required a sample size of 474 patients. Descriptive statistics were used to summarize patient demographics and the recommendations of the clinical pharmacists. If normally distributed, continuous values were expressed as mean with standard deviation (SD); in case of not-normal distribution, data were expressed as median with interquartile range (IQR). Chi-squared analysis, the Mann Whitney test or the unpaired Student t-test was used to compare the pre-intervention and post-intervention characteristics of patients and MEs (harmful or otherwise). We adjusted the analyses for differences in baseline medication characteristics. Error rates were plotted over time to examine the data visually and we used autoregressive integrated moving average (ARIMA) interrupted time series techniques to study the effect of the intervention. Statistical uncertainty was expressed by 95% confidence interval (95% CI) and a p value of 0.05 was considered statistically significant. All analyses were performed using SPSS software (PASW statistics version 22.0, IBM, Armonk, NY, USA).
Figure 1. Flow chart data collection

ME: Medication error

RESULTS

Patients and prescriptions

Patients were included from 01 July 2013 until 31 December 2013 (pre-intervention) and from 01 July 2014 until 31 December 2014 (post-intervention). We included 254 patients pre-intervention and 230 patients post-intervention; 7 patients were excluded due to missing files. Our total study population represented 1,915 admission days, during which 11,995 prescriptions were written and 28,496 medications were administered. There were significantly more patients with more than 5 prescriptions in the post-intervention period compared to the pre-intervention period (80% and 88% respectively, p = 0.02). The patients’ characteristics are summarized in Table 1.
Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Pre-intervention N = 254</th>
<th>Post-intervention N = 230</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>143 (56%)</td>
<td>133 (58%)</td>
</tr>
<tr>
<td>Age in months, median (IQR)</td>
<td>32.5 (98)</td>
<td>35.0 (106)</td>
</tr>
</tbody>
</table>

**Severity of illness**

<table>
<thead>
<tr>
<th>PRISM III, median (IQR)</th>
<th>2.5 (5)</th>
<th>3.0 (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ventilation, n (%)</td>
<td>98 (39%)</td>
<td>101 (44%)</td>
</tr>
<tr>
<td>Invasive ventilation days, median (IQR)</td>
<td>3.0 (4)</td>
<td>2.0 (3)</td>
</tr>
</tbody>
</table>

**Diagnosis category**

<table>
<thead>
<tr>
<th>Respiratory, n (%)</th>
<th>88 (35%)</th>
<th>72 (31%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective postsurgical, n (%)</td>
<td>89 (35%)</td>
<td>72 (31%)</td>
</tr>
<tr>
<td>Cardiac, n (%)</td>
<td>17 (7%)</td>
<td>30 (13%)</td>
</tr>
<tr>
<td>Neurological, n (%)</td>
<td>13 (5%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Trauma, n (%)</td>
<td>29 (11%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>2 (1%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Metabolic, n (%)</td>
<td>4 (2%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>12 (5%)</td>
<td>15 (7%)</td>
</tr>
</tbody>
</table>

**Admission**

<table>
<thead>
<tr>
<th>ICU length of stay in days, median (IQR)</th>
<th>2.0 (3)</th>
<th>2.0 (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs. – 7 days, n (%)</td>
<td>224 (88%)</td>
<td>209 (91%)</td>
</tr>
<tr>
<td>&gt;7 days, n (%)</td>
<td>30 (12%)</td>
<td>21 (9%)</td>
</tr>
</tbody>
</table>

**Medication during ICU admission**

<table>
<thead>
<tr>
<th>Prescriptions, median (IQR)</th>
<th>12.5 (20)</th>
<th>15.0 (19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 prescriptions, n (%)b,c</td>
<td>203 (80%)</td>
<td>202 (88%)</td>
</tr>
<tr>
<td>Administrations, median (IQR)</td>
<td>21.0 (40)</td>
<td>22.0 (38)</td>
</tr>
<tr>
<td>Patient with high-alert medication, n (%)</td>
<td>171 (67%)</td>
<td>161 (70%)</td>
</tr>
</tbody>
</table>

*IQR: Inter Quartile Range, ICU: Intensive Care Unit*

Medication errors

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 1.74 per 100 prescriptions. ARIMA analyses showed a stable incidence of MEs the pre-intervention period (β 0.10, 95% CI -0.03 to 0.23, p = 0.11). We observed a significant decline in the slopes between the pre-intervention and post-intervention period (β -0.21, 95% CI -0.30 to -0.04, p = 0.02), also after correction for patients with >5 prescriptions as a possible
confounder ($\beta = -0.21$, 95% CI $-0.41$ to $-0.02$, $p = 0.04$). Immediately after the start of the intervention, we observed a statistically non-significant decrease of 0.61 MEs per 100 prescriptions ($\beta = -0.61$, 95% CI $-1.31$ to $0.08$, $p = 0.07$), corresponding to 23% reduction of MEs. The results are visually presented in Figure 2 and the parameters estimates are summarized in Table 2.

Of the identified MEs prescribing errors occurred most frequently with incidences of 87% in the pre-intervention and 91% in the post-intervention period. Also, omissions of prescriptions and errors in dosages were common types of error. An overview of the results is presented in Table 3.

We explored differences in the incidence of MEs between patients whose medications were reviewed and discussed in the PICU team, compared to the patients without the medication review. This analysis showed a significant difference between the two groups (mean difference $-1.71$, 95% CI $-3.13$ to $-0.28$, $p = 0.03$), meaning the incidence of MEs per 100 prescriptions is significantly lower in patients with medication review than those without.

**Figure 2.** Medication errors per 100 prescriptions during the study periods

- : measured medication errors
- : trend lines

ME: Medication Error
Table 2. Interrupted time series analysis

<table>
<thead>
<tr>
<th>MEs per 100 prescriptions</th>
<th>( \beta ) (SE)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (( \beta_0 ))</td>
<td>1.92</td>
<td></td>
</tr>
<tr>
<td>Slope pre-intervention (( \beta_1 ))</td>
<td>0.10 (0.05)</td>
<td>-0.03 to 0.23 0.11</td>
</tr>
<tr>
<td>Slope post-intervention</td>
<td>-0.11 (0.06)</td>
<td>-0.25 to 0.02 0.08</td>
</tr>
<tr>
<td>Slope differences (( \beta_3 ))</td>
<td>-0.21 (0.07)</td>
<td>-0.30 to -0.04 0.02</td>
</tr>
<tr>
<td>Level change directly after intervention (( \beta_2 ))</td>
<td>-0.61 (0.28)</td>
<td>-1.31 to 0.08 0.07</td>
</tr>
</tbody>
</table>

Relative effect directly after intervention: 23%

\( \beta_1 \) estimates the pre-intervention slope.
\( \beta_2 \) estimates the difference between the observed level just after the intervention started and that predicted by the pre-intervention slope.
\( \beta_3 \) estimates the difference in slopes between the pre-intervention and post-intervention period.
ME: Medication Error, SE: Standard Error, CI: Confidence Interval

Table 3. Characteristics of the medication errors

<table>
<thead>
<tr>
<th>Medication process</th>
<th>Pre-intervention, 153 MEs</th>
<th>Post-intervention, 90 MEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription, n (%)</td>
<td>133 (87%)</td>
<td>82 (91%)</td>
</tr>
<tr>
<td>Administering, n (%)</td>
<td>11 (7%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Monitoring, n (%)</td>
<td>8 (5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Preparation, n (%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Type of ME</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omission, n (%)</td>
<td>91 (60%)</td>
<td>43 (48%)</td>
</tr>
<tr>
<td>Dosage, n (%)</td>
<td>25 (16%)</td>
<td>31 (34%)</td>
</tr>
<tr>
<td>Monitoring error, serum concentration, n (%)</td>
<td>7 (5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>30 (19%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>High-alert medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-alert medication involved in MEs, n (%)</td>
<td>21 (14%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>Consequences for patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No consequences, n (%)</td>
<td>130 (85%)</td>
<td>84 (93%)</td>
</tr>
<tr>
<td>Temporary harm, requiring intervention, n (%)</td>
<td>17 (11%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Temporary harm, prolonged PICU stay, n (%)</td>
<td>6 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Permanent harm, life threatening or fatal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ME: Medication Error, PICU: Pediatric Intensive Care Unit
Patient harm
Of the 153 MEs that had occurred in the pre-intervention period, we identified 23 harmful MEs (15%), corresponding with 0.34 per 100 prescriptions. In the post-intervention period 6 out of 90 MEs (7%) were identified as harmful, corresponding with 0.11 per 100 prescriptions. ARIMA analyses of the incidence of harmful MEs revealed no statistically significant differences in the slopes between the pre-intervention and post-intervention period ($\beta -0.01$, 95% CI $-0.17$ to $0.17$, $p = 0.88$). Also, no statistically significant differences were found in the number of harmful MEs in the post-intervention period directly following the intervention ($\beta -0.07$, 95% CI $-0.67$ to $0.53$, $p = 0.79$). Adjusted analyses for patients with >5 prescriptions did not alter the results.

The experts classified the observed harm as temporary and requiring intervention in 23 harmful MEs (79%) and temporary with prolonged PICU hospitalization in 6 harmful MEs (21%). None of the observed harmful MEs resulted in permanent harm or was considered life threatening or fatal. In 15 harmful MEs high-alert medications were involved: dopamine, opioids (including bupivacaine), propofol, potassium and total parenteral nutrition. Anti-epileptic drugs and furosemide were involved in 5 additional harmful events.

Recommendations made by the clinical pharmacist
During the post-intervention period, 230 intensive care patients were admitted to the PICU and 75 patients were reviewed (33%). The clinical pharmacists made 147 recommendations. The most common types of recommendation were dose adjustment (32%), discontinuation of a medication (23%) and monitoring of serum concentrations (22%) (Table 4).

Table 4. Recommendations by the clinical pharmacist

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>n=147</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose adjustment, n (%)</td>
<td>47 (32%)</td>
<td>Decrease dose Omeprazol, according to age &lt;1 yr.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase dose Paracetamol, according to weight &gt;40 kg.</td>
</tr>
<tr>
<td>Drug discontinuation, n (%)</td>
<td>34 (23%)</td>
<td>Stop potassium in case of hyperkalemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stop antibiotics after bacteriology culture came back negative.</td>
</tr>
<tr>
<td>Monitoring, serum concentration, n (%)</td>
<td>32 (22%)</td>
<td>Monitor Gentamycin serum levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor lactate levels in case of high dosage Propofol.</td>
</tr>
<tr>
<td>Start new drug, n (%)</td>
<td>18 (12%)</td>
<td>Start anti-epileptic drug after unintentional discontinuation (home medication).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Start vitamin D and K in newborn.</td>
</tr>
<tr>
<td>Administration, n (%)</td>
<td>7 (5%)</td>
<td>Switch of Total Parenteral Nutrition to central venous catheter.</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>9 (6%)</td>
<td>Correct prescription after confusion between Prednisol and Methylprednisol.</td>
</tr>
</tbody>
</table>
Of the 147 recommendations, 63% were accepted and given a follow-up within 24 hours. Another 28% of the recommendations were seriously considered but not accepted for various reasons (e.g. the patient’s situation had changed). No follow-up was given to 9% of the recommendations without reason.

DISCUSSION

Our study shows that the implementation of structured medication review, followed by timely feedback by a clinical pharmacist as part of the multidisciplinary team, resulted in a significant decreasing slope of the ME rate in a tertiary PICU. We also observed a decrease in medication-related patient harm, although this result was not statistically significant. The proactive role of the clinical pharmacist resulted in recommendations with a high acceptance rate.

We identified only one previous high-quality study that investigated interventions by a clinical pharmacist on a PICU [14]. This controlled before-after study by Kaushal et al. reported a reduction of serious MEs on a PICU from 29 to 6 per 1000 patient days (p < 0.01) after the introduction of a clinical pharmacist who provided information and advice to the PICU staff, assisted during preparation, administration and monitoring of medications, and supported storage and distribution. However, in that study the definition of serious MEs was limited to non-intercepted MEs and was therefore different from our broader definition. In addition, in the study of Kaushal et al. the clinical pharmacist was present fulltime on the PICU, while in our study the pharmacist spent approximately 3 hours per day on the PICU. Our study demonstrates that a comparable decrease in the incidence of MEs after the introduction of a clinical pharmacist can be achieved with a more cost-effective protocol.

Other studies that have investigated the effect of the presence of a clinical pharmacist on a PICU involved single-arm designs without a comparative control group, and focused on the recommendations and their acceptance by doctors and nurses rather than on the reduction of MEs [20-24]. Our finding that most recommendations of the clinical pharmacist concerned dosages is in accordance with the aforementioned studies, but the acceptance rate of the recommendations of 95% and 98% was higher than the 63% in our study [20,21,24].

In our study the clinical pharmacist was actively involved in the medication process of 1-2 patients per day, who were considered most at risk for MEs. Our results show the incidence of MEs per 100 prescriptions is significantly lower in patients with medication review than those without. This result suggests that the intervention has no effect in the non-reviewed patients, but this hypothesis must be investigated in future research. In addition, we found no significant effect of the interventions of the clinical pharmacist
on patient harm. This might be explained by the low baseline rate of harmful MEs, and our study may have been underpowered to detect a difference. Although the low number of harm incidents is consistent with previous studies [6,9], these results must be interpreted with caution. According to the study protocol, the experts classified patient harm based on patient information documented during the stay on the PICU and we did not perform a follow-up after transfer or discharge.

The combination of review and feedback is widely used to improve patient safety and generally leads to small but potentially important improvements in professional practice [25]. As part of the design of the study, the clinical pharmacist not only performed a medication review with bedside feedback, but also provided general clinical pharmacological information, gave instructions to and joined discussions with the PICU team on medication safety issues during the hours of presence. The latter activities might be considered as educational and teamwork interventions. Education has been shown to reduce MEs in children [26,27], while a multidisciplinary team results in clinical outcomes superior to those achieved by a monodisciplinary approach [28,29]. We did not investigate these interventions separately, and the effect on our results is unclear.

It can be expected that in the future computerized physician order entry (CPOE) systems will increasingly support the medication prescription process, possibly marginalizing the role of the clinical pharmacist. Although a CPOE reduces MEs [30,31], it is important to note that information technology seems to introduce new errors [32]. Ongoing research is necessary to determine if participation of a clinical pharmacist within the setting of a multidisciplinary team remains effective when the context changes. The new clinical role of a pharmacist might be considered as a financial burden for the organization. Economic evaluations suggest a cost avoidance effect of interventions by a clinical pharmacist, but robust comparative economic analyses are lacking [33,34]. Therefore, future research should focus on the economic costs and benefits of the participation of a clinical pharmacist on PICUs, such as the time investment of a clinical pharmacist, in relation to the medical costs and the extra resource utilization related to MEs. Another direction for future research should focus on the risk factors that lead to MEs and related harm in critically ill children. Several risk factors have been studied, such as age, severity of illness and surgery, but the existing studies are limited and report non-conclusive results [7,9,35,36]. Only the number of prescriptions seems to be an independent risk factor for MEs [9,37].

We recognize several potential limitations in our study. Firstly, we retrospectively reviewed clinical records to detect potential MEs (harmful or otherwise). The results of this retrospective method depended in part on the information that was documented by doctors and nurses. Although we combined this documentation with the incident
reports, this approach might have introduced an underestimation of MEs [38]. Secondly, blinding of the researchers was not complete during the process of identification of MEs, since the researchers knew whether the patient had been admitted during the pre-intervention or post-intervention period. However, neither researchers nor experts knew whether the medication for a specific patient had been reviewed by the clinical pharmacist. Thirdly, in an ITS study design data are collected at multiple time points before and after an intervention with a preferable 12-point data collection [39]. In our study data were collected at 6 points before the intervention. Although more data points might have increased the confidence in the study results, it is still in line with the Cochrane advice [40]. Finally, this was performed in a single-center study. Therefore, generalizability of the results might be limited in another clinical context and organization of the medication process.

In conclusion, the implementation of structured medication review, followed by feedback by a clinical pharmacist, as part of the multidisciplinary team resulted in a significant decreasing slope of the ME rate in pediatric patients admitted on a mixed PICU. The results of this study provide justification for expanding the PICU team with a part-time clinical pharmacist.

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REFERENCES


**APPENDIX 1. DEFINITIONS AND CLASSIFICATIONS IN SEVERITY OF MEDICATION ERRORS (NCC MERP)**

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**Medication error**

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures and systems, including prescribing; order communication; product labeling; packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use.

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**Harmful medication error**

Any medication error with potential for patient harm, but no patient harm occurred for whatever reason, e.g. the error was intercepted before it reached the patient or the error reached the patient but did not result in patient harm.

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**Harm**

Temporary or permanent impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting from this impairment, which requires intervention.

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**No error**

A: Circumstances or events that have the potential to cause error.

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**Error, no harm**

B: An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

C: **An error occurred that reached the patient but did not cause patient harm.**

D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

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**Error, harm**

E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial and prolonged hospitalization.

G: An error occurred that may have contributed to or resulted in permanent patient harm.

H: An error occurred that required intervention to sustain life.

I: An error occurred that may have contributed to or resulted in patient death.