Medication Safety in Children

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Dedicated to Christian, Maurin, Nino and my parents

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1 Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
ANZPIC	Australian and New Zealand Paediatric Intensive Care Registry
AKI	Acute kidney injury
ALAT	Alanin-amino-transferase
ASAT	Aspartat-amino-transferase
ATC	Anatomical therapeutical chemical classification
CI	Confidence Intervall
CPOE	Computerized physician order entry
CRP	C-reactive protein
die	Day
eGFR	Estimated glomerular filtration rate
f	Female
g	Gram
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl-transferase
ICU	Intensive care unit
Iv or i.v.	Intravenous (way of drug application)
kg	Kilogram
L	Litre
m	Male
MDSi	Minimal data set of the Swiss Society of Intensive Care Medicine
mg	Milligram
mcg	Microgram

mcmol	Micromole
mmol	Millimol
ME	Medication error
MODS	Multiple organ dysfunction syndrome
MPE	Medication prescribing error
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NSAID	Non-steroidal anti-inflammatory drugs
PCNE	Pharmaceutical Care Network Europe
PICU	Paediatric intensive care unit
PIM	Paediatric Index of Mortality Score
pRIFLE	Paediatric modified Risk, Injury, Failure, Loss, End-Stage criteria for renal failure
RR	Risk ratio
SD	Standard Deviation

2 Introduction

The issue of medication safety has received considerable attention in the last few years. Especially drug related problems (DRP) are a major safety issue. Several studies noted that the risks associated with the administration of drugs are high as it causes substantial mortality, morbidity and additional healthcare costs [1-3]. Hospital pharmacists are best placed to oversee the quality of the entire drug distribution, preparation and administration chain and can fulfil an important role in improving medication safety. Due to this fact, the pharmacist can improve the quality of pharmacotherapy.

Drug-related problems

The identification, prevention and resolution of DRPs are the core processes of pharmaceutical care. As defined by the Pharmaceutical Care Network Europe (PCNE), a DRP is an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes [4]. The term DRP contains adverse drug events (ADEs), adverse drug reactions (ADRs) and medication errors (ME). ADEs are defined as problems related to the use of a drug, but without evidence of the causality [5]. The definition of the term ADR covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from MEs and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicine [6]. MEs are defined as problems that involve a mistake in the process from the prescribing to the administration of the drug [5].

Children are thought to be at higher risk of DRPs than adults due to their physiology and immature mechanism of drug metabolism [7]. Some other factors that make

children vulnerable include the need of dosing calculation, the problems related to the inappropriate confection of drugs for children (with the need for special dilutions and manipulations of the drugs before application) and the high frequency of unlicensed and off label drug prescriptions [8].

Despite the awareness that children are at increased risk for DRPs, little is known about the epidemiology of these problems and where the gaps remain in our present knowledge. We undertook three studies to help provide a better understanding of (1) acute kidney injury as a possible ADE, (2) prescribing errors, which are considered as a subgroup of MEs and (3) high drug exposure as an important medication safety issue.

(1) Acute kidney injury as a possible adverse drug event

Acute kidney injury (AKI) is a devastating problem in critically ill children associated with an increased morbidity and mortality [9-11]. However AKI has not only been associated with increased mortality, but also with increased length of hospital stay, increased healthcare resource use and increased costs [10, 12-14]. In addition various drugs are currently being taken into consideration as possible causal factors of AKI in children [15]. Importantly, nephrotoxic medication exposure is becoming more prevalent as a primary cause of AKI, comprising approximately 16% of all paediatric inpatient causes of AKI [16]. The risk of developing AKI when any nephrotoxic medication is initiated and the additive risk of AKI development with multiple nephrotoxic medications are unknown. The outcomes of paediatric patients may be improved by identifying patients at risk for medication associated AKI. However, the true incidence of drug-induced nephrotoxicity is difficult to determine

because of the complexity of the clinical situation in critically ill children [17-19]. Nevertheless, this case control study may help to identify specific types of nephrotoxic drugs associated with a risk of developing AKI.

(2) Medication prescribing errors as a subgroup of medication errors

Medication errors (MEs) are common. Especially patients admitted to an intensive care unit (ICU) are at high risk for medication errors due to the critical nature of their illnesses, polypharmacy and the use of high-risk drugs [20]. Limited evidence suggests that the prevalence of ME and corresponding harm may be higher in children than in adults [21]. In addition, the majority of theses MEs are errors in prescribing [22]. Medication prescribing errors (MPEs) are much more important in children than in the adult population. In paediatric prescribing, more calculations are required as nearly all drugs have varying doses depending on the weight and/or bodysurface of the child. Additionally, drugs are often used unlicenced or off-label leading to less clear dosing guidance [23]. There have been two studies investigating paediatric prescribing errors in the UK, one showing an error rate of 5.3% of all medication orders and the other was not presenting an error rate [24, 25]. Other paediatric studies in USA and Australia found that prescribing errors occur in 0.4 to 1.9% of all written medication orders [26, 27] and cause harm in about 1% of all inpatients [24]. Ghaleb et al [28] carried out a prospective review of drug charts by pharmacists and researchers across five London hospitals over a 2-week period. This study found a prescribing error rate of 13%. Therefore, in order to improve patient-safety we need to know more about the frequency, the types and the severity of these MPEs.

(3) The number of drugs as an important issue of medication safety

The possibility that more care may also cause harm is unexpected and received little attention in the past [29]. Especially in intensive care units (ICU), patients receive twice as many drugs as patients in general care units and are therefore at high risk of an ADE or an ADR [30]. But principally the drug use in children should be clearly considered because the frequency of unlicensed and off label drug prescriptions is high [22]. In addition, the paediatric intensive care unit (PICU) is a setting where children are seriously ill and multiple drugs are prescribed. Some studies showed that particularly young children are at risk for a high drug exposure [31-34].
Our analysis should give some indications of patient related factors correlating with and probably influencing drug prescription in paediatric intensive care and the independent association of the number of drugs on the immediate patient outcome.

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3 Aims of the Thesis

The general aim of this thesis was to point out several important issues relating to medication safety in children.

The first focus of this thesis was to assess a potential association between drug use and the risk of developing acute kidney injury (AKI) in critically ill children with no pre-existing renal insufficiency at the University Children's Hospital Zürich.

The second focus of this thesis was to analyse medication prescribing errors (MPE) in critically ill children in the paediatric intensive care unit (PICU) at the University Children's Hospital Zürich. The specific objective of this study was to analyse the frequency, the type and the severity of such errors, with a view to reduce MPE and to improve patient safety.

The third focus of this thesis was to show the association between the number and profile of drugs applied in the first 24 hours of admission to PICU and socio-demographic, diagnostic and severity of illness parameters. The analysis should provide information on patient related factors correlating with and probably influencing drug prescriptions in paediatric intensive care.

4 Methods, Results and Discussion

The content of this dissertation is based on the subject of three publications. Thus, the following pages contain these three papers starting with the case-control study *'drugs as risk factors of acute kidney injury in critically ill children'*, continuing with the analysis of medication prescribing errors in critically ill children and ending with a retrospective study analysing the number and profile of ordered drugs and their association with socio-demographic, diagnostic and severity of illness parameters.

Drugs as Risk Factors of Acute Kidney Injury in Critically ill Children

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Abstract

Background

Acute kidney injury (AKI) is a serious condition in critically ill children. Nephrotoxic medication exposure is a common contributing factor to AKI, but little literature is available in paediatrics. The aim of the study was to assess a potential association between drugs and the risk of developing AKI.

Methods

We performed a retrospective case-control study in a paediatric intensive care unit (PICU). Cases were patients who developed AKI during PICU stay. Patients without AKI served as controls and were matched to cases on age category and gender in a one to one ratio.

Results

100 case-control pairs were included. Cases were not statistically different from controls with regard to median weight and main diagnoses, but differed with regard to the need of mechanical ventilation, the severity of illness, and the median length of PICU stay. Multivariate models revealed a statistically significantly higher risk of developing AKI for patients treated with Metamizol, Morphine, Paracetamol and Tropisetron. A similar risk could be shown for medication groups, namely glucocorticoids, betalactam antibiotics, opioids and non-steroidal anti-inflammatory drugs.

Conclusion

The results suggest that drugs are associated with acute renal dysfunction in critically ill children, but the multifactorial causes of AKI should be kept in mind.

Introduction

Acute kidney injury (AKI) is a serious condition in critically ill patients. Little literature is available on the association between drug therapy and AKI in the setting of paediatric intensive care.

AKI continues to represent a very common and potentially devastating problem in critically ill children. Recent studies have revealed that AKI may be an independent risk factor for mortality in critically ill children [1-3].

Furthermore, AKI has not only been associated with increased mortality, but also with increased length of hospital stay, increased healthcare resource use and increased costs in critical illness [4-7].

Previous paediatric studies have shown that the incidence of AKI ranges from 7% to 25% depending on the definition of AKI used and the population studied [8]. The variability in incidence and mortality rates of AKI is in part because no consensus exists regarding which definition should be used [1, 9]. Nonetheless, the available data suggest that the incidence of AKI in asphyxiated neonates is high, that non-oliguric AKI is common, and that AKI portends poor outcomes [10-14].

In addition various drugs are currently being taken into consideration as possible causal factors of AKI in children. Predisposing factors such as age, pharmacogenetics, underlying disease and concomitant medication determine and influence the severity of nephrotoxic insult [15]. The overall contribution of drugs to renal injury in the paediatric intensive care unit (PICU) is unknown because of the complexity of the clinical situation in critically ill children [8, 10, 16, 17].

Importantly, nephrotoxic medication exposure is becoming more prevalent as a primary cause of AKI, comprising approximately 16% of all paediatric inpatient

causes of AKI [18]. Health outcomes of paediatric patients may be improved by identifying patients at risk for medication associated AKI. Additionally medication selection may need to be altered to prevent poor outcomes or minimise risk caused by nephrotoxic medications[18].

The aim of the current study is (1) to assess a potential association between drug use and the risk of developing AKI in critically ill children with no pre-existing renal insufficiency, and (2) to identify the specific types of nephrotoxic drugs associated with a high risk of developing AKI.

Methods

Study population, data source and data categorisation

We performed a retrospective hospital-based case control study to determine the odds of medication exposure in critically ill children who developed AKI in the PICU at the University Children's Hospital in Zurich during 2010. The PICU is divided into a general PICU (9 beds) and a cardiac PICU (9 beds).

The study has been approved by the local Ethics Committee.

All patients who were admitted to the PICU between April and December 2010 were eligible to be included into the study. Demographic parameters (sex, age and weight) and factors relating to severity of illness (length of PICU stay, mechanical ventilation, Paediatric Index of Mortality 2 (PIM2)) [19] were surveyed by means of the minimal data set (MDSI) of the Swiss Society of Intensive care [20]. Information on drugs prescribed during PICU stay (according to the anatomical therapeutical chemical (ATC) classification), laboratory parameters (serum creatinine, albumine, aspartate-amino-transferase (ASAT), alanine-amino-transferase (ALAT), C-reactive protein (CRP)), main diagnosis (according to the Australian and New Zealand Paediatric Intensive Care Registry (ANZPIC) Diagnostic Codes) [21], were obtained from the electronic patient records or the order sheets. All medication orders were included in this analysis.

Age was categorised into five different age groups: neonates (0-4 weeks), infants (1-12 months), toddlers (1-4 years), children (5-11 years) and adolescents (> 12 years). The main diagnoses were categorised into the following groups: airway, cardiovascular, miscellaneous, neurological, or post procedural. Patients who were sent to the PICU after cardiac surgery were classified as post procedurals. Patients

who were first in the PICU and had then a cardiac surgery were classified as cardiovascular.

Paediatric Index of Mortality Score (PIM2) was categorised into three different strata related to the expected risk of mortality in percentages: category 1 (0-0.99%), category 2 (1.0%-9.99%) and category 3 (10%-100%) [22].

Medication exposure was defined as any medication a study subject received before developing AKI. Number of drugs was defined as the number of different drugs that a study subject received before developing AKI.

Case and Control definition

Cases were defined as any patient hospitalised in the PICU who developed an AKI described by stage 'Risk' or worse using the pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) definition (table 1) [3].

Table 1: AKI Definition using the estimated glomerular filtration rate criteria of the pRIFLE[i] definition

AKI Classification	**Estimated glomerular filtration rate (eGFR) criteria**
Risk (R)	Decrease by 25%
Injury (I)	Decrease by 50%
Failure (F)	Decrease by 75% or eGFR < 35 mL/min/1.73m^2

The lowest estimated glomerular filtration rate (eGFR) was calculated using the updated Schwartz formula and the peak Serum creatinine [23]. Baseline eGFR was assumed using the filtration rate by Guignard and Gouyon (table 2) [24].

Table 2: Baseline estimated glomerular filtration rate

age	**Baseline eGFR (mL/min/1.73 m^2)**
0 - 4 weeks	13
≥ 1 month - 3 months	50
≥ 3 months - 12 months	100
≥ 1 year	120

The maximal percent eGFR drop during treatment was calculated ((Baseline eGFR – lowest eGFR)/Baseline eGFR * 100) to determine the worst pRIFLE AKI category.

[i] The original pRIFLE definition also comprises urine output which was not assessed in this study. The categories ‚Loss' and ‚End Stage Kidney Disease' of the pRIFLE definiton, representing renal dysfunction of prolonged duration, were not assessed for this study.

Controls (no renal impairment) were matched to cases in a 1:1 ratio on age category and gender. Controls were recruited from the patients hospitalised during the same time period in PICU. Serum creatinine levels were measured for cases as well as for controls. If more than one control met matching criteria, the control with the nearest admission date to the case was selected.

Statistical analysis

Demographic variables were summarized using descriptive statistics. Differences between cases and controls were analysed using Fisher's exact test for categorical variables and Wilcoxon test (also known as Mann-Whitney U test) for continuous variables, because assumptions of normality could not always be satisfied. Continuous variables were expressed as median, categorical variables were expressed as proportions (%).

Multivariate conditional logistic regression models were then developed to evaluate the independent association between the administered drugs and the risk of AKI, controlling for potential confounding variables such as PIM2 score, length of PICU stay, mechanical ventilation and weight.

In a second step, we classified the most frequently administered drugs in eight pharmacologically different groups (drugs for cardiac stimulation, diuretics, glucocorticoids, betalactam antibiotics, opioids, non-steroidal anti-inflammatory drugs (NSAID), benzodiazepines and antithrombotic drugs).

We then ran a multivariate model including the medication groups, adjusted as well for the above mentioned potential confounding variables.

Statistical significance was defined as $p \leq 0.05$. Odds ratios (OR) are presented with a 95% confidence interval (CI). All of the data analyses were conducted using the software program SAS, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Characteristics of the patients

A total of 412 patient admissions were identified during the study period. Among these 412 patients 100 cases with AKI were identified, and the same number of matched controls resulting in a dataset of 200 patients. Male and female cases and controls were evenly distributed (50%). The case data set was not statistically different from the control data set in terms of median weight and main diagnoses (except the cardiovascular diagnosis). The detailed characteristics of the cases and the controls are displayed in table 3.

As reported in table 4, the cases were statistically different from the controls with regard to the severity of illness described by the PIM2 Score (except PIM2 Score category 2) and the median length of PICU stay (4 days vs 3 days). There was no statistically significant difference with regard to the need for mechanical ventilation (73% vs 60%).

Table 3: Patient characteristic of cases and controls (matching criteria: age category and gender)

Categories	**Number of cases N = 100**	**Number of controls N = 100**	**P-Value**
Age (in categories)			1.000
Neonates (0-4 weeks)	2	2	
Infants (1-12 months)	15	15	
Toddlers (1-4 years)	41	41	
Children (5-10 years)	24	24	
Adolescents (>10 years)	18	18	
Sex			1.000
Male	50	50	
Female	50	50	
Weight	**kg**	**kg**	**P-Value**
all	14 (0.8, 82)*	15 (3, 84)*	0.414
Neonates (0-4 weeks)	4 (3, 4)*	6 (3, 8)*	0.667
Infants (1-12 months)	5 (0.8, 10)*	6 (3, 8)*	0.507
Toddlers (1-4 years)	12 (7, 30)*	14 (7, 25)*	0.062
Children (5-10 years)	20 (11, 35)*	23 (16, 41)*	0.122
Adolescents (>10 years)	48 (7, 82)*	34 (4, 84)*	0.220
Main diagnosis	**Number of cases N = 100**	**Number of controls N = 100**	**P-Value**
Airway	5	7	0.766
Cardiovascular	37	18	0.004
Injury	12	16	0.541
Miscellaneous	13	12	1.000
Missings	2	3	1.000
Neurological	9	14	0.375
Post procedural	22	30	0.259

N = number of patients, * = range

Table 4: Severity of illness parameters of cases and controls

Categories	Number of cases N = 100	Number of controls N = 100	P-Value
Mechanical ventilation			0.072
Yes	73	60	
PIM2 Score			
Category 1 (0-0.99%)	22	43	0.003
Category 2 (1-9.99%)	64	50	0.151
Category 3 (10-100%)	14	4	0.026
Length of PICU stay (days)	4 (0, 49)*	3 (0, 79)*	0.002

N = number of patients, * = median and range

Drug exposure of cases and controls

Additionally, 53% of the cases were exposed to one or more drugs before onset of AKI , whereas only 13% of the controls were exposed to drugs. Similarly, cases had a greater number of different drugs. They received a median of 3 (range 0 to 25) different drugs before developing AKI. Both the number of different drugs received and medication exposure (drugs vs. no drugs) were associated with improved predictability for development of AKI.

Multivariate conditional logistic regression analysis

We developed a „single medication model“ to analyse the association between various drugs and the development of AKI. Parameters were adjusted for PIM2 score, length of PICU stay, mechanical ventilation and weight. Table 5 shows that patients treated with analgesics such as Metamizol, Morphine or Paracetamol and Tropisetron had a significantly greater odds ratio to develop AKI.

The second model (table 6) was a „medication group model“, which evaluated the association (odds ratio) between the eight most frequently administered medication groups and the development of AKI. Adjustments were made for the same parameters displayed above. Four of the eight drug groups namely betalactam

antibiotics, glucocorticoids, NSAID and opioids were associated with a statistically significantly increased risk for developing AKI. The other four groups did not show any association with acute renal dysfunction.

Table 5: Odds for the development of AKI: “single medication model”

Drugs	Number of cases	Number of controls	OR (95% CI)	P-Value
Metamizol	17	6	4.6 (1.36; 15.6)	0.014
Morphine	40	10	2.4 (1.02; 6.03)	0.042
Paracetamol	40	19	3.5 (1.47; 8.21)	0.005
Tropisetron	12	1	20.8 (1.98; 219)	0.011

Table 6: Odds for development of AKI: “medication group model”

Medication groups	Number of cases	Number of controls	OR (95% CI)	P-Value
Antithrombotic drugs	12	4	3.1 (0.65; 14.4)	0.158
Benzodiazepines	8	1	5.4 (0.58; 50.1)	0.137
Betalactam antibiotics	25	10	2.3 (1.03; 6.01)	0.043
Cardiac stimulation	22	11	1.8 (0.55; 5.58)	0.341
Diuretics	21	11	2.1 (0.76; 5.53)	0.158
Glucocorticoids	10	1	18.5 (1.75; 195)	0.015
NSAID	18	9	2.3 (1.08; 6.37)	0.027
Opioids	36	19	3.2 (1.35;7.75)	0.008

Discussion

In the current hospital-based case-control analysis we assessed the association between drug use and the risk of AKI in a paediatric intensive care setting. AKI-cases were three times more likely to be exposed to one or more drugs than the controls. In the wider setting of hospitalized paediatric patients, previous reports have noted that nephrotoxic medications are a common aetiological factor of AKI [18]. In our study, only few individual drugs were noted as being independently associated with the development of AKI in multivariate analyses. The identification of only few drugs associated with AKI lends support to the hypothesis that individual medication exposure may not be as important a risk factor for AKI than multiple medication exposure. Anyway, it is difficult to determine the overall contribution of drug-induced renal dysfunction due to the complexity of the clinical situation in critically ill patients. Nonetheless, a few studies revealed nephrotoxic medication groups such as NSAID, antibiotics, ACE-inhibitors, chemotherapeutics and diuretics [25-28]. Within our study population we could find evidence that some of the above mentioned drug groups are indeed involved in the development of AKI. In our study, children treated with NSAID had a two-fold higher risk (OR 2.3, 95% CI 1.08 to 6.37) of developing AKI. NSAID associated AKI has been previously reported in 54 infants and children in case reports or small case series [28]. Misurac et al. demonstrated in the largest series to date, that NSAIDs are a common cause of AKI in children [29].

The multivariate analysis provided evidence for an association between some other drug groups and AKI risk, such as betalactam antibiotics (OR 2.3, 95% CI 1.03 to 50.1), glucocorticoids (OR 18.5, 95% CI 1.75 to 196) and opioids (OR 3.2, 95% CI 1.35 to 7.75). These drugs are often used in the treatment of various diseases which

can directly impair renal function. It is difficult, though, to distinguish between the role of the underlying disease the drugs are used for, and the contribution of the drug itself. This phenomenon called ‘confounding by indication’ could also be an explanation why our analysis revealed Tropisetron (OR 20.8, 95% CI 1.98 to 219) as a potentially nephrotoxic drug. In view of the short term nature of the recommended treatment regimen of Tropisetron [30] the underlying disease is probably more to the fore than Tropisetron itself.

Very surprisingly, there was a significant association between Paracetamol use and AKI. Children who received Paracetamol had a three-fold higher relative risk (OR 3.5, 95% CI 1.47 to 8.21) of developing AKI than children who were not treated with Paracetamol. Paracetamol is widely used in children because its safety and efficacy are well established. However, the adverse effects of Paracetamol on the kidney are still being investigated, and data on renal toxicity in children are limited. Shahroor et al. looked at toxic effects of Paracetamol in paediatric use and described two children who developed severe hepatic damage combined with renal insufficiency [31]. Onay et al. described two children admitted to their hospital with acute nonoliguric renal failure temporally associated with ingestion of Paracetamol at therapeutic doses [32].

We did not find an association between ACE-inhibitors and aminoglycoside antibiotics and the development of AKI, as it is described in the literature [33-35]. This may be related to the tight monitoring of aminoglycoside blood levels and the repeated creatinine measurements in children on ACE-inhibitors.

Our study revealed that AKI-cases had an increased length of stay and mortality compared to AKI-free control patients. This finding is in line with various recent studies [36-38]. The need for mechanical ventilation was higher in cases compared to controls (73% vs 60%) a finding which is consistent with previously published data.

Akandari et al. reported that children with AKI had approximately twice the duration of mechanical ventilation compared to non-AKI patients [39]. The question remains whether these worse outcome parameters (length of stay, mortality, mechanical ventilation) are directly caused by AKI, or whether they are just related to increased co-morbid conditions which by themselves put children at increased risk for AKI. Recent studies suggest that the most common cause of AKI is multifactorial [37, 38, 40]. Because of the many different factors which are associated with AKI it is very difficult to show the independent role of drug exposure. We tried to take into account the co-morbidity of the patients as a cause of AKI. In the logistic regression analysis we included at least some indirect measures of co-morbidity, such as severity of illness at admission, mechanical ventilation and length of stay.

There are some well described populations at risk for AKI. Critically ill newborns with asphyxia are at great risk to develop AKI [12, 14, 40]. Furthermore, cardiovascular patients have been reported to be at higher risk of AKI. Our results also show a significant difference (P-Value 0.004) between cases and controls with regard to the main diagnosis cardiovascular disease, which is in accordance with the literature [39, 41]. Factors such as the complexity of the heart defect have previously been identified as risk factor for renal dysfunction in children [41]. In another recent study by Hui-Stickle et al., cardiac diseases were present in 30% of paediatric patients developing AKI [36].

Limitations

As with most case-control studies, matching is a difficult process and we were unable to match some patients on exact age, so that we matched them on age category. Although there could be a significant difference in age within categories, this is likely not clinically significant with regard to renal function. Additionally, the number of cases (N = 100) and the matched controls (N = 100) was rather small, which limits the possibility of doing subgroup analyses and which limits the interpretation of multivariate analyses. In our study, doses and durations of exposure to the drug before developing AKI were not taken into consideration.

The definition of AKI cases was based on a simplified pRIFLE criteria. Other renal function variables such as urine output were not comprised as definition criteria in our study. Due to our small case control study we just used one AKI stage (‘Risk’ and worse) and did not stratify the cases into ‘Risk’, ‘Injury’ and ‘Failure’ groups because this would make the interpretation of the results virtually impossible due to lack of statistical power in the various subgroups.

Conclusion

The results of this case-control analysis suggest that drugs are associated with acute renal dysfunction in paediatric intensive care, especially some critical medication groups such as betalactam antibiotics, glucocorticoids, opioids and NSAIDs. It is also important to underline the multifactorial aetiology of AKI. Our results emphasize the complexity of AKI development. Therefore early recognition of drug-induced renal dysfunction may alleviate some of the mortality that is associated with AKI in the PICU.

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Analysis of Medication Prescribing Errors in Critically ill Children

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Abstract

Medication prescribing errors (MPE) can result in serious consequences for patients. In order to reduce errors, we need to know more about the frequency, the type and the severity of such errors. We performed therefore a prospective observational study to determine the number and type of medication prescribing errors in critically ill children in a paediatric intensive care unit (PICU). Prescribing errors were prospectively identified by a clinical pharmacist. A total of 1'129 medication orders were analysed. There were 151 prescribing errors, giving an overall error rate of 14% (95% CI 11 to 16). The medication groups with the highest proportion of MPEs were antihypertensives, antimycotics and drugs for nasal preparation with error rates of each 50%, followed by antiasthmatic drugs (25%), antibiotics (15%) and analgesics (14%). 104 errors (70%) were classified as MPEs which required interventions and/or resulted in patient harm equivalent to 9% of all medication orders (95% CI 6.5 to 14.4). 45 MPEs (30%) did not result in patient harm.

Conclusion: With a view to reduce MPEs and to improve patient-safety, our data may help to prevent errors before they occur.

Introduction

In the current health care system, especially in neonatal and paediatric intensive care, medication errors are possibly an important source of morbidity [5, 15, 20, 32, 33, 40, 41] and efforts for improvement are paramount. Medication errors range from those with very serious consequences to those that have little impact on the patient. It has thus been suggested that the severity as well as the prevalence of errors should be taken into account [2]. Assessing the severity of errors increases the quality of information regarding the clinical relevance.

Children are a challenging group of patients because most drug dosages in paediatric medication are calculated individually, based on the patient's age, weight or body surface area. Furthermore, the frequency of unlicensed and off label drug prescriptions is about 50 to 70% depending on the method of analysis and the clinical setting [10].This may increase the potential for medication errors. Limited evidence suggests that the prevalence of medication errors and corresponding harm may be higher in children than in adults (1.1% vs 0.35%, $P< 0.001$) [20]. Especially patients admitted to an intensive care unit (ICU) are at high risk for medication errors due to the critical nature of their illnesses, polypharmacy and the use of high-risk drugs [21]. A review estimates that 5 to 27% of medication orders for children contain an error somewhere along prescribing, dispensing and administering. The review also estimates that there are 100 to 400 prescribing errors per 1000 patients [27]. There have been two studies investigating paediatric prescribing errors in the UK, one showing an error rate of 5.3% and the other not presenting error rates [28, 7]. Other studies in USA found that prescribing errors occur in 0.4 to 1.9% of all written medications orders [5, 27, 28] and cause harm in about 1% of all inpatients [7].

Ghaleb et al [18] carried out a prospective review of drug charts by pharmacists and researchers across five London hospitals over a 2-week period. This study found a prescribing error rate of 13%, which is higher than in previous studies.
However, a major problem with interpreting quantitative prescribing error studies is that the definition of an error used by the researchers is often ambiguous or not given at all. Often studies include all medication errors and do not distinguish clearly enough between prescribing errors and other types of errors [18].
The definition used in a study will impact directly on its result and therefore research in this area is particularly hard to interpret [16].
In addition, the different methods of detecting prescribing errors make it difficult to compare studies. Higher rates of prescribing errors were detected by retrospective reviews compared to prospective assessments. Spontaneous reporting and the use of retrospective trigger tools were not accurate to detect prescribing errors. [16]

To assess the epidemiology of MPEs in critically ill children may help to reduce serious errors in the use of prescribed drugs. Our goals were (1) to determine the rates of MPEs, (2) analyse the major types of errors and the drugs most commonly involved and (3) assess the severity of these errors.

Methods

Setting, study population and data source

We performed a prospective observational study to determine the number and type of medication prescribing errors in critically ill children in the paediatric intensive care unit (PICU) at the Children's Hospital in Zürich during a ten months period in 2010. Prescribing errors were prospectively identified by one of three clinical pharmacists as part of their routine prescription monitoring. The pharmacist reviews every order before the ward round. Only medication orders on Monday, Wednesday and Friday were included in this analysis, because only on these days a clinical pharmacist participates on the ward rounds. Ward rounds are held together with a senior physician, two residents and two nurses. The pharmacist told the medical and nursing PICU team which prescribing errors occurred in order to prevent harm to the patient.

The PICU is divided into a general PICU (9 beds) and a cardiac PICU (9 beds). The whole range of neonatal (also preterms), paediatric, surgical and cardiac surgical patients is admitted, excluding liver transplant patients. All up-to-date procedures are offered, including high-frequency oscillatory ventilation, inhaled nitric oxide (NO), renal replacement therapy (peritoneal dialysis and haemofiltration) and extra-corporeal-membrane-oxygenation (ECMO). About 25% of patients are neonates, mainly with cardiac and/or surgical pathologies. The study has been approved by the local Ethics Committee.

All patients who were admitted to the general PICU between April and December 2010 were eligible to be included into the study. Each readmission after 24 hours outside PICU was considered a new and separate case. Demographic parameters

(sex, age and weight) and factors relating to severity of illness (length of PICU stay, mechanical ventilation, Paediatric Index of Mortality 2 (PIM2) [36]) were surveyed by means of the minimal data set (MDSi) of the Swiss Society of Intensive care [43]. Information on drugs prescribed during PICU stay (according to the anatomical therapeutical chemical (ATC) classification), laboratory parameters (serum creatinine, albumine, aspartate-amino-transferase (ASAT), alanine-amino-transferase (ALAT), c-reactive protein (CRP)), main diagnosis (according to the Australian and New Zealand Paediatric Intensive Care Registry (ANZPIC) Diagnostic Codes [35]), were obtained from the electronic patient records or the order sheets.

Age was categorised into five different age groups: neonates (0-4 weeks), infants (≥1-12 months), toddlers (≥1-4 years), children (≥5-11 years), or adolescents (≥ 12 years).

The main diagnoses were categorised into the following groups: Airway, cardiovascular, gastrointestinal, infection, injury, miscellaneous, neurological, post procedural or renal [35].

PIM Score was categorised into three different strata related to the expected risk of mortality in percentages: category 1 (0-0.99%), category 2 (1.0%-9.99%), or category 3 (10%-100%) [39].

Number of medications was defined as the number of different drugs that a study subject received during the study period except the drugs kept in reserve.

Drugs were ordered by means of an excel order form without drug-drug interaction information. This order form was created by a resident of the PICU. Residents wrote prescriptions on a structured form using a lap-top computer at the bedside. There were some calculation aids, such as calculating the whole dose from the dose per kilogram body weight. For the preparation of continuous drips, standardised tables

were used, so that the residents only needed to order the amount of the medication per time (e.g.: adrenaline: 0.1 mcg/kg/min). All medication preparations were done by nurses. Regular orders, valid from 2 pm to 2 pm of the next day, were written on morning rounds and printed out. Additional orders, if required later than 2 pm, were written by hand on the back of the order form.

Medication prescribing error definition

For the purpose of this study, a clinically meaningful medication prescribing error (MPE) was defined as a prescribing decision or prescribing writing process, that results in an unintentional, significant reduction in the probability of treatment being timely and effective *or* increase in risk of harm, when compared with generally accepted practice. [4]

Identification and classification of medication prescribing errors

MPEs were classified according to an adapted Pharmaceutical Care Network Europe (PCNE) classification [30]. Only six of the eight primary domains of PCNE for causes of MPEs were used for the classification: drug selection (the cause of the MPE can be related to the selection of the drug), drug formulation (the cause of the MPE is related to the selection of the drug formulation), dose selection (the cause of the MPE can be related to the selection of the dosage schedule), treatment duration (the cause of the MPE is related to the duration of therapy), drug use process (the cause of the MPE can be related on the way the patient gets the drug administered) and other problems. The domain missing information (the cause of the MPE can be related to omitting information) was added. Additionally, sub domains were formed for each main domain which can be seen explanatory for the principal domains. The

other primary domains such as domains for problems and domains for interventions were not taken into account because we only wanted to classify prescribing errors.

Classification of the dosage

For calculation and verification of the correct drug dose the dosage booklet published by the Children's Hospital Zürich in 2009 was used [11]. This booklet contains dosages for regulatory approved drugs, as well as information on drugs which are not approved, but for which evidence or at least eminence based paediatric dosages are available. Was the drug dose not in the range given in the booklet, then the dose was considered to be wrong.

Classification of drug-drug interactions

Drug-drug interactions occur when the effect of one drug is changed by the presence of another drug.

All medication orders were screened for drug-drug interactions using the interaction screening program Pharmavista [13]. The program classifies the severities of drug-drug interactions into five categories: major, moderate, minor, insignificant, or of unidentified source. In this study, only the categories major, moderate and minor were taken into account for an inappropriate drug selection/drug dose.

Categorisation of medication prescribing errors by severity

A classification according to the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) was used [38] (Table 1). Each MPE was independently scored for error severity by a clinical pharmacist and by a senior intensive care physician. Any disagreements were resolved by a senior clinical pharmacist.

Table 1: Severity of medication prescribing error

[i]Major divisions	Subcategory	Description
Error, no harm	Category A	Circumstances that have the capacity to cause error
	Category B	Error did not reach the patient, because it was intercepted before or during administration process
	Category C	Error reached the patient but did not cause patient harm
Error, potential preventable ADE	Category D	Error reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
Error, preventable ADE	Category E	Error may have contributed to or result in temporary harm to the patient and required intervention
	Category F	Error may have contributed to or result in temporary harm to the patient and required initial or prolonged hospitalisation
	Category G	Error may have contributed to or resulted in permanent harm
	Category H	Error required intervention necessary to sustain life

Statistical analysis

Demographic variables were summarized using descriptive statistics. Differences between patients with MPEs and patients without MPEs were analysed using Fishers exact test for categorical variables and Wilcoxon test (also known as Mann-Whitney U test) for continuous variables, because assumptions of normality could not always be satisfied. Continuous variables were expressed as median, categorical variables were expressed as proportions (%).

The error rate was calculated as the percentage of errors relative to total drug orders with 95% confidence interval (CI).

In a second step, we classified the most frequently administered drugs in nine different groups (drugs for cardiac stimulation, diuretics, antiasthmathics, antibiotics, antiepileptics, antimycotics, analgesics, antihypertensives, or nasal preparations).

[i] Classification according to the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) [24]

We then calculated proportions of errors attributable to given medication groups with 95% CI.

All of the data analysis were conducted using the software program SAS, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Number and rates of medication prescribing errors

A total of 153 patients and 1'129 medication orders were analysed throughout the study period. There were 151 prescribing errors, giving an overall error rate of 14% (95% CI 11 to 16). Medication orders from 65 patients contain one or more MPEs. Dose selection errors were the most common type of MPEs with an error rate of 6.6% (95% CI 5.3 to 8.3) followed by drug selection errors with an error rate of 2.1% (95% CI 1.3 to 3.0). A list of the most frequent MPEs and their associated error rates is given in table 2.

Table 2: Number and error rates of medication prescribing errors

Categories	Number of MPEs (N(%))	Error rates (%)	95% CI for error rates
All	151 (100)	14	11; 16
Dose selection	75 (50)	6.6	5.3 ; 8.3
Dose too high	22 (15)	1.9	1.2 ; 2.9
Dose too low	17 (11)	1.5	0.9 ; 2.4
Drug formulation	7 (4.6)	0.6	0.2 ; 1.3
Drug selection	23 (15)	2.1	1.3; 3.0
pharmacodynamic interaction	9 (6.0)	0.8	0.4 ; 1.5
pharmacokinetic interaction	11 (7.3)	1.0	0.5 ; 1.7
Missing information	21 (14)	1.9	1.2; 2.8
Missing drug formulation	16 (11)	1.4	0.8; 2.3
Other Problems	18 (12)	1.6	0.9; 2.5
Treatment duration	0	0	0; 0.3

Drug categories associated with MPEs

The involvement of medication groups according to the ATC in MPEs is shown in table 3. The medication groups with the greatest proportion of MPEs were antihypertensives, antimycotics and drugs for nasal preparation with error rates of each 50%, followed by antiasthmatic drugs (25%), by antibiotics (15%) and by analgesics (14%).

Table 3: Medication groups associated with medication prescribing errors

Medication groups	Number of drug orders	Number of MPEs	Percentage of errors*	95% CI for error rates
Analgesics	301	43	14	11; 19
Antiasthmatics	20	5	25	8.7; 49
Antibiotics	130	19	15	9.0; 22
Antiepileptics	111	18	16.2	9.9; 24
Antihypertensives	14	7	50	23; 77
Antimycotics	6	3	50	12; 88
Diuretics	39	6	15	5.9; 31

Severity of medication prescribing errors

There was a high grade of accordance (96%) between the senior physician and the clinical pharmacist concerning the classification of the severity of the MPEs. Only six errors had to be solved by the senior pharmacist. The distribution of the severity ratings for MPEs showed that 104 errors (70%) were classified as MPEs which required interventions and/or resulted in patient harm (severity category D to H) equivalent to 9% of all medication orders (95% CI 6.5 to 14.4). 47 MPEs (30%) did not result in patient harm (severity categories A, B and C). The detailed distribution of the severity ratings is shown in table 4.

Table 4: Classification of medication prescribing errors regarding severity

Major divisions	Subcategory	Number of MPEs (N (%))	Error rates (%)	95% CI for error rates
Error, no harm	Category A	8 (5)	0.5	0.2 ; 1.2
	Category B	19 (12)	1.4	0.8 ; 2.3
	Category C	20 (13)	1.5	0.8; 2.4
Error, potential preventable ADE	Category D	81 (54)	7.0	5.6 ; 8.6
Error, preventable ADE	Category E	19 (13)	1.5	0.9 ; 2.4
	Category F	1 (1)	0.0	0.0 ; 2.5
	Category G	2 (1)	0.0	0.0 ; 0.6
	Category H	1 (1)	0.0	0.0 ; 0.5

Demographic differences in patients with and without MPEs

In general, demographic characteristics differed little between patients with or without MPEs . In particular, there were no differences regarding age, gender, weight (except for the category neonates) and main diagnoses (table 5).

However, as reported in table 6, the MPE-patient group was different from the group without MPEs with regard to the severity of illness described by the median length of PICU stay (7 days vs 3 days), the median length of mechanical ventilation (31 hours vs 2.7 hours), and the median number of prescribed drugs (9 drugs vs 5 drugs).

Table 5: Characteristics of patients with and without medication prescribing errors

Categories	All N = 153	Patients with MPE N = 65	Patients without MPE N = 88	P-Value
Age (in categories)				0.499
Neonates	47 (31%)	17 (26%)	30 (34%)	
Infants	31 (20%)	16 (25%)	15 (17%)	
Toddlers	25 (16%)	9 (14%)	16 (18%)	
Children	21 (14%)	8 (12%)	13 (15%)	
Adolescents	29 (19%)	15 (23%)	14 (16%)	
Sex				0.311
Male	97 (63%)	38 (58%)	59 (67%)	
Female	56 (37%)	27 (42%)	29 (33%)	
Weight	**Kg**	**kg**	**kg**	**P-Value**
all	9.5 (0.8, 84)	9.5 (0.8, 84)*	9.2 (1.3, 72)*	0.602
Neonates	3.0 (0.8, 8.4)*	2.5 (0.8, 4.2)*	3.1 (1.3, 8.4)*	0.050
Infants	6.4 (1.3, 10)*	6.4 (1.3, 9.5)*	6.4 (2.8, 10)*	0.984
Toddlers	14 (10, 30)*	14 (11, 30)*	13 (10, 17)*	0.649
Children	23 (16, 41)*	26 (16, 41)*	22 (16, 25)*	0.405
Adolescents	46 (14, 84)*	49 (18, 84)*	39 (14, 72)*	0.570
Main diagnosis				0.560
Airway	32 (21%)	14 (22%)	18 (21%)	
Cardiovascular	8 (5.2%)	5 (7.7%)	3 (3.4%)	
Gastrointestinal	14 (9.2%)	7 (11%)	7 (8.0%)	
Infection	2 (1.3%)	0 (0%)	2 (2.3%)	
Miscellaneous	28 (18%)	15 (23%)	13 (15%)	
Missings	2 (1.3%)	1 (1.5%)	1 (1.1%)	
Neurological	21 (14%)	7 (11%)	14 (16%)	
Post procedurals	29 (19%)	9 (14%)	20 (23%)	
Renal	5 (3.3%)	3 (4.6%)	2 (2.3%)	

N = number of patients, * = median with range

Table 6: Severity of illness parameters of patients with and without medication prescribing errors

Categories	**All** **N = 153**	**Patients with MPE** **N = 65**	**Patients without MPE** **N = 88**	**P-Value**
Mechanical ventilation (Yes)	91 (60%)	42 (65%)	49 (56%)	0.318
Length of mechanical ventilation (hours)	6.5 (0, 2762)*	31 (0, 2762)*	2.7 (0, 766)*	0.003
PIM2 score				0.055
Category 1 (0-0.99%)	57 (37%)	25 (38%)	32 (36%)	
Category 2 (1-9.99%)	80 (52%)	29 (45%)	51 (58%)	
Category 3 (10-100%)	16 (11%)	11 (17%)	5 (6%)	
Length of PICU stay(days)	4 (1, 116)*	7 (2, 116)*	3 (1, 20)*	<0.001
Number of medications	6 (1, 29)*	9 (1, 29)*	5 (1, 15)*	<0.001

N = number of patients, * = median and range

Discussion

The findings of our study support the notion that MPEs occur frequently with an overall error rate of 14%, a proportion which is higher than the one reported in adults of a tertiary care teaching hospital [26]. Much has been written on the importance of medication errors in paediatrics and in particular on prescribing errors [3, 9, 34, 17]. The error rate of 14% in the current study population is comparable to other published data [31, 6], even though a direct comparison of error rates across various studies is difficult due to variations in the definitions used and in the methodology. Davis [8] recently pointed out that reaching a generally accepted definition is difficult. The errors reported in our study were all identified by a pharmacist. Other studies have used reviews based on medical notes and have focused on those errors that resulted in patient harm [34, 24, 23]. We do not know whether the errors that result in patient harm differ substantially from those that are identified before harm can result. The main prescription error in our study was wrong dosing (overdosing or underdosing), with an error rate of 50% of all prescribing errors. This is in line with findings of most previous studies [15, 9, 25, 42]. The frequent need for dose calculations required in paediatrics for weight based dosing is most likely an important factor contributing to the high rates of dosing errors.

Other authors have found that incomplete medication orders are the most frequent prescribing error [18]. In our study missing information (error rate 14%) was located on third place. The reason for this discrepancy could be that in the other studies data were generally gathered on manual prescribing systems, whereas we gathered data from a “half-electronic” order form.

The second most common MPE in our study was the wrong selection of the drug (error rate 15%) potentially resulting in a drug-drug interaction. Risk factors for this may include the use of multiple drug therapies in critically ill children with multisystem disorders, making drug-drug and also drug-patient interactions more likely.

All these errors were more likely to occur among children with longer stay and greater medication exposure than for children with shorter stay and/or requiring fewer drugs. The association between length of stay and MPE may be explained by two different scenarios: (1) the longer the PICU stay the greater risk of a prescribing error; or (2) due to a MPE the PICU stay could be prolonged. It also appears that these errors could be a consequence of disease severity where the cases were more complicated and the prescription complex.

MPEs occurred across many different main diagnoses and were associated with a wide range of drugs. In our study antihypertensives, antimycotics and drugs for nasal preparation (e.g. Oxymetazolin Nasal Sprays) were most commonly involved in MPEs with an error rate of 50% each. These findings are not consistent with other published paediatric studies, where antibiotics, steroids, anticoagulants and hormones were the drugs most commonly related to MPEs [5, 26, 22, 1, 19]. These differences suggest that MPEs found in a PICU cannot be generalized to other children wards, and that different definition of MPEs result in differing rates of errors. Additionally, drugs less frequently prescribed by physicians such as antimycotics (only 6 orders out of 1’129 medication orders), drugs for nasal preparation (12 of 1’129) and antihypertensives (14 of 1’129) are less known and therefore more prone to errors. Another reason for the high error rate of antihypertensives may be related to the fact that this medication group is subjected to frequent changes in dosing,

which makes the prescribing process even more difficult. Overall, these drug categories should be emphasized in the ongoing education of the entire team.

In our study, analgesics were the medication group with the greatest number of MPEs (43 errors, 14%). These were the most frequently prescribed drugs in our PICU, and it is therefore not surprising that they accounted for more errors than other groups.

Antibiotics were the second most commonly prescribed medication group in our study and therefore also often involved in MPEs (error rate 15%). Nevertheless, error rates in other studies were often higher than 15%. The percentages in previous studies were as follows: Folli et al. 36% [15]; Struck et al. 34% [37]; Lesar et al. 40% [26] and Ross et al. 44% [33]. However, these studies cannot be directly compared to our study because they focussed on medication errors or interventions rather than on MPEs. Paediatric patients are important targets for efforts aiming at reducing unnecessary antibiotic use [37, 12].

With regard to error severity, our results showed that harmful or potentially harmful errors accounted for 66% of all MPEs. Although a direct comparison with other studies is hampered by differences between clinical settings, study designs and outcome definitions, we found studies which showed a similar proportion of harmful or potentially harmful errors [21, 29]. Other authors have found lower percentages, ranging from 17% to 36% [15, 14]. The estimation of severity of MPEs in our study was sometimes difficult. This is primarily because such classifications are rarely available in the literature. Therefore, the determination of severity was somewhat subjective. None of the studies mentioned any harmful effects on the patients, probably because the errors were corrected prior to administration.

Limitations

This study has several limitations. First, as a single-center study, the findings reflect the situation at only one specific PICU, which may reduce the generalizability of our findings to other clinical settings. Second, the errors reported here were all identified and classified by a clinical pharmacist who gave a feedback to the physician during the round which could introduce a bias into the study. Clinical pharmacists routinely analysed drug charts only on Monday, Wednesday and Friday and we cannot exclude the possibility of undetected MPEs, hence underestimating the incidence of MPEs per patient. However, this would not affect the incidence of MPEs per medication orders which we described in our study. Furthermore, we did not test for interobserver reliability between the pharmacists, but all pharmacists were experienced in clinical pharmacy and followed the same guidelines. Nevertheless, further work is needed to establish the reliability of the identification and documentation of prescribing errors by pharmacists. Third, most of the prescribers in our study were residents. It is unknown whether resident prescribing patterns are different from non-resident prescribers. Forth, we focused on incidence and characteristics of MPE's, as a basis for the introduction of preventive measures. In future studies, the mechanisms leading to MPE's should be analysed, such as human factors, sources for drug choice and dosing, interface between prescriber and prescription.

Conclusion

Our analysis of MPEs revealed that prescribing errors occurred in 14% of all prescriptions of this PICU. The most frequent errors were wrong dose selection (50%), wrong drug selection (15%), and missing information (14%). By evaluating the

types of MPEs and by analysing patient characteristics and medication groups most commonly involved, we were able to identify risk factors for MPEs. At high risk for MPEs were children who received medication groups such as antihypertensives, antimycotics, drugs for nasal preparation, antiasthmatics, antibiotics and analgesics. Long PICU stay and the need for long mechanical ventilation were additional risk factors.

With a view to reduce MPEs and to improve patient-safety, our data may help to prevent errors before they occur. In view of the importance of dosing errors, it seems to be necessary to strengthen the presence of clinical pharmacists as a key element in preventing prescribing errors and reducing patient harm. Even in settings with less resources, a clinical pharmacist can play an important role in enhancing medication safety, particularly in paediatric patients where calculations are often more complex.

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Drugs and their Association with Socio-demographic, Diagnostic and Severity of illness Parameters

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Abstract

Purpose

The number of drugs applied to a patient is an important parameter of medication safety. The aim of this study was to evaluate the association between the number and profile of drugs applied in the first 24 hours of paediatric intensive care unit (PICU) and socio-demographic, diagnostic and severity of illness parameters.

Methods

A retrospective observational study was performed to determine the number and profile of drugs and their association with socio-demographic, diagnostic and severity of illness parameters. Number of drugs was defined as the number of different drugs that a study subject received during the first 24 hours.

Results

During the study period, 1751 medication orders in the first 24 hours were included. The patients received a median of 4 (range 1; 25) different drugs. The most frequently prescribed drug groups were analgesics without opioids (19%), opioids (12%), betalactam antibiotics (12%) and cardiac stimulants (7%). There was a statistically significant association between the number of drugs and age, some diagnosis and the severity of illness parameters, respectively. Socio-economic status and sex was not associated with numbers of drugs. Three medication groups (cardiac stimulants, opioids and analgesics without opioids) showed a statistically significant association with the severity of illness parameters.

Conclusion

The number of drugs applied in the first 24 hours was independently associated with age, diagnosis and severity of illness parameters but not with sex and socio-economic factors. This indicates that in our setting children received the same intensity and quality of treatment, irrespective of their socio-economic background.

Introduction

The number of drugs applied to a patient is an important parameter of medication safety. Especially in children drug use should occur cautiously as the frequency of unlicensed and off label drug prescriptions has been reported to be about 50 to 70%, depending on the method of analysis used and on the clinical setting [1]. However, the research focus should not only lie on drug use, but also on the severity and the prevalence of diseases. The paediatric intensive care unit (PICU) is a setting in which children are seriously ill and therefore multiple drugs have to be prescribed.

The possibility that more care may also cause harm is somewhat unexpected and received little attention in the past [2]. Therefore, it is important to detect potential over treatment and to evaluate its reasons [3]. In intensive care units, patients receive twice as many drugs as patients in general care units and are therefore at high risk of an adverse drug event (ADE) or an adverse drug reaction (ADR) [4]. A previous meta-analysis reported that the number of drugs administered to children was a potential predictor for ADRs [5]. However, there was no difference in ADE and ADR rates in intensive care patients when adjusted for number of drugs used [3]. In neonatal intensive care, Warrier et al showed that Caucasian race, male sex, gestational age of less than 28 weeks and birth weight under 1000 g were risk factors for higher drug exposure [6]. In one study it has been recognised that the nature of the population under study affects patterns of drug utilisation, which in turn affects the nature and frequency of ADRs [7].

Published data show that drug exposure among sick children is high. Arlanda et al [8, 9] described extensive medication use in a neonatal intensive care unit population and reported that at least 15% of neonates were administered more than 10 drugs during their PICU stay. Another study found that the number of prescribed drugs was

highest in children aged less than two years [10]. The importance of a careful risk-benefit assessments before any medicine is prescribed is crucial to improve the safety of pharmacological treatments [11].

The aim of this study is to evaluate the association between the number and the profile of drugs applied in the first 24 hours of admission to PICU and socio-demographic, diagnostic and severity of illness parameters. The analysis should provide information on patient-related factors correlating with and probably influencing drug prescriptions in the first 24 hours and during the further course of patients in paediatric intensive care.

Methods

Study population and data source

We performed a retrospective observational study to determine the association between the number and profile of drugs ordered in the first 24 hours of admission to the PICU at the children's hospital in Zürich during April and December 2010 and demographic, severity of illness and diagnostic parameters. The PICU is divided into a general PICU (9 beds) and a cardiac PICU (9 beds).

The study has been approved by the local Ethics Committee.

All patients who were admitted to the PICU were eligible to be included into the study. Each readmission after 24 hours out of the PICU was considered a new and separate case. Demographic parameters (sex, age and weight) and factors relating to severity of illness (length of PICU stay, mechanical ventilation, Paediatric Index of Mortality 2 (PIM2) [12]) are surveyed by means of the minimal data set (MDSi) of the Swiss Society of Intensive care [13]. Information on drugs prescribed during PICU stay (according to the anatomical therapeutical chemical (ATC) classification), laboratory parameters (serum creatinine, albumine, aspartate-amino-transferase (ASAT), alanine-amino-transferase (ALAT), c-reactive protein (CRP)), main diagnosis (according to the Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry Diagnostic Codes [14]), were obtained from the electronic patient records or the order sheets. Only medication orders during the first 24 hours of PICU admission were included in this analysis.

Age was categorised into five different age groups: neonates (0-4 weeks), infants (1-12 months), toddlers (1-4 years), children (5-11 years) and adolescents (> 12 years).

The main diagnoses were categorised into the following groups: Airway, cardiovascular, gastrointestinal, infection, injury, miscellaneous, neurological, post procedural or renal.

PIM Score was categorised into four different strata related to the expected risk of mortality in percent: category 1 (0-0.99%), category 2 (1.0%-9.99%), category 3 (10%-49.99%) and category 4 (50%-100%) [13].

The socio-professional status of the parents was defined according to the classification of the Swiss Federal Office of Statistics [14]. Criteria for classification into different categories were occupation, professional position and education. On these criteria four groups were built: high, medium, low or unknown. Within couples, the higher status was considered as representative.

Nationality was categorised into four different groups according to the most common nationalities of the patients in the PICU: Swiss, German, East European, others.

Mother tongue was categorised into four different groups according to the most common languages spoken in the PICU-patients: German, other Swiss national language than German, East European, others.

Number of drugs was defined as the number of different drugs that a study subject received during the first 24 hours of PICU admission. All drugs, also drugs on demand, were included in this analysis except total parenteral nutrition, lipids and dialysate.

Statistical analysis

Demographic variables were summarized using descriptive statistics. Data were expressed as means with corresponding standard deviation (SD), as median and ranges, or as proportions (%).

The independent association between the number of administered drugs during the first 24 hours of admission and the socio-demographic, diagnostic and severity of illness parameters (main diagnosis, PIM Score, mechanical ventilation, length of PICU stay) was estimated by using multivariate Poisson regression analysis.

In a second step, we classified the most frequently administered drugs in sixteen different groups according to the ATC code step four. We then ran again a multivariate Poisson regression model including the medication groups and the factors PIM Score, mechanical ventilation and length of PICU stay.

Statistical significance was defined as $p \leq 0.05$. Risk ratios are presented with 95% CI. All of the data analysis were conducted using the software program SAS, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Characteristics of the patients

We identified a total of 359 patient admissions during the study period, and we included 1751 medication orders during the first 24 hours of admission in this analysis. 185 (52%) patients were admitted to the general PICU, whereas 174 (48%) patients were admitted to the cardiac PICU. Table 1 shows the socio-demographic characteristics of the patients and their parents and the corresponding numbers of drugs. The distribution of the diagnostic categories with corresponding numbers of drugs is shown in table 2, and table 3 provides data regarding the severity of illness parameters with corresponding numbers of drugs. The mean length of PICU stay of all analysed patients was 6.5 days (SD 10.2 days, median 4 days, range 1-116 days).

Table 1: Socio-demographic Characteristics

	N	%	Number of drugs		
			Mean	**SD**	**Median (Range)**
Age (in categories)					
Neonates (0-4 weeks)	92	26	3.11	2.17	2.50 (1; 12)
Infants (1-12 months)	88	24	4.84	2.49	4.00 (1; 12)
Toddlers (1-4 years)	76	21	4.14	2.47	4.00 (1; 15)
Children (5-10 years)	49	14	4.57	4.41	3.00 (1; 25)
Adolescents (>10 years)	54	15	4.78	2.83	4.00 (1; 12)
Sex					
Male	205	57	4.37	3.23	4.00 (1; 25)
Female	154	43	3.99	2.30	4.00 (1; 12)
Nationality					
Swiss	262	73	4.16	2.80	3,50 (1; 19)
German	15	4	4.27	1.98	4.00 (1; 8)
Eastern European	49	14	4.63	3.90	4.00 (1; 25)
Other	33	9	3.88	1.92	4.00 (1; 9)
Mother tongue					
German	318	89	4.04	2.61	3.00 (1; 19)
Swiss national language other than German	12	3	5.42	2.87	5.00 (1; 11)
Eastern European	22	6	6.00	5.25	5.50 (1; 25)
other	7	2	4.00	1.91	4.00 (2; 8)
Socio- Professional status					
high	49	14	4.33	2.63	3.00 (2; 8)
low	26	7	4.04	3.19	3.00 (1; 19)
medium	175	49	4.33	3.04	4.00 (1; 11)
unknown	109	30	3.98	2.64	3.00 (1; 25)

Table 2: Distribution of diagnostic categories

	N	**%**	**Number of drugs**		
Main Diagnosis			**Mean**	**SD**	**Median (Range)**
injury	18	6	3.00	2.14	2.00 (1; 7)
cardiovascular	120	34	4.52	3.44	4.00 (1; 25)
neurological	34	9	4.00	3.12	3.00 (1; 15)
airway	35	10	3.77	2.65	3.00 (1; 11)
renal	4	1	2.00	0.82	2.00 (1; 3)
gastrointestinal	16	5	4.19	2.23	4.00 (1; 8)
infection	2	1	4.50	0.71	4.50 (4; 5)
miscellaneous	39	11	4.44	3.06	3.00 (1; 12)
post procedural	80	23	4.40	2.19	4.00 (1; 12)

Table 3: Severity of illness parameter

		N	%	Number of drugs		
Mechanical Ventilation				**Mean**	**SD**	**Median (Range)**
	No	129	36	3.45	2.79	3.00 (1; 19)
	Yes	230	64	4.63	2.84	4.00 (1; 25)
PIM Score						
	Category 1 (0-0.99%)	124	35	4.06	2.61	3.00 (1; 12)
	Category 2 (1-9.99%)	199	55	4.11	2.88	4.00 (1; 25)
	Category 3 (10-49.99%)	32	9	5.19	3.68	4.00 (1; 19)
	Category 4 (50-100%)	4	1	5.50	2.38	4.50 (4; 9)

Most commonly ordered drug groups

We analysed a total of 1751 medication orders throughout the study period. The patients received a median of 4 (range 1; 25) different drugs. The most frequently prescribed drug groups were analgesics other than opioids (19%), opioids (12%), betalactam antibiotics (12%) and cardiac stimulants (7%).

Socio-demographic, diagnostic and severity of illness parameters associated with the number of drugs

The results of multivariable Poisson regression analysis are presented in table 4. There was no statistically significant association between the number of drugs and the socio-demographic parameters except for age; the older the children the more drugs they received. However, the analysis showed a statistically significant difference in the number of drugs across patients with different principal diagnoses. Compared with the main diagnosis injury, patients with a cardiovascular diagnosis were more likely (RR 1.35 [CI 95% 1.05; 1.86-]) to receive more drugs. Patients with the main diagnosis ‘post procedural’ or ‘miscellaneous’ also received more drugs compared to the injury patients (RR 1.36 (CI 95% 1.02; 1.84) and RR 1.49 (CI 95% 1.11; 2.05), respectively). According to the Poisson regression analysis the number

of drugs showed a statistically significant association with the severity of illness parameters mechanical ventilation (RR 1.35 (CI 95% 1.21; 1.54)) and length of PICU stay (RR 1.01 (CI 95% 1.00; 1.01)), but not with the PIM Score.

Table 4: Socio-demographic, diagnostic and severity of illness parameters associated with the number of drugs (multivariable regression analysis)

Risk factors	Risk ratio	95% CI	p- value
Age			
Neonates	1 (reference)		
Infants	0.95	0.87; 1.32	0.351
Toddlers	1.13	1.01; 1.25	0.050
Children	1.01	1.0; 1.02	0.013
Adolescents	1.07	0.98; 1.12	0.163
Gender (f)			
male	1 (reference)		
female	0.94	0.84; 1.04	0.25
Nationality			
Swiss	1 (reference)		
German	1.13	0.91; 1.42	0.270
Eastern European	1,10	0.76; 1.57	0.618
other	0,99	0.74; 1.31	0.938
Socio professional status			
high	1 (reference)		
low	0.96	0.74; 1.23	0.748
medium	1.03	0.88; 1.21	0.729
unknown	0.88	0.73; 1.05	0.145
Language			
german	1 (reference)		
Swiss national language other than German	0.93	0.62; 1.46	0.742
Eastern European	1.56	0.98; 2.56	0.068
other	1.50	0.92; 2.51	0.111
Main diagnosis			
injury	1 (reference)		
cardiovascular	1.38	1.05; 1.86	0.024
neurological	1.30	0.95; 1.80	0.103
airway	1.13	0.83; 1.57	0.457
renal	0.62	0.27; 1.23	0.211
gastrointestinal	1.20	0.84; 1.73	0.320
infection	1.20	0.54; 2.39	0.634
miscellaneous	1.49	1.11; 2.05	0.011
post procedural	1.36	1.02; 1.84	0.041
Factors of illness severity			
PIM Score category 1	1 (reference)		
PIM Score category 2	0.91	0.81; 1.03	0,148
PIM Score category 3	1.04	0.86; 1.26	0.660
Mechanical ventilation	1.35	1.21; 1.54	<0.001
Length of PICU stay	1.01	1.00; 1.01	<0.001

Medication groups and their association with severity of illness parameters

In a second step we ran a multivariable Poisson regression model in which we evaluated the association between various drug groups and the severity of illness parameters. Sixteen different drug groups were analysed. Only three groups (cardiac stimulants, opioids and analgesics without opioids) showed a statistically significant association with the severity of illness parameters. Tables 5 to 7 show the results of these three groups.

Table 5: Cardiac stimulants: association with severity of illness parameters

Risk factors		Risk ratio	95% CI	p- value
PIM Score category 1		1 (reference)		
PIM Score category 2		2.1	1.15; 4.01	0.019
PIM Score category 3		4.01	1.68; 9.68	0.002
Mechanical ventilation	Yes	1.93	1.08; 3.56	0.030
Length of PICU stay		1.03	1.01; 1.06	0.018

Table 6: Opioids: association with severity of illness parameters

Risk factors		Risk ratio	95% CI	p- value
PIM Score category 1		1 (reference)		
PIM Score category 2		1.37	1.27; 4.14	0.002
PIM Score category 3		1.54	1.27; 7.54	0.007
Mechanical ventilation	Yes	7.10	4.18; 12.43	<0.001
Length of PICU stay		0.98	0.95; 1.00	0.106

Table 7: Analgesics without opioids: association with severity of illness parameters

Risk factors		Risk ratio	95% CI	p- value
PIM Score category 1		1 (reference)		
PIM Score category 2		1.43	1.26; 5.05	< 0.000
PIM Score category 3		1.15	1.08; 16.61	< 0.000
Mechanical ventilation	Yes	2.16	1.28; 3.67	0.004
Length of PICU stay		0.99	0.97; 1.01	0.320

Discussion

Our study provides useful information on the number and type of drugs ordered during the first 24 hours of admission, and on socio-demographic, diagnostic and severity of illness parameters. Our data showed that the number of drugs was associated with age, diagnosis and certain severity of illness parameters, but not with sex or with socio-economic factors.

The results of this study further provide evidence that the likelihood of receiving a larger amount of drugs was higher if the patient had a cardiovascular, a post procedural or 'miscellaneous' diagnosis. These findings are interesting in light of a previous study by Costa G et al. [17] who reported that the risk of death increased four-fold by adding a drug with cardiac and/or vascular effect. Postoperative patients are also likely to have sedatives and analgesics which would put them to risk for ADRs.

As mechanical ventilation and length of PICU stay were both independently associated with a higher number of drugs (RR 1.35 (CI 95% 1.21; 1.54), RR 1.01 (CI 95% 1.00; 0.01) respectively) during the first 24 hours, the question arises whether a certain over-treatment may play a role. Importantly, in our multiple regression equation, we corrected for illness severity at admission (expected mortality) and for diagnosis. A patient exposed to more drugs in the first 24 hours may need to stay longer in PICU because of drug-related problems. We previously showed that the number of drugs was independently associated with mortality [15]. There is a certain risk that ADEs are treated with additional drugs. Previous studies showed a relationship between the number of drugs prescribed and the occurrence of ADRs [5, 18, 19]. Rashed A et al. [18] reported that patients with five or more drugs prescribed

during their hospital stay had a three times higher risk of developing ADRs compared to patients receiving one to four drugs. In our study, patients received a median of four (range 1; 25) different drugs. According to the literature, the drug combinations which are most often associated with ADRs are analgesics, antibiotics and opioids [20-22]. These drug groups were also most commonly prescribed to our study population. Therefore, it is important for physicians and pharmacists to be vigilant about these drug groups, especially in severely ill children. Careful evaluation of the indication of each drug should be a mandatory part of the prescribing and dispensing routine on the ward.

Regarding the association between the number of drugs and socio-demographic parameters (nationality, language and professional status), we could not find any statistically significant association. These findings are in line with some previous studies [23-25] reporting that applied medical resources did not differ according to race, gender and insurance. In contrast, there are studies which have documented an association between low household income or low parents' education and increased drug prescription in their children [26-28]. Ciofi degli Atte ML et al. [29] found that it is likely that paediatricians may be more cautious in prescribing drugs to a child with a highly educated mother, because she might be better informed about the potential side effects of drugs, thus resulting in paediatricians' feeling to be more pressured with regard to the appropriateness of the prescription. On the other hand, a study on diagnostic and treatment behaviour in children with chronic respiratory symptoms in the UK pointed in the opposite direction: in the least deprived areas, children without significant asthma symptoms were more likely to be on inappropriate medication [30]. In accordance to the findings in the present study, we showed in a previous study that once children enter tertiary health care, such as intensive care,

nationality and socio-economic factors no longer influence quality of health care delivery [31]. This suggests that the socio-professional status may have an influence on primary care, but not on drug treatment patterns in the PICU. PICU-admission represents a critical status of illness severity, in which differences in nationality or socio-professional status may not play a role.

Overall there were more male (57%) than female (43%) patients on our PICU. This gender distribution has been reported in other studies [11, 17, 25, 29]. In addition, in adult intensive care, it has been shown that men received an increased level of care [32]. Despite these differences, men did not have a better outcome [32]. Regarding the association between number of drugs and gender in PICU, a study reported a positive correlation between drug exposure and male gender [6]. In our study population, however, there was no evidence for a statistically significant difference between the numbers of drugs across gender.

When looking at the age in the multivariable Poisson regression model, the RR 1.13 (CI 95% 1.01; 1.25) for the age group ‘toddlers’, and the RR 1.01 (CI 95% 1.01; 1.02) for the age group ‘children’ indicated that older children were at a slightly increased likelihood of receiving more drugs than younger children. Similar findings were reported from other studies which revealed that older children had a tendency to have higher ADR frequency [11, 33]. However, these findings should be interpreted with caution. As we know, the pharmacokinetics and pharmacodynamics are particularly different in neonates and very young children. Warrier et al. [6] showed that especially male gender, gestational age under 28 weeks and birth weight under 1000 g were risk factors for higher drug exposure. The question remains whether the nature of the drug which is given to the children is more important rather than the age.

Limitations

This study has several limitations. First, the retrospective and observational approach depends on documentation by the clinical team and is therefore partly subjective. Second, we conducted this study in a general and cardiac PICU at a university hospital, so our results may have limited generalizability to non-academic PICUs. Third, possible misclassification of diagnoses and incomplete patients' records can not be ruled out entirely and has to be considered in the interpretation of the data.

Conclusion

In the current PICU-population, the number of drugs applied in the first 24 hours was independently associated with age, diagnosis and the severity of illness parameters 'mechanical ventilation' and 'length of PICU-stay', but not with sex and socio-economic factors. The association with the need of mechanical ventilation and length of stay may be compatible with the deleterious effects of overtreatment, but it may also reflect higher disease severity of these children requiring a more intense tretament. The most inflicted drug groups were analgesics, opioids and cardiac stimulants.

We did not find an association between drug exposure and socio-economic status and sex, indicating that in our setting children received the same intensity and quality of treatment, irrespective of their socio-economic background. This is in agreement with previous studies in tertiary health care, whereas in primary care inequalities of care may exist.

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5 Conclusions

Our studies reveal different risk factors associated with the administration of drugs in children. With a view to reduce these risk factors and improve patient safety, the data presented here help us to prevent errors before they occur. In addition, prevention of DRPs requires a team approach, where clinical pharmacists play an important role in optimizing drug therapy in critically ill children. Careful evaluation of each drug, precise prescription and the awareness of the most vulnerable population may improve patient's outcome.

Medication associated with acute kidney injury

AKI is an important risk factor for poor outcome in critically ill children [1]. In previous studies, medication exposure has been shown to be associated with the development of AKI [2-5]. Although the exact percentage of medication associated AKI is not known our case-control study reveals some critical medication groups which are independently associated with AKI. Medications that can cause kidney injury include betalactam antibiotics, glucocorticoids, opioids and NSAIDs. Careful monitoring especially of these drug groups is necessary because early recognition of drug-induced renal dysfunction may alleviate some of the morbidity and mortality that is associated with AKI in the PICU.

However, in our opinion, it is also important to underline the multifactorial origin of AKI. Our results emphasize the complexity of AKI development. Measures of illness severity such as high PIM score, mechanical ventilation and length of stay are additional independent risk factors of AKI in the PICU. This means, that special focus should be given on the management of these patients. Whereas the severity of illness cannot be prevented in most instances, effects from drug treatment may be

more amenable to intervention. Thus, whenever possible, preventive measures should be instituted and medications should always be evaluated when renal dysfunction is identified.

Analysis of medication prescribing errors

The main focus of this thesis was to identify risk factors for MPEs and to determine the frequency, the types and the severity of these errors. Our analysis revealed that the incidence of prescribing errors was 14% of all prescriptions in our PICU. This is higher than in an adult study [6], but similar to published data in children [7, 8]. It was not surprising that dosing errors (overdosing or underdosing) were the most frequent errors as for most drugs, dosing calculations are required. In view of the importance of the MPEs and especially dosing errors, it seems to be necessary to strengthen the presence of a clinical pharmacist in the PICU as a key element in preventing prescribing errors. When assessing the effects of pharmacist's interventions on prescribing error rates, the severity of errors should also be considered [9, 10]. Because the estimation of severity of our MPEs was sometimes difficult, it would be helpful to establish a method of measuring severity with acceptable international reliability and validity [11]. According to our study, special attention and precautions are appropriate when antihypertensives, antimycotics, drugs for nasal preparation, antiasthmatics, antibiotics and analgesics are administered. These drug groups accounted for 67% of the MPEs. In addition and not very surprisingly, long PICU stay and the need of long mechanical ventilation were additional risk factors for MPEs.

Thus, analysis and publication of MPEs are essential requirements for the development and implementation of a long-term strategy of quality improvement. Additionally, clinical pharmacist involvement is desirable in the prescribing process. Even in settings with less resources, a clinical pharmacist can play an important role

in enhancing medication safety, particularly in paediatric patients where calculations are often more complex.

Drugs and their association with socio-demographic, diagnostic and severity of illness parameters

The last part of this thesis focused on the number and profile of ordered drugs applied in the first 24 hours of admission to PICU which is also an important issue of medication safety. The identification of patient related factors associated with the number of drugs could help to improve patient's safety in the prescribing process. Longer PICU stay and the need of mechanical ventilation were associated with a larger number of drugs in the first 24 hours. Polypharmacy may increase ADRs and consecutively PICU stay [12, 13].Thus, it is important to review drug utilisation to identify drugs with increasing use. In our PICU particularly analgesics, opioids and cardiac stimulants should be kept in mind because they were associated with a longer PICU stay and mechanical ventilation. The study revealed also, that the types of main diagnosis such as cardiovascular and post procedural were independent predictors for a larger number of drugs. According to Costa G et al. [14] the risk of death increased four-fold by adding a drug with cardiac and/or vascular effect.

These findings indicate that in order to optimise patient's safety, healthcare professionals should keep the number of prescribed drugs as low as possible and pay particular attention to children at risk, such as long stay patients, patients with the need of mechanical ventilation and children with some critical main diagnoses. studies reveal different risk factors associated with the administration of drugs. With a view to reduce these risk factors and improve patient safety, the data presented here help us to prevent errors before they occur. In addition, prevention of DRPs requires a team approach, where clinical pharmacists play an important role in optimizing drug

therapy in critically ill children. Careful evaluation of the indication of each drug, precise prescription and the awareness of the most vulnerable population may improve patient's outcome.

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6 Publications

Glanzmann C, Vonbach P. Kinderspital Zürich betritt mit neuer online Plattform in der Schweiz Neuland [in German]; pharmaJournal 2012; 150(24): 10.

Glanzmann C, Vonbach P. www.kinderdosierungen.ch [in German and French], GSASA Journal 2012; 26(4); 132-3

Glanzmann C, Vonbach P. Medikamentendosierung bei Kindern – Datenbank unterstützt korrekte Dosierung [in German]. Competence 2012; 76(12): 28

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DOI: 10.1007/s00467-015-3180-9

Glanzmann C, Frey B, Meier CR, Vonbach P. Analysis of medication prescribing errors in critically ill children. Eur J Pediatr 2015;
DOI 10.1007/s00431-015-2542-4

Glanzmann C, Vonbach P, Meier CR, Frey B. Drugs and their association with socio-demographic, diagnostic and severity of illness parameters. Submitted

7 Poster Presentations

Kongress der Gesellschaft Schweizerischer Amts- und Spitalapotheker. Luzern, November 21 - 22, 2008. Jager M, Glanzmann C, Frey B, Baenziger O, Vonbach P. Optimization of the prescriptions on a paediatric intensive care unit through the pharmaceutical service [in German].

Joint annual meeting SGI / SGInf / SGSH / SGKPT / IGIP, Lausanne. September 1 - 3, 2010. Glanzmann C, Vonbach P, von Gunten V, Frey B, Berger C. Streamlining empirical antibiotic prescribing in paediatric intensive care.

Seizièmes Journées Franco-Suisses de Pharmacie Hospitalière. Sion, Novembre 18 - 19, 2010. Septembre 1 - 3, 2010. Glanzmann C, Vonbach P, von Gunten V, Frey B, Berger C, Streamlining empirical antibiotic prescribing in paediatric intensive care

16th Congress of the European Association of Hospital Pharmacists. Vienna, Austria, March 30 – April 1, 2011. Glanzmann C, Vonbach P, von Gunten V, Frey B, Berger C, Streamlining empirical antibiotic prescribing in paediatric intensive care.

GSASA – pharmaSuisse 2011 Kongress. 1. Schweizerischer Apothekerkongress. Interlaken, Switzerland, November 30 – December 1, 2011.
Glanzmann C, Bielicki J, Subotic U, Vonbach P, Berger C
Adherence to perioperative antimicrobial prophylaxis in a children’s hospital.

GSASA – pharmaSuisse 2011 Kongress. 1. Schweizerischer Apothekerkongress. Interlaken, Switzerland, November 30 – December 1, 2011. Vonbach P, Caduff Good A, Glanzmann C, Thoma R. Paediatric dosage booklet: from a crude text file to a sophisticated smartphone application?

Kongress der Gesellschaft Schweizerischer Amts- und Spitalapotheker. Baden, November 15 - 16, 2012. Vonbach P, Caduff Good A, Glanzmann C, Thoma R. kinderdosierungen.ch [in German].

18ièmes Journées Franco-Suisses de Pharmacie Hospitalière. Montreux, 28 - 29 Novembre, 2013 Vonbach P, Caduff Good A, Glanzmann C, Tuchschmid R, Aeschbacher S, Kussmann S, Fleury M. posologies-pediatriques.ch / kinderdosierungen.ch [in French].

GSASA – pharmaSuisse 2014 Kongress. 2. Schweizerischer Apothekerkongress. Interlaken, Switzerland, November 4, 2014. C Glanzmann, Vonbach P, Frey B, Meier C. Drugs as risk factors of acute kidney injury in critically ill children.

8 Oral Presentations

Teachingwoche Kinderspital Zürich, July 07, 2008. Dosisanpassung an Niereninsuffizienz.

Teachingwoche Kinderspital Zürich, May 26, 2009. Medikationsfehler – Strategien zur Vermeidung.

Teachingwoche Kinderspital Zürich, May 27, 2009. Biosimilars – Ähnliches ist nicht dasselbe.

IPS-Fortbildung Kinderspital Zürich, March 17, 2010. Antibiotika auf der Intensivstation.

Teachingwoche Kinderspital Zürich, September 07, 2010. 7 Steps to become a prescribing expert.

Teachingwoche Kinderspital Zürich. September 08, 2010. UAW's 2 Fallbeispiele.

Studentenkurs ETH, Kinderspital Zürich. November 24, 2010. Arzneimittelinformation.

Ärztefortbildung Kardiologie, Knderspital Zürich. November 30, 2010. UAWs.

IPS Pflege Fortbildung, Kinderspital Zürich. August 15 and 29, 2011. Tipps und Tricks der Arzneimittelliste.

Gemeinsamer Pädiatriekongress: fPmh, SGP, SGKC, SGKLPP, Montreux, Switzerland, September 1, 2011. Adherence to perioperative antimicrobial prophylaxis in a childrens hospital.

Teachingwoche Kinderspital Zürich. December 06, 2011. Fallbeispiel – 4 für alle Fälle.

Teachingwoche Kinderspital Zürich. December 08, 2011. Compliance mit Richtlinien: 2 Beobachtungsstudien.

Pflege Fortbildung, Kinderspital Zürich. December 13, 2011. Pharmakologie: Schmerz.

Teachingwoche Kinderspital Zürich, December 11, 2012. Lieferengpässe von Arzneimitteln.

Teachingwoche Kinderspital Zürich. December 12, 2012. Genetischer Polymorphismus.

FZK-Symosium, Kinderspital Zürich. March 21, 2013. Kinderdosierunge, individuell – wann und wie?

Frühlingsfortbildung der schweizerischen Interessensgesellschaft Notfallpflege. March 27, 2014. Kinderdosierungen – leicht gemacht?

9 Congress Participations

14th Congress of the European Association of Hospital Pharmacists. Barcelona, Spain, March 25 - 27, 2009.

15th Congress of the European Association of Hospital Pharmacists. Nice, France, March 26 - 27, 2010.

Joint annual meeting SGI / SGInf / SGSH / SGKPT / IGIP, Lausanne. September 1 - 3, 2010.

Gemeinsamer Pädiatriekongress: fPmh, SGP, SGKC, SGKLPP, Montreux, Switzerland, September 1, 2011.

GSASA – pharmaSuisse 2014 Kongress. 2. Schweizerischer Apothekerkongress. Interlaken, Switzerland, November 4, 2014.

10 Curriculum Vitae

Name	Corina Glanzmann
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Education

1985 – 1990	Primary school, Unterägeri (ZG)
1990 – 1998	Gymnasium Zug, leading to Matura Type B
1998 – 2003	Pharmacy Studies, Federal Institute of Technology Zurich
October, 2003	Federal Degree in Pharmacy
December, 2005	Certificate in Cambridge Advanced English
2010 –2011	Certificate of Advanced Studies in Biostatistics and Epidemiology, University Basel, Bern and Zürich
January 2010 to present	Dissertation, Division of Pharmacology and Toxicology, University Basel
July 2008 to June 2015	Hospital Pharmacy FPH

Professional experience

2003- 2005	Assistant chief pharmacist, Klus-Apotheke AG, Zürich
2006- 2007	Assistant chief pharmacist, Amavita-Apotheke, Buchs (AG)
June – October 2013	Internship, Kantonsapotheke Zürich
2007 to January 2015	Pharmacist, Children's University Hospital Zürich
March 2015 to present	Pharmacist, Kantonsapotheke Zürich
February 2008 to present	Lectures in pharmacology, Bachelor of Nursing Science, Zurich University of Applied Sciences Winterthur

Lectures

During my Pharmacy Studies, my postgraduate education in Hospital Pharmacy FPH and my Certificate of Advanced Studies in Biostatistics and Epidemiology I attended courses of the following lecturers:

Altorfer H, Amrhein N, Baltisberger M, Berger EG, Bohlius J, Borbély AA, Boutellier U, Corford J, Egger M, Folkers G, Gander B, Ganter C, Heusser-Gretler R, Hürzeler M, Inäbnit SO, Krähenbühl S, Kopp D, Kuehni C, Lengeler C, Lichtenteiger W, Marrer S, Meier B, Merkle HP, Minder B, Möhler H, Mühlebach S, Müntener M, Mütsch M, Obertüfer HK, Pannatier A, Rieder L, Surber C, Turnheer P, Winterhalter K, Wolfer D, Wunderli-Allenspach H, Zwahlen M