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High-alert medications for hospitalised paediatric patients – a two-step survey among paediatric clinical expert pharmacists in Germany

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Paediatric patients are more vulnerable to be harmed by medication errors compared to adults due to pharmacokinetic and pharmacodynamic changes in their development, individual dosing calculations, and manipulation of ready to-use products intended for adult patients. According to the Institute of Safe Medication Practices, there are some "drugs that bear a heightened risk of causing significant patient harm when they are used in error"; these drugs are called high-alert medications (HAM). The two-step survey among paediatric clinical expert pharmacists presented here aimed to compile a nation-wide HAM list. To provide detailed guidance, this survey followed a drug-based approach, resulting in specific potential drug related problems (DRPs) and associated recommendations for prevention. In contrast to this approach, in the first round of the survey two drug classes were included that both were rated as HAM (i.e. chemotherapy and parenteral nutrition). Twenty single drugs were identified as HAM, 65% of which were cardiovascular or neurological drugs. The paediatric expert pharmacists mentioned in total 216 potential DRPs; in particular, they identified potential administration-related problems (28% of all DRPs), dosing-related problems (26%), and drug-choice-related problems (18%, e.g. drug confusion and drug monitoring). Moreover, they suggested 275 potential interventions to address these DRPs. Two thirds of all interventions dealt with the preparation by the hospital pharmacy, standardisation of processes (e.g. labelling), and education or training. In conclusion, this survey provided a German paediatric high-alert medication list from a paediatric pharmacist point of view. Moreover, the experts mentioned for the first time specific potential DRPs and associated interventions to guide a local multidisciplinary approach for preventing medication-related harm in children.

1. Introduction

Paediatric drug therapy is characterised by age-dependent changes in pharmacokinetic and pharmacodynamic parameters compared to adult drug therapy (World Health Organization 2007). In addition, necessary manipulations with drug formulations (O'Brien et al. 2019) and individual dosing calculations (Avidan et al. 2014) enhance the patient's risk for harm-causing medication errors. This translates to up to 17 preventable adverse drug events per 1000 patient-days in paediatric inpatients and nearly double that amount in neonatal intensive care patients (Gates et al. 2018). A recent study found that 3.9% of all parenteral nutrition prescriptions on neonatal or paediatric intensive care units contained prescribing errors, that were prevented by a medication review. Of these errors, 12% could have resulted in harmful outcomes (Hermanspann et al. 2017). Interventions to prevent harm-causing medication errors are therefore crucial. Some drugs may be associated with a more pronounced risk for harm and were defined as High-Alert Medications (HAM). The Institute for Safe Medication Practices (ISMP) defined them as "drugs that bear a heightened risk of causing significant patient harm when they are used in error". Up to now, there were three approaches only to select HAM out of other drugs in paediatric therapy (Franke et al. 2009; Maaskant et al. 2013; Bataille et al. 2015). Specialized pharmacists are the group of healthcare professionals that overviews the whole medication-use process from prescription to bedside and in addition can provide drug-specific recommendations. To our knowledge, no other drug-specific recommendations were published in this field before, rather than general recommendations (Bataille et al. 2015).

Thus, the aims of this two-step survey were to develop a German paediatric high-alert medication list, provide potential specific Drug-Related Problems (DRP) and associated potential interventions.

2. Investigations and results

2.1. Response rate and respondents' characteristics

This survey was sent to pharmacists, who are specialised in paediatrics and working in a German university hospital (n=35). Additionally, pharmacists who were part of the paediatric committee of the "Federal Association of German Hospital Pharmacists", were included (n=7), resulting in a total of 42 pharmacists who were contacted to answer this survey. The first round was performed from December 2016 to February 2017 and resulted in 60% reply (25/42 persons); the second round of this survey took place from November 2018 to January 2019 – 40% of contacted persons replied (17/42 persons). The majority of respondents were specialised hospital pharmacists and had more than 15 years of professional experience. More details are displayed in Table 1.

2.2. High-alert medications

Thirty-nine different drugs and two drug classes (chemotherapy and parenteral nutrition) were extracted from three international surveys. Adopting a 75% threshold for HAM rating (Maaskant et al. 2013), 20 out 39 drugs (51%) and both drug classes were determined as HAM by the survey panel (see Figs. 1 and 2).

Table 1: Characteristics of survey respondents

Item	Round 1 (n=42)	Round 2 (n=42)
Respondents [n (% of invited pharmacists)]	25 (60%)	17 (40%)
Sex		
Male [n (%)]	6 (24%)	4 (24%)
Female [n (%)]	14 (56%)	8 (47%)
N.A. [n (%)]	5 (20%)	5 (29%)
Age		
Age of respondents [years, median (IQR)]	42 (33-48)	43 (36-53)
N.A. [n (%)]	7 (28%)	7 (41%)
Professional experience		
Years since pharmacist´s registration [median (IQR)]	17 (7-21)	16 (11-29)
N.A. [n (%)]	7 (28%)	4 (24%)
Professional training status		
Specialised hospital pharmacists [n (%)]	17 (68%)	12 (70%)
Not specialised hospital pharmacists [n (%)]	4 (16%)	2 (12%)
N.A. [n (%)]	4 (16%)	3 (18%)

N.A. = not available, IQR= interquartile range.

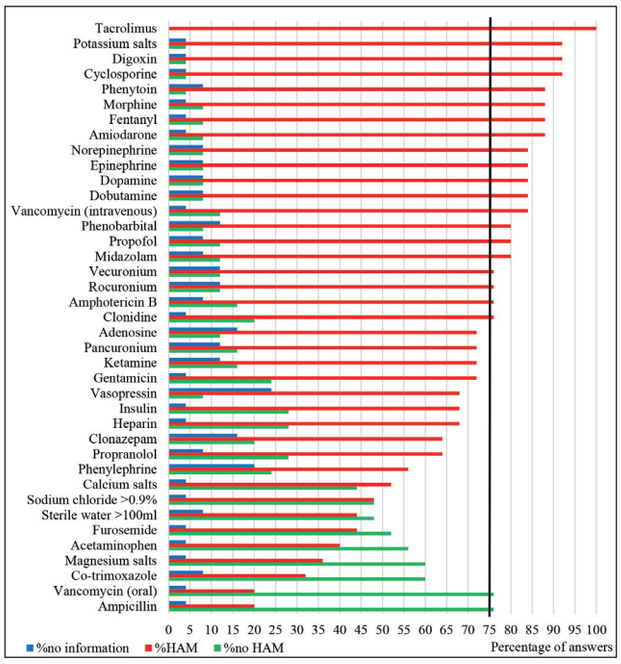

Fig. 1: The expert panel (n=25) rated 20 drugs as high-alert medications out of a total of 39 drugs. Black line marks 75% threshold. Green bar: no high-alert medication"; blue bar: "no information"; red bar: "high-alert medication".

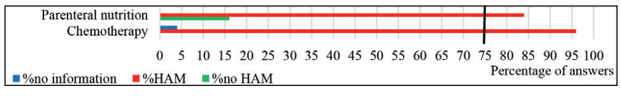

Fig. 2: Expert panel responses for two drug classes given in percentage of all answers (n=25). Black line marks 75% threshold. Green bar: no high-alert medication"; blue bar: "no information"; red bar: "high-alert medication".

The majority of drugs (13/20 drugs, 65%) resulted from two anatomical main groups: drugs addressing the cardiovascular (7 drugs) and the nervous system (6 drugs).

Twenty percent of respondents rated oral applied vancomycin as HAM (5/25 experts), whereas 84% did so with intravenous applied vancomycin (21/25 experts), indicating that the experts could differentiate between drugs that fit the definition for HAM and those that did not. However, the difference in ratings of oral and intravenous applied vancomycin did not reach statistical significance (Fisher-exact test, p=0.48).

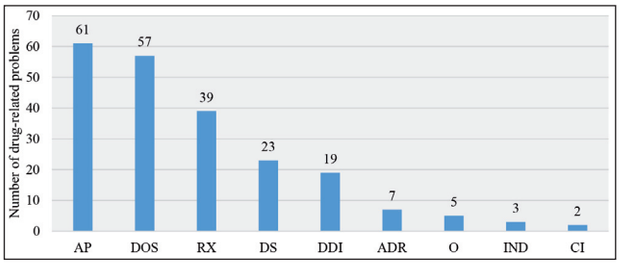

Fig. 3: Potential drug-related problem categories with frequency (total n=216) mentioned by survey panel and assigned to APS-Doc classification system (Hohmann, Eickhoff et al. 2012). AP= application/ administration, DOS= dosage, Rx= drug, DS= dosage form/ drug strength, DDI= drug-drug interaction, ADR= adverse drug reaction, O= other, IND= indication, CI= contraindication

2.3. Potential drug-related problems

In the second round of the survey, potential DRPs and possible interventions for prevention were enquired for the identified 20 HAM. The initially identified two drug classes were not included in the second round, as both classes comprise a multitude of single drugs. Thus, potential DRPs and associated interventions were supposed to show a wide variation.

In total, 216 potential DRPs were mentioned by the survey panel for the 20 HAM (median of 11 DRPs/drug [IQR 8-13 DRPs/drug], Table 2). The identified DRPs were categorised into the APS-Doc classification system as shown in fig. 3 (APS-Doc: German acronym for „Arzneimittelbezogene Probleme im Stationären Bereich"-Documentation [Drug-related problems in the inpatient setting]). Seventy-three percent of potential DRP (157/216 DRPs) could be categorised into three groups: problems regarding "application or administration" (e.g. crushing of sustained release tablets), "dosage" (e.g. tenfold errors), and "drug" (e.g. drug confusion or inadequate drug monitoring). Drug-drug interactions were mentioned only 19-times (9% of all DRPs) affecting ten single drugs, e.g. cyclosporine.

2.4. Potential interventions

The expert panel was invited to suggest potential interventions with respect to the potential DRPs via open-ended questions. This resulted in 166 DRPs for which at least one intervention was mentioned and 50 DRPs without associated interventions. In total, 275 interventions were named (1.7 interventions/DRP, a median of 14 interventions/drug [IQR 12-16 interventions/drug]). The interventions were iteratively categorised into nine groups (Table 3). These categories addressed three main groups of health care professionals, i.e. physicians, pharmacists, and nurses. The survey panel mentioned 8% of medication safety interventions to be carried out by physicians, 27% by pharmacists, and 12% by nurses. More than half of the interventions (52%) were not associated with a specific group. Sixty-five percent of interventions (179/275) addressed three topics: medication preparation by the hospital pharmacy, standardisation of processes (e.g. labelling), and education or training.

3. Discussion

This two-step survey identified for the first time high-alert medications (HAM) from a German hospital pharmacist's point of view. Using a drug-based approach, specific potential DRPs and associated interventions were identified. The results of this survey may help to improve paediatric medication safety by drug-specific and locally designed interventions.

A drug-based approach allowed researchers to ask the experts for specific potential DRPs and interventions. As a consequence, this method implied that drug groups (i.e. chemotherapy and parenteral nutrition) were missing in the second round of our survey. Simultaneously, we confirmed with the first-round results the rating as high-alert medication that is found by other research groups (Franke et al. 2009; Maaskant et al. 2013; Bataille et al. 2015).

Table 2:Potential drug-related problems and interventions associated with high-alert medications for hospitalised paediatric patients mentioned by expert panel

Drug	Drug.related problem category	n=	Drug-related problems: details	Potential intervention category	n=	Potential interventions: details
Amiodarone	AP	4	• Intravenous bolus rate too high • Wrong solvent choice for reconstitution (3x)	D	3	• Pre-printed label (including solvent) • Education/ training (2x)
				N.A.	1	• In case of emergency: bolus application
	DOS	4	• Calculation errors when unusual dosages for parenteral use or capsules are prescribed (2x)	B	3	• Ward-based pharmacist • Plausibility check before preparation • Preparation in hospital pharmacy
			• Dose prescription after loading dose not adequate	C	1	• Independent double-check after dosage calculation
			• Dosing error	D	4	• Digital documentation • Standardisation • Education/ training (2x)
	DDI	3	• Amiodarone inhibits cytochrome P450 enzymes (3x)	B	1	• Check for interactions
				D	1	• Education/ training
	DS	1	• Syringe pumps with different concentrations	D	1	• Standardised concentrations • Pre-printed label (including concentration)
	CI	1	• Disregard of contraindications	-	0	-
Amphotericin	DS	8	• Dosage confusion for liposomal and conventional amphotericin (8x)	A	4	• Unambiguous prescribing of amphotericin formulation and application form (4x)
				B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	3	• Storage of different amphotericin formulations separately • Double-check (2x)
				D	5	• Clear labelling (2x) • Education/ training (3x)
	AP	6	• Wrong solvent choice for reconstitution (2x) • Disregard of incompatibilities (2x) • Administration too fast (2x)	D	1	• Summarized handling instructions for reconstitution
	DOS	2	• Dosage error • Overdosing	A	1	• Standardised prescription
	IND	1	• Discontinuation too early	-	0	-
Cyclosporine	DDI	5	• Interactions via cytochrome P450 inhibition, e.g. with gentamicin or statins (5x)	B	2	• Pharmaceutical review (2x)
				D	2	• Programs available to perform drug-drug interaction checks • Education/ training
	RX	3	• Inadequate TDM • Inadequate generic substitution (2x)	D	3	• Education/ training (3x)
	DOS	2	• Dosing error • No adequate dose adjustment in case of renal failure	A	1	• Prescribing of standardised concentrations
				B	1	• Preparation in hospital pharmacy
	AP	1	• Administration-rate too high	D	1	• Education/ training
	ADR	1	• Disregard of toxicity	D	2	• TDM • Education/ training
Clonidine	AP	3	• Wrong reconstitution leads to wrong dosage • Accidental bolus or line flushing • Wrong syringe pump settings	B	4	• Preparation in hospital pharmacy (2x) • Unit-dose drug distribution • Ward-based pharmacist
				C	1	• Independent double-check
				D	3	• Standardised plan for dose tapering • Standardised assignment of central or peripheral venous catheter lines • Education/ training
	IND	2	• Hypertensive emergencies • Withdrawal symptoms via rapid discontinuation	D	2	• Monitoring of vital signs • Education/ training
	DOS	1	• Calculation errors	A	1	• Use of tables for enhanced switching between µg and mg
				C	1	• Independent double-check
	CI	1	• Disregard of coronary diseases	A	1	• Precise medical history and diagnostic approach
	DS	1	• Different concentrations of commercial medications	A	1	• Unambiguous prescription
	RX	1	• Confusion with clonazepam	D	1	• Clear labelling
Digoxin	RX	4	• Confusion with different cardiac glycosides (2x) • Incorrect monitoring (missed check of laboratory values, e.g. potassium; 2x)	A	1	• Prescription of commercial names
				D	3	• TDM • Laboratory controls of potassium • Education/ training
	DOS	2	• Dosage errors, e.g. in renal failure (2x)	D	1	• TDM
	DDI	2	• Disregard of potential interactions (2x)	D	1	• Education/ training

Dobutamine	RX	5	• Confusion with dopamine (5x)	B	1	• Pharmaceutical consultation in medication-use process
				C	1	• Storage separated from dopamine
				D	3	• Clear labelling (e.g. colour or tall-man lettering; 3x)
	DOS	3	• Calculation error (e.g. µg vs. mg; 2x) • Initial dose too high	D	1	• Pocket-sized card with common dosages
	DS	3	• Confusion of different concentrations (2x) or dosage forms	C	1	• Independent double-check
				D	2	• Clear labelling • Education/ training
	AP	4	• Wrong reconstitution leads to wrong dosage • Accidental bolus or line flushing • Disregard of incompatibilities, e.g. with heparin (2x)	C	1	• Catecholamine application via separate line
				D	4	• Standards assignment of drugs to intravenous lines • Education/ training (3x)
Dopamine	AP	2	• Accidental bolus via rinsing the lines or using the same line for different medications (2x)	B	2	• Preparation in hospital pharmacy • Ward-based pharmacist
				C	1	• Independent double-check
				D	4	• Standardisation • Standards assignment of drugs to intravenous lines • Education/ training (2x)
	DOS	2	• Dosage error (2x)	A	1	• Prescribing of standardised concentration
				B	1	• Preparation in hospital pharmacy
	RX	1	• Confusion with dobutamin	D	1	• Clear labelling
	DDI	1	• Interactions e.g. with linezolid	-	0	-
Epinephrine	DS	4	• Confusion of different concentrations in commercial products or infusion pumps (4x)	D	4	• Clear labelling with pre-printed labels • Standardised calculation forms • Education/ training (2x)
	RX	4	• Confusion (e.g. with norepinephrine; 4x)	C	1	• Storage separated from norepinephrine
				D	4	• Clear labelling (2x) • Education/ training (2x)
	AP	4	• Wrong concentration of infusion pump (2x) • Accidental bolus or line flushing • Wrong label on infusion pumps	B	3	• Ward-based pharmacist • Preparation in hospital pharmacy (e.g. ready-to-use syringes; 2x)
				C	1	• Independent double-check
				D	5	• Standardisation (3x) • Education/ training (2x)
	DOS	1	• Initial dose too high	-	0	-
	O	1	• Wrong storage	D	1	• Education /training
Fentanyl	DOS	4	• Tenfold errors • Overdosing due to different application forms or dosages at the same time (3x)	B	2	• Preparation in hospital pharmacy • Ward-based pharmacist
				C	1	• Independent double-check
				D	5	• Standardisation (e.g. infusion pump concentrations) • Education/ training (4x)
	RX	2	• Confusion with sufentanil • Wrong conversion when changing opioids	D	3	• Unambiguous communication • Consultation of local pain service • Education/ training
	DS	1	• Dose confusion (µg vs. mg)	A	1	• Prescribing of standardised concentration
	ADR	1	• Serotonin syndrome	D	1	• Education/ training
	AP	1	• Potential incompatibilities	D	1	• Education/ training
Midazolam	AP	5	• Wrong reconstitution leads to wrong dosage • Accidental bolus or line flushing • Incompatibilities (3x)	B	6	• Preparation in hospital pharmacy (3x) • Unit-dose drug distribution (2x) • Ward-based pharmacist
				C	1	• Independent double-check
				D	2	• Standardised infusion scheme • Education/ training
	DOS	1	• Dosing errors	A	1	• Prescribing of standardised concentrations
				B	1	• Preparation in hospital pharmacy
	RX	1	• Confusion with diazepam	C	1	• Storage separated from diazepam
				D	2	• Clear labelling • Consideration of local guidelines
	DDI	1	• Drug-drug interactions	-	0	-

Morphine	DOS	6	• Tenfold errors (2x) • Wrong reconstitution leads to wrong dosage • Fail to adjust doses to renal or hepatic function (2x) • Overdosing	B	3	• Ward-based pharmacist • Preparation in hospital pharmacy (2x)
				C	1	• Independent double-check
				D	6	• Standardisation of concentrations • Pocket-sized cards with common dosage • Establishing clinical decision support systems • Education/ training (3x)
	AP	3	• Wrong reconstitution leads to wrong dosage • Intravenous administration of oral product • Dose-dumping via crushing of extended-release tablets	B	4	• Unit-dose drug distribution • Preparation in hospital pharmacy (3x)
				D	2	• Education/ training (2x)
	DDI	1	• Drug-drug interactions with sedatives	-	0	-
Norepinephrine	AP	5	• Wrong reconstitution leads to wrong dosage (3x) • Accidental bolus or line flushing (2x)	A	2	• Prescribing of standardised concentrations (2x)
				B	3	• Ward-based pharmacist • Preparation in hospital pharmacy, e.g. of ready-to-use syringes (2x)
				C	1	• Independent double-check
				D	3	• Standardisation (2x) • Education/ training
	DOS	2	• Overdosing • Dosing error	A	1	• Prescribing of standardised concentrations
				B	1	• Preparation in hospital pharmacy
	DS	2	• Confusion of different concentrations (µg vs. mg; 2x)	D	2	• Establishing standardised calculation forms • Education/training
	RX	2	• Confusion with epinephrine (2x)	D	2	• Clear labelling • Education/ training
	ADR	1	• Extravasation	-	0	-
	O	1	• Wrong storage	D	1	• Education/ training
Phenobarbital	DOS	3	• Dosing error, e.g. tenfold errors (3x)	A	1	• Prescribing of standardised concentrations
				B	3	• Ward-based pharmacist • Preparation in hospital pharmacy (2x)
				C	1	• Independent double-check
				D	3	• Standardisation • Education/ training (2x)
	AP	2	• Administration rate of intravenous bolus too high • Wrong route of administration	D	2	• Education/ training (2x)
	ADR	1	• Extravasation	D	1	• Education/ training
	DDI	1	• Drug-drug interactions	-	0	-
Phenytoin	AP	5	• Wrong reconstitution leads to wrong dosage (2x) • Osmolality too high for peripheral administration • Wrong route of administration • Incompatibilities	B	4	• Unit-dose drug distribution (2x) • Preparation in hospital pharmacy (2x)
				D	3	• Preparation of handling instructions • Education/ training (2x)
	DOS	3	• Calculation errors when capsules are prescribed • Plasma level variations due to individual hepatic metabolism • Dosing errors	B	1	• Capsule compounding: independent double-check following dosage calculation
				D	1	• Education/ training
	DDI	2	• Drug-drug interactions (2x)	B	3	• Medication review • Unit-dose drug distribution • Preparation in hospital pharmacy
	RX	1	• Confusion with sound-alike medications	A	1	• Prescribing of drug (rather than commercial product)
	ADR	1	• Extravasation	D	1	• Education/ training
Potassium salts	DOS	6	• Overdosing (2x) • Under- or overdosing due to commercial product change (2x) • Dosing error (2x)	B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	3	• Independent double-check (3x)
				D	2	• Standardisation • Education/ training
	AP	6	• Wrong reconstitution leads to wrong dosage or accidental bolus (2x) • Confusion of intravenous products for peripheral vs. central administration (3x) • Wrong rate of infusion	B	4	• Unit-dose drug distribution (2x) • Preparation in hospital pharmacy (2x)
				C	1	• Independent double-check
				D	3	• Standardised dilutions • Arterial blood gas analysis • Education/ training
	RX	3	• Confusion with other infusions (e.g. saline; 3x)	B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	3	• Storage separated from other infusions • Independent double check (2x)
				D	2	• Standardisation • education/ training

Propofol	DS	3	• Confusion of different concentrations (1% and 2%; 3x)	B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	2	• Separated storage of propofol 1% and 2% • Independent double-check
				D	3	• Standardisation • Education/ training
	DOS	2	• Dosing error, e.g. overdosing (2x)	B	2	• Unit-dose drug distribution • Preparation in hospital pharmacy
	ADR	2	• Propofol infusion syndrome • potential addiction	D	2	• Reflected and short term use (2x)
	RX	2	• Confusion with etomidate (2x)	C	2	• Separated storage of propofol and etomidate • No simultaneous use of propofol and etomidate
				D	1	• Education/ training
	O	1	• Potential coagulation of emulsion due to expired product	D	1	• Clear labelling
Rocuronium	DOS	3	• Dosing error (2x) • Calculation error	A	1	• Prescribing of standardised concentration
				B	1	• Preparation in hospital pharmacy
				D	2	• Development of paediatric dosage guidelines • Standardisation
	RX	2	• Confusion with other medications (in case of emergency or sound-alike; 2x)	C	1	• Storage separated from sound-alike medications
				D	3	• Clear labelling • Education/ training (2x)
	AP	1	• Wrong reconstitution leads to wrong dosage	D	1	• Standardised reconstitution
	O	1	• Wrong storage	D	2	• Clear labelling • Education/ training
Tacrolimus	DOS	5	• No dose adjustment in case of renal failure • dosing error (3x) • No individualized dosing due to fixed doses of commercial products	A	4	• Ward-based pharmacist • Unit-dose drug distribution • Preparation in hospital pharmacy (2x)
				B	1	• Prescribing of standardised concentrations
	RX	4	• Missing TDM (2x) • Misinterpretation of TDM results • Inadequate generic substitutions	D	4	• Establishing TDM and preparing instructions for use (3x) • Education/ training
	AP	3	• Adsorption on PVC-containing infusion material (2x) • Disregard of incompatibilities	D	2	• Preparation of incompatibility lists including infusion set materials (2x)
	DDI	2	• Drug-drug interactions (2x)	B	2	• Unit-dose drug distribution • Preparation in hospital pharmacy
Vancomycin	AP	5	• Incompatibilities (2x) • Wrong reconstitution leads to wrong dosage (2x) • disregard of 1h minimal infusion period	D	4	• Local preparation and administration guideline (2x) • Education/ training (2x)
	DOS	3	• Dosing errors, e.g. tenfold errors (2x) • No dose adjustment in renal insufficiency	A	2	• Prescribing of standardised concentrations • Independent double-check of dosage prescription by more experienced physicians
				B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	1	• Independent double-check of dosage calculation by more experienced nurses
	RX	3	• Missing TDM (2x) • Misinterpretation of TDM results	B	2	• Ward-based pharmacist • Preparation in hospital pharmacy
				C	1	• Independent double-check
				D	4	• Establishment of TDM • Standardisation • Education/ training (2x)
	DDI	1	• Drug-drug interactions (e.g. with gentamicin)	-	0	• -
Vecuronium	DOS	2	• Dosage error (2x)	A	1	• Prescribing of standardised concentrations
				B	1	• Preparation in hospital pharmacy
	RX	1	• Confusion with sound-alike medications	C	1	• Separated storage from other sound-alike medications
				D	1	• Education/training
	AP	1	• Wrong preparation	D	1	• Local preparation and administration guideline
	O	1	• Wrong storage (room temperature vs. refrigerator)	-	0	• -

ADR= Adverse drug reaction, AP= Application/ administration errors, DOS= Dosage errors, DDI= Drug-drug interactions, DS= Dosage form/ drug strength, CI= Contraindications, IND= indication, Rx= Drug, O= Other, TDM= therapeutic drug monitoring, A= intervention category associated to physicians, B= intervention category associated to pharmacists, C= intervention category associated to nurses, D= general interventions.

To our best knowledge, there are three publications published up to now, that investigated high-alert medications in the paediatric setting (Franke et al. 2009; Maaskant et al. 2013, Bataille et al. 2015). These lists formed the foundation for our survey.

Tacrolimus is the only drug in the HAM list at hand that was rated by all survey experts to be a high-alert medication (100% agreement). Some of the potential reasons for this assessment were summarized in a recent review (Prytuła and van Gelder 2019). Tacrolimus is an immunosuppressant that posessees a narrow therapeutic window and a low and variable oral bioavailability that depends on the commercial product. It is mostly protein-bound and metabolized by CYP isoenzymes, both factors that pose a high risk for interactions. Beside others, the drug has the potential for nephrotoxic and gastrointestinal adverse reactions which affects other drug's pharmacokinetics (Prytuła and van Gelder 2019). In addition, medication errors when using this drug may increase the

Table 3: The survey panel proposed 275 interventions that were iteratively categorised into nine groups. Percentages do not sum to 100% because of rounding error

Intervention Category	Healthcare professional addressed	Intervention: details of category	Quantity [n (%)]
A1	Physicians	Prescribing by physician	23 (8%)
B1	Pharmacists	Pharmaceutical review	22 (8%)
B2		Preparation by hospital pharmacy	53 (19%)
C1	Nurses	Ward stock medication	9 (3%)
C2		Administration by nurses	24 (9%)
D1	General	Standardisation, labelling, or clinical decision support systems along the medication-use process	56 (20%)
D2		Universal interventions, e.g. drug monitoring or other laboratory measurement	17 (6%)
D3		Education or training	70 (25%)
N.A.	-	Not applicable, i.e. the intervention could not be sorted into one category	1 (0%)

risk for patient harm. The Institute for Safe Medication Practices summarized different categories of potential errors with tacrolimus in 2017. In particular, tenfold errors were named, look-alike errors, compounding errors, and confusion when more than one commercial product was prescribed to one patient (Institute for Safe Medication Practices 2017). The marked rating of tacrolimus by our expert panel underlines the risks for patient harm when using this drug. Therapeutic drug-monitoring is mandatory along with education of healthcare professionals. Other interventions like unit-dose drug distribution may complement the strategies as it was mentioned by our expert panel.

Many of the drugs in the list at hand are also mentioned in the paediatric literature. In concordance with Alghamdi et al. (2019), cardiovascular and neurological drugs were the second and third most mentioned drug classes. An analysis from incidents underlined this: most incident reports were related to the respiratory, cardiovascular and central nervous system and drug-related incidents formed nearly one fourth of all reports (Abbasi et al. 2018). Opioids are mentioned as HAM by different research groups (Institute for Safe Medication Practices Canada 2009; Nydert et al. 2020) and are also part of our final list (i.e. morphine and fentanyl). However, there are also some differences to be noted to drugs that are often considered "high-alert". Only 2/20 drugs are anti-infectives which were the most mentioned category in a recent systematic review (Alghamdi et al. 2019), namely amphotericin and vancomycin. The marked position of these two anti-infectives may be based on the need to adjust doses in renal insufficiency and differences in formulations, that are traditional go-to's for clinical pharmacists. In addition, insulin and heparin are missing from our list, that were mentioned by other groups (Franke et al. 2009; Institute for Safe Medication Practices Canada 2009; Maaskant et al. 2013; Bataille et al. 2015; Nydert et al. 2020). Insulin and heparin were rated as HAM by 68% of our experts, respectively. This was slightly below the cut-off of 75% that was used in reference to Maaskant et al. (2013). When comparing our data to that of Maaskant et al.'s Delphi-study, 79% and 75% of all experts rated insulin and heparin as HAM, respectively (Maaskant et al. 2013). This was slightly above or at the cut-off and may be explained by the interdisciplinary team (i.e. physicians, nurses, and pharmacists) that formed Maaskant et al's expert panel.

The types of potential DRPs summarised in this survey are seen from a pharmacist's point of view. Problems with dosing, application, confusion of drugs, and drug monitoring are pronounced in our survey. This is generally in line with Nydert et al.'s analysis of incident reports (Nydert et al. 2020). They identified 28% of all drug-related errors as dosing errors within the prescribing process. In the list at hand dosing errors were also the second-most mentioned error type with 26% of potential DRPs. Twenty-eight percent of the potential DRPs in our list were administration-related and therefore the most mentioned error type. Again, this is comparable to 36% in the investigation by Nydert et al. and also in line with Sutherland et al. (2019) who reported in a systematic review potential DRPs with administration to be more common in paediatric inpatients than prescribing-related problems (16.3% and 11.2%, respectively). Eighteen percent of all potential DRPs (n=39) were specified to be mainly based on drug-confusion and –monitoring; 23% were reported by Nydert et al. For 13 drugs in our final list (65%), look-alike or sound-alike errors were mentioned by the experts, including different concentrations of one drug, e.g. propofol. This underlines the great significance of this topic to prevent harm from the drug erroneously received, the drug erroneously not received, or both (Basco et al. 2016). Monitoring-based medication errors are rarely reported in literature. We identified the need to monitor drug-levels for four drugs (20% of all HAM, i.e. cyclosporine, digoxin, tacrolimus, and vancomycin). This corresponds to 4% of incident reports that were assigned to monitoring errors by Nydert et al. (2020).

When analysing the proposed interventions, 65% of them (179/275) were assigned to three groups: "Education or training", "Standardisation, labelling, or clinical decision support systems along the medication-use process", and "Preparation by hospital pharmacy". In a recent systematic review, educational interventions were seen to be often of short duration and limited effect (Koeck et al. 2021a). Intervention types may be classified according to the Hierarchy of Controls into interventions that substitute or isolate patients from a hazard risk (higher levels of control) and those that change the way healthcare professionals work (lower levels of control, e.g. education; The National Institute for Occupational Safety and Health 2015). Therefore, education should be best implemented along interventions that substitute risks for medication errors or isolate the patient from these risks (e.g. decision-support systems or computerised alerts). Standardised dilutions and ready-to-use preparations by hospital pharmacy were found to be effective as parts of bundle interventions (Koeck et al. 2021b). In general, the suggested interventions are in-line with a policy statement of the "American Academy of Pediatrics, Committee on Pediatric Emergency Medicine". Within this publication, 18 recommendations were published – 11 of which dealt with standardisations, four with education, and one recommendation explicitly supported the implementation of ward-based pharmacists (Benjamin et al. 2018). All three categories of interventions were frequently mentioned by our expert panel.

Germany shows a low pharmacist/100 beds ratio compared to other European countries; 0.4 compared to the European median 0.9 pharmacist/100 beds. In addition, only 20% of these pharmacists serve on hospital wards (Frontini et al. 2013), an even smaller part on paediatric wards. This in turn forms one motivation for our survey. A curriculum has to be developed to give more pharmacist the opportunity to specialize for paediatric care as it is already done in United Kingdom (Royal Pharmaceutical Society 2014). Within this curriculum one focus might be a German paediatric high-alert medication list. The survey at hand forms the foundation for this objective.

In conclusion, this survey provided for the first time a 20-item paediatric high-alert medication list from a German paediatric pharmacist point of view. Moreover, the experts suggested 216 specific potential DRPs and 275 associated interventions. This research may support a local multidisciplinary approach to identify and implement effective interventions to prevent medication-related harm in children.

Our survey data regarding potential DRPs and interventions indicates that medication safety in the paediatric setting cannot be performed by one group of health care professionals; 20% of all suggested potential interventions were assigned to physicians or nurses. More than half of all interventions could not be assigned to one group, but were of general character or had to be performed by more than one group. Errors may arise by "latent conditions" that result in harm-causing errors at some later point of the medication-use process (Reason 2000).

This survey may serve as a first step in the development of a German interdisciplinary consensus on high-alert medications.

Specialized pharmacists are the group of healthcare professionals that overviews the whole medication-use process from prescription to bedside and in addition can provide drug-specific recommendations. In a second step, this data may be supplemented on the one hand with prescription-specific problems (and interventions) reported by physicians and also with administration-specific topics reported by nurses.
Paediatric-specialised pharmacists in German university hospitals and the members of the paediatric committee of the "Federal Association of German Hospital Pharmacists" were requested to participate in this survey. The expertise of pharmacists from regional hospitals might be under-represented (5/40 hospitals, that were initially addressed). We did not perform an analysis for differences in characteristics for respondents and non-respondents. Despite this, we could reach via a personalised approach a response rate of 60% and 40% for the first and second survey round, respectively.

4. Experimental

4.1. Ethics approval and report structure

The study was registered with the local ethics commission (EK 165/17) and the study report was guided by the recommendations of the SURGE guideline (Grimshaw 2014).

4.2. Definitions

"High-alert medications" were defined as "drugs that bear a heightened risk of causing significant patient harm when they are used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients" (Institute for Safe Medication Practices 2018). DRPs were defined as events or circumstances "involving drug therapy that actually or potentially interferes with desired health outcomes" (Pharmaceutical Care Network Europe Association 2019). DRPs are seen as the topic to include medication errors (Ackroyd-Stolarz et al. 2006). Interventions were defined as "anything aimed at reducing medication errors" (Rinke et al. 2014).

4.3. Survey content

4.3.1. Literature search and data extraction

A literature search was performed with a pre-defined search term to identify existing HAM lists in the paediatric setting: (pediatrics[mh] OR pediatr*[tiab] OR paediatr*[tiab] OR child*[tiab] OR infant*[tiab] OR newborn*[tiab] OR toddler*[tiab] OR adolescenc*[tiab]) AND (high-alert[tiab] OR "high-risk medication"[tiab] OR "high-risk medications"[tiab] OR "high risk medication"[tiab] OR "high risk medications"[tiab]) AND eng[la]. This search led to 29 full-texts that were screened independently by two authors (S.S., J.A.K). After consensus, three full-texts containing lists of paediatric HAM were included that formed the foundation for this survey (Franke et al. 2009; Maaskant et al. 2013; Bataille et al. 2015). This survey aimed at recommendations at substance level that led to the exclusive extraction of drugs (rather than drug classes) from these three sources. Additionally, only drugs that are licensed in Germany were included. Finally, administration routes were ignored except for vancomycin (oral and intravenous form, see below). These data extraction criteria led to a HAM list of 39 drugs that were included in the first round of this survey.
The survey contained vancomycin in two different application forms (oral vs. intravenous). This was done to test the hypothesis, that the respondents applied the definition of HAMs (presented in the accompanying cover letter) to differentiate between drugs that fit the definition and those that did not. The survey`s author team rated intravenous applied vancomycin as HAM, because careful considerations are necessary to prevent serious adverse drug events (oto- and nephrotoxicity), e.g. correct sample collection for plasma level monitoring, interpretation of results, and/or dose adjustment if necessary. In contrast, orally applied vancomycin was interpreted by the author team not as HAM, because it is used in a fixed dose (e.g. 40mg/kg body weight three to four times daily). Plasma level monitoring is not necessary as the bioavailability of orally applied vancomycin is negligible. To test the hypothesis, the Chi^2- or Fisher-exact test was used (significance level $p<0.05$), whatever applicable.

4.3.2. First survey round

The expert panel used a four-point Likert-scale to classify a specific drug as HAM. The scale was endpoint-scaled with "1" that indicated full disagreement with this statement and "4" (full agreement). When a panel member could not assess a drug due to a lack of experience, a "not applicable" choice (N.A.) was given. The survey panel members were invited to add HAM to the list where necessary.

4.3.3. Second survey round

Using the results of the first round, the second-round survey was aimed at the elaboration of potential DRPs and associated interventions. To reduce the individual survey processing time for panel members, the drugs that resulted from the first round were randomly allocated to each person by using the software randlist (DatInf GmbH, Tübingen, Germany). So, each panel member only rated a randomly assigned proportion of the HAM, that were identified in the first round of the survey. The total number of drug assessments that had to be randomly assigned to the expert panel was calculated as followed: the number of high-alert medications were multiplied by the number of assessments per drug and divided by the estimated number of pharmacists who would return the survey (50% of 42 first-round pharmacists). After survey completion, the median of 8 assessments per drug resulted [IQR 7-9]. For each drug in the survey, the experts could name up to three potential DRPs that were individually considered to be associated with the highest risk for harm. In addition, the panel members were asked to propose potential interventions for each potential DRP.

4.4. Setting, survey participants, and conduction

4.4.1. Setting

Both rounds of the survey were addressed to 42 pharmacists, paediatric expert pharmacists in university hospitals as well as the paediatric committee members of the "Federal Association of German Hospital Pharmacists". The survey was sent to the chief pharmacists of all thirty-five German university hospitals to hand it to the local paediatric expert pharmacist. The chief pharmacists from two university hospitals were directly addressed and also the members of the paediatric committee coming from these hospitals to include the case that there was more than one specialized paediatric pharmacist. Five pharmacists from regional hospitals were invited as they were part of the paediatric committee.

4.4.2. Survey participants

Demographic data was recorded, like age, gender, years of professional experience and potential formal specialisation. Survey non-respondents were not consulted afterwards, so differences of respondents and non-respondents could not be investigated.

4.4.3. Conduction

The surveys of both rounds were sent by mail to the chief pharmacists of each university hospital pharmacy or directly addressed to the paediatric committee members. Each survey was accompanied by a cover letter, that explained the aims of the survey, contained contact data, and stated that all data would be handled confidentially and analysed in an anonymous way. A pre-test was performed before mail-out to optimise the survey. There were no incentives offered for participation. The mail-out was supported by several reminder e-mails.

4.5. Data collection and analysis

To define HAMs out of the four-point Likert scale (first round of survey), the scale was divided in two parts where ratings at 3 or 4 points of the scale indicated a HAM and 1 or 2 points rejected this statement. Based on the Delphi-study by Maaskant et al. (2013), a specific drug was included in the final list, when at least 75% of the participants rated it as HAM.
The suggested potential DRPs in the second round of the survey were independently classified by one person (S.S.) according to APS-Doc (APS-Doc: German acronym for „Arzneimittelbezogene Probleme im Stationären Bereich"-Documentation [Drug-related problems in the inpatient setting]; Hohmann et al. 2012). Another person (J.A.K) amended the classification when necessary. Discrepancies in classification were resolved through discussion. Two subcategories were added to the APS-Doc classification, one to the category "application" (AP8: "missing or wrong labelling") and one to the category "other" (O3: "wrong storage"), as these were not represented initially.
Potential interventions were iteratively categorised into a self-developed four-step model representing three target groups of health care professionals along the medication-use process for a specific intervention by one person (S.S.) and amended by a second one (J.A.K). These target groups were physicians (category A) for prescription, pharmacists (category B) for pharmaceutical analysis, dispensing and storing medications, and nurses (category C) for medication preparation and administration. The three categories were supplemented by a fourth more general group of interventions (category D). This approach was inspired by the categorisation of interventions along the medication-use process by Bataille et al. (2015). When a proposed intervention could be assigned to one group of healthcare professionals (categories A-C), this was in favour to a category D assignment. In case of repeated DRPs or interventions by different experts, this was summarized to provide a clear overview. The number of experts who suggested a specific DRP or intervention is provided along with the text in Table 2.
Metric data was shown with numbers and percentages or median and interquartile range, whatever applicable.

Conflicts of interest: None declared.

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