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ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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TITLE PAGE

ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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Key Words: drug toxicity; pharmacovigilance; drug monitoring; intensive care; pediatrics; patient safety.

ABSTRACT

Objective: To identify the rates and risk factors of adverse drug events (ADEs) in children under intensive care.

Design: Prospective, observational study.

Setting: Pediatric intensive care unit of a tertiary care teaching hospital.

Patients: 239 patients with a mean age of 67.5 months representing 1818 days of hospitalization in intensive care unit .

Interventions: Active search of charts and electronic patient records using indicative parameters ("triggers"). The statistical analysis involved linear and logistic regression.

Measurements and Main Results: The average PICU stay was 7.6 days. There were 110 proven, probable, and possible ADEs in 84 patients (35.1%). We observed 138 instances of triggers. The major classes of drugs associated with events were: antibiotics (n = 41), diuretics (n = 24), antiseizures (n = 23), sedatives and analgesics (n = 17), and steroids (n = 18). The number of drugs administered was most related to the occurrence of ADEs and also to the length of stay ($p < 0.001$). The occurrence of an ADE may result in an increase in the length of stay by 1.5 days per event. Patient aged less than 48 months also proved to be at significant risk for ADEs, with an odds ratio of 1.84 (confidence interval - 95% CI - 1.07 to 3.15, $p = 0.025$). The number of drugs administered also correlated with the number of ADEs ($p < 0.0001$). The chance of having at least one ADE increased linearly as the patient was administered more drugs.

Conclusions: The use of multiple drugs as well as lower patient age favor the occurrence of ADEs, which in turn may result in increasing the length of PICU hospitalization. The active search provides a systematic approach to the problem.

INTRODUCTION

The use of medication in children and infants is a matter of great concern largely due to the vulnerability of their constantly changing and developing homeostasis, as well as the unique mechanisms by which different children respond to injuries. There are important differences in absorption, distribution, metabolism and excretion of drugs during childhood and early adolescence.[1] In addition, several medications have not exhibited safety in the pediatric age group, while others are prescribed differently than recommended for adults; key differences include dose and frequency of administration, presentation of the drug, route of administration, or indication for use in childhood (i.e. "off-label" use), and each of these factors can vary depending on the age of the child.[2] In the majority of instances, recommended doses of drugs used in children are based on extrapolations from adult doses, related only to weight, body surface area, and age, often ignoring their pharmacokinetic and pharmacodynamic properties; this results in increased susceptibility of children to drug-related adverse events.[1-4]

Reports documenting the incidence of adverse drug events in the pediatric population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with high morbidity and mortality.[5] Hospitalized children may be at a higher risk of an adverse event, as doses, drug safety, and effectiveness are often difficult to determine.[6] Kaushal and colleagues identified that the potential frequency of ADEs in children is three times higher than a previous study focused on ADEs in adults, however, the rate of avoidable

ADEs was similar.[4] In intensive care units, multiple, potentially hazardous drugs are routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics; as the risk of an ADE increases by 1.7% for each additional drug used,[5] it is far more likely that adverse reactions will occur in the ICU.

There are few studies documenting safety in drug administration in children in the ICU. The primary objective of this study was to describe ADEs in children admitted to the pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As a second objective, we attempted to identify risk factors for such events and tools that could detect them early.

MATERIALS AND METHODS

We conducted a preliminary survey over a period of 22 days in March 2004 to identify the number of admissions required to effectively report ADEs in the PICU, a unit of 13 beds, with average occupation of 80%. Based on the results of this survey, we determined that it would then be necessary to study 150 admissions to reach a stable estimate of the incidence of ADEs and explore possible risk factors using a multivariate analysis (approximately 10 ADEs for each variable potentially associated). The study population consisted of consecutive admissions to the PICU between October 1, 2005 and March 31, 2006. The strategy to identify ADEs was through an active search, using pre-established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or flag, found when reviewing a patient's medical chart, that requires further investigation to determine the presence or absence of an adverse event.[7,8] The following methodology was undertaken:

1. The admission form for each new patient in the PICU was entered by two trained intensive care pediatricians;

2. The following records for each patient were reviewed, guided by triggers indicative of adverse events:

- Laboratory tests (electronic database);

- Clinical annotations;

- Nursing annotations;

- Prescription;

3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable, possible, or doubtful;[9]

4. Analysis of all proven, probable and possible ADEs.

The study included only unavoidable ADEs, that is, only those that occurred during normal use of a drug, and not the result of a human error,[10] as well as those classified as moderate to severe according to the World Health Organization guidelines.[11] The study protocol was reviewed and approved by the Ethics Committee of the institution prior to the start of data collection (protocol number 485/56/2005). Because of the observational nature of the study, without any interference in therapy, informed consent was waived.

Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the odds ratios (OR) by logistic regression. We used a linear regression model for the variables, "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent), and "PICU stay" (dependent). Significance of differences between means was obtained with the T test. Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was considered statistically significant. We calculated the positive predictive value of pre-established parameters as triggers for the search of adverse events.

RESULTS

In our pilot survey, we identified 20 adverse events of moderate to severe intensity over a period of 22 days in March 2004, which we calculated to represent at least 5 events per 100 patient-days.

In our actual study, there were 244 admissions to the PICU during the period between October 1, 2005 and March 31, 2006. Four patients were excluded because they were adult organ donors and one patient was excluded due to age > 18 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of 9.5 days.

The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%). Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%), neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac disease (n = 12, 5%).

There were 110 proven, probable, or possible ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were prevalent at admission and the remaining 71 (64.5%) occurred subsequent to PICU admission (Table 1). The identification of these 110 ADEs was triggered by 138 positive occurrences of indicative parameters (triggers) as shown in table 2, with their predictive positive values. Table 3 shows the observed ADEs and related drugs.

The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24), antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9),

bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5), hormonal analogues (4), antipyretics (4), and others (5). There was a significant difference between the mean length of stay (LOS) between patients with and without ADEs (11.1 vs. 5.3 days, $p < 0.0001$). Using multivariate linear regression, we attempted to define the relationship between several variables and LOS. The only independent variables remaining in the final model that affect LOS were the number of ADEs ($p = 0.089$, slope coefficient 1.49) and the number of drugs ($p < 0.001$, slope coefficient 0.83, $R^2 = 0.104$); other variables did not show any significant relationship. If significant, the slope coefficient indicates that an ADE would result in an increase in PICU hospitalization by 1.49 days. We hypothesized that this may be relevant with a longer period of observation. We extrapolated our results to 480 patients (the expected number of admissions in one year); using the obtained standard deviations of 9.5 for the dependent variable (LOS) and 0.72 for the independent variable (ADE), we determined that the probability of increasing the LOS by 1.5 days for each ADE is 70%. For two years (~1000 patients), the probability reached 94%.

Gender, the presence of chronic disease, and age, were analyzed as possible risk factors for the incidence of ADEs; for males, the odds ratio (OR) was 1.46 ($p = 0.16$); for the presence of a chronic disease, the OR was 1.47 ($p = 0.30$), and none of the individual chronic conditions displayed an increased risk for ADEs; however, patient age less than 48 months proved to be a significant risk factor, with an OR of 1.84 (95% CI: 1.07 - 3.15, $p = 0.025$).

The number of drugs received by each patient correlated with the number of ADEs ($R^2 = 0.13$, $p < 0.0001$). The likelihood of at least one ADE became significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, p =

0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1, $p < 0.0001$) with 11 concomitant drugs. The same was observed for the occurrence of more than one ADE (Table 4).

In our multivariate analysis, we observed a positive interaction in patients aged less than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01) or the use of five drugs (OR = 2.46; CI 95%: 1.26-4.80, p = 0.008), in the occurrence of at least one ADE. This interaction remained significant, with discrete elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI: 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001 for the use of 9 drugs). There was no significant interaction between use of five or more drugs and the occurrence of more than one ADE.

In addition, mean "survival" without ADEs (time from admittance to the PICU until the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for patients younger than 48 months (p = 0.017).

DISCUSSION

Determining the occurrence of adverse events in an intensive care environment is a complex undertaking. The symptoms of the event may overlap the underlying disease and may be caused by several unrelated factors including the pharmacokinetic profile of the drug, unknown drug allergies of each patient, or human error. These difficulties may serve as an explanation for why many events are not recognized as ADEs. Frequently, other drugs are administered in an attempt to solve the problem created by the ADE, without the specific diagnosis of an ADE. While some events are easily attributed to certain drugs,

there are several possible and poorly documented events and some are completely unknown and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE, including age and certain comorbidities, such as the presence of renal or hepatic impairment. In addition drug-related factors such as toxicity, time of administration, dosage, and duration of use, are variables that can also impact the probability of ADEs. In addition, new drugs that have just completed phase III clinical trials may not have been powered to detect rare events.[12] In general, if we don't look for ADEs, it is unlikely that we will find them.[13]

In the absence of reliable empirical methods for detection of ADEs, formal and logical tools can help differentiate an ADE from a symptom caused by exacerbations in a patient's underlying condition. The most widely accepted formal instrument to obtain this is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some included events may not have been ADEs. However, to prove an ADE according to the algorithm, it is necessary to re-administer the drug and observe the event again, or obtain serum levels that are known to be toxic. The first option is strongly discouraged and the second may be technically impossible or unavailable. However, we excluded the "doubtful" events (score equal to or less than 1) from our analysis and some of these events may have actually been ADEs.

The incidence of observed events (35.1% of admissions) is much higher than those reported in adult patients hospitalized in ICUs (around 9%).[14] Furthermore, we found that younger children under the age of 48 months, which constitute approximately half the patient sample, were more likely to have ADEs. This was particularly significant with the administration of over five drugs at the same time, and also resulted in an ADE earlier in

the patient's ICU stay. The high incidence of ADEs also highlights the importance of an active search focused on triggers to detect ADEs in children: Holdsworth et al reported ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart review by a pharmacist).[15] Takata et al. performed a search focused on triggers and reported 11.1 events/100 inpatients, almost double that of the retrospective study. These authors indicated that performing a search focused on specific circumstances associated with ADEs in specific elements of the patient's chart can increase the rates of observed ADEs.[16] We wish to highlight that our study evaluated severely ill children under intensive care receiving multiple drugs (up to 18), and the chances of developing an ADE is therefore, more likely. In addition, comparing event rates is also challenging and potentially misleading as definitions of ADEs are unclear among studies, ranging from a benign and transient alteration of electrolytes to vital organ damage.[10]

We investigated whether ADEs may have an impact on the LOS in the PICU; if an increase was observed, we can conclude that the ADEs caused harm to the patient. Our sample did not have the power to implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however, calculations based on standard deviations observed in our sample showed a high probability that this would be true in a longer-term study. In addition to patient harm, there are significant costs associated with patient stays in the ICU: An increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at $600.00 (American dollars) each day, ADEs amount to $198,000 per year, which is a considerable sum for our public health system. In principle, the events occurred as a result of habitual use of drugs and were therefore "inevitable", however, a systematic approach could convert some ADEs from inevitable to avoidable. A good example cited by Kane-Gill et al[10] describes bleeding caused by the correct dose of heparin in a patient being

monitored by partial thromboplastin time and would be classified as inevitable. If an investigation identified that the laboratory has changed their method for thromboplastin time and failed to communicate the necessary adjustment, the error would become preventable. More studies on pharmacokinetics and drug interactions in children are required to define optimal dosing regimens and reduce ADEs.

CONCLUSIONS

The use of focused and active search engines can provide a systematic approach to identify ADEs in PICUs. The use of multiple drugs as well as lower patient age favors the occurrence of ADEs, which in turn may result in increasing the length of PICU hospitalization.

REFERENCES

1. Niederhauser VP. Prescribing for children: issues in pediatric pharmacology. *Nurse Pract* 1997;22(3):16-18.

2. Hussain E, Kao E. Medication safety and transfusion errors in the ICU and beyond. *Crit Care Clin* 2005;21:91-110.

3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-471.

4. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285:2114-2120.

5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.

6. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;84:438-441.

7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003;12(3):194–200.

8. Resar RK, Rozich JD, Classen DC. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care* 2003;12(suppl 2):ii39 –ii45.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther* 30 (2): 239–245.

10. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med* 2012;40(3):823-8.

11. World Health Organization (WHO). Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III. Geneva; 1995.

12. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001;94(4):370-3.

13. Kelly WN. How Can I Recognize an Adverse Drug Event. Available online at: *http://www.medscape.org/viewarticle/569794*. Accessed Feb 1, 2012.

14. Vargas E, Terleira A, Hernando F, Perez E, Cordon C, Moreno A, Portoles A. Effect of adverse drug reactions on length of stay in surgical intensive care units. *Crit Care Med* 2003;31(3):694-8.

15. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med* 2003;157(1):60–65.

16. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-3.

Table 1 – Distribution of prevalent and incident adverse events according to causality.

ADE	Prevalent	Incident	TOTAL
Proven	0	5	5
Probable	12	32	44
Possible	27	34	61
TOTAL	39	71	110

Table 2 – Indicative parameters of ADEs used for active search.

Indicative parameters ("Triggers")	**Number of occurrences**	**Positive predictive value**
Hematological alterations	8	5.79%
Biochemical alterations	64	46.37%
Cardiac alterations	17	12.3%
Antihistamines	5	3.62%
Corticoids	2	1.45%
Allergic reactions	11	7.97%
Non-programmed endotracheal intubation	1	0.72%
Level of consciousness degradations	2	1.45%
Drug interactions	8	5.80%
Antiseizures prescription	2	1.45%
Drug intolerance	0	0%
Non-programmed suspension of drug	1	0.72%
Fever	0	0%
Sudden death	0	0%
Serum level alteration	0	0%
Aminophylline / adrenaline prescription	0	0%
Antidotes prescription	3	2.17%

Others	14	10.14%

Table 3 – Observed adverse drug events (ADEs) and related drugs

Adverse Drug Events (ADEs)	N	Related drugs
Hyponatremia	27	furosemide, fentanyl, carbamazepine, vigabatrin topiramate, hydrochlorothiazide, somatostatin, vancomycin, rifampicin, ranitidine, phenytoin
Hyperglycemia	17	dexamethasone, hydrocortisone, methylprednisolone, terbutaline, tacrolimus
Hypokalemia	13	amphotericin b, terbutaline, furosemide, ranitidine
Skin rash and urticaria	11	vancomycin, dipyrone, cefepime, ceftriaxone, levetiracetam, dipyrone, rasburicase
Hypoventilation/desaturation of oxygen	6	midazolam, propofol, fentanyl, morphine, diazepam
Bradycardia	4	midazolam
Hypotension	4	midazolam, furosemide, thiopental, chlorpromazine
Liver enzyme abnormalities	4	meropenem, carbamazepine, amlodipine, carvedilol, clonidine, amitriptyline, phenobarbital
Hypertension	3	prednisone tacrolimus, dopamine
Increased BUN and creatinine	3	vancomycin, tacrolimus
Seizure	2	hydrocortisone, liposomal amphotericin B, cefepime
Tachycardia	2	terbutaline
Anemia	2	ketoprofen, paracetamol
Extrasystole	2	carvedilol, terbutaline
Increased number of platelets	2	Meropenem, ceftriaxone
Vomiting	2	Nitroprusside, tacrolimus
Cardiorespiratory arrest	1	dipyrone
Thrombocytopenia	1	dipyrone
Apnea	1	phenytoin
Leukopenia	1	imipenem
Stevens-Johnson syndrome	1	trimethoprim / sulfamethoxazole
Eosinophilia	1	ceftriaxone

Table 4 – Odds ratios related to the concomitant use of medications.

	Occurrence of at least one ADE			Occurrence of more than one ADE		
Number of drugs	*Odds ratio*	95% CI	*P*	*Odds ratio*	95% CI	*P*
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.0,3	1.69-5.40	0.0002	3.28	1.06-10.07	0.037
7	3.69	2.11-6.46	< 0.0001	2.95	1.14-7.60	0.025
8	3.84	2.24-6.80	< 0.0001	3.35	1.34-8.35	0.009
9	4.40	2.29-8.45	< 0.0001	3.14	1.24-7.90	0.015
10	6.48	2.85-14.77	< 0.0001	3.69	1.36-9.99	0.010
11	7.26	2.77-19.01	< 0.0001	5.55	1.98-15.52	0.001

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ABSTRACT

Objectives: To describe adverse drug events (ADEs) in children under intensive care, identify risk factors and tools that can detect ADEs early, and the impact on length of stay (LOS).

Design: Prospective, observational study.

Setting: Pediatric intensive care unit of a tertiary care teaching hospital.

Patients: 239 patients with a mean age of 67.5 months representing 1818 days of hospitalization in intensive care unit .

Interventions: Active search of charts and electronic patient records using triggers. The statistical analysis involved linear and logistic regression.

Measurements and Main Results: The average LOS was 7.6 days. There were 110 proven, probable, and possible ADEs in 84 patients (35.1%). We observed 138 instances of triggers. The major classes of drugs associated with events were: antibiotics (n = 41), diuretics (n = 24), antiseizures (n = 23), sedatives and analgesics (n = 17), and steroids (n = 18). The number of drugs administered was most related to the occurrence of ADEs and also to the length of stay ($p < 0.001$). The occurrence of an ADE may result in an increase in the length of stay by 1.5 days per event, but this was not statistically significant in this sample. Patient aged less than 48 months also proved to be at significant risk for ADEs, with an odds ratio of 1.84 (confidence interval - 95% CI - 1.07 to 3.15, $p = 0.025$). The number of drugs administered also correlated with the number of ADEs ($p < 0.0001$). The chance of having at least one ADE increased linearly as the patient was administered more drugs.

Conclusions: The use of multiple drugs as well as lower patient age favors the occurrence of ADEs. The active search described here provides a systematic approach to this problem.

INTRODUCTION

The use of medication in children and infants is a matter of great concern largely due to the vulnerability of their constantly changing and developing homeostasis, as well as the unique mechanisms by which different children respond to injuries. There are important differences in absorption, distribution, metabolism and excretion of drugs during childhood and early adolescence.[1] In addition, several medications have not exhibited safety in the pediatric age group, while others are prescribed differently than recommended for adults; key differences include dose and frequency of administration, presentation of the drug, route of administration, or indication for use in childhood (i.e. "off-label" use), and each of these factors can vary depending on the age of the child.[2] Most of times, recommended doses of drugs used in children are based on extrapolations from adult doses, related only to weight, body surface area, and age, often ignoring their pharmacokinetic and pharmacodynamic properties; this results in increased susceptibility of children to drug-related adverse events.[1-4]

Reports documenting the incidence of adverse drug events in the pediatric population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with high morbidity and mortality.[5] Hospitalized children may be at a higher risk of an adverse event, as doses, drug safety, and effectiveness are often difficult to determine.[6] Kaushal and colleagues identified that the potential frequency of ADEs in children is three times higher than a previous study focused on ADEs in adults, however, the rate of avoidable ADEs was similar.[4] In intensive care units, multiple, potentially hazardous drugs are

routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics; as the risk of an ADE increases by 1.7% for each additional drug used,[5] it is far more likely that adverse reactions will occur in the ICU.

There are few studies documenting safety in drug administration in children in the ICU. The primary objective of this study was to describe ADEs in children admitted to the pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary objectives, we attempted to identify risk factors for such events and tools that could detect them early as well as determine if there was impact on LOS.

MATERIALS AND METHODS

We conducted a preliminary survey over a period of 22 days in March 2004 to identify the number of admissions required to effectively report ADEs in the PICU, a unit of 13 beds, with average occupation of 80%. Based on the results of this survey, we determined that it would then be necessary to study 150 admissions to reach a stable estimate of the incidence of ADEs and explore possible risk factors using a multivariate analysis (approximately 10 ADEs for each variable potentially associated). The study population consisted of consecutive admissions to the PICU between October 1, 2005 and March 31, 2006. The strategy to identify ADEs was through an active search, using pre-established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or flag, found when reviewing a patient's medical chart, that requires further investigation to determine the presence or absence of an adverse event.[7,8] Using this method, specific events, such as prescription or abrupt discontinuation of certain medications, prescription of antidotes, and some laboratory tests, serve as indicators for further investigation. Several triggers have been described in the literature,[8] and therefore we chose and adapted the ones

that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows these triggers and the rationale for their use. The positive predictive value (PPV) of each trigger was calculated as the number of times that each trigger identified an ADE, divided by the total number of times the triggers were identified in the active search.

The following methodology was undertaken for active search:

1. The admission form for each new patient in the PICU was entered by two trained intensive care pediatricians; data were reviewed by 2 authors (Drs. Silva and Shibata) and consolidated in agreement.

2. The following records for each patient were reviewed, guided by triggers indicative of adverse events:

- Laboratory tests (electronic database);
- Clinical annotations;
- Nursing annotations;
- Prescription;

3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable, possible, or doubtful;[9]

4. Analysis of all proven, probable and possible ADEs.

The study included only unavoidable ADEs, that is, only those that occurred during normal use of a drug, and not the result of a human error,[10] as well as those classified as moderate to severe according to the World Health Organization (WHO) guidelines: By this definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears after administration of a drug at doses normally used for prophylaxis, diagnosis or treatment of a disease. A moderate reaction is one that requires modification of therapy and may require specific treatment; a severe reaction is potentially fatal and requires specific

treatment, requires or prolongs hospitalization.[11] We analyzed only those ADEs that appeared after admission. ADEs that appeared after admission but were related to drugs that the patient was receiving before being admitted were defined as due to “prevalent drug”. This definition eliminated, for example, ADEs due to chemotherapy already present before admission in patients with cancer. ADEs related to drugs introduced after admission were classified as due to "incident drug". The study protocol was reviewed and approved by the Ethics Committee of the institution prior to the start of data collection (protocol number 485/56/2005). Because of the observational nature of the study, without any interference in therapy, informed consent was waived.

Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the odds ratios (OR) by logistic regression. A multinomial logistic regression model was performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number of drugs” because they have been significantly correlated with the incidence of ADEs.[5] Some studies have shown a lower risk for ADEs in male children.[12] Chronic illness is an important variable due to the continuous use of various drugs and the presence of organ dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS" (dependent). Significance of differences between means was obtained with the T test. Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was considered statistically significant.

RESULTS

In our pilot survey, we identified 20 adverse events of moderate to severe intensity over a period of 22 days in March 2004, which we calculated to represent at least 5 events per 100 patient-days.

In our actual study, there were 244 admissions to the PICU during the period between October 1, 2005 and March 31, 2006. Four patients were excluded because they were adult living-donors for liver transplant, and one patient was excluded due to age > 18 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of 9.5 days.

The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%). Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%), neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83), postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures, digestive bleeding, dehydration, renal failure, hypertension, and others.

We observed 138 occurrences of triggers, as shown in Table 2, with their predictive positive values. These triggers led to the identification of 110 proven, probable, or possible ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after

PICU admission or "incidents" (Table 3). Table 4 shows the observed ADEs and related drugs.

Gender, the presence of chronic disease, age, and administration of at least five drugs were included in a multinomial logistic regression analysis as independent variables for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the individual chronic conditions displayed an increased risk for ADEs; however, patient age less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01) in the occurrence of at least one ADE. This interaction remained significant, with discrete elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI: 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001 for the use of 9 drugs).

In a bivariate analysis, the number of drugs received by each patient correlated with the number of ADEs (R2 = 0.13, p < 0.0001). The likelihood of at least one ADE became significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the occurrence of more than one ADE (Table 5).

There was a significant difference between the mean LOS between patients with and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75

(p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS. However, this increase was not maintained when other confounding variables were added in the multivariate regression model. The only independent variables remaining in the final model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and the number of drugs (p < 0.001; slope coefficient 0.83; R2 = 0.104); The slope coefficient could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but the study did not have the power to demonstrate it. A sample calculation showed that in order for this fact to be significant in a larger sample, it would take 1000 patients to achieve p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the dependent variable "LOS" and 0.72 for independent "number of ADEs". Other variables did not show any significant relationship.

In addition, mean "survival" without ADEs (time from admittance to the PICU until the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for patients younger than 48 months (p = 0.017).

The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24), antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9), bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5), hormonal analogues (4), antipyretics (4), and others (5).

DISCUSSION

Determining the occurrence of adverse events in an intensive care environment is a complex task. The symptoms of the event may overlap the underlying disease and may be caused by several unrelated factors including the pharmacokinetic profile of the drug, unknown drug allergies of each patient, or human error. These difficulties may serve as an

explanation for why many events are not recognized as ADEs. Frequently, other drugs are administered in an attempt to solve the problem created by the ADE, without the specific diagnosis. While some events are easily attributed to certain drugs, there are several possible and poorly documented events and some are completely unknown and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE, including age and certain comorbidities, such as the presence of renal or hepatic impairment. Drug-related factors such as toxicity, time of administration, dosage, and duration of use are variables that can also impact the probability of ADEs. In addition, new drugs that have just completed phase III clinical trials may not have been powered to detect rare events.[13] In general, if we don't look for ADEs, it is unlikely that we will find them.[14]

In the absence of reliable empirical methods for detection of ADEs, formal and logical tools can help differentiate an ADE from a symptom caused by exacerbations in a patient's underlying condition. The most widely accepted formal instrument to obtain this is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some included events may not have been ADEs. However, to prove an ADE according to the algorithm, it is necessary to re-administer the drug and observe the event again, or obtain serum levels that are known to be toxic. The first option is strongly discouraged and the second may be technically impossible or unavailable. However, we excluded the "doubtful" events (score equal to or less than 1) from our analysis and some of these events may have actually been ADEs.

Most of our patients had chronic diseases, which may contribute to a higher incidence of ADEs, due to the use of multiple medications. This population of chronic patients reflects the current reality of Brazilian university hospitals. We observed no

significant difference in ADE incidence between patients with and without chronic diseases, which can be explained by the exclusion of events prior to PICU admission and was more likely related to the medications used regularly.

The incidence of observed events (35.1% of admissions) is much higher than those reported in adult patients hospitalized in ICUs (around 9%).[15] Furthermore, we found that younger children under the age of 48 months, which constitute approximately half the patient sample, were more likely to have ADEs. This was particularly significant with the administration of over five drugs at the same time, and also resulted in an ADE earlier in the patient's ICU stay. The high incidence of ADEs also highlights the importance of an active search focused on triggers to detect ADEs in children: Holdsworth et al reported ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart review by a pharmacist).[16] Takata et al. performed a search focused on triggers and reported 11.1 events/100 inpatients, almost double that of the retrospective study. These authors indicated that performing a search focused on specific circumstances associated with ADEs in specific elements of the patient's chart can increase the rates of observed ADEs.[17] The methodology we used in this study (definition of triggers and daily search in the records of patients) is a simple way to perform an active search for ADEs. Triggers can be individualized for each hospital setting according to the most frequently used medications. PPVs can be determined through a simple calculation that assists in the choice of triggers that are most useful in each unit. We observed higher PPVs for biochemical alterations; in an automated process, the system of the laboratory itself could alert for possible ADEs.

We wish to highlight that our study evaluated severely ill children under intensive care receiving multiple drugs (up to 18), and the chances of developing an ADE is therefore, more likely. In addition, comparing event rates is also challenging and potentially

misleading as definitions of ADEs are unclear among studies, ranging from a benign and transient alteration of electrolytes to vital organ damage.[10]

We investigated whether ADEs may have an impact on the LOS in the PICU. The most important limitation of the study was that our sample did not have the power to implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however, calculations based on standard deviations observed in our sample showed a high probability that this would be true in a longer-term study. In addition to possible patient harm, there are significant costs associated with patient stays in the ICU: An increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at $600.00 (American dollars) each day, ADEs amount to $198,000 per year, which is a considerable sum for our public health system. In principle, the events occurred as a result of habitual use of drugs and were therefore "inevitable"; however, a systematic approach could convert some ADEs from presumably inevitable to avoidable. A good example cited by Kane-Gill et al[10] describes bleeding caused by the correct dose of heparin in a patient being monitored by partial thromboplastin time and would be classified as inevitable. If an investigation identified that the laboratory has changed their method for thromboplastin time and failed to communicate the necessary adjustment, the error would become preventable. More studies on pharmacokinetics and drug interactions in children are required to define optimal dosing regimens and reduce ADEs.

Another limitation of the study was the short time of observation, which did not include the seasonality of respiratory diseases. A positive aspect of the study was the analysis of a PICU population in a country outside Europe and North America, therefore making it possible to analyze ADEs due to drugs such as dipyrone. We hope that our study will contribute to a future systematic approach to this subject in developing countries.

CONCLUSIONS

The use of multiple drugs as well as lower patient age favors the occurrence of ADEs, which in turn may result in an increase in the length of PICU hospitalization. The use of an active search using triggers can provide a systematic approach to identify ADEs in PICUs.

REFERENCES

1. Niederhauser VP. Prescribing for children: issues in pediatric pharmacology. *Nurse Pract* 1997;22(3):16-18.

2. Hussain E, Kao E. Medication safety and transfusion errors in the ICU and beyond. *Crit Care Clin* 2005;21:91-110.

3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-471.

4. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285:2114-2120.

5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.

6. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;84:438-441.

7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003;12(3):194–200.

8. Resar RK, Rozich JD, Classen DC. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care* 2003;12(suppl 2):ii39 –ii45.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30 (2): 239–245.

10. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med* 2012;40(3):823-8.

11. World Health Organization (WHO). Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III. Geneva; 1995.

12. Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. Adverse drug reactions in children-a systematic review. *PLoS One*. 2012;7(3):e24061.

13. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001;94(4):370-3.

14. Kelly WN. How Can I Recognize an Adverse Drug Event. Available online at: http://www.medscape.org/viewarticle/569794. Accessed Feb 1, 2012.

15. Vargas E, Terleira A, Hernando F, Perez E, Cordon C, Moreno A, Portoles A. Effect of adverse drug reactions on length of stay in surgical intensive care units. *Crit Care Med* 2003;31(3):694-8.

16. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med* 2003;157(1):60–65.

17. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-3.

Table 1 – rationale for the use of triggers

Triggers	Rationale for use
Hematological alterations	Anemia, leukopenia, and thrombocytopenia are adverse reactions of various drugs
Biochemical alterations	Hyponatremia, hypokalemia, elevated BUN and creatinine are common events with various drugs
Cardiac alterations	Tachycardia is common, for example, with beta-adrenergic agents, which can cause other arrhythmias; bradycardia may occur with beta-blockers
Antihistamines	Indicator of allergic reaction
Corticoids	Potential indicator of allergic reaction
Allergic reactions	Frequently reported adverse events
Non-programmed endotracheal intubation	Potential indicator of respiratory depression, common, for example, with benzodiazepines
Level of consciousness degradations	Common with benzodiazepines, anticonvulsants
Drug interactions	For example, hypotension and lethargy caused by concomitant administration of sedatives and anticonvulsants
Antiseizures prescription	Potential indicative of unexpected seizure, when using medications that may lead to changes in electrolytes and seizures, like amphotericin B
Drug intolerance	For example, vomiting and diarrhea, frequent events with various medications, such as antibiotics
Non-programmed suspension of drug	Indicative of intolerance or adverse reaction
Fever	Adverse event of drugs such as amphotericin B
Sudden death	Already reported with drug combinations containing dipyrone
Serum level alteration	for monitored drugs such as vancomycin and phenobarbital, with a

	narrow therapeutic range and potentially toxic at high levels
Aminophylline / adrenaline prescription	Potential indicators of severe allergic reactions
Antidotes prescription	For example, the use of flumazenil may indicate adverse events due to the use of benzodiazepines
Others	Adverse events discovered in the review of medical records, and that does not fit in any trigger, being the trigger the event itself

Table 2 – Occurrences of triggers used for active search.

Triggers	**Number of occurrences**	**Positive predictive value**
Hematological alterations	8	5.79%
Biochemical alterations	64	46.37%
Cardiac alterations	17	12.3%
Antihistamines	5	3.62%
Corticoids	2	1.45%
Allergic reactions	11	7.97%
Non-programmed endotracheal intubation	1	0.72%
Level of consciousness degradations	2	1.45%
Drug interactions	8	5.80%
Antiseizures prescription	2	1.45%
Drug intolerance	0	0%
Non-programmed suspension of drug	1	0.72%
Fever	0	0%
Sudden death	0	0%
Serum level alteration	0	0%
Aminophylline / adrenaline prescription	0	0%
Antidotes prescription	3	2.17%
Others	14	10.14%

Table 3 – Distribution of prevalent-drug and incident-drug adverse events according to causality.

ADE	Prevalent-drug	Incident-drug	TOTAL
Proven	0	5	5
Probable	12	32	44
Possible	27	34	61
TOTAL	39	71	110

Table 4 – Observed adverse drug events (ADEs) and related drugs

Adverse Drug Events (ADEs)	N	Related drugs
Hyponatremia	27	furosemide, fentanyl, carbamazepine, vigabatrin topiramate, hydrochlorothiazide, somatostatin, vancomycin, rifampicin, ranitidine, phenytoin
Hyperglycemia	17	dexamethasone, hydrocortisone, methylprednisolone, terbutaline, tacrolimus
Hypokalemia	13	amphotericin b, terbutaline, furosemide, ranitidine
Skin rash and urticaria	11	vancomycin, dipyrone, cefepime, ceftriaxone, levetiracetam, dipyrone, rasburicase
Hypoventilation/desaturation of oxygen	6	midazolam, propofol, fentanyl, morphine, diazepam
Bradycardia	4	midazolam
Hypotension	4	midazolam, furosemide, thiopental, chlorpromazine
Liver enzyme abnormalities	4	meropenem, carbamazepine, amlodipine, carvedilol, clonidine, amitriptyline, phenobarbital
Hypertension	3	prednisone tacrolimus, dopamine
Increased BUN and creatinine	3	vancomycin, tacrolimus
Seizure	2	hydrocortisone, liposomal amphotericin B, cefepime
Tachycardia	2	terbutaline
Anemia	2	ketoprofen, paracetamol
Extrasystole	2	carvedilol, terbutaline
Increased number of platelets	2	Meropenem, ceftriaxone
Vomiting	2	Nitroprusside, tacrolimus
Cardiorespiratory arrest	1	dipyrone
Thrombocytopenia	1	dipyrone
Apnea	1	phenytoin
Leukopenia	1	imipenem
Stevens-Johnson syndrome	1	trimethoprim / sulfamethoxazole
Eosinophilia	1	ceftriaxone

Table 5 – Odds ratios related to the concomitant use of medications.

	Occurrence of at least one ADE			Occurrence of more than one ADE		
Number of drugs	*Odds ratio*	95% CI	*P*	*Odds ratio*	95% CI	*P*
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.0,3	1.69-5.40	0.0002	3.28	1.06-10.07	0.037
7	3.69	2.11-6.46	< 0.0001	2.95	1.14-7.60	0.025
8	3.84	2.24-6.80	< 0.0001	3.35	1.34-8.35	0.009
9	4.40	2.29-8.45	< 0.0001	3.14	1.24-7.90	0.015
10	6.48	2.85-14.77	< 0.0001	3.69	1.36-9.99	0.010
11	7.26	2.77-19.01	< 0.0001	5.55	1.98-15.52	0.001

TITLE PAGE

ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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Key Words: drug toxicity; pharmacovigilance; drug monitoring; intensive care; pediatrics; patient safety.

ABSTRACT

Objectives: To describe adverse drug events (ADEs) in children under intensive care, identify risk factors and tools that can detect ADEs early, and the impact on length of stay (LOS).

Design: Prospective, observational study.

Setting: Pediatric intensive care unit of a tertiary care teaching hospital.

Patients: 239 patients with a mean age of 67.5 months representing 1818 days of hospitalization in intensive care unit .

Interventions: Active search of charts and electronic patient records using triggers. The statistical analysis involved linear and logistic regression.

Measurements and Main Results: The average LOS was 7.6 days. There were 110 proven, probable, and possible ADEs in 84 patients (35.1%). We observed 138 instances of triggers. The major classes of drugs associated with events were: antibiotics (n = 41), diuretics (n = 24), antiseizures (n = 23), sedatives and analgesics (n = 17), and steroids (n = 18). The number of drugs administered was most related to the occurrence of ADEs and also to the length of stay ($p < 0.001$). The occurrence of an ADE may result in an increase in the length of stay by 1.5 days per event, but this was not statistically significant in this sample. Patient aged less than 48 months also proved to be at significant risk for ADEs, with an odds ratio of 1.84 (confidence interval - 95% CI - 1.07 to 3.15, $p = 0.025$). The number of drugs administered also correlated with the number of ADEs ($p < 0.0001$). The chance of having at least one ADE increased linearly as the patient was administered more drugs.

Conclusions: The use of multiple drugs as well as lower patient age favors the occurrence of ADEs. The active search described here provides a systematic approach to this problem.

INTRODUCTION

The use of medication in children and infants is a matter of great concern largely due to the vulnerability of their constantly changing and developing homeostasis, as well as the unique mechanisms by which different children respond to injuries. There are important differences in absorption, distribution, metabolism and excretion of drugs during childhood and early adolescence.[1] In addition, several medications have not exhibited safety in the pediatric age group, while others are prescribed differently than recommended for adults; key differences include dose and frequency of administration, presentation of the drug, route of administration, or indication for use in childhood (i.e. "off-label" use), and each of these factors can vary depending on the age of the child.[2] Most of times, recommended doses of drugs used in children are based on extrapolations from adult doses, related only to weight, body surface area, and age, often ignoring their pharmacokinetic and pharmacodynamic properties; this results in increased susceptibility of children to drug-related adverse events.[1-4]

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There are few studies documenting safety in drug administration in children in the ICU. The primary objective of this study was to describe ADEs in children admitted to the pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary objectives, we attempted to identify risk factors for such events and tools that could detect them early as well as determine if there was impact on LOS.

MATERIALS AND METHODS

We conducted a preliminary survey over a period of 22 days in March 2004 to identify the number of admissions required to effectively report ADEs in the PICU, a unit of 13 beds, with average occupation of 80%. Based on the results of this survey, we determined that it would then be necessary to study 150 admissions to reach a stable estimate of the incidence of ADEs and explore possible risk factors using a multivariate analysis (approximately 10 ADEs for each variable potentially associated). The study population consisted of consecutive admissions to the PICU between October 1, 2005 and March 31, 2006. The strategy to identify ADEs was through an active search, using pre-established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or flag, found when reviewing a patient's medical chart, that requires further investigation to determine the presence or absence of an adverse event.[7,8] Using this method, specific events, such as prescription or abrupt discontinuation of certain medications, prescription of antidotes, and some laboratory tests, serve as indicators for further investigation. Several triggers have been described in the literature,[8] and therefore we chose and adapted the ones

that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows these triggers and the rationale for their use. The positive predictive value (PPV) of each trigger was calculated as the number of times that each trigger identified an ADE, divided by the total number of times the triggers were identified in the active search.

The following methodology was undertaken for active search:

1. The admission form for each new patient in the PICU was entered by two trained intensive care pediatricians; data were reviewed by 2 authors (Drs. Silva and Shibata) and consolidated in agreement.

2. The following records for each patient were reviewed, guided by triggers indicative of adverse events:

- Laboratory tests (electronic database);
- Clinical annotations;
- Nursing annotations;
- Prescription;

3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable, possible, or doubtful;[9]

4. Analysis of all proven, probable and possible ADEs.

The study included only unavoidable ADEs, that is, only those that occurred during normal use of a drug, and not the result of a human error,[10] as well as those classified as moderate to severe according to the World Health Organization (WHO) guidelines: By this definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears after administration of a drug at doses normally used for prophylaxis, diagnosis or treatment of a disease. A moderate reaction is one that requires modification of therapy and may require specific treatment; a severe reaction is potentially fatal and requires specific

treatment, requires or prolongs hospitalization.[11] We analyzed only those ADEs that appeared after admission. ADEs that appeared after admission but were related to drugs that the patient was receiving before being admitted were defined as due to “prevalent drug”. This definition eliminated, for example, ADEs due to chemotherapy already present before admission in patients with cancer. ADEs related to drugs introduced after admission were classified as due to "incident drug". The study protocol was reviewed and approved by the Ethics Committee of the institution prior to the start of data collection (protocol number 485/56/2005). Because of the observational nature of the study, without any interference in therapy, informed consent was waived.

Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the odds ratios (OR) by logistic regression. A multinomial logistic regression model was performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number of drugs” because they have been significantly correlated with the incidence of ADEs.[5] Some studies have shown a lower risk for ADEs in male children.[12] Chronic illness is an important variable due to the continuous use of various drugs and the presence of organ dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS" (dependent). Significance of differences between means was obtained with the T test. Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was considered statistically significant.

RESULTS

In our pilot survey, we identified 20 adverse events of moderate to severe intensity over a period of 22 days in March 2004, which we calculated to represent at least 5 events per 100 patient-days.

In our actual study, there were 244 admissions to the PICU during the period between October 1, 2005 and March 31, 2006. Four patients were excluded because they were adult living-donors for liver transplant, and one patient was excluded due to age > 18 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of 9.5 days.

The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%). Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%), neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83), postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures, digestive bleeding, dehydration, renal failure, hypertension, and others.

We observed 138 occurrences of triggers, as shown in Table 2, with their predictive positive values. These triggers led to the identification of 110 proven, probable, or possible ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after

PICU admission or "incidents" (Table 3). Table 4 shows the observed ADEs and related drugs.

Gender, the presence of chronic disease, age, and administration of at least five drugs were included in a multinomial logistic regression analysis as independent variables for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the individual chronic conditions displayed an increased risk for ADEs; however, patient age less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01) in the occurrence of at least one ADE. This interaction remained significant, with discrete elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI: 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001 for the use of 9 drugs).

In a bivariate analysis, the number of drugs received by each patient correlated with the number of ADEs (R2 = 0.13, p < 0.0001). The likelihood of at least one ADE became significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the occurrence of more than one ADE (Table 5).

There was a significant difference between the mean LOS between patients with and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75

(p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS. However, this increase was not maintained when other confounding variables were added in the multivariate regression model. The only independent variables remaining in the final model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and the number of drugs (p < 0.001; slope coefficient 0.83; R2 = 0.104); The slope coefficient could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but the study did not have the power to demonstrate it. A sample calculation showed that in order for this fact to be significant in a larger sample, it would take 1000 patients to achieve p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the dependent variable "LOS" and 0.72 for independent "number of ADEs". Other variables did not show any significant relationship.

In addition, mean "survival" without ADEs (time from admittance to the PICU until the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for patients younger than 48 months (p = 0.017).

The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24), antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9), bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5), hormonal analogues (4), antipyretics (4), and others (5).

DISCUSSION

Determining the occurrence of adverse events in an intensive care environment is a complex task. The symptoms of the event may overlap the underlying disease and may be caused by several unrelated factors including the pharmacokinetic profile of the drug, unknown drug allergies of each patient, or human error. These difficulties may serve as an

explanation for why many events are not recognized as ADEs. Frequently, other drugs are administered in an attempt to solve the problem created by the ADE, without the specific diagnosis. While some events are easily attributed to certain drugs, there are several possible and poorly documented events and some are completely unknown and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE, including age and certain comorbidities, such as the presence of renal or hepatic impairment. Drug-related factors such as toxicity, time of administration, dosage, and duration of use are variables that can also impact the probability of ADEs. In addition, new drugs that have just completed phase III clinical trials may not have been powered to detect rare events.[13] In general, if we don't look for ADEs, it is unlikely that we will find them.[14]

In the absence of reliable empirical methods for detection of ADEs, formal and logical tools can help differentiate an ADE from a symptom caused by exacerbations in a patient's underlying condition. The most widely accepted formal instrument to obtain this is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some included events may not have been ADEs. However, to prove an ADE according to the algorithm, it is necessary to re-administer the drug and observe the event again, or obtain serum levels that are known to be toxic. The first option is strongly discouraged and the second may be technically impossible or unavailable. However, we excluded the "doubtful" events (score equal to or less than 1) from our analysis and some of these events may have actually been ADEs.

Most of our patients had chronic diseases, which may contribute to a higher incidence of ADEs, due to the use of multiple medications. This population of chronic patients reflects the current reality of Brazilian university hospitals. We observed no

significant difference in ADE incidence between patients with and without chronic diseases, which can be explained by the exclusion of events prior to PICU admission and was more likely related to the medications used regularly.

The incidence of observed events (35.1% of admissions) is much higher than those reported in adult patients hospitalized in ICUs (around 9%).[15] Furthermore, we found that younger children under the age of 48 months, which constitute approximately half the patient sample, were more likely to have ADEs. This was particularly significant with the administration of over five drugs at the same time, and also resulted in an ADE earlier in the patient's ICU stay. The high incidence of ADEs also highlights the importance of an active search focused on triggers to detect ADEs in children: Holdsworth et al reported ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart review by a pharmacist).[16] Takata et al. performed a search focused on triggers and reported 11.1 events/100 inpatients, almost double that of the retrospective study. These authors indicated that performing a search focused on specific circumstances associated with ADEs in specific elements of the patient's chart can increase the rates of observed ADEs.[17] The methodology we used in this study (definition of triggers and daily search in the records of patients) is a simple way to perform an active search for ADEs. Triggers can be individualized for each hospital setting according to the most frequently used medications. PPVs can be determined through a simple calculation that assists in the choice of triggers that are most useful in each unit. We observed higher PPVs for biochemical alterations; in an automated process, the system of the laboratory itself could alert for possible ADEs.

We wish to highlight that our study evaluated severely ill children under intensive care receiving multiple drugs (up to 18), and the chances of developing an ADE is therefore, more likely. In addition, comparing event rates is also challenging and potentially

misleading as definitions of ADEs are unclear among studies, ranging from a benign and transient alteration of electrolytes to vital organ damage.[10]

We investigated whether ADEs may have an impact on the LOS in the PICU. The most important limitation of the study was that our sample did not have the power to implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however, calculations based on standard deviations observed in our sample showed a high probability that this would be true in a longer-term study. In addition to possible patient harm, there are significant costs associated with patient stays in the ICU: An increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at $600.00 (American dollars) each day, ADEs amount to $198,000 per year, which is a considerable sum for our public health system. In principle, the events occurred as a result of habitual use of drugs and were therefore "inevitable"; however, a systematic approach could convert some ADEs from presumably inevitable to avoidable. A good example cited by Kane-Gill et al[10] describes bleeding caused by the correct dose of heparin in a patient being monitored by partial thromboplastin time and would be classified as inevitable. If an investigation identified that the laboratory has changed their method for thromboplastin time and failed to communicate the necessary adjustment, the error would become preventable. More studies on pharmacokinetics and drug interactions in children are required to define optimal dosing regimens and reduce ADEs.

Another limitation of the study was the short time of observation, which did not include the seasonality of respiratory diseases. A positive aspect of the study was the analysis of a PICU population in a country outside Europe and North America, therefore making it possible to analyze ADEs due to drugs such as dipyrone. We hope that our study will contribute to a future systematic approach to this subject in developing countries.

CONCLUSIONS

The use of multiple drugs as well as lower patient age favors the occurrence of ADEs, which in turn may result in an increase in the length of PICU hospitalization. The use of an active search using triggers can provide a systematic approach to identify ADEs in PICUs.

REFERENCES

1. Niederhauser VP. Prescribing for children: issues in pediatric pharmacology. *Nurse Pract* 1997;22(3):16-18.

2. Hussain E, Kao E. Medication safety and transfusion errors in the ICU and beyond. *Crit Care Clin* 2005;21:91-110.

3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-471.

4. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285:2114-2120.

5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.

6. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;84:438-441.

7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003;12(3):194–200.

8. Resar RK, Rozich JD, Classen DC. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care* 2003;12(suppl 2):ii39 –ii45.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30 (2): 239–245.

10. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med* 2012;40(3):823-8.

11. World Health Organization (WHO). Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III. Geneva; 1995.

12. Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. Adverse drug reactions in children-a systematic review. *PLoS One*. 2012;7(3):e24061.

13. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001;94(4):370-3.

14. Kelly WN. How Can I Recognize an Adverse Drug Event. Available online at: http://www.medscape.org/viewarticle/569794. Accessed Feb 1, 2012.

15. Vargas E, Terleira A, Hernando F, Perez E, Cordon C, Moreno A, Portoles A. Effect of adverse drug reactions on length of stay in surgical intensive care units. *Crit Care Med* 2003;31(3):694-8.

16. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med* 2003;157(1):60–65.

17. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-3.

Table 1 – rationale for the use of triggers

Triggers	Rationale for use
Hematological alterations	Anemia, leukopenia, and thrombocytopenia are adverse reactions of various drugs
Biochemical alterations	Hyponatremia, hypokalemia, elevated BUN and creatinine are common events with various drugs
Cardiac alterations	Tachycardia is common, for example, with beta-adrenergic agents, which can cause other arrhythmias; bradycardia may occur with beta-blockers
Antihistamines	Indicator of allergic reaction
Corticoids	Potential indicator of allergic reaction
Allergic reactions	Frequently reported adverse events
Non-programmed endotracheal intubation	Potential indicator of respiratory depression, common, for example, with benzodiazepines
Level of consciousness degradations	Common with benzodiazepines, anticonvulsants
Drug interactions	For example, hypotension and lethargy caused by concomitant administration of sedatives and anticonvulsants
Antiseizures prescription	Potential indicative of unexpected seizure, when using medications that may lead to changes in electrolytes and seizures, like amphotericin B
Drug intolerance	For example, vomiting and diarrhea, frequent events with various medications, such as antibiotics
Non-programmed suspension of drug	Indicative of intolerance or adverse reaction
Fever	Adverse event of drugs such as amphotericin B
Sudden death	Already reported with drug combinations containing dipyrone
Serum level alteration	for monitored drugs such as vancomycin and phenobarbital, with a

	narrow therapeutic range and potentially toxic at high levels
Aminophylline / adrenaline prescription	Potential indicators of severe allergic reactions
Antidotes prescription	For example, the use of flumazenil may indicate adverse events due to the use of benzodiazepines
Others	Adverse events discovered in the review of medical records, and that does not fit in any trigger, being the trigger the event itself

Table 2 – Occurrences of triggers used for active search.

Triggers	**Number of occurrences**	**Positive predictive value**
Hematological alterations	8	5.79%
Biochemical alterations	64	46.37%
Cardiac alterations	17	12.3%
Antihistamines	5	3.62%
Corticoids	2	1.45%
Allergic reactions	11	7.97%
Non-programmed endotracheal intubation	1	0.72%
Level of consciousness degradations	2	1.45%
Drug interactions	8	5.80%
Antiseizures prescription	2	1.45%
Drug intolerance	0	0%
Non-programmed suspension of drug	1	0.72%
Fever	0	0%
Sudden death	0	0%
Serum level alteration	0	0%
Aminophylline / adrenaline prescription	0	0%
Antidotes prescription	3	2.17%
Others	14	10.14%

Table 3 – Distribution of prevalent-drug and incident-drug adverse events according to causality.

ADE	Prevalent-drug	Incident-drug	TOTAL
Proven	0	5	5
Probable	12	32	44
Possible	27	34	61
TOTAL	39	71	110

Table 4 – Observed adverse drug events (ADEs) and related drugs

Adverse Drug Events (ADEs)	N	Related drugs
Hyponatremia	27	furosemide, fentanyl, carbamazepine, vigabatrin topiramate, hydrochlorothiazide, somatostatin, vancomycin, rifampicin, ranitidine, phenytoin
Hyperglycemia	17	dexamethasone, hydrocortisone, methylprednisolone, terbutaline, tacrolimus
Hypokalemia	13	amphotericin b, terbutaline, furosemide, ranitidine
Skin rash and urticaria	11	vancomycin, dipyrone, cefepime, ceftriaxone, levetiracetam, dipyrone, rasburicase
Hypoventilation/desaturation of oxygen	6	midazolam, propofol, fentanyl, morphine, diazepam
Bradycardia	4	midazolam
Hypotension	4	midazolam, furosemide, thiopental, chlorpromazine
Liver enzyme abnormalities	4	meropenem, carbamazepine, amlodipine, carvedilol, clonidine, amitriptyline, phenobarbital
Hypertension	3	prednisone tacrolimus, dopamine
Increased BUN and creatinine	3	vancomycin, tacrolimus
Seizure	2	hydrocortisone, liposomal amphotericin B, cefepime
Tachycardia	2	terbutaline
Anemia	2	ketoprofen, paracetamol
Extrasystole	2	carvedilol, terbutaline
Increased number of platelets	2	Meropenem, ceftriaxone
Vomiting	2	Nitroprusside, tacrolimus
Cardiorespiratory arrest	1	dipyrone
Thrombocytopenia	1	dipyrone
Apnea	1	phenytoin
Leukopenia	1	imipenem
Stevens-Johnson syndrome	1	trimethoprim / sulfamethoxazole
Eosinophilia	1	ceftriaxone

Table 5 – Odds ratios related to the concomitant use of medications.

	Occurrence of at least one ADE			Occurrence of more than one ADE		
Number of drugs	*Odds ratio*	95% CI	*P*	*Odds ratio*	95% CI	*P*
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.0,3	1.69-5.40	0.0002	3.28	1.06-10.07	0.037
7	3.69	2.11-6.46	< 0.0001	2.95	1.14-7.60	0.025
8	3.84	2.24-6.80	< 0.0001	3.35	1.34-8.35	0.009
9	4.40	2.29-8.45	< 0.0001	3.14	1.24-7.90	0.015
10	6.48	2.85-14.77	< 0.0001	3.69	1.36-9.99	0.010
11	7.26	2.77-19.01	< 0.0001	5.55	1.98-15.52	0.001

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ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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TITLE PAGE

ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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Key Words: drug toxicity; pharmacovigilance; drug monitoring; intensive care; pediatrics; patient safety.

ABSTRACT

Objectives: To describe adverse drug events (ADEs) in children under intensive care, identify risk factors and tools that can detect ADEs early, and the impact on length of stay (LOS).

Design: Prospective, observational study.

Setting: Pediatric intensive care unit of a tertiary care teaching hospital.

Patients: 239 patients with a mean age of 67.5 months representing 1818 days of hospitalization in intensive care unit .

Interventions: Active search of charts and electronic patient records using triggers. The statistical analysis involved linear and logistic regression.

Measurements and Main Results: The average LOS was 7.6 days. There were 110 proven, probable, and possible ADEs in 84 patients (35.1%). We observed 138 instances of triggers. The major classes of drugs associated with events were: antibiotics (n = 41), diuretics (n = 24), antiseizures (n = 23), sedatives and analgesics (n = 17), and steroids (n = 18). The number of drugs administered was most related to the occurrence of ADEs and also to the length of stay ($p < 0.001$). The occurrence of an ADE may result in an increase in the length of stay by 1.5 days per event, but this was not statistically significant in this sample. Patient aged less than 48 months also proved to be at significant risk for ADEs, with an odds ratio of 1.84 (confidence interval - 95% CI - 1.07 to 3.15, $p = 0.025$). The number of drugs administered also correlated with the number of ADEs ($p < 0.0001$). The chance of having at least one ADE increased linearly as the patient was administered more drugs.

Conclusions: The use of multiple drugs as well as lower patient age favors the occurrence of ADEs. The active search described here provides a systematic approach to this problem.

INTRODUCTION

The use of medication in children and infants is a matter of great concern largely due to the vulnerability of their constantly changing and developing homeostasis, as well as the unique mechanisms by which different children respond to injuries. There are important differences in absorption, distribution, metabolism and excretion of drugs during childhood and early adolescence.[1] In addition, safety of several medications has not been properly evaluated in the pediatric age group, while others are prescribed differently than recommended for adults; key differences include dose and frequency of administration, drug formulation, route of administration, or indication for use in childhood (i.e. "off-label" use), and each of these factors can vary depending on the age of the child.[2] Most of times, recommended doses of drugs used in children are based on extrapolations from adult doses, related only to weight, body surface area, and age, often ignoring their pharmacokinetic and pharmacodynamic properties; this results in increased susceptibility of children to drug-related adverse events.[1-4]

Reports documenting the incidence of adverse drug events in the pediatric population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with high morbidity and mortality.[5] Hospitalized children may be at a higher risk of an adverse event, as doses, drug safety, and effectiveness are often difficult to determine.[6] Kaushal and colleagues identified that the potential frequency of ADEs in children is three times higher than a previous study focused on ADEs in adults, however, the rate of avoidable ADEs was similar.[4] In intensive care units, multiple, potentially hazardous drugs are

routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics; as the risk of an ADE increases by 1.7% for each additional drug used,[5] it is far more likely that adverse reactions will occur in the ICU.

There are few studies documenting safety in drug administration in children in the ICU. The primary objective of this study was to describe ADEs in children admitted to the pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary objectives, we attempted to identify risk factors for such events and tools that could detect them early as well as determine if there was impact on LOS.

MATERIALS AND METHODS

We conducted a preliminary survey over a period of 22 days in March 2004 to identify the number of admissions required to effectively report ADEs in the PICU, a unit of 13 beds, with average occupation of 80%. Based on the results of this survey, we determined that it would then be necessary to study 150 admissions to reach a stable estimate of the incidence of ADEs and explore possible risk factors using a multivariate analysis (approximately 10 ADEs for each variable potentially associated). The study population consisted of consecutive admissions to the PICU between October 1, 2005 and March 31, 2006. The strategy to identify ADEs was through an active search, using pre-established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or flag, found when reviewing a patient's medical chart, that requires further investigation to determine the presence or absence of an adverse event.[7,8] Using this method, specific events, such as prescription or abrupt discontinuation of certain medications, prescription of antidotes, and some laboratory tests, serve as indicators for further investigation. Several triggers have been described in the literature,[8] and therefore we chose and adapted the ones

that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows these triggers and the rationale for their use. The positive predictive value (PPV) of each trigger was calculated as the number of times that each trigger identified an ADE, divided by the total number of times the triggers were identified in the active search.

The following methodology was undertaken for active search:

1. The admission form for each new patient in the PICU was entered by two trained intensive care pediatricians; data were analyzed and consolidated by 2 authors (Drs. Silva and Shibata).

2. The following records for each patient were reviewed, guided by triggers indicative of adverse events:

- Laboratory tests (electronic database);
- Clinical annotations;
- Nursing annotations;
- Prescription;

3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable, possible, or doubtful;[9]

4. Analysis of all proven, probable and possible ADEs.

The study included only unavoidable ADEs, that is, only those that occurred during normal use of a drug, and not the result of a human error,[10] as well as those classified as moderate to severe according to the World Health Organization (WHO) guidelines: By this definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears after administration of a drug at doses normally used for prophylaxis, diagnosis or treatment of a disease. A moderate reaction is one that requires modification of therapy and may require specific treatment; a severe reaction is potentially fatal and requires specific

treatment, requires or prolongs hospitalization.[11] We analyzed only those ADEs that appeared after admission. ADEs that appeared after admission but were related to drugs that the patient was receiving before being admitted were defined as due to “prevalent drug”. This definition eliminated, for example, ADEs due to chemotherapy already present before admission in patients with cancer. ADEs related to drugs introduced after admission were classified as due to "incident drug". The study protocol was reviewed and approved by the Ethics Committee of the institution prior to the start of data collection (protocol number 485/56/2005). Because of the observational nature of the study, without any interference in therapy, informed consent was waived.

Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the odds ratios (OR) by logistic regression. A multinomial logistic regression model was performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number of drugs” because they have been significantly correlated with the incidence of ADEs.[5] Some studies have shown a lower risk for ADEs in male children.[12] Chronic illness is an important variable due to the continuous use of various drugs and the presence of organ dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS" (dependent). Significance of differences between means was obtained with the T test. Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was considered statistically significant.

RESULTS

In our pilot survey, we identified 20 adverse events of moderate to severe intensity over a period of 22 days in March 2004, which we calculated to represent at least 5 events per 100 patient-days.

In our actual study, there were 244 admissions to the PICU during the period between October 1, 2005 and March 31, 2006. Four patients were excluded because they were adult living-donors for liver transplant, and one patient was excluded due to age > 18 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of 9.5 days.

The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%). Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%), neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83), postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures, digestive bleeding, dehydration, renal failure, hypertension, and others.

We observed 138 occurrences of triggers, as shown in Table 2, with their predictive positive values. These triggers led to the identification of 110 proven, probable, or possible ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after

PICU admission or "incidents" (Table 3). Table 4 shows the observed ADEs and related drugs.

Gender, the presence of chronic disease, age, and administration of at least five drugs were included in a multinomial logistic regression analysis as independent variables for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the individual chronic conditions displayed an increased risk for ADEs; however, patient age less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01) in the occurrence of at least one ADE. This interaction remained significant, with discrete elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI: 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001 for the use of 9 drugs).

In a bivariate analysis, the number of drugs received by each patient correlated with the number of ADEs (R^2 = 0.13, p < 0.0001). The likelihood of at least one ADE became significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the occurrence of more than one ADE (Table 5).

There was a significant difference between the mean LOS between patients with and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75

(p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS. However, this increase was not maintained when other confounding variables were added in the multivariate regression model. The only independent variables remaining in the final model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and the number of drugs (p < 0.001; slope coefficient 0.83; R^2 = 0.104); The slope coefficient could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but the study did not have the power to demonstrate it. A sample calculation showed that in order for this fact to be significant in a larger sample, it would take 1000 patients to achieve p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the dependent variable "LOS" and 0.72 for independent "number of ADEs". Other variables did not show any significant relationship.

In addition, mean "survival" without ADEs (time from admittance to the PICU until the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for patients younger than 48 months (p = 0.017).

The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24), antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9), bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5), hormonal analogues (4), antipyretics (4), and others (5).

DISCUSSION

Determining the occurrence of adverse events in an intensive care environment is a complex task. The symptoms of the event may overlap the underlying disease and may be caused by several unrelated factors including the pharmacokinetic profile of the drug, unknown drug allergies of each patient, or human error. These difficulties may serve as an

explanation for why many events are not recognized as ADEs. Frequently, other drugs are administered in an attempt to solve the problem created by the ADE, without the specific diagnosis. While some events are easily attributed to certain drugs, there are several possible and poorly documented events and some are completely unknown and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE, including age and certain comorbidities, such as the presence of renal or hepatic impairment. Drug-related factors such as toxicity, time of administration, dosage, and duration of use are variables that can also impact the probability of ADEs. In addition, new drugs that have just completed phase III clinical trials may not have been powered to detect rare events.[13] In general, if we don't look for ADEs, it is unlikely that we will find them.[14]

In the absence of reliable empirical methods for detection of ADEs, formal and logical tools can help differentiate an ADE from a symptom caused by exacerbations in a patient's underlying condition. The most widely accepted formal instrument to obtain this is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some included events may not have been ADEs. However, to prove an ADE according to the algorithm, it is necessary to re-administer the drug and observe the event again, or obtain serum levels that are known to be toxic. The first option is strongly discouraged and the second may be technically impossible or unavailable. However, we excluded the "doubtful" events (score equal to or less than 1) from our analysis and some of these events may have actually been ADEs.

Most of our patients had chronic diseases, which may contribute to a higher incidence of ADEs, due to the use of multiple medications. This population of chronic patients reflects the current reality of Brazilian university hospitals. We observed no

significant difference in ADE incidence between patients with and without chronic diseases, which can be explained by the exclusion of events prior to PICU admission and was more likely related to the medications used regularly.

The incidence of observed events (35.1% of admissions) is much higher than those reported in adult patients hospitalized in ICUs (around 9%).[15] Furthermore, we found that younger children under the age of 48 months, which constitute approximately half the patient sample, were more likely to have ADEs. This was particularly significant with the administration of over five drugs at the same time, and also resulted in an ADE earlier in the patient's ICU stay. The high incidence of ADEs also highlights the importance of an active search focused on triggers to detect ADEs in children: Holdsworth et al reported ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart review by a pharmacist).[16] Takata et al. performed a search focused on triggers and reported 11.1 events/100 inpatients, almost double that of the retrospective study. These authors indicated that performing a search focused on specific circumstances associated with ADEs in specific elements of the patient's chart can increase the rates of observed ADEs.[17] The methodology we used in this study (definition of triggers and daily search in the records of patients) is a simple way to perform an active search for ADEs. Triggers can be individualized for each hospital setting according to the most frequently used medications. PPVs can be determined through a simple calculation that assists in the choice of triggers that are most useful in each unit. We observed higher PPVs for biochemical alterations; in an automated process, the system of the laboratory itself could alert for possible ADEs.

We wish to highlight that our study evaluated severely ill children under intensive care receiving multiple drugs (up to 18), and the chances of developing an ADE is

therefore, more likely. In addition, comparing event rates is also challenging and potentially misleading as definitions of ADEs are unclear among studies, ranging from a benign and transient alteration of electrolytes to vital organ damage.[10]

We investigated whether ADEs may have an impact on the LOS in the PICU. The most important limitation of the study was that our sample did not have the power to implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however, calculations based on standard deviations observed in our sample showed a high probability that this would be true in a longer-term study. In addition to possible patient harm, there are significant costs associated with patient stays in the ICU: An increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at $600.00 (American dollars) each day, ADEs amount to $198,000 per year, which is a considerable sum for our public health system. In principle, the events occurred as a result of habitual use of drugs and were therefore "inevitable"; however, a systematic approach could convert some ADEs from presumably inevitable to avoidable. A good example cited by Kane-Gill et al[10] describes bleeding caused by the correct dose of heparin in a patient being monitored by partial thromboplastin time and would be classified as inevitable. If an investigation identified that the laboratory has changed their method for thromboplastin time and failed to communicate the necessary adjustment, the error would become preventable. More studies on pharmacokinetics and drug interactions in children are required to define optimal dosing regimens and reduce ADEs.

Another limitation of the study was the short time of observation, which did not include the seasonality of respiratory diseases. A positive aspect of the study was the analysis of a PICU population in a country outside Europe and North America, therefore making it possible to analyze ADEs due to drugs such as dipyrone. In Brazil, the reporting

of ADEs is incipient. The online system provided by the health authority only receives notifications, which are not mandatory. Active search is not utilized, even in private institutions. We hope that our study will contribute to a future systematic approach to this subject in developing countries.

CONCLUSIONS

The use of multiple drugs as well as lower patient age favors the occurrence of ADEs, which in turn may result in an increase in the length of PICU hospitalization. The use of an active search using triggers can provide a systematic approach to identify ADEs in PICUs.

REFERENCES

1. Niederhauser VP. Prescribing for children: issues in pediatric pharmacology. *Nurse Pract* 1997;22(3):16-18.

2. Hussain E, Kao E. Medication safety and transfusion errors in the ICU and beyond. *Crit Care Clin* 2005;21:91-110.

3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-471.

4. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285:2114-2120.

5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.

6. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;84:438-441.

7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003;12(3):194–200.

8. Resar RK, Rozich JD, Classen DC. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care* 2003;12(suppl 2):ii39 –ii45.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30 (2): 239–245.

10. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med* 2012;40(3):823-8.

11. World Health Organization (WHO). Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III. Geneva; 1995.

12. Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. Adverse drug reactions in children-a systematic review. *PLoS One*. 2012;7(3):e24061.

13. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001;94(4):370-3.

14. Kelly WN. How Can I Recognize an Adverse Drug Event. Available online at: *http://www.medscape.org/viewarticle/569794*. Accessed Feb 1, 2012.

15. Vargas E, Terleira A, Hernando F, Perez E, Cordon C, Moreno A, Portoles A. Effect of adverse drug reactions on length of stay in surgical intensive care units. *Crit Care Med* 2003;31(3):694-8.

16. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med* 2003;157(1):60–65.

17. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-3.

Table 1 – rationale for the use of triggers

Triggers	Rationale for use
Hematological alterations	Anemia, leukopenia, and thrombocytopenia are adverse reactions of various drugs
Biochemical alterations	Hyponatremia, hypokalemia, elevated BUN and creatinine are common events with various drugs
Cardiac alterations	Tachycardia is common, for example, with beta-adrenergic agents, which can cause other arrhythmias; bradycardia may occur with beta-blockers
Antihistamines	Indicator of allergic reaction
Corticoids	Potential indicator of allergic reaction
Allergic reactions	Frequently reported adverse events
Non-programmed endotracheal intubation	Potential indicator of respiratory depression, common, for example, with benzodiazepines
Level of consciousness degradations	Common with benzodiazepines, anticonvulsants
Drug interactions	For example, hypotension and lethargy caused by concomitant administration of sedatives and anticonvulsants
Antiseizures prescription	Potential indicative of unexpected seizure, when using medications that may lead to changes in electrolytes and seizures, like amphotericin B
Drug intolerance	For example, vomiting and diarrhea, frequent events with various medications, such as antibiotics
Non-programmed suspension of drug	Indicative of intolerance or adverse reaction

Fever	Adverse event of drugs such as amphotericin B
Sudden death	Already reported with drug combinations containing dipyrone
Serum level alteration	for monitored drugs such as vancomycin and phenobarbital, with a narrow therapeutic range and potentially toxic at high levels
Aminophylline / adrenaline prescription	Potential indicators of severe allergic reactions
Antidotes prescription	For example, the use of flumazenil may indicate adverse events due to the use of benzodiazepines
Others	Adverse events discovered in the review of medical records, and that does not fit in any trigger, being the trigger the event itself

Table 2 – Occurrences of triggers used for active search.

Triggers	**Number of occurrences**	**Positive predictive value**
Hematological alterations	8	5.79%
Biochemical alterations	64	46.37%
Cardiac alterations	17	12.3%
Antihistamines	5	3.62%
Corticoids	2	1.45%
Allergic reactions	11	7.97%
Non-programmed endotracheal intubation	1	0.72%
Level of consciousness degradations	2	1.45%
Drug interactions	8	5.80%
Antiseizures prescription	2	1.45%
Drug intolerance	0	0%
Non-programmed suspension of drug	1	0.72%
Fever	0	0%
Sudden death	0	0%
Serum level alteration	0	0%
Aminophylline / adrenaline prescription	0	0%
Antidotes prescription	3	2.17%
Others	14	10.14%

Table 3 – Distribution of prevalent-drug and incident-drug adverse events according to causality.

ADE	Prevalent-drug	Incident-drug	TOTAL
Proven	0	5	5
Probable	12	32	44
Possible	27	34	61
TOTAL	39	71	110

Table 4 – Observed adverse drug events (ADEs) and related drugs

Adverse Drug Events (ADEs)	N	Related drugs
Hyponatremia	27	furosemide, fentanyl, carbamazepine, vigabatrin topiramate, hydrochlorothiazide, somatostatin, vancomycin, rifampicin, ranitidine, phenytoin
Hyperglycemia	17	dexamethasone, hydrocortisone, methylprednisolone, terbutaline, tacrolimus
Hypokalemia	13	amphotericin b, terbutaline, furosemide, ranitidine
Skin rash and urticaria	11	vancomycin, dipyrone, cefepime, ceftriaxone, levetiracetam, dipyrone, rasburicase
Hypoventilation/desaturation of oxygen	6	midazolam, propofol, fentanyl, morphine, diazepam
Bradycardia	4	midazolam
Hypotension	4	midazolam, furosemide, thiopental, chlorpromazine
Liver enzyme abnormalities	4	meropenem, carbamazepine, amlodipine, carvedilol, clonidine, amitriptyline, phenobarbital
Hypertension	3	prednisone tacrolimus, dopamine
Increased BUN and creatinine	3	vancomycin, tacrolimus
Seizure	2	hydrocortisone, liposomal amphotericin B, cefepime
Tachycardia	2	terbutaline
Anemia	2	ketoprofen, paracetamol
Extrasystole	2	carvedilol, terbutaline
Increased number of platelets	2	Meropenem, ceftriaxone
Vomiting	2	Nitroprusside, tacrolimus
Cardiorespiratory arrest	1	dipyrone
Thrombocytopenia	1	dipyrone
Apnea	1	phenytoin
Leukopenia	1	imipenem

Stevens-Johnson syndrome	1	trimethoprim / sulfamethoxazole
Eosinophilia	1	ceftriaxone

Table 5 – Odds ratios related to the concomitant use of medications.

	Occurrence of at least one ADE			Occurrence of more than one ADE		
Number of drugs	*Odds ratio*	95% CI	*P*	*Odds ratio*	95% CI	*P*
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.0,3	1.69-5.40	0.0002	3.28	1.06-10.07	0.037
7	3.69	2.11-6.46	< 0.0001	2.95	1.14-7.60	0.025
8	3.84	2.24-6.80	< 0.0001	3.35	1.34-8.35	0.009
9	4.40	2.29-8.45	< 0.0001	3.14	1.24-7.90	0.015
10	6.48	2.85-14.77	< 0.0001	3.69	1.36-9.99	0.010
11	7.26	2.77-19.01	< 0.0001	5.55	1.98-15.52	0.001

TITLE PAGE

ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A PROSPECTIVE COHORT

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Key Words: drug toxicity; pharmacovigilance; drug monitoring; intensive care; pediatrics; patient safety.

ABSTRACT

Objectives: To describe adverse drug events (ADEs) in children under intensive care, identify risk factors and tools that can detect ADEs early, and the impact on length of stay (LOS).

Design: Prospective, observational study.

Setting: Pediatric intensive care unit of a tertiary care teaching hospital.

Patients: 239 patients with a mean age of 67.5 months representing 1818 days of hospitalization in intensive care unit .

Interventions: Active search of charts and electronic patient records using triggers. The statistical analysis involved linear and logistic regression.

Measurements and Main Results: The average LOS was 7.6 days. There were 110 proven, probable, and possible ADEs in 84 patients (35.1%). We observed 138 instances of triggers. The major classes of drugs associated with events were: antibiotics (n = 41), diuretics (n = 24), antiseizures (n = 23), sedatives and analgesics (n = 17), and steroids (n = 18). The number of drugs administered was most related to the occurrence of ADEs and also to the length of stay ($p < 0.001$). The occurrence of an ADE may result in an increase in the length of stay by 1.5 days per event, but this was not statistically significant in this sample. Patient aged less than 48 months also proved to be at significant risk for ADEs, with an odds ratio of 1.84 (confidence interval - 95% CI - 1.07 to 3.15, $p = 0.025$). The number of drugs administered also correlated with the number of ADEs ($p < 0.0001$). The chance of having at least one ADE increased linearly as the patient was administered more drugs.

Conclusions: The use of multiple drugs as well as lower patient age favors the occurrence of ADEs. The active search described here provides a systematic approach to this problem.

INTRODUCTION

The use of medication in children and infants is a matter of great concern largely due to the vulnerability of their constantly changing and developing homeostasis, as well as the unique mechanisms by which different children respond to injuries. There are important differences in absorption, distribution, metabolism and excretion of drugs during childhood and early adolescence.[1] In addition, safety of several medications has not been properly evaluated in the pediatric age group, while others are prescribed differently than recommended for adults; key differences include dose and frequency of administration, drug formulation, route of administration, or indication for use in childhood (i.e. "off-label" use), and each of these factors can vary depending on the age of the child.[2] Most of times, recommended doses of drugs used in children are based on extrapolations from adult doses, related only to weight, body surface area, and age, often ignoring their pharmacokinetic and pharmacodynamic properties; this results in increased susceptibility of children to drug-related adverse events.[1-4]

Reports documenting the incidence of adverse drug events in the pediatric population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with high morbidity and mortality.[5] Hospitalized children may be at a higher risk of an adverse event, as doses, drug safety, and effectiveness are often difficult to determine.[6] Kaushal and colleagues identified that the potential frequency of ADEs in children is three times higher than a previous study focused on ADEs in adults, however, the rate of avoidable ADEs was similar.[4] In intensive care units, multiple, potentially hazardous drugs are

routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics; as the risk of an ADE increases by 1.7% for each additional drug used,[5] it is far more likely that adverse reactions will occur in the ICU.

There are few studies documenting safety in drug administration in children in the ICU. The primary objective of this study was to describe ADEs in children admitted to the pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary objectives, we attempted to identify risk factors for such events and tools that could detect them early as well as determine if there was impact on LOS.

MATERIALS AND METHODS

We conducted a preliminary survey over a period of 22 days in March 2004 to identify the number of admissions required to effectively report ADEs in the PICU, a unit of 13 beds, with average occupation of 80%. Based on the results of this survey, we determined that it would then be necessary to study 150 admissions to reach a stable estimate of the incidence of ADEs and explore possible risk factors using a multivariate analysis (approximately 10 ADEs for each variable potentially associated). The study population consisted of consecutive admissions to the PICU between October 1, 2005 and March 31, 2006. The strategy to identify ADEs was through an active search, using pre-established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or flag, found when reviewing a patient's medical chart, that requires further investigation to determine the presence or absence of an adverse event.[7,8] Using this method, specific events, such as prescription or abrupt discontinuation of certain medications, prescription of antidotes, and some laboratory tests, serve as indicators for further investigation. Several triggers have been described in the literature,[8] and therefore we chose and adapted the ones

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2. The following records for each patient were reviewed, guided by triggers indicative of adverse events:

- Laboratory tests (electronic database);
- Clinical annotations;
- Nursing annotations;
- Prescription;

3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable, possible, or doubtful;[9]

4. Analysis of all proven, probable and possible ADEs.

The study included only unavoidable ADEs, that is, only those that occurred during normal use of a drug, and not the result of a human error,[10] as well as those classified as moderate to severe according to the World Health Organization (WHO) guidelines: By this definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears after administration of a drug at doses normally used for prophylaxis, diagnosis or treatment of a disease. A moderate reaction is one that requires modification of therapy and may require specific treatment; a severe reaction is potentially fatal and requires specific

treatment, requires or prolongs hospitalization.[11] We analyzed only those ADEs that appeared after admission. ADEs that appeared after admission but were related to drugs that the patient was receiving before being admitted were defined as due to “prevalent drug”. This definition eliminated, for example, ADEs due to chemotherapy already present before admission in patients with cancer. ADEs related to drugs introduced after admission were classified as due to "incident drug". The study protocol was reviewed and approved by the Ethics Committee of the institution prior to the start of data collection (protocol number 485/56/2005). Because of the observational nature of the study, without any interference in therapy, informed consent was waived.

Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the odds ratios (OR) by logistic regression. A multinomial logistic regression model was performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number of drugs” because they have been significantly correlated with the incidence of ADEs.[5] Some studies have shown a lower risk for ADEs in male children.[12] Chronic illness is an important variable due to the continuous use of various drugs and the presence of organ dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS" (dependent). Significance of differences between means was obtained with the T test. Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was considered statistically significant.

RESULTS

In our pilot survey, we identified 20 adverse events of moderate to severe intensity over a period of 22 days in March 2004, which we calculated to represent at least 5 events per 100 patient-days.

In our actual study, there were 244 admissions to the PICU during the period between October 1, 2005 and March 31, 2006. Four patients were excluded because they were adult living-donors for liver transplant, and one patient was excluded due to age > 18 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of 9.5 days.

The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%). Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%), neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83), postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures, digestive bleeding, dehydration, renal failure, hypertension, and others.

We observed 138 occurrences of triggers, as shown in Table 2, with their predictive positive values. These triggers led to the identification of 110 proven, probable, or possible ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after

PICU admission or "incidents" (Table 3). Table 4 shows the observed ADEs and related drugs.

Gender, the presence of chronic disease, age, and administration of at least five drugs were included in a multinomial logistic regression analysis as independent variables for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the individual chronic conditions displayed an increased risk for ADEs; however, patient age less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01) in the occurrence of at least one ADE. This interaction remained significant, with discrete elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI: 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001 for the use of 9 drugs).

In a bivariate analysis, the number of drugs received by each patient correlated with the number of ADEs (R^2 = 0.13, p < 0.0001). The likelihood of at least one ADE became significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the occurrence of more than one ADE (Table 5).

There was a significant difference between the mean LOS between patients with and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75

(p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS. However, this increase was not maintained when other confounding variables were added in the multivariate regression model. The only independent variables remaining in the final model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and the number of drugs (p < 0.001; slope coefficient 0.83; R^2 = 0.104); The slope coefficient could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but the study did not have the power to demonstrate it. A sample calculation showed that in order for this fact to be significant in a larger sample, it would take 1000 patients to achieve p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the dependent variable "LOS" and 0.72 for independent "number of ADEs". Other variables did not show any significant relationship.

In addition, mean "survival" without ADEs (time from admittance to the PICU until the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for patients younger than 48 months (p = 0.017).

The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24), antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9), bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5), hormonal analogues (4), antipyretics (4), and others (5).

DISCUSSION

Determining the occurrence of adverse events in an intensive care environment is a complex task. The symptoms of the event may overlap the underlying disease and may be caused by several unrelated factors including the pharmacokinetic profile of the drug, unknown drug allergies of each patient, or human error. These difficulties may serve as an

explanation for why many events are not recognized as ADEs. Frequently, other drugs are administered in an attempt to solve the problem created by the ADE, without the specific diagnosis. While some events are easily attributed to certain drugs, there are several possible and poorly documented events and some are completely unknown and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE, including age and certain comorbidities, such as the presence of renal or hepatic impairment. Drug-related factors such as toxicity, time of administration, dosage, and duration of use are variables that can also impact the probability of ADEs. In addition, new drugs that have just completed phase III clinical trials may not have been powered to detect rare events.[13] In general, if we don't look for ADEs, it is unlikely that we will find them.[14]

In the absence of reliable empirical methods for detection of ADEs, formal and logical tools can help differentiate an ADE from a symptom caused by exacerbations in a patient's underlying condition. The most widely accepted formal instrument to obtain this is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some included events may not have been ADEs. However, to prove an ADE according to the algorithm, it is necessary to re-administer the drug and observe the event again, or obtain serum levels that are known to be toxic. The first option is strongly discouraged and the second may be technically impossible or unavailable. However, we excluded the "doubtful" events (score equal to or less than 1) from our analysis and some of these events may have actually been ADEs.

Most of our patients had chronic diseases, which may contribute to a higher incidence of ADEs, due to the use of multiple medications. This population of chronic patients reflects the current reality of Brazilian university hospitals. We observed no

significant difference in ADE incidence between patients with and without chronic diseases, which can be explained by the exclusion of events prior to PICU admission and was more likely related to the medications used regularly.

The incidence of observed events (35.1% of admissions) is much higher than those reported in adult patients hospitalized in ICUs (around 9%).[15] Furthermore, we found that younger children under the age of 48 months, which constitute approximately half the patient sample, were more likely to have ADEs. This was particularly significant with the administration of over five drugs at the same time, and also resulted in an ADE earlier in the patient's ICU stay. The high incidence of ADEs also highlights the importance of an active search focused on triggers to detect ADEs in children: Holdsworth et al reported ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart review by a pharmacist).[16] Takata et al. performed a search focused on triggers and reported 11.1 events/100 inpatients, almost double that of the retrospective study. These authors indicated that performing a search focused on specific circumstances associated with ADEs in specific elements of the patient's chart can increase the rates of observed ADEs.[17] The methodology we used in this study (definition of triggers and daily search in the records of patients) is a simple way to perform an active search for ADEs. Triggers can be individualized for each hospital setting according to the most frequently used medications. PPVs can be determined through a simple calculation that assists in the choice of triggers that are most useful in each unit. We observed higher PPVs for biochemical alterations; in an automated process, the system of the laboratory itself could alert for possible ADEs.

We wish to highlight that our study evaluated severely ill children under intensive care receiving multiple drugs (up to 18), and the chances of developing an ADE is

therefore, more likely. In addition, comparing event rates is also challenging and potentially misleading as definitions of ADEs are unclear among studies, ranging from a benign and transient alteration of electrolytes to vital organ damage.[10]

We investigated whether ADEs may have an impact on the LOS in the PICU. The most important limitation of the study was that our sample did not have the power to implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however, calculations based on standard deviations observed in our sample showed a high probability that this would be true in a longer-term study. In addition to possible patient harm, there are significant costs associated with patient stays in the ICU: An increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at $600.00 (American dollars) each day, ADEs amount to $198,000 per year, which is a considerable sum for our public health system. In principle, the events occurred as a result of habitual use of drugs and were therefore "inevitable"; however, a systematic approach could convert some ADEs from presumably inevitable to avoidable. A good example cited by Kane-Gill et al[10] describes bleeding caused by the correct dose of heparin in a patient being monitored by partial thromboplastin time and would be classified as inevitable. If an investigation identified that the laboratory has changed their method for thromboplastin time and failed to communicate the necessary adjustment, the error would become preventable. More studies on pharmacokinetics and drug interactions in children are required to define optimal dosing regimens and reduce ADEs.

Another limitation of the study was the short time of observation, which did not include the seasonality of respiratory diseases. A positive aspect of the study was the analysis of a PICU population in a country outside Europe and North America, therefore making it possible to analyze ADEs due to drugs such as dipyrone. In Brazil, the reporting

of ADEs is incipient. The online system provided by the health authority only receives notifications, which are not mandatory. Active search is not utilized, even in private institutions. We hope that our study will contribute to a future systematic approach to this subject in developing countries.

CONCLUSIONS

The use of multiple drugs as well as lower patient age favors the occurrence of ADEs, which in turn may result in an increase in the length of PICU hospitalization. The use of an active search using triggers can provide a systematic approach to identify ADEs in PICUs.

REFERENCES

1. Niederhauser VP. Prescribing for children: issues in pediatric pharmacology. *Nurse Pract* 1997;22(3):16-18.

2. Hussain E, Kao E. Medication safety and transfusion errors in the ICU and beyond. *Crit Care Clin* 2005;21:91-110.

3. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med J Aust* 1995;163:458-471.

4. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001;285:2114-2120.

5. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001;52:77-83.

6. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995;84:438-441.

7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003;12(3):194–200.

8. Resar RK, Rozich JD, Classen DC. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care* 2003;12(suppl 2):ii39 –ii45.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30 (2): 239–245.

10. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients. *Crit Care Med* 2012;40(3):823-8.

11. World Health Organization (WHO). Council for International Organizations of Medical Sciences. Guidelines for preparing core clinical safety information on drug from CIOMS Working Group III. Geneva; 1995.

12. Smyth RM, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, Williamson P. Adverse drug reactions in children-a systematic review. *PLoS One*. 2012;7(3):e24061.

13. Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001;94(4):370-3.

14. Kelly WN. How Can I Recognize an Adverse Drug Event. Available online at: *http://www.medscape.org/viewarticle/569794*. Accessed Feb 1, 2012.

15. Vargas E, Terleira A, Hernando F, Perez E, Cordon C, Moreno A, Portoles A. Effect of adverse drug reactions on length of stay in surgical intensive care units. *Crit Care Med* 2003;31(3):694-8.

16. Holdsworth MT, Fichtl RE, Behta M, et al. Incidence and impact of adverse drug events in pediatric inpatients. *Arch Pediatr Adolesc Med* 2003;157(1):60–65.

17. Takata GS, Mason W, Taketomo C, Logsdon T, Sharek PJ. Development, testing, and findings of a pediatric-focused trigger tool to identify medication-related harm in US children's hospitals. *Pediatrics* 2008;121(4):e927-3.

Table 1 – rationale for the use of triggers

Triggers	Rationale for use
Hematological alterations	Anemia, leukopenia, and thrombocytopenia are adverse reactions of various drugs
Biochemical alterations	Hyponatremia, hypokalemia, elevated BUN and creatinine are common events with various drugs
Cardiac alterations	Tachycardia is common, for example, with beta-adrenergic agents, which can cause other arrhythmias; bradycardia may occur with beta-blockers
Antihistamines	Indicator of allergic reaction
Corticoids	Potential indicator of allergic reaction
Allergic reactions	Frequently reported adverse events
Non-programmed endotracheal intubation	Potential indicator of respiratory depression, common, for example, with benzodiazepines
Level of consciousness degradations	Common with benzodiazepines, anticonvulsants
Drug interactions	For example, hypotension and lethargy caused by concomitant administration of sedatives and anticonvulsants
Antiseizures prescription	Potential indicative of unexpected seizure, when using medications that may lead to changes in electrolytes and seizures, like amphotericin B
Drug intolerance	For example, vomiting and diarrhea, frequent events with various medications, such as antibiotics
Non-programmed suspension of drug	Indicative of intolerance or adverse reaction

Fever	Adverse event of drugs such as amphotericin B
Sudden death	Already reported with drug combinations containing dipyrone
Serum level alteration	for monitored drugs such as vancomycin and phenobarbital, with a narrow therapeutic range and potentially toxic at high levels
Aminophylline / adrenaline prescription	Potential indicators of severe allergic reactions
Antidotes prescription	For example, the use of flumazenil may indicate adverse events due to the use of benzodiazepines
Others	Adverse events discovered in the review of medical records, and that does not fit in any trigger, being the trigger the event itself

Table 2 – Occurrences of triggers used for active search.

Triggers	**Number of occurrences**	**Positive predictive value**
Hematological alterations	8	5.79%
Biochemical alterations	64	46.37%
Cardiac alterations	17	12.3%
Antihistamines	5	3.62%
Corticoids	2	1.45%
Allergic reactions	11	7.97%
Non-programmed endotracheal intubation	1	0.72%
Level of consciousness degradations	2	1.45%
Drug interactions	8	5.80%
Antiseizures prescription	2	1.45%
Drug intolerance	0	0%
Non-programmed suspension of drug	1	0.72%
Fever	0	0%
Sudden death	0	0%
Serum level alteration	0	0%
Aminophylline / adrenaline prescription	0	0%
Antidotes prescription	3	2.17%
Others	14	10.14%

Table 3 – Distribution of prevalent-drug and incident-drug adverse events according to causality.

ADE	Prevalent-drug	Incident-drug	TOTAL
Proven	0	5	5
Probable	12	32	44
Possible	27	34	61
TOTAL	39	71	110

Table 4 – Observed adverse drug events (ADEs) and related drugs

Adverse Drug Events (ADEs)	N	Related drugs
Hyponatremia	27	furosemide, fentanyl, carbamazepine, vigabatrin topiramate, hydrochlorothiazide, somatostatin, vancomycin, rifampicin, ranitidine, phenytoin
Hyperglycemia	17	dexamethasone, hydrocortisone, methylprednisolone, terbutaline, tacrolimus
Hypokalemia	13	amphotericin b, terbutaline, furosemide, ranitidine
Skin rash and urticaria	11	vancomycin, dipyrone, cefepime, ceftriaxone, levetiracetam, dipyrone, rasburicase
Hypoventilation/desaturation of oxygen	6	midazolam, propofol, fentanyl, morphine, diazepam
Bradycardia	4	midazolam
Hypotension	4	midazolam, furosemide, thiopental, chlorpromazine
Liver enzyme abnormalities	4	meropenem, carbamazepine, amlodipine, carvedilol, clonidine, amitriptyline, phenobarbital
Hypertension	3	prednisone tacrolimus, dopamine
Increased BUN and creatinine	3	vancomycin, tacrolimus
Seizure	2	hydrocortisone, liposomal amphotericin B, cefepime
Tachycardia	2	terbutaline
Anemia	2	ketoprofen, paracetamol
Extrasystole	2	carvedilol, terbutaline
Increased number of platelets	2	Meropenem, ceftriaxone
Vomiting	2	Nitroprusside, tacrolimus
Cardiorespiratory arrest	1	dipyrone
Thrombocytopenia	1	dipyrone
Apnea	1	phenytoin
Leukopenia	1	imipenem

Stevens-Johnson syndrome	1	trimethoprim / sulfamethoxazole
Eosinophilia	1	ceftriaxone

Table 5 – Odds ratios related to the concomitant use of medications.

	Occurrence of at least one ADE			Occurrence of more than one ADE		
Number of drugs	*Odds ratio*	95% CI	*P*	*Odds ratio*	95% CI	*P*
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.0,3	1.69-5.40	0.0002	3.28	1.06-10.07	0.037
7	3.69	2.11-6.46	< 0.0001	2.95	1.14-7.60	0.025
8	3.84	2.24-6.80	< 0.0001	3.35	1.34-8.35	0.009
9	4.40	2.29-8.45	< 0.0001	3.14	1.24-7.90	0.015
10	6.48	2.85-14.77	< 0.0001	3.69	1.36-9.99	0.010
11	7.26	2.77-19.01	< 0.0001	5.55	1.98-15.52	0.001