



**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.

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3 **Conclusions:** The use of multiple drugs as well as lower patient age favor the occurrence
4 of ADEs, which in turn may result in increasing the length of PICU hospitalization. The
5 active search provides a systematic approach to the problem.
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10 11 12 **INTRODUCTION**

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14 The use of medication in children and infants is a matter of great concern largely due to the
15 vulnerability of their constantly changing and developing homeostasis, as well as the
16 unique mechanisms by which different children respond to injuries. There are important
17 differences in absorption, distribution, metabolism and excretion of drugs during childhood
18 and early adolescence.¹ In addition, several medications have not exhibited safety in the
19 pediatric age group, while others are prescribed differently than recommended for adults;
20 key differences include dose and frequency of administration, presentation of the drug,
21 route of administration, or indication for use in childhood (i.e. "off-label" use), and each of
22 these factors can vary depending on the age of the child.² In the majority of instances,
23 recommended doses of drugs used in children are based on extrapolations from adult doses,
24 related only to weight, body surface area, and age, often ignoring their pharmacokinetic and
25 pharmacodynamic properties; this results in increased susceptibility of children to drug-
26 related adverse events.¹⁻⁴
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46 Reports documenting the incidence of adverse drug events in the pediatric
47 population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with
48 high morbidity and mortality.⁵ Hospitalized children may be at a higher risk of an adverse
49 event, as doses, drug safety, and effectiveness are often difficult to determine.⁶ Kaushal
50 and colleagues identified that the potential frequency of ADEs in children is three times
51 higher than a previous study focused on ADEs in adults, however, the rate of avoidable
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3 ADEs was similar.⁴ In intensive care units, multiple, potentially hazardous drugs are
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5 routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics;
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7 as the risk of an ADE increases by 1.7% for each additional drug used,⁵ it is far more likely
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9 that adverse reactions will occur in the ICU.
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13 There are few studies documenting safety in drug administration in children in the
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15 ICU. The primary objective of this study was to describe ADEs in children admitted to the
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17 pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As a second objective,
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19 we attempted to identify risk factors for such events and tools that could detect them early.
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22 23 24 **MATERIALS AND METHODS**

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26 We conducted a preliminary survey over a period of 22 days in March 2004 to
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28 identify the number of admissions required to effectively report ADEs in the PICU, a unit
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30 of 13 beds, with average occupation of 80%. Based on the results of this survey, we
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32 determined that it would then be necessary to study 150 admissions to reach a stable
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34 estimate of the incidence of ADEs and explore possible risk factors using a multivariate
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36 analysis (approximately 10 ADEs for each variable potentially associated). The study
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38 population consisted of consecutive admissions to the PICU between October 1, 2005 and
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40 March 31, 2006. The strategy to identify ADEs was through an active search, using pre-
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42 established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or
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44 flag, found when reviewing a patient's medical chart, that requires further investigation to
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46 determine the presence or absence of an adverse event.^{7,8} The following methodology was
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48 undertaken:
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55 1. The admission form for each new patient in the PICU was entered by two trained
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57 intensive care pediatricians;
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3 2. The following records for each patient were reviewed, guided by triggers indicative of
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5 adverse events:
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8 - Laboratory tests (electronic database);
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10 - Clinical annotations;
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14 - Prescription;
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17 3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable,
18 possible, or doubtful;⁹
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21 4. Analysis of all proven, probable and possible ADEs.
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24 The study included only unavoidable ADEs, that is, only those that occurred during
25 normal use of a drug, and not the result of a human error,¹⁰ as well as those classified as
26 moderate to severe according to the World Health Organization guidelines.¹¹ The study
27 protocol was reviewed and approved by the Ethics Committee of the institution prior to the
28 start of data collection (protocol number 485/56/2005). Because of the observational nature
29 of the study, without any interference in therapy, informed consent was waived.
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38 Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the
39 odds ratios (OR) by logistic regression. We used a linear regression model for the variables,
40 "ADEs", "Presence of chronic disease", "Age", "Gender", "Number of drugs"
41 (independent), and "PICU stay" (dependent). Significance of differences between means
42 was obtained with the T test. Variables involving time were analyzed using the Kaplan-
43 Meier method, and $p < 0.05$ was considered statistically significant. We calculated the
44 positive predictive value of pre-established parameters as triggers for the search of adverse
45 events.
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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),

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3 bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5),
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5 hormonal analogues (4), antipyretics (4), and others (5). There was a significant
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7 difference between the mean length of stay (LOS) between patients with and without ADEs
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9 (11.1 vs. 5.3 days, $p < 0.0001$). Using multivariate linear regression, we attempted to define
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11 the relationship between several variables and LOS. The only independent variables
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13 remaining in the final model that affect LOS were the number of ADEs ($p = 0.089$, slope
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15 coefficient 1.49) and the number of drugs ($p < 0.001$, slope coefficient 0.83, $R^2 = 0.104$);
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17 other variables did not show any significant relationship. If significant, the slope coefficient
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19 indicates that an ADE would result in an increase in PICU hospitalization by 1.49 days. We
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21 hypothesized that this may be relevant with a longer period of observation. We extrapolated
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23 our results to 480 patients (the expected number of admissions in one year); using the
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25 obtained standard deviations of 9.5 for the dependent variable (LOS) and 0.72 for the
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27 independent variable (ADE), we determined that the probability of increasing the LOS by
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29 1.5 days for each ADE is 70%. For two years (~1000 patients), the probability reached
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31 94%.
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39 Gender, the presence of chronic disease, and age, were analyzed as possible risk
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41 factors for the incidence of ADEs; for males, the odds ratio (OR) was 1.46 ($p = 0.16$); for
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43 the presence of a chronic disease, the OR was 1.47 ($p = 0.30$), and none of the individual
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45 chronic conditions displayed an increased risk for ADEs; however, patient age less than 48
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47 months proved to be a significant risk factor, with an OR of 1.84 (95% CI: 1.07 - 3.15, $p =$
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49 0.025).
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53 The number of drugs received by each patient correlated with the number of ADEs
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55 ($R^2 = 0.13$, $p < 0.0001$). The likelihood of at least one ADE became significant when the
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57 patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI: 1.14 – 4.20, $p =$
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3 0.018). We observed a linear elevation of the chance of an occurrence of an ADE as the
4 patient was administered more medications, achieving an OR of 7.26 (95% CI: 2.77 - 19.1,
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8 $p < 0.0001$) with 11 concomitant drugs. The same was observed for the occurrence of more
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10 than one ADE (Table 4).

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13 In our multivariate analysis, we observed a positive interaction in patients aged less
14 than 48 months and concomitant administration of at least five drugs (OR = 2.05, 95% CI:
15 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
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17 the occurrence of at least one ADE. This interaction remained significant, with discrete
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19 elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI:
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21 1.15-3.60, $p = 0.014$, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, $p < 0.0001$
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23 for the use of 9 drugs). There was no significant interaction between use of five or more
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25 drugs and the occurrence of more than one ADE.
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32 In addition, mean “survival” without ADEs (time from admittance to the PICU until
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34 the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for
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36 patients younger than 48 months ($p = 0.017$).
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41 **DISCUSSION**

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43 Determining the occurrence of adverse events in an intensive care environment is a
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45 complex undertaking. The symptoms of the event may overlap the underlying disease and
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47 may be caused by several unrelated factors including the pharmacokinetic profile of the
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49 drug, unknown drug allergies of each patient, or human error. These difficulties may serve
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51 as an explanation for why many events are not recognized as ADEs. Frequently, other
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53 drugs are administered in an attempt to solve the problem created by the ADE, without the
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55 specific diagnosis of an ADE. While some events are easily attributed to certain drugs,
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3 there are several possible and poorly documented events and some are completely unknown
4 and rare. There are also a multitude of patient-specific risk-factors leading to the occurrence
5 of an ADE, including age and certain comorbidities, such as the presence of renal or
6 hepatic impairment. In addition drug-related factors such as toxicity, time of administration,
7 dosage, and duration of use, are variables that can also impact the probability of ADEs. In
8 addition, new drugs that have just completed phase III clinical trials may not have been
9 powered to detect rare events.¹² In general, if we don't look for ADEs, it is unlikely that we
10 will find them.¹³

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

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48 The incidence of observed events (35.1% of admissions) is much higher than those
49 reported in adult patients hospitalized in ICUs (around 9%).¹⁴ Furthermore, we found that
50 younger children under the age of 48 months, which constitute approximately half the
51 patient sample, were more likely to have ADEs. This was particularly significant with the
52 administration of over five drugs at the same time, and also resulted in an ADE earlier in
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3 the patient's ICU stay. The high incidence of ADEs also highlights the importance of an
4 active search focused on triggers to detect ADEs in children: Holdsworth et al reported
5 ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart
6 review by a pharmacist).¹⁵ Takata et al. performed a search focused on triggers and reported
7 11.1 events/100 inpatients, almost double that of the retrospective study. These authors
8 indicated that performing a search focused on specific circumstances associated with ADEs
9 in specific elements of the patient's chart can increase the rates of observed ADEs.¹⁶ We
10 wish to highlight that our study evaluated severely ill children under intensive care
11 receiving multiple drugs (up to 18), and the chances of developing an ADE is therefore,
12 more likely. In addition, comparing event rates is also challenging and potentially
13 misleading as definitions of ADEs are unclear among studies, ranging from a benign and
14 transient alteration of electrolytes to vital organ damage.¹⁰

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16 We investigated whether ADEs may have an impact on the LOS in the PICU; if an
17 increase was observed, we can conclude that the ADEs caused harm to the patient. Our
18 sample did not have the power to implicate ADEs as a causative factor in prolonging PICU
19 stays by 1.5 days; however, calculations based on standard deviations observed in our
20 sample showed a high probability that this would be true in a longer-term study. In addition
21 to patient harm, there are significant costs associated with patient stays in the ICU: An
22 increase of 1.5 days per event results in an additional 330 days per year. Estimating cost at
23 \$600.00 (American dollars) each day, ADEs amount to \$198,000 per year, which is a
24 considerable sum for our public health system. In principle, the events occurred as a result
25 of habitual use of drugs and were therefore "inevitable", however, a systematic approach
26 could convert some ADEs from inevitable to avoidable. A good example cited by Kane-
27 Gill et al¹⁰ describes bleeding caused by the correct dose of heparin in a patient being

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3 monitored by partial thromboplastin time and would be classified as inevitable. If an
4 investigation identified that the laboratory has changed their method for thromboplastin
5 time and failed to communicate the necessary adjustment, the error would become
6 preventable. More studies on pharmacokinetics and drug interactions in children are
7 required to define optimal dosing regimens and reduce ADEs.
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14 15 16 17 **CONCLUSIONS**

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19 The use of focused and active search engines can provide a systematic approach to identify
20 ADEs in PICUs. The use of multiple drugs as well as lower patient age favors the
21 occurrence of ADEs, which in turn may result in increasing the length of PICU
22 hospitalization.
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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%
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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, dipyrrone, cefepime, ceftriaxone, levetiracetam, dipyrrone, 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	dipyrrone
Thrombocytopenia	1	dipyrrone
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.

Number of drugs	Occurrence of at least one ADE			Occurrence of more than one ADE		
	<i>Odds ratio</i>	95% CI	<i>P</i>	<i>Odds ratio</i>	95% CI	<i>P</i>
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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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.

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

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12 The use of medication in children and infants is a matter of great concern largely
13 due to the vulnerability of their constantly changing and developing homeostasis, as well as
14 the unique mechanisms by which different children respond to injuries. There are important
15 differences in absorption, distribution, metabolism and excretion of drugs during childhood
16 and early adolescence.¹ In addition, several medications have not exhibited safety in the
17 pediatric age group, while others are prescribed differently than recommended for adults;
18 key differences include dose and frequency of administration, presentation of the drug,
19 route of administration, or indication for use in childhood (i.e. "off-label" use), and each of
20 these factors can vary depending on the age of the child.² Most of times, recommended
21 doses of drugs used in children are based on extrapolations from adult doses, related only to
22 weight, body surface area, and age, often ignoring their pharmacokinetic and
23 pharmacodynamic properties; this results in increased susceptibility of children to drug-
24 related adverse events.¹⁻⁴
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43 Reports documenting the incidence of adverse drug events in the pediatric
44 population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with
45 high morbidity and mortality.⁵ Hospitalized children may be at a higher risk of an adverse
46 event, as doses, drug safety, and effectiveness are often difficult to determine.⁶ Kaushal
47 and colleagues identified that the potential frequency of ADEs in children is three times
48 higher than a previous study focused on ADEs in adults, however, the rate of avoidable
49 ADEs was similar.⁴ In intensive care units, multiple, potentially hazardous drugs are
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3 routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics;
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5 as the risk of an ADE increases by 1.7% for each additional drug used,⁵ it is far more likely
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7 that adverse reactions will occur in the ICU.
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10 There are few studies documenting safety in drug administration in children in the
11 ICU. The primary objective of this study was to describe ADEs in children admitted to the
12 pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary
13 objectives, we attempted to identify risk factors for such events and tools that could detect
14 them early as well as determine if there was impact on LOS.
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24 MATERIALS AND METHODS

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26 We conducted a preliminary survey over a period of 22 days in March 2004 to
27 identify the number of admissions required to effectively report ADEs in the PICU, a unit
28 of 13 beds, with average occupation of 80%. Based on the results of this survey, we
29 determined that it would then be necessary to study 150 admissions to reach a stable
30 estimate of the incidence of ADEs and explore possible risk factors using a multivariate
31 analysis (approximately 10 ADEs for each variable potentially associated). The study
32 population consisted of consecutive admissions to the PICU between October 1, 2005 and
33 March 31, 2006. The strategy to identify ADEs was through an active search, using pre-
34 established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or
35 flag, found when reviewing a patient's medical chart, that requires further investigation to
36 determine the presence or absence of an adverse event.^{7,8} Using this method, specific
37 events, such as prescription or abrupt discontinuation of certain medications, prescription of
38 antidotes, and some laboratory tests, serve as indicators for further investigation. Several
39 triggers have been described in the literature,⁸ and therefore we chose and adapted the ones
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3 that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows
4 these triggers and the rationale for their use. The positive predictive value (PPV) of each
5 trigger was calculated as the number of times that each trigger identified an ADE, divided
6 by the total number of times the triggers were identified in the active search.
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10 The following methodology was undertaken for active search:

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13 1. The admission form for each new patient in the PICU was entered by two trained
14 intensive care pediatricians; data were reviewed by 2 authors (Drs. Silva and Shibata) and
15 consolidated in agreement.
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22 2. The following records for each patient were reviewed, guided by triggers indicative of
23 adverse events:
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25 - Laboratory tests (electronic database);
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27 - Clinical annotations;
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29 - Nursing annotations;
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31 - Prescription;
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34 3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable,
35 possible, or doubtful;⁹
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39 4. Analysis of all proven, probable and possible ADEs.
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43 The study included only unavoidable ADEs, that is, only those that occurred during
44 normal use of a drug, and not the result of a human error,¹⁰ as well as those classified as
45 moderate to severe according to the World Health Organization (WHO) guidelines: By this
46 definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears
47 after administration of a drug at doses normally used for prophylaxis, diagnosis or
48 treatment of a disease. A moderate reaction is one that requires modification of therapy and
49 may require specific treatment; a severe reaction is potentially fatal and requires specific
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3 treatment, requires or prolongs hospitalization.¹¹ We analyzed only those ADEs that
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5 appeared after admission. ADEs that appeared after admission but were related to drugs
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7 that the patient was receiving before being admitted were defined as due to “prevalent
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9 drug”. This definition eliminated, for example, ADEs due to chemotherapy already present
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11 before admission in patients with cancer. ADEs related to drugs introduced after admission
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13 were classified as due to "incident drug". The study protocol was reviewed and approved
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15 by the Ethics Committee of the institution prior to the start of data collection (protocol
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17 number 485/56/2005). Because of the observational nature of the study, without any
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19 interference in therapy, informed consent was waived.
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25 Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the
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27 odds ratios (OR) by logistic regression. A multinomial logistic regression model was
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29 performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of
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31 drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number
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33 of drugs” because they have been significantly correlated with the incidence of ADEs.⁵
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35 Some studies have shown a lower risk for ADEs in male children.¹² Chronic illness is an
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37 important variable due to the continuous use of various drugs and the presence of organ
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39 dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of
40
41 chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS"
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43 (dependent). Significance of differences between means was obtained with the T test.
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45 Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was
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47 considered statistically significant.
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55 RESULTS

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3 In our pilot survey, we identified 20 adverse events of moderate to severe intensity
4 over a period of 22 days in March 2004, which we calculated to represent at least 5 events
5 per 100 patient-days.
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10 In our actual study, there were 244 admissions to the PICU during the period
11 between October 1, 2005 and March 31, 2006. Four patients were excluded because they
12 were adult living-donors for liver transplant, and one patient was excluded due to age > 18
13 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU
14 hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of
15 9.5 days.
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24 The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients
25 (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%).
26 Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most
27 prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%),
28 neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac
29 disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83),
30 postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of
31 consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures,
32 digestive bleeding, dehydration, renal failure, hypertension, and others.
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46 We observed 138 occurrences of triggers, as shown in Table 2, with their predictive
47 positive values. These triggers led to the identification of 110 proven, probable, or possible
48 ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5
49 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were
50 due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after
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3 PICU admission or “incidents” (Table 3). Table 4 shows the observed ADEs and related
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5 drugs.
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8 Gender, the presence of chronic disease, age, and administration of at least five
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10 drugs were included in a multinomial logistic regression analysis as independent variables
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12 for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p
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14 = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the
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16 individual chronic conditions displayed an increased risk for ADEs; however, patient age
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18 less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19
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20 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and
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22 concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01)
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24 in the occurrence of at least one ADE. This interaction remained significant, with discrete
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26 elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI:
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28 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001
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30 for the use of 9 drugs).
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37 In a bivariate analysis, the number of drugs received by each patient correlated with
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39 the number of ADEs (R^2 = 0.13, p < 0.0001). The likelihood of at least one ADE became
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41 significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI:
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43 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an
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45 ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI:
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47 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the
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49 occurrence of more than one ADE (Table 5).
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53 There was a significant difference between the mean LOS between patients with
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55 and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model
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57 (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75
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3 (p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS.
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6 However, this increase was not maintained when other confounding variables were added
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8 in the multivariate regression model. The only independent variables remaining in the final
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10 model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and
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12 the number of drugs (p < 0.001; slope coefficient 0.83; R² = 0.104); The slope coefficient
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14 could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but
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16 the study did not have the power to demonstrate it. A sample calculation showed that in
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18 order for this fact to be significant in a larger sample, it would take 1000 patients to achieve
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20 p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the
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22 dependent variable “LOS” and 0.72 for independent “number of ADEs”. Other variables
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24 did not show any significant relationship.
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29 In addition, mean “survival” without ADEs (time from admittance to the PICU until
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31 the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for
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33 patients younger than 48 months (p = 0.017).
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36 The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24),
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38 antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9),
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40 bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5),
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42 hormonal analogues (4), antipyretics (4), and others (5).
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48 **DISCUSSION**

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50 Determining the occurrence of adverse events in an intensive care environment is a
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52 complex task. The symptoms of the event may overlap the underlying disease and may be
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54 caused by several unrelated factors including the pharmacokinetic profile of the drug,
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56 unknown drug allergies of each patient, or human error. These difficulties may serve as an
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3 explanation for why many events are not recognized as ADEs. Frequently, other drugs are
4 administered in an attempt to solve the problem created by the ADE, without the specific
5 diagnosis. While some events are easily attributed to certain drugs, there are several
6 possible and poorly documented events and some are completely unknown and rare. There
7 are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE,
8 including age and certain comorbidities, such as the presence of renal or hepatic
9 impairment. Drug-related factors such as toxicity, time of administration, dosage, and
10 duration of use are variables that can also impact the probability of ADEs. In addition, new
11 drugs that have just completed phase III clinical trials may not have been powered to detect
12 rare events.¹³ In general, if we don't look for ADEs, it is unlikely that we will find them.¹⁴
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27 In the absence of reliable empirical methods for detection of ADEs, formal and
28 logical tools can help differentiate an ADE from a symptom caused by exacerbations in a
29 patient's underlying condition. The most widely accepted formal instrument to obtain this
30 is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5
31 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some
32 included events may not have been ADEs. However, to prove an ADE according to the
33 algorithm, it is necessary to re-administer the drug and observe the event again, or obtain
34 serum levels that are known to be toxic. The first option is strongly discouraged and the
35 second may be technically impossible or unavailable. However, we excluded the "doubtful"
36 events (score equal to or less than 1) from our analysis and some of these events may have
37 actually been ADEs.
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53 Most of our patients had chronic diseases, which may contribute to a higher
54 incidence of ADEs, due to the use of multiple medications. This population of chronic
55 patients reflects the current reality of Brazilian university hospitals. We observed no
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3 significant difference in ADE incidence between patients with and without chronic
4 diseases, which can be explained by the exclusion of events prior to PICU admission and
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6 was more likely related to the medications used regularly.
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10 The incidence of observed events (35.1% of admissions) is much higher than those
11 reported in adult patients hospitalized in ICUs (around 9%).¹⁵ Furthermore, we found that
12 younger children under the age of 48 months, which constitute approximately half the
13 patient sample, were more likely to have ADEs. This was particularly significant with the
14 administration of over five drugs at the same time, and also resulted in an ADE earlier in
15 the patient's ICU stay. The high incidence of ADEs also highlights the importance of an
16 active search focused on triggers to detect ADEs in children: Holdsworth et al reported
17 ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart
18 review by a pharmacist).¹⁶ Takata et al. performed a search focused on triggers and reported
19 11.1 events/100 inpatients, almost double that of the retrospective study. These authors
20 indicated that performing a search focused on specific circumstances associated with ADEs
21 in specific elements of the patient's chart can increase the rates of observed ADEs.¹⁷ The
22 methodology we used in this study (definition of triggers and daily search in the records of
23 patients) is a simple way to perform an active search for ADEs. Triggers can be
24 individualized for each hospital setting according to the most frequently used medications.
25 PPVs can be determined through a simple calculation that assists in the choice of triggers
26 that are most useful in each unit. We observed higher PPVs for biochemical alterations; in
27 an automated process, the system of the laboratory itself could alert for possible ADEs.
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52 We wish to highlight that our study evaluated severely ill children under intensive
53 care receiving multiple drugs (up to 18), and the chances of developing an ADE is
54 therefore, more likely. In addition, comparing event rates is also challenging and potentially
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3 misleading as definitions of ADEs are unclear among studies, ranging from a benign and
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5 transient alteration of electrolytes to vital organ damage.¹⁰
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8 We investigated whether ADEs may have an impact on the LOS in the PICU. The
9
10 most important limitation of the study was that our sample did not have the power to
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12 implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however,
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14 calculations based on standard deviations observed in our sample showed a high probability
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16 that this would be true in a longer-term study. In addition to possible patient harm, there are
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18 significant costs associated with patient stays in the ICU: An increase of 1.5 days per event
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20 results in an additional 330 days per year. Estimating cost at \$600.00 (American dollars)
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22 each day, ADEs amount to \$198,000 per year, which is a considerable sum for our public
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24 health system. In principle, the events occurred as a result of habitual use of drugs and were
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26 therefore "inevitable"; however, a systematic approach could convert some ADEs from
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28 presumably inevitable to avoidable. A good example cited by Kane-Gill et al¹⁰ describes
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30 bleeding caused by the correct dose of heparin in a patient being monitored by partial
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32 thromboplastin time and would be classified as inevitable. If an investigation identified that
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34 the laboratory has changed their method for thromboplastin time and failed to communicate
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36 the necessary adjustment, the error would become preventable. More studies on
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38 pharmacokinetics and drug interactions in children are required to define optimal dosing
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40 regimens and reduce ADEs.
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48 Another limitation of the study was the short time of observation, which did not
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50 include the seasonality of respiratory diseases. A positive aspect of the study was the
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52 analysis of a PICU population in a country outside Europe and North America, therefore
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54 making it possible to analyze ADEs due to drugs such as dipyrene. We hope that our study
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56 will contribute to a future systematic approach to this subject in developing countries.
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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.

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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.

Number of drugs	Occurrence of at least one ADE			Occurrence of more than one ADE		
	<i>Odds ratio</i>	95% CI	<i>P</i>	<i>Odds ratio</i>	95% CI	<i>P</i>
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.

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

11
12 The use of medication in children and infants is a matter of great concern largely
13 due to the vulnerability of their constantly changing and developing homeostasis, as well as
14 the unique mechanisms by which different children respond to injuries. There are important
15 differences in absorption, distribution, metabolism and excretion of drugs during childhood
16 and early adolescence.¹ In addition, several medications have not exhibited safety in the
17 pediatric age group, while others are prescribed differently than recommended for adults;
18 key differences include dose and frequency of administration, presentation of the drug,
19 route of administration, or indication for use in childhood (i.e. "off-label" use), and each of
20 these factors can vary depending on the age of the child.² Most of times, recommended
21 doses of drugs used in children are based on extrapolations from adult doses, related only to
22 weight, body surface area, and age, often ignoring their pharmacokinetic and
23 pharmacodynamic properties; this results in increased susceptibility of children to drug-
24 related adverse events.¹⁻⁴
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43 Reports documenting the incidence of adverse drug events in the pediatric
44 population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with
45 high morbidity and mortality.⁵ Hospitalized children may be at a higher risk of an adverse
46 event, as doses, drug safety, and effectiveness are often difficult to determine.⁶ Kaushal
47 and colleagues identified that the potential frequency of ADEs in children is three times
48 higher than a previous study focused on ADEs in adults, however, the rate of avoidable
49 ADEs was similar.⁴ In intensive care units, multiple, potentially hazardous drugs are
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3 routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics;
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5 as the risk of an ADE increases by 1.7% for each additional drug used,⁵ it is far more likely
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7 that adverse reactions will occur in the ICU.
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10 There are few studies documenting safety in drug administration in children in the
11 ICU. The primary objective of this study was to describe ADEs in children admitted to the
12 pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary
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14 objectives, we attempted to identify risk factors for such events and tools that could detect
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16 them early as well as determine if there was impact on LOS.
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24 MATERIALS AND METHODS

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26 We conducted a preliminary survey over a period of 22 days in March 2004 to
27 identify the number of admissions required to effectively report ADEs in the PICU, a unit
28 of 13 beds, with average occupation of 80%. Based on the results of this survey, we
29 determined that it would then be necessary to study 150 admissions to reach a stable
30 estimate of the incidence of ADEs and explore possible risk factors using a multivariate
31 analysis (approximately 10 ADEs for each variable potentially associated). The study
32 population consisted of consecutive admissions to the PICU between October 1, 2005 and
33 March 31, 2006. The strategy to identify ADEs was through an active search, using pre-
34 established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or
35 flag, found when reviewing a patient's medical chart, that requires further investigation to
36 determine the presence or absence of an adverse event.^{7,8} Using this method, specific
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38 events, such as prescription or abrupt discontinuation of certain medications, prescription of
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40 antidotes, and some laboratory tests, serve as indicators for further investigation. Several
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42 triggers have been described in the literature,⁸ and therefore we chose and adapted the ones
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3 that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows
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5 these triggers and the rationale for their use. The positive predictive value (PPV) of each
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7 trigger was calculated as the number of times that each trigger identified an ADE, divided
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9 by the total number of times the triggers were identified in the active search.
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12 The following methodology was undertaken for active search:

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14 1. The admission form for each new patient in the PICU was entered by two trained
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16 intensive care pediatricians; data were reviewed by 2 authors (Drs. Silva and Shibata) and
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18 consolidated in agreement.
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22 2. The following records for each patient were reviewed, guided by triggers indicative of
23
24 adverse events:

- 25 - Laboratory tests (electronic database);
- 26
- 27 - Clinical annotations;
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- 29 - Nursing annotations;
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- 31 - Prescription;
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36 3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable,
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38 possible, or doubtful;⁹

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40 4. Analysis of all proven, probable and possible ADEs.
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43 The study included only unavoidable ADEs, that is, only those that occurred during
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45 normal use of a drug, and not the result of a human error,¹⁰ as well as those classified as
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47 moderate to severe according to the World Health Organization (WHO) guidelines: By this
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49 definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears
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51 after administration of a drug at doses normally used for prophylaxis, diagnosis or
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53 treatment of a disease. A moderate reaction is one that requires modification of therapy and
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55 may require specific treatment; a severe reaction is potentially fatal and requires specific
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3 treatment, requires or prolongs hospitalization.¹¹ We analyzed only those ADEs that
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5 appeared after admission. ADEs that appeared after admission but were related to drugs
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7 that the patient was receiving before being admitted were defined as due to “prevalent
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9 drug”. This definition eliminated, for example, ADEs due to chemotherapy already present
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11 before admission in patients with cancer. ADEs related to drugs introduced after admission
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13 were classified as due to “incident drug”. The study protocol was reviewed and approved
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15 by the Ethics Committee of the institution prior to the start of data collection (protocol
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17 number 485/56/2005). Because of the observational nature of the study, without any
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19 interference in therapy, informed consent was waived.
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25 Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the
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27 odds ratios (OR) by logistic regression. A multinomial logistic regression model was
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29 performed with the variables “Presence of chronic disease”, “Age”, “Gender”, “Number of
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31 drugs” (independent) and “ADEs” (dependent). We chose the variables “Age” and “number
32
33 of drugs” because they have been significantly correlated with the incidence of ADEs.⁵
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35 Some studies have shown a lower risk for ADEs in male children.¹² Chronic illness is an
36
37 important variable due to the continuous use of various drugs and the presence of organ
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39 dysfunction. We used also a linear regression model for the variables “ADEs”, “Presence of
40
41 chronic disease”, “Age”, “Gender”, “Number of drugs” (independent), and “LOS”
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43 (dependent). Significance of differences between means was obtained with the T test.
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45 Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was
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47 considered statistically significant.
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55 RESULTS

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3 In our pilot survey, we identified 20 adverse events of moderate to severe intensity
4 over a period of 22 days in March 2004, which we calculated to represent at least 5 events
5 per 100 patient-days.
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10 In our actual study, there were 244 admissions to the PICU during the period
11 between October 1, 2005 and March 31, 2006. Four patients were excluded because they
12 were adult living-donors for liver transplant, and one patient was excluded due to age > 18
13 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU
14 hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of
15 9.5 days.
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20 The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients
21 (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%).
22 Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most
23 prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%),
24 neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac
25 disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83),
26 postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of
27 consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures,
28 digestive bleeding, dehydration, renal failure, hypertension, and others.
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45 We observed 138 occurrences of triggers, as shown in Table 2, with their predictive
46 positive values. These triggers led to the identification of 110 proven, probable, or possible
47 ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5
48 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were
49 due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after
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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

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3 (p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS.
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5 However, this increase was not maintained when other confounding variables were added
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7 in the multivariate regression model. The only independent variables remaining in the final
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9 model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and
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11 the number of drugs (p < 0.001; slope coefficient 0.83; R² = 0.104); The slope coefficient
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13 could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but
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15 the study did not have the power to demonstrate it. A sample calculation showed that in
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17 order for this fact to be significant in a larger sample, it would take 1000 patients to achieve
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19 p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the
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21 dependent variable “LOS” and 0.72 for independent “number of ADEs”. Other variables
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23 did not show any significant relationship.
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29 In addition, mean “survival” without ADEs (time from admittance to the PICU until
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31 the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for
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33 patients younger than 48 months (p = 0.017).
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36 The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24),
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38 antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9),
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40 bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5),
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42 hormonal analogues (4), antipyretics (4), and others (5).
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48 DISCUSSION

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50 Determining the occurrence of adverse events in an intensive care environment is a
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52 complex task. The symptoms of the event may overlap the underlying disease and may be
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54 caused by several unrelated factors including the pharmacokinetic profile of the drug,
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56 unknown drug allergies of each patient, or human error. These difficulties may serve as an
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3 explanation for why many events are not recognized as ADEs. Frequently, other drugs are
4 administered in an attempt to solve the problem created by the ADE, without the specific
5 diagnosis. While some events are easily attributed to certain drugs, there are several
6 possible and poorly documented events and some are completely unknown and rare. There
7 are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE,
8 including age and certain comorbidities, such as the presence of renal or hepatic
9 impairment. Drug-related factors such as toxicity, time of administration, dosage, and
10 duration of use are variables that can also impact the probability of ADEs. In addition, new
11 drugs that have just completed phase III clinical trials may not have been powered to detect
12 rare events.¹³ In general, if we don't look for ADEs, it is unlikely that we will find them.¹⁴
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27 In the absence of reliable empirical methods for detection of ADEs, formal and
28 logical tools can help differentiate an ADE from a symptom caused by exacerbations in a
29 patient's underlying condition. The most widely accepted formal instrument to obtain this
30 is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5
31 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some
32 included events may not have been ADEs. However, to prove an ADE according to the
33 algorithm, it is necessary to re-administer the drug and observe the event again, or obtain
34 serum levels that are known to be toxic. The first option is strongly discouraged and the
35 second may be technically impossible or unavailable. However, we excluded the "doubtful"
36 events (score equal to or less than 1) from our analysis and some of these events may have
37 actually been ADEs.
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53 Most of our patients had chronic diseases, which may contribute to a higher
54 incidence of ADEs, due to the use of multiple medications. This population of chronic
55 patients reflects the current reality of Brazilian university hospitals. We observed no
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3 significant difference in ADE incidence between patients with and without chronic
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5 diseases, which can be explained by the exclusion of events prior to PICU admission and
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8 was more likely related to the medications used regularly.
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10 The incidence of observed events (35.1% of admissions) is much higher than those
11 reported in adult patients hospitalized in ICUs (around 9%).¹⁵ Furthermore, we found that
12 younger children under the age of 48 months, which constitute approximately half the
13 patient sample, were more likely to have ADEs. This was particularly significant with the
14 administration of over five drugs at the same time, and also resulted in an ADE earlier in
15 the patient's ICU stay. The high incidence of ADEs also highlights the importance of an
16 active search focused on triggers to detect ADEs in children: Holdsworth et al reported
17 ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart
18 review by a pharmacist).¹⁶ Takata et al. performed a search focused on triggers and reported
19 11.1 events/100 inpatients, almost double that of the retrospective study. These authors
20 indicated that performing a search focused on specific circumstances associated with ADEs
21 in specific elements of the patient's chart can increase the rates of observed ADEs.¹⁷ The
22 methodology we used in this study (definition of triggers and daily search in the records of
23 patients) is a simple way to perform an active search for ADEs. Triggers can be
24 individualized for each hospital setting according to the most frequently used medications.
25 PPVs can be determined through a simple calculation that assists in the choice of triggers
26 that are most useful in each unit. We observed higher PPVs for biochemical alterations; in
27 an automated process, the system of the laboratory itself could alert for possible ADEs.
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53 We wish to highlight that our study evaluated severely ill children under intensive
54 care receiving multiple drugs (up to 18), and the chances of developing an ADE is
55 therefore, more likely. In addition, comparing event rates is also challenging and potentially
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3 misleading as definitions of ADEs are unclear among studies, ranging from a benign and
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5 transient alteration of electrolytes to vital organ damage.¹⁰
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8 We investigated whether ADEs may have an impact on the LOS in the PICU. **The**
9
10 **most important limitation of the study was** that our sample did not have the power to
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12 implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however,
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14 calculations based on standard deviations observed in our sample showed a high probability
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16 that this would be true in a longer-term study. In addition to **possible** patient harm, there are
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18 significant costs associated with patient stays in the ICU: An increase of 1.5 days per event
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20 results in an additional 330 days per year. Estimating cost at \$600.00 (American dollars)
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22 each day, ADEs amount to \$198,000 per year, which is a considerable sum for our public
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24 health system. In principle, the events occurred as a result of habitual use of drugs and were
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26 therefore "inevitable"; however, a systematic approach could convert some ADEs from
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28 **presumably** inevitable to avoidable. A good example cited by Kane-Gill et al¹⁰ describes
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30 bleeding caused by the correct dose of heparin in a patient being monitored by partial
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32 thromboplastin time and would be classified as inevitable. If an investigation identified that
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34 the laboratory has changed their method for thromboplastin time and failed to communicate
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36 the necessary adjustment, the error would become preventable. More studies on
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38 pharmacokinetics and drug interactions in children are required to define optimal dosing
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40 regimens and reduce ADEs.
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48 **Another limitation of the study was the short time of observation, which did not**
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50 **include the seasonality of respiratory diseases. A positive aspect of the study was the**
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52 **analysis of a PICU population in a country outside Europe and North America, therefore**
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54 **making it possible to analyze ADEs due to drugs such as dipyron. We hope that our study**
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56 **will contribute to a future systematic approach to this subject in developing countries.**
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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.

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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, dipyron, cefepime, ceftriaxone, levetiracetam, dipyron, 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	dipyron
Thrombocytopenia	1	dipyron
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.

Number of drugs	Occurrence of at least one ADE			Occurrence of more than one ADE		
	<i>Odds ratio</i>	95% CI	<i>P</i>	<i>Odds ratio</i>	95% CI	<i>P</i>
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



**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.

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

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12 The use of medication in children and infants is a matter of great concern largely due to the
13 vulnerability of their constantly changing and developing homeostasis, as well as the
14 unique mechanisms by which different children respond to injuries. There are important
15 differences in absorption, distribution, metabolism and excretion of drugs during childhood
16 and early adolescence.¹ In addition, safety of several medications has not been properly
17 evaluated in the pediatric age group, while others are prescribed differently than
18 recommended for adults; key differences include dose and frequency of administration,
19 drug formulation, route of administration, or indication for use in childhood (i.e. "off-label"
20 use), and each of these factors can vary depending on the age of the child.² Most of times,
21 recommended doses of drugs used in children are based on extrapolations from adult doses,
22 related only to weight, body surface area, and age, often ignoring their pharmacokinetic and
23 pharmacodynamic properties; this results in increased susceptibility of children to drug-
24 related adverse events.¹⁻⁴
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43 Reports documenting the incidence of adverse drug events in the pediatric
44 population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with
45 high morbidity and mortality.⁵ Hospitalized children may be at a higher risk of an adverse
46 event, as doses, drug safety, and effectiveness are often difficult to determine.⁶ Kaushal
47 and colleagues identified that the potential frequency of ADEs in children is three times
48 higher than a previous study focused on ADEs in adults, however, the rate of avoidable
49 ADEs was similar.⁴ In intensive care units, multiple, potentially hazardous drugs are
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3 routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics;
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5 as the risk of an ADE increases by 1.7% for each additional drug used,⁵ it is far more likely
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7 that adverse reactions will occur in the ICU.
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10 There are few studies documenting safety in drug administration in children in the
11 ICU. The primary objective of this study was to describe ADEs in children admitted to the
12 pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary
13 objectives, we attempted to identify risk factors for such events and tools that could detect
14 them early as well as determine if there was impact on LOS.
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24 MATERIALS AND METHODS

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26 We conducted a preliminary survey over a period of 22 days in March 2004 to
27 identify the number of admissions required to effectively report ADEs in the PICU, a unit
28 of 13 beds, with average occupation of 80%. Based on the results of this survey, we
29 determined that it would then be necessary to study 150 admissions to reach a stable
30 estimate of the incidence of ADEs and explore possible risk factors using a multivariate
31 analysis (approximately 10 ADEs for each variable potentially associated). The study
32 population consisted of consecutive admissions to the PICU between October 1, 2005 and
33 March 31, 2006. The strategy to identify ADEs was through an active search, using pre-
34 established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or
35 flag, found when reviewing a patient's medical chart, that requires further investigation to
36 determine the presence or absence of an adverse event.^{7,8} Using this method, specific
37 events, such as prescription or abrupt discontinuation of certain medications, prescription of
38 antidotes, and some laboratory tests, serve as indicators for further investigation. Several
39 triggers have been described in the literature,⁸ and therefore we chose and adapted the ones
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3 that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows
4 these triggers and the rationale for their use. The positive predictive value (PPV) of each
5 trigger was calculated as the number of times that each trigger identified an ADE, divided
6 by the total number of times the triggers were identified in the active search.
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10 The following methodology was undertaken for active search:

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13 1. The admission form for each new patient in the PICU was entered by two trained
14 intensive care pediatricians; data were analyzed and consolidated by 2 authors (Drs. Silva
15 and Shibata).
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22 2. The following records for each patient were reviewed, guided by triggers indicative of
23 adverse events:
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25 - Laboratory tests (electronic database);
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27 - Clinical annotations;
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29 - Nursing annotations;
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31 - Prescription;
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35 3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable,
36 possible, or doubtful;⁹
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39 4. Analysis of all proven, probable and possible ADEs.
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43 The study included only unavoidable ADEs, that is, only those that occurred during
44 normal use of a drug, and not the result of a human error,¹⁰ as well as those classified as
45 moderate to severe according to the World Health Organization (WHO) guidelines: By this
46 definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears
47 after administration of a drug at doses normally used for prophylaxis, diagnosis or
48 treatment of a disease. A moderate reaction is one that requires modification of therapy and
49 may require specific treatment; a severe reaction is potentially fatal and requires specific
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3 treatment, requires or prolongs hospitalization.¹¹ We analyzed only those ADEs that
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5 appeared after admission. ADEs that appeared after admission but were related to drugs
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7 that the patient was receiving before being admitted were defined as due to “prevalent
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9 drug”. This definition eliminated, for example, ADEs due to chemotherapy already present
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11 before admission in patients with cancer. ADEs related to drugs introduced after admission
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13 were classified as due to “incident drug”. The study protocol was reviewed and approved
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15 by the Ethics Committee of the institution prior to the start of data collection (protocol
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17 number 485/56/2005). Because of the observational nature of the study, without any
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19 interference in therapy, informed consent was waived.
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25 Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the
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27 odds ratios (OR) by logistic regression. A multinomial logistic regression model was
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29 performed with the variables “Presence of chronic disease”, “Age”, “Gender”, “Number of
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31 drugs” (independent) and “ADEs” (dependent). We chose the variables “Age” and “number
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33 of drugs” because they have been significantly correlated with the incidence of ADEs.⁵
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35 Some studies have shown a lower risk for ADEs in male children.¹² Chronic illness is an
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37 important variable due to the continuous use of various drugs and the presence of organ
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39 dysfunction. We used also a linear regression model for the variables “ADEs”, “Presence of
40
41 chronic disease”, “Age”, “Gender”, “Number of drugs” (independent), and “LOS”
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43 (dependent). Significance of differences between means was obtained with the T test.
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45 Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was
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47 considered statistically significant.
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55 RESULTS

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3 In our pilot survey, we identified 20 adverse events of moderate to severe intensity
4 over a period of 22 days in March 2004, which we calculated to represent at least 5 events
5 per 100 patient-days.
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10 In our actual study, there were 244 admissions to the PICU during the period
11 between October 1, 2005 and March 31, 2006. Four patients were excluded because they
12 were adult living-donors for liver transplant, and one patient was excluded due to age > 18
13 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU
14 hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of
15 9.5 days.
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24 The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients
25 (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%).
26 Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most
27 prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%),
28 neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac
29 disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83),
30 postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of
31 consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures,
32 digestive bleeding, dehydration, renal failure, hypertension, and others.
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46 We observed 138 occurrences of triggers, as shown in Table 2, with their predictive
47 positive values. These triggers led to the identification of 110 proven, probable, or possible
48 ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5
49 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were
50 due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after
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3 PICU admission or “incidents” (Table 3). Table 4 shows the observed ADEs and related
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6 drugs.

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8 Gender, the presence of chronic disease, age, and administration of at least five
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10 drugs were included in a multinomial logistic regression analysis as independent variables
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12 for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p
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14 = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the
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16 individual chronic conditions displayed an increased risk for ADEs; however, patient age
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18 less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19
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20 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and
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22 concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01)
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24 in the occurrence of at least one ADE. This interaction remained significant, with discrete
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26 elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI:
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28 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001
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30 for the use of 9 drugs).
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37 In a bivariate analysis, the number of drugs received by each patient correlated with
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39 the number of ADEs ($R^2 = 0.13$, p < 0.0001). The likelihood of at least one ADE became
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41 significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI:
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43 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an
44
45 ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI:
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47 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the
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49 occurrence of more than one ADE (Table 5).
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54 There was a significant difference between the mean LOS between patients with
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56 and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model
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58 (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75
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3 (p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS.
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6 However, this increase was not maintained when other confounding variables were added
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8 in the multivariate regression model. The only independent variables remaining in the final
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10 model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and
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12 the number of drugs (p < 0.001; slope coefficient 0.83; R² = 0.104); The slope coefficient
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14 could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but
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16 the study did not have the power to demonstrate it. A sample calculation showed that in
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18 order for this fact to be significant in a larger sample, it would take 1000 patients to achieve
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20 p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the
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22 dependent variable “LOS” and 0.72 for independent “number of ADEs”. Other variables
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24 did not show any significant relationship.
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29 In addition, mean “survival” without ADEs (time from admittance to the PICU until
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31 the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for
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33 patients younger than 48 months (p = 0.017).
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36 The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24),
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38 antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9),
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40 bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5),
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42 hormonal analogues (4), antipyretics (4), and others (5).
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48 **DISCUSSION**

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50 Determining the occurrence of adverse events in an intensive care environment is a
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52 complex task. The symptoms of the event may overlap the underlying disease and may be
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54 caused by several unrelated factors including the pharmacokinetic profile of the drug,
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56 unknown drug allergies of each patient, or human error. These difficulties may serve as an
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3 explanation for why many events are not recognized as ADEs. Frequently, other drugs are
4 administered in an attempt to solve the problem created by the ADE, without the specific
5 diagnosis. While some events are easily attributed to certain drugs, there are several
6 possible and poorly documented events and some are completely unknown and rare. There
7 are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE,
8 including age and certain comorbidities, such as the presence of renal or hepatic
9 impairment. Drug-related factors such as toxicity, time of administration, dosage, and
10 duration of use are variables that can also impact the probability of ADEs. In addition, new
11 drugs that have just completed phase III clinical trials may not have been powered to detect
12 rare events.¹³ In general, if we don't look for ADEs, it is unlikely that we will find them.¹⁴
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27 In the absence of reliable empirical methods for detection of ADEs, formal and
28 logical tools can help differentiate an ADE from a symptom caused by exacerbations in a
29 patient's underlying condition. The most widely accepted formal instrument to obtain this
30 is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5
31 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some
32 included events may not have been ADEs. However, to prove an ADE according to the
33 algorithm, it is necessary to re-administer the drug and observe the event again, or obtain
34 serum levels that are known to be toxic. The first option is strongly discouraged and the
35 second may be technically impossible or unavailable. However, we excluded the "doubtful"
36 events (score equal to or less than 1) from our analysis and some of these events may have
37 actually been ADEs.
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53 Most of our patients had chronic diseases, which may contribute to a higher
54 incidence of ADEs, due to the use of multiple medications. This population of chronic
55 patients reflects the current reality of Brazilian university hospitals. We observed no
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3 significant difference in ADE incidence between patients with and without chronic
4 diseases, which can be explained by the exclusion of events prior to PICU admission and
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6 was more likely related to the medications used regularly.
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10 The incidence of observed events (35.1% of admissions) is much higher than those
11 reported in adult patients hospitalized in ICUs (around 9%).¹⁵ Furthermore, we found that
12 younger children under the age of 48 months, which constitute approximately half the
13 patient sample, were more likely to have ADEs. This was particularly significant with the
14 administration of over five drugs at the same time, and also resulted in an ADE earlier in
15 the patient's ICU stay. The high incidence of ADEs also highlights the importance of an
16 active search focused on triggers to detect ADEs in children: Holdsworth et al reported
17 ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart
18 review by a pharmacist).¹⁶ Takata et al. performed a search focused on triggers and reported
19 11.1 events/100 inpatients, almost double that of the retrospective study. These authors
20 indicated that performing a search focused on specific circumstances associated with ADEs
21 in specific elements of the patient's chart can increase the rates of observed ADEs.¹⁷ The
22 methodology we used in this study (definition of triggers and daily search in the records of
23 patients) is a simple way to perform an active search for ADEs. Triggers can be
24 individualized for each hospital setting according to the most frequently used medications.
25 PPVs can be determined through a simple calculation that assists in the choice of triggers
26 that are most useful in each unit. We observed higher PPVs for biochemical alterations; in
27 an automated process, the system of the laboratory itself could alert for possible ADEs.
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55 We wish to highlight that our study evaluated severely ill children under intensive
56 care receiving multiple drugs (up to 18), and the chances of developing an ADE is
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3 therefore, more likely. In addition, comparing event rates is also challenging and potentially
4 misleading as definitions of ADEs are unclear among studies, ranging from a benign and
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6 transient alteration of electrolytes to vital organ damage.¹⁰
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10 We investigated whether ADEs may have an impact on the LOS in the PICU. The
11 most important limitation of the study was that our sample did not have the power to
12 implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however,
13 calculations based on standard deviations observed in our sample showed a high probability
14 that this would be true in a longer-term study. In addition to possible patient harm, there are
15 significant costs associated with patient stays in the ICU: An increase of 1.5 days per event
16 results in an additional 330 days per year. Estimating cost at \$600.00 (American dollars)
17 each day, ADEs amount to \$198,000 per year, which is a considerable sum for our public
18 health system. In principle, the events occurred as a result of habitual use of drugs and were
19 therefore "inevitable"; however, a systematic approach could convert some ADEs from
20 presumably inevitable to avoidable. A good example cited by Kane-Gill et al¹⁰ describes
21 bleeding caused by the correct dose of heparin in a patient being monitored by partial
22 thromboplastin time and would be classified as inevitable. If an investigation identified that
23 the laboratory has changed their method for thromboplastin time and failed to communicate
24 the necessary adjustment, the error would become preventable. More studies on
25 pharmacokinetics and drug interactions in children are required to define optimal dosing
26 regimens and reduce ADEs.
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50 Another limitation of the study was the short time of observation, which did not
51 include the seasonality of respiratory diseases. A positive aspect of the study was the
52 analysis of a PICU population in a country outside Europe and North America, therefore
53 making it possible to analyze ADEs due to drugs such as dipyrene. In Brazil, the reporting
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3 of ADEs is incipient. The online system provided by the health authority only receives
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5 notifications, which are not mandatory. Active search is not utilized, even in private
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7 institutions. We hope that our study will contribute to a future systematic approach to this
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9 subject in developing countries.
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12 13 14 15 **CONCLUSIONS**

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

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3	Fever	Adverse event of drugs such as
4		amphotericin B
5	Sudden death	Already reported with drug
6		combinations containing dipyrone
7	Serum level alteration	for monitored drugs such as
8		vancomycin and phenobarbital, with a
9		narrow therapeutic range and
10		potentially toxic at high levels
11	Aminophylline / adrenaline prescription	Potential indicators of severe allergic
12		reactions
13	Antidotes prescription	For example, the use of flumazenil
14		may indicate adverse events due to the
15		use of benzodiazepines
16	Others	Adverse events discovered in the
17		review of medical records, and that
18		does not fit in any trigger, being the
19		trigger the event itself
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28 *Table 2 – Occurrences of triggers used for active search.*

29 Triggers	30 Number of occurrences	31 Positive predictive value
32 Hematological alterations	8	5.79%
33 Biochemical alterations	64	46.37%
34 Cardiac alterations	17	12.3%
35 Antihistamines	5	3.62%
36 Corticoids	2	1.45%
37 Allergic reactions	11	7.97%
38 Non-programmed endotracheal	1	0.72%
39 intubation		
40 Level of consciousness	2	1.45%
41 degradations		
42 Drug interactions	8	5.80%
43 Antiseizures prescription	2	1.45%
44 Drug intolerance	0	0%
45 Non-programmed suspension of	1	0.72%
46 drug		
47 Fever	0	0%
48 Sudden death	0	0%
49 Serum level alteration	0	0%
50 Aminophylline / adrenaline	0	0%
51 prescription		
52 Antidotes prescription	3	2.17%
53 Others	14	10.14%
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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.

Number of drugs	Occurrence of at least one ADE			Occurrence of more than one ADE		
	<i>Odds ratio</i>	95% CI	<i>P</i>	<i>Odds ratio</i>	95% CI	<i>P</i>
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.03	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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3 **TITLE PAGE**
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5 **ADVERSE DRUG EVENTS IN A PEDIATRIC INTENSIVE CARE UNIT: A**
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7 **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.

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

11
12 The use of medication in children and infants is a matter of great concern largely due to the
13 vulnerability of their constantly changing and developing homeostasis, as well as the
14 unique mechanisms by which different children respond to injuries. There are important
15 differences in absorption, distribution, metabolism and excretion of drugs during childhood
16 and early adolescence.¹ In addition, safety of several medications has not been properly
17 evaluated in the pediatric age group, while others are prescribed differently than
18 recommended for adults; key differences include dose and frequency of administration,
19 drug formulation, route of administration, or indication for use in childhood (i.e. "off-label"
20 use), and each of these factors can vary depending on the age of the child.² Most of times,
21 recommended doses of drugs used in children are based on extrapolations from adult doses,
22 related only to weight, body surface area, and age, often ignoring their pharmacokinetic and
23 pharmacodynamic properties; this results in increased susceptibility of children to drug-
24 related adverse events.¹⁻⁴
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43 Reports documenting the incidence of adverse drug events in the pediatric
44 population range from 4.3% to 16.7%; 12.2% of these events being serious in nature, with
45 high morbidity and mortality.⁵ Hospitalized children may be at a higher risk of an adverse
46 event, as doses, drug safety, and effectiveness are often difficult to determine.⁶ Kaushal
47 and colleagues identified that the potential frequency of ADEs in children is three times
48 higher than a previous study focused on ADEs in adults, however, the rate of avoidable
49 ADEs was similar.⁴ In intensive care units, multiple, potentially hazardous drugs are
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3 routinely administered, such as inotropes, sedation medications, analgesia, and antibiotics;
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5 as the risk of an ADE increases by 1.7% for each additional drug used,⁵ it is far more likely
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7 that adverse reactions will occur in the ICU.
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10 There are few studies documenting safety in drug administration in children in the
11 ICU. The primary objective of this study was to describe ADEs in children admitted to the
12 pediatric ICU (PICU) of a tertiary care hospital in Sao Paulo, Brazil. As secondary
13 objectives, we attempted to identify risk factors for such events and tools that could detect
14 them early as well as determine if there was impact on LOS.
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24 MATERIALS AND METHODS

25 We conducted a preliminary survey over a period of 22 days in March 2004 to
26 identify the number of admissions required to effectively report ADEs in the PICU, a unit
27 of 13 beds, with average occupation of 80%. Based on the results of this survey, we
28 determined that it would then be necessary to study 150 admissions to reach a stable
29 estimate of the incidence of ADEs and explore possible risk factors using a multivariate
30 analysis (approximately 10 ADEs for each variable potentially associated). The study
31 population consisted of consecutive admissions to the PICU between October 1, 2005 and
32 March 31, 2006. The strategy to identify ADEs was through an active search, using pre-
33 established parameters ("triggers"). A "trigger" can be defined as an occurrence, prompt, or
34 flag, found when reviewing a patient's medical chart, that requires further investigation to
35 determine the presence or absence of an adverse event.^{7,8} Using this method, specific
36 events, such as prescription or abrupt discontinuation of certain medications, prescription of
37 antidotes, and some laboratory tests, serve as indicators for further investigation. Several
38 triggers have been described in the literature,⁸ and therefore we chose and adapted the ones
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3 that seemed more consistent with the drugs commonly used in our PICU. Table 1 shows
4 these triggers and the rationale for their use. The positive predictive value (PPV) of each
5 trigger was calculated as the number of times that each trigger identified an ADE, divided
6 by the total number of times the triggers were identified in the active search.
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10 The following methodology was undertaken for active search:

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13 1. The admission form for each new patient in the PICU was entered by two trained
14 intensive care pediatricians; data were analyzed and consolidated by 2 authors (Drs. Silva
15 and Shibata).
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22 2. The following records for each patient were reviewed, guided by triggers indicative of
23 adverse events:
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25 - Laboratory tests (electronic database);
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27 - Clinical annotations;
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29 - Nursing annotations;
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31 - Prescription;
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35 3. The Naranjo algorithm was applied to classify the cause of the ADE: proven, probable,
36 possible, or doubtful;⁹
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39 4. Analysis of all proven, probable and possible ADEs.
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43 The study included only unavoidable ADEs, that is, only those that occurred during
44 normal use of a drug, and not the result of a human error,¹⁰ as well as those classified as
45 moderate to severe according to the World Health Organization (WHO) guidelines: By this
46 definition (WHO), ADE is any detrimental or undesirable event, unintended, which appears
47 after administration of a drug at doses normally used for prophylaxis, diagnosis or
48 treatment of a disease. A moderate reaction is one that requires modification of therapy and
49 may require specific treatment; a severe reaction is potentially fatal and requires specific
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3 treatment, requires or prolongs hospitalization.¹¹ We analyzed only those ADEs that
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5 appeared after admission. ADEs that appeared after admission but were related to drugs
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7 that the patient was receiving before being admitted were defined as due to “prevalent
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9 drug”. This definition eliminated, for example, ADEs due to chemotherapy already present
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11 before admission in patients with cancer. ADEs related to drugs introduced after admission
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13 were classified as due to "incident drug". The study protocol was reviewed and approved
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15 by the Ethics Committee of the institution prior to the start of data collection (protocol
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17 number 485/56/2005). Because of the observational nature of the study, without any
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19 interference in therapy, informed consent was waived.
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25 Statistical analysis was performed using SPSS and Microsoft Excel, obtaining the
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27 odds ratios (OR) by logistic regression. A multinomial logistic regression model was
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29 performed with the variables "Presence of chronic disease", "Age", "Gender", "Number of
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31 drugs" (independent) and "ADEs" (dependent). We chose the variables “Age” and “number
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33 of drugs” because they have been significantly correlated with the incidence of ADEs.⁵
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35 Some studies have shown a lower risk for ADEs in male children.¹² Chronic illness is an
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37 important variable due to the continuous use of various drugs and the presence of organ
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39 dysfunction. We used also a linear regression model for the variables "ADEs", "Presence of
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41 chronic disease", "Age", "Gender", "Number of drugs" (independent), and "LOS"
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43 (dependent). Significance of differences between means was obtained with the T test.
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45 Variables involving time were analyzed using the Kaplan-Meier method, and $p < 0.05$ was
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47 considered statistically significant.
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55 RESULTS

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3 In our pilot survey, we identified 20 adverse events of moderate to severe intensity
4 over a period of 22 days in March 2004, which we calculated to represent at least 5 events
5 per 100 patient-days.
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10 In our actual study, there were 244 admissions to the PICU during the period
11 between October 1, 2005 and March 31, 2006. Four patients were excluded because they
12 were adult living-donors for liver transplant, and one patient was excluded due to age > 18
13 years. We analyzed the remaining 239 patients, representing a total of 1818 days of PICU
14 hospitalization. The average length of stay was 7.6 days with a standard deviation (SD) of
15 9.5 days.
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19 The mean age was 67.5 months (median 51 months, range 1-243), and 113 patients
20 (47.2%) were younger than 48 months. Ninety-four of the 239 patients were male (39.3%).
21 Only 39 of the 239 patients did not have a chronic disease at admission (16.3%); the most
22 prevalent chronic diseases were cancer (n = 48, 20%), hepatic disease (n = 37, 15.4%),
23 neurological disease (n = 28, 11.7%), respiratory disease (n = 28, 11.7 %), and cardiac
24 disease (n = 12, 5%). Admissions were mostly due to respiratory failure (n = 83),
25 postoperative of neurosurgical, general, or cardiac surgery (n = 52), decreased level of
26 consciousness (n = 14), or sepsis/septic shock (n = 28). Other causes were seizures,
27 digestive bleeding, dehydration, renal failure, hypertension, and others.
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31 We observed 138 occurrences of triggers, as shown in Table 2, with their predictive
32 positive values. These triggers led to the identification of 110 proven, probable, or possible
33 ADEs in 84 patients (35.1%) during the six month study period, resulting in a rate of 60.5
34 ADEs / 1,000 patient-days; 21 patients had more than one ADE. Thirty-nine ADEs were
35 due to prevalent drugs and the remaining 71 (64.5%) were related to drugs introduced after
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3 PICU admission or “incidents” (Table 3). Table 4 shows the observed ADEs and related
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5 drugs.
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8 Gender, the presence of chronic disease, age, and administration of at least five
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10 drugs were included in a multinomial logistic regression analysis as independent variables
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12 for the incidence of ADEs (dependent variable); for males, the odds ratio (OR) was 1.31 (p
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14 = 0.33); for the presence of a chronic disease, the OR was 0.71 (p = 0.35), and none of the
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16 individual chronic conditions displayed an increased risk for ADEs; however, patient age
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18 less than 48 months proved to be a significant risk factor, with an OR of 2.1 (95% CI: 1.19
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20 - 3.72, p = 0.01). There was a positive interaction in patients aged less than 48 months and
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22 concomitant administration of at least five drugs (OR = 2.05, 95% CI: 1.18-3.57, p = 0.01)
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24 in the occurrence of at least one ADE. This interaction remained significant, with discrete
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26 elevation of the OR until 9 concomitant drugs were administered (OR = 2.03, 95% CI:
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28 1.15-3.60, p = 0.014, for age < 48 months; and OR = 4.69, 95% CI: 2.41-9.15, p < 0.0001
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30 for the use of 9 drugs).
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37 In a bivariate analysis, the number of drugs received by each patient correlated with
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39 the number of ADEs ($R^2 = 0.13$, p < 0.0001). The likelihood of at least one ADE became
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41 significant when the patient was given at least 5 drugs at the same time (OR 2.19 – 95% CI:
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43 1.14 – 4.20, p = 0.018). We observed a linear elevation of the chance of an occurrence of an
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45 ADE as the patient was administered more medications, achieving an OR of 7.26 (95% CI:
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47 2.77 - 19.1, p < 0.0001) with 11 concomitant drugs. The same was observed for the
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49 occurrence of more than one ADE (Table 5).
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53 There was a significant difference between the mean LOS between patients with
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55 and without ADEs (11.1 vs. 5.3 days, p < 0.0001). In a bivariate linear regression model
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57 (LOS as the dependent variable and ADEs as independent), the slope coefficient was 2.75
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3 (p = 0.001), meaning that each ADE corresponded to an increase of 2.75 days in the LOS.
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6 However, this increase was not maintained when other confounding variables were added
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8 in the multivariate regression model. The only independent variables remaining in the final
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10 model that affected LOS were the number of ADEs (p = 0.089; slope coefficient 1.49) and
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12 the number of drugs (p < 0.001; slope coefficient 0.83; R² = 0.104); The slope coefficient
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14 could indicate an increase in LOS of 1.49 days for each ADE, if statistically significant, but
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16 the study did not have the power to demonstrate it. A sample calculation showed that in
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18 order for this fact to be significant in a larger sample, it would take 1000 patients to achieve
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20 p < 0.05 with a power of 0.94, considering the observed standard deviation of 9.5 for the
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22 dependent variable “LOS” and 0.72 for independent “number of ADEs”. Other variables
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24 did not show any significant relationship.
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29 In addition, mean “survival” without ADEs (time from admittance to the PICU until
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31 the occurrence of an ADE) was 19 days for patients older than 48 months and 11.2 days for
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33 patients younger than 48 months (p = 0.017).
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36 The drug classes involved in ADEs were: antibiotics (n = 41), diuretics (24),
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38 antiseizures (23), sedatives and analgesics (17), steroids (18), antihypertensives (9),
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40 bronchodilators (8), gastric protectors (3), immunosuppressives (4), vasoactive drugs (5),
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42 hormonal analogues (4), antipyretics (4), and others (5).
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48 DISCUSSION

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50 Determining the occurrence of adverse events in an intensive care environment is a
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52 complex task. The symptoms of the event may overlap the underlying disease and may be
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54 caused by several unrelated factors including the pharmacokinetic profile of the drug,
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56 unknown drug allergies of each patient, or human error. These difficulties may serve as an
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3 explanation for why many events are not recognized as ADEs. Frequently, other drugs are
4 administered in an attempt to solve the problem created by the ADE, without the specific
5 diagnosis. While some events are easily attributed to certain drugs, there are several
6 possible and poorly documented events and some are completely unknown and rare. There
7 are also a multitude of patient-specific risk-factors leading to the occurrence of an ADE,
8 including age and certain comorbidities, such as the presence of renal or hepatic
9 impairment. Drug-related factors such as toxicity, time of administration, dosage, and
10 duration of use are variables that can also impact the probability of ADEs. In addition, new
11 drugs that have just completed phase III clinical trials may not have been powered to detect
12 rare events.¹³ In general, if we don't look for ADEs, it is unlikely that we will find them.¹⁴
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27 In the absence of reliable empirical methods for detection of ADEs, formal and
28 logical tools can help differentiate an ADE from a symptom caused by exacerbations in a
29 patient's underlying condition. The most widely accepted formal instrument to obtain this
30 is the Naranjo algorithm; however, this tool is also not without bias: in our sample, only 5
31 of 110 ADEs were classified as "proven" or definite (scores 9 and 10). Therefore, some
32 included events may not have been ADEs. However, to prove an ADE according to the
33 algorithm, it is necessary to re-administer the drug and observe the event again, or obtain
34 serum levels that are known to be toxic. The first option is strongly discouraged and the
35 second may be technically impossible or unavailable. However, we excluded the "doubtful"
36 events (score equal to or less than 1) from our analysis and some of these events may have
37 actually been ADEs.
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53 Most of our patients had chronic diseases, which may contribute to a higher
54 incidence of ADEs, due to the use of multiple medications. This population of chronic
55 patients reflects the current reality of Brazilian university hospitals. We observed no
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3 significant difference in ADE incidence between patients with and without chronic
4 diseases, which can be explained by the exclusion of events prior to PICU admission and
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6 was more likely related to the medications used regularly.
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10 The incidence of observed events (35.1% of admissions) is much higher than those
11 reported in adult patients hospitalized in ICUs (around 9%).¹⁵ Furthermore, we found that
12 younger children under the age of 48 months, which constitute approximately half the
13 patient sample, were more likely to have ADEs. This was particularly significant with the
14 administration of over five drugs at the same time, and also resulted in an ADE earlier in
15 the patient's ICU stay. The high incidence of ADEs also highlights the importance of an
16 active search focused on triggers to detect ADEs in children: Holdsworth et al reported
17 ADE rates of 6 per 100 admissions (ICU and pediatric ward, determined using a chart
18 review by a pharmacist).¹⁶ Takata et al. performed a search focused on triggers and reported
19 11.1 events/100 inpatients, almost double that of the retrospective study. These authors
20 indicated that performing a search focused on specific circumstances associated with ADEs
21 in specific elements of the patient's chart can increase the rates of observed ADEs.¹⁷ The
22 methodology we used in this study (definition of triggers and daily search in the records of
23 patients) is a simple way to perform an active search for ADEs. Triggers can be
24 individualized for each hospital setting according to the most frequently used medications.
25 PPVs can be determined through a simple calculation that assists in the choice of triggers
26 that are most useful in each unit. We observed higher PPVs for biochemical alterations; in
27 an automated process, the system of the laboratory itself could alert for possible ADEs.
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55 We wish to highlight that our study evaluated severely ill children under intensive
56 care receiving multiple drugs (up to 18), and the chances of developing an ADE is
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3 therefore, more likely. In addition, comparing event rates is also challenging and potentially
4 misleading as definitions of ADEs are unclear among studies, ranging from a benign and
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6 transient alteration of electrolytes to vital organ damage.¹⁰
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10 We investigated whether ADEs may have an impact on the LOS in the PICU. The
11 most important limitation of the study was that our sample did not have the power to
12 implicate ADEs as a causative factor in prolonging PICU stays by 1.5 days; however,
13 calculations based on standard deviations observed in our sample showed a high probability
14 that this would be true in a longer-term study. In addition to possible patient harm, there are
15 significant costs associated with patient stays in the ICU: An increase of 1.5 days per event
16 results in an additional 330 days per year. Estimating cost at \$600.00 (American dollars)
17 each day, ADEs amount to \$198,000 per year, which is a considerable sum for our public
18 health system. In principle, the events occurred as a result of habitual use of drugs and were
19 therefore "inevitable"; however, a systematic approach could convert some ADEs from
20 presumably inevitable to avoidable. A good example cited by Kane-Gill et al¹⁰ describes
21 bleeding caused by the correct dose of heparin in a patient being monitored by partial
22 thromboplastin time and would be classified as inevitable. If an investigation identified that
23 the laboratory has changed their method for thromboplastin time and failed to communicate
24 the necessary adjustment, the error would become preventable. More studies on
25 pharmacokinetics and drug interactions in children are required to define optimal dosing
26 regimens and reduce ADEs.
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50 Another limitation of the study was the short time of observation, which did not
51 include the seasonality of respiratory diseases. A positive aspect of the study was the
52 analysis of a PICU population in a country outside Europe and North America, therefore
53 making it possible to analyze ADEs due to drugs such as dipyrene. **In Brazil, the reporting**
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3 of ADEs is incipient. The online system provided by the health authority only receives
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5 notifications, which are not mandatory. Active search is not utilized, even in private
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7 institutions. We hope that our study will contribute to a future systematic approach to this
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9 subject in developing countries.
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14 15 CONCLUSIONS

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

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

Number of drugs	Occurrence of at least one ADE			Occurrence of more than one ADE		
	<i>Odds ratio</i>	95% CI	<i>P</i>	<i>Odds ratio</i>	95% CI	<i>P</i>
5	2.19	1.14-4.2	0.018	2.38	0.67-8.38	0.175
6	3.03	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