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Article

Adverse reactions caused by antimicrobials in hospitalized pediatric patients: causality and avoidability analysis

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In pediatrics, drug therapy is commonly performed through adaptations of the dosage forms to adult use, increasing the risk of adverse drug reactions. In this context, studies assessing the severity and avoidability of the adverse reactions in children, especially those caused by antimicrobials, are still scarce. This work aimed to investigate suspected antimicrobial adverse reactions (ATM-ADRs) in pediatric patients admitted to a public hospital in northeastern Brazil, focusing on causality and avoidability analysis. A cohort study was carried out over a period of six months in a 64-bed pediatric unit. The incidence of suspected adverse reactions caused by antimicrobials was 14.65%. Most reactions were rated as *probable* (89.13%), with *moderate* severity (84.78%) and *possibly avoidable* (45.65%). The analysis indicated that the use of a larger number of medications ($p<0.0001$) and longer hospital stay ($p=0.004$) were related to the occurrence of ATM-ADR. Our findings demonstrated that almost half of the suspected reactions could be prevented and that the antimicrobial's clinical management is relevant in this context. Besides, increasingly accurate adverse reaction classification instruments are essential. These results can support the development of therapeutic guidelines addressed to a safe and effective pharmacotherapy in the pediatric area.

Keywords: Adverse drug reactions. Pediatrics. Antimicrobials. Causality. Avoidability.

INTRODUCTION

Children are in constant anatomical, biochemical and physiological changes during their development in their various age groups, which may result in pharmacokinetic and pharmacodynamic differences compared to adults (Becker, Leeder, 2010; Fernandez *et al*., 2011; Santos, Heineck, 2012). These factors, added to the use of a large number of medications, prolonged hospital stay, and the *off label* use of drugs, increase the risk of Adverse Drug Reactions (ADRs) (Andrade *et al*., 2017).

An ADR can be defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of dose regimen, or withdrawal of the product" (Edwards, Aronson, 2000). ADRs contribute to increased morbidity and mortality, hospital admissions, and health system costs (Qing-Ping *et al*., 2014; Cliff-Eribo, Sammons, Choonara, 2016). Particularly in pediatrics, due to the lack of clinical trials in children, drug therapy is commonly performed through adaptations of the dosage forms for use in adults, which

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may compromise the bioavailability and efficacy of the medication, as well as bring a higher risk of adverse events occurrence (Tuleu, Breitkreutz, 2013).

Antimicrobial drugs are the most used drugs in pediatrics (Principi, Esposito, 2016). A systematic review found a 0.6 to 16.8% variation in the incidence of ADRs in hospitalized children, mainly caused by antimicrobials (Smyth *et al.,* 2012). In Brazil, antimicrobials were also the most involved drug class (41%) in suspected ADRs reported in children (Lima *et al.,* 2019).

However, studies evaluating the severity and avoidability of ADRs in children are scarce (Smyth *et al.,* 2012). In addition, the studies use variable methods concerning validity and reliability, with a wide range of results. Identification and analysis of the risks related to the use of medications in pediatrics, as well as the causality, avoidability, and severity classifications, are essential for the elaboration of strategies for prevention, diagnosis, and management of adverse reactions in this population.

Thus, this study aimed to investigate the suspicions of adverse reactions caused by antimicrobials in pediatric patients admitted to a public hospital in northeastern Brazil regarding causality, avoidability, and severity.

MATERIAL AND METHODS

Design and subjects

A prospective cohort study was conducted to investigate the occurrence of antimicrobial adverse reactions (ATM-ADR) in children admitted to a hospital located in northeastern Brazil. Its pediatric unit has 64 beds. Data collection included children admitted from December 2018 to May 2019, who were hospitalized for at least 48 hours and used at least one antimicrobial. Surgical patients were excluded.

Data collection

Data collection was performed exclusively on medical records. The project was submitted to the Research Ethics Committee of the Institute of Health and Hospital Management, approved with opinion number 3.027.780.

The following clinical data were collected: age, weight, gender, drug allergy, and previous medication use (residence or previous hospital). The medications used during hospitalization were checked and recorded every 48 hours: drug name, dosage form, route of administration, indication, dose, dates, and times when it was administered and period of suspension.

Intensive monitoring was performed, every 48h on weekdays and 72h on weekends, in patients enrolled in this study. The follow-up consisted of reading medical records, focusing on the medical and nursing evolution and reading laboratory tests.

After ATM-ADR suspicion identified, the cases were followed to collect complementary information every 24h (72h on weekends) until the end of the symptoms, the patient was discharged or transferred. Data collected: description and evolution of the event, including duration, time from administration of the suspected drug to ATM-ADR occurrence, relevant measures for reaction evaluation (laboratory tests and observations), specific treatment and action taken (drug withdrawal, antagonist prescription), outcome (recovery, death, lengthening of hospitalization).

Data were entered directly into a research-specific spreadsheet prepared using Microsoft Excel 2018 (Microsoft Corporation), without the use of any paper collection instrument.

Data classification

Each suspicion of ATM-ADR was classified according to a) causality, using the Liverpool Causality Assessment Tool (LCAT) (Gallagher *et al.*, 2011); b) avoidability, using the Liverpool Avoidability Assessment Tool (LAAT) (Bracken *et al.*, 2017); c) severity, using an adapted scale (Hartwig, Siegel, Schneider, 1992), in which ATM-ADRs were categorized as *Fatal* (resulted directly or indirectly in patient's death), *Severe (*caused permanent damage or significant hemodynamic instability or resulted in a patient being transferred to a higher level of care), *Moderate* (required specific treatment or discontinuation of the suspected drug) or *Mild* (no conduct required or change in dose or frequency of the suspected medicinal product). The ATM-ADRs were classified regarding the

system involved using the *Adverse Reaction Terminology* from the World Health Organization (WHO, 1997).

Data Analysis

The following independent variables were analyzed as risk factors for the occurrence of ATM-ADR (dependent variable): age, gender, previous history of allergy/ADR, length of stay, and the number of medications administered to patients.

Statistical analysis was performed using the IBM SPSS statistical software. The *chi-square test* was used to establish the relationship between gender and the occurrence of ADRs. Age and the number of medications were correlated, the *student's* t test was used. And the Kruskal-Wallis test was used to relate the hospitalization days with the occurrence of ADR. Binary logistic regression was used to assess the associated risk with the parameters that obtained a statistically significant difference in the previous tests. A 95% confidence interval (CI 95%) was considered. A p-value <0.05 was selected as the statistical significance level for all analyses.

RESULTS AND DISCUSSION

A total of 314 patients met the study inclusion and exclusion criteria. The incidence of suspected ATM-ADRs was 14.65% (n=46). Most children who had a suspicion of ATM-ADRs used between 3 and 4 medications (41.03%, n=16). In terms of gender distribution, 51.28% (n=20) of the children with ATM-ADRs were male. 38.46% (n=15) of the suspected ATM-ADRs occurred in children aged 0 to 1 year old, and 20.51% (n=8) involved children aged 2 to 5 years old. The mean length of stay of the patients who had ATM-ADRs was 25.94 days (Table I). The main medications involved in the suspected reactions were ceftriaxone (32.08%, n=17) and oxacillin (26.41%, n=14). The main events observed were gastrointestinal system disorders and skin and appendages disorders, with 50.91% (n=28) and 29.09% (n=16) of the cases.

Table I - Demographic and clinical data of the monitored patients in public hospital patients in northeastern Brazil (From December 2018 to May 2019)

		Presented ATM-ADR[a]		Did not present ATM-ADR		p-value
		n	%	n	%	
Age group (years old)	0-1	15	38.46	109	39.64	-
	2-5	8	20.51	73	26.54	
	6-10	6	15.38	35	12.73	
	11-15	5	12.82	42	15.27	
	16-17	5	12.82	16	5.82	
Age mean		5.82 (CI[b]: 3.89 – 7.75)		4.94 (CI: 4.3 – 5.57)		0.391[d]
Gender	Male	20	51.28	142	51.64	0.967[e]
	Female	19	48.72	133	48.36	
Allergy	Yes	4	10.26	20	7.27	0.518[f]
	No	35	89.74	255	92.73	

Table I - Demographic and clinical data of the monitored patients in public hospital patients in northeastern Brazil (From December 2018 to May 2019)

		Presented ATM-ADR[a]		Did not present ATM-ADR		p-value
		n	%	n	%	
Number of medications in use	1-2	7	17.95	129	46.9	-
	3-4	16	41.03	84	30.55	
	5-6	7	17.95	32	11.67	
	>6	9	23.07	30	10.9	
Mean of medications in use		5.59 (CI: 4.18 – 6.99)		3.38 (CI: 3.09 – 3.67)		<0.0001 (OR:1.225; p<0.0001)[g]
		25.94 (CI: 14.47-37.42)		14.91 (CI: 12.61- 17.2)		0.004 (OR:1.017, p=0.009)[g]
Total		**39**	**100**	**275**	**100**	

[a]ATM-ADR (antimicrobial adverse reaction); [b]CI (confidence interval) [c]OR (*odds ratio*) [d]student's t-test; [e]chi square test; [f]fisher's exact test, [g]binary logistic regression.

The incidence of ATM-ADRs found in our study (14.65%) is higher than the mean reported in the literature (Smyth *et al.*, 2012; de las Salas *et al.*, 2016). It was most likely due to intensive monitoring methodology, which enabled the visualization of a greater number of ATM-ADRs, many of which would not have been spontaneously reported by the multi-professional team. The antimicrobial class's focus may also have contributed to the frequency obtained, given that this class of medications is more associated with the occurrence of ADRs in Brazil (Lima *et al.*, 2019).

Ceftriaxone and oxacillin were the antimicrobials most implicated as possible causes of reactions, as already reported in other studies (Shalviri, Yousefian, Gholami, 2012; Lima *et al.*, 2019). The risk related to the use of ceftriaxone is relevant, and the literature highlights the occurrence of events considered severe, such as an anaphylactic reaction and cardiac arrest (Shalviri, Yousefian, Gholami, 2012). In turn, oxacillin can cause elevated transaminases, fever, rash, and leukopenia, causing reactions in more than 30% of the exposed patients (Souza *et al.*, 2007).

The most common adverse reactions were gastrointestinal system disorders and skin and appendages disorders, especially diarrhea and pruritus/rash. The reactions that affect these systems are routinely observed among patients and are prolifically reported in the literature (Fonteles *et al.*, 2009; Gallagher *et al.*, 2012; Khan *et al.*, 2016). However, the fact that they are the most observed reactions is due not only to the frequency of occurrence but also to the fact that they are more easily identified when compared to changes in vital parameters and test results.

There were no statistically significant differences related to gender, previous allergy report, or age and suspected ATM-ADRs (p>0.05). The lack of statistical relevance of gender to the incidence of ATM-ADRs was previously reported in the literature (Andrade *et al.,* 2017). Regarding age, other studies have found similar age distributions to those reported here, with reactions mainly affecting children up to 1-year old (Khan *et al.*, 2016; Lima *et al.*, 2019). The physiological and immune system immaturity seems to have some relationship with the high incidence of reactions observed in this age group (Vázquez-Alvarez *et al.*, 2017). Nevertheless, the patient's mean age with and without adverse reaction was similar, which also did not allow to infer the existence of any associated risk with age.

On the other hand, the analysis indicated that the use of a larger number of medications (p<0.0001) and longer hospital stay (p=0.004) were related to the occurrence

of reactions. For each unit of medication added in the patient's prescription, the chance of ADRs increased by 22.5% ($p<0.0001$, *odds ratio* = 1.225). It was also observed that each additional day of hospitalization increased the chance of ADRs by 1.7% ($p=0.009$, *odds ratio* = 1.017).

The increase in the number of prescribed drugs is a predictive factor for the occurrence of ATM-ADRs (Smyth *et al*., 2012). This is probably due to the cumulative risk of each drug used, the presence of drug interactions, and the greater susceptibility to prescribing and administration errors during hospitalization (Andrade *et al*., 2017). Also, hospital stay length was significantly longer in patients with suspected ATM-ADRs, making it possible to establish a relationship between the increase in hospitalization days and the occurrence of adverse reactions, which was expected due to longer exposure to active substances with the potential to trigger ADRs.

Regarding causality, the LCAT instrument tends to classify ADRs as *probable* (89.13%) (Table II). This tool's tendency towards *probable*, other than *possible*, as observed in previous studies, is a promising result. A precise instrument is necessary, once an accurate diagnosis of the ADRs can be helpful to reduce their occurrence, making a positive impact for the health services and the patients (Khan *et al*., 2016; Mouton *et al*., 2017; Behera *et al*., 2018).

Table II - Classification of the suspected ATM-ADRs[a] in public hospital patients in northeastern Brazil (From December 2018 to May 2019)

	Classification	n	%
Causality	Defined	2	4.35
	Probable	41	89.13
	Possible	3	6.52
Severity	Mild	6	13.04
	Moderate	39	84.78
	Severe	1	2.17
Avoidability	Definitely avoidable	5	10.87
	Possibly avoidable	21	45.65
	Unavoidable	20	43.48
	Total	**46**	**100**

[a]ATM-ADR (antimicrobial adverse reaction).

Most reactions were rated as *moderate* (84.78%) for severity (Table II). This classification means that the treatment had to be discontinued, or that drugs had to be introduced to treat the adverse reaction, which may have contributed to the prolongation of hospitalizations, leading to increased treatment costs, as well as causing a negative impact on the health and social situation of the patients and their relatives (Souza *et al*., 2007; Fonteles *et al*., 2009; Raut *et al*., 2015).

A single reaction was classified as severe. It was a reaction to the treatment of leprosy with clofazime and dapsone, in which the patient had a series of symptoms that threatened his life and prevented the continuation of treatment, as fever, anemia, elevated transaminases, bilirubin and LDH and icterus. Although rare, reactions to dapsone are usually severe, leading to the interruption or change of pharmacotherapy and, in some cases, death (Guragain, Upadhahyay, Bhattarai, 2017).

As for avoidability, most reactions were possibly avoidable (45.65%), which means they don't have specific guidelines to prevent them, but there must be information in the literature that can be applied to avoid them (Table II). In the cases of diarrhea described, for example, a prescription of probiotics like *Saccharomyces boulardii* is indicated as an effective and safe approach to prevent cases of diarrhea associated with antimicrobial use in children and adolescents, both during treatment and within 14 days after suspension (Guo *et al*., 2019) (Table III).

Table III - ATM-ADR[a] cases in public hospital patients in northeastern Brazil (From December 2018 to May 2019)

Antibiotic/Number of cases	ADR	Causality	Severity
Definitely Avoidable			
Oxacillin (3); PipeTazo[b] (1)	Gastric irritation	Probable	Moderate
Vancomycin (1)	Phlebitis	Probable	Moderate
Possibly avoidable			
Ceftriaxone/Oxacillin (1); Ceftriaxone/Clindamycin (1); Ceftriaxone (4); PipeTazo (4); PipeTazo/ Vancomycin (1); Meropenem (1); Oxacillin (1); Azithromycin (1); Ampicillin (1); Clindamycin (1)	Diarrhea	Probable	Moderate
Meropenem (1)	Diarrhea	Possible	Moderate
Ceftriaxone/Clindamycin (1); Ceftriaxone (2)	Diarrhea	Probable	Mild
Ceftriaxone/Oxacillin (1)	Colitis	Probable	Moderate
Unavoidable			
Ceftriaxone/Oxacillin (1); Ceftriaxone (3); Oxacillin (1); Vancomycin (1); PipeTazo (1);	Rash	Probable	Moderate
Ceftriaxone (1); Meropenem (1)	Rash	Defined	Moderate
Ceftriaxone (1); Oxacillin (1)	Phlebitis	Probable	Moderate
Ceftriaxone/Oxacillin (1); Oxacillin (1)	Elevated transaminases	Probable	Moderate
Cephalexin (1)	Facial edema	Probable	Mild
Oxacillin (1); Cefepime (1)	Eosinophilia	Possible	Mild
Oxacillin (1)	Pruritus	Probable	Moderate
Oxacillin (1)	Laryngospasm	Probable	Moderate
Dapsone + Clofazimine (1)	Multiple symptoms	Probable	Severe
RIPE[c] (1)	Gastric irritation	Probable	Moderate

[a]ATM-ADR (antimicrobial adverse reaction); [b]PipeTazo (piperacillin + tazobactam); [c]RIPE (Rifampicin + isoniazid + pyrazinamide + ethambutol)

The reactions classified as *unavoidable* (43.48%) were mostly idiosyncratic reactions, not explained by the pharmacodynamics of the drug (Table II). Thus, due to the impossibility of predicting their occurrence, there were no means available to prevent the occurrence of these ATM-ADRs.

The reactions rated as *definitely avoidable* (10.87%) were those in which there was established medical conduct that could have been followed to prevent the reaction from occurring (Table II). In four cases, the use of a gastric protector could have prevented symptoms of gastric irritation due to the use of antimicrobials (oxacillin and piperacillin + tazobactam) associated with non-steroidal anti-inflammatory drugs (ketoprofen). The patients' clinical condition was considered in the evaluation, and a proton pump inhibitor was expected to be included in the treatment to prevent ulcers (Mungan, Pınarbaşı, Şimşek, 2017; Sandhu, Fass, 2018). In another case, the correct dilution of vancomycin antibiotic (<5 mg/ml) could have prevented phlebitis, since its pH may damage the venous access vessel (Bauters *et al.*, 2012; Milutinović, Simin, Zec, 2015).

The fact that this was a study conducted in a single hospital, the short period of data collection, and the possibility of variations among observers when using the classification instruments are some limitations of our study. However, our results are relevant for pediatric care, considering that avoidable reactions are still poorly evaluated in the studies, and it has proven to be a meaningful cause of hospitalizations and an increase in the length of stay. Moreover, preventing avoidable reactions can save health systems' money as they are a significant source of spending (Formica *et al.*, 2018).

CONCLUSION

Our findings demonstrated that many suspected reactions could be prevented and that the clinical management of antimicrobials, including aspects of drug quantity and quality, is relevant in this context.

Knowledge about the occurrence and avoidability of ADRs helps promote new strategies to avoid them in the future, as well as the improvement of existing ones and this study can contribute to developing therapeutic guidelines that make the drug therapy process safer and more effective in the pediatric population.

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