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Characterization of potential drug interactions with antimicrobials in a pediatric intensive care unit, Western Amazon

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Abstract

Objective: Characterize the occurrence of potential drug interactions (PDIs) involving antimicrobials in a pediatric intensive care unit (PICU) in Acre state, Western Amazon. **Methods**: The cross-sectional study analyzed 246 prescriptions from patients up to 11 years old, made in the first 24 hours of hospitalization. Consultations about PDIs were made using Truven Health Analytics Micromedex® Solutions 2.0. classifying according to severity. **Results**: In the 246 prescriptions analyzed, 28 types of antimicrobials were found, the most prescribed were: ceftriaxone 32.7% (n = 123) and ampicillin 9.3% (n = 35). When analyzing in Micromedex® the information about all the drugs prescribed in this sample, it was obtained in 56% (n = 139) of the prescriptions, 435 PDIs of 64 different types, already described in the literature involving only antimicrobials and antimicrobials with other groups of drugs. Among antimicrobials, ampicillin 28% (n = 26) and gentamicin 23.7% (n = 22) were the most often related to PDIs and in 54.7% (n = 238), the severity of these PDIs it was moderate. **Conclusion**: We conclude that the PDIs found in the PICU, although well documented, are of serious concern due to their potential effects. The results presented stimulate actions that can guarantee greater safety for hospitalized pediatric patients.

Keywords: antibiotics; drug interactions; children; pharmacoepidemiology; polypharmacy; intensive care unit

Caracterização de potenciais interações medicamentosas com antimicrobianos em unidade de terapia intensiva pediátrica, Amazônia Ocidental

Resume

Objetivo: Caracterizar a ocorrência de potenciais interações medicamentosas (PIMs) envolvendo antimicrobianos em uma unidade de terapia intensiva pediátrica (UTIP) no estado do Acre, Amazônia Ocidental. **Métodos**: O estudo transversal analisou 246 prescrições de pacientes com até 11 anos, feitas nas primeiras 24 horas de internação. As consultas sobre PDIs foram feitas usando Truven Health Analytics Micromedex® Solutions 2.0. classificando de acordo com a gravidade. **Resultados**: Nas 246 prescrições analisadas, foram encontrados 28 tipos de antimicrobianos, os mais prescritos foram: ceftriaxona 32,7% (n = 123) eampicilina 9,3% (n = 35). Ao analisar no Micromedex® as informações sobre todos os medicamentos prescritos nesta amostra, foi obtido em 56% (n = 139) das prescrições, 435 PIMs de 64 tipos diferentes, já descritos na literatura envolvendo antimicrobianos . Entre os antimicrobianos, ampicilina 28% (n = 26) e gentamicina 23,7% (n = 22) foram os mais frequentemente relacionados às PIMs e em 54,7% (n = 238), a gravidade dessas PIMs foi moderada. **Conclusão**: Concluímos que os PIMs encontrados na UTIP, embora bem documentados, são preocupantes devido aos seus potenciais efeitos. Os resultados apresentados estimulam ações que possam garantir maior segurança ao paciente pediátrico hospitalizado.

Palavras-chave: antibióticos; interações medicamentosas; crianças; farmacoepidemiologia; polifarmácia; unidade de terapia intensiva

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Introduction

Potential drug interactions (PDIs) are pharmacological responses, in which the effects of medications may be altered by simultaneous administration with other medicines, foods or drugs[1], leading to unfavorable responses not expected for in the therapeutic regimen or even presenting some benefit clinical significance[2]. The PDIs are mostly observed in intensive care units (ICU), due to the high prevalence of polypharmacy and the critical condition of patients related to neurological, cardiovascular and post-surgical problems[3,4]. The use of antimicrobials stands out mainly due to invasive procedures (catheters, probes, respirators, among others) and resistant bacteria. In the case of pediatrics, there is also the aggravation of prescriptions with medications not suitable for children[5].

The absence of pharmaceutical forms suitable for pediatrics, the use of drugs not legally approved for use in children and the lack of adequate presentations for them lead to unsafe drug therapy. Especially in Pediatric Intensive Care Units (PICU), there is a high prevalence of prescriptions with medicines not suitable for children, including antimicrobials, due to the severity of infections, the critical condition of hospitalized patients, the greater number of invasive procedures, and a higher incidence of resistant bacteria[5]. In general, medicines use in children has been based mainly on extrapolations and adaptations of the use in adults, information obtained from observational studies, and expert consensus in the field[6].

In this context, it is emphasized that pediatric patients are more vulnerable than adults to developing adverse events (AE) due to how they react to medicines and because they do not yet have the processes of biotransformation and elimination of well-matured drugs. Considering the above, and because there is little data on the topic in the literature, this study proposed to characterize the occurrence of PDIs involving antimicrobials in a pediatric intensive care unit (PICU) in the Western Amazon.

Methods

The study was carried out in Children's Hospital (Hospital da Criança), in Rio Branco city (Acre state), which has about 370,550 inhabitants. Approximately 44% of the population is in the age group from 0 to 16 years. According to IBGE data, it is the sixth largest city in the North Region and the 66th largest in Brazil[7].

Children's Hospital is a state reference in pediatrics, being the only one with PICU. The PICU has been operating since October 2011 with a multidisciplinary patient support team following RDC 7/20108. However, without the support of a pharmacist for this hospital sector. The hospital has ten intensive care beds, two semi-intensive beds, and 60 infirmary beds and attends to inter-municipal patients. According to data from the Hospitalization Service (Serviço de Internação Hospitalar), the occupancy rate is eight beds/day. The hospital accepts children from 29 days to 16 years of age referred from the emergency service of the Urgency and Emergency Hospital of Rio Branco (Hospital de Urgência e Emergência de Rio Branco - HUERB) and Emergency Care Units (Unidades de Pronto Atendimento- UPA's).

The study is cross-sectional and consisted of an analysis of the pharmacological aspects of the medical prescription of pediatric patients admitted to the hospital's PICU, during 12 months from August 2014 to July 2015, whose parents authorized the participation. Prescriptions were used in the first 24 hours of hospitalization, and it was decided to study patients up to 11 years old, because above this age, individuals are considered to be pharmacological adults[9].

The sample size was calculated considering the 319 PICU admissions that occurred in 2013 and a 50% prevalence of antimicrobial use. The 50% value can be explained through the central limit theory, which states that as we increase the sample size, the sample mean will be closer to the population mean[10,11]. The confidence interval used was 95% and the margin of error was 3%, due to the small number of beds and very low daily turnover. The sample was calculated by entering these data into the Epi Info™ 7.2[12] program resulting in a sample of 246 patients.

Queries about PDIs were made using *Truven Health Analytics Micromedex® Solutions 2.0* (*Web Applications Access*)[13] which is a database availa ble free of charge through the Journal's Portal from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes). The name of the drugs used in the prescriptions was inserted in the tab "drug interactions" to check if there was cross information between them that resulted in PDIs. The software classifies the PDIs according to severity, and the existing documentation in the literature (Table 1).

For the analysis of Pearson's correlation between the number of drugs prescribed and the number of PDIs found, we used the SPSS[14] *software* version 2010 at a 5% significance level.

This research was authorized by the Research Ethics Committee of the Federal University of Acre (CEP-UFAC) under number CAAE 31104114.1.000.5010.

Table 1. Information provided by *Truven Health Analytics Micromedex® Solutions 2.0*, according to severity, documentation, and an example of the drug interaction.

Severity	Documentation	Example of drug interaction
Contraindicated: drugs are contraindicated for concomitant use	Reasonable: the available documentation is unsatisfactory, but pharmacological considerations lead clinicians to suspect the existence of interaction, or the documentation is good for a pharmacologically similar drug.	Fluconazole x Ondansetron
Important: The interaction can be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects	Excellent: controlled studies bring clarity about the information.	Clarithromycin x Midazolam
Moderate: The interaction can result in an exacerbation of the patient's condition and/or require a change in treatment.	Good: the documentation strongly suggests the existence of interaction, but there is a lack of properly controlled studies	Azithromycin x Fentanyl
Secondary: The interaction can limit clinical effects. Manifestations may include an increase in the frequency or severity of side effects, but it will generally not require a major change in therapy.		Ampicilin x Gentamicin

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Results

Of the 246 patient prescriptions analyzed, 435 PDIs were found. Of these, 64 involved antimicrobials and were presented in Table 1 according to severity. In total, 101 types of drugs from the most diverse pharmacological groups were prescribed, including 28 types of antimicrobials, distributed in 14 different classes, of which the most prescribed were: ceftriaxone 32.7% (n = 123), ampicillin 9.3 % (n = 35), oxacillin 7.7% (n = 29), vancomycin 7.4% (n = 28), ceftazidime 5.9% (n = 22), gentamicin 5.6% (n = 21) followed by the other pharmacological groups 31.4% (n = 118).

Of the prescriptions analyzed, about 89% (n = 219) received at least five drugs, seven of which were the average number of drugs prescribed. The correlation between number of drugs and PDIs which was positive and moderate (r = 0.482 **).

Discussion

The identification of PDIs through the use of software detects only the probable existence of this, but, it cannot affirm that the patient will have an AE arising from this use[15]. Even so, this study can contribute to demonstrating that the reference service for the pediatric population of the State of Acre, presents prescriptions with risks of PDIs.

The frequency of PDIs in hospital prescriptions is a permanent risk, mainly in the ICU, due to polypharmacy. In pediatric patients it is a serious problem because the therapy and the adverse effects of the drugs are usually based on the extrapolation of the results of clinical trials in adults, given the scarcity of studies in this age group, which makes them even more vulnerable to PDIs and this justifies observational studies in this population[16].

This study showed data similar to the findings by Paiva and Moura, 2012[16] and Cortes and Silvino[17], performed with elderly patients admitted to the ICU where all prescriptions had PDIs. This is due to the influence of factors related to the research location (outpatient, hospital), the therapeutic classes involved, the characteristics of the investigated sample (age, sex, pathophysiological status, type of diet), the mode of medication administration (dose, route, interval, and sequence of administration), the professionals' habits regarding prescriptions and the irrational use of medications. The risk of PDIs tends to increase in the hospital setting because new drugs are often added to existing therapy[4,18].

The association between drug interaction and the number of drugs is well documented in the literature. It is estimated that interactions occur in 3 to 5% of patients who receive few drugs and, when 10 to 20 drugs are administered, this rate can reach 20% [19,20]. According to Cortes and Silvino[17]the polypharmacy increases the average

Table 2. Potential drugs interactions (PDIs) involving antimicrobials in the prescriptions of patients admitted to the pediatric intensive care unit (PICU) by severity, Rio Branco – Acre, 2014-2015.

Severity	PDI	Effect	Documentation	N (%)
Contraindicated	Fluconazole x Ondansetron	Increases the risk of QT prolongation	Reasonable	1 (1,6)
Important	Clarithromycin x Midazolam	Increases exposure to midazolam by prolonging sedation	Excellent	5 (7,8)
Important	Clarithromycin x Fentanyl	Increases the risk of fentanyl poisoning	Reasonable	4 (6,3)
Important	Furosemide x Gentamicin	May result in increased plasma and tissue concentrations of gentamicin and additive effect of nephro and ototoxicity	Good	2 (3,1)
Important	Clarithromycin x Clonazepam	Increases the risk of exposure to CYP3A substrate and risk of intoxication	Reasonable	1 (1,6)
Important	Clarithromycin x Dexamethasone	Can decrease exposure to clarithromycin and increase exposure to dexamethasone	Reasonable	1 (1,6)
Important	Clarithromycin x Digoxin	May increase the risk of digitalis poisoning	Excellent	1 (1,6)
Important	Fluconazole x Fentanyl	Increases the risk of Fentanyl poisoning	Reasonable	1 (1,6)
Important	Fluconazole x Metronidazole	Increases the risk of QT prolongation and arrhythmias	Reasonable	1(1,6)
Important	Gentamicin x Rocuronium	May result in a larger or prolonged neuromuscular block that can lead to respiratory depression and paralysis	Good	1 (1,6)
Moderate	Fluconazole x Omeprazole	Increases plasma omeprazole concentrations	Excellent	6 (9,4)
Moderate	Ciprofloxacin x Ferrous Sulfate	May reduce the effect of ciprofloxacin	Reasonable	2 (3,1)
Moderate	Fluconazole x Midazolam	Increases midazolam concentration and potential midazolam poisoning	Excellent	2 (3,1)
Moderate	Azithromycin x Fentanyl	May increase or prolong the effects of opioids (CNS depression and respiratory depression)	Good	1 (1,6)
Moderate	Ciprofloxacin x Phenytoin	May increase or decrease serum phenytoin concentrations	Good	1 (1,6)
Moderate	Clarithromycin x Methylprednisolone	May increase the side effects of methylprednisolone	Good	1 (1,6)
Moderate	Clarithromycin x Rocuronium	May result in a larger or prolonged neuromuscular block	Reasonable	1 (1,6)
Moderate	Erythromycin x Methylprednisolone	Increases the risk of adverse effects induced by steroids	Good	1 (1,6)
Moderate	Metronidazole x Phenytoin	May increase the risk of Phenytoin poisoning or decrease plasma Metronidazole levels	Reasonable	1 (1,6)
Secondary	Ampicillin x Gentamicin	Decreases the effectiveness of aminoglycoside	Good	17 (26,6)
Secondary	Ampicillin x Amikacin	Decreases the effectiveness of aminoglycoside	Good	9 (14,1)
Secondary	Amikacin x Penicillin	Decreases the effectiveness of aminoglycoside	Good	1 (1,6)
Secondary	Albendazole x Dexamethasone	Potentializes the risk of adverse effects of albendazole	Good	1 (1,6)
Secondary	Gentamicin x Oxacillin	Decreases the effectiveness of aminoglycoside	Good	1 (1,6)
Secondary	Gentamicin x Penicillin	Decreases the effectiveness of aminoglycoside	Good	1 (1,6)
Total				64 (100)

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number of PDIs from 2.3 to 12.9%, however, in our study we were unable to confirm the above observations due to the low number of patients with a high number of prescription drugs. Although drug interactions are currently one of the most important topics in pharmacology for the clinical practice of health professionals, the frequency of clinically important interactions is poorly described in the literature[2]. In this study, most PDIs were of moderate severity and have reasonable documentation, that is, the interaction may result in an exacerbation of the patient's condition or require a change in treatment. Among the interactions, it should be noted that, of these, no documentation was classified as excellent, which justifies the need for further studies that can improve the quality of this information, aiming at patient safety.

Ampicillin, gentamicin, and amikacin are among the antimicrobials that were most involved in PDIs, as shown by Piedade *et al*.[21] and Queiroz *et al.*[22]. One reason is because, according to the protocols of the Brazilian Society of Pediatrics, these drugs are widely used in children admitted to PICUs and Neonatal ICUs in empirical treatments, due to the low resistance induction, high sensitivity of gram-negative rods to amikacin, in addition to their wide availability and low cost. The cautious use of aminoglycosides due to the risk of nephro and ototoxicity should be considered, especially when in use with other potentially nephro and ototoxic drugs such as vancomycin[23].

Furosemide classified as a Potentially Hazardous Drug (Medicamento Potencialmente Perigoso - MPP) by the Institute for Safe Practices in the Use of Medicines (Instituto para práticas Seguras no Uso dos Medicamentos - ISMP)[24] was among the five drugs most involved in PDI, including antimicrobials, as well as in Queiroz *et al*.[22] studies. According to Oliveira and Lima-Dellamora[25], this medication is among the drugs that have reports in the literature of serious interactions and need monitoring during use.

In this work, PDI was also observed involving other pharmacological groups, here mainly represented by midazolam and fentanyl, in agreement with studies by Cedraz et al.[20], for being the drugs of choice for sedation and analgesia in patients undergoing invasive procedures[26]. For Cortes and Silvino[17], medications such as fentanyl and midazolam, appear to be more likely to generate this type of AE.

The drugs found in our results are similar to the findings of Lima *et al.*[27], and are closely related to the occurrence of ADR (Adverse Drug Reactions). Due to the fact that the research was carried out only in the prescription of the first 24 hours, it was not possible to verify their occurrence, which can be the object of observation in future works. Reports involving antimicrobials show the relevance of new studies that address pediatric pharmacoepidemiology and safety in this group of patients[27].

This study has some limitations including the fact that it was performed in only one PICU with few beds, a short period of time analyzed (one year), and the age group cut-off point where children up to 11 years old. The presentation of medical records, with erasures, lack of data on medications, and lack of information on the patient's clinical condition is also a limitation of the research. Even with these limitations, as this is the first study on PDIs in a reference service for the State of Acre, these results represent a local situational diagnosis, allowing planning and intervention actions that can guarantee greater safety for hospitalized pediatric patients.

Conclusion

The PDIs found in the PICU, despite being well documented, are of serious concern due to their potential effects. The data in this study call attention to the fact that PICUs can implement pharmacovigilance actions in services according to the law, where there is control in prescriptions, with supervision of the pharmacist present in multidisciplinary teams, as provided by law, in order to minimizePDIs. Thus, the importance of the role of the pharmacist in preventing drug interactions, often resulting from prescription errors is highlighted, since the prevention of drug combinations that may be harmful to patients would be a better strategy than retrospective verification.

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Collaborators

FLJ: study design, Project administration and writing original draft. AFB and LAKM: data analysis and writing original draft and review. SCP and SPOGB: data collection and review the manuscript.

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Conflict of interests statement

The authors declare no conflict of interests.

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