



Research Article

Prevalence and Severity of Potential Drug-Drug Interactions in Pediatric Intensive Care Unit Prescriptions of a Tertiary Care Teaching Hospital in Odisha, India

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Abstract

Background: To accomplish a specific therapeutic purpose, drugs are frequently used in combination, which can result in drug-drug interactions (DDIs). Information about potential drug-drug interactions (PDDIs) should be made available to healthcare providers. **Objective:** To clarify the drug interaction (DI) trend, the relation with polypharmacy, and the degree of severity at IMS and SUM Hospitals, India. To determine the prevalence, severity, and pattern of PDDIs and to assess their association with the number of concurrent medications. **Methods:** In this prospective cross-sectional study we examined the pediatric prescriptions of children (one month to 15 years) who were admitted to the pediatric intensive care unit (PICU). PDDIs were identified using drug interaction checking software and categorized according to severity (unknown, minor, moderate, and major); the number of concurrent medications per prescription was recorded and its relationship with polypharmacy. The predicted clinical consequences of adverse DIs were measured. **Results:** We discovered 482 PDDIs out of 101 prescriptions, of which 64.9% were moderate, 19.29% were minor, 12.4% were unknown, and 7.67% were major. Age and severity were non-significantly associated with potential DDIs ($p=0.61$), while the number of concurrent drugs was positively associated with the PDDIs/prescription. Third-generation cephalosporins, ureidopenicillin, carbapenem, and aminoglycosides accounted for 39% of PDDIs, followed by salbutamol (20.12%) and antiepileptic medications (18.67%). Low potassium (11.2%) was the most common predictable consequence. **Conclusions:** The results may help with the planning and execution of future research as well as the monitoring and prevention of PDDIs associated with adverse events in PICU.

Keywords: Concurrent drugs; Drug interactions; Pediatric intensive care units.

انتشار وشدة التفاعلات المحتملة بين الأدوية في وصفات وحدات العناية المركزة للأطفال في مستشفى تعليمي للرعاية الثالثية في أوديشا، الهند

الخلاصة

الخلفية: لتحقيق هدف علاجي محدد، تستخدم الأدوية غالباً معاً، مما قد يؤدي إلى تداخلات دواء (DDIs). يجب توفير معلومات حول التفاعلات المحتملة بين الأدوية (PDDIs) لمقدمي الرعاية الصحية. **الهدف:** توضيح اتجاه تفاعل الأدوية (DI)، والعلاقة مع الأدوية المتعددة، ودرجة شدة الحالة في مستشفيات IMS و SUM في الهند. تحديد انتشار وشدة ونمط اضطرابات شخصية المفردة في الاضطراب وتقييم ارتباطها بعدد الأدوية المتزامنة. **الطرائق:** في هذه الدراسة المقطعية المستقبلية، فحصنا وصفات للأطفال (من شهر إلى 15 سنة) الذين تم إدخالهم إلى وحدة العناية المركزة للأطفال (PICU). تم تحديد حالات اضطراب الشخصية الجزئية باستخدام برنامج فحص تداخل الأدوية وتصنيفها حسب الشدة (غير معروفة، طفيفة، متوسطة، وكبيرة)؛ تم تسجيل عدد الأدوية المتزامنة لكل وصفة طبية وعلاقتها بالأدوية المتعددة. تم قياس العواقب السريرية المتوقعة لنتائج المؤشرات السلبية (DIs). **النتائج:** اكتشفنا 482 حالة من أصل 101 وصفة طبية، منها 64.9% متوسطة، 19.29% طفيفة، 12.4% غير معروفة، و 7.67% رئيسية. كان العمر والشدة مرتبطين بشكل غير دلالي بتأثيرات DDI المحتملة ($p=0.61$)، بينما كان عدد الأدوية المتزامنة مرتبطاً إيجابياً ب PDDIs/الوصفة الطبية. شكلت السيفالوسبورينات من الجيل الثالث، واليوريدوبينيلين، والكاربامبينيم، والأمينوجليكوسيدات 39% من PDDIs، تليها سالبوتامول (20.12%) وأدوية مضادة للصرع (18.67%). كان انخفاض البوتاسيوم (11.2%) هو النتيجة الأكثر شيوعاً المتوقعة. **الاستنتاجات:** قد تساعد النتائج في التخطيط وتنفيذ الأبحاث المستقبلية وكذلك في مراقبة والوقاية من حالات PDDI المرتبطة بالأحداث السلبية في وحدات العناية المركزة لعلاج الأطفال الداخليين.

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INTRODUCTION

Drug-drug interactions (DDIs) occur when one medication affects another's metabolism, absorption, excretion, or distribution (referred to as pharmacokinetic interactions) or increases or decreases the efficacy of another (known as pharmacodynamic interactions) [1]. DDIs are more likely to occur in critically sick patients for a variety of reasons, including the use of several medications, the complexity of the disease, associated organ

dysfunction, and the complexity of the pharmacotherapy [2]. Polypharmacy is one of the major risk factors for causing PDDIs; this may lead to treatment failure, adverse medication responses, toxicities, or decreased therapeutic efficacy. These outcomes raise patient morbidity and mortality as well as healthcare expenses [3]. Due to their distinct physiology from adults, children are more susceptible to PDDIs when polypharmacy in the pediatric population rises [4]. Because of their complicated medication regimens and the physiological

dysfunction brought on by their illnesses, critical patients are more likely to experience PDDIs [5,6]. Apart from polypharmacy, a variety of other factors, including age, sex, underlying medical conditions, prescriptions from several doctors, unlicensed or off-label prescriptions, and prescribing medications with limited therapeutic indices, may also have an impact on the occurrence of PDDIs [7,8]. In the PICUs, the combination of many medications and the occurrence of drug interactions are sometimes inevitable and necessary throughout the patient stabilization process, diagnosis, and specialized therapy; however, this raises the risk of toxicity and may decrease the effectiveness of the therapy [3,9,10]. When one medication considerably changes the effects of another that was previously or simultaneously provided, it's referred to as a DDI. PDDI is the theoretical possibility that a concurrently administered medication could physiologically change the pharmacological effects of another medication [9]. When one medication is utilized to maximize the effects of another, such as when ascorbic acid and non-heme iron are administered concurrently, DDIs may help clinical management [9,11]. Unwanted DDIs, however, are linked to ADE and longer hospital stays [12,13]. Compared to adult studies, there are fewer PDDI studies on children. Also, data regarding the prevalence and pattern of potential drug-drug interactions in critically ill children in Indian tertiary care settings remain limited [4]. Also, knowledge of drug interactions among medical practitioners plays a vital role in prescribing optimum drugs for obtaining maximum therapeutic advantage. Identifying them is crucial since they may have a detrimental effect on the patient as well as raise hospital stays and expenses [14, 15]. Our goals were to determine the severity of PDDIs at a tertiary care hospital's PICU, establish the association between the number of concurrent drugs with the number of PDDIs per prescription, and also fill the knowledge gap among the physicians regarding the concept of computerized drug-interaction alert systems (DIAS) by using databases, which might reduce some extent of potential interactions.

METHODS

Study design, setting, and duration

This one-year cross-sectional observational study is done prospectively at the prescription level between August 2024 and August 2025 at the PICU of a tertiary care hospital at a medical facility in eastern India named IMS & SUM Hospital, Odisha. The data was collected using prescriptions from patients admitted to the PICU. Each prescription represented a single patient admission to the PICU, and duplicate prescriptions from the same patient were excluded to avoid clustering bias. Data from the prescriptions of patients admitted to the PICU between the ages of one month and fifteen years was collected following the acquisition of signed informed consent from parents and, if applicable, approval from the patients in accordance with our institutional ethics committee

guidelines. Prescriptions with intravenous fluids, blood products, supplemental diets, topical treatments, electrolyte solutions, parenteral and enteral nutrition, and prescriptions with less than two medications were not included in the analysis. Every prescription's DDI was evaluated using the DDInter 2.0 [16] online drug-drug interaction database and categorized according to their severity as unknown, minor, moderate, and major. The drug combinations should be rigorously avoided because the major interactions were clinically significant; moderate interactions could worsen the state of the patient and/or require a change in treatment; unknown interactions implied that the description of the interaction was either incomplete or inadequate; and even minor interactions were typically not necessary because they were not clinically significant, as they do not require therapeutic adjustments.

Ethical approval

The Institutional Ethical Committee of IMS & SUM Hospital (Ref. no./IEC/IMS.SH/SOA/2024/773) approved the study design.

Statistical analysis

The sample size was calculated using the standard formula for estimating a single population proportion: $n = Z^2 \alpha p (1-p)/e^2$. Where n represents the required sample size, Z_{α} is the Z value corresponding to the desired confidence interval (1.96 for a 95% confidence interval), p represents the estimated prevalence of potential drug-drug interactions obtained from previous literature, and e represents the margin of error. Based on a previously reported prevalence of potential drug-drug interactions of 8.7%, the sample size was calculated using a 95% confidence interval and a 5% margin of error [17]. This results in a minimum required sample size of approximately 101 prescriptions. Therefore, a total of 101 prescriptions from the PICU meeting the inclusion criteria during the study period were included in the analysis. The chi-square test was used to establish the association between the patient's age and the severity of potential drug-drug interactions. The association between the number of concurrent drugs and the number of PDDIs per prescription was established by linear regression. Figures and tables were utilized as needed. All the analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), and 95% confidence intervals (95% CI) were computed. It was considered statistically significant if $p < 0.05$.

RESULTS

Of 101 prescriptions evaluated, there were 482 PDDIs, which are potential drug-drug interactions that could occur when two or more medications are prescribed together. A total of 698 medications were used in the 101 prescriptions. 6.91 medications were prescribed on average. Distribution of PDDIs was more common in prescriptions for those under five

years old (71.78%, n= 346) and those under one year old (36.30%, n= 175), and the number declined as people became older. The study population demographic details are tabulated in Table 1.

Table 1: Association between patient age and severity of potential drug-drug interactions (Chi-square test)

Patients age (year)	Mod/major PDDI (%)	Unknown/Minor PDDI (%)	Total (%)	p-value
<1	125(71.4)	50(28.6)	175(36.3)	0.61
1-5	123(71.9)	48(28.1)	171(35.4)	
6-10	64(79.01)	17(20.9)	81(16.9)	
11-15	39(70.9)	16(29.1)	55(11.4)	

Of 482 PDDIs, 313 (64.9%) were "moderate" in severity, with "minor" PDDIs coming next (n= 93, 19.29%), followed by "unknown" PDDIs (n= 39, 12.4%) and "major" PDDIs (n= 37, 7.67%). Prescriptions containing six to ten medications had the highest number of PDDIs (n= 290; 60.16%); nevertheless, prescriptions including more than ten medications had the highest average number of PDDIs per prescription (7.8), as indicated in Table 2.

Table 2: Number of potential drug-drug interactions and the number of concurrent medications per prescription

Concurrent drugs (Number)	Prescription Quantity (n=101)	No. of PDDI (n=482) n(%)	PDDIs/prescription (average)
2-5	33	76(15.7)	2.30
6-10	53	290(60.16)	5.48
>10	15	116(24.06)	7.8

The most frequently used medication in the interaction was antibiotics (3rd generation cephalosporins, ureidopenicillin, carbapenem, and aminoglycosides) (n= 188; 39%), followed by salbutamol (n= 97, 20.12%) and antiepileptic drugs (n= 90, 18.67%), as shown in Figure 1. In linear regression analysis, the correlation between the length of stay in the PICU and the number of medications prescribed (≥ 5) and the severity of PDDI (moderate, major) is not statistically significant, with p-values of 0.110 and 0.138.

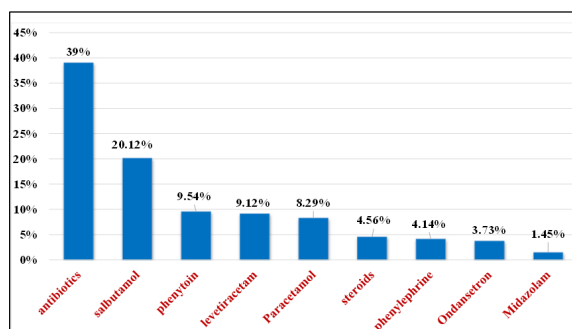


Figure 1: Commonly used drugs involved in potential drug-drug interactions.

When salbutamol, a β_2 agonist, and a glucocorticoid were given together, the most typical potential outcome was low potassium (n= 54, 11.2%). The administration of gentamicin resulted in hypomagnesemia (n= 30, 6.2%) and anticonvulsant therapeutic failure due to enzyme induction (n= 29, 6.01%). This reported outcome represents a predicted

potential outcome identified through the drug interaction database DDInter 2.0 rather than a clinically verified effect.

DISCUSSION

In the Indian context, polypharmacy is a common practice that mostly depends on the type of sickness, concomitant conditions, heredity, economic position, and malnutrition. According to WHO criteria, the average number of pharmaceuticals per person was between 1.4 and 2.4. Many medications have the potential to interact with other drugs or substances when prescribed simultaneously. Siddarama *et al.* reported that patients were prescribed an average of 9.82 drugs, indicating polypharmacy [18]. According to the current survey, individuals were administered an average of 6.91 drugs, indicating the presence of polypharmacy. Similar to the finding of Rao *et al.*, where PDDIs were more prevalent in patients younger than five years old (75.43%), and 346 prescriptions (71.78%) for this age group had more PDDIs [19], after that the number decreased as the age grew. In contrast, the probabilities of major PDDI exposure were considerably greater in the age range of 6–12 years ($p= 0.008$) according to observations by Ismail *et al.* [20]. According to the PDDIs' severity evaluation (using DDInter 2.0), the majority of PDDIs (64.9%) were moderately severe, with minor (19.29%) and major (7.67%) coming next. These findings were in line with Dai *et al.* and Rao *et al.*, the bulk of drug interaction studies carried out in this group [3,19]. The frequency of PDDIs was shown to be correlated with the quantity of medications administered. It shows that interactions were more frequent in prescriptions with six to ten drugs (60.16%), although there were more PDDIs on average per prescription in those with more than ten drugs (7.8/prescription). These findings are in line with another study by Sherin and Udaykumar, which declared that as the number of concurrent drugs grew, so did the typical quantity of PDDIs for each prescription [21]. Numerous other research has shown that a rise in PDDIs is associated with an increase in polypharmacy [22-24]. In our study it was found that antibiotics were most commonly involved in causing drug-drug interactions (39%), followed by salbutamol (20.12%) and antiepileptic drugs (18.67%). These results were consistent with another study that found that the most commonly interfering medications were systemic anti-infectives, followed by the respiratory system class of medications such as caffeine, adrenaline, and salbutamol [25]. However, the most common medications linked to PDDIs in a study by Langerva *et al.* were immunosuppressants and antiepileptics [26]. A higher number of medications and greater PDDI severity were observed among children with longer stays in the PICU; however, this association was not statistically significant, in contrast to another study where the association between longer stays in the PICU with more severe (major and contraindicated) PDDI & the number of drugs used was statistically significant [27]. The most frequently identified potential clinical consequence of PDDIs in

our study was hypokalemia (11.2%), predicted with the co-administration of salbutamol and glucocorticoids. This was followed by potential hypomagnesemia (6.2%) associated with gentamicin use and possible anticonvulsant therapeutic failure (6.01%) due to enzyme-inducing drug combinations. These outcomes were predicted based on drug-drug interaction screening software and represent theoretical pharmacodynamic effects rather than laboratory-confirmed clinical events. These results are consistent with those of Rao *et al.*, where the clinically relevant potential outcome was hypokalemia (13.71%), which was primarily caused by an interaction between salbutamol and corticosteroids [19]. According to a study by Baniyadi *et al.*, where a clinically relevant possible outcome was an extension of the QTc interval that was lab confirmed [17].

Study limitations

There were various shortcomings in our study that could not be excluded. The study was conducted in only one tertiary care teaching hospital, which may limit the generalizability of the findings to other hospitals or regions. The sample size analyzed in the study was small, which may not represent the true burden and pattern of PDDIs in PICU. The study was conducted over one year, which may not capture seasonal variations in disease patterns and prescribing practices. The analysis was conducted at the prescription level rather than the patient level, which may introduce prescription-level bias and may not fully capture patient-specific clinical variations. The study relied on a single interaction-checking database (DDInter 2.0), and the identified interactions along with possible outcomes represent theoretical predictions rather than clinically validated interactions. Therefore, the clinical relevance of the detected interactions could not be confirmed. The statistical analysis was performed using Microsoft Excel, though it does not offer sophisticated analytical features. Due to the small sample size and prescription-level dataset, multivariate modelling was not statistically appropriate.

Conclusion

The present study identified a high prevalence of potential drug-drug interactions in prescriptions from the pediatric intensive care unit, with moderate interactions constituting the majority. Polypharmacy was common, with an average of 6.91 medications per prescription, and more drugs was associated with an increased number of PDDIs. Although no statistically significant association was observed between PDDI severity, number of drugs prescribed, and length of PICU stay, the findings emphasize the value of careful medication review and the use of drug interaction screening tools to support safer prescribing practices in critically ill pediatric patients. Further multicenter studies with large sample sizes and clinical outcome assessments are recommended to better understand

the clinical impact of PDDIs in pediatric intensive care settings.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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