Potential Drug-Drug Interactions and their Associated Factors at the University Children's Hospital in Syria: A Cross-Sectional Study

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ABSTRACT

Objective: Polypharmacy among pediatric inpatients is common and exposes children to the risk of drug-drug interactions (DDIs). This study aimed to characterize potential DDIs (pDDIs) and their associated risk factors among pediatric inpatients.

Methods: A cross-sectional study was conducted over six months at the University Children's Hospital in Damascus. A total of 575 children taking two drugs or more participated. pDDIs were checked using Lexi-Interact® software. pDDIs within risk category B (No action needed), C (Monitor therapy), D (Modify regimen), and X (Avoid combination) were included. Logistic regression was used to identify factors associated with pDDIs.

Results: At least one pDDI was detected in 49.7% of children. Overall, 744 pDDIs were identified. The majority of pDDIs were within risk category C (71.6%), followed by D (14%), B (12.8%), and X (1.6%). The most common pDDIs were: aminoglycosides - penicillins (n=56), aminoglycosides - cephalosporins (n=27), and vitamin D analogs - calcium salts (n=23). The number of prescribed drugs and nervous system drugs were significantly associated with the presence of pDDIs.

Conclusion: pDDIs among pediatric inpatients were prevalent. The majority of the pDDIs were within risk category C, which necessitates therapy monitoring and necessary action to avoid adverse consequences.

Keywords: Drug-drug interactions, pediatrics, pediatric inpatients, drug safety, Syria.

INTRODUCTION

Pharmacotherapy in children requires special interest due to differences in both pharmacokinetics and pharmacodynamics and insufficient evaluation of the use of many drugs compared to adults. Pediatric polypharmacy is defined as the concurrent use of two or more medications [1]. Polypharmacy is common among pediatric patients, with a higher prevalence in inpatient settings compared to outpatient settings, likely due to the complexity of children's health conditions in hospitals [1]. While polypharmacy may be necessary for pediatric disease management, it does expose children to the risk of drug-drug interactions (DDIs). According to previously published studies, potential drug-drug interactions (pDDIs) are prevalent among pediatric inpatients [2].

pDDIs are a risk factor for the occurrence of adverse drug reactions (ADRs) [3,4,5]. Data on the contribution of pDDIs to the development of ADRs in pediatrics is scarce, but a higher number of prescribed medicines have been found to lead to a higher rate of ADRs in children. DDIs are a possible explanation for this association [6,7]. Additionally, pDDIs were associated with longer stays in pediatric intensive care units [8]. Moreover, 57% of ADRs detected in children in neuropsychiatric units were due to DDIs [9].

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Detecting and understanding pDDIs is fundamental in preventing their adverse consequences. So far, pDDIs among pediatric inpatients in Syria have not been investigated. Real-world data would enhance the awareness of physicians and pharmacists about pDDIs and their significance in children.

OBJECTIVES

The current study aimed to assess the frequency, types, and risk factors of pDDIs among children in the largest children's hospital in Syria.

METHODS

Study design and setting

A cross-sectional study was conducted over a six-month period between March and September 2018 in the public pediatric ward at the University Children's Hospital (UCH) in Damascus. UCH in Damascus is a public teaching hospital and the largest pediatric hospital in Syria. The public pediatric ward includes 116 beds and provides care for children with various diseases including cardiac, neurological, gastrointestinal, orthopedic, renal, and metabolic diseases. UCH does not have a clinical pharmacist on-site.

Ethical considerations

This study was approved by the Scientific Research Council at the Arab International University (Decision No. 7/6, August 16, 2017). Administrative permission was obtained from the hospital for access to patients' charts and for conducting analyses.

Data source

Prescriptions for admitted children were collected once a week. As children were divided according to their diseases and ages into 22 rooms, stratified random sampling was utilized to select patients from every room in a ratio of 1:2:3 for rooms occupied by 1-3, 4-5, and 6-8 patients respectively. If distinct prescriptions were found for the same patient/admission, only one prescription was selected for inclusion in the sample. Children prescribed fewer than two medications were excluded from the study.

The following demographic data were collected from the patient charts for each child: age, gender, length of stay, and the number of prescribed drugs. Children were divided into the following age groups based on the International Conference on Harmonisation (ICH) E11 classifications [10]:

- Newborn infants (0–28 days)
- Infants and toddlers (>28 days–23 months)
- Preschool children (2–5 years)
- School age children (6–11 years)
- Adolescents (12–16 years)

Data on all prescribed drugs, with the exception of sodium chloride and glucose intravenous solutions, were collected. Drugs were classified according to the first level of the Anatomical Therapeutic Chemical (ATC) classification system [11].

Screening for DDIs

Drug interactions were checked using Lexi-Interact® software, a product of Wolters Kluwer. Lexi-Interact® is an online software that has demonstrated high sensitivity and specificity [12,13]. Detected pDDIs were classified according to risk rating, severity, and reliability level as indicated by the software.

Lexi-Interact® assigns DDIs with risk rates of A, B, C, D, and X according to the action required to manage the DDI, as follows: A: No known interaction, B: No action needed, C: Therapy monitoring is recommended, D: Therapy modification is considered, and X: The combination should be avoided. DDIs with a risk rating of A were not considered in the analysis of this study.

Regarding severity level, DDIs are classified by Lexi-Interact® into: Major (the interaction may be life-threatening or cause permanent damage), Moderate (the patient's condition may deteriorate, requiring additional care or extended hospitalization), and Minor (the interaction is not medically detrimental).

Additionally, the dependability of the DDIs is categorized by the software based on the quality and quantity of supporting medical literature. This is broken down into: Excellent, Good, Fair, and Poor.

Statistical analysis

Descriptive statistics were used to analyze the population characteristics and the pDDIs.

Univariate and multivariate binary logistic regression analyses were performed to assess the factors potentially associated with pDDIs. The occurrence of a pDDI was the dependent variable. The predictor variables tested included: gender, age, duration of stay, and the number of prescribed medicines. ATC codes prescribed for ≥10% of the patients were also included. Variables with a univariate P-value <0.1 were included in the multivariate analysis. Predictor variables in the multivariate analysis with a P-value of ≤0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS v22.

RESULTS

Study population and prescriptions data

A total of 577 children admitted to the public pediatric ward between March and September 2018 were included in the study. Figure 1 illustrates the data collection flow throughout the study.

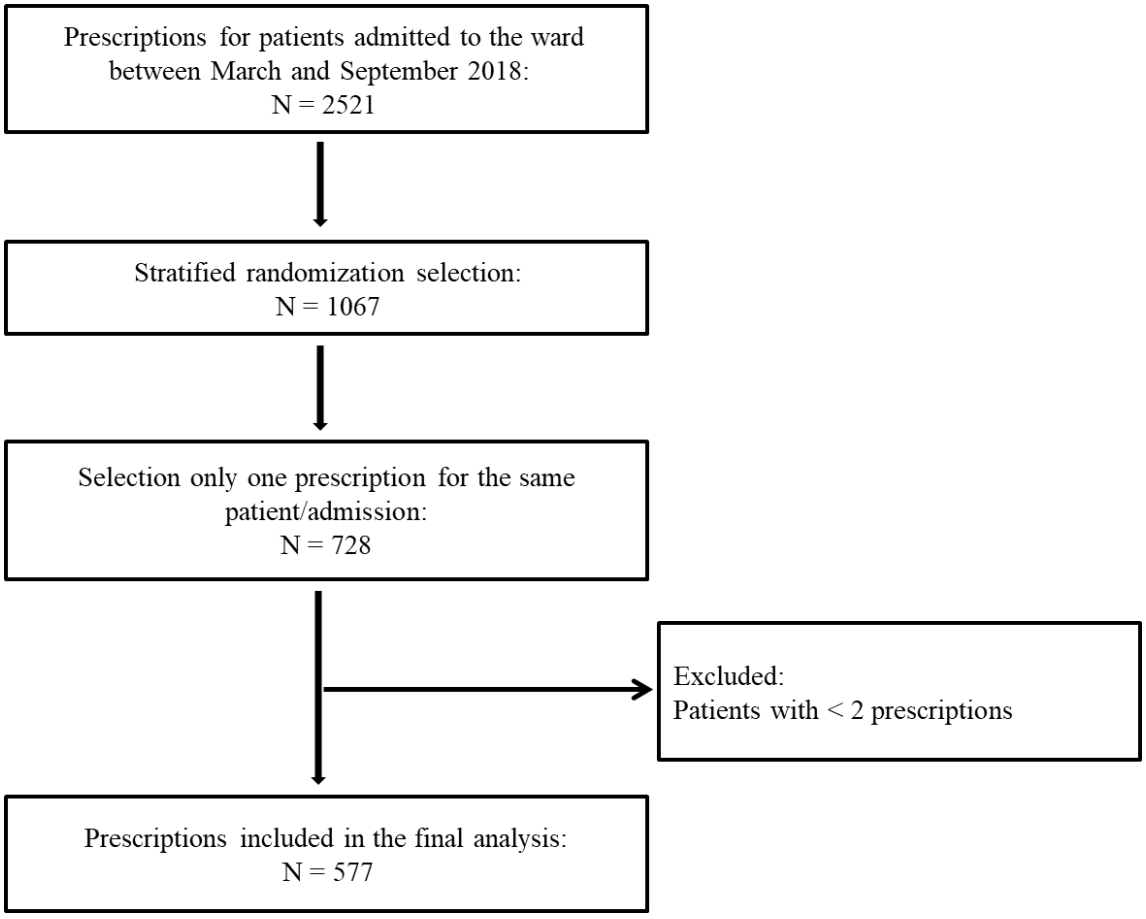

Figure 1: Data collection flow

The demographic and clinical characteristics of the children are presented in Table 1. Out of the study population, 328 (56.8%) were boys. The median age was 1.5 years, with a range from one day to 14 years old. The

largest proportion of the population were infants and toddlers, accounting for 313 (54.2%) of the subjects. The median duration of stay in the hospital was ten days, ranging from one to 133 days.

Table 1: Demographic and clinical characteristics of patients (N=577)

Characteristics	Value
Age (year), median (range)	1.5 (0-14)
Gender, n (%)	
Male	328 (56.8%)
Female	249 (43.2%)
Age groups, n (%)	
Newborn infants	5 (0.9%)
Infants and toddlers	313 (54.2%)
Pre-school children	120 (20.8%)
School age children	117 (20.3)
Adolescents	22 (3.8%)
Duration of stay in the hospital, median (range)	10 (1-133)
Duration of stay in the hospital, n (%)	
1-3	74 (12.8%)
4-7	116 (20.1%)
≥ 8	387 (67.1%)
Prescribed medication per patient, median (range)	4 (2-14)
Prescribed medication per patient, n (%)	
2-4	358 (62%)
5-9	192 (33.3%)
≥ 10	27 (4.7%)
ATC code, n (%)	
ATC code "A" (Alimentary tract and metabolism)	360 (62.4%)
ATC code "B" (Blood and blood forming organs)	147 (25.5%)
ATC code "C" (Cardiovascular system)	122 (21.1%)
ATC code "D" (Dermatologicals)	30 (5.2%)
ATC code "H" (Systemic hormonal preperations)	133 (23.1%)
ATC code "J" (Antiinfectives for systemic use)	487 (84.4%)
ATC code "L" (Antineoplastic and immunomodulating agents)	6 (1%)
ATC code "M" (Musculo-skeletal system)	55 (9.5%)
ATC code "N" (Nervous system)	236 (40.9%)
ATC code "P" (Antiparasitic products, insecticides and repellents)	2 (0.3%)
ATC code "R" (Respiratory system)	30 (5.2%)
ATC code "S" (Sensory organs)	17 (2.9%)
ATC code "V" (Various)	5 (0.9%)

In total, 2,587 drugs were prescribed with a median of four drugs per patient, ranging from two to fourteen drugs. The largest proportion of children, 358 (62%), received between two and four drugs. Drugs with ATC code "J" (Antiinfectives for systemic use) had the highest prescription rate, with 84.4% of children receiving at least one drug with an ATC code of "J".

Characteristics of pDDIs

There were 287 children (49.7%) who had at least one pDDI. In total, 744 pDDIs were identified. Among patients with pDDIs, the median number of pDDIs per patient was two, ranging from one to fifteen. The majority of detected pDDIs were of risk rate C (71.6%). The distribution of pDDIs according to their risk rating is presented in Table 2.

Table 2: Distribution of pDDIs according to their risk rating

Risk rate	Number of pDDIs (%)
B	95 (12.8%)
C	533 (71.6%)
D	104 (14.0%)
X	12 (1.6%)

The majority of the detected pDDIs, 568 (76.4%), had moderate severity, while 101 (13.6%) and 74 (9.9%) had minor and major severity respectively.

The most common pDDIs were aminoglycosides with penicillins (56 instances), aminoglycosides with cephalosporins (27 instances), and vitamin D analogs with calcium salts (23 instances).

The most common pDDIs in each risk category are presented in Table 3.

Factors associated with pDDIs

The association between patient characteristics and the occurrence of pDDIs in both univariate and multivariate analyses is presented in Table 4. According to the univariate model, the exposure to pDDIs was significantly associated with the number of prescribed drugs and ATC codes "B" (Blood and blood-forming organ drugs), "C" (Cardiovascular system drugs), "J" (Antiinfectives for systemic use), "H" (Systemic hormonal preparations), and "N" (Nervous system drugs).

The multivariate model indicated a significant association between the number of prescribed drugs and the presence of pDDIs. The adjusted odds ratio (AOR) increased from 5.80 (95% CI 3.64-9.26) in patients prescribed between five and nine drugs to 35.86 (95% CI 4.52-284.69) in patients prescribed ≥10 drugs. Patients prescribed drugs with ATC code "N" (Nervous system drugs) had a higher risk of having a pDDI (AOR=2.82, 95% CI 1.87-4.27).

Table 3: The most commonly detected pDDIs in each risk category

pDDI	No.	Severity	Level of evidence	clinical effect
Risk rate X				
VitD analogs - VitD analogs	5	Moderate	Fair	↑ Adverse/toxic effect of VitD
Carbamazepine - Linezolide	3	Major	Fair	Risk of serotonin syndrome
Domperidone - Fluconazole	2	Major	Fair	↑ QTc-prolonging effect, ↑ Serum level of domperidone
Domperidone - Itraconazole	1	Major	Fair	↑ Serum level of domperidone
Gentamicin - Amikacin	1	Moderate	Good	↑ Nephrotoxicity and/or neurotoxicity
Risk rate D				
Dexamethasone - Phenytoin	16	Major	Fair	↓ Serum level of dexamethasone
Aminoglycosides - Vancomycin	14	Moderate	Fair	↑ Nephrotoxicity and/or neurotoxicity
Al/Mg hydroxide - Corticosteroids	9	Moderate	Fair	↓ Bioavailability of oral corticosteroids
Carbapenems - Valproic acid	5	Major	Good	↓ serum level of valproate products
Calcium carbonate - Prednisolone	4	Moderate	Fair	↓ Bioavailability of oral prednisolone
Calcium Salts - Levothyroxine	4	Moderate	Fair	↓ Therapeutic effect of levothyroxine
Risk rate C				
Aminoglycosides - Penicillins	56	Moderate	Excellent	↓ Serum level of aminoglycosides
Aminoglycosides - Cephalosporins	27	Moderate	Excellent	↑ Nephrotoxic effect of aminoglycosides, ↓ Serum level of aminoglycosides
VitD analogs - Calcium Salts	23	Moderate	Fair	↑ Adverse/toxic effect of VitD
Digoxin - Furosemide	17	Moderate	Fair	↑ Adverse/toxic effect of digoxin
Allopurinol - Furosemide	15	Moderate	Fair	↑ Adverse/toxic effect of allopurinol
Amlodipine - Calcium salts	15	Moderate	Excellent	↓ Therapeutic effect of amlodipine
Risk rate B				
Ondansetron - Paracetamol	17	Minor	Fair	↓ Analgesic effect of paracetamol
Iron - VitE	11	Minor	Fair	↓ Therapeutic effect of iron
Ciprofloxacin - Fluconazole	7	Minor	Fair	↑ QTc-prolonging effect
Aminoglycosides - Clindamycin	5	Minor	Poor	↑ Nephrotoxic effect of aminoglycosides
Metronidazole - Ondansetron	5	Minor	Fair	↑ QTc-prolonging effect

Table 4: Risk factors associated with potential drug–drug interactions

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	AOR (95% CI)	P value
Gender				
Female	Reference			
Male	1.12 (0.80-1.55)	0.517		
Age groups				
Newborn infants	Reference			
Infants and toddlers	0.60 (0.10-3.63)	0.576		
Pre-school children	0.60 (0.10-3.74)	0.587		
School age children	0.99 (0.16-6.17)	0.994		
Adolescents	0.46 (0.06-3.35)	0.444		
Number of prescribed drugs				
2-4	Reference		Reference	
5-9	7.95 (5.28-11.96)	<0.001*	5.80 (3.64-9.26)	<0.001*
≥10	57.86 (7.75-431.72)	<0.001*	35.86 (4.52-284.69)	0.001*
Duration of stay (days)				
1-3	Reference			
4-7	1.33 (0.74-2.39)	0.338		
≥8	1.25 (0.76 – 2.06)	0.383		
ATC code "A" (Alimentary tract and metabolism)	1.30 (0.93-1.83)	0.125		
ATC code "B" (Blood and blood forming organs)	1.61 (1.10-2.35)	0.014*	1.15 (0.71-1.88)	0.573
ATC code "C" (Cardiovascular system)	3.02 (1.96-4.64)	<0.001*	1.69 (0.97-2.94)	0.066
ATC code "J" (Antiinfectives for systemic use)	1.88 (1.18-2.96)	0.008*	1.31 (0.76-2.25)	0.331
ATC code "H" (Systemic hormonal preperations)	2.51 (1.67-3.78)	<0.001*	1.59 (0.96-2.63)	0.070
ATC code "N" " (Nervous system)	2.76 (1.96-3.89)	<0.001*	2.82 (1.87-4.27)	<0.001*

AOR adjusted odds ratio, OR odds ratio

* P-value is statistically significant

DISCUSSION

This study is the first to characterize pDDIs among pediatric inpatients in Syria. Nearly half of the children in the study had at least one pDDI. The majority of detected pDDIs fell within risk category C (71.6%). Both the number of prescribed drugs and receiving drugs with an ATC code of "N" (Drugs for nervous system) were significantly associated with the occurrence of pDDIs.

Almost half of the children (49.7%) had at least one pDDI. This is similar to the results of previous studies, wherein 42% to 52.3% of pediatric inpatients were found to have at least one pDDI [1,14,15,16]. However, the percentage of children exposed to pDDIs in our study was much higher compared to that in Langerová et al.'s study (3.83%)[17]. This difference might be partially due to variations in the inclusion criteria and the software used to detect pDDIs. Langerová et al. utilized the INFOPHARM Drug Interactions Compendium® computer program in

their study. An evaluation of INFOPHARM's performance could not be found in the literature. On the other hand, Lexi-Comp, which was used in our study, has been found to have a higher sensitivity compared to many other drug-drug interaction software programs [13].

The majority of detected pDDIs in our study (71.6%) were within risk category C, followed by risk categories D (14.0%), B (12.8%), and X (1.6%). This differed from the results of Bebitoğlu et al., who used the same DDI checker [16]. According to Bebitoğlu's study, 44.8% and 42.7% of pDDIs were within risk categories B and A respectively, whereas 8.4% and 4.1% of the pDDIs were classified under risk categories C and D respectively. No pDDIs were detected in risk category X.

This discrepancy might be partially explained by differences in the inclusion/exclusion criteria of the two studies. pDDIs within risk category A were excluded from our study, whereas 42.7% of the pDDIs in Bebitoğlu's study fell into risk category A. Additionally, vitamins were excluded from the analysis in Bebitoğlu's study, whereas they were included in our study and were often involved in pDDIs under risk category C, such as Vitamin D analogs with calcium salts.

Furthermore, the medical conditions of children in our study were likely more complex compared to those in Bebitoğlu et al.'s study. This is indicated by the longer length of stay in our study (ten days versus 5.1±2.0 days in Bebitoğlu et al.'s study), and a much higher proportion of children who were prescribed ≥5 medications (38% versus 5.6%).

Consequently, children in our study were prescribed different medications and combinations. For instance, to treat infections, children were often prescribed combinations such as aminoglycosides with penicillins, aminoglycosides with cephalosporins, and aminoglycosides with vancomycin. These largely contributed to the proportion of pDDIs under risk categories C and D.

The most common pDDI in our study involved a combination of aminoglycosides and penicillins, which have a moderate severity and fall into risk category C. The interaction between aminoglycosides and penicillins, which may decrease the serum concentration of aminoglycosides, has also been reported as a common pDDI in previous pediatric studies [18,19,20]. This interaction is particularly significant when penicillin and aminoglycoside are in contact over a prolonged period of time, such as in patients with renal dysfunction. In this case, treatment monitoring is recommended, especially in severely ill patients [21].

The second most common pDDI was between aminoglycosides and cephalosporins, which was also found to have moderate severity and to fall into risk category C. This pDDI has also been among the most common pDDIs detected in previous pediatric studies [22,23]. The combination of aminoglycosides and cephalosporins is synergistically nephrotoxic, necessitating careful monitoring for signs of nephrotoxicity [24,25]. Additionally, cephalosporins may inactivate aminoglycosides [26]. However, this is expected to be clinically significant only in patients with severely impaired renal function [27,28].

The third most common pDDI was between vitamin D analogs and calcium salts. The severity of this pDDI is moderate and it falls into risk category C, requiring monitoring of serum calcium concentrations and signs/symptoms of hypercalcemia.

In this study, both the number of prescribed drugs and ATC code "N" (Drugs for nervous system) were found to be significantly associated with the presence of pDDIs. The number of prescribed drugs has previously been identified as a risk factor for the presence of pDDIs in pediatric wards [14,17]. Studies assessing the association between medication groups and the presence of pDDIs among children are scarce. However, Langerová et al. found a significant association between antiepileptic drugs (ATC code: N03) and the presence of pDDIs among pediatric inpatients [17].

Although a high proportion of children in this study were exposed to pDDIs, the majority of pDDIs fell within risk category C (71.6%) and were of moderate severity (76.4%). This implies that most pDDIs are not expected to be life-threatening or cause permanent damage. However, additional care and therapy monitoring are required, especially in the presence of risk factors or other pDDIs with similar potential adverse effects. According to published literature, not all pDDIs result in actual DDIs or ADRs, but life-threatening and fatal ADRs can develop [29]. Therefore, pediatricians should be informed about pDDIs and a plan should be developed at the hospital level to avoid the adverse effects of pDDIs.

It is important to draw the attention of clinicians to the significant association between the occurrence of pDDIs, the number of prescribed drugs, and the prescribing of drugs for the nervous system. We also suggest a protocol be developed to manage the most frequently detected pDDIs in all risk categories each time the involved combination is prescribed. However, screening for pDDIs with every prescription of more than one drug is recommended to detect less common pDDIs and to avoid adverse consequences. This could be better achieved with the support of clinical pharmacists. Clinical pharmacists are qualified to perform medication reviews, detect drug-related problems including DDIs, and intervene to avoid negative impacts on patients [30,31].

A limitation of this study is that the clinical outcomes of the pDDIs were not evaluated. Furthermore, the drug interaction checker used in the study detects pDDIs between each pair of drugs without considering the influence of additional drugs on the pDDIs. As a result, the severity of some pDDIs may have been underestimated. Another limitation is the single-center design of the study, which limits the generalizability of its findings. Moreover, both newborn infants and adolescents were not sufficiently represented in the study, due to the small percentages of these age groups in the sample. Future research to assess actual DDIs in multiple pediatric settings, including different age groups, is needed.

CONCLUSION

Almost half of the pediatric inpatients in our study had at least one pDDI. The number of drugs and drugs with ATC code "N" (Drugs for nervous system) showed a significant association with the presence of pDDIs. Clinicians at the hospital are advised to exercise caution when prescribing for patients with these risk factors to detect and assess any potential pDDIs. The majority of the detected pDDIs fell within risk category C, necessitating therapy monitoring and nimble response as needed to avoid adverse consequences. Future investigations to evaluate the actual impact of pDDIs on pediatric inpatients are recommended.

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التداخلات الدوائية المحتملة والمتنبّئات المرتبطة بحدوثها في مشفى الأطفال الجامعي في سورية: دراسة مقطعية

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ملخص

هدف الدراسة: إعطاء الأدوية المتعددة للأطفال المرضى ممارسة شائعة وتُعرّض الأطفال لخطر التداخلات الدوائية (DDIs). تهدف هذه الدراسة إلى توصيف الـ DDIs المحتملة (pDDIs) وعوامل الخطورة المرتبطة بها لدى الأطفال المقبولين في المستشفى.

المنهج البحثي: أجريت دراسة مقطعية لمدة 6 أشهر في مشفى الأطفال الجامعي بدمشق. ضمّت الدراسة 577 طفلاً يتلقون دواءين أو أكثر. استُخدم برنامج Lexi-Interact® لتحرّي pDDIs. شمل التحليل الـ pDDIs من الفئات: B (لا حاجة لاتخاذ إجراء)، C (مراقبة المعالجة)، D (تعديل الجرعات)، وX (تجنب المشاركة). استُخدم الانحدار اللوجستي لتحديد عوامل الخطورة المرتبطة بـ DDIs.

النتائج: تم الكشف عن وجود pDDI واحد على الأقل لدى 49.7% من الأطفال. بلغ عدد الـ pDDIs ما مجموعه 744 تداخلاً دوائياً. تنتمي معظم الـ pDDIs إلى فئة الخطورة C (71.6%)، تليها التداخلات من الفئة D (14%)، B (12.8%) وX (1.6%). أكثر الـ pDDIs تكراراً: الأمينوغليكوزيدات – البنسلينات (56 مشاركة)، الأمينوغليكوزيدات – السيفالوسبورينات (27 مشاركة) و فيتامين د – أملاح الكالسيوم (23 مشاركة). شملت العوامل المؤثرة على وجود pDDIs كلاً من عدد الأدوية الموصوفة ووصف دواء من زمرة الأدوية العصبية.

الاستنتاجات: معدّل الـ pDDIs لدى الأطفال في المشفى مرتفع. معظم الـ pDDIs من فئة الخطورة C، مما يستدعي مراقبة العلاج واتخاذ الإجراء المناسب لتجنب التبعات الضارة.

الكلمات الدالة: التداخلات الدوائية، طب الأطفال، الأطفال في المشفى، مأمونية الدواء، سورية.

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