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Evaluation of potential drug-drug interactions in a pediatric population

Çocuk kliniğinde potansiyel ilaç-ilaç etkileşimlerinin değerlendirilmesi

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The known about this topic

Considering the principles of rational drug use which considers the efficacy, safety, suitability and the cost of medication during treatment regimens would also prevent the occurrence of many drug-drug interactions. This is especially important for pediatric population, where the pharmacokinetic parameters of the medications are very different from adult population. There is scarce data on drug-drug interactions and pharmacokinetics profiles in pediatric population due to ethical and practical limitations.

Contribution of the study

The results of this study give detailed information about the abundance of potential clinically significant drug-drug interactions and their mechanisms in a Pediatric clinic. The studies performed on adult population extrapolated to the pediatric population may result in under or over prediction of the severity of drug-drug interactions. Therefore the prevalence of potential drug-drug interactions in hospitalized pediatric patients and main drug classes involved in severe potential drug-drug interactions in pediatric population are presented.

Abstract

Aim: A large number of medications are prescribed in pediatric clinics and this leads to the development of drug–drug interactions (DDI) that may complicate the course of the disease. The aim of the study was to identify the prevalence of potential drug–drug interactions, to categorize main drug classes involved in severe drug–drug interactions and to highlight clinically relevant DDIs in a pediatric population.

Material and Methods: A total of 1500 prescriptions during the 12-month study period were retrospectively reviewed; 510 prescriptions that comprised two or more drugs were included in study. The presence of potential drug–drug interactions was identified by using the Lexi-Interact database and categorized according to severity: A (unknown), B (minor), C (moderate), D (major), and X (contraindicated).

Results: There were 1498 drugs in 510 prescriptions; 253 of these (49.6%) included 2 drugs, 228 (44.7%) included 3–4 drugs, and 29 (5.6%) included ≥5 drugs. A total of 634 (42%) potential drug–drug interactions were idenfied. Among those, 271 (42.7%) were catego-

Öz

Amaç: Çocuk kliniklerinde çok sayıda ilaç reçete edilmektedir ve bu durum hastalığın seyrini kötüleştirebilecek ilaç-ilaç etkileşimlerinin oluşmasına neden olabilmektedir. Bu çalışmanın amacı, potansiyel ilaç-ilaç etkileşimlerinin yaygınlığını ve ciddi etkileşime giren başlıca ilaç gruplarını belirlemek ve çocuk yaş grubunda klinik olarak önemli ilaç-ilaç etkileşimlerini vurgulamaktır.

Gereç ve Yöntemler: 12 aylık çalışma döneminde toplam 1 500 reçete geriye dönük olarak incelendi; bunlar içerisinden iki ya da daha fazla ilaç içeren 510 reçete çalışmaya alındı. Potansiyel ilaç-ilaç etkileşimlerinin varlığı, Lexi-Interact veritabanı kullanılarak belirlendi ve ciddiyetine göre sınıflandı: A (bilinmeyen), B (minor), C (orta), D (major) ve X (kontrendike).

Bulgular: 510 reçetede toplam 1498 ilaç vardı; bunların 253'ü (%49,6) 2 ilaç, 228'i (%44,7) 3–4 ilaç ve 29'u (%5,6) ≥5 ilaç içermekte idi. Toplam 634 (%42) potansiyel ilaç-ilaç etkileşimi belirlendi. Bunlardan 271'i (%42,7) A, 284'ü (%44,8) B, 53'ü (%8,4) C ve 26'sı (%4,1) D grubu

Cont. ➡

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rized as A, 284 (44.8%) as B, 53 (8.4%) as C, and 26 (4.1%) as D. There was no potential risk for X interaction. Anti-infectives (36%) were the most commonly prescribed drug classes involved in C and/or D categories. Clarithromycin was the most commonly interacting agent that interfered with budesonide.

Conclusion: It is noteworthy that a significant number of drugs causing potential drug–drug interactions are prescribed together in pediatric clinics. Increasing the awareness of physicians on this issue will prevent potential complications and ensure patient safety.

Keywords: Drug-drug interactions, pediatric, pharmacology, prescriptions

etkileşim olarak sınıflandırıldı. X etkileşimi içeren risk saptanmadı. C ya/ya da D kategorisinde en yaygın reçete edilen ilaç grubu anti-infektifler (%36) idi. Klaritromisin, budesonide ile etkileşen ve en sık etkileşime giren ilaç idi.

Çıkarımlar: Çocuk kliniklerinde potansiyel ilaç-ilaç etkileşimlerine neden olan ilaçların sıklıkla birlikte reçete edilmesi dikkat çekicidir. Klinisyenlerin bu konudaki farkındalığının arttırılması olası komplikasyonları önleyecek ve hasta güvenliğini artıracaktır.

Anahtar sözcükler: Farmakoloji, ilaç-ilaç etkileşimi, pediatrik, reçete

Introduction

Many pediatric patients receive multiple medications for their treatments and this condition can potentially lead to drug–drug interactions (DDIs) and may further complicate the course of the diseases in pediatrics clinics. As the pharmacokinetics of drugs in pediatric patients is different from adults, the drug interactions in pediatric population require more attention compared with adults (1). The changes in excretion and elimination processes may prolong the half-life of metabolized drugs and this may cause toxicity problems (2).

Hospitalized patients are at an increased risk of potential DDIs due to the multiple medications prescribed, and their illnesses can also cause physiological changes that may further affect both pharmacokinetic and pharmacodynamic responses (3). Drug–drug interactions may cause treatment failure and adverse drug reactions that can complicate the course and clinical picture of diseases severity (4).

There are scarce data on DDIs and pharmacokinetics profiles in pediatric population due to ethical and practical limitations (1, 5). The results of a pediatric database analysis in the United States showed that approximately half of hospitalized children were exposed to a potential DDI, of which 41% were considered 'major' according to the Micromedex DRUG-REAX classification system (6). The prevalence of potential DDIs was also investigated in children admitted to emergency departments and it was reported to be as high as 61% (7). Moreover, studies performed on adult populations extrapolated to the pediatric population may result in under or over prediction of the severity of DDIs (5).

The aim of this study was to identify the prevalence of potential DDIs in hospitalized pediatric patients, to categorize the main drug classes involved in severe DDIs, and to highlight clinically relevant DDIs in the pediatric population.

Material and Methods

This single-center, retrospective, cross-sectional study included pediatric patients aged between 1 week and 18 years, who were hospitalized for more than 24 hours in Haydarpaşa Numune Health Practice and Research Center Pediatrics Clinic between January 2016 and December 2016. One thousand five hundred prescriptions were reviewed during the 12-month study period. Five hundred ten prescriptions included two or more drugs and these prescriptions were included in the study. Prescriptions including topical drugs, electrolytes, vitamins, and insulin were excluded. The drugs administered during hospitalization were retrospectively analyzed after obtaining institutional clinical research ethics committee approval (Document No.: HNEAH-KAEK 2017/KK/53, Date: 24.04.2017). The study was conducted in accordance with the Declaration of Helsinki.

The drugs were further classified according to the anatomical therapeutic chemical (ATC) classification (8). Data about demographic characteristics, primary diagnosis and comorbidities, medical prescriptions, and clinical and laboratory features if necessary were collected from the patients' medical records. Diagnostic classifications were performed according to the tenth revision of the International Classification of Disease.

The presence of potential DDIs was identified by using the Lexi-Interact database and categorized according to severity: A (unknown), B (minor), C (moderate), D (major), and X (contraindicated) (Appendix 1) (9). As A and B interactions were considered as minor, the drugs showing C and D interactions were considered clinically important pDDIs for further analysis. The SPSS statistical software (Version 22, SPSS Inc., Chicago, II, USA) was used for descriptive analysis of the data.

Results

The demographic and clinical characteristics of the included patients are summarized in Table 1. Nearly half the patients (46%, n=234) were aged under one year and 40% were aged between four weeks and one year.

The most common primary diagnosis was respiratory system diseases (n=297, 58%), followed by infectious (n=68, 13%), urinary system (n=61, 12%), gastrointestinal system

Table 1. Clinical and demographic characteristics of the patients

Clinical and demographic data	n	%
Number of patients	510	
Age distribution		
0–4 weeks	29	5.7
>4 weeks- 1 year	205	40.2
>1–3 years	72	14.1
>4–6 years	61	12.0
>6–14 years	97	19.0
>14 years	46	9.1
Sex (male/female)	256 (50.2)/254 (49.8)	
Length of stay in hospital, day (mean±SD)	5.1±2.0	
Length of stay in ICU, day (mean±SD)	2.5±1.0	

SD: Standard deviation; ICU: Intensive care unit

(n=42, 8%), central nervous system (n=30, 6%) diseases, and hematologic disorders (n=12, 2.4%).

There were 1498 drugs in 510 prescriptions; 253 of these (49.6%) included 2 drugs, 228 (44.7%) included 3–4 drugs, and 29 (5.6%) included ≥5 drugs. A total of 634 (42%) potential DDIs were idenfied. Among those, 271 (42.7%) were categorized as A, 284 (44.8%) as B, 53 (8.4%) as C and 26 (4.1%) as D. There was no potential risk for X interaction. The distribution of interaction categories according to the number of drugs in prescriptions is presented on Figure 1.

Of the total 1498 administered drugs, 158 of them (10.5%) were involved in potential C and/or D categories. The main drug classes involved in C and/or D interactions

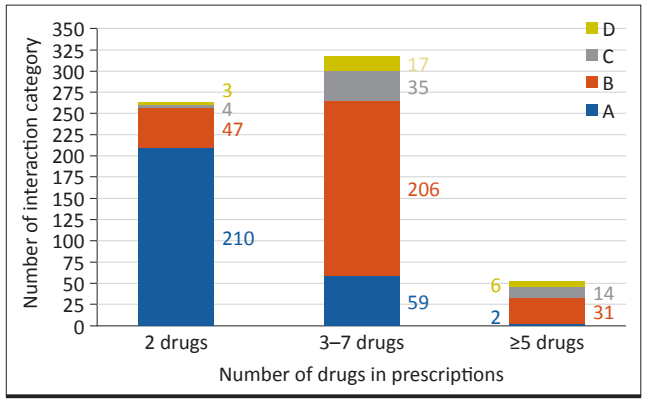

Figure 1. The distribution of interaction categories according to the number of drugs in prescriptions is presented

were anti-infectives (36%), followed by agents of the central nervous system (19%), respiratory system (16%), endocrinology (13.3%), cardiovascular (9.5%) drugs, non-steroidal anti-inflammatory drugs (NSAIDs) (3.8%), and gastrointestinal system drugs (2.5%). Among the 158 drugs involving in C and/or D interactions, there were 110 different pharmacologically active substances, and 34 different interacting medications were identified (Table 2).

Seventy-nine out of 634 potential DDIs (12.5%) were classified as C and/or D interactions. Of the 79 potential DDIs with a severity rating of C and/or D, 34 were unique drug pairs (a specific combination of interacting medication that is counted once). The drug pairs causing C and/or D interactions are presented in Table 3.

Clarithromycin was the most common interacting drug with 37 times affecting budesonide (n=20), methylprednisolone (n=14), dexamethasone (n=2), and midazo-

Table 2. Drug classes specific medications associated with C and/or D interactions, and the frequency of interactions

Drug classes (frequency of interactions)	Specific medications (frequency of interactions)
Anti-infective drugs (n=57)	Clarithromycin (n=37), ceftriaxone (n=4), amikacin (n=3), streptomycin (n=3), vancomycin (n=2), rifampicin (n=2), gentamicin (n=1), isoniazid (n=2), meropenem (n=1), cefepime (n=1), colistin (n=1)
Central nervous system drugs (n=30)	Levetiracetam (n=8), phenobarbital (n=7), midazolam (n=5), valproic acid (n=3), fentanyl (n=2), clonazepam (n=1), phenytoin (n=1), diazepam (n=1), pheni ramine (n=1), sertraline (n=1)
Respiratory system drugs (n=25)	Salbutamol (n=2), budesonide (n=23)
Endocrine drugs (n=21)	Methylprednisolone (n=17), prednisolone (n=2), dexamethasone (n=2)
Cardiovascular system drugs (n=15)	Furosemide (n=10), enalapril (n=3), digoxin (n=1), captopril (n=1)
NSAIDS (6)	Acetylsalicylic acid (n=1), ibuprofen (n=5)
Gastrointestinal drugs (n=4)	Aluminium hydroxide and magnesium carbonate antacid (n=3), ursodeoxycholic acid (n=1)

NSAID: Non-steroidal anti-inflammatory drugs

Table 3. Drug classes of clinically significant potential drug-drug interactions

Drug class (n)	Drug	Potential drug for interaction		Category of interaction
		Drug	n	
Anti-infective (48)	Clarithromycin	Budesonide	20	C
	Clarithromycin	Methylprednisolone	14	D
	Clarithromycin	Dexamethasone	2	D
	Clarithromycin	Midazolam	1	D
	Ceftriaxone	Streptomycin	2	C
	Rifampicin	Isoniazid	1	C
	Rifampicin	Valproic acid	1	D
	Isoniazid	Valproic acid	1	C
	Ceftriaxone	Gentamicin	1	C
	Ceftriaxone	Amikacin	1	C
	Cefepime	Amikacin	1	C
	Streptomycin	Ibuprofen	1	C
	Meropenem	Valproic acid	1	D
	Vancomycin	Colistin	1	D
Central nervous system (13)	Phenobarbital	Levetiracetam	5	C
	Phenobarbital	Midazolam	2	D
	Phenytoin	Midazolam	1	D
	Fentanyl	Sertraline	1	C
	Fentanyl	Pheniramine	1	D
	Diazepam	Levetiracetam	1	C
	Midazolam	Levetiracetam	1	C
	Clonazepam	Levetirecetam	1	C
Endocrine system (7)	Methylprednisolone	Ibuprofen	3	C
	Budesonid	Furosemide	3	C
	Prednisolon	Furosemide	1	C
Cardiovascular system (4)	Furosemide	Enalapril	2	C
	Furosemide	Digoxin	1	C
	Furosemide	Captopril	1	C
Gastrointestinal system (3)	Aluminium hydroxide and magnesium carbonate antacid	Amikacin	1	C
	Aluminium hydroxide and magnesium carbonate antacid	Prednisolone	1	D
	Aluminium hydroxide and magnesium carbonate antacid	Ursodeoxycholic acid	1	D
Respiratory system (2)	Salbutamol	Furosemide	2	C
Nonsteroidal anti-inflammatory drugs (2)	Acetylsalicylic acid	Enalapril	1	C
	Ibuprofen	Vancomycin	1	C

lam (n=1) (Table 3). Critical potential DDIs (D category) were detected between rifampicin and valproic acid, meropenem and valproic acid, and between vancomycin and colistin (Table 3). The other frequently interacting drug class was the central nervous system drugs including levetiracetam (n=8), phenobarbital (n=7) and midazolam (n=5). The other most commonly interacting medications were budesonide (n=23), methylprednisolone (n=17), furosemide (n=10) and ibuprofen (n=5) (Table 2 and 3).

Discussion

This study evaluated the frequency of clinically important potential DDIs (C and D risk categories) in hospitalized

pediatric patients. In terms of severity, most interactions were minor and no potential risk for contraindication was detected. The drug classes and specific medications that have potential for interaction are identified to highlight the importance of these interactions, which may result in the occurrence of adverse drug reactions, noncompliance to treatment, failure in treatment, and increased duration of hospitalization. As irrational drug use is one of the risk factors for the development of adverse reactions, frequently noted potential DDIs should be considered by physicians for patient safety (10).

The main risk factor for adverse drug reaction occurrence in the pediatric population is the increase in the number of prescription drugs (11). In this study, the number of patients prescribed two or more drugs were 510 among 1500 prescriptions; 253 of these (49.6%) included 2 drugs, 228 (44.7%) included 3–4 drugs, and 29 (5.6%) included ≥5 drugs. The frequency of C and D interactions were the highest among the prescriptions including 3–4 drugs. In line with previous studies, both in adult and pediatric populations (12, 13), increased numbers of total daily medications were associated with a greater potential DDI in our study population. These findings indicate that pediatric prescriptions should contain the smallest possible number of medications to prevent possible drug interactions (13).

The prevalence of potential DDIs (42%) was found be lower than the reported findings of other studies in pediatric hospitals in Mexico (61%) and Philadelphia (49%), but higher than the prevalence of DDIs found in other pediatric studies (3.8%) (5–7, 14). This wide variability in the reported prevalence of DDIs in different studies can be explained by the included population, the underlying medical conditions of the involved patients, the study design, and the software used for their identification (6, 12). In our study, a total of 634 potential DDIs were identified in all 1498 patients, out of which 8.4% were 'moderate,' 4.1% were 'major,' without any 'contraindicated' pDDIs. This ratio was lower than the results found in another study that reported 57.3% moderate and 18% major DDIs (D and X, respectively) (15). Another study reported that contraindicated DDIs occurred in 5%, major DDIs in 41%, moderate DDIs in 28%, and minor DDIs in 11% of all hospitalizations (6). Also, it was reported that the ratio of 'contraindicated' DDI was 0.2%, 'serious' DDIs were 7.5%, and 'significant-monitor closely' were 62.8% (7). The large difference in the prevalence of clinically important potential drug interactions might be due to the critical medical conditions of pediatric inpatients, which make them more susceptible to the administration of multiple drugs, complex treatment regimens, and care by physicians of different specialties for consultations (15, 16). In addition, hospitalized pediatric patients are vulnerable to medication-related issues because of off-label prescribing of drugs, lack of therapeutic profiles for rare drugs, and weight-based dosing strategies. Our study may reflect developments in the practice of physicians over time with previous valuable efforts and their awareness.

In our study, the most common diagnoses were respiratory system diseases, infectious diseases were also commonly encountered in children, and anti-infective agents and drugs used in the respiratory system and central nervous system were the main drug classes involved in C and D interactions. In accordance with previous studies (2, 13, 17, 18), the present study revealed that anti-infective agents (36.1%) were the most prescribed agents in pediatric patients. It was followed by central nervous system (19%) and respiratory system drugs (15.8%), which are also associated with clinically significant adverse drug reactions and interactions. It has also been shown that opioids are involved in nearly 25% of all DDIs, followed by anti-infective agents (17%), and neurologic agents (15%), similar to our results (5, 6). We found central nervous system drugs (19%) to be the second most common prescribed drugs.

There is a wide range of different consequences that could be predicted according to DDI mechanisms. The results of potential DDIs may be due to pharmacokinetic mechanisms such as induction or activation of the metabolizing enzymes causing a decrease or increase of the serum concentration of the object drug or pharmacodynamic reactions related to receptors, both resulting in additive effects such as hypotension, CNS depression, and adverse effects (19).

The results of the current study revealed that the most common potential drug-drug interactions were between clarithromycin and budesonide and methylprednisolone, in terms of the pharmacokinetic interactions. It was reported in another study that frequent potential moderate interactions were also noted between clarithromycin and corticosteroids (10.7%) (13). Regarding the concomitant administration of such drugs, their effectiveness may be altered by metabolizing enzyme CYP3A4 inhibition. Therefore, monitoring of drug interactions is especially important in children with asthma attacks. In addition, the rational use of antibiotics is an important issue in our country, where the prescription of antibiotics requires close monitoring for both maintaining efficacy, preventing resistance, and reducing cost. The inhibition or activation of drug-metabolizing enzymes and alterations in gastrointestinal absorption of antibiotics are also the

most common mechanisms often associated with antimicrobial interactions (19–21).

Another important interaction includes the interaction of meropenem (anti-infective agent) with valproic acid, and rifampicin with valproic acid. These interactions may decrease the efficacy of valproic acid. There is a risk of nephrotoxicity with concomitant use of streptomycin with ibuprofen and vancomycin with colistin. Also, concomitant use of ceftriaxone with streptomycin or gentamicin or amikacin may lead to nephrotoxicity due to potential interactions (9).

The second most common interaction was found between antiepileptic drugs; phenobarbital-levetiracetam, phenobarbital-midazolam, and also between phenytoin and midazolam. Diazepam-levetiracetam, midazolam-levetiracetam, and clonazepam-levetiracetam interactions may result in increased central nervous system depression and subsequent toxicity.

The cardiovascular drug groups are among the most frequent drugs involved in DDIs (22, 23). Hypopotassemia and hypotension may develop as a result of DDIs with the use of different groups of cardiovascular drugs (24). In our study, enalapril use with acetylsalicylic acid was also detected in one patient, which may increase the risk of nephrotoxicity. Concomitant use of steroids with diuretic furosemide may also lead to increased hypopotassemia and furosemide use with agents acting on the cardiovascular system such as digoxin and captopril combination lead to digoxin toxicity and an increased hypotensive effect, respectively.

Considering the current profile of interactions, prevention measures should include strategies such as dosage adjustment considering pharmacokinetics, avoidance of group use, observation of the therapeutic response, and clinical monitoring for the early detection of adverse effects (25). Identifying and finding the exact cause of common potential DDIs could help physicians to understand clinical situations in which co-administration is acceptable, to motivate them to monitor for potential adverse drug effects, and to adjust dose regimens when adverse drug reactions occur. This requires participation of clinical pharmacologists in the multidisciplinary team, to evaluate the pharmacotherapy of patients, especially in populations with special needs such as pediatrics or geriatrics. Clinical pharmacologists are highly competent on these problems and have a unique insight into the possible mechanism related with drug use (26). It is now well known that rational drug use considers the efficacy, safety, suitability, and the cost of medication use during treatment regimens. Consideration to the principles of rational drug use would also prevent the occurrence of many DDIs. This is especially important for pediatric population, in which the pharmacokinetic parameters of medications are very different from the adult population (27).

The limitation of this study was that the clinical outcomes related to DDIs are not presented because the data were collected from hospital records and analyzed retrospectively. In addition, the data were collected only from a single dedicated center and the generalization of these results to all centers is relatively hard. The Lexi-Interact program is commonly preferred by Turkish physicians and available in many hospitals due to its accessibility; however, the use of different software could also provide more accurate results (28).

The setting of the current study is a tertiary care hospital that is a referral center in Istanbul and reported interactions related to the most commonly prescribed drugs could provide information for other pediatricians. Interactions reported in the present study may alert physicians and lead to alterations in their treatment choices to reduce clinical problems and complications caused by such interactions.

In conclusion, while prescribing medications in the pediatric population, physicians should be aware of potential pharmacodynamic and pharmacokinetic drug interactions and treatment regimens should be adjusted accordingly. Highlighting the possible severe interactions of drug classes may increase the awareness of physicians about patient safety, and the categories of DDIs according to drug classes may help physicians prevent possible clinically significant DDIs.

Ethics Committee Approval: Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee Approval (document no: HNEAH-KAEK/2017/KK/53, date: 24.04.2017).

Informed Consent: Informed consent was not obtained because the study was conducted retrospectively.

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References

1. Salem F, Rostami-Hodjegan A, Johnson TN. Do children have the same vulnerability to metabolic drug–drug interactions as adults? A critical analysis of the literature. J Clin Pharmacol 2013; 53: 559–66.
2. Martinbiancho J, Zuckermann J, Dos Santos L, Silva MM. Profile of drug interactions in hospitalized children. Pharm Pract (Granada) 2007; 5: 157–61.
3. Papadopoulos J, Smithburger PL. Common drug interactions leading to adverse drug events in the intensive care unit: management and pharmacokinetic considerations. Crit Care Med 2010; 38: S126–35.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279: 1200–5.
5. Salerno SN, Burckart GJ, Huang SM, Gonzalez D. Pediatric Drug-Drug Interaction Studies: Barriers and Opportunities. Clin Pharmacol Ther 2019; 105: 1067–70.
6. Feinstein J, Dai D, Zhong W, Freedman J, Feudtner C. Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. Pediatrics 2015; 135: e99–e108.
7. Morales-Ríos O, Jasso-Gutiérrez L, Reyes-López A, Garduño-Espinosa J, Muñoz-Hernández O. Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico. PLoS One 2018; 13: e0190882.
8. WHO Collaborating Centre. ATC/DDD Index 2020. Available from: https://www.whocc.no/atc_ddd_index/.
9. Lexicomp. Lexi-Interact Online App. Available from https://www.uptodate.com/contents/search (accessed August 2018).
10. World Health Organization. Action Programme onEssential Drugs. Model guide to good prescribing. Geneva: WHO; 1991.
11. Andrade PH, Santos AD, Souza CA, Lobo IM, da Silva WB. Risk factors for adverse drug reactions in pediatric inpatients: a systematic review. Ther Adv Drug Saf 2017; 8: 199–210.
12. Dai D, Feinstein JA, Morrison W, Zuppa AF, Feudtner C. Epidemiology of Polypharmacy and Potential Drug-Drug Interactions Among Pediatric Patients in ICUs of U.S. Children's Hospitals. Pediatr Crit Care Med 2016; 17: e218–28.
13. Masukawa YM, Veríssimo GB, Vianello Richtzenhain MH, Alessandra L. Drug interactions in children with respiratory diseases in the pediatric unit of a teaching hospital in Brazil. Rev Cubana Pediatr 2016; 88: 166–81.
14. Langerová P, Prokeš M, Konvalinka M, Fürstová J, Urbánek K. Incidence of potential drug interactions in medication prescriptions for children and adolescents in the University Hospital Olomouc, Czech Republic. Eur J Pediatr 2013; 172: 631–8.
15. Hassanzad M, Arenas-Lopez S, Baniasadi S. Potential Drug-Drug Interactions Among Critically Ill Pediatric Patients in a Tertiary Pulmonary Center. J Clin Pharmacol 2018; 58: 221–7.
16. Womer J, Zhong W, Kraemer FW, et al. Variation of opioid use in pediatric inpatients across hospitals in the U.S. J Pain Symptom Manage 2014; 48: 903–14.
17. Baniasadi S, Fahimi F, Shalviri G. Developing an adverse drug reaction reporting system at a teaching hospital. Basic Clin Pharmacol Toxicol 2008; 102: 408–11.
18. Meiners MM, Bergsten-Mendes G. Drug prescription for hospitalized pediatric patients: how can the quality be evaluated? [Article in Portuquese]. Rev Assoc Med Bras 1992; 47: 332-7.
19. Baxter K. Stockley's drug interactions. 8th ed. London: Pharmaceutical Press; 2008.p. 2–11.
20. Pereira JM, Paiva JA. Antimicrobial drug interactions in the critically ill patients. Curr Clin Pharmacol 2013; 8: 25–38.
21. Del Rosso JQ. Oral antibiotic drug interactions of clinical significance to dermatologists. Dermatol Clin 2009; 27: 91–4.
22. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence

of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med 2008; 19: 413–20.
23. Magro L, Conforti A, Del Zotti F, et al. Identification of severe potential drug-drug interactions using an Italian general-practitioner database. Eur J Clin Pharmacol 2008; 64: 303–9.
24. Ganeva M, Gancheva T, Troeva J, Kiriyak N, Hristakieva E. Clinical relevance of drug-drug interactions in hospitalized dermatology patients. Adv Clin Exp Med 2013; 22: 555–63.
25. Hansten PD. Drug interaction management. Pharm World Sci 2003; 25: 94–7.
26. Moore N. The role of the clinical pharmacologist in the management of adverse drug reactions. Drug Saf 2001; 24: 1–7.
27. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults. Pharmaceutics 2011; 3: 53–72.
28. Kheshti R, Aalipour M, Namazi S. A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract 2016; 5: 257–63.

Appendix 1. The definition of each risk rating of Lexi-Interact data fields

Risk rating	Action	Description
A	No Interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Modify regimen	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

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