Evaluation of Potential Drug-Drug Interactions in Hospitalized Pediatric Patients with Bronchitis Diagnosis: A Retrospective Study

Neda Taner*, Müferiye Eskitoğlu, Betül Şirin

Department of Clinical Pharmacy, School of Pharmacy, İstanbul Medipol University, İstanbul, Turkey.

Received: 2023-01-17, Revised: 2023-03-19, Accepted: 2023-03-25, Published: 2023-03-31

Abstract

Background: Acute bronchitis is one of the most common infectious diseases in children and a major cause of hospital admissions. Treatment of acute bronchitis is usually symptomatic, analgesics and antipyretics are often used. The simultaneous intake of drugs brings pharmacological interactions with it. These interactions are important for the success of the treatment. The aim of our investigation is to determine the prevalence and severity of possible drug interactions; draw attention to drug interactions in children and adolescents.

Methods: This study was conducted on 99 patients, 48 males and 51 females, with bronchitis hospitalized between 2019 and 2021 in Rize, Turkey. Patient records were retrospectively evaluated, and drug interactions were determined using database Medscape data by clinical pharmacists. Data was analyzed by SPSS 15.0v. statistical program $p<0.05$ was considered significant. The severity of the interactions was assessed as an alternative to serious use, close monitoring and minor interactions.

Results: In this study, it was found that the mean age of the patients was 5.17 ± 2.31 years. A total of 69 drug-drug interactions were identified, most of which (63.6%) were identified on the 'Close Monitor', and the interaction rate at the 'Serious Use Alternative' level was found to be 16.2%. There was no interaction in some patients in this study; but some patients experienced up to 4 interactions.

Conclusion: Healthcare professionals should be more cautious about polypharmacy and more aware of the rational use of drugs. By raising awareness of drug interactions among healthcare professionals, drug interactions can be minimized.

J Pharm Care 2023; 11(1): 25-31.

Keywords: Rational Drug Use; Bronchitis; Pediatrics; Drug-Drug Interaction

Introduction

Acute bronchitis is one of the most common types of infection in children, especially children under the age of 5, and a leading cause of hospitalization. Although acute bronchitis is caused by viruses at a high rate of 90%, it can rarely be caused by bacteria at a rate of only 10% (1).

Bronchitis can come in a variety of forms, such as acute, chronic, non-obstructive or obstructive, non-allergic or allergic. Acute bronchitis can be defined as inflammation of the tracheobronchial tree. With this inflammation, edema develops in the mucous membrane of the respiratory tract and an increase in bronchial secretion is observed (2). Acute bronchitis can be mostly wheezing, sometimes suppurative or nonsuppurative. It is a disease characterized by fever and cough. In bronchitis, there is inflammation in the bronchi due to viral or bacterial causes.

Treatment of acute bronchitis is usually symptomatic, ibuprofen for analgesia and fever are often used. For chronic bronchitis, the use of albuterol as bronchodilator and inhaled corticosteroids such as methylprednisolone are effective treatments (3).

Rational use of drug (RUD) is defined as a set of rules that ensure patients receive their drugs according to their clinical needs, in the dose that suits their personal needs,

Corresponding Author: Dr Neda Taner
Address: Istanbul Medipol University, School of Pharmacy Department of Clinical Pharmacy, Kavacık South Campus, Göztepe Dist. Atatürk Str. No.40, 34810, Beykoz-Istanbul-Turkey. Tel: +44485442299
Email: ntaner@medipol.edu.tr

in sufficient time, and at the lowest cost for both the society and them (4).

A special procedure should be applied to pediatric patients if the principles of RDU in children are met (5). The FDA has approved only a quarter of the children's drugs on the market as suitable for use in pediatric patients. Although many drugs on the market are not approved for use in infants and children, they appear to be used. This is because studies on pediatric dosage forms are limited and their market shares are small compared to adults (6).

If many pediatric patients take more than one drug for their treatment, this can lead to potential drug interactions. Since pharmacokinetics of the drug differs between adults and pediatrics, pediatric patients are at greater risk for drug interactions than adults. Drug interactions can lead to treatment failure and adverse drug reactions complicating the course and clinical picture of the disease in pediatric clinics.

Considering that pediatric patients are exposed to a high rate of drug-drug interactions, treatment planning based on the principles of rational drug use is expected to significantly reduce the incidence of drug-drug interactions.

In this study to determine the prevalence and severity of possible pediatric drug-drug interactions; the aim is to draw attention to drug-drug interactions in the pediatric population.

Methods

In current study, data from a private hospital in the central district of Rize, Turkey were used. At the time of the data used in our study while 3 pediatricians were in the hospital, one of pediatrician quit his job. Following the application submitted to Ethics Committee for Non-Interventional Research of Istanbul Medipol University, Ethics Committee approval was given unanimously with letter number E108400 72.021617 in dated 05/04/2021 and decision number 397 and 01/04/2021.

For this retrospective study, the necessary permissions and approvals were obtained from the hospital's chief physician in order for us to access the data. This study covers the records among January 2019 and January 2021. The research started with the determination of the inclusion criteria for the selection of the patient group. These criteria were arranged as the patients were in the 2-11 pediatric age range, were diagnosed with bronchitis, and their order included 2 or more drugs. 99 pediatric patients meeting all these criteria were included in our study. The adequacy level of the number of patients included in the study was measured by performing G power factor analysis. In this study, orders of 99 pediatric patients who were hospitalized in this date range were retrospectively analyzed.

In our study, no distinction was made between physicians. Our aim is to investigate whether there is an interaction between the drugs used in the treatment of pediatric patients. Topical drugs, vitamins, and electrolytes were excluded from the study when searching for drug interactions. When testing medicinal products with more than one active ingredient, the number of active ingredients was considered.

The drugs used in the treatment of acute bronchitis and clinical recommendations are shown in Table 1.

Table 1. Pharmacotherapy in the treatment of acute bronchitis and clinical recommendations.

Clinical recommendation	Evidence assessment
Antibiotics should not be routinely used in the treatment of acute bronchitis unless they are of bacterial origin.	B
If people had acute bronchitis, but not pneumonia or tuberculosis, and had been sick for less than 30 days; treatments were antibiotics, including certain examples as deoxycycline, erythromycin, trimethoprim/sulfamethoxazole, azithromycin, cefuroxime, amoxicillin and co-amoxiclav	
The following treatments may be considered to treat bronchitis-related symptoms:	
Antitussives (dextromethorphan, codeine, hydrocodone) / 6 years and older	C
Beta-agonist inhalers/wheezing patients	
High-dose inhaled corticosteroids	B
Echinacea	B
Pelargonium	B
Dark honey	B
The following drugs should not be used to manage symptoms associated with bronchitis:	
Expectorants	B
Beta-agonist inhalers/patients without wheezing	B
Antitussives/under six years old	C

A = consistent, quality patient-centered evidence; B = patient-centered evidence of inconsistent or limited quality; C = consensus, evidence for disease, usual practice, expert opinion, or case series. (23)

Eligible patients for our study were selected by reviewing patients' retrospective medical records from the hospital pharmacy's Meddata database. Then the name, surname, gender, age, drug number in the medication list of the selected patients were transferred to a file and saved. The drug Interactions section of the Medscape database was used to search for drug interactions in the patients included in our study. Drug interactions were reviewed for each patient in the Medscape database by clinical pharmacists.

Interactions have been divided into three main groups based on their severity; starting with,

1. Serious (Use alternative),
2. Should be monitored (Monitor Closely),
3. Minor (Minor) and, added to patient information records that were previously created.

Three different programs have also been used to verify these interactions and the accuracy of the interactions has been confirmed. These Programs Are: Drugs.com, Rx Media Pharma, Drugbank Online.

SPSS 15.0v. for Windows was used for statistical analysis. Descriptive statistics; numbers and percentages for categorical variables and numeric variables such as mean, standard deviation, minimum, maximum, median, interquartile range. As the numeric variables did not satisfy the normal distribution condition, Mann Whitney's U test was used in two groups and Kruskal Wallis' test was used in more than two groups. Mann Whitney's U test was used in the subgroup analysis. In our study, the alpha statistical significance level was accepted as $p<0.05$.

Results

This study was conducted on 99 pediatric patients aged 2-11 years hospitalized for more than 24 hours, diagnosed with bronchitis. Of the patient group, 48.5% were male and 51.5% female. The number of drugs in the patient order was 5.44 ± 1.97. The age ranges were 29.3% 3 and under, 47.5% 4-6, 23.2% 7 years and over. Groups of drugs based on the severity of the interaction are shown in Table 2.

Table 2. Interactions seen in drug groups according to severity

Interaction grades	Interactions	n	%	Mechanism	Formulation
Serious-Use Alternative	Clarithromycin+Methylprednisolone	16	16.16	effecting CYP3A4 metabolism	suspension,vial
	Clarithromycin+Methylprednisolone	1	1.01	increase QTc interval	suspension,vial
Monitor Closely	Potassium Chloride+Albuterol	50	50.5	albuterol decreases the serum potassium	vial, inhalation
	Clarithromycin+Montelukast	11	11.1	affecting CYP3A4 metabolism	suspension, tablet
	Claritromycin+Mometasone	4	4.04	affecting CYP3A4 metabolism	suspension, nasal
	İbuprofen+Albuterol	2	2.02	decrease serum potassium	suspension, inhalation
	İbuprofen+Methylprednisolone	2	2.02	increased risk of GI ulceration	suspension, vial
	Clarithromycin+Fluticasone	2	2.02	affecting CYP3A4 metabolism	suspension, inhalation
	Albuterol+Terbutalin	1	1.01	decrease serum potassium	inhalation
Minor	Methylprednisolone+Montelukast	20	20.2	affecting CYP3A4 metabolism	vial, tablet
	Methylprednisolone+Lansoprazol	1	1.01	affecting CYP3A4 metabolism	vial, capsule

As was mentioned in Table 1, Table 2 indicates the records of bacterial infections being diagnosed as the cause of bronchitis in prescriptions interacting with antibiotics.
In this study, the number of interactions was positively correlated with the number of drugs ordered ($p<0.001$). No statistically significant correlation was found between the number of interactions and age ($p=0.271$). The relationship is shown in Table 3.

Table 3. The relationship between the number of interactions and the number of drugs and age.

	Number of Interactions	
	r	*p**
Age	0.113	0.265
Number of Medicines	0.718	<0.001

* Spearman Correlation Analysis

Pediatric patients are exposed to multiple medications during their hospital stay (7). Polypharmacy is defined as the simultaneous use of several drugs. Polypharmacy is a significant risk factor for the development of drug-related adverse drug reactions events in the pediatric population (8). While drug interactions lead to treatment failure and increased side effects, adverse drug reactions are the leading cause of increased morbidity and mortality (9). Although no interactions were observed in some patients in this study, there were also patients with up to 4 interactions. These numerical interaction ratios are shown in Figure 1.

Figure 1. Ratios of interaction counts.

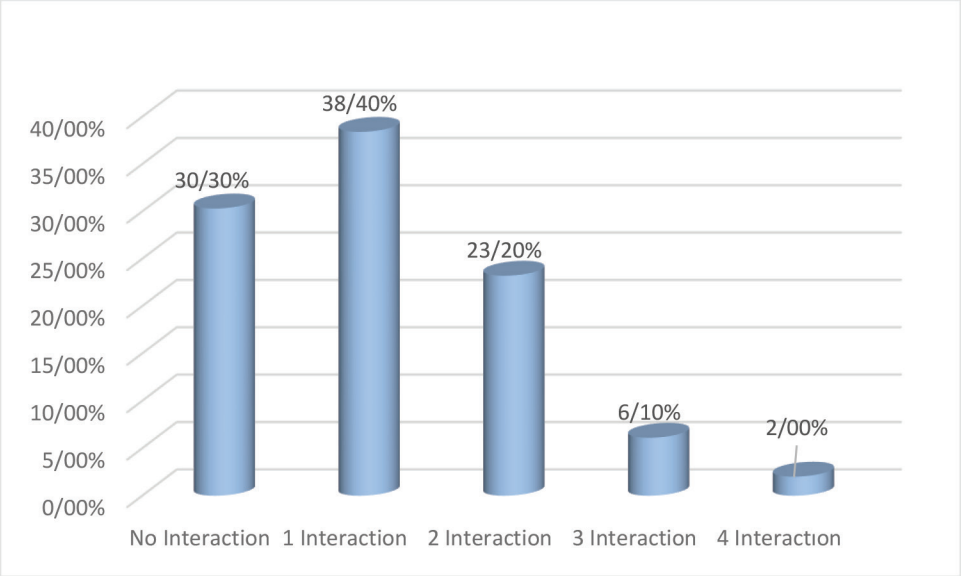
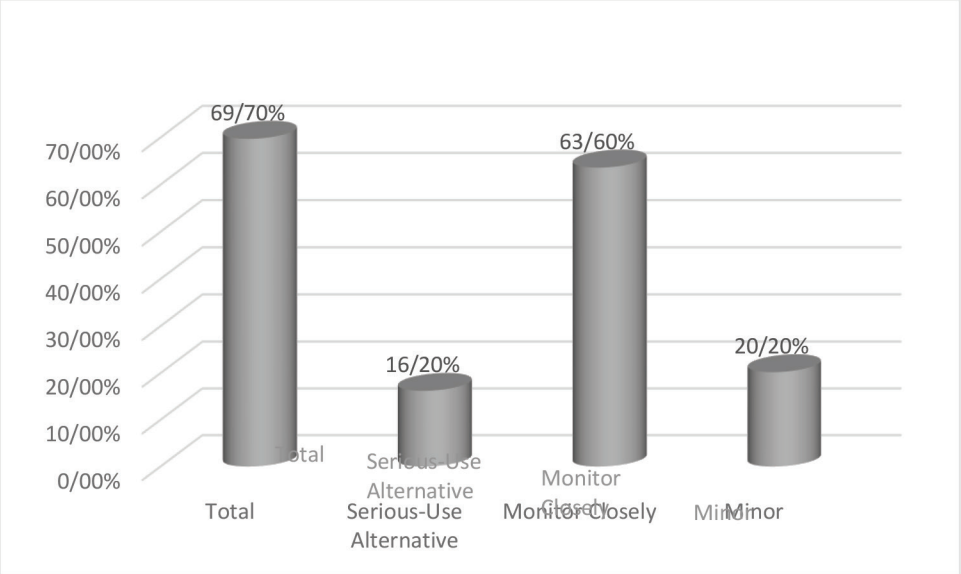


Figure 2. Presence relationship of numbers and interaction types.



Discussion

A pediatric retrospective study reported that pediatric ICU patients were exposed to an average of 10 different medications per day (10,11). In a study in the United States, it was shown that approximately 41% of hospitalized children were exposed to a potential drug interaction, considered important (12).

A total of 99 pediatric patients were included in our study and the average number of medications per patient was found to be 5.44 ± 1.97. In another study, this rate was 4.6

± 2.8 (13) since the number of drugs per patient is close to our study. Moreover, a statistically significant difference was found in the number of drugs in the treatment protocol according to the age groups of our study (p = 0.001).

In this study, patients ranged in age from 2-11, 29 individuals aged 3 years and younger, 47 individuals aged 4-6 years and older, and 23 individuals aged 7 years and older with composite gender percentages of 48.5% male and 51.5% female. In several similar studies, the profile of female patients was found to be close to the rate in our study and higher than that of male patients (14-15).

In this study, which aimed to assess drug interactions in hospitalized pediatric patients, interactions were detected in 69.7% of patients and no interactions were observed in 30.3% of patients. 16.2% of these interactions are serious, 63.6% are monitored and 20.2% are minor. Another study found these rates to be 17% severe, 56% moderate, and 27% mild (16). Terzioglu et al., Holm et al., and Choi et al., a similar interaction rate was observed with our study based on severity classification (17-19).

The average number of interactions per patient was found to be 1.11 ± 0.98 with at least 1 and at most 4 interactions, and this result was also supported by the study result of Medina Barajas et al., (13). This result indicates that the rates of drug interactions per patient are close on average. However, in order to come to a clearer conclusion, it would be correct to compare the results of studies conducted on large populations.

An increase in the number of prescription drugs is a risk factor for adverse drug reactions (20). In our study, the number of interactions observed in patients was found to be positive and statistically significant correlated with the number of drugs in the order. In the study by Terzioğlu et al., the highest interaction was observed in prescriptions containing 3-4 drugs (12). Based on these results, it can be stated that as the number of drugs used in the treatment of patients increases, the frequency of the interaction also increases.

When we review the data of our study, it was determined that the drug pair with the greatest interaction was potassium chloride and albuterol. Methyl prednisolone-montelukast is second, followed by the drug pairs clarithromycin-methyl prednisolone.

In our study, it was observed that no interaction was observed in 30.3% of patients. When these patients were examined in more detail, it was noted that they were ambulatory patients and that the combination dexamethasone + epinephrine was mainly used in their treatment to open the airways and relieve breathing.

Today, the incidence of potential drug interactions continues to increase day by day. Drug interactions are important contributors to the prevention of morbidity and mortality in healthcare settings (21). In the literature, there has been a significant increase in the use of vitamins in children and adults in recent years. Vitamins are substances with important pharmacological activities. They can cause drug interactions by interacting with other drugs used by the patient (22) The rate of potential vitamin interactions was studied in a cross-sectional study conducted in Canada from this study concluded that more than one-third of children had more than one potential interaction (22,23). As vitamins were excluded from the study, this question was not mentioned.

Most often, drug interactions (DDI) are the cause of adverse drug reactions. Drug interaction follow-up by the pharmacist is an important issue. The role of pharmacists is to facilitate the maintenance, development and ongoing evaluation of risk reduction programs of ADRs by detecting, evaluating and reporting suspected ADR cases. This was demonstrated by a new study which concluded that the ADR report is an essential part of monitoring and evaluating the activities carried out in hospitals (24).

Likewise, in our retrospective study, we evaluated drug interactions in 2-11-year-old pediatric patients diagnosed with bronchitis. As a result of our study, it was found that there were mostly moderate drug interactions as well as severe interactions, which do not need to be counted. When reviewing the literature for our research, the paucity of drug interaction studies in pediatric patients became apparent. As our study is limited to bronchitis and a certain age group, it is believed that drug interactions in pediatric patients can be interpreted more accurately if large studies are conducted, including more patient populations, diverse group'sdrugs and various diseases.

Contemporary pharmacy services include all aspects of clinical pharmacy services as a major theme. Thus, all the professional divisions, from the community pharmacy to the hospital pharmacy, essentially bring together clinical pharmacy services. In this context, the pharmacist, as a member of the multidisciplinary team, can make a significant contribution by monitoring the prescribed treatment and detecting interactions, to reducing drug-related problems and optimizing the pharmacotherapy of these patients.

There are two basic processes for pharmacists to play a protective role in managing drug interactions. The first is the communication and mutual consultation process that must be maintained with physicians during clinical intervention processes (prescription or post-prescription). The second is to inform the patient about drug interactions by the pharmacist during the pharmaceutical care services that must be provided to the patient. When all of these processes are generally challenged to answer what pharmacists should do about drug interaction management options, "what to do" should include the following as clues: Understand and evaluate an approach on how to completely avoid the drug interaction; Know how to adjust the dose of the drugs; Give appropriate information about spaced dosing times to avoid interactions; Monitoring for early diagnosis; Provide information about the patient's risk factors that increase the risk of a negative outcome; Improve computerized screening systems; Select the appropriate clinical outcome from the excessive number of drug interactions on systems; Understand differences

in drug classes that are not managed properly.

Based on the results of this study, it can be concluded that the majority of patients are exposed to drug interactions with a moderate majority. In particular, as in the drug couple potassium chloride and albuterol, the drug should be used with caution and monitoring from such interactions. At the same time, there are serious interactions that cannot be counted as little observed in the couple clarithromycin and methylprednisolone, it is recommended to use alternative drugs.

This study concluded that as the number of drugs in the prescription increases, so does the number of drug interactions. For this reason, it is believed that when the minimum and most effective number of drugs is used, the frequency of drug interactions decreases. This should be considered when planning drug treatment.

The results of this study do not retrospectively include medical-pharmaceutical clinical collaboration. It turns out that drug combinations in prescriptions prescribed by doctors cause drug interactions, and no information is received from pharmacists as awareness. Therefore, it can be concluded that there is no shared role between physicians and pharmacists in ensuring patient safety in terms of hospital pharmacy and clinical pharmacy services. The basis for this inference is understood from the drug combinations used in the treatment. Drug interactions that can be easily avoided and managed with the cooperation of doctors and pharmacists have not been prevented. Again, this finding indirectly demonstrates the importance of clinical pharmacy services in terms of medical practices and health economics.

Finally, the healthcare sector is an area that needs to be done collaboratively and with care. Physician, pharmacist and nurse stakeholders need to work together and communicate to reduce the occurrence of adverse events and drug interactions. The workload of health workers is quite high due to the intensity of work and the lack of personnel. To facilitate this communication, a section warning of drug interactions that may occur in the patient can be added to the system. Only services that assess drug interactions in the treatment of patients can be housed in hospital pharmacy units. This is important in terms of reducing physician workload and increasing patient efficiency from treatment. At the same time, educational seminars and conferences can be organized for healthcare professionals to show the necessary importance of drug interactions.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

References

1. Fleming DM, Elliot AJ. The management of acute bronchitis in children. Expert Opin Pharmacother. 2007;8(4):415-426.
2. Bülbül, Y. Akut bronşit tedavisi. Treatment of acute bronchitis. Avaibile from: https://verem.org.tr/uploads/pdf/23kongre/akut_bronsit.pdf Accesed May 06, 2021.
3. Carolan PL. Pediatric bronchitis. Avaibile from: https://emedicine.medscape.com/article/1001332-overview Accesed May 26, 2021.
4. Alp H, Türk S, Yılmaz S, MutluTiryaki Ü, Yiğitbaşı M. Rational drug use. Mustafa Kemal Üniversitesi Tıp Dergisi. 2018; 9(33): 20-28.
5. Karataş N, Kaya A, İşler A. Akılcı ilaç kullanımın çocuk sağlığına etkileri. The effects of rational drug use onchild health. 2 nd International Health Sciences and Life Congress. 2019
6. Baktır G, Pala Z. Çocuklarda ilaç kullanımı. Medication use in pediatrics. Meslek İçi Sürekli Eğitim Dergisi. 2012; 60-68.
7. Matthys H, Kamin W, Funk P, Heger M. Pelargonium sidoides preparation (EPs 7630) in the treatment of acute bronchitis in adults and children. Phytomedicine. 2007;14 Suppl 6:69-73.
8. 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(1):e99-e108.
9. Yeh ML, Chang YJ, Yeh SJ, et al. Potential drug-drug interactions in pediatric outpatient prescriptions for newborns and infants. Comput Methods Programs Biomed. 2014;113(1):15-22.
10. Salerno SN, Burckart GJ, Huang SM, Gonzalez D. Pediatric Drug-Drug Interaction Studies: Barriers and Opportunities. Clin Pharmacol Ther. 2019;105(5):1067-1070.
11. 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(5):e218-e228.
12. Bebitoğlu BT, Oğuz E, Nuhoğlu Ç, et al. Evaluation of potential drug-drug interactions in a pediatric population. Turk Pediatri Ars. 2020;55(1):30-38.
13. Medina-Barajas F, Vázquez-Méndez E, Pérez-Guerrero EE, et al. Pilot study: Evaluation of potential drug-drug interactions in hospitalized pediatric patients. Pediatr Neonatol. 2020;61(3):279-289.
14. Holm J, Eiermann B, Kimland E, Mannheimer B. Prevalence of potential drug-drug interactions in Swedish pediatric outpatients. PLoS One. 2019;14(8):e0220685. Published 2019 Aug 5.
15. Chen Y, Liu J, Larson E. Temporal trends and factors associated with pediatric hospitalizations with respiratory infection. J Asthma. 2016;53(1):15-18.
16. Işık M N, Dalgıç N, Okuyan B, Yıldırmak ZY,

Sancar M. Hastanede yatan pediatrik hastalarda ilaç tedavisinin incelenmesi: klinik eczacı önerileri. Evaluation of drug therapy in hospital pediatric patients: Recommandation of clinical pharmacists. J Pediatr Inf. 2020;14(4):237-243.

17. Martinbiancho J, Zuckermann J, Dos Santos L, Silva MM. Profile of drug interactions in hospitalized children. Pharm Pract (Granada). 2007;5(4):157-161.
18. Choi YH, Lee IH, Yang M, et al. Clinical significance of potential drug-drug interactions in a pediatric intensive care unit: A single-center retrospective study. PLoS One. 2021;16(2):e0246754.
19. Andrade PHS, Santos ADS, Souza CAS, Lobo IMF, da Silva WB. Risk factors for adverse drug reactions in pediatric inpatients: a systematic review. Ther Adv Drug Saf. 2017;8(6):199-210.
20. Day RO, Snowden L, McLachlan AJ. Life-threatening drug interactions: what the physician needs to know. Intern Med J. 2017;47(5):501-512.
21. Goldman RD, Vohra S, Rogovik AL. Potential vitamin-drug interactions in children: at a pediatric emergency department. Paediatr Drugs. 2009;11(4):251-7.
22. Yu SM, Kogan MD, Gergen P. Vitamin-mineral supplement use among preschool children in the United States. Pediatrics. 1997;100(5):E4.
23. Albert RH. Diagnosis and treatment of acute bronchitis. Am Fam Physician. 2010;82(11):1345-1350.
24. Alqurbi MMA, Atiah MAQ. The role of clinical pharmacists in reducing adverse drug reactions. Int J Med Developing Countries. 2020;4(1):236–239.

PLEASE CITE THIS PAPER AS:

Taner N, Eskitoğlu M, Şirin B. Evaluation of Potential Drug-Drug Interactions in Hospitalized Pediatric Patients with Bronchitis Diagnosis: A Retrospective Study. J Pharm Care 2023; 11(1): 25-31.