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Evaluation of the frequency and characteristics of drug hypersensitivity reactions in hospitalized children: Real life-cohort study

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ABSTRACT

Introduction: There are limited data regarding the characteristics and management of drug hypersensitivity reactions (DHR) in hospitalized children. This study aims to determine the prevalence, clinical features, and management of DHRs in pediatric inpatients.

Methods: Children who had pediatric allergy consultation for suspected DHR during hospitalization in Ankara Bilkent City Hospital between August 1, 2020, and July 30, 2021, were included. Patient and reaction characteristics, culprit drugs, and management strategies were recorded. When possible, diagnostic tests (skin or provocation tests) were performed after discharge.

Results: Among the 14,090 hospitalized children, 165 (72% male, median age: 106 months) underwent consultation for 192 suspected DHRs with 246 drugs. Cutaneous eruptions were the most common (94.3%). There was anaphylaxis in 40 patients and severe cutaneous adverse drug reaction in 4 patients (drug rash with eosinophilia and systemic symptoms in 3, acute generalized exanthematous pustulosis in 1). Antimicrobials were the leading cause (78.4%, n = 193/246). In 48 reactions, 60 (24%) culprit drugs could be readministered with close follow-up or desensitization (n = 12). In total, 186 suspected drugs were discontinued, and 115 were replaced with alternative drugs. After discharge, 38 provocation tests (2 positives) and 36 skin tests (1 positive prick test, 1 positive intradermal test, and 1 positive patch test) were performed.

Discussion/conclusions: The incidence of suspected DHR among pediatric inpatients was approximately 1.1%. Skin symptoms were the most common manifestation. Twenty-four percent of suspected drugs could be continued during hospitalization. Patients with DHR during hospitalization should be evaluated with a drug allergy work-up unless there are contraindications to testing.

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INTRODUCTION

Adverse drug reactions (ADR) were reported in 10–20% of hospitalized patients. Only 3% of patients encountered a new ADR in the hospital.[1] Drug hypersensitivity reactions (DHR) is a significant health problem for inpatients, causing life-threatening reactions, prolonged hospital stays, and necessitating the use of broader spectrum and more expensive drugs.[1,2] Few studies on DHR, which occurred *de novo* at the hospital, and their management in pediatric inpatients have been published.[3,4]

Our first aim was to contribute to the literature by documenting the patient and reaction characteristics of pediatric inpatients with an allergy/immunology consultation for suspected DHR in Ankara Bilkent City Hospital during 1 year and the frequency of new-onset DHR in inpatient children. Our second aim was to evaluate difficulties in the diagnosis, treatment, and management of DHR in inpatient children.

METHODS

Study population

Ankara Bilkent City Hospital is the largest tertiary pediatric hospital in Turkey, with 700 beds, including all pediatric subspecialties. All patients aged 0–18 years admitted to Ankara Bilkent City Hospital between August 1, 2020, and July 30, 2021, and received consultation from the Pediatric Allergy/Immunology Clinic for suspected DHR during their present hospitalization were included. The patients were followed up during hospitalization, after which their diagnostic tests were planned; follow-up was continued in the allergy outpatient clinic.

Study procedures

The same physicians recorded the patients' socio-demographic characteristics, reasons for hospital admission, characteristics of the suspected allergic reaction, and information related to the suspected culprit drug using the standard DHR questionnaire.[5] Complete blood count (CBC), liver and kidney function tests, acute phase reactants, tryptase, specific IgE (penicillin V, penicillin G, ampicillin, and amoxicillin) [only for immediate reactions], viral serology, and skin biopsy results were recorded.

Consent was obtained from the families (and patients $>$ 9 years) for participation in the study and all diagnostic tests. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision number: E1-20-863).

Classification of reactions

Drug reactions were primarily classified based on time of onset (at or within 1 h of drug intake, after 1–6 h, and after $>$6 h) and categorized as immediate or non-immediate.[6,7] Anaphylaxis and its severity were defined according to the criteria stated in the European Academy of Allergy & Clinical Immunology (EAACI) position paper and World Allergy Organization (WAO) anaphylaxis guidance 2020, Drug rash with eosinophilia and systemic symptoms (DRESS) was defined according to the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, and acute generalized exanthematous pustulosis (AGEP) was investigated according to the EuroSCAR scoring system.[8–10] Other cutaneous manifestations (Symmetrical drug-related intertriginous and flexural exanthema, fixed drug eruption, maculopapular exanthema [MPE], Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]) of drug hypersensitivity were defined according to the EAACI position paper criteria.[11]

Adverse drug reaction probability scale (Naranjo score)

Total scores range from -4 to $+13$; the reaction was considered definite if the score was 9 or

higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.[12]

Identification of suspected drugs

Suspected drugs were defined as those taken in the preceding <1 h for patients with immediate reaction findings (1– 24h for non-steroid antiinflammatory drugs [NSAİD] reactions), after >1 h and within the last ≥1 day for patients with MPE, within 2–6 weeks for DRESS, within 4–28 days for SJS/TEN, and within 1–12 days for AGEP.[6]

Contributing factors and laboratory investigations during hospitalization

In patients with anaphylaxis, tryptase was analyzed within the first hour of the reaction. Tryptase was accepted as high if it was >11.4 or 1.2x basal tryptase + 2 ng/ml.[10] In patients for whom viral infection could not be ruled out, viral serology (COVID-19, parvovirus, cytomegalovirus [CMV], Epstein-Barr virus [EBV], hepatitis, and respiratory viral panel) was performed.

In-hospital approach after drug reactions

The patients were followed and treated according to protocols based on international guidelines, especially EAACI/European Network on Drug Allergy (ENDA) and our national guidelines, and modified according to the patient's conditions.[13–17] If DHR was suspected, the primary approach was to perform a risk/benefit analysis, in order to decide to discontinue the suspected drug and use a non-cross-reactive alternative.[6] However, in some patients, the suspected drug could not be discontinued or was re-administered after interruption. In patients with mild or subjective symptoms, the drug was resumed after testing the initial dosage with a two-step graded challenge test (we gave 1/10 of the dosage, and after 30 min, if there were not any reactions, we gave 9/10 of the dosage).[7,18] In patients with mild reactions and no signs of danger, the drug was continued using the "treating-through" approach.[19,20] If a DHR was strongly suspected, the reaction was immediate and moderately severe (signs of anaphylaxis or acute recurrent generalized urticaria), and no suitable alternative was available, the drug was re-administered after desensitization according to an EAACI protocol or other effective protocol from the literature.[16] Desensitization was not attempted in severe cutaneous adverse drug reactions (SCAR).

Allergological work-up

Patients whose drug(s) were discontinued at the time of reaction were invited for outpatient follow-up and diagnostic testing after discharge. Diagnostic tests were scheduled for 4–6 weeks after non-severe DHR and 6 months after DRESS reactions. Diagnostic tests were not performed on patients with anaphylaxis who were desensitized during hospitalization, with severe reactions, or when consent could not be obtained.

Diagnostic testing could not be performed on patients who died, were medical tourists, or underwent bone marrow transplantation after the reaction. Patients with immediate reactions other than anaphylaxis were tested using prick and intradermal tests with the culprit drug(s). Drug provocation tests (DPT) were performed only if these tests were negative. Skin prick, intradermal, or patch testing was performed using the doses recommended in the EAACI guidelines.[21]

The ENDA guidelines were used to determine indications, contraindications, and administration of DPT.[15] In case of any reaction during a challenge, the test was terminated immediately, appropriate interventions were provided, and the test was considered positive.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY). Categorical values were not normally distributed and were presented as the median and interquartile range (IQR; 25th–75th percentiles). The χ^2 square test was used to compare nonparametric data; the Mann-Whitney U test was used for comparisons among non–normally distributed continuous variables and independent samples t test for normally distributed continuous variables. A p-value of <0.05 was considered significant. Predictive factors were analyzed with univariate and multivariate logistic regression analysis. The multivariate logistic regression analysis included variables with $p < 0.2$ in the univariate analysis and factors thought to be predictive of adverse drug hypersensitivity reaction occurrence during hospitalization. The results

are expressed as odds ratio (OR) and 95% confidence interval (CI).

RESULTS

During the study period, 14,090 children had 24,627 admissions to our hospital. Of these inpatients, 58.1% (n = 8181) were male; the median age was 3 years (IQR: 0–11), and the median length of hospital stay was 3 days (IQR: 1–6).

The study included 165 inpatients (1.1%) who had consultations for 192 suspected DHRs (0.77% of all hospitalizations, n = 192/24,627). Five patients had reactions to different drugs on 3 different dates; 17 patients had reactions to different drugs on 2 different dates.

The study group (n:165) was 72% male (n = 119/165), and the median age was 10.2 years (IQR: 3.9–15.4 years) (Table 1).

The most common reasons for hospital admission were infectious diseases (36.4%) and hemato-oncological diseases (30.7%); others were surgical diseases (12.5%), neurology (5.2%), metabolism (1%), allergy immunology (4.7%), nephrology (2.1%), cardiology (4.2%), and gastroenterology (3.1%) related diseases.

Characteristics of reactions

The median reaction time between ingestion of the drug and occurrence of the reaction was 5 min (IQR 1–120 min). Reactions occurred during or within the first hour of taking the suspected drug in 121 patients and more than 6 h later in 27 patients (Table 2).

Skin findings were most common during the reaction (94.3%; n = 181/192). Of the patients with only cutaneous symptoms (n = 149, 77.6%), the most common symptom was isolated MPE (n = 66), followed by isolated urticaria (n = 52). Reactions with only urticaria were more likely than those with only MPE to occur with non-antibiotic drugs (28% vs. 9%, $p = 0.021$) and were less likely to have multiple-drug reactions (17% vs. 33%, $p = 0.043$).

A total of 40 anaphylaxis reactions (21 severe, 16 moderate, and 3 mild) were detected in 38

Sex (male), n (%)	119 (72)
Age at reaction (years), median (IQR)	10.2 (3.9–15.4)
Distribution of age at reaction n (%)	
0–24 month	43 (26.1)
25–71 month	25 (15.2)
72–143 month	43 (26.1)
≥144 month	54 (32.7)
Chronic diseases, n (%)	102 (61.8)
Allergic diseases, n (%)	29 (17.6)
Atopic dermatitis	10 (6.1)
Asthma	12 (7.3)
Allergic rhinitis	7 (0.1)
Food allergy	6 (3.6)
Previous drug allergy, n (%)	22 (13.3)
Drug allergy in family, n (%)	5 (3)
Allergic diseases in family, n (%)	18 (10.9)

Table 1. Demographic characteristics (n = 165)

Time from drug intake to reaction onset (hours), n (%)	
≤1	124 (64.5)
>1–6	43 (22.3)
>6	25 (13)
Type of reaction, n (%)	
Only cutaneous involvement	**148 (77.1)**
Urticaria	52
Angioedema	13
MPE	66
Rash	26
Anaphylaxis	**40**
- according to WAO and EAACI criteria	36
- according to WAO criteria	4
- **SCAR**	**4**
- DRESS	3
- AGEP	1
Day of inpatient at the time of reaction	8 (2–24.5)

Table 2. Characteristics of reactions (N = 192) *AGEP, Acute generalized exanthematous pustulosis; DRESS, Drug rash with eosinophilia and systemic symptoms; MPE, Maculopapular exanthema*

patients. Culprit drugs were 17 antibiotics (3 vancomycin, 2 ceftriaxone, 2 amikacin, 1 sulperazon, 1 clindamycin, 1 ertapenem, 1 meropenem, 1 ciprofloxacin, 4 ampicillin, 1 metronidazole), 6 antifungal (4 amphotericin-B, 1 fluconazole, and 1 voriconazole), 9 chemotherapeutics (4 L-asparaginase, 1 peg-asparaginase, 1 anti-tymocyte globulin [ATG], 1 clofarabine, 1 busulfan, 1 ATG), 3 biological agents (2 rituximab, 1 infliximab), 1 enzyme (idursulfase), 1 NSAID (ibuprofen), 2 Proton pump inhibitors (2 omeprazole), and 1 ranitidine in anaphylaxis reactions. Tryptase was tested in 39 reactions (median: 5.5 IQR: 2.9–9.9). However, tryptase was elevated in 6 patients (median: 19.5 IQR: 11.8–20.5).

SCAR was detected in 4 patients, DRESS in 3 patients, and AGEP in 1 patient. Details of the patients with SCAR are shown in Table 3.

Comparison of patients with and without chronic diseases

Anaphylaxis was more frequent (23.7% vs. 10%), but MPE was less frequent (28% vs. 44%) in patients with chronic diseases than in patients without chronic diseases (p: 0.021, 0.029, respectively). In addition, reactions with antibiotics were less frequent in patients with chronic diseases than those without chronic diseases ($p < 0.001$).

Viral serology and laboratory results

Viral serology was examined in 67 patients. Viral infection was detected in 23 (COVID-19 n:9, mycoplasma n:4, parvovirus n:2, adenovirus n:2, EBV n:2, CMV n:2, and enterovirus/rhinovirus n:2) (supplement Table 1). Of these 23 patients, the drug was discontinued without replacement in 10 patients, 2 patients were able to continue the current medication, and 11 were switched to an alternative drug.

Suspected drugs

During the study, 382,099 individual drugs were used for inpatient children. The ratio of drugs associated with suspected DHR to the total number of drugs used in the hospital was 0.06% (n = 246/382,099) (Fig. 1).

Types of SCAR	Age (year)/ gender	Cause of hospitalization	Suspected Drug (day of using drug)	RegiSCAR or EuroSCAR score	Symptoms and laboratory findings	Treatment	Allergy Test after discharge
DRESS 1	8/M	Pneumonia	Teicoplanin (16)	7	Fever MPE Eosinophilia Viral serology:negative ALT/AST:high Biopsy+	Prednisolone	Teicoplanin patch planned
DRESS 2	8/M	Urinary tract infection	SAM (23) Cefotaxime (8)	6	Fever MPE Eosinophilia Atypic lymphocyte Viral serology:negative ALT/AST: high	Prednisolone	SAM patch: negative
DRESS 3	11/M	Osteomyelitis	SAM (29) Teicoplanin (9)	6	Fever MPE Eosinophilia Atypic lymphocyte Viral serology:negative ALT/AST: high	Prednisolone	SAM and Teicoplanin patch planned
AGEP 1	6/M	Meningitis + urinary tract infection (operated spina bifida)	Vancomycin (7) Meropenem (6) Amikacin (6)	9	Fever Typical pustules Typical erythema Typical distribution Postpustular desquamation No mucosal involvement PMNL = 12,000/mm^3 Resolved <15 days	Topical steroid	Meropenem reused (in another hospital) Vancomycin patch negative Amikacin patch positive

Table 3. Characteristics of patients with severe cutaneous drug reactions (n = 4). *AGEP, Acute generalized exanthematous pustulosis; DRESS, Drug rash with eosinophilia and systemic symptoms; F, female; M, male; PMNL, poly morpho nuclear leucocyte; SAM, Sulbactam ampicillin*

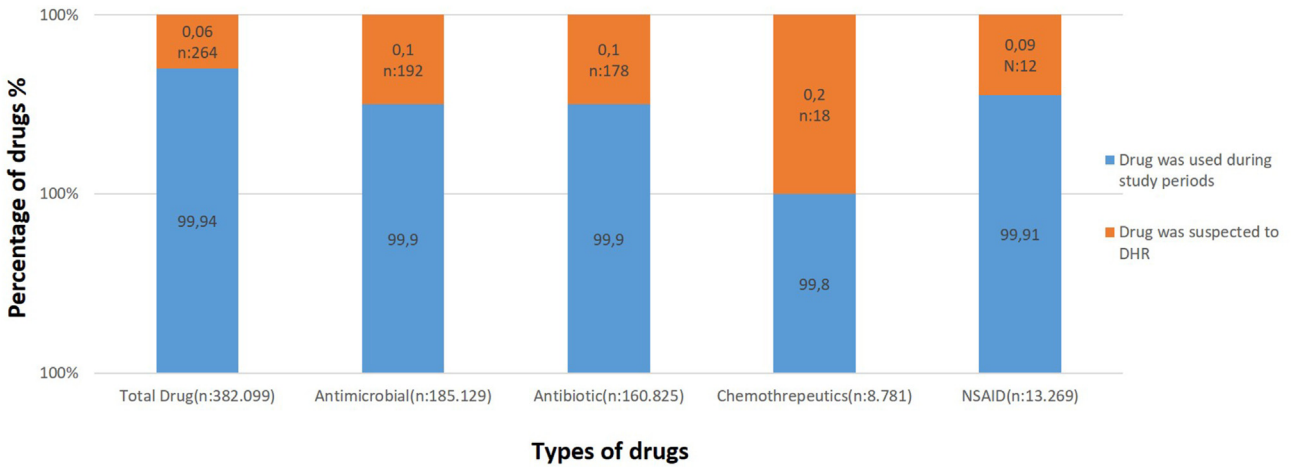

Fig. 1 Ratios of suspected drugs to total number of drugs used

In 177 (92%) of the 192 reactions, the patients had received multiple drugs. Although a single drug was administered at the time of reaction in 151 (78.6%), there were multiple suspected drugs in 41 reactions (21.3%) because more than 1 drug was given consecutively before the reaction (4 drugs in 2 reactions, 3 drugs in 9 reactions, and 2 drugs in 30 reactions). Therefore, there were 246 suspected drugs for the 192 reactions. Suspected drugs were most frequently antimicrobials (78%, n = 192/246), especially antibiotics (72.3%, n = 178/246) (Table 4). Reactions in patients using multiple drugs were most commonly associated with combinations of antibiotics (n = 31), followed by antibiotics and NSAID combinations (n:8).

Approach and treatment at the time of the drug reaction

Symptomatic treatment was provided with antihistamines in 166 (86.5%), steroids in 66 (34.4%),

Types of drugs	All reactions, n (%) (n = 246)	Reactions with single drug (n = 151)	Reactions with multiple drugs[a] (n = 95)
Antimicrobials	192 (78)	108 (71.5)	84 (88)
Antibiotics	178 (72)	98 (64.9)	80 (84)
Beta-lactam	101 (41)	63 (41.7)	38 (40)
Non-beta-lactam	77 (31)	35 (23)	42 (44)
Antifungal	12 (4.8)	8 (5)	4 (4.2)
Antiviral	2 (0.8)	2 (13)	-
Chemotherapeutics	18 (7.3)	16 (10.5)	2 (2)
NSAIDs	13 (5.2)	6 (3.9)	7 (7)
Antiepileptics	7 (2.8)	6 (3.9)	1 (1)
Biologics	5 (2)	5 (3.3)	-
PPI or H2 Blockers	4 (1.6)	4 (2.6)	-
Others[b]	7 (2.8)	6 (3.9)	1 (1)

Table 4. Types of drugs responsible for hypersensitivity reactions. *NSAID, Non-steroidal anti-inflammatory drug; PPI, Proton pump inhibitor.* [a]*Total 95 suspected drugs in 41 reactions (2 drugs in 30, 3 drugs in 9, and 4 drugs in 2 reactions).* [b]*Anesthetics (n = 2), enzyme (n = 1), N-acetylcysteine (n = 1), allopurinol (n = 1), ilioprost (n = 1), iohexol (n = 1)*

salbutamol in 3 (1.6%), and epinephrine in 36 reactions (all anaphylaxis). Four reactions required transfer to intensive care.

A total of 186 drugs suspected in 148 reactions were discontinued, and 115 were substituted with alternative drugs. Sixty suspected drugs in 48 reactions could not be discontinued.

In 13 (6.7%) reactions with low suspicion of DHR, 14 drugs (4 meropenem, 2 vancomycin, 1 teicoplanin, 1 voriconazole, 1 diazepam, 1 sulbactam ampicillin, 1 sulperazon, 1 cefotaxime, 1 ATG, 1 rituximab) could be reintroduced with a two-step graded challenge. All these reactions involved only cutaneous symptoms.

In 23 (13.9%) patients who had MPE suspected to be DHR, but no danger signs and when the drug was absolutely necessary, 34 drugs could be continued using the treating-through strategy. Median ages were 4.5 (1.5–12) years; 65% were male (n:15/23). These patients were hospitalized for hemato-oncological diseases (n:8), surgical disease (n:7), infectious disease (n:4), cardiological disease (n:2), and neurological disease (n:2). Maculopapular eruption was the only symptom in all reactions. There were no other symptoms. The median number of days of drugs used at the time of reaction was 4 (IQR: 2–7). The median time interval between drug intake and reaction occurrence was 30 min (IQR: 5–180 min); 17 reactions occurred with a single drug, 6 with multiple drugs (1 with 4 drugs, 3 with 3 drugs, and 2 with 2 drugs). Of the reactions, 27 occurred with antibiotics, 2 with antiepileptics, 2 with chemotherapeutics, 1 with NSAID, 1 with iloprost, and 1 with antifungal drugs. Treating through was used successfully in all.

In 12 (6%) reactions (anaphylaxis n:8, recurrent generalized urticaria n:4) with a high suspicion of DHR to a necessary drug with no alternative, 12 drugs (3 ATG, 2 rituximab, 2 amphotericin-B, 2 infliximab, 1 clofarabine, 1 idursulfase, and 1 busulfan) were administered with desensitization.

Post-discharge allergological work-up

Specific-IgE (penicillin G, penicillin V, ampicillin, amoxicillin) was negative in 45 immediate reactions. Skin tests were performed with 36 drugs. There was 1 positive prick test with lansoprazole (esomeprazole was identified as an alternative drug by challenge) and 1 positive intradermal test with omeprazole (1:10 dilution was positive; lansoprazole was identified as an alternative drug by challenge after a negative skin test). There was 1 positive patch test (for AGEP) with amikacin (2.5 mg/ml). (Supplement Table 2: showed skin test concentrations of drugs).

DPT was performed with 38 drugs (in 31 reactions), and 2 tests were positive, both with cefpodoxime (used for ceftriaxone-induced reactions because it has a side chain similar to ceftriaxone and can be used orally). (Supplement 2: showed dosage of DPT).

Final status of suspected multiple-drug allergy

The median Naranjo scores of the patients were 5 (IQR: 4–7). The Naranjo score was detected >9 (definite) in 18 patients, from 5 to 8 (probable) in 115 patients, and between 1 and 4 (possible) in 59 patients.

Of the 41 reactions (21.3%) that occurred after receiving more than 1 drug simultaneously, multiple-drug hypersensitivity (MDH) was ruled out in 16 patients (39%). In 7 patients, the drug could be continued while in the hospital; in 9 patients, MDH could be ruled out with post-discharge allergy workup. MDH with different drugs on different dates (in 22 patients with 49 reactions) was ruled out for 15 of the patients. The final status of all reactions is summarized in Fig. 2.

Factors increasing the occurrence of adverse drug hypersensitivity reactions in hospitalized patients

In multivariate logistic regression analysis, being >10 years old, hospitalized due to hematologic disease, and hospitalized due to infectious diseases were the predictive factors for ADR. Gender and hospitalized due to surgical disease were also included in the analysis but they were not found to be significant predictive factors (Table 5).

DISCUSSION

To our knowledge, this is the first prospective cohort study of DHRs in pediatric inpatients. The prevalence of suspected DHR was approximately 1.1% in hospitalized children. Cutaneous

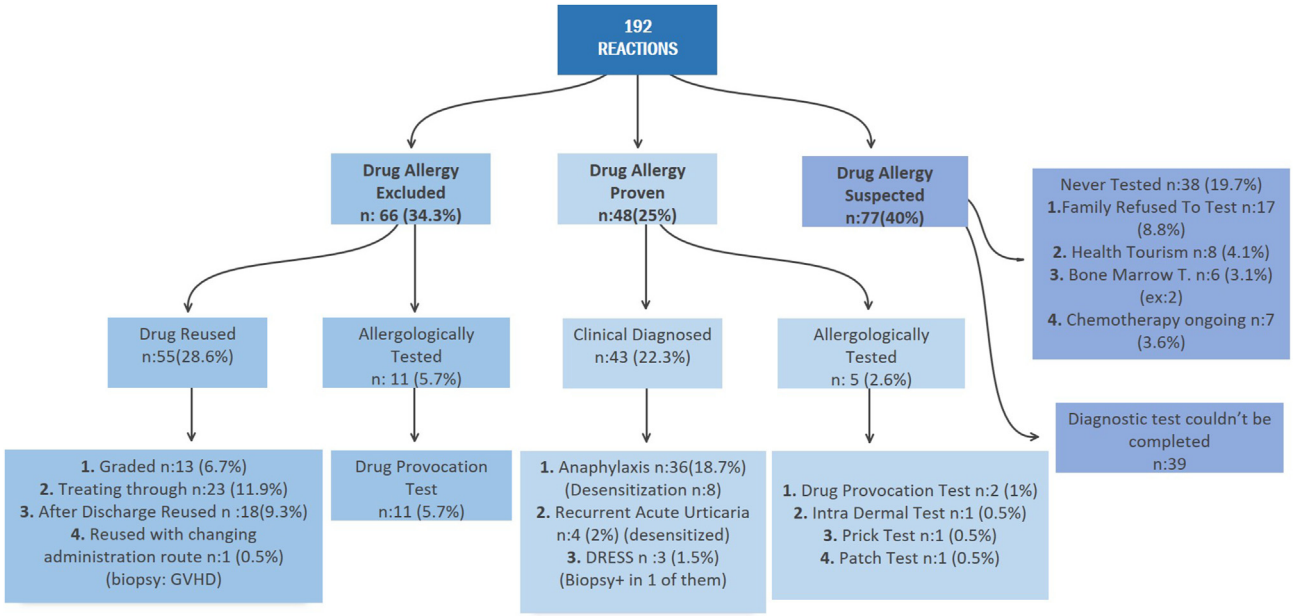

Fig. 2 Final status of reactions

symptoms were the most common manifestations, and antimicrobials were the most common suspected drugs. We were able to continue 24% of the suspected drugs during the children's hospital stay.

The prevalence of inpatient DHR was previously reported as 0.4–1.14% in studies including mostly adults.[3,22-25] We evaluated in-hospital DHRs among pediatric inpatients over 1 year and determined that 1.1% of all hospitalized patients were given allergy consultations for suspected DHRs. DHR could be confirmed in 25% (n = 48) of these reactions and could be ruled out in 34% (n = 66), either during hospitalization (24%) or after discharge (10%).

On a per-drug basis, 0.06% of all drugs used in the hospital during our study period resulted in consultations for suspected DHR. This rate increased to 0.1% in antimicrobials and antibiotics and to 0.2% in chemotherapeutics. Consistent with previous studies,[4,26] antimicrobials were the most commonly suspected drugs (48%). The high frequency of suspected DHR with antimicrobials may be due to the high frequency of admissions

	Univariant			Multivariant		
	OR	95%CI	*P*	OR	95%CI	*P*
≥10 years old	2.41	1.77–3.28	0.000	1.73	1,25–2.39	0.001
Gender (male)	1.264	0.91–1.23	0.150	1.24	0.89–1.73	0.167
Hospitalized because of hematological disease	23.06	16.47–32.28	0.000	27.92	19.28–40.43	0.000
Hospitalized because of infectious diseases	3.9	2.81–5.3	0.000	5.65	3.96–8.06	0.000
Hospitalized because of surgical diseases	0.416	0.265–0653	0.000	1.26	0.75–2.11	0.306

Table 5. Factors increasing the occurrence of adverse drug hypersensitivity reactions in hospitalized patients

for infection in pediatric patients and the fact that antimicrobials are the most commonly used drugs.

Although chemotherapeutics accounted for only 2.2% of all drugs used in the hospital during the study period, they were the second most common drug group suspected to cause DHR. This may be associated with a higher risk of DHR in cancer patients[26,27] or T-cell imbalance caused by chemotherapeutics.[28]

Hospitalized patients often use multiple drugs at the same time, which can increase the risk of reactions due to drug interactions and make it difficult to determine the culprit drug. In such cases, the most suspicious drug, based on the type and timing of the reaction, should first be determined and discontinued. Two studies evaluating MDH in outpatients reported that MDH could be confirmed in 2.5% and 2.7% of patients.[29,30] Furthermore, the most common combinations that caused MDH were combinations of antibiotics and combinations of antibiotics and NSAIDs.[29,30] In this study of pediatric inpatients, 21.3% of reactions occurred after the simultaneous intake of multiple drugs; the most common combinations were of 2 antibiotics, followed by an antibiotic and NSAID. The high prevalence of antibiotic combinations may be attributable to inpatients using multiple antibiotics more frequently than outpatients. We excluded MDH in 16 (39%) of the 41 reactions that occurred with multiple drugs simultaneously. Among children whose reactions occurred with different drugs on different dates (n = 22), MDH was ruled out in 68.1% (n:15).

Similar to previous studies, MPE was the most common symptom, followed by urticaria.[3,25,26] Skin findings occur in many childhood infections, causing difficulties in distinguishing between DHR and infection.[2,27] In our study, viral serology was performed in 67 patients and was positive in 23 of them (COVID-19 n:9, mycoplasma n:4, parvovirus n:2, adenovirus n:2, EBV n:2, CMV n:2, and enterovirus/rhinovirus n:2). However, the detection of acute infection does not rule out DHR.[27] Ten patients discontinued the drug without substitution, 11 patients were switched to an alternative drug, and 2 patients were able to continue using the drug.

Previously, the recommended primary approach to a DHR was to discontinue the culprit drug and treat the acute reaction.[6] However, considering the clinical and financial implications, in some cases where there is no alternative treatment or the alternative treatment is not sufficiently safe and effective, re-administration of the suspected drug may be necessary. It has been reported that DHR can be safely ruled out with a 1 or 2-step graded challenge in selected cases with low suspicion of DHR.[7,18,31] In our study, 14 drugs in 13 (6.7%) reactions with low clinical suspicion of DHR were re-administered with a 2-step graded challenge while the patient was in the hospital.

Continuing the suspected drug by "treating through" reactions without danger signs after performing a careful risk–benefit assessment is also an option in the management of DHR.[19,20] Trautmann et al. used the treating-through approach with 18 adults who developed MPE during intravenous antibiotic treatment and could continue the drug in 12 patients.[20] In our study, 34 drugs were successfully continued by treating through in 34.8% (n = 23/66) of the reactions with isolated MPE; 27 (79%) occurred with antibiotics. The most common causes of patients who managed with treating through were hemato-oncological diseases (34.7%) and surgical diseases (30.4%). To our knowledge, our study includes the largest number of cases of suspected DHR in pediatric inpatients managed by treating through. Because drug options are limited in pediatric patients, our study provides encouraging results for treating through patients with suspected DHR without red-flag findings.[19]

Desensitization of the culprit drug is an essential option in severe reactions where there is no alternative to the suspected drug, or the alternative drug is more toxic.[16] In our study, desensitization was achieved with 12 drugs implicated in 12 reactions and subsequently re-administered successfully.

We detected that being >10 years old, being hospitalized due to a hematologic disease, and due to infectious diseases were the predictive factors for ADR. However, our hospital is one of the biggest hospitals in Turkey and patients hospitalized with hemato-oncological diseases are more frequent according to other hospitals; this could

increase the median age of patients who had ADR in our study. Previous studies have indicated that cancer is a risk factor for cutaneous ADR among hospitalized patients. They also reported that anti-infective drugs were the most common cause of ADR.[26] Therefore, our results were supported by this data.

The primary limitation of this study is that it was conducted during the COVID-19 pandemic. In addition, the simultaneous administration of multiple drugs in inpatients and the frequency of clinical and laboratory findings resembling DHR in infectious diseases and hematology/oncology patients presented challenges in differential diagnosis, making it difficult to arrive at a definitive diagnosis. Furthermore, we were unable to perform a complete allergy work-up in all patients because some of them died, returned to their native country after treatment, underwent stem cell transplantation, had a prolonged course of disease, and treatment or consent could not be obtained for allergological tests. The most compelling aspect of the study is that it is the first real-life study to comprehensively examine DHR in pediatric inpatients, all of whom were evaluated by the allergy clinic. The fact that it was a single-center study also prevented possible data loss and differing approaches.

CONCLUSIONS

The incidence of suspected DHR was approximately 1.1% in pediatric inpatients in our hospital during the study period. Cutaneous symptoms were the most common, and most culprit drugs were anti-infectives. Of the suspected drugs, 24% could be continued during hospitalization, with 17.7% administered by "treating through." Patients with DHR during hospitalization should be evaluated with an allergy workup unless testing is contraindicated.

Abbreviations

AGEP, Acute Generalized Exanthematous Pustulosis; CBC, Complete blood count; DHR, Drug Hypersensitivity Reactions; DRESS, Drug Rash with Eosinophilia and Systemic Symptoms; DPT, Drug Provocation Test; EAACI/ENDA, European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy; IgE, Total Immunoglobulin E; MPE, Maculopapuler Exantem; MDH, Multi Drug Hypersensitivity; SCAR, Severe Cutaneous Adverse Reactions; sIgE, Specific Immunglobulin E; SJS/TEN, Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; SPT, Skin Prick Test

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Availability of data and materials

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Author contributions

All author were contributed to the all stages (concept, design, data collection and processing, analysis and interpretation, literature search and write) of the article.

Statements of ethics

Consent was obtained from the families (and patients >12 years) for participation in the study and all diagnostic tests. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision number: E1-20-863).

Agreement to publish

All authors agree to publish. All authors have given permission for publication.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100893.

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