

The controversy of drug hypersensitivity in patients with cystic fibrosis and review of the literature

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Abstract

Background: Cystic fibrosis (CF) is reported to be a risk factor for drug hypersensitivity. However, there are conflicting data about true prevalence of drug hypersensitivity in children with CF.

Methods: The suspicious drug hypersensitivity reactions (DHRs) of children with CF were enquired by the European Network for Drug Allergy (ENDA) questionnaire, and skin tests and/or drug provocation tests were performed according to the established guidelines.

Results: Two hundred and nineteen children (48.9% boys; median [IQR] age, 8.4 years [4.8–12.4 years]) with cystic fibrosis were included in the study, among which 22 patients with 24 suspected DHRs were evaluated. Most of the suspected DHRs were of non-immediate ($n = 16$, 66.6%) type, and the offending drugs were amoxicillin-clavulanic acid ($n = 7$), macrolides ($n = 4$), trimethoprim-sulfamethoxazole (TMP/SMX) ($n = 2$), piperacillin-tazobactam ($n = 1$), pancrelipase ($n = 1$), and ursodeoxycholic acid ($n = 1$). Eight (33.3%) of the DHRs were classified as immediate (ceftriaxone [$n = 2$], ceftazidime [$n = 2$], meropenem [$n = 1$], AmBisome [$n = 2$], and vancomycin [$n = 1$]). The main clinical presentations were maculopapular eruption (41.6%) and urticaria (37.5%), accompanied by angioedema (8.3%), flushing (12.5%), and vomiting (8.3%). Nine skin tests (with beta-lactam protocol in 6 patients) and 24 DPTs were performed, and none of the skin tests revealed a positive result; however, 2 DPTs with TMP/SMX were positive.

Conclusion: Actual drug hypersensitivity was demonstrated in 2 of 219 patients (0.9%) with non-beta-lactam antibiotics. These results conflict with previous researches that showed higher drug hypersensitivity rates but are consistent with some recent studies. Allergological diagnostic workup is mandatory in patients with cystic fibrosis in case of a suspicious DHR.

KEYWORDS

actual drug allergy, challenge tests, cystic fibrosis, drug hypersensitivity reactions, skin prick tests

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1 | INTRODUCTION

Cystic fibrosis (CF) is an inherited disease caused by mutations in the cystic fibrosis transmembrane conductance regulator protein, which may affect all mucus-producing organs in the body.¹ The survival of patients with CF increased considerably by early diagnosis of the disease enhanced monitoring and earlier recognition of deterioration of organ function, and detection and prompt treatment of airway infections.²

Antibiotics are crucial components of CF management for prophylaxis and suppression of chronic infections and treatment of the acute worsening of CF-related pulmonary symptoms, called pulmonary exacerbations. Infections caused by pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* require repetitive, aggressive, long-term, and broad-spectrum antibiotic treatments in either inhaled, oral, or parenteral way, to preserve lung function.³ Besides, polypharmacy is common due to other systemic complications of the disease, including pancreatic enzymes, mucolytics, ursodeoxycholic acid, proton pump inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, and many others.^{4–6}

Frequent exposure to drugs, especially antibiotics, might cause the development of drug hypersensitivity reactions (DHRs) with both serious health and economic consequences. In patients with cystic fibrosis, the epidemiological studies concerning DHRs mainly pointed out beta-lactam antibiotics. Nevertheless, there are conflicting data that while some studies reported a higher prevalence (28.8–61.9%),^{7–9} other studies described similar results to general population (0.71–2.3%).^{10–12}

Therefore, in this study, we aimed to evaluate any suspected DHR in children with cystic fibrosis to determine the prevalence of confirmed DHRs and the culprit drugs, and to analyze the risk factors that may facilitate the occurrence of DHRs. Additionally, we reviewed the literature concerning the prevalence of DHRs in patients with cystic fibrosis to investigate the subject further.

2 | METHODS

We included children with cystic fibrosis, who were followed at the Hacettepe University, the Department of Pediatric Pulmonology. This study was performed in accordance with the protocol approved by the local ethics committee (Hacettepe University, GO 15/811), and all parents/guardians provided written informed consent.

We carried out a self-designed questionnaire survey including demographic factors (age at CF diagnosis, cystic fibrosis transmembrane conductance regulator [CFTR] mutation results, years of follow-up, history of allergic diseases and DHRs, and detailed data about chronically used medications [the onset and duration of use, administration route]) and reviewed medical records to note the hospitalizations due to lower respiratory tract infections and/or number of parenteral AB used within the last year, average annual use of oral antibiotics, complications related to CF, and chronic colonizations

Key Message

Due to the chronic nature of cystic fibrosis, the patients are frequently exposed not only to antibiotics but also to NSAIDs, proton pump inhibitors, and others. The incidence of drug hypersensitivity among children with cystic fibrosis does not seem to be higher than the incidence in the general population. Non-beta-lactam antibiotic hypersensitivity is important in patients with cystic fibrosis, which requires diagnostic workup.

(*Pseudomonas aeruginosa*, *Staphylococcus aureus*). In case of history or of new occurrence of any suspicious DHR, the patients were evaluated by the pediatric allergy department.

2.1 | Study measurements

In the pediatric allergy department, DHRs were enquired with the European Network for Drug Allergy (ENDA) questionnaire.¹³ Briefly, the detailed information on medications used and clinical manifestations of DHRs (general, cutaneous [pruritus, urticaria, angioedema, flushing, rash], respiratory [cough, dyspnea, wheezing, chest tightness, stridor, difficulty in swallowing], cardiovascular [chest pain, blood pressure, and/or heart rate changes], gastrointestinal [nausea, vomiting, abdominal pain], neurologic [seizure, loss of consciousness]), type of DHR [immediate (<1–6 h) and non-immediate/delayed (≥6 h)], drugs used to treat DHR, and the response were recorded.^{13,14}

2.2 | Allergological workup

If the DHR was of the immediate-type, we performed skin testing with the culprit drug, histamine (10 mg/ml of histamine phosphate, Allergopharma) as positive, and 0.9% sterile saline as negative controls on the volar surface of the forearm.^{13,15} If the skin prick test was negative, an intradermal testing (IDT) with the culprit drug starting with minimum non-irritating concentration was performed and assessed after 20 min.¹⁵ The test was considered as positive, if a wheal of at least 3 mm greater in diameter than that of saline, accompanied by erythema, was formed. The evaluation of beta-lactam allergy was based on the European Academy of Allergy and Clinical Immunology recommendations for the skin prick test (SPT) and an intradermal test (IDT) as amoxicillin and other semi-synthetic penicillins (20 mg/ml), cephalosporins (20 mg/ml), major (benzylpenicilloyl-octa-L-lysine, 0.04 mg/ml) and minor (sodium benzylpenilloate, 0.5 mg/ml) determinants (Diater S.A.), and benzylpenicillin (10,000 IU/ml). In low-risk non-immediate reactions with beta-lactams, direct provocation with the culprit drug without prior skin testing was preferred.¹⁴ In case of delayed HSRs, a delayed reading of IDT was done, if applicable.¹³

2.3 | Drug provocation tests

The children underwent drug provocation tests (DPTs) in case of mild or moderate index DHR, if the initial SPT and IDT revealed negative results. The patients were directly provoked with the culprit medication, when there was no parenteral form of the drug proper for SPT/IDT (eg, NSAIDs), or when there were no standard ST protocols established (eg, clarithromycin).¹⁶ Oral form of the drug was preferred for DPT, and the doses and intervals were determined according to the established protocols.¹⁷ The patient was administered the total daily dose, who was age- and weight-adjusted, in four or five divided doses.^{14,17} The positive DPT was defined as the development of any objective physical symptom of a DHR concerning cutaneous (urticaria, maculopapular rash, flushing, which occurred during the DPT or within 48 hrs), respiratory, gastrointestinal, and cardiovascular

system.^{13,14} For non-immediate reactions, a 1-day protocol was performed to protect patients from longer exposure to antimicrobials.

2.4 | Statistical analysis

Statistical analyses were done using SPSS software version 21 (SPSS, Inc.). The demographic factors of CF patients and the reactions were described as frequencies for categorical variables. The values were given as medians (interquartile ranges) for data that did not show a normal distribution.

3 | RESULTS

Two hundred and nineteen children (48.9% boys; median [IQR] age, 8.4 years [4.8–12.4 years]) with cystic fibrosis were included in the study. The median age at diagnosis of CF was 3^{2–6} months; the duration of follow-up was 5.8 (3.3–10.1) years (Table 1). Seventy-six (24.7%) patients carried at least one Δ F508 mutation, whereas nearly half of the children were demonstrated to have other mutations. Some of the children were colonized chronically with *Pseudomonas aeruginosa* ($n = 36$, 16.5%) and *Staphylococcus aureus* ($n = 56$, 25.6%). Nearly all patients (99%) were using medications chronically (Table 2); two hundred and fourteen (97.7%) of them received at least one course of antibiotics within last year. One fourth of the patients were administered at least one course of parenteral antibiotic treatment in hospital in the last 1 year.

Twenty-two patients were referred to the pediatric allergy department with 24 suspected drug-related hypersensitivity reactions

TABLE 1 Demographic characteristics of the CF cohort

Characteristics	<i>n</i> = 219
Age (yrs)	8.4 (4.8–12.4) ^a
Male gender (%)	108 (48.9)
Age at diagnosis (mos)	3 (2–6) ^a
Follow-up period (yrs)	5.8 (3.3–10.1) ^a
Concomitant atopic disease (%)	21 (9.6)
Asthma	11 (5)
Family history for atopic disease (%)	36 (16.4)
Family history for drug HSRs (%)	11 (5)
Mutations	
Δ F508 homozygote	40 (18.3)
Δ F508 heterozygote	36 (16.4)
Other mutations	117 (53.4)
No mutation detected	26 (11.9)
Complications (%)	
Chronic liver disease	46 (21)
Gastroesophageal reflux	8 (3.6)
Allergic bronchopulmonary aspergillosis	9 (4.1)
CF-related diabetes	4 (1.8)
Osteoporosis	6 (2.7)
Antibiotic courses within last yr, PO (≥ 1 /yr) (%)	214 (97.7)
≥ 3 courses/yr	108 (49.3)
Median number/yr	2 (2–4) ^a
Hospitalization for pneumonia within last year (≥ 1 /yr) (%)	59 (26.9)
Antibiotic courses within last year, parenteral (≥ 1 /yr)	59 (26.9)
Chronical colonization of airways (%)	81 (36.9)
<i>Pseudomonas aeruginosa</i>	36 (16.5)
<i>Staphylococcus aerius</i>	56 (25.6)

Abbreviations: HSRs, hypersensitivity reactions; mos, months; PO, per os; yrs, years.

^aMedian (interquartile range).

TABLE 2 Chronically used medications

Medications	<i>n</i> = 219 (%)
Pulmonary	
Recombinant human DNase	213 (97.3)
Inhaled antibiotics	28 (12.8)
Colimycin	12 (5.5)
Tobramycin	16 (7.3)
Inhaled bronchodilator	18 (8.2)
Inhaled corticosteroids	12 (5.5)
Azithromycin	1 (0.5)
Hypertonic saline	2 (0.9)
Inhaled mannitol	2 (0.9)
Others	
Pancreatic enzymes	211 (96.3)
Vitamin supplement	217 (99)
Ursodeoxycholic acid	46 (21)
Proton pump inhibitors	23 (10.5)
Insulin	4 (1.8)
Bisphosphonates	1 (0.5)

(Figure 1). The route of administration of these drugs was mainly oral ($n = 13$) than parenteral ($n = 9$). Most of the suspected DHRs were of non-immediate ($n = 16$, 66.6%) type, and the offending drugs were amoxicillin-clavulanic acid ($n = 7$), macrolides ($n = 4$), trimethoprim-sulfamethoxazole (TMP/SMX) ($n = 2$), piperacillin-tazobactam ($n = 1$), pancrelipase ($n = 1$), and ursodeoxycholic acid ($n = 1$). Eight (33.3%) of the DHRs were classified as immediate (ceftriaxone [$n = 2$], ceftazidime [$n = 2$], meropenem [$n = 1$], AmBisome [$n = 2$], and vancomycin [$n = 1$]). The clinical presentations were maculopapular eruption (41.6%) and urticaria (37.5%), accompanied by angioedema (8.3%), flushing (12.5%), and vomiting (8.3%). None of the patients experienced anaphylaxis or severe cutaneous adverse reactions.

We performed 9 skin tests (with beta-lactam protocol in six patients) and 24 DPTs to determine the actual drug allergy (Figure 1). None of the skin tests revealed a positive result; however, 2 DPTs with TMP/SMX were positive. A 12-year-old boy (CF mutation Q720X/Q720X) developed generalized maculopapular eruption on the second day of TMP/SMX treatment, after 3–4 h of ultimate dose, which resolved within 2 days of cessation of the drug at the ages of seven and eleven. The patient presented with maculopapular

eruption again after 6 h of DPT with TMP/SMX. A 9-year-old girl (CF mutation E92K) experienced generalized urticaria and angioedema of face, 4 h after the last dose of TMP/SMX on Day 3 of the treatment. The DHR resolved upon the administration of antihistamine and systemic corticosteroid within 6 h. The skin testing with TMP/SMX (0.8 mg/ml)¹⁸ was negative; nevertheless, the DPT confirmed generalized urticaria had occurred 2 h after administration of TMP/SMX, suggesting that the TMP/SMX was the culprit drug.

In summary, actual drug hypersensitivity was demonstrated in two of two hundred and nineteen patients (0.9%) treated with non-beta-lactam antibiotics after diagnostic workup for DHRs. Due to the low prevalence of actual drug hypersensitivity in our cohort, we were not able to define any risk factor for occurrence of DHRs in children with cystic fibrosis.

4 | DISCUSSION

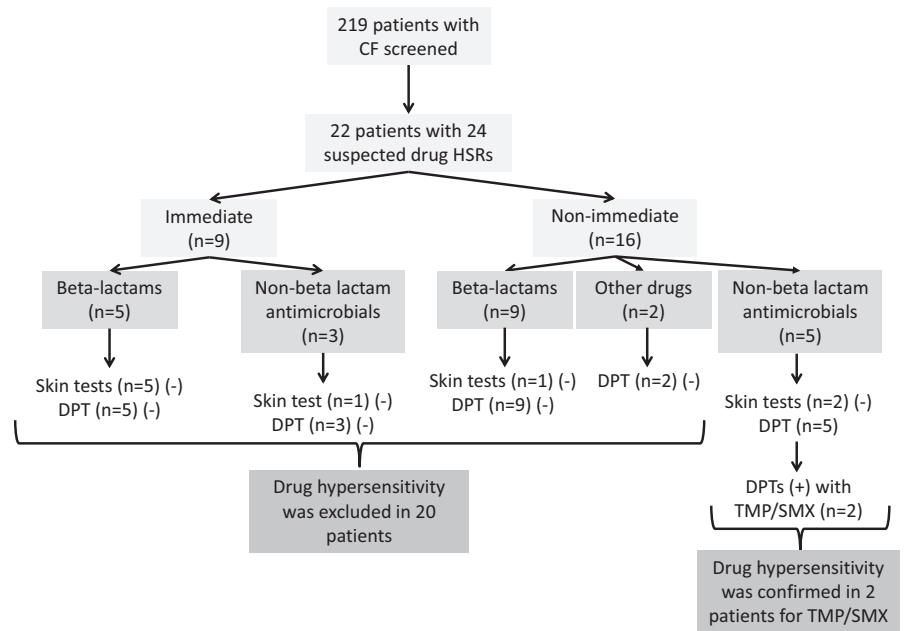
In this study, 10.04% of our patients with cystic fibrosis underwent diagnostic workup due to symptoms suggesting any drug-related

TABLE 3 Summary of studies concerning prevalence of DHRs in CF

Author, year	Study design	Sample size	Age group	Drugs involved
Koch C et al, 1991 ⁹	Retrospective	121	Adults+ Children Mean: male, 20 yrs, female, 18.2 yrs	Beta-lactams
Pleasant RA et al, 1994 ⁸	Retrospective	90	Adults	Beta-lactams
Wills R et al, 1998 ²¹	Retrospective	53	Children Mean, 9.5 yrs Range, 0.2–22.2 yrs	Beta-lactams Non-beta-lactams
Burrow JA et al, 2007 ²²	Retrospective	150	Adults Median, 26 yrs Range, 17–57 yrs	Beta-lactams
Caimmi S et al, 2012 ¹⁰	Prospective	171	Adults +children Mean, 21.2±11.2 yrs	Beta-lactams
Roehmel JF et al, 2014 ⁷	Retrospective	100	Adults +children Mean, 27.9±10.8 yrs	Parenteral Beta-lactams Non-beta-lactams
Matar R et al, 2014 ¹¹	Retrospective	701	Children Mean, 11.2 yrs Range, 1.4–18.6 yrs	Beta-lactams
Braun C et al, 2020 ¹²	Retrospective	601	Adults +children	Beta-lactams Non-beta-lactams
Tugcu GD et al, 2021	Retrospective +prospective	219	Children Median, IQR 8.4 (4.8–12.4) yrs	Antibiotics Other drugs

Abbreviations: ADR, adverse drug reaction; yrs, years; rxns will be reactions.

FIGURE 1 Flowchart of the study



Methodology	HSRs	Prevalence	Notes
Medical records	75 patients, 125 ADR 53 (42.4%) ADR; immediate	61.9% (75/125)	31 (25.6%) patients reacted ≥one beta-lactam class
Medical records	Rash Drug-induced fever	28.8% (26/90)	
Medical records Questionnaire-based	18 patients, 61 ADR 1 bronchospasm 5 angioedema	34% (18/53)	IV route, most allergenic ≥20 iv courses→↑ADR risk
Medical records, Questionnaire-based	54 patients, 93 ADR 37 (40%) ADR; early	36% (54/150)	20 (13.4%) patients reacted ≥one beta-lactam class ≥20 iv courses, older age (>25 yrs)→↑ADR risk
ENDA questionnaire, Allergological workup	Proven ADR; immediate	2.3% (4/171)	24 patients were consulted due to a history of DHRs
Medical records, ENDA questionnaire	60 patients, 185 ADR 162 (88%) ADR; immediate 15% anaphylaxis	60% (60/100)	↑years of Pseudomonas colonization, ↑annual dose of Abs→↑ADR risk
Medical records, Allergological workup	9 children, 23 ADR 13 (56.5%) ADR; immediate 9 rxns, anaphylaxis	(5/701)	Totally, 19 children were consulted, 9 cases were confirmed for drug allergy. In study center (n = 701), 5 of 8 cases were confirmed.
Medical records, Allergological workup	13 patients, 13 ADR 7 (53.8%) ADR; immediate 2 ADR, anaphylaxis 3 (23%) ADR; fixed drug eruption	2.16% (13/601)	4 children and 9 adults were confirmed. 9 cases, beta-lactams all. 3 cases, TMP/SMX all. 1 case, vancomycin all. No risk factor identified
Medical records, ENDA questionnaire, Allergological workup	2 patients, 3 ADR Proven ADR; non-immediate	(2/219)	22 patients were consulted, 2 cases were confirmed for drug allergy. 2 cases, TMP/SMX all.

hypersensitivity reaction, and we confirmed drug hypersensitivity in 0.9% of the study population. Unlike previous studies, none of the children exhibited beta-lactam hypersensitivity; instead, a non-beta-lactam antibiotic, TMP/SMX, was the culprit agent responsible for DHRs.

There are limited data concerning the prevalence of confirmed DHRs in general population. Rebelo et al. demonstrated parentally reported drug allergy prevalence to be 4.6% in children and diagnostic workup confirmed drug allergy in 0.2% of the study population.¹⁹ In a population-based study concerning school-aged children, the true frequency of immediate-type drug hypersensitivity was shown as 0.11%.²⁰ In the present study, the prevalence of DHRs was similar to that of the general population, but lower than the prevalence of DHRs compared with some previous studies (28.8–61.9%).^{7–9,21}

Since there are contradictory results about the frequency of DHRs in the literature, we summarized these studies in Table 3 for comparison. In earlier studies, the prevalence of DHRs in patients with CF ranged between 28.8 and 61.9%.^{7–9,21,22} There might be a number of explanations for this. The majority of patients with cystic fibrosis included in those studies were only adults or adults and children. Burrows et al. demonstrated that the age of the patients with CF, who experienced a DHR, was older and a higher proportion of patients older than 25 years had DHRs compared with younger patients. Furthermore, higher number of antibiotic courses was associated not only with higher risk of antibiotic allergy, but also with allergy to more than one antibiotic.²² However, Roehmel et al. showed that DHRs were drug-specific and dependent on cumulative annual dose.⁷ The definitions of DHRs might not fit all of the criteria for DHRs defined in guidelines. Pleasant et al. described the DHRs as rash and drug-induced fever in their study.⁸ Besides, the clinical presentations of DHRs were not detailed in most of these studies. Probably the most important problem in these studies was that the guidelines defined for allergy assessment steps were not followed; most studies were retrospective and based on questionnaires and/or medical records, and skin tests or DPTs were not performed for the confirmation of true drug allergy.^{7–9,21,22} It is well known that only a minority of suspected DHRs were proved to be accurate drug allergy.¹⁹

It is encouraging that our results are consistent with the findings of the more recent studies by Matar et al.,¹¹ Braun et al.,¹² and Caimmi¹⁰ et al. ranging between 0.71 and 2.3%. Caimmi et al. conducted skin tests and DPTs on 14% of the hundred and seventy-one patients with suggestive DHR due to beta-lactam antibiotics, and 2.3% of the study cohort was diagnosed as immediate-type beta-lactam allergy.¹⁰ The reason for higher frequency of DHRs in cystic fibrosis is believed to be due to the repetitive antibiotic administrations that may result in increased risk of sensitization.^{7,21,22} However, recurrent exposure to drugs, especially by courses longer than applied to everyone, might contribute to the development of tolerance.¹¹ Our patients also used antibiotics frequently. One fourth of our patients were hospitalized due to pneumonia, which was treated by parenteral antibiotics within the last year. Although we did not have the data related to the total number of antibiotic courses up to the child's age, in the last year, nearly all of the patients

consumed antibiotics at least once and half of the cases used antibiotics more than twice.

One unanticipated finding was that there were no cases with beta-lactam hypersensitivity; besides, two patients were diagnosed as TMP/SMX hypersensitivity (0.9%). Recently, in a population of six hundred and one patients with cystic fibrosis, the prevalence of TMP/SMX hypersensitivity was indicated as 0.49% and shown as the second class of antibiotics responsible for DHRs.¹² Self-reported sulfa allergy ranged between 0.07 and 2.7% in different populations.^{23–25} Twenty-five percent of our patients were colonized with *S. aureus*, and TMP/SMX is the preferred treatment in our pulmonology department. Although we do not have recorded data on the frequency of use of different antibiotics, children with cystic fibrosis use more TMP/SMX than most other pediatric patients that may lead to sensitization. In addition, increased antigenicity to sulfamethoxazole in sulfamethoxazole-hypersensitive patients with cystic fibrosis was demonstrated.²⁶ T cells from sulfamethoxazole-hypersensitive patients with cystic fibrosis were stimulated with oxidative metabolites of sulfamethoxazole more than sulfamethoxazole-hypersensitive patients without cystic fibrosis in terms of higher secretion of IFN- γ , IL-6, and IL-10. Additionally, recurrent infections might enhance sulfamethoxazole metabolite formation, thereby increasing protein adduct formation associated with the stimulation of sulfamethoxazole-responsive T cells.²⁶ In view of the results of these studies, physicians dealing with cystic fibrosis should be more vigilant about DHRs due to TMP/SMX HRs, which was an understudied area.

To our knowledge, this is the first study that focused on the prevalence of any drug hypersensitivity reaction in patients with cystic fibrosis. In the present work, we extensively inquired patients and reviewed medical records for DHRs related to drugs other than beta-lactam and non-beta-lactam antibiotics. Due to the chronic nature of cystic fibrosis, the patients were frequently exposed not only to antibiotics but also to NSAIDs, proton pump inhibitors, and others.⁶ The administration of the offending drug or cross-reactive ones in chronic or repetitive treatment schedules enhances the risk for DHRs. Actual drug allergy was shown to be more frequent in patients with chronic diseases.^{27,28} However, we were unable to demonstrate hypersensitivity to drugs other than antibiotics.

There are some limitations of this study. We did not have detailed information about the classes of antibiotics and NSAIDs and the duration of treatment courses used during lifetime. The study had both retrospective and prospective aspects that some of the diagnostic tests might not have been done with optimal timing.

As adverse drug reactions accumulate over time, the physicians will try to manage their patients with CF with a limited number of treatment options. Therefore, it is crucial to assess cases according to the established diagnostic protocols. When evaluating patients with CF for DHRs, attention should be paid not only to beta-lactam allergies but also to other drug allergies.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Gokcen Dilsa Tugcu: Data curation (equal); Investigation (equal); Resources (equal); Software (equal); Visualization (supporting); Writing – review & editing (supporting). **Nagehan Emiralioglu:** Resources (supporting); Supervision (supporting); Visualization (equal); Writing – original draft (supporting); Writing – review & editing (supporting). **Ebru Yalçın:** Writing – review & editing (supporting). **Umit Murat Sahiner:** Writing – review & editing (supporting). **Deniz Dogru:** Writing – review & editing (supporting). **Bulent Enis Sekerel:** Methodology (equal); Project administration (equal); Supervision (equal); Visualization (equal); Writing – review & editing (equal). **Ugur Ozcelik:** Resources (equal); Supervision (equal); Visualization (equal); Writing – review & editing (equal). **Nural Kiper:** Writing – review & editing (supporting). **Ozge Soyer:** Conceptualization (lead); Formal analysis (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (lead); Writing – review & editing (lead).

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