Proven Non- β -Lactam Antibiotic Allergy in Children

Hakan Guvenir^a Emine Dibek Misirlioglu^a Murat Capanoglu^a Emine Vezir^a
Muge Toyran^a Can Naci Kocabas^b

^aDepartment of Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Training and Research Hospital, Ankara, and ^bDivision of Pediatric Allergy and Immunology, Department of Children's Health and Diseases, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey

Key Words

Allergy · Drug provocation tests · Hypersensitivity · Intradermal tests · Non- β -lactam antibiotics · Pediatric allergy · Skin prick tests

Abstract

Background: Parallel to the increasing use of non- β -lactam (NBL) antibiotics, allergic reactions to this drug group seem to increase. Data about NBL antibiotic hypersensitivity in children are limited. The aim of this study is to evaluate characteristic reactions to NBL antibiotics in children. **Method:** Patients with suspected NBL allergy were assessed between 2011 and 2015. Characteristics of the reactions and results of skin and drug provocation tests (DPTs) were recorded. **Results:** In total, 96 patients aged 75.15 ± 56.77 months (range: 3–208) were assessed. Clarithromycin (63.6%) was the most common cause of reactions reported. After ingestion of NBL antibiotics, maculopapular rash, urticaria/angioedema and anaphylaxis presented in 48.9, 40.7 and 10.4% of the patients, respectively. Tests were performed in 85 patients. Intradermal tests were positive in 3 patients (clarithromycin, ciprofloxacin and cotrimoxazole) and DPT was positive in 1 patient (clarithromycin). Eleven patients could not be tested.

Seven patients had severe anaphylaxis, and 4 patients with urticaria/angioedema had to take their medications at the time of the reaction so desensitization was performed. When only patients confirmed by tests were evaluated, NBL allergy was 4.7% (4/85) in our study group. However, when patients who could not be tested, but were regarded as suffering from drug hypersensitivity according to clinical findings, were included, the frequency of NBL allergy was 15.6% (15/96). **Conclusion:** Most of the children with suspected NBL do not have true hypersensitivity. The frequency of confirmed hypersensitivity is low, and thus a detailed history should be taken from patients with suspected NBL hypersensitivity and DPTs should be performed in patients without contraindications.

© 2016 S. Karger AG, Basel

Introduction

The most common causes of drug-related hypersensitivity reactions in children are β -lactam antibiotics. However, non- β -lactam (NBL) antibiotics may also induce hypersensitivity reactions, with a prevalence estimated at 1–3% in the general population [1].

Most publications on allergy to antibiotics have focused on hypersensitivity to β -lactams, while studies on reactions to NBLs involve only case reports or small series of patients [2]. Especially data about NBL hypersensitivity in children are very limited.

As a matter of fact, only a minority of reported NBL reactions are true hypersensitivity reactions. In population-based questionnaire surveys among children in different countries, parent-reported drug hypersensitivity ranged from 2.8 to 5.4%, of which 10–20% were associated with NBL antibiotics, but only 7.8–36% of suspected reactions could be confirmed by skin and/or provocation tests [3–5].

A detailed history taking and careful physical examination are the most essential steps toward an accurate diagnosis of drug-induced reactions. The diagnostic skin prick and intradermal tests for NBL antibiotics lack validation. Therefore, the gold standard for the diagnosis of drug hypersensitivity is a drug provocation test (DPT) [6].

The aim of this study was to evaluate the characteristics and test results of children evaluated in our clinic for suspected NBL hypersensitivity.

Patients and Methods

This study was conducted in the pediatric allergy department. We included patients who were admitted with a suspicion of NBL antibiotic allergy and were evaluated by skin test and/or DPT between January 1, 2011, and June 15, 2015. The local ethics committee approved the study design and protocol.

The initial drug allergy workup started with the standardized European Network of Drug Allergy (ENDA) questionnaire on drug allergy [7]. A detailed history included the spectrum and timing of symptoms, dose and route of administration, concomitant medication, and history and timing of previous hypersensitivity reactions. Coexisting chronic diseases and family history of drug allergy were also recorded.

Reactions occurring within the first hour were labeled as 'immediate reactions', mostly manifesting clinically as urticaria, angioedema, rhinitis, bronchospasm and anaphylaxis; the ones occurring later (after 1 h) were labeled as 'nonimmediate reactions', manifesting clinically as maculopapular eruptions and delayed-appearing urticaria/angioedema [8].

The definition of anaphylaxis and the level of severity were defined and classified according to the criteria suggested in the EAACI Task Force position paper on the management of anaphylaxis in childhood [9].

If the history of suspected reaction was compatible with drug hypersensitivity, skin tests (prick test and intradermal test) and DPT to the suspected drug were proposed. These tests were performed at least 1 month after the initial reaction. Use of antihistamine medications and other drugs that could affect skin tests or DPT were discontinued 1 week before the test. Written informed consent was obtained from the caregivers.

Table 1. Drug concentrations for skin prick and intradermal tests

NBL antibiotics	Drug concentrations for skin prick tests	Drug concentrations for intradermal tests, mg/ml
Clarithromycin	without dilution	0.05
Cotrimoxazole	without dilution	0.8
Ciprofloxacin	0.006 mg/ml	0.006
Gentamicin	without dilution	4
Metronidazole	2 mg/ml	0.02
Rifampicin	without dilution	0.002

Exclusion Criteria

Patients who had a history of severe life-threatening drug reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome or drug reactions with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, nephritis, pneumonitis, hepatitis and vasculitis) were excluded as DPT was contraindicated.

Skin Tests for Drugs

Patients were subjected to skin prick and intradermal tests to the suspected drugs (the drug concentrations used in skin prick tests and intradermal tests are shown in table 1) [10]. Isotonic saline solution was used for dilution. All drugs were initially tested on the volar forearm by a skin prick test, and reactions were considered positive when a wheal diameter ≥ 3 mm compared to the negative control (with surrounding erythema) was present 20 min later [11].

When skin prick tests yielded negative results, 0.02 ml of the parenteral drug solution was injected intradermally on volar forearm skin. Readings were made 20 min after injections. Results were considered positive when an increase ≥ 3 mm in wheal diameter, accompanied by erythema, was noticed. Histamine at 10 mg/ml and 0.9% NaCl were used as positive and negative controls, respectively [11].

Drug Provocation Tests

ENDA guidelines for DPTs were carefully followed. A provocation test involved administering the suspected drug at divided doses every 30 min, until a cumulative dose close to the age-/weight-adjusted daily dose of the drug was achieved. The provocation was given maximally in 5 doses in order to prevent the possibility of patient desensitization. The test was discontinued in the event of any reaction. Administration was open and performed by a physician with full resuscitation backup [12]. The DPT was considered positive if any objective symptoms or signs (e.g. urticaria, angioedema, circulatory depression, wheezing and rhonchi) were documented. After the last dose had been administered without a reaction, the patient was kept under surveillance for at least 2 h and told to continue to use the drug in two divided doses for 5 days at home for patients with delayed reactions. The tests were considered negative if no reaction occurred at the end of this time [12].

Statistical Analyses

Statistical analyses were performed using the SPSS-22 statistical software package (SPSS, Inc., Chicago, Ill., USA) for Windows.

The definitions were provided as numbers and percentages for discrete variables and means and standard deviations for continuous variables.

Results

During the study period, 96 patients were admitted to our clinic with suspected NBL antibiotic allergy. The mean age of the patients was 75.15 ± 56.77 months [range 3–208, median 72, interquartile range (IQR) 19–109]; 51 patients (53.1%) were male.

At presentation, history was compatible with immediate reactions for 38 (39.6%) patients and with anaphylaxis in 10 of these 38 patients [10.4%: cotrimoxazole ($n = 3$), teicoplanin ($n = 3$), vancomycin ($n = 1$), ciprofloxacin ($n = 1$), colistin ($n = 1$) and gentamicin ($n = 1$)]. Clarithromycin was the most commonly suspected drug (63.6%). The time interval between drug intake and reaction was 257.81 ± 300.96 min (range: 5–1,440, median 180, IQR 60–360). Characteristics of the patients and reactions are given in table 2.

Skin Prick and Intradermal Tests

Skin prick and intradermal tests were performed in 79 of the remaining 85 patients. Skin prick tests were negative in all patients, while intradermal tests were positive to clarithromycin, ciprofloxacin and cotrimoxazole in 3 patients. Six patients could not be tested, because these drugs cannot be applied as intravenous solutions. Therefore, DPTs were performed in these 6 patients and 76 patients with negative skin tests. The algorithm of the study is shown in figure 1.

Drug Provocation Tests

Eighty-two DPTs were performed. Mean age of the patients at the time of provocation was 80.11 ± 56.93 months (range: 6–213, median 70, IQR 24.75–118.75). The time interval between the initial reaction and drug provocation was 7.23 ± 20.69 months (range: 1–173, median 2, IQR 2–5). Only 1 patient showed a positive reaction. The patient with reported clarithromycin hypersensitivity had a maculopapular eruption during DPT and was diagnosed as true hypersensitivity. Patient characteristics are listed in table 3.

Patients Diagnosed Based on History

Eleven patients were diagnosed with NBL antibiotic hypersensitivity based on clinical history (table 3). Seven patients had severe anaphylaxis (3 to teicoplanin, 1 to vancomycin, 1 to ciprofloxacin, 1 to colistin and 1 to cotrimoxazole). These patients could not be tested. In addition,

Table 2. Characteristics of the patients and reactions ($n = 96$)

Characteristics	Patients, n (%)
<i>History of reactions to NBL</i>	
Macrolides	65 (67.9)
Clarithromycin	61 (63.6)
Azithromycin	4 (4.3)
Sulfonamides	14 (14.6)
Cotrimoxazole	14 (14.6)
Glycopeptides	5 (5.2)
Teicoplanin	3 (3.1)
Vancomycin	2 (2.1)
Antituberculous drugs	3 (3.1)
Isoniazid	2 (2.1)
Rifampicin	1 (1)
Imidazole antibiotics	3 (3.1)
Metronidazole	2 (2.1)
Albendazole	1 (1)
Quinolones	3 (3.1)
Ciprofloxacin	3 (3.1)
Aminoglycosides	1 (1)
Gentamicin	1 (1)
Polymyxins	1 (1)
Colistin	1 (1)
Oxazolidinones	1 (1)
Linezolid	1 (1)
<i>Type of reactions</i>	
Maculopapular exanthema	47 (48.9)
Urticaria	28 (29.2)
Urticaria and angioedema	7 (7.3)
Angioedema	4 (4.2)
Anaphylaxis	10 (10.4)
<i>Allergic disease</i>	
Asthma	12 (12.5)
Allergic rhinitis	4 (4.1)
Asthma and allergic rhinitis	2 (2.1)
Acute recurrent urticaria	2 (2.1)
<i>Skin prick test</i>	
Atopy	8 (8.3)
<i>Family history of drug allergy</i>	
NBL antibiotic	3 (3.1)

tion, 6 of them had to take their medication, so they were desensitized. Four patients had recurrent urticaria/angioedema most likely due to vancomycin, linezolid, isoniazid and albendazole. They could not be tested because they were taking antihistaminics and they had to take their antibiotics; thus these patients were also desensitized.

Frequency of NBL Hypersensitivity

When only patients confirmed by tests were evaluated, the frequency was 4.7% (4/85) in our study. However,

Fig. 1. Diagnostic algorithm of the study. ID = Intradermal; DPT = drug provocation test.

Table 3. Characteristics of the patients with diagnosed NBL hypersensitivity

Patient No.	Age at reaction, months	Gender	Culprit drug in history	Reaction type	Atopic disease	Skin prick test	Intradermal test to suspected drug	DPT	Age at provocation, months	Time interval between reaction and test, months	Reaction of DPT
<i>Patients diagnosed according to intradermal test/DPT</i>											
1	167	M	clarithromycin	MPE	allergic rhinitis	pollen atopy	negative	clarithromycin	168	1	MPE ¹
2	30	F	clarithromycin	urticaria	asthma	none	positive	ND	ND	ND	ND
3	15	F	cotrimoxazole	MPE	none	none	positive	ND	ND	ND	ND
4	147	F	ciprofloxacin	anaphylaxis	asthma	none	positive	ND	ND	ND	ND
<i>Patients diagnosed based on history</i>											
5	8	F	cotrimoxazole	anaphylaxis	none	ND	ND	ND			
6	6	F	colistin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
7	156	M	teicoplanin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
8	142	M	teicoplanin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
9	156	M	teicoplanin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
10	19	M	vancomycin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
11	89	F	vancomycin	urticaria and angioedema	none	ND	ND	desensitization was performed with culprit drug			
12	156	M	ciprofloxacin	anaphylaxis	none	ND	ND	desensitization was performed with culprit drug			
13	96	M	linezolid	urticaria and angioedema	none	ND	ND	desensitization was performed with culprit drug			
14	180	F	isoniazid	urticaria and angioedema	none	ND	ND	desensitization was performed with culprit drug			
15	87	M	albendazole	urticaria and angioedema	none	None	ND	desensitization was performed with culprit drug			

MPE = Maculopapular eruption; ND = not done. ¹ MPE presented 300 min after the 5th DPT dose (300 mg).

when patients who could not be tested but had hypersensitivity based on clinical findings were included, the frequency of NBL allergy was 15.6% (15/96).

Discussion

In this study, the frequency of patients diagnosed with NBL allergy was 15.6%. The most common suspected allergy-inducing NBL antibiotic was clarithromycin (63.6%); however, the frequency of confirmed clarithromycin hypersensitivity was found to be only 2.1%.

Among all NBL antibiotics, cotrimoxazole, which belongs to the sulfonamide family, has been shown to be the most common drug suspected to be associated with hypersensitivity reactions. Reactions are rarely IgE mediated, while fixed drug eruption and maculopapular rash are the most common presentations [13]. It has been estimated that reactions to cotrimoxazole occur in approximately 3% of the general population, 12–40% of which are patients with AIDS [6]. In a prospective study including children, rashes occurred in 8.5% of the patients prescribed cotrimoxazole [14]. In two studies including different age groups of children, the frequency of hypersensitivity reactions caused by sulfonamides was found to be 1.6 and 9.9% based on history [4, 5]. In our study, cotrimoxazole was the second most commonly suspected agent (14/96, 14.6%), and confirmed hypersensitivity was found to be 14.2% (2/14). In 1 patient, hypersensitivity was confirmed by intradermal skin test. The other patient had anaphylaxis.

Compared to sulfonamides, macrolides have been less frequently associated with hypersensitivity reactions [15, 16]. In a study conducted by Lange et al. [4], the ratio of reported macrolide hypersensitivity was 8.2% in children. In addition, it has been shown that most of the children with reported hypersensitivity could tolerate macrolides, and macrolide hypersensitivity was confirmed in only 6.2–15.5% of the reported cases [17, 18]. In another study in children in our country, the frequency of confirmed macrolide hypersensitivity was 27.2% (3/11) [19]. In this study, the number of patients is lower than in ours, and all confirmed cases had immediate reactions. In our study, macrolide reactions were reported in 67.9%; however, only 2 of 61 reactions could be confirmed as hypersensitivity (2/61, 3.3%). Barni et al. [18] reported confirmed azithromycin hypersensitivity in 47.3% and concluded that azithromycin is a more potent allergen than clarithromycin in children. However, in our study, none of the 4 patients with reactions suspected to be caused by azithromycin had a positive reaction during evaluation. The difference in the

frequency of reactions may be caused by the varied usage of macrolides among countries and genetic factors.

Hypersensitivity to quinolones is not frequent [2, 6, 20]. In a study conducted by Blanca-López et al. [21], which included 218 adult patients, 32.1% of the suspected cases were confirmed. In our study, 2 of 3 suspected hypersensitivity reactions caused by ciprofloxacin were confirmed. One patient had a history of anaphylaxis and a positive intradermal test. The other had severe anaphylaxis to ciprofloxacin and was therefore not tested.

Antituberculous drugs, isoniazid and rifampicin were other NBL antibiotics causing reactions in our study. One of 2 patients who had a history of hypersensitivity reactions to isoniazid had a negative DPT. The other patient had a remarkable history of urticaria and angioedema with isoniazid; he was diagnosed with hypersensitivity and was desensitized. One patient who had a history of reactions to rifampicin had a negative DPT. The frequency of hypersensitivity reactions caused by antituberculous drugs are between 0.1 and 20% in the literature, and pyrazinamide has been associated with a higher risk of hypersensitivity [2, 6]. None of our patients had a history of hypersensitivity to pyrazinamide in our study.

There are little data about glycopeptide antibiotics, vancomycin and teicoplanin. Although the red man syndrome is a frequent side effect of vancomycin treatment, real hypersensitivity reactions and anaphylaxis are rarely reported [6, 16]. In our study, 3 patients had a history of severe anaphylaxis caused by teicoplanin and 1 patient by vancomycin. Another patient had a history of urticaria and angioedema due to vancomycin. Skin tests and provocation could not be performed in these patients and they were desensitized.

In our study, 3 patients had a history of allergic reactions to metronidazole and to albendazole, both drugs belonging to the nitroimidazole family. The 2 patients with hypersensitivity reactions to metronidazole had negative skin and provocation tests. The other patient had recurrent urticaria and angioedema with albendazole. Since their parents did not consent, he could not be tested and was desensitized. There are no published reports of pediatric cases with hypersensitivity reactions caused by metronidazole and albendazole.

One patient with a history of gentamicin-related urticaria had a negative intradermal test. Previous studies have shown that aminoglycoside antibiotics (especially neomycin) lead to contact skin reactions on topical applications. The number of pediatric cases with a history of topical/systemic reactions caused by gentamicin and streptomycin is limited [6, 22].

One patient with a history of recurrent urticaria and angioedema caused by linezolid, an oxazolidinone, and another patient with a history of anaphylaxis caused by colistin could not be tested; both were diagnosed clinically. Hypersensitivity to these drugs was not reported in children in the literature. Adult data are limited to case reports.

The strength of our study is the prospective design, the high number of patients included and the use of DPT, which is the gold standard for the diagnosis of drug allergy. Blind placebo-controlled challenges may be better than an open challenge in the diagnosis of drug hypersensitivity [23], but only 1 patient in our study had a positive reaction, but this point has apparently not affected outcome. The very low frequency of positive reactions in our DPTs may be due to the fact that patients with clear hy-

persensitivity could not be tested. Most of the patients tested had nonimmediate reactions, and the frequency of positive DPTs is lower for nonimmediate reactions [24].

In conclusion, in children, the percentages of both clinical history and confirmed hypersensitivity caused by NBL antibiotics fall behind β -lactam antibiotics and non-steroidal anti-inflammatory drugs. The frequency of confirmed hypersensitivity is low and thus in patients with suspected NBL hypersensitivity detailed history taking and DPT should be performed.

Disclosure Statement

There are no sources of funding to declare.

References

- 1 Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology: Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–273.
- 2 Sánchez-Borges M, Thong B, Blanca M, Ensina LF, González-Díaz S, Greenberger PA, Jares E, Jee YK, Kase-Tanno L, Khan D, Park JW, Pichler W, Romano A, Jaén MJ: Hypersensitivity reactions to non beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy. *World Allergy Organ J* 2013;31:6:18.
- 3 Kidon MI, See Y: Adverse drug reactions in Singaporean children. *Singapore Med J* 2004;45:574–577.
- 4 Lange L, Koningsbruggen SV, Rietschel E: Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. *Pediatr Allergy Immunol* 2008;19:634–638.
- 5 Orhan F, Karakas T, Cakir M, Akkol N, Bahat E, Sonmez FM, Gedik Y: Parental-reported drug allergy in 6- to 9-yr-old urban school children. *Pediatr Allergy Immunol* 2008;19:82–85.
- 6 Kuyucu S, Mori F, Atanaskovic-Markovic M, Caubet JC, Terreehorst I, Gomes E, Brockow K; Pediatric Task Force of EAACI Drug Allergy Interest Group: Hypersensitivity reactions to non-beta-lactam antibiotics in children: an extensive review. *Pediatr Allergy Immunol* 2014;25:534–543.
- 7 Demoly P, Kropf R, Bircher A, Pichler WJ: Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. *Allergy* 1999;54:999–1003.
- 8 Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W, Sanchez-Borges M, Shiohara T, Thong BY: International Consensus on drug allergy. *Allergy* 2014;69:420–437.
- 9 Vetander M, Helander D, Lindquist C, Hedlin G, Alfvén T, Ostblom E, Nilsson C, Lilja G, Wickman M: Classification of anaphylaxis and utility of the EAACI Taskforce position paper on anaphylaxis in children. *Pediatr Allergy Immunol* 2011;22:369–673.
- 10 Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, Bircher A, Blanca M, Bonadonna B, Campi P, Castro E, Cernadas JR, Chiriac AM, Demoly P, Grosber M, Gooi J, Lombardo C, Mertes PM, Mosbech H, Nasser S, Pagani M, Ring J, Romano A, Scherer K, Schnyder B, Testi S, Torres M, Trautmann A, Terreehorst I; ENDA/EAACI Drug Allergy Interest Group: Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702–712.
- 11 Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P: General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45–51.
- 12 Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P: European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity: Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003;58:854–863.
- 13 Schnyder B, Pichler WJ: Allergy to sulfonamides. *J Allergy Clin Immunol* 2013;131:256–257.
- 14 Ibia EO, Schwartz RH, Wiedermann BL: Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol* 2000;136:849–854.
- 15 Araujo L, Demoly P: Macrolides allergy. *Curr Pharm Des* 2008;14:2840–2862.
- 16 Tilles SA, Slatore CG: Hypersensitivity reactions to non-beta-lactam antibiotics. *Clin Rev Allergy Immunol* 2003;24:221–228.
- 17 Mori F, Barni S, Pucci N, Rossi E, Azzari C, de Martino M, Novembre E: Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Ann Allergy Asthma Immunol* 2010;104:417–419.
- 18 Barni S, Butti D, Mori F, Pucci N, Rossi ME, Cianferoni A, Novembre E: Azithromycin is more allergenic than clarithromycin in children with suspected hypersensitivity reaction to macrolides. *J Investig Allergol Clin Immunol* 2015;25:128–132.
- 19 Arikoglu T, Aslan G, Batmaz SB, Eskandari G, Helvacı I, Kuyucu S: Diagnostic evaluation and risk factors for drug allergies in children: from clinical history to skin and challenge tests. *Int J Clin Pharm* 2015;37:583–591.
- 20 Blanca-López N, Andreu I, Torres Jaén MJ: Hypersensitivity reactions to quinolones. *Curr Opin Allergy Clin Immunol* 2011;11:285–291.
- 21 Blanca-López N, Ariza A, Doña I, Mayorga C, Montañez MI, García-Campos J, Gomez F, Rondón C, Blanca M, Torres MJ: Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. *Clin Exp Allergy* 2013;43:560–567.
- 22 Romano A, Caubet JC: Antibiotic allergies in children and adults: from clinical symptoms to skin testing diagnosis. *J Allergy Clin Immunol Pract* 2014;2:3–12.
- 23 Aberer W, Kränke B: Provocation tests in drug hypersensitivity. *Immunol Allergy Clin North Am* 2009;29:567–584.
- 24 Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P: Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 2012;42:123–130.