allergies

Article

The Role of Medical History and Allergic Tests in the Analysis of Antibiotic Allergy in the Pediatric Population

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Abstract: According to parental reports, about 10% of children are believed to be allergic to at least one antibiotic, leading to the prescription of second line medications. This incurs higher costs, results in less effective treatments, and contributes to global concern of antibiotic resistance. De-labeling programs could mitigate these problems. The primary objectives of this study were to assess the proportion of children that tolerate the suspected antibiotic well through allergy testing and, secondly, to examine which information in their medical history correlates with a positive test result. Children with a history of antibiotic allergy were categorized into high- and low-risk groups for immediate allergic reaction. The latter underwent oral provocation testing (OPT), while the high-risk group underwent the test only after negative skin tests (STs). In total, 76.8% of children tolerated the tested antibiotic well. Among children with positive OPT, two (8.0%) had to receive adrenaline for symptom resolution. Children who had exhibited suspected symptoms within one hour after antibiotic administration, and those with a history of asthma or food allergy, had an increased risk of positive allergic testing ($p < 0.05$). In conclusion, the adoption of a standardized protocol for an antibiotic allergy de-labeling program is essential for every allergy department.

Keywords: antibiotic allergy; immediate type reaction; de-labeling; pediatric population; oral provocation testing; skin tests

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1. Introduction

In the pediatric population, the utilization of antibiotics is prevalent, especially in the early years of life when respiratory infections are more frequent [1]. Most infections can be treated with common antibiotics; however, in the case of a reported allergy, advanced medicines are preferred. However, these medications are not always the optimal choice. Approximately 50% of children labeled as allergic to a specific antibiotic end up being treated with a drug that is not recommended for their infection [2]. Additionally, these antibiotics are often more expensive, are associated more frequently with adverse effects, and contribute to the development of antibiotic-resistant microorganisms and a longer hospitalization period [1,3–6].

Individuals undergoing treatment with broad-spectrum antibiotics are at an elevated risk of infections with resistant organisms, including *Clostridium difficile*, *methicillin-resistant Staphylococcus aureus (MRSA)*, and *vancomycin-resistant Enterococcus (VRE)* [4]. The World

Health Organization (WHO) recognizes antibiotic resistance as one of the biggest health challenges nowadays [7]. According to a recent research article, in 2019 antimicrobial resistance led to more than 1.27 million deaths and was associated with about 5 million deaths worldwide [8].

Hence, scientists have recently been suggesting shorter courses of antibiotic, which are equally effective [8–10]. An alternative approach to deal with resistance to antibiotics is to administer advanced antimicrobials exclusively to children with confirmed allergies.

Administering advanced medicines also represents a significant burden on public resources. The utilization of advanced antibiotics comes with higher costs both in terms of the actual drug and the associated healthcare infrastructure. In a related study, Yilu Dong et al. examined the potential cost savings associated with implementing a de-labeling program in a pediatric unit in the U.S.A. The study estimated a cost reduction of approximately $618,653 over an 8 year period [11]. According to another multicenter study, the projected lifetime cost for an individual identified as antibiotic allergic before the age of 10 is $1893 higher than for a non-allergic person [12].

Allergy to at least one antibiotic is reported to affect about 10–25% of the population [13]. The allergy label to antibiotics is often acquired during childhood, with approximately 75% of individuals being identified as allergic to penicillin before the age of three years [14]. Eventually, after allergological evaluation, more than 90% of them can tolerate the antibiotic without any problem [15,16]. There are two main reasons for that. Firstly, in many cases, the primary symptom that raises the suspicion of drug allergy is a cutaneous rash that could be attributed to a viral infection itself or to the interaction between a virus and an antibiotic, as is observed in Epstein-Barr virus (EBV) infection, and not to a real allergic reaction [17,18]. The second reason is the potential development of tolerance to the antibiotic over time. Over 80% of patients with an IgE-mediated allergy will acquire tolerance within the next decade, while T-cell mediated events may not recur upon subsequent exposure to the same antibiotic [16].

The introduction of a de-labeling program could probably mitigate the inappropriate use of advanced antibiotics. It is crucial for de-labeling to be implemented early in life to avoid perpetuating this issue into adulthood. In the past, oral provocation testing (OPT) was only performed on patients with previously negative skin tests (STs) [2]. Indeed, STs' specificity is about 97.4%, which means that a positive STs can define a person as allergic to a specific antibiotic [19]. However, STs have limited sensitivity, particularly in cases of delayed skin reactions [20]. A comparative study found that only 9% of patients with non-immediate allergic reactions and positive OPT had previously tested positive on STs [21]. Additionally, STs are time-consuming and can be distressing for young children. Regarding laboratory in vitro testing, this testing is not effective in defining antibiotic allergy, as the existing data are controversial and limited in the pediatric population [22,23]. Conversely, OPT is considered a safe and straightforward method, as the majority of children undergoing this test do not exhibit severe symptoms [24]. For these reasons, it is preferable to perform OPT directly on individuals considered low risk for IgE antibiotic allergy and to conduct STs only in children who have experienced a reaction that is likely IgE-mediated.

The time that clinical manifestations occurred is a useful tool to distinguish reactions as high or low risk for immediate-type allergic reaction. If they happened within the first hour after medicine administration, they are likely immediate-type allergic reactions, whereas if clinical manifestations appeared after the first 72 h, they are probably T-cell mediated reactions. However, this distinction is not absolute, as immediate-type allergic reactions may sometimes manifest with a delay up to 6 h after antibiotic intake, while delayed allergic reactions can occur within the first 8–12 h [25–27].

The aim of this study was to evaluate the possibility of removing allergy labels for antibiotics in children and to explore the risk factors linked to positive allergy testing.

2. Materials and Methods

2.1. Patient Sample

We examined 112 children aged older than 12 months and younger than 16 years who visited the Pediatric Allergy Department of the Athens General Hospital "Attikon" between 18 December 2019 and 1 December 2023. They were referred due to allergy to at least one antimicrobial agent. OPT was regarded as the gold standard method for evaluating drug allergies, and as part of this study, children with reported allergies to multiple antibiotics underwent allergic tests for only one antibiotic.

2.2. Exclusion Criteria

Children with psychomotor delay, chronic urticaria, or uncontrolled asthma and immunosuppressed children were excluded by this study. Furthermore, individuals who had experienced severe allergic reactions, such as toxic epidermal necrolysis or Stevens-Johnson syndrome, were also not included in the studied population. The OPT was considered reliable if the child showed no signs or symptoms of infection during testing and if 4–6 weeks had passed since a possible hypersensitivity reaction. Additionally, none of the children had received antihistamines or corticosteroids for at least one week preceding the skin or OPT test.

2.3. Allergy Testing

We classified children into low and high-risk groups for immediate-type allergic reactions based on the time at which they exhibited suspicious symptoms. Any reactions occurring within the initial six hours following antibiotic administration were deemed possible immediate-type allergic reactions [25]. We further identified children as very high risk if they exhibited suspicious symptoms within one hour after antibiotic administration. In the high-risk group, the assessment commenced with the skin prick test (SPT) and intradermal test (IDT). A small amount of suspected allergens, normal saline (negative marker), and histamine (positive marker) were applied to the inner surface of children's forearms with a 20–30 min interval between the two kinds of tests. In our study, the allergens included amoxicillin, amoxicillin–clavulanic acid, cefuroxime, cefprozil, and cefaclor. We administered 0.05 mL of a concentration of 20 mg/mL for amoxicillin or amoxicillin–clavulanic acid and 2 mg/mL for cephalosporins [28]. The skin tests were evaluated at 15–20 min and were considered positive if the skin reaction exceeded 3 mm compared to the negative control [29]. Only if skin tests were negative, the OPT was subsequently conducted. If the skin tests were positive, the child was considered as allergic to the specific antibiotic and their parents were advised to avoid its administration. Children who were considered as a low-risk population underwent direct OPT.

The OPT was conducted by administering the suspected antibiotic at the maximum daily dose, divided into two doses (10% and 90% of total amount) with a one-hour interval between them. The administered antibiotics included amoxicillin, amoxicillin-clavulanic acid, cefuroxime, cefprozil, cefaclor, and clarithromycin. After the OPT, the children remained under observation at the Pediatric Allergy Department for a minimum of three hours after the last dose. The protocol was based on the previously described OPT method [30]. Subsequently, the provocation test extended for an additional three-day period, with an at-home administration of the antimicrobial agent at the maximum therapeutic dose. If the child manifested symptoms indicating allergic reaction at any stage of the OPT, the test was interrupted and considered as positive. For the purpose of our study, a positive allergic test was defined as either a positive ST or a positive OPT. Children who initially tolerated the suspected antibiotic well, but subsequently did not take it for three consecutive days due to reasons unrelated to an allergic reaction were excluded from the final analysis.

2.4. Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics 28.0 software. Initially, a descriptive statistical analysis of the entire sample data was conducted. Subsequently, appropriate statistical tools were applied to investigate potential correlations between variables. Mean values (Mean) and standard deviations (SD) were used to describe quantitative variables, while absolute (N) and relative (%) frequencies were employed to describe qualitative variables. The study utilized Fisher's exact test for potential correlations among qualitative variables and the Student's *t*-test for independent samples to compare quantitative variables between two groups. Prior to multivariate analysis, a comprehensive univariate analysis was conducted to identify potential predictor variables associated with positive allergy testing. Variables with a significance level less than 0.1 were considered for inclusion in the multivariate logistic regression model. All significance levels are two-tailed, and statistical significance was set at 0.05.

2.5. Ethics

All procedures conducted adhered to the ethical set by the committee on human experimentation and were in alignment with the Helsinki Declaration of 1975, as revised in 2008. Written consent was obtained from the parents of all participants after providing a comprehensive explanation of the study's objectives. Patient anonymity was strictly preserved. The research protocol, along with the written informed consent form, received approval from the scientific and ethics committee of the hospital.

3. Results

In total, we examined 112 children and 47 subjects (42.0%) were girls. The mean age of the total population was 5 years (1–16 years). The possible allergic reaction was presented in a mean age of 3 years old. The most frequently reported antibiotics were amoxicillin (48.2%) and amoxicillin/clavulanic acid (42.9%). Less frequently were reported allergies to second generation cephalosporins (6.3%) and macrolides (2.7%). In twenty-three subjects (20.5%), there was an allergy to more than one antibiotic, while six of children (5.4%) had presented with more than one episode after the administration of the same antibiotic. Almost all children (111, 99.1%) had received the responsible antibiotic orally and 106 out of 112 children (94.6%) presented symptoms after receiving antibiotic for their first time.

The main reason for prescribing the responsible antibiotic was upper respiratory tract infection (URTI) (71.2%). Overall, respiratory infection, regardless of focus, accounted for 89.3%. Three (2.7%) children had received the responsible antibiotic for skin infection, two (1.8%) for urinary tract infection, three (2.7) for other types of infection, and three (2.7%) for unknown reasons.

All children had presented maculopapular exanthema or urticaria, while six of them (5.4%) had presented with angioedema as well. In no case did parents reference symptoms affecting the respiratory, cardiovascular, or gastrointestinal systems. In the majority of cases, symptoms resolved after the administration of antihistamine drugs (80 individuals/71.4%), while 11 (9.8%) patients discontinued the antibiotic without further intervention. Corticosteroids were administered in 12 cases (10.7%) and none of the patients had received adrenaline. Hospitalization was required for 14 (12.5%) children. As for the duration of symptoms, parents of 21 children (18.7%) reported that the symptoms resolved in less than 24 h. In 81 (72.3%) children, the symptoms' duration was less than a week and only in 10 (8.9%) children did the symptoms persist for more than a week.

These symptoms presented in 13 individuals (11.6%) within the first hour and in 42 subjects (37.5%) within the first 6 h. These children were categorized as high risk for an immediate allergic reaction and underwent STs as the initial allergic testing.

As for the individual history of the studied children, 16 (14.3%) of them reported the presence of allergic asthma, 14 (12.5%) reported allergic rhinitis, and 38 (33.9%) had atopic dermatitis, respectively. Allergy history to other antibiotics was reported by 23 (20.5%) children and allergy to any other factor except for medications was reported by 15

(13.4%) subjects. A family history of allergy to any antibiotic was noted in only 12 (10.7%) of the children.

The clinical characteristics of the patients in relation to their assigned group are outlined in Table 1.

Table 1. Characteristics of high- and low-risk groups, related to the individual, family, and episode-specific medical history.

	Low Risk (N = 70)	**High Risk (N = 42)**	***p* Value**
Female sex	32 (45.7%)	15 (35.7%)	0.299
Current age	6.27 ± 3.40	6.23 ± 3.62	0.951
Age of episode	3.93 ± 2.40	3.20 ± 2.54	0.138
More frequently reported antibiotic (amoxicillin)	35 (50.0%)	19 (45.2%)	0.730
Route of drug administration (per os)	70 (100%)	41 (97.6%)	0.195
Reason for antibiotic prescription *: Respiratory infection	59 (84.2%)	41 (97.6%)	**0.027**
Urinary infection	1 (1.4%)	1 (2.4%)	0.713
Skin infection	3 (4.3%)	0 (0.0%)	0.174
Symptoms *: Maculopapular exanthema or urticaria	70 (100%)	42 (100%)	1.000
Angioedema	4 (5.7%)	2 (4.8%)	0.828
Duration of suspicious symptoms (<24 h) *	10 (14.3%)	11 (26.2%)	0.118
Treatment *: Discontinuation of antibiotic	9 (12.9%)	4 (9.5%)	0.594
Antihistamine drugs	54 (77.1%)	35 (83.3%)	0.432
Corticosteroids	7 (10.0%)	2 (4.8%)	0.324
Hospitalization	7 (10.0%)	7 (16.7%)	0.302
Allergy to other antibiotics	13 (18.6%)	10 (23.8%)	0.506
Food allergy	10 (14.3%)	5 (11.9%)	0.720
Asthma	7 (10.0%)	9 (21.4%)	0.094
Allergic rhinitis	6 (8.6%)	8 (19.0%)	0.105
Atopic dermatitis	23 (32.9%)	15 (35.7%)	0.757
Family history of antibiotic allergy	5 (7.1%)	7 (16.7)	0.115

* Data refer to the episode that was considered as a potential allergic reaction.

Characteristics such as gender, age, a medical or family history of allergy to other antibiotics, a medical history of food allergy, asthma, or allergic rhinitis, and atopic dermatitis were similarly frequent in both groups. The only statistically significant difference between the two groups was the reason for administering the responsible antibiotic. High-risk individuals were more likely to have received antibiotic treatment for respiratory infection than those in the low-risk group.

STs were ultimately performed on forty-two children, and three (7%) of them tested positive. These children were considered allergic to the tested antibiotic. OPT was performed in 109 children and 22 (19.6%) had a positive test result. Nine subjects (40.9%) experienced a reaction within the first hour of receiving the suspected medication, six (27.3%) on the first day, and seven (31.8%) in the subsequent days. One child (0.9%) did not complete the test because parents did not administer the antibiotic at home. This child was excluded from further statistical analysis. The remaining 86 (76.8%) children had negative OPT and managed to get de-labeled. The findings are illustrated in Figure 1.

Regarding the presented symptoms, seven individuals (31.8%) exhibited gastrointestinal symptoms, such as vomiting or abdominal pain, thirteen (59.0%) displayed urticaria or maculopapular exanthema, and two (9.0%) reported a fainting sensation without a decrease in blood pressure or an increase in heart rate. It is noteworthy that the last two children had been categorized as high risk, and their symptoms successfully resolved after adrenaline administration.

In total, 25 participants had positive test results (22.3%). The primary characteristics of children concerning their final categorization as allergic or non-allergic to drugs are

illustrated in Table 2. Children with a food allergy or a history of asthma were more likely to exhibit positive results in allergic testing. Moreover, if the suspected episode occurred at an earlier age or if parents reported the presentation of suspicious symptoms within six hours after antibiotic administration, the likelihood of testing positive also increased for the individual.

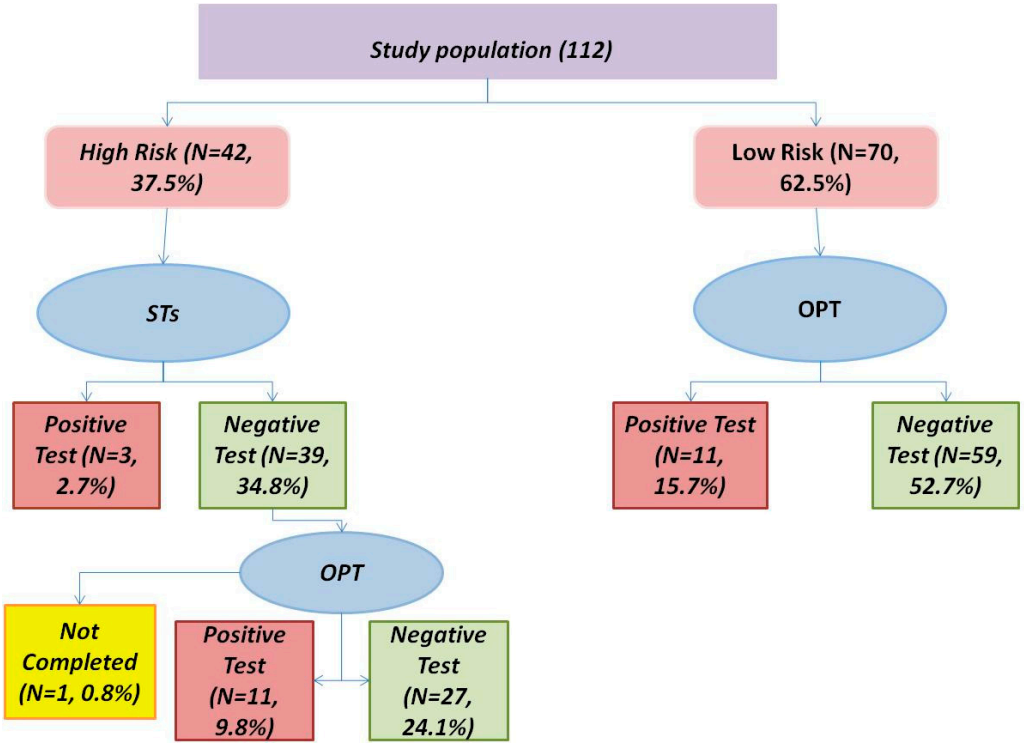

Figure 1. Results after allergic testing.

Table 2. Characteristics of participants that tested positive and negative, related to the individual, family, and episode medical history.

	Tested Negative (N = 86)	Tested Positive (N = 25)	*p* Value
Female sex	37 (43.0%)	10 (40.0%)	0.788
Current age	6.18 ± 3.58	6.36 ± 3.09	0.818
Age of episode	3.87 ± 2.69	2.94 ± 1.35	**0.021**
Reason for antibiotic prescription: respiratory infection	78 (90.7%)	21 (84.0%)	0.342
Duration of suspicious symptoms (<24 h)	14 (16.3%)	7 (28.0%)	0.188
Allergy to another antibiotic	14 (16.3%)	8 (32.0%)	0.83
Food allergy	8 (9.3%)	7 (28.0%)	**0.016**
Asthma	8 (9.3%)	7 (28.0%)	**0.016**
Allergic rhinitis	9 (10.5%)	4 (16.0%)	0.449
Atopic dermatitis	27 (31.4%)	10 (40.0%)	0.422
Family history of antibiotic allergy	9 (10.5%)	3 (12.0%)	0.828
High-risk group	27 (31.4%)	14 (56.0%)	**0.025**

According to the multivariate analysis, the variables demonstrating a correlation with an elevated risk of positive testing were food allergy, allergy to other antibiotics, and a history of asthma. High-risk children also showed a correlation with increased odds for positive testing; however, the significance level, although approaching conventional thresholds ($p = 0.065$), did not achieve statistical significance at the accepted level of 0.05. However, children who presented symptoms within one hour after antibiotic administration had

significantly increased odds for positive allergic tests (OR = 6.956, 95% C.I. 1.772–27.302, $p = 0.005$). Results of univariate and multivariate analyses are illustrated in Table 3.

Table 3. Univariate and multivariate analyses of studied variables.

	Univariate OR (95%CI)	***p* Value**	**Multivariate OR (95%CI)**	***p* Value**
Female sex	0.883 (0.356–2.187)	0.788		
Current age	1.015 (0.894–1.153)	0.816		
Age of episode	0.820 (0.648–1.038)	0.100	0.872 (0.667–1.141)	0.319
Reason for antibiotic prescription: respiratory infection	0.538 (0.148–1.963)	0.348		
Duration of suspicious symptoms (<24 h)	2.000 (0.704–5.681)	0.193		
Allergy to another antibiotic	2.420 (0.875–6.690)	0.088	1.820 (0.573–5.784)	0.310
Food allergy	3.792 (1.217–11.814)	**0.022**	4.885 (1.377–17.336)	**0.014**
Asthma	3.792 (1.217–11.814)	**0.022**	4.028 (1.094–14.824)	**0.036**
Allergic rhinitis	1.630 (0.456–5.819)	0.452		
Atopic dermatitis	1.457 (0.580–3.656)	0.423		
Family history of antibiotic allergy	1.167 (0.291–4.684)	0.828		
High risk	2.781 (1.118–6.920)	0.028	2.583 (0.943–7.074)	0.065
Very high risk			6.956 (1.772–27.302)	**0.005**

4. Discussion

In our study, the majority of children were categorized as low risk for immediate-type allergy (62.5%). The only criterion used to categorize children into low- and high-risk groups was the time they presented the suspicious symptom. If it occurred within the first 6 h after antibiotic administration, they were considered high risk. The sole differing characteristic between groups, more prevalent in the high-risk group ($p = 0.027$), was the administration of the suspected antibiotic for treating respiratory infections. This is plausible, given that respiratory viruses are likely to interact with the antibiotic and trigger the appearance of rashes soon after its administration [18,31,32].

A significant percentage of children (76.8%) demonstrated good tolerance to the tested medication. This percentage was lower than expected based on the majority of the current literature (>90%) [33,34]. However, there are also other studies that present percentages similar to our findings [35,36]. In our study, the population included a substantial proportion of high-risk children (37.5%), enhancing the probability of having genuine allergy to the examined antibiotic. Additionally, the OPT test spanned 4 days, enhancing the method's sensitivity [37]. The STs showed a sensitivity of 20%, aligning closely with the existing literature [19]. In children with positive STs or OPT a further recommendation was made for repeat allergological testing in 5 years [16].

Regarding positive allergic testing, children had a younger age when the suspicious episode occurred, were more likely to report food allergy or asthma, and were more frequently classified into the high-risk group. However, following multivariate analysis, an increased risk for positive testing was observed only in children with a history of allergy to other factors or asthma. Being asthmatic or having food allergy indicates a predisposition of the organism to exhibit an allergic reaction to foreign antigens [38,39]. Therefore, it is reasonable for these children to be at an increased risk for antibiotic allergy.

In our study, we considered as high-risk children those who reported the onset of suspicious symptoms within 6 h of taking the antibiotic. The reason we chose to extend the time limit to 6 h is that the history was taken retrospectively, and we wanted a broader time frame for parents. Additionally, we aimed to conduct OPTs with great safety, particularly because children in the low-risk group had not undergone ST. When a multivariate analysis was conducted, considering potential risk factors and setting the time limit for symptom onset at one hour, significant increased odds ratios were found. This indicates that children who exhibit suspicious symptoms within one hour after antibiotic administration are at an increased risk of testing positive.

Family history has also been identified as a risk factor for positive testing in other studies [35,36,40–42]. For instance, a recent study in Portugal discovered that a family history of antibiotic allergy was significantly more frequently reported in children with a positive OPT [42]. According to a relevant systematic review, there are some polymorphisms in some genes that correlate with increased risk for immediate allergic reactions to beta lactams [41]. In our study, children allergic and non-allergic to antibiotics did not differ in their family history of antibiotic allergy. This may be due to the size of our sample or it could be attributed to the presence of specific genes that predispose for antibiotic allergy in some populations and not in others. Additionally, our population consisted of patients with allergies to all kinds of antibiotics, and not only beta lactams.

Female sex, the age at the time of the possible allergic reaction, a history of allergy to other antibiotics, atopic dermatitis, and rhinitis have been identified as risk factors in some studies, while others found no correlation [43–48]. In our study we did not observe a correlation between these factors and an increased risk of positive allergic testing. This discrepancy in the literature underscores a substantial gap in current knowledge.

Finally, children who had been administered the responsible antibiotic for respiratory infections had a higher frequency of negative test results, albeit the difference was not statistically significant. This is reasonable, since, as already noted, respiratory viruses may independently provoke rash. However, respiratory infections are the most common reason for antibiotic prescription and as a result, the majority of participants had received the antimicrobial agent for this purpose. Hence, the lack of statistically significant difference might be attributed to this prevalence [1,32].

This study has certain limitations. Firstly, it was a cross-sectional study that relied on the children's history as reported by parents, introducing potential recall bias. Furthermore, the categorization of the study population into high and low risk was solely determined by the timing of symptoms after antibiotic administration. The development of a protocol that could classify children into high and low risk by considering additional risk factors might prove beneficial for future studies. Additionally, the small sample size and the single center design and implementation of the study, as well as the lack of long-term tolerance follow-up, constrain the generalization of our findings. These limitations underscore the necessity for further research to address these gaps.

5. Conclusions

The percentage of children with good tolerance to the tested antibiotic was significantly high and exceeded 75%. Furthermore, children who displayed symptoms within an hour of antibiotic administration, as well as those with a medical history of asthma or food allergies, showed a notable increase in the likelihood of testing positive. Last but not least, it was demonstrated that a 6 h timeframe serves as a safe limit for direct OPT without the need for a preceding ST. However, additional studies are needed to identify more factors that increase the risk of antibiotic allergy. These data could be integrated into standardized protocols aiming for individual de-labeling from childhood, offering both individual and societal benefits.

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Informed Consent Statement: Written consent was obtained from the parents of all participants after providing a comprehensive explanation of the study's objectives.

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