Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Risk Stratification of Penicillin Allergy Labeled Children: A Cross-Sectional Study from Jordan

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Background: Implementing allergy testing among children with a reported history of penicillin allergy could be challenging, particularly in developing countries with limited resources. This study screened and risk-stratified the likelihood of true penicillin allergy among children labeled with penicillin allergy in Jordan.

Methods: A web-based survey, completed by parents, assessed history, type, and severity of penicillin allergic reactions, including age at diagnosis, symptoms, time to the reaction, reaction's course and resolution, and received medical evaluation/testing. Low-risk allergic symptoms were defined as vomiting, diarrhea, headache, dizziness, itching, rash, cough, or runny nose without evidence of anaphylaxis or severe cutaneous reactions.

Results: A total of 530 parents of "penicillin allergy"-labeled children completed the survey. Of these, 86.4% reported allergic reactions to penicillin and 13.6% reported avoidance of penicillin due to family history. Among the former, 52.2% were male, 67.3% were three years old or younger when the reported reaction was established, and 68.3% experienced exclusively low-risk symptoms. Overall, skin rash was the most reported symptom (86.0%). High-risk symptoms were reported in 31.5% of children. About two-thirds (64.0%) of children were reported to have experienced symptoms after the first exposure to penicillin. The most common indication for antibiotic use was a throat infection (63.8%). Asthma comorbidity was significantly higher among high-risk (24.8%) compared low-risk group (11.5%).

Conclusion: In Jordan, many parent-reported penicillin allergic reactions seem to be clinically insignificant and unlikely to be verifiable, which can adversely affect patients' care and antimicrobial stewardship. An appropriate clinical history/evaluation is a key step in identifying true immunoglobulin E-mediated allergic reactions and risk stratifying patients for either de-labeling those with obviously non-immune–mediated reactions or identifying candidates for direct oral challenge test.

Keywords: children, drug hypersensitivity, drug resistance, Jordan, penicillin resistance

Introduction

Penicillin is one of the most reported antibiotic drug implicated in eliciting hypersensitivity reactions with a prevalence of 10% in general population.[1] Nevertheless, many patients are believed not to be truly allergic and are amenable to the safe use of penicillin.[2,3]

Inaccurate penicillin allergy labeling is associated with increased potential for the utilization of costly, broad-spectrum, or second- or third-line antibiotics.[4] It may also increase the risk of antimicrobial resistance which currently represents the fundamental challenge against the use of successful antimicrobial therapy in developing countries.[5,6] Hospitalized patients with an unverified history of penicillin allergy were reported to experience longer hospital stays and to develop serious drug-resistant infections, such as methicillin-resistant Staphylococcus *aureus* (MRSA) and Clostridium *difficile*.[5–7] Active attention to evaluating old and inaccurate penicillin allergies and de-labeling strategies are, therefore, important milestones in antimicrobial stewardship programs. Accordingly, one of the recommendations by

Received: 19 February 2024
Accepted: 7 August 2024
Published: 22 August 2024

the American Academy of Allergy, Asthma, and Immunology (AAAAI) in the Choosing Wisely program, in 2014, was that "physicians should not overuse non-β-lactam antibiotics" in patients with a history of penicillin allergy without "an appropriate evaluation".[8]

The appropriate evaluation of penicillin allergy cases depends largely on careful history- taking. An accurate structured history includes a detailed description of symptoms, the timing of the reaction, course of the reaction, treatment of the reaction, concurrent exposure to other drugs, and presence of relevant comorbidities. These factors play a key role in distinguishing between a true allergic reaction, whether IgE-mediated or non-IgE-mediated, and other non-allergic adverse reactions. Studies have shown that between 30% and 63% of drug allergy labels can be removed after an appropriate interview, which would be particularly useful if the availability and implementation of skin testing is lacking. This will have a substantial impact on both the quality of care and antimicrobial stewardship.[9–11]

Further, almost 40% of patients with antibiotic allergy labels have low-risk allergy history, which makes them candidates for a direct oral challenge without the need to perform skin testing.[10] Studies demonstrated the safety and efficacy of direct oral challenge to penicillin without prior skin testing in low-risk patients.[12–14] In resource-limited clinical settings, such as those in most developing countries, including Jordan, this is a critical approach that can save time and effort upon administering penicillin to children who report potential allergic reactions. Yet, little is known about risk stratification or history-based assessment in most developing countries. The current study aimed to screen and risk stratify the likelihood of a true penicillin allergy by parents of "penicillin-allergic" labeled children, and to clarify the characterization and severity of the reaction and the likelihood of causality.

Methods

Study Design

In this observational cross-sectional study, we developed a survey containing essential clinical questions adapted from expert opinion, published studies, and guidelines to screen and risk stratify the likelihood of a true penicillin allergy.[12,15–17]

Tool

The survey was completed by either parent to clarify penicillin allergies by providing information related to the type and severity of the reaction.

The first question confirmed if the child had experienced a reaction to penicillin antibiotics, or if parents were avoiding penicillin antibiotics due to any other reason. Allergy-related questions included: the age of the child when the allergy was diagnosed, gender, antibiotic administered, the indication of antibiotic prescription, a list of allergy symptoms, time to allergic reaction from the first dose, reaction course and resolution, reaction recurrence, whether the child was evaluated by an allergist or pediatrician or underwent allergy testing, antibiotic re-use, a parent, healthcare personnel, or both diagnosed the allergy.

Parents who reported skin rash were asked to identify the rash type utilizing a set of pictures representing different types of rashes. Parental responses evaluated children who had a penicillin allergy label, differentiated true immunologically based penicillin allergies from a nonspecific or non-immunological reaction, identified clinical presentations and severity of penicillin allergy, and stratified children into low-risk or high-risk groups, based on the history of parent-reported clinical presentations (symptoms) associated with penicillin allergy.

Any history suggesting potentially life-threatening IgE-mediated symptoms, respiratory, or cardiovascular involvement, such as difficulty in breathing, wheezing, drop in blood pressure, facial, throat or lip swelling, or severe cutaneous adverse reactions, was considered a high-risk symptom. Low-risk symptoms referred to clinical presentations that are likely non-immunological reactions such as vomiting, diarrhea, headache, dizziness, itching, rash, cough, or runny nose without any symptom suggesting anaphylaxis. This classification was based on the reported symptoms and reaction severity with the potential for severe IgE-mediated or a T-cell-driven reaction. Any symptom suggesting a potentially life- threatening reaction, either IgE-mediated or T-cell driven, was considered a high-risk symptom. While low-risk symptoms referred to clinical presentations that are likely non- immunological and not likely to represent severe reactions (without angioedema,

severe cutaneous involvement such as mucosal ulceration, or systemic symptoms).[1,12–16] Severe cutaneous adverse reaction such as blisters and peeling of skin and mucous membranes suggestive of severe T-cell-mediated reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms.

Study population

The online survey link was distributed using special social media parental groups between September and November 2021. These groups were Facebook groups where parents usually share experiences related to their children's well-being including medication allergies. Some of these groups were related to allergies while others were related to general well-being of the children. Parents were asked to participate if they had a child with any type of self-reported penicillin allergy and had avoided penicillin antibiotics. Subjects were then administered the online survey by directing parents to a Google form link housing the survey questions. Before the beginning of the survey, parents were informed about the purpose of the survey and were provided an online consent for participation. This study was approved by the institutional review board of Yarmouk University (no. RD/119/12/1575) under the Faculty of Research (no. 2/2021). Our study complies with the Declaration of Helsinki.

Patient and Public Involvement Statement

Neither patient nor public were involved in the design or conduction of this study.

Data analysis

Data was extracted from Google forms and imported into EXCEL for quality control before analyses took place using SPSS version 26. Frequency distribution of the main variables, using frequency and percentages (%) as well as means and standard deviations (SD), was conducted as appropriate. The distribution of children by risk group (low vs high risk) was assessed using a chi-square test. Alpha level was set at 0.05 for statistical significance.

Results

Rates of Parent-Reported Symptoms of Previous Penicillin Allergic Reactions

A total of 530 parents participated in the study and self-reported being a parent of a child with a penicillin allergy-label and the avoidance of penicillin antibiotics. Of which, 86.4% (n=458) reported a history of clinical allergic reaction to penicillin antibiotics, and 13.6% (n=72) reported avoidance of penicillin due to, only, a family history of β-lactam hypersensitivity. Among the group with a history of allergic reactions, 52.2% (n=239) were male and more than two-thirds (n=308, 67.3%) were 3 years or younger at the onset of the reaction and "penicillin allergy label" acquisition (Table 1).

Table 1 Demographics of the Study Population (n=458)

	n (number)	% *(percentage)*
Age when reaction reported		
1 to 6 months	74	*16.2*
7 to 12 months	100	*21.8*
1 to 3 years	134	*29.3*
4 to 6 years	75	*16.4*
7 to 9 years	24	*5.2*
10 to 13 years	26	*5.7*
14 to 16 years	25	*5.5*
Total	***458***	***100***
Gender		
Girls	219	*47.8*
Boys	239	*52.2*
Total	***458***	***100***

Risk Stratification of Parent-Reported Symptoms of Penicillin Allergic Reactions

Based on the severity of the reported allergy symptoms and their consistency with true allergy, we stratified participants into two risk groups: low-risk and high-risk symptom groups. Exclusively low-risk symptoms were the most reported (68.3%, n=313) (Table 2). Overall, skin rash (86.0%, n=394) and itching (30.6%, n=140) were the most reported low-risk symptoms (Table 2). The gastrointestinal symptoms, such as diarrhea (13.3%, n=61) and vomiting (10.9%, n=50), were not as common. Among those with skin rash, the maculopapular rash was the most identified type (58.3%, n=267) indicative of a mild cutaneous reaction, while the urticarial eruption was reported only in 19.0% of children (n=87). About one-third of parents (31.7%, n=145) reported one or more high-risk symptoms, with facial swelling (29.5%, n=135) being the most frequently reported symptom, followed by difficulty breathing (n=53, 11.6%) and lip swelling (n=43, 9.4%). The distribution of risk groups by age and gender showed no statistically significant differences (Table 3).

Types of Parent-Reported Penicillin and Therapeutic Indications

While 39.1% of parents did not remember the type of penicillin administered at the time of the reaction, amoxicillin and amoxicillin/clavulanate were the most frequent culprit antibiotics recalled (88.0%). Throat infection was the most commonly reported indication for an antibiotic prescription when the reaction occurred (67.2%, n=308). To a lesser extent, children were given the penicillin antibiotic for ear and chest infections (n=79, 17.2% and n=65, 14.2%, respectively) (Table 4).

The percentage of first exposure to penicillin was higher among high-risk (71.0%), compared to low-risk group participants (60.7%), albeit this difference was not statistically significant (p=0.097) (Table 5). Similarly, the percentage

Table 2 Distribution of Children by Parent-Reported Allergy Symptoms [a] (n=458)

Presence of Symptoms[a]				
Clinical Presentation	**No**		**Yes**	
	n	**%**	**n**	**%**
Low Risk Symptoms			**313**	**68.3%**
Itching	318	*69.4%*	140	*30.6%*
Skin rash*	64	*14.0%*	394	*86.0%*
Urticaria	371	*81.0%*	87	*19.0%*
Maculopapular rash	191	*41.7%*	267	*58.3%*
Non-specific rash	418	*91.3%*	40	*8.7%*
Diarrhea	397	*86.7%*	61	*13.3%*
Vomiting	408	*89.1%*	50	*10.9%*
Cough	429	*93.7%*	29	*6.3%*
Runny Nose	432	*94.3%*	26	*5.7%*
Dizziness	437	*95.4%*	21	*4.6%*
High Risk Symptoms			**145**	**31.7%**
Facial swelling	323	*70.5%*	135	*29.5%*
Difficulty Breathing	405	*88.4%*	53	*11.6%*
Lip swelling	415	*90.6%*	43	*9.4%*
Wheezing	428	*93.4%*	30	*6.6%*
Mouth Blisters	436	*95.2%*	22	*4.8%*
Skin Peeling	433	*94.5%*	25	*5.5%*
Throat Swelling	437	*95.4%*	21	*4.6%*
Hypotension	451	*98.5%*	7	*1.5%*

Notes: [a] more than one symptom could be selected (items are not mutually exclusive). * Percentage calculated for skin rash categories is from the total study population.

Table 3 Distribution by Risk Group and by Age and Gender

	Low-Risk		High-Risk		*P-value*
	n	%	n	%	
Age					*0.333*
1 to 6 months	43	*58.1%*	31	*41.9%*	
7 to 12 months	74	*74.0%*	26	*26.0%*	
1 to 3 years	90	*67.2%*	44	*32.8%*	
4 to 6 years	53	*70.7%*	22	*29.3%*	
7 to 9 years	19	*79.2%*	5	*20.8%*	
10 to 13 years	18	*69.2%*	8	*30.8%*	
14 to 16 years	16	*64.0%*	9	*36.0%*	
Gender					*0.940*
Female	150	*68.5%*	69	*31.5%*	
Male	163	*68.2%*	76	*31.8%*	

Table 4 Distribution of Children-Data by Indication for Antibiotic Use

Indication[b]	n	%
Throat Infection	308	*67.2%*
Ear infection	79	*17.2%*
Chest Infection	65	*14.2%*
Fever without a known reason	38	*8.3%*
Urine infection	12	*2.6%*
Do not remember	27	*5.9%*
Skin infection	13	*2.8%*
Other	37	*8.1%*

Notes: [b]Indication for Antibiotic Use Reported by Parents. The items are not mutually exclusive. More than one indication could be selected.

Table 5 Distribution by Risk Group and by Penicillin Use and Time of Symptom Onset

	Risk Group					
	Total	**Low-Risk**		**High-Risk**		***P-value***
		n	%	n	%	
First-Time Penicillin Use						
Do not Remember	52	38	*12.2%*	14	*9.7%*	
No	113	85	*27.2%*	28	*19.3%*	*0.097*
Yes	293	190	*60.7%*	103	*71.0%*	
Total	458	313	*100.0%*	145	*100.0%*	
Time of Symptom Onset						
Less than 1 hour	145	98	*31.3%*	47	*32.4%*	
Less than 6 hours	122	87	*27.8%*	35	*24.1%*	
Less than 24 hours	71	47	*15.0%*	24	*16.6%*	*0.097*
More than 24 hours	75	51	*16.3%*	24	*16.6%*	
Do not remember	45	30	*9.6%*	15	*10.3%*	

of parents who reported that the symptoms occurred within one hour of drug administration was similar in both risk groups (low risk: 31.3%, high risk: 32.4%, p=0.097).

Less than one-quarter (n=68, 21.7%) of children in the low-risk group visited an emergency department (ED), of those only two (2.9%, 2/68) received an epinephrine injection. Among the high-risk group, 26.9% (n=39) of children visited an ED, of which seven (17.9%, 7/39) received an epinephrine injection.

When asked if the child underwent an allergy evaluation, 40.2% (n=184) of parents stated that their children were penicillin-allergy labeled without any further evaluation by health care providers. However, 27.9% (n=128) of children were evaluated and diagnosed by a general practitioner and 28.2% (n=129) by a pediatrician. In only 3.7% of children, the diagnosis was made by an allergist. Diagnostic procedures for penicillin allergy were not performed in most children (74.5%).

Penicillin Allergic Reactions and Comorbidities

In terms of comorbidities, over one-third of the children (40%, n=183) had a history of other allergic diseases (Table 6). Children in the high-risk group (24.8%) were significantly twice as likely to have asthma compared to their counterparts in the low-risk group (11.5%) (p=0.002). However, children with food allergies were significantly higher in the low-risk group (9.6%) compared to their counterparts in the high-risk group (2.1%) (p-value =0.003) (Table 6).

Discussion

The current study screened children with potential penicillin allergy and risk-stratified them to identify the likelihood of a true penicillin allergy. The results suggest that about two-thirds (68.3%) of children with parent-reported penicillin allergy labels had experienced exclusively low-risk symptoms. These children are appropriate candidates for a direct oral amoxicillin challenge, to confirm current penicillin tolerance, thereby overcoming the need for allergy testing which is not routinely available in Jordan. These results are in line with studies addressing penicillin allergy histories where between 50 and 70% of patients with parent-reported penicillin allergy have symptoms unlikely to be consistent with true allergy[1,10,18.] This reflects on the global impact of identifying penicillin allergy using risk stratification through detailed history taking, especially in resource-limited countries. Accordingly, quality improvement in the health services that apply for screening for penicillin allergy implemented within developed countries could be of an added value to Jordan. Clinical guidelines for the proper identification of medication allergies could be utilized in developed countries as similar results of reported in the current study were inline with the global literature. Cutaneous eruptions were the most reported symptoms (86%), of which, the maculopapular rash was the most identified type. Previous data noted that mild cutaneous reactions including non-specific, maculopapular rash and hives were the most frequent reported clinical history in percentages between 37% and 90%.[10,18] This type of rash is explained as being benign and non -IgE-mediated cutaneous adverse reaction to the administered antibiotic but is not considered to belong to true drug allergy.[19] Furthermore, viral infections are the most common cause of maculopapular eruptions in children, and thus a concurrent infection could be the cause of this rash.[20,21] Moreover, the presence of an underlying viral infection, such as those caused by Epstein- Barr

Table 6 Comorbid Allergic Disorders Among Children[c]

Risk Group					
Comorbid Allergic Disorders	**Low-Risk**		**High-Risk**		***P-value***
	n	**%**	**n**	**%**	
Asthma	36	*11.5%*	36	*24.8%*	*0.002*
Allergic Rhinitis	51	*16.3%*	22	*15.2%*	*0.760*
Eczema	27	*8.6%*	11	*7.6%*	*0.707*
Food Allergy	30	*9.6%*	3	*2.1%*	*0.003*

Notes: [c] More than 1 indication could be selected (items are not mutually exclusive).

virus (EBV), cytomegalovirus, or human herpes virus 6, is a risk factor for the occurrence of penicillin-induced maculopapular rash.[18,22,23]

Studies have indicated a very high incidence of antibiotic-induced skin reactions in patients with acute infections with EBV that may reach more than 90% of patients.[24] Several studies also demonstrated that skin rash associated with amoxicillin is rarely reproducible with allergy testing and that it is a common benign adverse reaction that does not require discontinuation of the medication.[18,25] While the development of urticaria could be a result of an IgE-mediated reaction, isolated urticaria that is not accompanied by high-risk symptoms is also considered a low-risk symptom since urticaria is more frequent due to other causes than a true penicillin allergy.[18,26] In our study, the majority of reported urticaria (83%) was isolated. Accordingly, distinguishing the underlying cause of the skin rash is a critical issue that pediatricians should consider before informing parents of any potential penicillin allergic reaction. Parents should also consider this possibility before deciding that their child is allergic. Although penicillin is estimated to cause between 0.7% and 10% of all cases of anaphylaxis, the incidence of these potentially life-threatening reactions to penicillin is very low (estimated at 1 in 100,000).[27,28] In our study, less than a third of parents reported one or more high-risk allergy symptoms, and a small subset of children had a history consistent with a high-risk reaction, such as those with IgE-mediated anaphylactic reactions that are associated with respiratory or cardiovascular involvement (ie, wheezing, difficulty breathing, hypotension, etc). This type of reaction is generally classified as an immediate reaction that occurs within one hour of receiving the medication.[27,29,30] However, this chronological classification is somewhat controversial and certain guidelines suggest that immediate reactions can be elicited within up to six hours after drug administration.[31] However, one-third of the reported reactions (33.2%) in the high-risk group in this study were delayed after six hours of drug administration which does not reflect true IgE-mediated reactions. This inconsistency highlights the need for immediate evaluation and proper documentation of any suspected penicillin allergy.

In children, acute otitis media is the most common indication for antibiotic therapy in the outpatient setting.[32] Our results showed that throat infection was the most common indication for penicillin antibiotic administration (67.2%) and only 17.2% of children received the antibiotic for an ear infection. Over 60% of children in the low-risk group and more than two-thirds (71%) of the high-risk group were taking penicillin for the first time. This is not consistent with the immunologically mediated hypersensitivity reactions to drugs that usually required sensitization from previous exposure.[33] Most penicillin allergy labels are acquired in early childhood and most children are penicillin-allergy labeled before their third birthday.[34] Similarly, our results found that 67.2% of penicillin allergy labels are obtained by the age of three years with no significant difference between low- and high-risk groups. Notably, about one-half of penicillin-allergy labeled children in our study were diagnosed by parents without formal medical involvement or evaluation and more than half of the children were diagnosed by a general practitioner or a pediatrician. Primary care physicians are often the first point of contact for patients with a drug reaction history. Unfortunately, a paucity of skills and knowledge of drug allergy approaches and diagnoses is recognized among primary care physicians and pediatricians.[35–37] Drug hypersensitivity reactions require a structured diagnostic process and potentially further evaluation by allergy specialists.[38] In our study, only 4.3% of children have been evaluated and diagnosed by an allergist and 2.6% underwent a diagnostic procedure that exclusively consisted of a skin prick test but none of the children had an oral drug challenge test. Previous reports have shown that a small percentage of patients (less than 10%) who are suspected to have drug allergies received allergists' consultations and diagnostic tests were performed infrequently.[36,38] Our results call for increasing awareness of the role of accurate history taking in de-labeling of penicillin allergy children. A structured training in this category could benefit a wide range of physicians, especially, pediatricians, in properly labeling pediatric patients especially in the emergency rooms. This could be part of the continuous medical education and re-certification programs. As well, pediatricians, primary care physicians, and pharmacists could implement a de-labeling program at healthcare services that lack allergy specialist.

Limitations

We acknowledge that this study had a few limitations. At first, it was conducted using an online survey so the results may not be generalizable. Still, the results showed the urgent need to implement screening and allergy testing to ensure those labeled for allergies are appropriately labeled or de-labeled. This study also utilized reporting of allergies and related

symptoms by parents. This may lead to the misidentification of symptoms. Accordingly, future studies should recruit patients from healthcare facilities and conduct a clinical assessment of signs and symptoms and compare them to parent-reported signs and symptoms. In addition, future investigations should focus on testing for allergic reactions by an allergist to be able to properly estimate symptom severity. Regardless of the limitations, the current investigation pointed to the critical need in educating healthcare providers and parents on issues related to true penicillin allergy.

Conclusion

Many children with parent-reported penicillin allergy had inconsistent histories with true penicillin allergic reactions. Insufficient penicillin allergy assessment by healthcare professionals will lead to inaccurate penicillin allergy labels and unnecessary treatment with alternative agents. There is a need for validated approaches to penicillin allergy diagnosis that starts with using a structured allergy history assessment to help differentiate true allergic reactions from adverse reactions. The use of history and risk stratification is a simple and feasible rule that accurately identifies low-risk penicillin symptoms that do not require formal allergy testing. Subsequently, this decreases the need for the time-consuming, costly, and sometimes unavailable penicillin skin testing.

Abbreviations

EBV, Epstein–Barr Virus; n, Number; %, percentage.

Data Sharing Statement

Data are available with the corresponding author and could be requested for a rational reason.

Acknowledgments

We would like to thank all parents who participated in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Faculty of Research at Yarmouk University [grant number 2/2021]. The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript. The payment was distributed for research activities to cover logistics and data collection design and maintenance. No payments were personally received by any of the authors.

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this article.

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