

Antibiotic oral provocation challenge in children

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Abstract

Aim

The main objective of this study was to see how many of the children, with a suspected antibiotic allergy, developed an allergic or adverse reaction to a drug provocation test.

Methods

Data on children that had undergone a drug provocation test for a suspected antibiotic allergy were compiled retrospectively for the period from 2007–2018. The median age at the first provocation was 2.25 years (1.5–5.7). Standardised questionnaires, the children's parents had answered before the provocation, were used to evaluate the originally suspected allergic reaction, previous health, atopic diseases and family history.

Results

Ninety-two (6.4%) of the 1440 children showed a possible mild allergic reaction. Sixty-four of the 92 children underwent a second drug provocation test 1–2 years later. At that time, only eleven developed a positive- or a possible-delayed reaction.

Conclusion

An immediate moderate or severe allergic reaction was excluded in all cases of suspected antibiotic allergy in this study. Our study indicates that an oral drug provocation test is safe. It may be appropriate to wait for 6 months or more after the initial event of ADR before these tests are performed. A second oral provocation

1–2 years after the first one shows that ADRs are outgrown in most children.

Abbreviations

IgE

Immunoglobulin E

Key Notes

The study was conducted to determine how many children labelled with an antibiotic allergy reacted when given the suspected antibiotic.

At first test, 6.4% showed a mild possible allergic reaction and when tested again 1–2 years later, only 17.2% had a mild reaction.

Most children with a history of a mild reaction to antibiotics seem to tolerate the same antibiotic later

1 INTRODUCTION

Penicillin allergy is frequently suspected in children. It is estimated that up to 10% of adults believe that they have a penicillin allergy.^{1, 2} Interestingly, however, the majority of them tolerate antibiotics on provocation.^{3, 4} Most children admitted to an emergency department in the USA because of a suspected penicillin allergy had minor symptoms. Most of them were receiving the ongoing penicillin treatment for acute otitis media (AOM) and were less than 3 years of age.⁵ It is difficult to verify ADRs by clinical information alone and this explains why it is important to have well-functioning guidelines for testing penicillin allergy.

Generally, symptoms of drug allergy can be divided into early and late. The early ones appear within 1 h after the drug has been taken. The most common symptoms are urticaria, angioedema, asthma and breathing difficulties. These symptoms are mostly mediated through IgE and can become life-threatening.^{6, 7} This type of allergy can be diagnosed with cutaneous tests or blood allergy tests for the penicillin components.⁸ Anaphylaxis caused by antibiotics is very rare and should be managed by allergy specialists. A good guideline is reported by Macocic et al. in an EAACI position paper.⁹

Delayed antibiotic allergy reactions appear after some hours and are T-cell-mediated. The most common symptoms are mild skin rashes, maculopapular eruptions and urticaria.¹⁰ Examples of serious T-cell-mediated delayed reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis.¹¹ Although around 10% of children develop rashes when treated with antibiotics,¹² the majority have only mild rashes. In many cases, they are not mediated through immunological mechanisms. In adults, these symptoms are more likely to be

allergic than they are in children. This can be explained by the fact that young children experience contact with different viruses early in their lives, This leads to different immunological responses compared with adults and skin eruptions are common.¹³

A diagnosis of an antibiotic allergy cannot solely be determined by clinical data. The history, especially the type of symptoms and duration, is important. The available tests are mostly used to exclude an IgE-mediated allergy, which can be life-threatening. Tests include intracutaneous skin testing, which is not practical for children.

1.1 Measurements of IgE antibodies to different antibiotics and oral provocation tests are preferred for children

A suspected penicillin allergy calls for the use of antibiotics that are often more expensive and can increase the risk of inducing bacterial resistance to the drug used. It is, therefore, of great interest to have the appropriate guidelines to confirm or exclude the drug allergy diagnosis.

2 MATERIAL AND METHODS

Fourteen hundred and forty children, aged from five months to 18 years, were included in this retrospective observational study that covered the period from 2007 to 2018, Table 1. The children, 679 girls (47%) and 761 boys (53%), were called in for an antibiotic provocation test at the outpatient department at the Children's Hospital in Reykjavik, Iceland. Sixty-four of the 92 children who reacted after the first provocation were repeated the tests 1–2 years after the first one. Of those 28 who did not participate, some had moved abroad, others refused participation and a few had already been given the suspected antibiotic.

TABLE 1. Demographics of the 1440 children

Characteristic	Number
Male	761 (53%)
Female	679 (47%)
Age at inclusion, years, median/IQR	2.25 (1.5–5.7)*

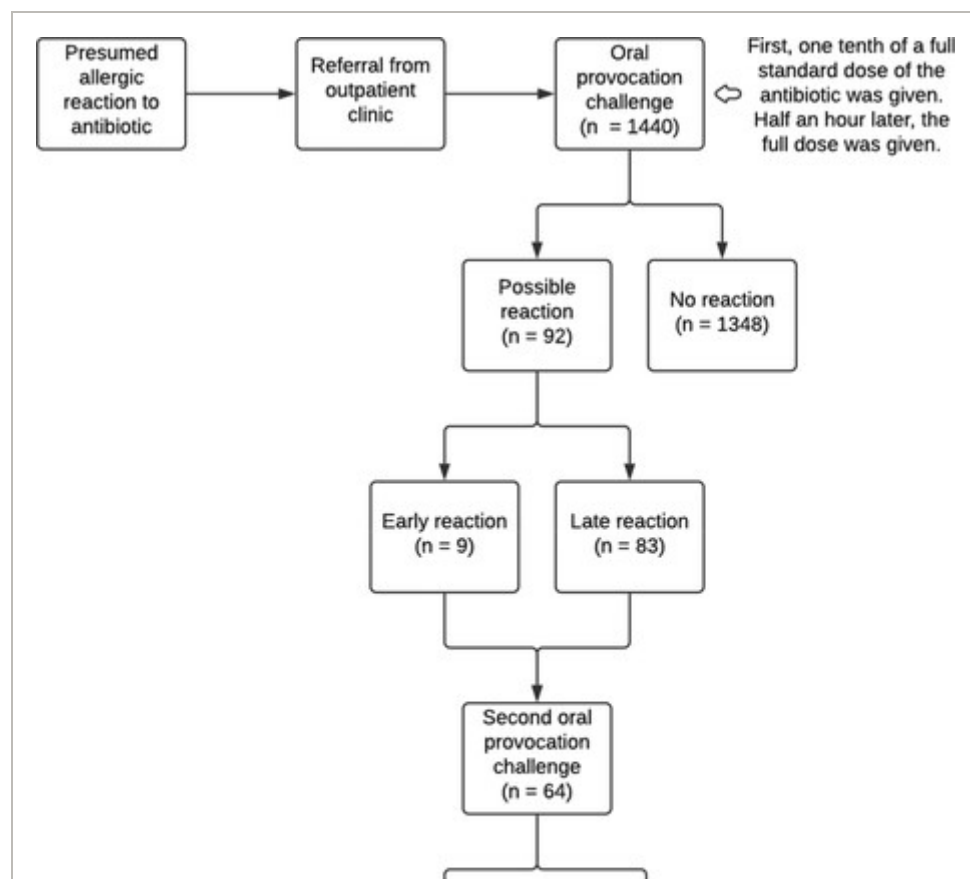
Atopic diseases**	Yes (%)	No (%)	Unknown (%)
Atopic dermatitis	308 (21.4)	439 (30.5)	693 (48.1)
Asthma/wheezing	351 (24.4)	395 (27.4)	694 (48.2)
Another allergy***	171 (11.9)	1153 (80.1)	116 (8.0)

*Interquartile range.

**Answers relating to atopic dermatitis and asthma were only available for around 50% of the children. This is because these questions were added a few years after the initiation of the study period.

***IgE-mediated allergy (food, pollen, animals, etc.).

The children participating in this study were mostly referred from outpatient clinics. During the study period, all the children met the same study nurse who performed the oral provocation test. A paediatric allergy specialist also participated. Prior to the provocation test, parents answered a standardised questionnaire about the type of drug used, the diagnosis that led to the antibiotic treatment, the type of drug reaction, when the reaction started and for how many days it lasted. Questions were answered about atopic diseases amongst the children and their parents. All the children underwent a stepwise drug provocation at the Children's Hospital in Reykjavik, Iceland, Figure 1. The child received one-tenth of a full standard dose of the same antibiotic that had originally been given. Half an hour later, the second dose was given. The doses were based on the child's weight. After the second dose, the child was observed for 1 h. If no reaction was observed, the child was discharged from the hospital. Within the next 24 h, the parents were contacted to confirm whether a possible late reaction had occurred. Children who had a positive oral provocation challenge were registered for a repeated oral challenge test a year or two later. The procedure of the provocation was the same and doses of antibiotics were also correlated to the children's weight, see Figure 1.



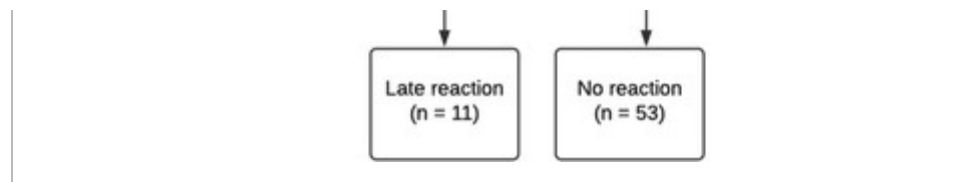


FIGURE 1

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Protocol illustrating the procedure of the oral drug provocation

2.1 Statistical analysis

When the provocation test was performed, all the data were registered in Microsoft Excel and in the patients' medical notes. The Excel data were exported to the R Studio tools version 1.1.419, 2018, for statistical analysis. Descriptive data are presented as median and Interquartile range. A comparison was carried out with the chi-square test. The level of significance was set at $p < 0.05$. Missing data from the second oral provocation challenge were excluded from the statistical analysis.

2.2 Ethics

This study was approved by the hospital ethics committee, the Icelandic Data Protection Authority and the Chief Medical Officer at Landspítali University Hospital.

3 RESULTS

Of all the children tested, 44.3% were <2 years. Children <5 years accounted for 72.6%, whilst 82.6% were <8 years. Ninety-two (6.4%) of the 1440 children showed a possible allergic reaction. Nine (0.6%) developed a reaction within one hour. A late reaction was found in 83 children. All 92 children had mild reactions, Figure 1.

Eight hundred and seventy of the 1440 children underwent the provocation test less than 6 months after the event with antibiotic treatment. These children were more likely to have a positive provocation test result compared with those that were tested later ($p = 0.047$). Sixty-four (69.6%) of the 92 children who had mild reactions, proceeded to a second provocation test 1–2 years after the first one. A late mild reaction, mostly rashes, was seen in 11 (17.2%) children, whilst 53 (82.8%) did not develop any reaction. Twenty-eight children could not be reached at that time or did not show up.

The diagnoses and use of antibiotics are shown in Table 2. The most common known causes of antibiotic treatment were AOM and an infection caused by streptococcus group A. According to the questionnaire, the most common symptoms were rashes and 1317 (91.5%) had them. Most rashes (71.2%) appeared during the first three days after starting treatment. Itching was reported in 559 (38.8%), Table 2.

TABLE 2. Illustrates diagnosis, use of antibiotics and symptoms of the 1440 children

Diagnosis	Number (%)
AOM	649 (45.1)
Streptococcal infection	142 (9.9)
Pneumonia	78 (5.4)
Sinusitis	49 (3.4)
Other infections	294 (20.4)
Unknown cause	228 (15.8)
Type of antibiotics	
Amoxicillin	646 (44.9)
Amoxicillin with clavulanic acid	588 (40.8)
Other penicillin's	112 (7.8)
Cephalosporins	58 (4.0)
Other antibiotics	36 (2.5)
Symptoms related to antibiotics	
Rashes	1317 (91.5)
Itching	559 (38.8)

4 DISCUSSION

The true, provocation-verified incidence of drug allergy in children, especially in the younger ones, is much lower than that reported by parents. A correct diagnosis is important for both the patient and society. It is estimated that about 10% of the population have been diagnosed with a possible allergy to antibiotics, especially penicillin. Many of them have been given the diagnosis in childhood.¹⁴ It is, therefore, important to have a clear and safe guideline to rule out or verify a suspected allergy. Amongst the 1440 children, rashes were by far the most common signs in our study and were found in 91.5% of all the children. The most common diagnosis leading to treatment with antibiotics was AOM. AOM is common during the first 3 years of life.

Respiratory tract viruses can be isolated or diagnosed from the middle ear and from the nasopharyngeal area in many young children with AOM.¹⁵ It is, therefore, possible that a

viral infection leads to a significant number of rashes. Guidelines for the treatment of uncomplicated AOM differ in different countries in the world. The trend in Europe is to delay antibiotic treatment in children older than 12 months of age, bearing in mind that the infection is often self-cured and is caused by common respiratory tract viruses. The second most frequent diagnosis in our group was streptococcal infection. It is also well known that streptococci can induce rashes and urticaria, like the typical scarlatina rash.

By far the most common antibiotic used (85.7%) in our material was amoxicillin with or without clavulanic acid. Reports have been published about a possible interaction between this antibiotic or clavulanic acid and the infectious agent, leading to rashes of different kinds. However, recent studies report very little connection between rashes and the use of amoxicillin.¹⁶

In our study, 5.8% developed a late reaction and only 0.6% had an immediate mild reaction to the provocation test. This result is comparable with those in other studies. Mills and co-workers confirmed that 5.9% of children suspected of having an amoxicillin allergy developed a mild-immediate or non-immediate reaction after provocation with amoxicillin.^{16, 17} In our study, significantly more children showed a positive reaction if they were tested less than 6 months after the initial reaction ($p = 0.047$). This can possibly be explained by immunological mechanisms that resolve within this time limit.

To our knowledge, we are the first to perform a second provocation test amongst the individuals that reacted after the initial one. The provocation test was performed 1–2 years after the initial provocation. Only 17.2% developed a mild late reaction. If these numbers are correct, we can estimate that around 1% of the 1440 children in our study could have a long-lasting mild reaction that can be connected to the given antibiotic. Mill et al. followed up 250 children that had been labelled as having an allergy to amoxicillin but had been negative in their provocation test. During a 3-year period, 55 of them were treated with amoxicillin. Only six or 10.9% of them developed mild non-immediate skin reactions.¹⁷ We believe that, if the supposed allergic reaction to the antibiotic is mild, the doctor can prescribe the same antibiotic again to the patient 6 months after the event or later when needed.

5 CONCLUSION

The majority of the children in our study were less than 5 years of age. None had had anaphylactic, life-threatening or major adverse reactions to antibiotics. Our study indicates that it is safe to perform an oral antibiotic provocation test after a mild possible allergic reaction. It is more likely to have a negative provocation if performed more than 6 months after the event and around 99% of the children do not have long-standing adverse reactions to antibiotics. Our study indicates that children with a mild reaction to antibiotics can be prescribed the same antibiotic later. Children that have an immediate reaction or anaphylaxis should be evaluated by a family doctor or an allergy specialist for further consideration.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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