AN UPDATE ON THE MANAGEMENT OF ANTIBIOTIC ALLERGY IN CHILDREN

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ABSTRACT
Suspensions of antibiotic allergy are very common in children, but true allergic reactions are rare and clearly overdiagnosed, representing a major public health problem. Indeed, viral skin rashes are very common, and children are falsely labeled as ‘penicillin allergic’ mostly because of fear of an anaphylactic reaction. Highlighting the most recent literature, this current review focuses on the management of the child with a possible antibiotic allergy. Systematic approaches have been proposed for the management of children with a suspicion of antibiotic allergy. Although essential, clinical history is not sufficient and a complete allergic work-up is required in all children with a suspicion of antibiotic allergy. Allergological tests will be adapted, depending if an immediate or a non-immediate reaction is suspected. The drug provocation test is considered the gold standard and has gained in importance, particularly in children developing a benign rash during a beta-lactam treatment. However, this test is associated with a potential risk of severe reaction, has relevant cost and is time-consuming. Several new diagnostic tests are currently under investigation and provide promising results. An accurate diagnosis of antibiotic allergy is important not only to avoid severe allergic reactions but also to decrease the number of patients incorrectly labelled as allergic to antibiotics.

INTRODUCTION
Associated with substantial morbidity and mortality as well as increased medical costs, drug hypersensitivity is considered a major public health problem. Any drug is potentially associated with a risk of allergic reaction, but antibiotics and particularly beta-lactams (BLs) are the most common cause of drug hypersensitivity reactions in the paediatric population. This is mainly due to the fact that antibiotics are among the most widely and heavily prescribed drugs for children worldwide, but also to the intrinsic capacity of these drugs to elicit hypersensitivity reactions. Regarding the incidence of antibiotic hypersensitivity in children, epidemiological data are sparse and most of the studies rely on the history, ignoring the underlying mechanisms and leading to overestimation of the true incidence.

Overall, the risk of developing an allergy during BL treatment is estimated to range between 2.5 and 10.2%. The vast majority of allergic reactions to antibiotic are mild and limited to the skin, with the most common manifestations being maculopapular or delayed-urticarial rashes. Although the exact mechanism of these reactions is not yet well defined, they are believed to be T-cell-mediated. Rarely, patients may develop more severe reactions associated with antibiotic intake, including potentially life-threatening IgE-mediated reactions as well as severe non-immediate reactions, such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematic pustulosis (AGEP) and drug-induced hypersensitivity syndrome (DIHS). Although the incidence of these reactions is low, with an estimated incidence ranging between 2 and 7 per million people per year, proper identification is fundamental as they are associated with a high mortality rate. This review addresses the most recent literature regarding the management of suspicion of antibiotic allergy in children.

DIAGNOSTIC DIFFICULTIES
In clinical practice, children who experience adverse reactions after antibiotic intake are often labelled as being allergic and, most of the time, this diagnosis persists into adulthood. Approximately 10% of patients report suspected allergic reactions to BLs, but an allergic reaction is confirmed in less than 10% of those cases. This discrepancy is mainly due to terminology confusion between ‘allergic reactions’ and ‘adverse reactions’ to the antibiotic. The term ‘allergy’ refers only to adverse immunological reactions to antibiotics, either antibody-mediated or cell-mediated, and should be distinguished from other adverse reactions that do not have an immune basis. From a medical point of view, this overdiagnosis of allergic reactions is mainly due to the major difficulties involved in correctly characterising these reactions. Often the diagnosis of allergy is related to excessive caution, mostly fear of a severe anaphylactic reaction. In clinical practice, one of the key challenges is to distinguish a real allergic allergy from a viral rash. Skin rashes are very common in children, with an estimated incidence of approximately 150 cases per 10 000 and viral infections are the most common cause of maculopapular or urticarial eruptions, regardless of any medication intake. In addition, allergic reactions could be facilitated by concomitant disease, especially viral infection. The best-known example is an Epstein Barr virus (EBV) infection, known as a risk factor for cutaneous drug reactions. Accurate diagnosis of antibiotic allergy is important not only to prevent serious
or even life-threatening reactions, but also to avoid unnecessary drug restriction resulting in increased resistance to antibiotics and increased health costs. Currently the diagnosis of antibiotic allergy is based on the clinical history, in vivo tests (i.e. skin tests), in vitro tests (i.e. specific IgE, basophil activation tests, lymphocyte transformation tests) with drug provocation tests (DPT) considered the gold standard.

**DIAGNOSTIC TOOLS**

**CLINICAL HISTORY**

In allergology, the clinical history is an essential step of the diagnostic process. The aim is to identify the responsible drug and to classify the reaction as immediate or non-immediate, as this suggests the underlying immunological mechanisms and thus will direct the diagnostic procedure. This classification is based on the delay between drug intake and occurrence of the reaction, i.e. immediate reactions occurring within an hour of taking the drug and non-immediate reactions occurring between an hour and 72 hours after the last dose. Although rare, severe reactions are associated with a high mortality rate and should not be missed. Therefore, clinical evaluation should focus on identification of severity signs including symptoms of anaphylaxis, but also skin pain or burning, extension of the lesion (>60% of the body surface area), dusky or purpuric macules, atypical target lesions, blisters or epidermal detachment, positive Nikolsky’s sign, involvement of mucosal membranes, facial oedema, lymphadenopathy, arthralgia and high fever (i.e. >40°C). Of note, laboratory tests indicating a more severe reaction include mainly abnormal liver-function tests and eosinophilia. To improve the clinical history, a questionnaire was developed by ENDA (European Network for Drug Allergy). Although it is one of the main steps of diagnosis of antibiotic allergy, it has been shown that the clinical history alone is not predictive of an antibiotic allergy.

**IN VIVO AND IN VITRO TESTS**

Skin tests are important tools in the diagnosis of antibiotic allergy, particularly helpful to identify patients at higher risk of developing immediate, potentially life-threatening reactions. These tests can be performed at any age and should be done apart from a reaction, and ideally not when the antibiotics are urgently needed. In addition to immediate reactions, skin tests have been used to diagnose reactions associated with delayed hypersensitivity. They can be done by the prick method, intradermally or by using patches. The choice of method will be adapted to the type of reaction suspected, i.e. immediate versus non-immediate (see section on the management of a child with suspicion of antibiotic allergy). Regarding BL antibiotics, skin-prick tests and intradermal tests are relatively well standardised and will include the major and minor determinants (i.e. PPL and MDM, respectively), as well as the incriminated antibiotic itself to increase the sensitivity. Of note, non-irritative concentrations have been determined for all BL antibiotics. If the exact molecule is not known, amoxicillin should be used as a representative of the BL class. Recent studies highlighted the role of clavulanic acid in several immediate reactions. It has been proposed to test this component, particularly in children with negative skin tests to amoxicillin.

Regarding the diagnosis of non-BL antibiotics, fewer data are available. Sulphonamides and macrolides are among the most commonly implicated antibiotics in paediatric drug allergy after BLs, although the exact incidence is not known. The most important issue in diagnosis is that skin tests are not standardised and most of the diagnosis relies on DPT. In the testing of non-standardised drug preparations, false-positives can occur from irritating properties of the incriminated drug. However, non-irritating intradermal skin test concentrations are reported for some of these non-BL antibiotics. Regarding patch testing, solutions are prepared by mixing the incriminated drug in petrolatum at a concentration of 5%.

Concerning in vitro tests, the indications are currently limited. Although less sensitive than skin tests, blood specific IgE to BL antibiotics (RAST or ELISA) have been shown to add diagnostic value in patients with a suspicion of immediate reaction and negative skin tests. Several other in vitro tests are still under validation, i.e. mainly lymphocyte transformation tests, lymphocyte activation tests and basophil activation tests. Although several studies have shown promising results, these tests are not recommended in clinical practice yet and need further validation by large studies.

**DRUG PROVOCATION TEST (DPT)**

Considered as the gold standard, the DPT involves careful administration of the offending drug and it is used to confirm or deny a drug allergy with the best sensitivity. Unfortunately, protocols are not standardised among different countries. In any case, the allergist will decide if this test is indicated and the protocol will be adapted depending on the risk and the type of reaction suspected, i.e. immediate versus non-immediate. Because of potential risk of anaphylaxis, the DPT has to be done in a secure environment (trained personnel on-site and emergency drugs available). This test is contraindicated in severe non-immediate reaction (i.e. SJS, TEN, AGEP and DIHS).
MANAGEMENT OF A CHILD WITH SUSPICION OF ANTIBIOTIC ALLERGY

NON-IMMEDIATE HYPERSENSITIVITY
Non-immediate reactions occur more than 1 hour after antibiotic intake and involve mainly the skin, maculopapular and delayed-urticarial skin rashes being the most common clinical manifestations. As discussed above, the differential diagnosis is broad in patients who develop skin rash during antibiotic treatment. Skin rashes are very common in children and viruses are the main cause, independently of any drug intake. It has been shown that the vast majority of children with a negative subsequent DPT tested positive for viral infection (mostly enteroviruses (picornavirus)) potentially responsible for the index rash.18 As no test has been validated so far to differentiate between a viral and a drug-induced exanthema, the diagnosis will be based on a complete allergy work-up.19 In patients developing a benign skin rash (i.e. without any severe signs), a DPT with the incriminated antibiotic has been demonstrated to be the most important test.20-22 Indeed, several recent paediatric studies have demonstrated the limited contribution of skin testing in diagnosis of non-immediate reactions to BL, i.e. delayed reading intradermal or/and patch tests.14-16,40,43,44 Although the negative predictive value was found to be high (above 90%), a low sensitivity (around 2-10%) was reported. A DPT without previous skin testing has been shown to be a relatively safe procedure in children with a history of mild cutaneous eruption to BL (Fig. 1a).14-16,45,46 However, the clinician should be certain that the initial reaction was a benign rash, excluding a severe reaction. This level of certainty is only reached if the clinician observed the reaction first hand or has a clear documentation of the rash in the medical record. If there is any doubt, skin tests are recommended, mainly to exclude an immediate reaction (Fig. 1b). Large studies including paediatric patients have confirmed the high negative predictive value of DPT to BLs and most of the patients reacting after a negative DPT developed mild non-immediate reactions. This information should reassure patients and their doctors in prescribing antibiotics for patients with negative allergy work-up.

Regarding severe non-immediate reactions (i.e. SJS, TEN, AGEP and DIHS), the DPT is formally contraindicated. Patch and intradermal tests have been suggested as useful to diagnose these severe reactions.23-25 However, these tests are associated with risk of triggering a systemic reaction and should be reserved for patients with a low pretest risk, and if the antibiotic is indispensable.

IMMEDIATE HYPERSENSITIVITY
In children, immediate reactions to antibiotics are rare, with an estimated incidence of 0.01%.26 As they are associated with a potentially life-threatening risk, a correct diagnosis is of major importance. These reactions have been shown to be IgE-mediated and occur less than 1 hour after the last dose.

Patients developing immediate reaction to antibiotic present with the classic manifestations of anaphylaxis, i.e. urticaria and/or angio-oedema, rhinitis, wheezing and hypotension. After a detailed history, assessment of immediate reaction is mainly based on skin tests, i.e. immediate reading prick and intradermal tests (Fig. 2). Ideally, skin tests should be performed 4-6 weeks after the reaction18 and, in any case, as soon as possible because of the loss of sensitivity of these tests over time.18 It is important to note that safety of skin testing has been confirmed recently in a large cohort of paediatric patients.16 The negative predictive value of skin tests is very high (>90%), but the main issue with skin testing is the lack of data on the positive predictive value because of ethical concerns about challenging these patients with the incriminated antibiotic.15,16,44,49 Serum specific IgE is still the most common in vitro method for evaluating immediate reactions. Some cases have been reported with negative skin tests and positive IgE; specific IgE is therefore still recommended in addition to skin testing in order to improve the sensitivity of the allergy work-up.23-25,50 If these tests are negative, a DPT is recommended. Increased doses of the incriminated antibiotic are administered gradually, under medical supervision with emergency drugs available.
Clinical history of immediate reaction to BL

Prick tests and IDT
(PPL, MDM, amoxicillin + incriminated BL)

Specific IgE (penicillin/amoxicillin)

Drug provocation test (incriminated BL)
(if not known, amoxicillin)

No allergy

Fig. 2. Algorithm for the diagnosis of immediate allergic reactions to beta-lactams. IDT = intradermal tests; BL = beta-lactams.

CROSS-REACTIVITY BETWEEN BLS
If a BL allergy has been confirmed, identification of well-tolerated BLS is important to provide primary care physicians with an alternative. In the case of confirmed benign non-immediate reaction to a BL, other antibiotics from the same class can be administered safely. In patients with proved immediate hypersensitivity to a BL, potential cross-reactivity must be taken into account before prescribing an antibiotic belonging to the BL class. Regarding carbapenems, skin tests should be considered before a DPT under medical supervision. Monobactams (i.e. aztreonam) are very weakly cross-reactive with other BLS and generally well tolerated by patients with penicillin allergy. The only exception is ceftazidime as it shares an identical side chain and has shown some cross-reactivity potential. Second- or third-generation cephalosporins may also be considered as they have demonstrated less cross-reactivity to penicillin than first-generation agents, particularly those with dissimilar side chains to the offending penicillin. Nevertheless, Romano et al. found that 25% of subjects with cephalosporin allergy had positive results to penicillins. The authors conclude that in patients requiring alternative BLS, pretreatment skin tests are advisable because negative results indicate tolerability of the incriminated BL.

CONCLUSION
Several recent publications have confirmed that antibiotic allergies are rare and clearly overdiagnosed in children. The proper identification, evaluation and management of patients with a reported history of antibiotic allergy are essential components of patient care. Indeed, overdiagnosis has a major impact on public health, particularly the development of resistance by unnecessary use of broad-spectrum antibiotics and increased medical costs. If allergy is suspected, the child should be referred to an allergist in order to perform a complete allergy work-up, based on carefully selected diagnostic tests depending on whether an immediate or non-immediate reaction is suspected. The DPT remains the gold standard and has gained in importance, particularly in children presenting with a benign rash while taking antibiotics. However, new diagnostic tests are required to assess the presence and severity of an antibiotic allergy as the DPT potentially exposes subjects to a significant risk of severe anaphylactic reactions, and is time consuming and costly.

Declaration of conflict of interest
The authors declare no conflict of interest.

Acknowledgement

REFERENCES

ETHICS CPD QUESTIONNAIRE

ASSENT TO PARTICIPATE IN HEALTHCARE RESEARCH ( see p. 145)

In order to obtain 3 Ethics CEUs, you have to obtain 70% or more for answering the following questions. The questionnaire can only be answered online at www.allergyusa.org. Log in to the members section by entering your user name and password (obtainable from the ALLSA office). Click on My CPD to access the Ethics section where you can view the article and access the questionnaire. Please note that you have only two opportunities to submit the questionnaire so please check answers carefully.

1. True or false: The assent for research participation that is provided by a child is not legally binding.
2. True or false: It is unjust to include children who cannot provide consent for participation in research.
3. Choose ONE correct answer: Conducting research upholds the principle of beneficence to:
   a) The child who is taking part
   b) Current and future generations of children
   c) Both of the above
4. Choose ONE correct answer: Ethics committees use the following ethical principles when approving research:
   a) Beneficence
   b) Non-maleficence
   c) Both of the above

5. True or false: In the UK, children under the age of 16 can consent to treatment without their parents’ knowledge.
6. Choose ONE correct answer: The lower age limit for Gillick competence is:
   a) 10
   b) 12
   c) There is no lower age limit
7. True or false: There have been successful cases in the law courts of children dissenting from treatment that their parents agree to.
8. True or false: Consent/assent is dynamic and may be withdrawn during the course of a trial.
9. True or false: Children who take part in research always benefit from participation.
10. True or false: If a trial has been given ethical approval then the health care practitioner does not need to consider whether participation is in the best interests of a specific child.

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