Taking a Rational Approach to a Reported Antibiotic Allergy

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Abstract: Up to 10% of hospitalized patients have an antibiotic allergy label in their medical file, most frequently concerning penicillins. However, the vast majority of reported allergies to antibiotics does not represent a "true" allergy but are due to drug intolerance, idiosyncratic reactions or symptoms of the concurrent infectious disease. Since antibiotic allergy labels result in deviation from first-choice antimicrobial therapy, tackling the issue of incorrect antibiotic allergy labelling, already at young age, is a core element of antibiotic stewardship. In this article, we describe the structured approach to the patient with a presumed antibiotic allergy with emphasis on key elements of allergy-specific history taking and the limited risk of cross-allergic reactions between beta-lactam subclasses.

Key Words: allergy, antibiotic stewardship, cross-allergic reaction, side effects, antibiotic agents

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Physicians are often confronted with antibiotic allergy labels in a setting where this immediately hinders the selection of optimal antimicrobial treatment. An allergy to an antibiotic from the beta-lactam class, penicillin or amoxicillin, is reported in up to 10% of hospitalized patients.[1,2] In clinical practice, these labels are one of the foremost reasons why commonly used beta-lactams are avoided even if they constitute the first choice of therapy. Selection of an alternative—often broader spectrum—antibiotic may have a negative impact on disease outcome, may lead to increased risk of toxicity and contributes to the development of antimicrobial resistance (AMR).[3] Tackling the issue of incorrect antibiotic allergy labelling, that is, when the patient is not allergic, is now considered a both important and reachable aim of antibiotic stewardship. This as well applies to the field of pediatric medicine since antibiotic allergy labels are registered from a very young age onward and often taken into adulthood.[4] A recent study reported that if an antibiotic allergy label was present in the medical file, it had been registered before the age of 3-years-old in >75% of the children.[5] The overuse of broad-spectrum antimicrobials caused by incorrect allergy labels can be reduced substantially if adequate action is undertaken. However, no comprehensive guidelines are currently available for the systematic approach to this problem.

THE DEFINITION OF ANTIBIOTIC ALLERGY AND ANTIBIOTIC ALLERGY LABELLING IN REAL-LIFE PRACTICE

Adverse drug reactions are categorized as type A and type B reactions. Whereas type A "on-target" reactions are predictable from the pharmacologic effect of the drug, type B "off-target" reactions are unpredictable from the known pharmacology of the drug. Allergies reside under type B reactions and per definition are mediated by the immune system. According to the original classification by Gell and Coombs, allergic reactions are divided in 4 subcategories: type I, II, III and IV.[6] More applicable in clinical practice is the overlapping classification into *immediate-type* reaction and *delayed-type* allergic reactions (see Table 1 and link to video content).

However, any type of sign or symptom during a course of antibiotics that is incompletely understood by patients, parents, guardians or healthcare workers can easily lead to an antibiotic allergy label. Despite the above classifications based on pathogenesis, it can be challenging at the bedside to discriminate between a (past) "true" allergic reaction and a history of signs and symptoms that represent something else than an allergic reaction to an antibiotic. By far, the largest proportion of side effects falsely reported as an antibiotic allergy fall into the category of mild drug intolerance reactions.[7] Other categories concern idiosyncratic reactions, for example, the rash that may occur upon amoxicillin treatment during Epstein–Barr virus infection, or disease symptoms that are mistaken for an allergic reaction to medication.

When deciding about the choice of antimicrobial therapy for an individual patient, it is warranted that physicians are well informed about the probability of the presence of a "true" allergy, in particular a type I (immediate-type) or a severe form of delayed-type allergy. In these situations, repeated exposure can be life-threatening, while in other situations reexposure is relatively safe.

ANTIBIOTIC ALLERGY LABELLING

Multiple studies in patients that reported a penicillin allergy showed that on average only in 10% of the study population, the presence of a "true" type I allergy could be confirmed with skin tests.[8] The assumption that all patients with an antibiotic allergy label are actually allergic leads to unnecessary use of less effective and/or broader spectrum antimicrobial regimens, prolonged hospital admission and higher healthcare costs.[9] In addition, incorrect labelling—particularly at pediatric age—unduly limits options for future antimicrobial treatment because physicians often experience a barrier to act against earlier decisions made by colleagues. Therefore, in times of increasing AMR and the antibiotic stewardship imperative of using small-spectrum antibiotics as much as possible, incorrect labelling of antibiotic allergies needs to be counteracted.[10]

To aid future decisions on antibiotic therapy, the antibiotic allergy label itself should contain detailed information, for example, about the involved antibiotic, date and time of first symptoms, the timing of the reaction after start of treatment, all signs and symptoms, the duration of the reaction and performed interventions (see below). Several studies have reported that the label information is often incomplete.[11,12]

HISTORY TAKING BEFORE SKIN TESTING

To take a specific allergy history is the standard first step in the approach of the patient with a presumed antibiotic allergy.[1,8] Collecting first-hand information from caregivers or other persons who witnessed the allergic reaction at the time can be extremely valuable. Information obtained from the medical file, the pharmacy registers or

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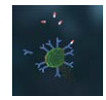
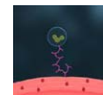
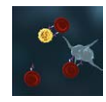
TABLE 1. General Classification and Pathogenesis of (Antibiotic) Allergies

Type According to Gell Land Coombs Classification[6]	Immediate- or Delayed-type Allergy* (Relative Frequency)	Mechanism	Link to Pathogenesis Animation *Press Control Key + Click On Icon to Follow Link*
Type I	Immediate (common)	IgE-mediated reaction based on cross-linking of IgE on the surface of mast cells and subsequent degranulation	
Type II	Delayed (rare)	Antigen binding to IgM or IgG antibody on cell surfaces	
Type III	Delayed (rare)	Deposition of antibody–antigen complexes in tissues and capillaries with subsequent inflammation	
Type IV	Delayed (common)	T-cell activation by specific antigens	

*Immediate type: first symptoms typically occur <1 hours after exposure; delayed-type first symptoms occur predominantly >6 hours after exposure. In allergies to antibiotics, part of the molecular structure of the antibiotic functions as the antigen

by a call to the family physician can further add to the insight whether it may concern a "true" allergy. In Table 2, the key elements of the allergy history are listed. Similarly, information with regard to—intended or unintended—reexposure to the antibiotic or structurally similar antibiotics with potential cross-reactivity needs to be obtained.

Based on the collected information, skin tests for the evaluation of a reported antibiotic allergy are needed only in a selected group of patients.[13] Skin testing can be unpleasant and not easy to perform in younger children. Although the negative predictive value is high for penicillin allergy, most data have been obtained in adults and may not be applicable to children.[14] Currently, clinical strategies are shifting toward directly performing a drug provocation test. Cumulating data indicate that using provocation tests—without prior skin testing is an effective and safe strategy in children with a history of nonserious reactions to penicillin and amoxicillin.[13,15,16] Skin tests should still be considered first-line diagnostics if the history reveals a serious reaction and/or an immediate-type allergy is suspected. Further research is needed to more clearly guide the choice for drug provocation tests only versus skin tests followed by drug provocation in individual patients.

TIME ELAPSED SINCE AN ALLERGIC REACTION

There are only a few studies that indicate that the time elapsed since the last reported reaction influences the risk of a repeated reaction upon a new exposure to the same antibiotic.[17] These data are only available for penicillin and amoxicillin. In a study performed by Blanca et al, approximately 80% of participants had lost skin test reactivity to penicillin after 10 years.[18] Unfortunately, not all these patients thereafter received an oral provocation test, which is regarded the golden standard for excluding type I allergy. The combination of skin prick- and intradermal allergy testing for penicillin allergy is considered to yield high negative predictive values. Therefore, it is generally assumed that the risk of an allergic reaction gradually wanes over time and is considerably lower after more than 10 years have passed since the initial reaction.[19] Nevertheless, in an elective setting, skin tests (after severe reactions) and/or oral provocation tests should always be considered to confirm or rule out a presumed immediate-type penicillin allergy.[20]

CROSS-ALLERGIC REACTIONS BETWEEN BETA-LACTAM ANTIBIOTICS

Before 1980, a rate of over 10% of cross-allergic reactions was reported in patients allergic to penicillin that were administered cephalosporins. It is now known that these reactions can predominantly be attributed to contamination of cephalosporin preparations with penicillin moieties during the production process. From a recent review of studies performed after 1980, it becomes clear that the probability of a cross-allergic reaction in patients with a

TABLE 2. Key Eelements in the Allergy History

Elements	Explanation
Antibiotic	*It is important to specify the antibiotic as this may have consequences for decision-making. For example: Frequently a "penicillin allergy" is reported, without specification of the type of penicillin (amoxicillin, flucloxacillin, etc.).*
Years past	*The probability of a serious immediate-type penicillin allergy is lower when the reaction occurred many years ago, in particular >10 years.*
Symptoms	*A detailed description of symptoms helps to discriminate allergic from nonallergic reactions and identify the allergy type. Urticaria, angioedema, stridor and syncope point toward IgE-mediated allergy. An exanthema could be caused by a delayed-type allergy but can also be a side effect or a symptom of the infection itself.*
Time line	*The time line is helpful to differentiate between immediate- and delayed-type allergy.* • *The time between administration of the drug (first dose) and start of symptoms. In immediate-type reactions, symptoms appear within 1 hour in the majority of cases. Start of symptoms after >6 hours in unlikely an immediate-type allergy.* • *The time between cessation of the drug (last dose) and disappearance of symptoms. If the drug is discontinued in immediate-type reactions, symptoms disappear within 24 hours. In delayed-type reactions, symptoms may persist for days to weeks.*
Observation	*Where the symptoms assessed by a healthcare worker? Retrieving the notes in the medical file helps to assess the type of reaction and the severity of the reaction.*
Alternative causes	*The rash in viral infection may mimic delayed-type hypersensitivity. Viral and bacterial, especially streptococcal infections may also cause acute urticaria. Furthermore, comedication should be reviewed to assess alternative causes.*
Consequences	*Whether the child was hospitalized or not helps to assess the severity of the reaction. Both immediate and delayed reactions may cause severe symptoms. Need for adrenaline or intubation points toward immediate-type allergy.*
Reexposure	*The antibiotic—or an antibiotic from the same group—may have already been readministered despite the allergy label. For example, because the healthcare provider was unaware of the label. The symptoms (or absence of symptoms) after reexposure can guide decision-making and delabeling.*
Testing	*Has the child been tested for antibiotic allergies in the past. What were the results?*

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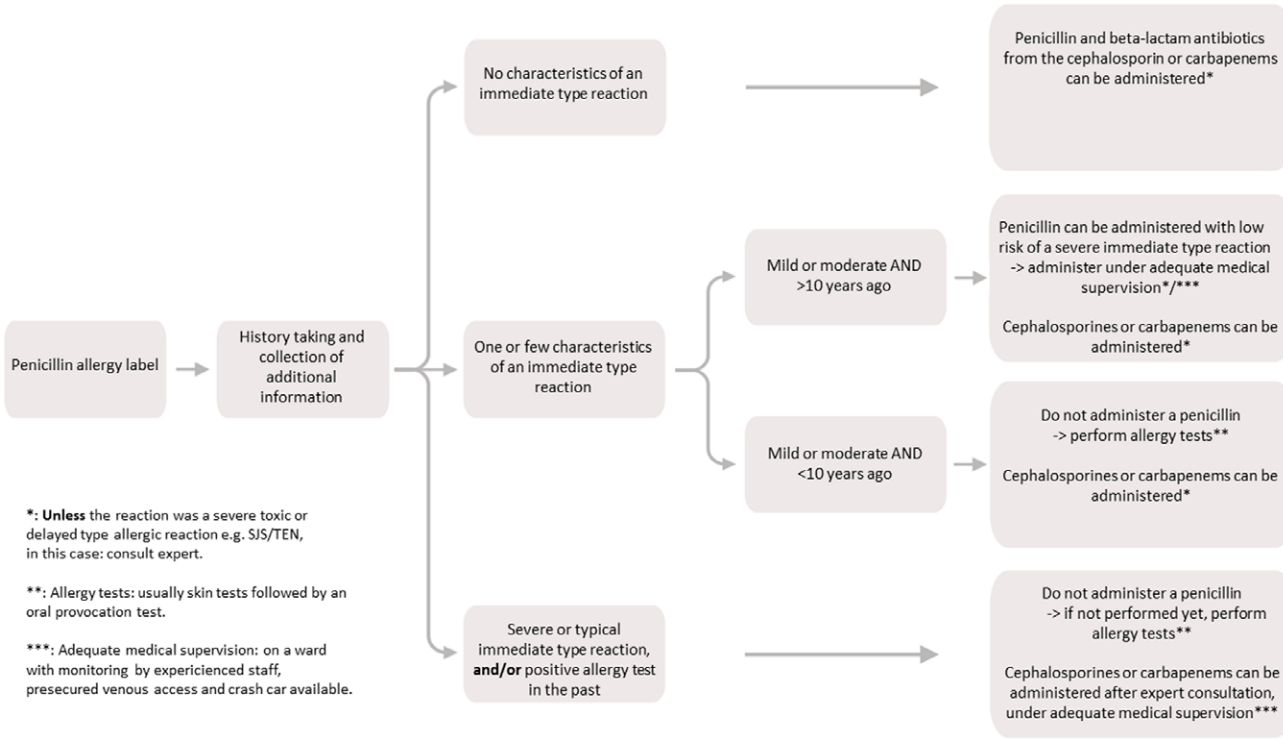

FIGURE 1. Algorithmic approach to a reported allergy to a penicillin.

history of penicillin allergy and a positive skin prick test is approximately 2%.[20] Notably, not all these reactions included features of anaphylaxis or anaphylactic shock. The majority of immediate-type allergic reactions after exposure to penicillin is evoked by penicilloyl polylysine (PPL), also known as the major determinant. This molecular structure is formed when the beta-lactam ring degrades and binds to serum proteins. Although cephalosporins contain a classic beta-lactam structure, no PPL is formed upon degradation. For cephalosporins, the side chains are in fact the major determinants as is PPL for simple beta-lactam antibiotics. Therefore, the potential for a cross-allergic reaction is based on the similarity of the side chains of penicillin and cephalosporins.[21] Hence, the risk of cross-allergic reaction can be minimized by prescribing a cephalosporin without a similar chain as the penicillin in the antibiotic allergy label.[21,22] Only a limited number of investigations assessed the risk of a cross-allergic reaction caused by using a carbapenem in the presence of a skin test–proven penicillin allergy. A recent study in adults, using both skin tests and intravenous provocation tests, showed that the risk of a cross-allergic reaction in this situation is extremely low.[23]

AN ALGORITHMIC APPROACH TO THE PATIENT WITH A PRESUMED ANTIBIOTIC ALLERGY

Some studies have piloted the use of bedside skin testing in infectious disease consultation of patients with a presumed antibiotic allergy, but this is not yet a commonly available service.[24] Importantly, in many situations', allergy tests are not required for optimizing the antimicrobial regimen and the debate about their applicability and positive predictive value in children remains. After obtaining detailed information, including the allergy history, a practical approach based on risk stratification and drug challenge under medical supervision (i.e., provocation) can be implemented in most hospital settings. If based on history taking, the presumed allergic reaction can be classified as a mild toxic reaction or nonimmune-mediated intolerance, or simply as a symptom of the disease itself, the patient may be safely reexposed to the same antibiotic.

In case of a potential immediate-type reaction, the decision should depend on the severity of the reaction as well as the time elapsed since the reaction occurred (see Fig. 1 for our suggested flow diagram for reported allergy to penicillin). In this scenario, a rechallenge should always take place under medical supervision and circumstances in which adequate action can be undertaken if an anaphylactic reaction occurs. Importantly, this requires presence of experienced medical personnel, presecured venous access and presence of a crash car on the ward.

After a severe type IV (or other delayed-type) allergic reaction, or a severe toxic reaction, the presumed causative antibiotic should not be rechallenged. Examples are Stevens–Johnson syndrome, toxic epidermal necrolysis, tubulointerstitial nephritis or DRESS (drug reaction with eosinophilia and systemic symptoms).

SUMMARY AND RECOMMENDATIONS

Most (>90%) of the reported adverse reactions to antibiotics do not represent a "true" allergy and effort should be undertaken to identify those that are not. Thereby, optimal antimicrobial therapy can be provided. As compared to alternative regimens, the first choice of antimicrobial therapy is often more effective and has a lower risk of unwanted side effects. This is also beneficial in terms of controlling healthcare costs and counteracting the downward spiral of development of AMR. Even without performing allergy skin tests, a rational decision can be made on how to act upon a reported allergy to an antibiotic. Careful history taking and the search for additional relevant data are key elements in this process. When penicillins cannot be prescribed due to suspected immediate-type allergy, cephalosporins or carbapenems with dissimilar side

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chains are often reasonable alternatives with a very limited risk of a cross-allergic reaction. Removal of the antibiotic allergy label in the medical file is an important action once the presence of the antibiotic allergy is disproved.

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