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Drug Allergy (C Mayorga, Section Editor)

Diagnostic Approximation to Delabeling Beta-Lactam Allergic Patients

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Abstract

Purpose of review Beta-lactam antibiotics constitute first-choice drugs for bacterial infections, although the high rate of hypersensitivity reactions constitutes a worldwide health problem. The public health implications of beta-lactam (BL) allergy are enormous as the self-reported penicillin allergy has been associated with antimicrobial resistance, increased cost to health systems, intensive care admission, and death. Therefore, an accurate and rapid diagnosis is crucial.

Recent findings The diagnostic work-up is mainly based on the performance of an accurate clinical history, skin tests, drug provocation tests and, in some cases, in vitro tests. In recent years, there has been a growing interest on the role of computerized clinical decision support systems to stratify the risk for performing classical diagnostic work-up and in the design of mathematical diagnostic algorithms based on clinical history predictors that would permit the avoidance of high-risk procedures such as skin and drug provocation tests. A precise diagnosis of BL allergy will allow defining phenotypes and endotypes.

Summary Nowadays, clinical guidelines that use data from the clinical history are not able to delabel patients, although they can be useful in an urgent situation. True delabeling is still based on the performance of in vivo tests, although differences on the pattern of BL consumption cause differences in the diagnostic approach among different countries.

Introduction

Beta-lactam (BLs) antibiotics still constitute first-choice drugs for treating bacterial infections [1]. Nevertheless, their prescription is limited by a high rate of hypersensitivity reactions, which currently constitutes a worldwide health problem affecting up to 10% of the general population [2]. Hypersensitivity reactions to drugs are defined as adverse effects of drugs that clinically resemble allergic reactions. The term drug allergy must only be applied to those for which a definite immunological mechanism (either drug-specific antibody or T cell) is demonstrated [3]. BLs are the drugs in which an immunological mechanism has been most frequently described with reactions being either immediate (i.e., occurring within 1–6 h after the last drug administration) or non-immediate (i.e., occurring at least 1 h after the initial drug administration in sensitized patients, but usually after several hours or even days) [3].

BLs include a wide spectrum of chemical structures that share a common beta-lactam ring. In Europe, the group of antibiotics most commonly consumed is BLs, specifically amoxicillin (AX) [4, 5], and therefore this drug is also the most frequent BL involved in hypersensitivity reactions in adults and children [6]. Anaphylaxis represents 0.015–0.004% of all drug reactions in general population [7] and AX is the trigger of 75% of all fatal anaphylactic episodes in the USA per year [8]. However, in Northern Europe, Penicillin V is still the BL most frequently involved, being non-immediate reactions the most frequent clinical picture [9].

The public health implications of BL allergy are enormous. The self-reported penicillin allergy has been associated with antimicrobial resistance, increased cost, intensive care admission, and death [10–12]. This is especially important if we consider that after an allergological work-up, less than 30% of adults and 10% of children are confirmed as allergic [13, 14]. Therefore, delabeling patients allergic to BLs has become a main challenge not only for allergists but also for infectious disease physicians [15•] and general practitioners [16•]. Patients with a reported penicillin allergy are more often treated with fluoroquinolones, clindamycin, vancomycin, glycopeptides, and aminoglycosides [17]. Compared with non-allergic patients, those wrongly labeled as allergic to penicillin have a longer duration of hospitalization and present increased rates of infections caused by *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* [12, 18].

Therefore, an accurate and rapid diagnosis is crucial to improve the correct use of antibiotic therapy, increase patient security, and reduce costs to health systems. A precise diagnosis able to characterize phenotypes and endotypes is mainly based on the performance of skin tests (STs) and drug provocation tests (DPTs), tools that are time-consuming and not exempt of risk [19]. In this manuscript, we are going to analyze the different approaches for diagnosing BL allergic patients.

BL allergy diagnosis

Given the unfavorable clinical outcomes of being labeled as penicillin allergic, several centers in the USA have proposed beta-lactam STs as an antibiotic stewardship to exclude allergy and promote the use of BLs in patients with reported allergy; in the case of the negativity of STs, the BL could be administered [20, 21]. This recommendation is based on the high negative predictive

value of STs reported by American studies [22, 23]. However, European studies indicated that between 8.4 and 30.7% of skin-negative patients reacted on drug challenge [13, 24–26]. This is likely due to the preferring prescription and consumption in Europe, especially in Southern Europe, of AX, AX–clavulanic acid (CLV) and cephalosporins [27], and the health system organization. As a result, adverse events may occur at a higher rate in European populations if only STs were used. Therefore, an adequate allergy evaluation should be necessary in order to exclude beta-lactam allergy [3, 28, 29].

The diagnostic work-up in suspected hypersensitivity reactions to BLs is based on in vivo and in vitro tests selected on the basis of clinical manifestations (immediate or non-immediate reaction). In order to reach an adequate diagnosis, an exhaustive clinical history is essential, followed by STs. In vitro tests can be used when available. Clinical history is important in order to differentiate between non-specific adverse events (e.g., headache, gastrointestinal symptoms) and drug hypersensitivity reactions. Drug hypersensitivity reactions include adverse events mediated or not by immunological mechanisms that clinically resemble allergic reactions [3]. Allergic reactions to drugs are those in which it is possible to demonstrate a specific immunological mechanism. Drug hypersensitivity reactions are classified as immediate or non-immediate/delayed depending on their onset during treatment. Typical symptoms of immediate reactions include urticaria, angioedema, bronchospasm, or anaphylaxis. Immediate drug hypersensitivity reactions to BLs are generally induced by an IgE mechanism. The most frequent clinical manifestations of non-immediate reactions include maculopapular exanthems and delayed urticaria. In these reactions, a delayed T cell-dependent mechanism can be implied. The allergological evaluation is important in order to demonstrate the specific immunological mechanism involved.

The allergological evaluation would not be indicated in the case of symptoms non-suggestive of hypersensitivity or allergy, and BLs could be administered. However, the history can be imprecise in many cases as the patient is evaluated many years after the reaction and up to one-third of patients with vague symptoms have positive STs [30]. Since the clinical history is often not reliable and the sensitivity of STs and in vitro tests is not optimal, a DPT may be required to establish the diagnosis.

Besides, DPTs can be used to study cross-reactivity in order to assess the tolerance to other BLs. Patients with immediate reactions to BLs can be allergic to several antibiotics, to a subgroup of drugs with side chain similarities, or just to a single drug. In general, evidence indicates that, regardless of the BL inducing the clinical reaction, the first evaluation should be made with benzylpenicillin (BP) and, if positive, the subject must be classified as allergic to BLs. But if this initial evaluation is negative, the patient should be tested with the culprit drug. If this is positive, the patient is diagnosed as selectively allergic to the culprit drug. If we do not know the culprit BL, the first evaluation should be made with an aminopenicillin.

In non-immediate hypersensitivity reactions to BLs, DPT is an important diagnostic tool since both delayed reading intradermal tests and patch tests have low sensitivity (5–9% for both) [31, 32]. However, DPT is contraindicated in patients with a history of severe cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome, or toxic epidermal necrolysis [33].

A DPT should be done only after performing STs, and when these are negative. However, DPTs may be recommended, without previous STs, in children with a history of mild cutaneous reactions, since most of them are not allergic reactions but viral exanthemas. Recent studies have demonstrated the safety of this approach in children who have not presented anaphylactic reactions or non-immediate severe cutaneous reactions [14, 34, 35]. Therefore, the Pediatric Task Force of European Academy of Allergy and Clinical Immunology (EAACI) in the Drug Allergy Interest group recommended DPT (without STs) for children with a history of mild exanthema to penicillins [6].

The European Network for Drug Allergy (ENDA) has designed various diagnostic algorithms for the evaluation of immediate [29] and non-immediate reactions [36]. Although with limitations, these algorithms are still useful in the evaluation of patients with a history of allergy to BL antibiotics (Fig. 1).

In vivo tests

Skin tests

For immediate reactions, BL ST includes skin prick test (SPT) and if negative, intradermal testing (IDT) [37]. For non-immediate reactions, both patch tests (PT) and delayed reading of IDT can be used [36–38], although they are not as standardized as for immediate reactions. ST should be performed by experienced personnel in the performance and interpretation of such testing [37].

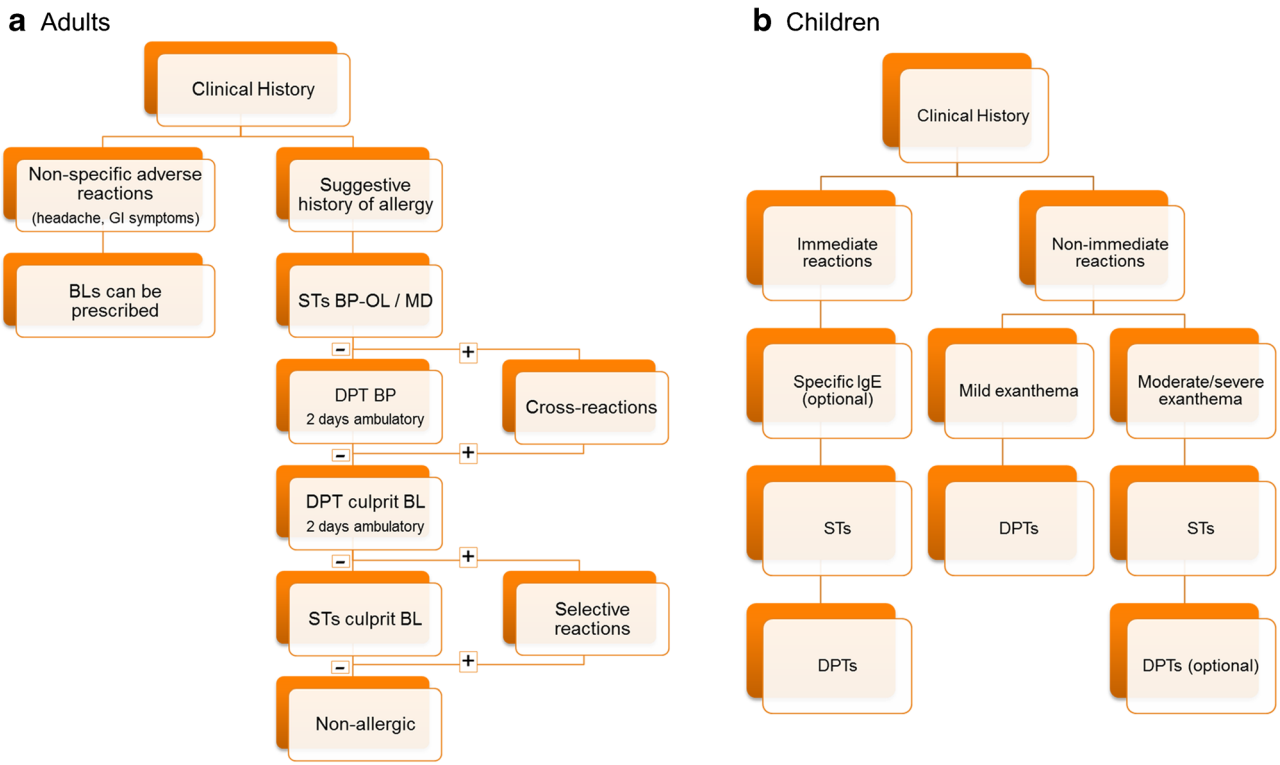

Fig. 1. Schematic representation of the algorithms used in the diagnosis of BL reactions in adults (**a**) and children (**b**).

Haptens classically available for STs are the major and minor determinants of penicillin. A metabolite of the β-lactam core structure of penicillins, benzylpenicilloyl, is considered the major antigenic determinant, which is commercially available as a multivalent antigen with 12–15 penicilloyl moieties coupled to a synthetic peptide consisting of 20 lysine residues (benzylpenicilloyl-poly-L-lysine; PPL, Pre-Pen®, AllerQuest LLC, Plainville, CT, USA). The minor determinants consist of sodium benzylpenicilloate, and benzylpenicilloic acid, which make up the minor determinant mixture (MDM). Recently, a purer and more stable benzylpenicilloyl octa-L-lysine (BP-OL) and the most stable minor determinant, sodium benzylpenilloate (penilloate) called "minor determinant" (MD), have been commercialized, known as "Diagnostic Allergy Penicillin" (DAP®, Diater) [39].

The percentage of positive responses in ST to major and minor determinants has decreased over time reflecting changes in patterns of prescription [13, 28, 40, 41, 42•, 43], with an increase in the incidence of specific reactions to side chains of semisynthetic penicillins such as AX or cephalosporins in the last years [40]. Indeed, the inclusion of AX in ST could increase positivity to up to 70% nowadays [40]. Nevertheless, major and minor determinants of BP continue to play a key role in diagnosis, as they induce a positive response in 60% of cases even in populations in which the predominant intake BL is AX [39]. However, there are discrepancies about the need to include BP in ST [44, 45]. Recently, an increase in the use of β-lactamase inhibitors has led to an increasing incidence of selective hypersensitivity reactions to CLV [46–48]. Therefore, the inclusion of CLV in STs is needed, obtaining a sensitivity up to 18.7% in SPT and up to 81.2% in IDT [46, 47].

For non-immediate reactions, sensitivity has been estimated as less than 10% with PT, which may be due to the poor penetration of some reagents in the skin. Late reading of IDT appears to be more sensitive [14, 31, 32, 38], as it has been reported to be up to 12% for benzylpenicillin and 39% for aminopenicillins [36]. The diagnostic value of the addition of penicillin determinants in evaluating non-immediate reactions is limited [49]. Recommended doses for skin testing are shown in Table 1.

Systemic reactions may occur in 3% of subjects reporting immediate reactions in whom IDT has been performed, especially when multiple BL derivatives are tested simultaneously and when the highest recommended concentration is used, reaching in these cases up to 11% [41, 50–52]. Therefore, in patients with severe immediate reactions, IDT should be started on serial dilutions of up to 1000 times [53]. Systemic reactions to PT are quite rare [54];

Table 1. Reagents and doses recommended for BL STs

Reagent	Dose
BP-OL	0.04 mg/mL (8.64×10^{-5} mol/L)
MD	0.5 mg/mL (1.5×10^{-3} mol/L)
AX, CLV	20 mg/mL
Cephalosporins	2–20 mg/mL

BP-OL, benzylpenicillin-octa-lysine; *MD*, minor determinant; *AX*, amoxicillin; *CLV*, clavulanic acid

thus, they have been proposed as first-line tests in severe systemic cutaneous reactions [54, 55].

For immediate reactions, sensitivity of STs decreases over time; however, after a new contact with BL, subjects can become positive again (re-sensitization), although this percentage is unknown. For this reason, the re-evaluation after 4–6 weeks is recommended in patients with suggestive history of a BL-induced immediate reaction with negative ST and in vitro tests, and good tolerance in DPT in order to rule out study-induced re-sensitization [40]. Nevertheless, several studies report that the rate of re-sensitization after treatment with oral penicillins is comparable to the rate of sensitization, being estimated in 1 to 16% [56, 57]. Therefore, it has not been recommended by all authors to repeat penicillin ST in patients with a history of penicillin allergy if at least one course of oral penicillins has been tolerated [50]. However, data on re-sensitization after parenteral penicillins are more limited and repeating penicillin ST may be considered [50]. Regarding non-immediate reactions, there is evidence that sensitization is long-lasting [36].

Drug provocation test

Since sensitivity and specificity of ST and in vitro methods are not 100%, DPT is considered to be the gold standard for establishing the diagnosis of allergy as well as for assessing tolerance to potentially cross-reactive drugs in order to look for alternative treatments [33, 58]. It is not a risk-free procedure and it should be performed after a risk–benefit analysis and by trained personnel in a clinical setting where resuscitation facilities are available. DPT should not be performed in cases reporting previous severe life-threatening reactions (anaphylaxis, SJS/TEN) [33].

DPT is usually performed in a single blind manner by escalating doses until achieving the therapeutic one. There is a direct association between the dose to which the patient reacts and the type of reaction: the higher the dose to which the patient reacts, the greater the interval between the administration of the drug and the onset of the reactions [59]. Recently, DPT with AX without prior STs has been proposed in children with history of mild cutaneous reactions due to the very low rate of positive penicillin STs [35, 60•].

It is important to note that tolerance to drug in DPT does not rule out the possibility of an allergic reaction to the drug in the future. Indeed, it has been reported that up to 8% of patients developed reactions despite tolerating the culprit drug in DPT [61].

In vitro tests

Immunoassays

Quantification of drug-specific IgE (sIgE) in serum by immunoassay is the most used in vitro test to diagnose immediate reactions to BL [62••]. This technique is based on the detection of the complex formed between the drug sIgE present in patients' sera and the drug–carrier protein conjugate coupled to a solid phase. Levels of sIgE bound are detected with a secondary anti-human IgE antibody labeled with any detectable property, such as fluorescence or radioactivity [62••].

ImmunoCAP FEIA, which uses fluorescent reagents, is the most used commercial method to quantify sIgE to BL. However, it is only available for several penicillins, such as BP, Penicillin V, AX, and ampicillin and for only one cephalosporin, cefaclor [63•]. The availability for only few BL has led to the development of in-house immunoassays such as Sepharose-radioimmunoassay (RIA) and radioallergosorbent test (RAST) that, although with more sensitivity, have the inconvenience of the use of radioactive materials [62••, 63•].

Sensitivity of immunoCAP FEIA is rather low and variable depending on the BL involved, ranging from 0 to 50% [64–66]. However, although this test shows a high specificity (83.3–100%) [64], reports of false positive results exist, especially for Penicillin V (26%) [67], and in patients with high total IgE levels [68]. This may be due to the presence of an unspecific identification of IgE to non-clinically relevant molecules that forms similar adducts to those included in the test for BL or the presence of anti-IgE auto-antibodies, sometimes found in severe atopic disorders. In contrast, in-house RAST has shown higher sensitivity (42.9–75%) but lower specificity (67.7–83.3%) in the evaluation of penicillins and cephalosporins [64].

Basophil activation test

This assay uses flow cytometry to determine the basophil activation after drug stimulation in vitro. The lack of standardized procedures on commercial kits [69] has led to the use of in-house protocols with a high variability, especially regarding the markers used for selecting basophils and assessing activation. Two main molecules are used to determine activation, CD63 and CD203c [62••], although each one can represent the best option depending on the drug tested [70, 71]. Another issue is the existence of up to 10–20% of "non-responders" patients, those that present negative activation with positive control, in whom the test cannot be interpreted [69].

In the evaluation of BL patients, sensitivity of basophil activation test (BAT) ranges from 50 to 77.7% and specificity from 89 to 97% [66, 72, 73, 74•]. These differences can be due to differences in the characteristics of patients analyzed in each study or to the no inclusion of the exact metabolite recognized by the IgE [75]. Nevertheless, BAT is recommended for diagnosing immediate reactions to BLs and, although it is not used in routine clinical practice, can be complementary to in vivo and to other in vitro tests [62••, 76••].

Histamine release test

This test is based on the detection of histamine release by human basophils after in vitro incubation of blood with the culprit. Histamine release test (HRT) has been used for the evaluation of immediate reactions to clavulanic acid (CLV), showing a sensitivity of 55% and a specificity of 85% [77]. This test, as well as BAT, is useful in the diagnosis of CLV allergy, due to the absence of methods for the detection of sIgE. Despite these promising results, further research must be conducted to standardize the use of HRT for diagnosing allergic reactions to BL.

Lymphocyte transformation test

This is the main in vitro test used for evaluating non-immediate reactions to drugs. It is based on the proliferation of drug-specific T cells from patients upon

stimulation with the drugs. Lymphocyte transformation test (LTT) in general has shown to have better sensitivity than skin testing for diagnosing this type of reactions [62••, 78]. The clinical manifestation can influence the sensitivity and specificity of the test, being of higher value for the evaluation of maculopapular exanthema, fixed drug eruption, acute generalized exanthematous pustulosis, and DRESS [62••, 79] than for SJS/TEN [79].

In the evaluation of BL allergy, sensitivity and specificity range from 58 to 88.8% and 85 to 100%, respectively [62••]. Some studies have included the use of dendritic cells as professional antigen-presenting cells in the evaluation of reactions induced by AX, increasing the sensitivity of the test from 22 to 88% [80]. Another modification of the protocol has been the inclusion of co-factors (i.e., from infectious diseases) that were present during the in vivo allergic reaction, such as TLR agonists. Its inclusion in the evaluation of reactions induced by AX has increased sensitivity from 40.5 to 80.7%, with little change in specificity (from 72.7 to 78.6%) [81].

Enzyme-linked immunosorbent spot

Enzyme-linked immunosorbent spot (ELISpot) is another valuable in vitro test to diagnose non-immediate drug reactions focused in the analysis of the effector response. This assay allows the visualization of the secretory products of individual cells after drug stimulation, such as cytokines and cytotoxic markers [62••]. ELISpot assay has the advantages of being able to detect very few reactive cells [62••] even several years after the reaction occurred [82], and the possibility of determining more than one cytokine in the same assay, improving the accuracy of the test and reducing the number of cells that must be used [79, 83]. The determination of the secretion of IFN-γ in the evaluation of non-immediate reactions induced by AX has shown a sensitivity ranging from 13 to 91% [62••].

Sensitivity and specificity of the different in vitro tests that can be used in allergy diagnosis are shown in Table 2.

Clinical history and mathematical models

Given that allergy tests are not readily available in many hospitals, in recent years, the interest in stratification of patients labeled as allergic to penicillins has been growing. In that sense, several guidelines have been developed in order to identify low-risk patients in whom penicillins or other BLs could be used.

Table 2. Sensitivity and specificity reported in different studies for the main in vitro test used in BL allergy diagnosis

Test		Sensitivity	Specificity	Ref
Immunoassay	ImmunoCAP	0–50%	83.3–100%	[64–66]
	RAST	42.9–75%	67.7–83.3%	[64]
BAT		50–77.7%	89–97%	[66, 72–74]
HRT		55%	85%	[77]
LTT		58–88.8%	85–100%	[62••]
ELISpot		13–91%	83–100%	[62••]

RAST, radioallergosorbent test; *BAT*, basophil activation test; *HRT*, histamine release test; *LTT*, lymphocyte transformation test; *ELISpot*, enzyme-linked immunospot assay

Blumenthal et al. [18, 84••] have designed a computerized guideline-based drug allergy history and classified patients in three categories: (i) clinical history of immediate (IgE-mediated), (ii) clinical history of non-immediate reaction, and (iii) unlikely clinical history of allergy. The recommendation was to perform a DPT with a third- or fourth-generation cephalosporin or carbapenems in the first category, to avoid all BLs in the second category, and to perform DPT with penicillin or first- or second-generation cephalosporin without previous ST. The implementation of this guideline led to an increase in the use of BL. Most patients were switched to third- and fourth-generation cephalosporins. However, performing DPTs with cephalosporins does not rule out the label of penicillin allergy as an accurate delabeling could only be definite when clinical tolerance has been demonstrated to the culprit penicillin. Other limitations of this study are the relatively small sample size and the retrospective data collection.

Krishna et al. in the UK described a similar computerized method of risk stratification based on both nature and severity of the reaction, and presence or absence of cardio-respiratory comorbidity that may potentially impact on the severity of allergic reaction and on the response to treatment during DPT. Patients were classified as "low risk" in these cases: (i) history suggested mainly non-specific symptoms, indicating a non-immunological reaction and (ii) in patients with non-severe non-immediate exanthema in the absence of severe asthma, uncontrolled chronic obstructive pulmonary disease, and unstable cardiac disease as comorbidities. Patients were categorized as "high risk" if they reported any one of the following: (i) rash ≤ 1 h after first dose; (ii) isolated hypotension; (iii) upper and/or lower airway involvement and/or other clinical features suggestive of anaphylaxis. In patients considered to be at "low risk," tolerance to the suspected antibiotic would be definitively delabeled. The approach in "high risk" patients and in patients with a history of severe non-immediate systemic reactions (e.g., SJS, TENS, AGEP, DRESS syndrome) was similar to the one proposed by Blumenthal. Recently, the authors analyzed retrospectively data of 231 patients studied in their allergy center due to a suspected penicillin allergy [85]. Based on index reaction and comorbidities, patients were classified into "low risk" and "high risk." The negative predictive value for successful delabeling in the "low risk" group was 94%. Predictors for true penicillin allergy were history of anaphylaxis, hospitalization, and ≤ 5 years since the index reaction. The authors concluded that risk stratification can play an important role in delabeled patients with "low risk" of penicillin allergy. The main limitations of this study were that it is a single-center retrospective study with a relatively small cohort of patients. The authors stated that a prospective large multi-center study for validation is needed.

Also in recent years, there has been a growing interest in designing mathematical diagnostic algorithms based on clinical history predictors [86••, 87], on the basis that this would permit the avoidance of high-risk procedures such as STs and DPTs. Soria et al. [88] designed a clinical decision-making algorithm for penicillin allergy based on anamnesis. In their study, results were compared with results of penicillin allergy work-up. Allergy work-up diagnosed penicillin hypersensitivity in 41/259 patients (15.8%). A clinical algorithm based on the clinical history misclassified 3/41 (3.7%) truly allergic patients. The authors concluded that although the risk of misclassification is low, they could not recommend the use of this algorithm in general practice due to the risk to

misclassify patients with having immediate allergy to penicillins. However, the authors consider the algorithm could be useful in emergency situations in hospital settings.

Chiriac et al. [86••] designed a predictive model by two different methods: multivariate logistic regression and decision tree methods. The study included a retrospective and a prospective phase. In the prospective phase, they identified some clinical variables predicting risk for BL allergy through multivariate analysis. The most important variable was clinical history of anaphylactic shock. However, the overall performance of the models was poor. The best performances of logistic regression with a model containing 9 clinical history predictors were sensitivity 51% and specificity 75%. Regarding the decision tree, more than half of the allergic patients (70.5% on retrospective data and 56.4% on prospective data) were misclassified. Santurino et al. [87] designed a retrospective model using logistic regression and their performances were a bit better. They construct a model that included 8 variables in the medical history and they tested patients with reactions to several active principles. For a cutoff point of 0.5, the model using 90% of the sample correctly classified 81.8% of active principles. The model applied to the remaining 10% of the sample correctly classified 77.5%. No prospective evaluation was performed and cases misclassified as non-allergic are not discussed. In addition, the study included patients with a suspected allergy but not confirmed diagnosis, and the sample size of patients with allergy to BLs was low [89].

Therefore, despite the efforts made in recent years, currently there is no sufficiently validated predictive model for the diagnosis of hypersensitivity to BL antibiotics based on clinical history. Other potential methods to identify predictors of beta-lactam allergy may be artificial intelligence tools (e.g., machine learning, artificial neural networks), as they have been useful for prediction in other areas on medicine.

Conclusions

BLs are the first-choice drugs for most bacterial infections, with amoxicillin being the most frequently consumed in Europe. This wide consumption is associated with a high rate of BL allergy, constituting a worldwide health problem. The diagnosis of AX allergy is complex and, more importantly, time- and resource-consuming. Moreover, when AX allergy is confirmed or cannot be excluded, alternative antibiotics, such as quinolones, macrolides, or aminoglycosides, must be prescribed, and this forced switch is associated with reduced efficacy, prolonged treatment cycles and hospitalization periods, and increased costs and toxicity. Importantly, these alternative antibiotics are also main drivers of bacterial resistance.

Delabeling patients allergic to BLs is actually a necessity and different algorithms and guidelines based on clinical stratification have been developed in the last decade. However, from all recent studies, we can conclude that:

1. Until now, there is no clinical guideline using data only from the clinical history able to delabel patients with a clinical history of BL allergy, although they can be useful for giving alternative antibiotics in an urgent situation.
2. As the clinical history is often unreliable, true delabeling is still based on the performance of ST and DPT. Moreover, this needs to be clearly documented

in the clinical records to avoid new studies.

3. There are differences in the diagnostic approach between the USA and Europe and even between North and South Europe. These differences are mainly based on the pattern of BL consumption and the organization of the health system. To avoid risky procedures, this fact needs to be taken into account when using a specific diagnostic protocol.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
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