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Review

Management of reported beta lactam hypersensitivity in the emergency department setting

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SUMMARY

Severe antibiotic allergies are rare and widely overestimated. In children who present to the pediatric emergency department (ED) an antibiotic allergy is reported in 10% of cases, and frequency reaches 20-25%. in hospitalized patients. A true immune-mediated antibiotic hypersensitivity can be confirmed in only 5% of these patients. Many parents report their children as suspected to have "penicillin allergy" without clearly remembering or understanding the reaction and frequently this suspicion is uncritically accepted as a true allergy and reported in diaries and medical records. Methods for "delabeling" cases of uncertain diagnosis are an important goal of the healthcare system given the fact that a false beta lactam diagnosis leads to antibiotic resistance, prescription of not equally effective drugs with higher costs and long-lasting diseases. Furthermore, especially for a child it is not ethically acceptable to receive a wrong diagnosis that lasts their entire life.

This article provides practical guidance for correct management of an overestimated problem that does not promote judicious antibiotic use.

KEYWORDS Beta lactam antibiotics, Beta lactam allergy, Delabeling, Allergy, Diagnosis

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INTRODUCTION

Beta-lactam antibiotics (BLs), which include penicillins, cephalosporins, carbapenems and monobactams, are the class of antibiotics most frequently causing hypersensitivity reactions (HSRs) [1]. The first BL to be involved in HSRs was benzylpenicillin, followed over the years by other penicillins such as ampicillin, cloxacillin and amoxicillin, which is now the most frequently implicated. More recently, allergies to cephalosporins, carbapenems, monobactams and clavulanic acid have been often reported [2,3]. Within BLs, penicillins (with amoxicillin at the top of the list) are effective, safe and the most widely used for the most common bacterial respiratory infections in children. They should be avoided only when a true allergy is strongly suspected.

HSRs to antibiotics are rare and often overreported [4]. About 10% of parents report a drug allergy in their children and BLs are the most frequently suspected [5]. In medical records, patients are often defined as allergic to antibiotics on the basis of an unverified, vague, and long-standing

(e.g. > 10 years) history of reactions reported by parents. Undefined skin rashes are the most common complaint. Of note, it is often difficult to distinguish between maculo-papular exanthema due BLs, and viral exanthema and urticaria is more often related to infections than to drug HSRs. In most cases (> 95%), children labelled "allergic" to BLs are found to be non-allergic when a proper diagnostic work-up is performed [6-8].

In children labelled as allergic, the choice of an antibiotic therapy represents a crucial challenge. Approximately half of all hospitalized patients receive antibiotics and 10-15% of patients with previous reported penicillin allergy receive second-line broad-spectrum antibiotics, even when first-line treatment is a BL [9]. This increases the risk of treatment failure and adverse events. It also plays a role in the growth of antimicrobial resistance in hospital and community settings (methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus) and may cause *Clostridium difficile* infections. Furthermore, these patients have prolonged hospital stays, which can contribute to increased health care costs [10]. An accurate diagnosis needs an accurate history with details about the reason why the antibiotic was prescribed, the dose, the interval time between antibiotic administration and the reaction, any previous use of the same drug, any treatment administered and the recovery time. Unfortunately, the history reported by caregivers may lead to inaccurate or overestimated reactions. Therefore, clinical history cannot be a reliable diagnostic tool and it is unable to accurately differentiate allergic from non-allergic individuals. Skin tests, patch tests and in vitro tests (e.g. serum-specific IgE assays) can be helpful in assessing BL hypersensitivity. When an allergy test is positive, the drug provocation test (DPT) is considered to be unnecessary for diagnosis. However, the DPT is often necessary to confirm the suspected diagnosis of drug-induced HSR and is still considered the gold standard. Diagnostic tests should be performed within 1-6 months from the suspected reaction to minimize the risk of false negative results [11]. Further studies are needed to provide data supporting the regulation of DPT protocols in children with suspected HSR to BL. The number of given doses and the duration of DPT (especially in non-immediate reactions) to achieve an adequate compromise between safety, time consuming and potential side effects should be defined [11].

When a diagnosis of antibiotic hypersensitivity is made, the second step is to find a safe and effective alternative drug. Usually, if BL hypersensitivity is suspected, the entire class is avoided due to fear of cross-reactions, and alternative non-BL antibiotics are used. If an alternative BL is needed, structural similarities or identities between the culprit and the alternative drug should be avoided [12-14]. This article aims to provide pediatricians with a practical approach to manage these patients in hospital and community settings.

MANAGEMENT OF IMMEDIATE REACTIONS

The majority of IgE-mediated reactions to drugs are "immediate reactions" occurring from 0 to 6 h after administration of the culprit drug (in rare cases up to 12 hours). Delayed reactions occur after 6 hours and up to several days after the last administration of the culprit drug [15,16]. Clinically-significant IgE-mediated hypersensitivity can typically present within the first hour after oral exposure and always within 30 minutes of a parenteral exposure [17,18]. Anaphylactic reactions to penicillins are rare, with an estimated frequency of 0.01-0.05% [19]. In an emergency situation, the physician must take rapid decisions on the drug to prescribe in the best safety conditions to patients with a history of BL reaction who did not perform allergy tests.

The medical history that remains the first step for diagnosis of to BLs should be reevaluated not only to establish a first diagnosis, but especially to estimate the probability of a future severe allergic reaction, which may vary considerably in individual cases [20]. Although there is no consistent definition of "low-risk and high risk drug reactions", identification of higher and lower risk patients when there is concern for a type I IgE-mediated reaction is essential [21] (Tab. I). The management of patients with suspected HSR to BLs is based on their risk profile. Subjects who experienced severe reactions, or who have a high likelihood of experiencing a severe reaction if re-exposed to the culprit BL, can be classified at high risk. Subjects who experienced mild reactions, or who have a low likelihood of experiencing a more severe reaction than the index reaction in case of re-exposure to the culprit drug, can be classified as low risk [10].

It is also important when choosing the drug to be used that the doctor knows the probability of cross reactivity between BLs. The risk of

TABLE I. Risk stratification of immediate drug allergic reactions (modified from [21]).

Severe risk (particularly within the last 5 years)	Low Risk
Any of the following severe symptoms within 1 hour. (probability is highest when two or more occur together)	Remote history of symptoms not suggestive of severe reaction, > 5-10 y ago
Disseminated hives/urticaria	Delayed onset urticaria (> 6 h following dosing)
Angioedema/Swelling of face/ throat	Urticaria only, expecially if > 5-10 y ago
Shortness of breath, wheezing, coughing	Self-limited mild exanthem
Shock	Itching, dizziness only
Weak pulse	Gastrointestinal symptoms only
Loss of consciousness/ confusion	Family history of penicillin allergy only
Severe gastrointestinal symptoms (diarrhea, vomiting)	Avoidant from fear of allergy only
Recurrent reactions to drugs	

clinical cross-reactivity between penicillins and cephalosporins is still a controversial issue and in many cases overestimated. It varies from 0 to 38%, depending on the similarity between chemical structures [12]. Risk for cross reactions between BLs decreases greatly if the similarity of side chains is taken into account. The cross reactivity between penicillins and cephalosporins and between different cephalosporins is generally mediated by similarities in side-chain structures rather than the structure of the BL core. Cross-reactivity between penicillins and cephalosporins with different side chains is low [14]. Thus, cephalosporins with side chains dissimilar to penicillin or amoxicillin cannot be associated with an increased risk of allergic reactions in penicillin or amoxicillin allergic patients [22].

Of note, a meta-analysis of studies performed between 1966 and 2005, which compared hypersensitivity reactions to cephalosporins in penicillin-allergic and non-penicillin-allergic patients, reported a significant increase (odds ratio = 4.8) in allergic reactions to all first-generation cephalosporins, but no increase with second- or third generation cephalosporins in penicillin allergic patients [23]. Using the Drug Allergy and Hypersensitivity Database Cohort, in 143 patients with proven BL allergy the prevalence of cefuroxime hypersensitivity reactions was 6.3% [24]. Cross-reactivity occurs between cephalexin and amoxicillin that share similar side chains [25].

Regarding cross-reactivity between cephalosporins, the greatest risk occurs when cephalosporins with similar side chains are used and it is quite low in drugs with dissimilar side chains [26] (Fig. 1). The cross-reactivity among cephalosporins may be mainly linked with the R1 side chains. Cases of cross reactivity related to the R2 side chain are rare [25]. Cross-reactivity between penicillins or cephalosporins and monobactams is very low (< 1%). However, cross reactions between aztreonam and ceftazidime due to the homology of side chains are quite frequent [27]. Cross reactions between penicillins or cephalosporins and carbapenems are very rare [28].

In the emergency setting in patients with higher risk for reactions and in absence of a confirmed allergy diagnosis, the doctor's behavioral patterns might be suggested as follows [8,29]:

If the index reaction was to a penicillin (penicillin G, penicillinase resistant penicillins, amoxicillin, piperacillin) it can be considered to administer a full dose of a 3rd/4th/5th generation cephalosporin.

If the index reaction was to 1st/2nd generation cephalosporins, possible options are full dose of aztreonam, or carbapenems, or 3rd/4h/5h generation cephalosporins with dissimilar side chains using test dose procedure. This modality consists of a two-step intravenous or oral challenge with 10% of the therapeutic dose, followed by either 90% after 30-60 min of administration [8]. However, the duration and dosage of test doses remains controversial among experts.

If the index reaction was to 3rd/4th/5th generation cephalosporins, possible options are full dose of aztreonam (unless original reaction was to ceftazidime), full dose of carbapenems, or test dose procedure with penicillin antibiotics or 1st/2nd generation cephalosporins with dissimilar side chains.

In patients at lower risk of reactions the suspected drug may be re-administered in a full dose, with subsequent observation of the child for at least 2 hours after administration. However, it must also be considered that the safety of the patient achieved with these procedures can never reach 100%. After resolution of the acute reaction, in cases where an antibiotic other than the suspected one has been administered, it is always advisable to refer the child to the allergist for a drug allergy work-up [30].

MANAGEMENT OF DELAYED REACTIONS

In a pediatric age, most HSRs are delayed, usually occurring after 6 hours from exposure [18]. The most frequent type of delayed HSRs is benign maculopapular exanthema (MPE). Rarely, delayed HSRs can also present in severe forms, usually appearing > 24 hours after exposure but up to two or more weeks. The temporal overlapping onset between mild and severe forms underlines the importance of careful monitoring even of the child with MPE, since in 2-6.7% they can evolve into a severe cutaneous adverse reactions (SCAR) [31].

BLs are often administered during viral infections with possible bacterial co-infection. It is significant that 75% of children with reported BLs allergy were diagnosed before the age of 3 years when these conditions are more frequent and that most patients who report an allergy to BLs have received this "label" due to a delayed benign skin reaction.

Most skin eruptions are due to an infectious agent, in particular viruses that infiltrate tissues and cause direct cytopathic damage [32]. Viruses are also able to promote or exacerbate HSR rashes [33]. However, there are some clinical and diagnostic features that can help the clinician to distinguish between them, as reported by Mori et al. [34].

The classic and most reported delayed HSRs is MPE, which accounts for 35% of all HSRs in a pediatric age [35]. MPE has an estimated incidence around 158.3/10,000 cases, with a high incidence in children under 4 years of age (over 350/10.000 cases) [35,36]. Most MPEs are mild, transient, characterized by maculopapular elements with limited cutaneous extension (less than 50% of skin), without systemic symptoms and with usually self-resolving evolution. They start in the first week of exposure to the drug (4-21 days) and resolve within a few days or weeks after drug suspension. It should be remembered, however, that in a previously sensitized child, the manifestations can appear more quickly, even after a few hours from the first dose and reach their maximum extent in 24-48 hours with subsequent exposures to the drug. Infectious urticaria is also often mistakenly diagnosed as drug-induced urticaria due to the similarity of skin lesions. However, the temporal dynamics (not immediate correlation with the exposure and the persistence of the lesions even after discontinuation of the drug) and some characteristics of the lesions (such as a polymorphic appearance of the lesions) should help in the differential diagnosis.

When dealing with suspected delayed HSRs, clinicians must know how to promptly identify patients who are at risk for severe reactions and the presence of signs and symptoms of danger (Tab. II) [7,4,10,37]. Determination of MPE severity is reported in Table III [38].

TABLE II. Danger signs, risk factors for drug allergic delayed reactions (modified from [7,4,10,37]).

Danger signs and symptoms	Patients at high risk of severe delayed reactions
Skin reactions	Patients with a history of severe or life-threatening reaction (immediate or delayed) to an antibiotic (e.g. Stevens-Johnson syndrome or skin rash with blistering or mucosal involvement)
Intense facial involvement	Patients with positive skin test
Atypical target lesions	Patients with recurrent reactions or reactions to multiple antibiotics
Bullous lesions	**Patients at low risk of severe delayed reactions**
Small vesicles or crusts	History of isolated symptoms of intolerance (nausea, vomiting, diarrhea or headache)
Diffuse dark red or grey purple erythema	History of mild skin reactions, especially if occurred more than 5 years before the evaluation
Extensive pustulosis	Local reactions at the injection site
Skin pain or burning	History of unknown reactions that occurred long time ago without characteristics of immediate IgE-mediated reactions
Systemic reactions	Family history of antibiotic allergy
Involvement of the mucous membranes	
Generalized lymphadenopathy	
Hepatitis	
Nephritis	
Pneumonitis	
Fever > 38.5°C	
Modifications in blood cell counts (anemia, granulocytopenia, neutrophilia, eosinophilia, thrombocytopenia)	
Hypocomplementemia	

TABLE III. Severity of Maculo Papular Exanthema (MPE) (modified from [38]).

Mild	Moderate	Severe
Not urticarial	Duration 7 days	Involving > 50% of the body surface and systemic symptoms
Involving less than 50% of the body surface	Requiring topical/sistemic steroids	Mucosal involvment
Without danger signs	Involving > 50% of the body surface	Clinical signs or symptoms compatible with SCARs
Occurring more than 6 h after the drug intake	Not systemic symptoms	
Duration, < 7-days	Mild MPE with severe comorbidities (for example mastocytosis, significant cardiac or pulmonary diseases)	
Not requiring hospitalization or systemic treatment other than antihistamines		

The Primary Care Pediatrician (PCP) is usually the parent's first contact in the event of a HSR. It is important that the PCP is able to recognize the type of reaction, its severity and the need for immediate referral to a specialist. The PCP should also know how to manage mild HSRs in the outpatient setting during the acute event and thereafter for future courses of antibiotics [39].

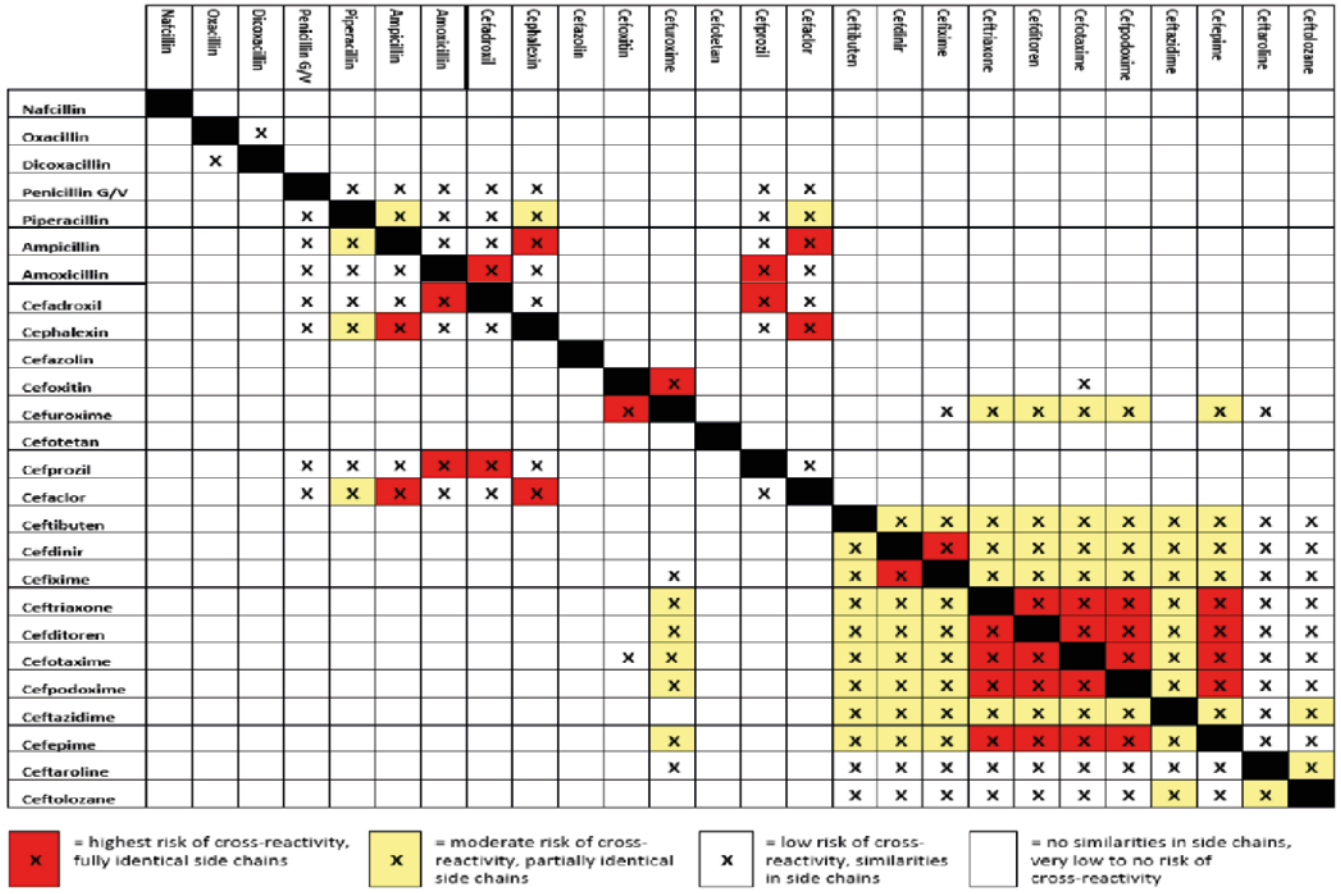

FIGURE 1. Side chains structural similarities between b-lactam drugs and risk of hypersensitivity reactions (adapted from [26]).

In acute setting of mild delayed reactions, such as in MPE, if the PCP deems no risk for progressing to severe delayed HSRs, it can be considered to continue with the same BL and ensure a close clinical follow-up along with supportive treatment, such as antihistamines in case of itching [4]. When in doubt about the benign nature or there is the need for antibiotic switching, it is preferable to avoid other aminopenicillins and first generation cephalosporins with an amino group (for example cefaclor or cephalexin) according to Figure 1, while in more severe exanthemas it is preferable to change the class of antibiotics avoiding all penicillins and cephalosporins [39].

After resolution of the acute event, it is imperative not to label the child as allergic and promptly arrange an evaluation on BL tolerance with the parents' consent. When it is certain that the child had had a mild delayed HSRs to BLs, it is possible to proceed with a direct DPT, without carrying out skin or serological tests [38]. Once the PCP has identified those children at low risk of HSRs it has been proven safe to perform a DPT at well-being status with a full dose of BLs in the ambulatory setting, with a two hour observation period and with emergency care facilities promptly available. If no immediate reactions occur, the child can be sent back home and continue the BL for at least 5 days [40]. Strict follow-up of the child is mandatory, since in a minority of cases (< 5%) the rash may recur, although usually with the same severity of the index reaction [41].

Since skin tests have shown a low diagnostic accuracy in mild delayed MPE, DPT for BLs represents the gold standard for diagnosis of HSRs [42]. It assesses both tolerance to the suspected drug and reassures parents on the safety of the therapy. The DPT can be performed directly starting with the therapeutic dose (1-step or 2- or 3-step protocol). It has already been demonstrated that more than 90% of cases, MPE does not recur upon subsequent exposure to the antibiotic, even in immediate mild HSRs [43] and in any case with manifestations that are no more severe than the index ones. Consequently, further doses are necessary to induce the clinical manifestations, and further doses are always taken at home. On these grounds, therefore, the PCP might simply prescribe a BL again when needed and then deal with the "allergy" issue only in the small percentage of children who will show the skin reaction again.

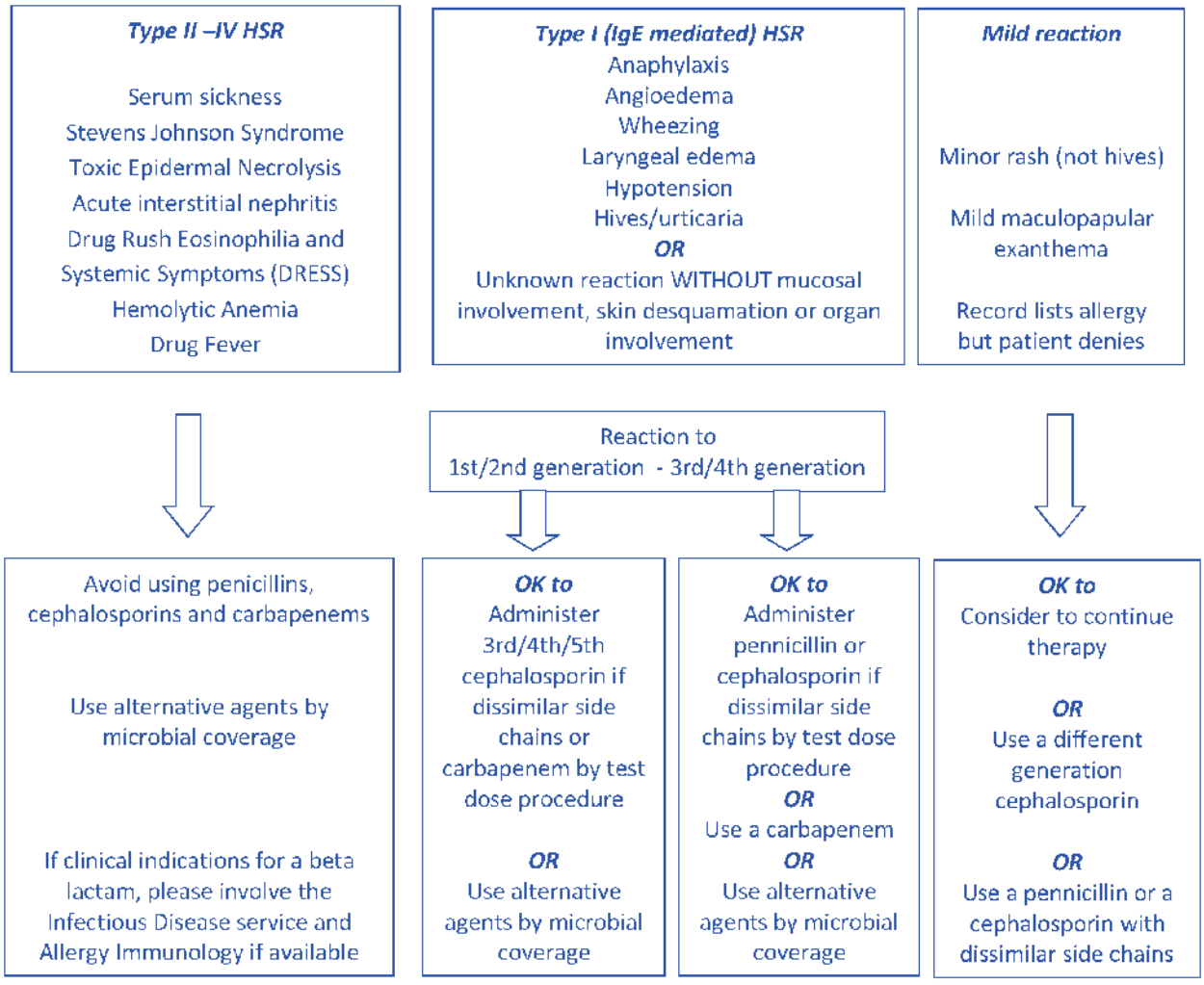

FIGURE 2. Suggested pathways in cases of suspected beta lactam hypersensitivity. (modified from [8]).

CONCLUSIONS

BLs antibiotics are the most common triggers of drug allergies, but may cause rare severe reactions (e.g. anaphylaxis). Many patients report suspected BL hypersensitivity and misdiagnosis is frequent. While clinical pathways for drug allergy risk stratification have provided major advancements in the field of BL allergy evaluation and antibiotic stewardship, they have also highlighted the need for evidence-based predictive models to develop data-driven point-of-care clinical decision rules that define true risk of penicillin or beta-lactam allergy. An algorithm can be used in the context of the "doctor behavioral patterns" (Fig. 2) [8]. Delabeling programs for BLs HSRs must include information campaigns, including pocket size reminder cards programs of administration of drugs by general physicians. The patient's medical history is essential for all delabeling procedures, especially for risk stratification. Definition of low risk remains a subject of controversy but stratification of patients at high or low risk may be useful to rule out hypersensitivity to BLs. These procedures reduce the need for skin testing and/or comprehensive allergy counseling.

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Conflict of interest statement

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Ethical considerations

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