



Risk stratification in beta-lactam allergy

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Abstract

Purpose of Review Beta-lactams (BLs) are among the most commonly prescribed and effective antibiotics. Given the fact that overdiagnosis of penicillin allergy constitutes a major public health problem by increasing health costs and contributing to overall antibiotic resistance, removing BL allergy label is crucial.

Recent Findings Delabeling penicillin allergy as an essential component of antimicrobial stewardship is a hot topic. Despite several clinical risk factors and genetic characteristics proposed to predict BL allergy, it is still unclear what exactly constitutes a risk. Recently, a great deal of interest has been focused in the design of risk stratification and implementing pathways in order to classify the risk based on the clinical history. Appropriate risk stratification is critical to ensure that high-risk patients are referred to allergy specialist for further diagnostic assessment, whereas direct drug provocation tests can be safely employed in low-risk patients.

Summary Many patients labeled as allergic to BLs are able to tolerate these drugs. The huge burden of penicillin allergy can be tackled by integrating risk-based and traditional testing strategies into antibiotic stewardship programs. Promising potential methods to accurately assess BL allergy risk will require collaborative multimodal approaches including risk stratification pathways with validated tools.

Introduction

Beta-lactams (BLs) are preferred as first choice drugs in the treatment of many bacterial infections and hence the most widely used antibiotics all over the world [1]. BLs, which include penicillins, cephalosporins, carbapenems, and monobactams, are the most common antibiotic classes reported to cause allergic reactions [2]. Due to the heterogeneity in BL prescription patterns and diagnostic protocols, BL antibiotic allergy prevalence shows variation with a range of 0.7 to 10% among populations [3]. BL allergy is confirmed in 6.8 to 15.9% of the children with a history of reaction to BLs [4–6]. Penicillins are the most common drugs causing drug allergy among BLs both in adults and children [7, 8]. However, the studies comprising thorough diagnostic work-up have shown that penicillin allergy is largely overestimated [6, 9, 10]. Over the last years, there is a trend of increase in the consumption of amoxicillin and cephalosporins rather than penicillins [11, 12]. Amoxicillin and amoxicillin-clavulanic acid (CLV) constitute almost 50% of drug allergy reports in Europe [13]. Recently, an increase in the number of patients has been reported with selective immediate allergic reactions to CLV which may be related to their increased utilization [14].

BL allergy is classified as immediate reaction (IR) or non-immediate reaction (NIR) based on the time interval between the first dose of the therapeutic

course and the onset of the symptoms [15, 16]. IRs are defined as those which typically appear within 1 h but may occur up to 6 h after the last therapeutic dose and generally manifest as symptoms such as urticaria with or without angioedema; respiratory symptoms such as rhinitis, cough, bronchospasm, and dyspnea; and gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea, or as anaphylaxis [16, 17].

NIRs are defined as reactions which appear more than 1 h after the first dose of therapeutic course and generally up to several hours or days of treatment [16–18]. The most common clinical presentations of NIRs which are usually associated with a T cell-mediated allergic mechanism are delayed appearing urticaria/angioedema and maculopapular exanthems. BLs are also culprit drugs in other hypersensitivity reactions such as fixed drug eruption, symmetric drug-related intertriginous flexural exanthema (SDRIFE), serum sickness-like reactions, and type 2 reactions such as cytopenia and nephritis [16, 19]. Rarely, severe cutaneous adverse reactions (SCARs) occur which include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) [20, 21].

Conventional diagnostic approach to BL allergy

The diagnostic work-up protocol of BL allergy depends on the clinical symptoms and chronology of the reactions and includes a detailed and standardized questionnaire, physical examination, skin tests such as skin prick test (SPT), intradermal test (IDT) and patch test, in vitro tests, and drug provocation tests (DPTs) [22–24]. Diagnostic tests should be performed after a time

interval of at least 3–6 weeks from the index reaction and preferably done before 6 to 12 months [17].

IgE-mediated mechanisms are responsible for most of the IRs where SPTs and early reading of IDTs are used as a first step in the diagnosis [25]. The conventional skin test panel for the assessment of BL allergy includes penicillin reagents (major and minor penicillin determinants and benzylpenicillin), amoxicillin, and the culprit BL. Major (benzylpenicilloyl-poly-L-lysine, PPL, Pre-Pen®, AllerQuest LLC, Plainville, CT, USA, and benzylpenicilloyl-octa-L-lysine, BP-OL, DAP®, Diater) and minor (the only commercially available form is sodium benzylpenilloate, DAP®, Diater) determinants of penicillin have a central role in BL allergy diagnosis [17, 26]. However, due to the alterations in the prescription pattern of BLs, the diagnostic approaches and the sensitivity of the skin tests are changing over time [27]. Torres et al. demonstrated that the addition of amoxicillin in skin test panel has been reported to increase the test positivity up to 70% [28]. The positive predictive (PPV) and negative predictive values (NPV) of penicillin skin tests with these reagents were found to be approximately 50% and more than 93% in adults, respectively [29, 30]. Recently, the role of CLV has increased in BL allergies, so it has also been recommended to test this antibiotic in skin tests (CLV, Diater®) [31]. In this regard, the use of CLV in skin tests has shown that more than 30% of patients with an IR to amoxicillin-CLV are selective reactors for CLV [32, 33]. A previous research by Ibanez et al. demonstrated that overall specificity was very high (98.3%) for IDT, whereas sensitivity was extremely low (9.1%) in children evaluated for penicillin allergy [34]. In a recent study, a double-blind penicillin skin testing with PPL and benzylpenicillin was performed before DPT with amoxicillin in children with a history of mild type penicillin reaction to determine the predictive values of skin tests. The sensitivity and specificity of penicillin skin tests for reacting to amoxicillin challenge were found as 20% and 90%, respectively [35].

Regarding the unreliability of clinical history and low sensitivity of skin tests and in vitro tests, a DPT is the gold standard to establish the diagnosis. DPTs with the culprit BL is suggested in patients with a history of allergic reaction to BLs presenting with negative skin tests [8, 18, 20]. It should be carried out under medical supervision by experienced personnel who are able to deal with anaphylaxis. Undoubtedly, DPTs are contraindicated in patients with a history of severe anaphylaxis [17]. In vitro tests such as serum tryptase, basophil activation test, and determination of drug-specific IgE could be useful in severe IRs [8, 16, 22]. However, the sensitivity of immunoCAP assay which is the mostly used method to measure sp IgE to BL is low, ranging from 0 to 50% due to the BL used [36, 37]. The sensitivity and specificity of basophil activation test have been reported to be in a range of 50 to 77% and 89 to 97%, respectively [38, 39].

Patch tests and delayed reading of IDTs (after 24, 48, and 72 h) are used in the first step of diagnosis of non-immediate allergic reactions which are thought to be mediated by T cells [23]. The sensitivity of patch tests is lower than IDTs depending on the vehicle and the drug used [15]. Caubet et al. demonstrated that IDTs have poor diagnostic values with a sensitivity of 50% in children with a benign non-immediate allergic reaction to BLs [40]. Another study by Caubet et al. showed a sensitivity of 66.7% and a PPV

of 36.4% for IDTs but a good specificity (91.5%) and a high NPV (97.4%) in children with mild non-immediate BL reactions [4]. Regarding that IDT confers a high relapse risk in SCARs, patch tests are proposed as the first-line assessment [17]. In vitro tests such as lymphocyte transformation test and enzyme-linked immunosorbent spot assay can also be used for T cell-mediated reactions [26, 41]. In the context of BL allergy assessment, sensitivity and specificity of lymphocyte transformation test range from 58 to 88.8% and 85 to 100%, respectively [41]. Since the diagnostic value of skin tests is low, the diagnosis of NIRs due to BLs is often confirmed or excluded with DPTs, which are contraindicated in patients with a history of SCAR [4, 8, 17].

Historical risk factors that predict confirmed BL allergies

Despite a growing number of studies attempting to identify the clinical characteristics and risk factors involved in BL allergy, it is still unclear what exactly constitutes a risk for the development of BL allergy [34, 42]. In this sense, several clinical factors giving rise to the risk of BL allergy have been reported in the literature including older age [6, 43]; anaphylaxis or respiratory or cardiovascular involvement [20, 44–47]; angioedema during the index reaction [43]; any reaction within 1 h after last or first dose [44, 47]; a reaction history within the last 12 months [45, 48, 49], requirement for an emergency department visit, treatment, or hospitalization [46]; a family history of drug allergy [49–51]; and atopic background and presence of asthma [43, 52].

Allergic drug reactions are infrequent during childhood due to the immaturity of the immune system and less frequent exposure to drugs compared to adults [42, 53]. In a previous study, given that the older children were less likely to pass the DPT, the age at the time of the reaction was reported as a significant risk factor for BL allergy. Regarding that younger children have more viral infections compared to older ones, it is not an unexpected result [43]. Most studies among adults show that women have a higher incidence of drug allergies compared to men due to the differences in pharmacokinetic, immunological, and hormonal factors [9, 54, 55]. However, pediatric studies reported that the female gender was not a risk factor for drug allergy among children [5, 50, 56].

Many studies have shown that an anaphylaxis history was among the strongest predictive factors for confirmed BL allergies [44, 46–48]. Patients presenting with anaphylaxis after BL administration are more likely to have positive skin tests and DPTs reflecting the higher specificity of anaphylaxis for true IgE-mediated reactions rather than other presentations [45]. Since angioedema was more common in true allergic reactions, it was also found as a significant clinical finding associated with DPT failure in a recent study [43]. IRs have been reported to have a high probability of being confirmed compared to NIRs after diagnostic assessment [6]. Moreover, the time elapsed since the index reaction was indicated as an important variable particularly in the context of IgE-mediated reactions due to loss of sensitization over time [46]. Consistent with this data, Siew et al. demonstrated that a time interval of less than 1 year since the index reaction significantly increased the

risk of having immediate type BL allergy. The authors also pointed out that hospitalization history for the index reaction was a significant predictor for BL allergy [45]. An index reaction treated with corticosteroids was found to be associated with penicillin allergy [34].

A family history of drug allergy is mentioned in a few studies in which the predictors of immediate type BL allergies were mostly linked to IgE pathway, atopy, and antigen presentation, both in children and adults [42, 49–51, 57]. In a genome-wide association study, single-nucleotide polymorphisms within HLA-DRA and HLA-DRB5 predicted skin test positivity to amoxicillin and penicillins [58]. Recently, HLA-B*48:01 was found to be strongly associated with IRs to BLs [59].

Atopy is not considered to be associated with a higher risk of drug allergy, but it may contribute to more severe allergic reactions [56, 60]. The results are contradictory in the context of BL allergy, and some studies found no relation [5, 6], whereas others reported increased [52] or decreased [61] risk among atopic children and adults. A candidate gene approach showed that polymorphisms in genes related to atopy such as IL-4, IL-4R alpha, IL-13, and IL-10 were predictors of BL allergy among adults [42, 51, 62, 63]. Moreover, asthma was found as a significant risk factor for DPT failure, whereas the presence of food allergy was marginally significant in children with amoxicillin allergy [43].

Many of these risk factors could not be reproduced in other studies pointing out that there are some population-specific risk factors [5, 34]. Hence, there is a great need for further studies focusing on predictors of BL allergy based on the clinical risk factors and genetic characteristics which may target personalized medicine and contribute to antibiotic management strategies.

Recent risk stratification and management guidelines for BL allergies

Given the fact that penicillin allergy labels are highly prevalent and mostly inaccurate, antimicrobial stewardship strategies have been the focus of global healthcare [26, 64]. Overdiagnosis of penicillin allergy alters treatment decisions leading to suboptimal antibiotic preferences that are often less effective and more toxic with significant side effects [47, 65]. Unfortunately, patients with an inconsistent history of penicillin allergy are given broad-spectrum antimicrobial agents which give rise to infection risk with *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* [19, 66, 67]. Besides that, being labeled as having a penicillin allergy contributes to the risk for a prolonged length of hospital stay and more frequent hospital admissions [68]. On the other hand, the overestimation of penicillin allergy is related to increased costs with poor socioeconomic consequences. Regarding these drawbacks, a great deal of effort has been directed towards BL allergy delabeling in an attempt to reduce antimicrobial resistance and facilitate the antimicrobial stewardship [47, 64, 69, 70].

Recently, a growing interest has been focused in the design of clinical decision support systems, risk stratification, and implementing pathways in order to ensure optimal antibiotic stewardship [19, 30, 47, 48, 64, 65]. Appropriate risk stratification is of the utmost importance as a way to ensure that high-risk patients are referred to allergy specialist for further diagnostic assessment, whereas direct DPTs can be safely employed in low-risk patients [17, 47, 48, 71].

Regarding the importance but also uncertainty of “low-risk” criteria, variable risk stratification tools have been developed across different centers [47, 65, 68, 72]. Shenoy et al. published a practical risk stratification tool for penicillin allergy assessment indicating the low-risk histories as isolated non-allergic symptoms, such as gastrointestinal symptoms, or a family history of a penicillin allergy alone, or symptoms of pruritus without rash, or unknown remote (> 10 years) reaction without features of IgE-mediated symptoms. The authors defined a moderate-risk history consisting of urticaria or other pruritic rashes or symptoms suggestive of an IgE-mediated reaction but not anaphylaxis and a high-risk history including anaphylaxis, recurrent penicillin reactions, positive penicillin skin testing, or hypersensitivities to multiple BLs [65].

An important potential barrier to widespread implementation of penicillin allergy assessment is the lack of externally validated tools to stratify the risk for penicillin allergies [73••]. In this regard, Devchand et al. validated a BL allergy risk assessment tool based on the index reaction with the aim to identify low-risk patients suitable to direct DPTs. The assessment tool demonstrated a sensitivity and specificity highest for direct delabeling the reactions unlikely to be immune-mediated and also a good sensitivity for immediate allergic reactions [72]. In a recent study by Trubiano et al., a clinical decision rule was created and also validated to identify low-risk patients potentially amenable to direct DPT. The significant predictors related to penicillin allergy were the presence of anaphylaxis/angioedema or SCAR, time since reaction ≤ 5 years, and whether treatment was required. They stated that a validated clinical decision rule could be helpful to predict low-risk penicillin allergy [74•].

The high burden of penicillin allergy can be tackled by integrating risk-based strategies into antibiotic stewardship programs [30, 64, 73••]. However, some pitfalls exist in designing and implementing BL allergy pathways. First of all, they are not standardized, and none can ideally discriminate patients who are truly allergic. Also, risk stratification algorithms should take into account the information of current clinical stability and comorbidities for selection of diagnostic interventions, as well as the historical reaction details. However, some pathways indicate clinical instability as an exclusion criterion, and the others are designed irrespective of clinical condition [47, 75]. On the other hand, it is unclear in most of the reported pathways whether unknown remote reactions should be interpreted as high or low risk. In the light of these key considerations, pathways should be adapted to patient-specific risks as well as local geographic features regarding BL allergy epidemiology, prescribing practices, and cross-reactivity patterns [73••].

Recently, a European Academy of Allergy and Clinical Immunology (EAACI) position paper provided a risk stratification in BL allergy in which the high-risk patients are classified according to index reaction as subjects with a serious reaction history, or likely to experience a severe reaction if re-expose to the culprit drug, while those who had not severe reactions, or unlikely to experience a serious reaction in case of re-exposure, are considered as low risk [17]. In detail, anaphylaxis, hypotension, laryngeal edema, bronchospasm, urticaria and/or angioedema, and generalized erythema are defined as high risk for IRs. For NIRs, severe maculopapular exanthema (widespread rash that may develop into erythroderma; > 1-week duration, with systemic involvement), specific organ manifestations, systemic vasculitis/serum sickness-like reaction, drug-induced autoimmune diseases, SJS, TEN, DRESS, AGEP, and generalized bullous fixed drug eruption were classified as high-risk situations [17].

In light of the recent accumulating evidences derived from EAACI position paper [17] and risk stratification studies [19, 30, 47, 48, 64, 65, 71, 76, 77], low-risk patients can be defined as those with a history of symptoms nausea, diarrhea, or headache in isolation [17, 19, 30, 47, 48, 64, 65, 76, 77] or symptoms of pruritus without rash [17, 19, 64, 71] or benign rash such as mild maculopapular rash [17, 47, 48, 71] or remote (> 5–10 years) unknown reaction not suggestive of an IR [19, 30, 64, 65, 71] or no treatment required or treated with antihistamines only [19] or a family history of a penicillin allergy alone [19, 64, 65] or tolerance with re-exposure to the responsible drug since the index reaction [47]. The characteristics of studies focusing on low-risk historical situations in BL allergy are presented in Table 1. High-risk criteria can be defined as reactions with upper or lower airway involvement (wheezing, laryngeal edema) [17, 47, 48, 64, 76, 77]; hypotension [17, 30, 47, 76, 77]; anaphylaxis [17, 30, 47, 48, 64, 65, 71]; systemic steroid or epinephrine use [19, 30]; positive penicillin skin testing [65, 71]; recurrent penicillin reactions [65] or reactions to multiple BLs [65]; emergency visit or hospital admission [19]; reaction with organ involvement, profound skin desquamation, or mucosal involvement such as SJS, TEN, AGEP, and DRESS; immune-mediated liver or kidney injury; and drug-induced immune cytopenia and serum sickness-like reaction [17, 19, 30, 47, 64, 76]. Also, unstable or compromised respiratory or hemodynamic condition should be regarded as high risk even in the context of a low-risk history since it has the potential for giving rise to poor consequences [47, 65, 71]. Although urticaria was considered as a high-risk situation according to EAACI position paper [17], in a few studies, patients presenting with urticaria or other pruritic rashes treated with antihistamine or reactions with features of IgE (e.g., swelling) but not anaphylaxis were defined as moderate-risk [30, 65, 71]. The other moderate-risk criteria identified in those studies were anaphylaxis or positive penicillin skin testing 5 or more years ago [71] or unknown reaction < 5 years ago [71].

In view of recent findings, the management of patients with suspected BL allergy has to depend on the patient's risk profile and accessibility of an allergy assessment [17]. In patients who experienced BL side effects such as nausea, vomiting, and headache that are mislabeled as allergic or those who

Table 1 Definition of low-risk historical situations in beta-lactam risk stratification studies

	Low-risk definition
Shenoy E, et al. 2019 [65]	-Isolated reactions, unlikely allergic (gastrointestinal symptoms, headache) -Pruritis without rash -Remote (>10 years) unknown reactions without features of IgE -Family history of penicillin allergy only
Krishna MT, et al. 2017 [47]	-Gastrointestinal symptoms only -Benign rash only (urticaria, exanthematous rash, angioedema) > 1 h after first dose -Poorly described symptoms but not deemed serious ± well controlled asthma, COPD, stable cardiac comorbidity -Presyncope only (after oral dose) -AX or co-amoxiclav has been tolerated since index episode
Blumenthal KG, et al. 2019 [19]	-Family history only -Non-allergic symptoms (headache) -Tested positive without exposure -Itching only -No therapy was needed -Remote reactions (> 10 years ago) -Antihistamines used -Cutaneous symptoms only
Stone CA, et al. 2020 [64]	-Remote history of symptoms, not suggestive severe reaction (> 5–10 years ago) -Delayed onset urticaria (> 6 h after dosing) -Urticaria only, > 5–10 years ago -Self limited mild exanthem -Gastrointestinal symptoms only -Family history of penicillin allergy only -Avoidant from fear of allergy only
Blumenthal KG, et al. 2019 [71]	-Reaction with features of IgE, 5 or more years ago -Mild non-IgE cutaneous reactions (e.g., maculopapular rash, pruritis) -Unknown reaction
Castells M, et al. 2019 [30]	-A history of nausea, diarrhea, or headache in isolation -A remote or unknown history of penicillin allergy
Macy E, et al. 2018 [48]	-Penicillin associated symptoms occurring more than 12 months ago -Any benign rash -Gastrointestinal symptoms -Headaches -Other benign somatic symptoms -Unknown history
Vyles D, et al. 2017 [76]	Runny nose or cough or headache Nonhive rash Urticarial rash in the absence of other high risk symptoms Itching Nausea, vomiting, or diarrhea No symptoms but family history of penicillin allergy
Romano A, et al. 2020 [17]	-Isolated generalized pruritus -Isolated gastrointestinal symptoms -Local urticaria to parenteral administration -Contact dermatitis -Palmar exfoliative exanthema -Fixed drug eruption -Delayed-appearing urticaria -SDRIFE -Mild-moderate maculopapular exanthema

AX amoxicillin, **COPD** chronic obstructive pulmonary disease, **SDRIFE** symmetric drug-related intertriginous flexural exanthema

have only a family history of allergy or may have been re-exposed and tolerated successfully the culprit drug since the index reaction, BL allergy labels can be removed without testing. Despite the differences in the definition of low-risk allergy phenotypes, recent studies and guidelines have confirmed that a direct DPT under medical observation without prior skin tests is appropriate and can be safely applied in patients with low-risk history [65, 68, 78–85]. Undoubtedly, patients with high-risk history should be evaluated by allergy specialists. In this regard, moderate-high-risk patients can be evaluated with classical diagnostic algorithm, including skin tests and subsequent DPTs if skin test results are negative. Moreover, if penicillin is urgently required for patients with a high probability of experiencing anaphylaxis, a desensitization procedure can be employed [64, 65]. Recent EAACI position paper also provides an algorithmic approach when an antibiotic therapy is urgently required and referral to an allergist is not feasible. In all these cases, a non-BL alternative antibiotic can be given, and in case of a need for an alternative BL, cross-reactivity patterns should be taken into account [17]. Undoubtedly, patients with SCARs should avoid all penicillins and BLs until further detailed testing [17, 30].

Conclusion

Regarding that BL allergy is often overestimated leading to treatment failures and poor socioeconomic outcomes, delabeling is critical for global public health. The enormous burden of penicillin allergy can be handled by integrating risk-based and traditional testing strategies into antibiotic stewardship programs. It is worth noting that appropriate risk stratification is essential to ensure that the high-risk patients are referred for further diagnostic assessment, whereas direct DPTs can be safely employed in low-risk patients. In that sense, there is a great need for collaborative multimodal approaches to accurately assess BL allergy risk by incorporating risk stratification pathways with validated tools into clinical practice as well as to determine the potential for generalizability in different populations.

Declarations

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.

Conflict of Interest

The authors declare no competing interests.

References and Recommended Reading

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

- Of importance
- Of major importance

1. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol*. 2016;137:1148–53. <https://doi.org/10.1016/j.jaci.2015.10.026>.
2. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol*. 2012;108:88–93. <https://doi.org/10.1016/j.anai.2011.11.006>.
3. Doña I, Barrionuevo E, Blanca-Lopez N, Torres MJ, Fernandez TD, Mayorga C, et al. Trends in hypersensitivity drug reactions: more drugs, more response patterns, more heterogeneity. *J Investig Allergol Clin Immunol*. 2014;24:143–53.
4. Caubet JC, Kaiser L, Lemaître B, Fellay B, Gervais A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*. 2011;127:218–22. <https://doi.org/10.1016/j.jaci.2010.08.025>.
5. Ponvert C, Perrin Y, Bados-Albiero A, Le Bourgeois M, Karila C, Delacourt C, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol*. 2011;22:411–8. <https://doi.org/10.1111/j.1399-3038.2011.01169.x>.
6. Zambonino MA, Corzo JL, Muñoz C, Requena G, Ariza A, Mayorga C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol*. 2014;25:80–7. <https://doi.org/10.1111/pai.12155>.
7. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy*. 2012;42:123–30. <https://doi.org/10.1111/j.1365-2222.2011.03887.x>.
8. Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71:149–61. <https://doi.org/10.1111/all.12774>.
9. Doña I, Blanca-Lopez N, Torres MJ, Garcia-Campos J, Garcia-Nunez I, Gomez F, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol*. 2012;22:363–71.
10. Moreno E, Laffond E, Munoz-Bellido F, Gracia MT, Macias E, Moreno A, et al. Performance in real life of the European network on drug allergy algorithm in immediate reactions to beta-lactam antibiotics. *Allergy*. 2016;71:1787–90. <https://doi.org/10.1111/all.13032>.
11. Zetts RM, Stoesz A, Smith BA, Hyun DY. Outpatient antibiotic use and the need for increased antibiotic stewardship efforts. *Pediatrics*. 2018;141: e20174124. <https://doi.org/10.1542/peds.2017-4124>.
12. Blanca M. Allergic reactions to penicillins. A changing world? *Allergy*. 1995;50:777–82. <https://doi.org/10.1111/j.1398-9995.1995.tb05048.x>.
13. Torres MJ, Montanez MI, Ariza A, Salas M, Fernandez TD, Barbero N, et al. The role of IgE recognition in allergic reactions to amoxicillin and clavulanic acid. *Clin Exp Allergy*. 2016;46:264–74. <https://doi.org/10.1111/cea.12689>.
14. Blanca-Lopez N, Perez-Alzate D, Ruano F, Garcimartin M, de la Torre V, Mayorga C, et al. Selective immediate responders to amoxicillin and clavulanic acid tolerate penicillin derivative administration after confirming the diagnosis. *Allergy*. 2015;70:1013–9. <https://doi.org/10.1111/all.12636>.
15. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol*. 2011;127:67–73. <https://doi.org/10.1016/j.jaci.2010.11.047>.
16. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy*. 2014;69:420–37. <https://doi.org/10.1111/all.12350>.
17. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams- an EAACI position paper. *Allergy*. 2020;75:1300–15. <https://doi.org/10.1111/all.14122>.
18. Torres MJ, Adkinson NF Jr, Caubet JC, Khan DA, Kidon MI, Mendelson L, et al. Controversies in drug allergy: beta-lactam hypersensitivity testing. *J Allergy Clin Immunol Pract*. 2019;7:40–5. <https://doi.org/10.1016/j.jaip.2018.07.051>.
19. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393:183–98. [https://doi.org/10.1016/S0140-6736\(18\)32218-9](https://doi.org/10.1016/S0140-6736(18)32218-9).
20. Macy E, Romano A, Khan D. Practical management of antibiotic hypersensitivity in 2017. *J Allergy Clin Immunol Pract*. 2017;5:577–86. <https://doi.org/10.1016/j.jaip.2017.02.014>.
21. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med*. 2003;139:683–93. <https://doi.org/10.7326/0003-4819-139-8-200310210-00012>.

22. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*. 2009;64:183–93. <https://doi.org/10.1111/j.1398-9995.2008.01916.x>.
23. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. *Allergy*. 2004;59:1153–60. <https://doi.org/10.1111/j.1398-9995.2004.00678.x>.
24. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy*. 2003;58:961–72. <https://doi.org/10.1034/j.1398-9995.2003.00280.x>.
25. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI drug allergy interest group position paper. *Allergy*. 2013;68:702–12. <https://doi.org/10.1111/all.12142>.
26. Torres MJ, Moreno E, Fernandez-Santamaria R, Dona I, Fernandez TD. Diagnostic approximation to delabeling betalactam allergic patients. *Curr Treat Options Allergy*. 2019;6:56–70. <https://doi.org/10.1007/s40521-019-0202-z>.
27. Torres MJ, Celik G, Whitaker P, Atanaskovic-Markovic M, Barbaud A, Bircher A, et al. A EAACI drug allergy interest group survey on how European allergy specialists deal with β -lactam allergy: heterogeneity in practice. *Allergy*. 2019;74:1052–62. <https://doi.org/10.1111/all.13721>.
28. Torres MJ, Romano A, Mayorga C, Moya MC, Guzman AE, Reche M, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy*. 2001;56:850–6. <https://doi.org/10.1034/j.1398-9995.2001.00089.x>.
29. Solensky R, Jacobs J, Lester M, Lieberman P, McCafferty F, Nilsson T, et al. Penicillin allergy evaluation: a prospective, multicenter, open label evaluation of a comprehensive penicillin skin test kit. *J Allergy Clin Immunol Pract*. 2019;7:1876–85. e3. <https://doi.org/10.1016/j.jaip.2019.02.040>.
30. Castells M, Khan DA, Phillips EJ. Penicillin Allergy. *N Engl J Med*. 2019;381:2338–51. <https://doi.org/10.1056/NEJMr1807761>.
31. Salas M, Laguna JJ, Doña I, Barrionuevo E, Fernandez-Santamaria R, Ariza A, et al. Patients taking amoxicillin-clavulanic can become simultaneously sensitized to both drugs. *J Allergy Clin Immunol Pract*. 2017;5:694–702.e3. <https://doi.org/10.1016/j.jaip.2017.02.007>.
32. Torres MJ, Ariza A, Mayorga C, Doña I, Blanca-Lopez N, Rondon C, et al. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. *J Allergy Clin Immunol*. 2010;125(502–5):e2. <https://doi.org/10.1016/j.jaci.2009.11.032>.
33. Sánchez-Morillas L, Pérez-Ezquerro PR, Reaño-Martos M, Laguna-Martínez JJ, Sanz ML, Martínez LM. Selective allergic reactions to clavulanic acid: a report of 9 cases. *J Allergy Clin Immunol*. 2010;126:177–9. <https://doi.org/10.1016/j.jaci.2010.03.012>.
34. Ibáñez MD, Rodríguez Del Río P, Lasa EM, Joral A, Ruiz-Hornillos J, Muñoz C, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy: from clinical history to challenge tests. *Ann Allergy Asthma Immunol*. 2018;121:235–44. <https://doi.org/10.1016/j.anai.2018.05.013>.
35. Labrosse R, Paradis L, Samaan K, Lacombe-Barrios J, Paradis J, Bégin P, et al. Sensitivity and specificity of double-blinded penicillin skin testing in relation to oral provocation with amoxicillin in children. *Allergy Asthma Clin Immunol*. 2020;16:57. <https://doi.org/10.1186/s13223-020-00449-7>.
36. Fontaine C, Mayorga C, Bousquet PJ, Arnoux B, Torres MJ, Blanca M, et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate β -lactam allergy. *Allergy*. 2007;62:47–52. <https://doi.org/10.1111/j.1398-9995.2006.01268.x>.
37. Blanca M, Mayorga C, Torres MJ, Reche M, Moya MC, Rodriguez JL, et al. Clinical evaluation of Pharmacia CAP System™ RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy*. 2001;56:862–70. <https://doi.org/10.1034/j.1398-9995.2001.00995.x>.
38. Sanz ML, Gamboa PM, Antepara I, Uasuf C, Vila L, Garcia-Aviles C, et al. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to betalactam antibiotics. *Clin Exp Allergy*. 2002;32:277–86. <https://doi.org/10.1046/j.1365-2222.2002.01305.x>.
39. Torres MJ, Padial A, Mayorga C, Fernandez T, Sanchez-Sabate E, Cornejo-Garcia JA, et al. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. *Clin Exp Allergy*. 2004;34:1768–75. <https://doi.org/10.1111/j.1365-2222.2004.02110.x>.
40. Caubet JC, Frossard C, Fellay B, Eigenmann PA. Skin tests and in vitro allergy tests have a poor diagnostic value for benign skin rashes due to beta-lactams in children. *Pediatr Allergy Immunol*. 2015;26:80–2. <https://doi.org/10.1111/pai.12314>.
41. Mayorga C, Celik G, Rouzair P, Whitaker P, Bona-donna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI drug allergy interest group position paper. *Allergy*. 2016;71:1103–34. <https://doi.org/10.1111/all.12886>.
42. Ariza A, Fernández TD, Mayorga C, Blanca M, Torres MJ. Prediction of hypersensitivity to antibiotics: what factors need to be considered? *Expert Rev Clin Immunol*. 2013;9:1279–88. <https://doi.org/10.1586/1744666X.2013.852957>.
43. Faitelson Y, Boaz M, Dalal I. Asthma, family history of drug allergy, and age predict amoxicillin allergy in children. *J Allergy Clin Immunol Pract*.

- 2018;6:1363–7. <https://doi.org/10.1016/j.jaip.2017.11.015>.
44. Chiriac AM, Wang Y, Schrijvers R, Bousquet PJ, Mura T, Molinari N, et al. Designing predictive models for beta-lactam allergy using the drug allergy and hypersensitivity database. *J Allergy Clin Immunol Pract*. 2018;6:139–48.e2. <https://doi.org/10.1016/j.jaip.2017.04.045>.
45. Siew LQC, Li PH, Watts TJ, Thomas I, Ue KL, Caballero MR, et al. Identifying low-risk beta-lactam allergy patients in a UK tertiary centre. *J Allergy Clin Immunol Pract*. 2019;7:2173–81.e1. <https://doi.org/10.1016/j.jaip.2019.03.015>.
46. Mohamed OE, Beck S, Huissoon A, Melchior C, Heslegrave J, Baretto R, et al. A retrospective critical analysis and risk stratification of penicillin allergy delabeling in a UK specialist regional allergy service. *J Allergy Clin Immunol Pract*. 2019;7:251–8. <https://doi.org/10.1016/j.jaip.2018.05.025>.
47. Krishna MT, Huissoon AP, Li M, Richter A, Pillay DG, Sambanthan D, et al. Enhancing antibiotic stewardship by tackling “spurious” penicillin allergy. *Clin Exp Allergy*. 2017;47:1362–73. <https://doi.org/10.1111/cea.13044>.
48. Macy E, Vyles D. Who needs penicillin allergy testing? *Ann Allergy Asthma Immunol*. 2018;121:523–9. <https://doi.org/10.1016/j.anai.2018.07.041>.
49. Dias de Castro E, Carolino F, Carneiro-Leão L, Barbosa J, Ribeiro L, Cernadas JR. Allergy to beta-lactam antibiotics in children: risk factors for a positive diagnostic work-up. *Allergol Immunopathol (Madr)*. 2020;48:417–23. <https://doi.org/10.1016/j.aller.2020.01.005>.
50. Arikoglu T, Aslan G, Batmaz SB, Eskandari G, Helvacı I, Kuyucu S. Diagnostic evaluation and risk factors for drug allergies in children: from clinical history to skin and challenge tests. *Int J Clin Pharm*. 2015;37:583–91. <https://doi.org/10.1007/s11096-015-0100-9>.
51. Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetic risk factors of self-reported penicillin allergy. *J Allergy Clin Immunol*. 2008;122:152–8. <https://doi.org/10.1016/j.jaci.2008.03.037>.
52. Chambel M, Martins P, Silva I, Palma-Carlos S, Romeira AM, Leiria PP. Drug provocation tests to betalactam antibiotics: experience in a paediatric setting. *Allergol Immunopathol (Madr)*. 2010;38:300–6. <https://doi.org/10.1016/j.aller.2010.01.005>.
53. Demoly P, Bousquet J. Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol*. 2001;1:305–10. <https://doi.org/10.1097/01.all.0000011031.16814.e0>.
54. Kurt E, Demir AU, Cadirci O, Yildirim H, Pinar ET. Immediate-type drug hypersensitivity and associated factors in a general population. *Allergol Immunopathol (Madr)*. 2011;39:27–31. <https://doi.org/10.1016/j.aller.2010.02.009>.
55. Anderson GD. Gender differences in pharmacological response. *Int Rev Neurobiol*. 2008;83:1–10. [https://doi.org/10.1016/S0074-7742\(08\)00001-9](https://doi.org/10.1016/S0074-7742(08)00001-9).
56. Gomes ER, Kuyucu S. Epidemiology and risk factors in drug hypersensitivity reactions. *Curr Treat Options Allergy*. 2017;4:239–57. <https://doi.org/10.1007/s40521-017-0128-2>.
57. Gueant-Rodriguez RM, Romano A, Beri-Dexheimer M, Viola M, Gaeta F, Gueant JL. Gene-gene interactions of IL13 and IL4RA variants in immediate allergic reactions to betalactam antibiotics. *Pharmacogenet Genomics*. 2006;16:713–9. <https://doi.org/10.1097/01.fpc.0000230409.00276.44>.
58. Guéant JL, Romano A, Cornejo-García JA, Oussalah A, Chery C, Blanca-López N, et al. HLA-DRA variants predict penicillin allergy in genome-wide fine-mapping genotyping. *J Allergy Clin Immunol*. 2015;135:253–9. <https://doi.org/10.1016/j.jaci.2014.07.047>.
59. Singvijarn P, Manuyakorn W, Mahasirimongkol S, Wattanapokayakit S, Inunchot W, Wichukchinda N, et al. Association of HLA genotypes with Beta-lactam antibiotic hypersensitivity in children. *Asian Pac J Allergy Immunol*. 2019. <https://doi.org/10.12932/AP-271118-0449>.
60. Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. *Clin Rev Allergy Immunol*. 2003;24:201–20. <https://doi.org/10.1385/CRIAI.24:3:201>.
61. Jares EJ, Baena-Cagnani CE, Sanchez-Borges M, Ensina LF, Arias-Cruz A, Gómez M, et al. Drug-induced anaphylaxis in Latin American countries. *J Allergy Clin Immunol Pract*. 2015;3:780–8. <https://doi.org/10.1016/j.jaip.2015.05.012>.
62. Cornejo-García JA, Guéant-Rodriguez RM, Torres MJ, Blanca-Lopez N, Tramoy D, Romano A, et al. Biological and genetic determinants of atopy are predictors of immediate-type allergy to betalactams, in Spain. *Allergy*. 2012;67:1181–5. <https://doi.org/10.1111/j.1398-9995.2012.02867.x>.
63. Guglielmi L, Fontaine C, Gougat C, Avinens O, Eliaou JF, Guglielmi P, et al. IL-10 promoter and IL4-Ralpha gene SNPs are associated with immediate beta-lactam allergy in atopic women. *Allergy*. 2006;61:921–7. <https://doi.org/10.1111/j.1398-9995.2006.01067.x>.
64. Stone CA Jr, Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. *Allergy*. 2020;75:273–88. <https://doi.org/10.1111/all.13848>.
65. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321:188–99. <https://doi.org/10.1001/jama.2018.19283>.
66. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol*. 2014;133:790–6. <https://doi.org/10.1016/j.jaci.2013.09.021>.
67. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based

- matched cohort study. *BMJ*. 2018;361:k2400. <https://doi.org/10.1136/bmj.k2400>.
68. Rose MT, Slavin M, Trubiano J. The democratization of de-labeling: a review of direct oral challenge in adults with low-risk penicillin allergy. *Expert Rev Anti Infect Ther*. 2020;18:1143–53. <https://doi.org/10.1080/14787210.2020.1792775>.
 69. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis*. 2013;26:526–37. <https://doi.org/10.1097/QCO.000000000000006>.
 70. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis*. 2017;65:166–74. <https://doi.org/10.1093/cid/cix244>.
 71. Blumenthal KG, Huebner EM, Fu X, Li Y, Bhattacharya G, Levin AS, et al. Risk-based pathway for outpatient penicillin allergy evaluations. *J Allergy Clin Immunol Pract*. 2019;7:2411–2414.e1. <https://doi.org/10.1016/j.jaip.2019.04.006>.
 72. Devchand M, Urbancic KF, Khumra S, Douglas AP, Smibert O, Cohen E, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract*. 2019;7:1063–5.e5. <https://doi.org/10.1016/j.jaip.2018.07.048>.
 - 73.●● Chiriac AM, Banerji A, Gruchalla RS, Thong BYH, Wickner P, Mertes PM, et al. Controversies in drug allergy: drug allergy pathways. *J Allergy Clin Immunol Pract*. 2019;7:46–60.e4. <https://doi.org/10.1016/j.jaip.2018.07.037>.
- This is an excellent expert consensus document which reviews current pathways and important considerations in implementing and evaluating beta-lactam allergy pathways.**
- 74.● Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med*. 2020;180:745–52. <https://doi.org/10.1001/jamainternmed.2020.0403>.
- Among the important studies that searched for the predictive factors for penicillin allergy. The authors developed and validated a penicillin allergy clinical decision rule that enabled the risk assessment of patient-reported penicillin allergy.**
75. Blumenthal KG, Wickner PG, Hurwitz S, Pricco N, Nee AE, Laskowski K, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol*. 2017;140:154–61.e6. <https://doi.org/10.1016/j.jaci.2017.02.005>.
 76. Vyles D, Chiu A, Simpson P, Nimmer M, Adams J, Brousseau DC. Parent-reported penicillin allergy symptoms in the pediatric emergency department. *Acad Pediatr*. 2017;17:251–5. <https://doi.org/10.1016/j.acap.2016.11.004>.
 77. Vyles D, Antoon JW, Norton A, Stone CA Jr, Trubiano J, Radowicz A, et al. Children with reported penicillin allergy: public health impact and safety of delabeling. *Ann Allergy Asthma Immunol*. 2020;124:558–65. <https://doi.org/10.1016/j.anai.2020.03.012>.
 78. Moral L, Caubet JC. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: time to change the paradigm? *Pediatr Allergy Immunol*. 2017;28:724–7. <https://doi.org/10.1111/pai.12800>.
 79. Vyles D, Adams J, Chiu A, Simpson P, Nimmer M, Brousseau DC. Allergy testing in children with low-risk penicillin allergy symptoms. *Pediatrics*. 2017;140:e20170471. <https://doi.org/10.1542/peds.2017-0471>.
 80. Mustafa SS, Conn K, Ramsey A. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. *J Allergy Clin Immunol Pract*. 2019;7:2163–70. <https://doi.org/10.1016/j.jaip.2019.05.037>.
 81. Mill C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr*. 2016;170:e160033. <https://doi.org/10.1001/jamapediatrics.2016.0033>.
 82. Blanca-Lopez N, Atanaskovic-Markovic M, Gomes ER, Kidon M, Kuyucu S, Mori F, et al. An EAACI task force report on allergy to beta-lactams in children: clinical entities and diagnostic procedures. *Pediatr Allergy Immunol*. 2021. <https://doi.org/10.1111/pai.13529>.
 83. Iammatteo M, Arango S, Ferastraorau D, Akbar N, Lee AY, Cohen HW, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract*. 2019;7:236–43. <https://doi.org/10.1016/j.jaip.2018.05.008>.
 84. Pouessel G, Winter N, Lejeune S, Thumerelle C, Deschildre A. Oral challenge without skin testing in children with suspected non-severe betalactam hypersensitivity. *Pediatr Allergy Immunol*. 2019;30:488–90. <https://doi.org/10.1111/pai.13048>.
 85. Prieto A, Muñoz C, Bogas G, Fernández-Santamaría R, Palomares F, Mayorga C, et al. Single-dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to beta-lactams. *Allergy*. 2021. <https://doi.org/10.1111/all.14800>.

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