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NEWS AND VIEWS

Algorithms in Allergy and Clinical Immunology

# An algorithm for the diagnosis of beta-lactam allergy, 2024 update

The diagnostic work-up for diagnosing betalactam (BL) allergy includes clinical history, skin test (ST), in vitro tests (specific immunoglobulin E (sIgE) and basophil activation test (BAT) for immediate reactions (IRs), and lymphocyte transformation test (LTT) for non-immediate reactions (NIRs)), and drug provocation test (DPT)[1,2] (Figure 1).

Regarding ST and in vitro tests, a recent metanalysis including studies conducted in patients reporting a penicillin allergy show a ST sensitivity of 31% and specificity of 97%, and sIgE sensitivity of 19% and specificity of 97%. This data mainly reflect the low frequency of true BL allergy.[3] In fact, in studies including truly allergic patients, STs showed a higher sensitivity, reaching up to 60–70% in IRs and 20% in NIRs.[1] sIgE in patients experiencing IRs confirmed by positive STs showed sensitivity values of 39%–52%, with false-positive results to penicillin G in up to 16% of cases.[4] A recent metanalysis gave a BAT sensitivity of 51% and specificity of 89%.[5] Recently, it has been demonstrated that CD203c as activation marker in BAT showed a good confirmatory power, especially for amoxicillin allergy.[6,7] The diagnostic value of LTT for NIRs has been evaluated only in few papers, displaying a sensitivity of 53–65% and specificity of 94–96%.[1] Both BAT and LTT cannot be considered as a routine element of clinical practice due to the complex procedures and the lack of standardization, however they may be useful as a complemmentary diagnostic tool.[1,6] In fact, in vitro tests are recommended to be performed before in vivo tests when evaluating patients with severe reactions.[1,6]

Considering that in vitro and skin testing lack 100% negative predictive value, DPT is the gold standard for diagnosis.[1,2] DPT protocols are far from being standardized and vary among studies in terms of dose steps, time intervals between incremental doses, and days of dosing. The whole allergological work-up, in general, takes several days.[8] However, taking into account the low proportion of patients who are truly allergic, faster pathways has been proposed such as direct DPT without previous STs. This procedure has shown to be safe on multiple large studies performed in children,[9,10] and more recently, in adults,[11,12] giving a prevalence of reactions lower than 7%, being less than 0.1% severe. In fact, direct penicillin DPT has been recently advocated by UK and Asia guidelines.[13,14] It is important to highlight that in all the subjects included in those studies performing a direct DPT, the risk of being true allergic was low. In consequence, risk stratification has emerged as an important tool for adapting the diagnostic strategy to the perceived probability of being truly allergic, whilst still maintaining the safety for the patient, with the aim of optimizing investigations in terms of efficiency and resources. However, nowadays there is still no broad consensus on the risk stratification of subjects labelled as BL allergic.[1,8,14,15] Therefore, over recent years, interest has grown in the development of validated point-of-care assessment tools that, based on the information obtained from clinical history, generate a quantitative scoring scale for stratifying patients into risk categories, with 'low-risk' patients able to proceed straight to direct DPT. In that sense, a clinical decision rule called PEN-FAST has shown a high negative predictive value of 96% in delabeling patients in USA and Australia,[16] and a direct oral DPT with penicillin showed to be safe (only 0.5% reacted in DPT experiencing mild cutaneous symptoms) and effective in those estratified as low-risk (PEN-FAST score less than 3).[17] Current efforts are focused in the validation and optimization of these tools in ethnically diverse populations,[18,19] as well as for providing not only allergist-designed guidance but also for non-allergists.

Another matter of debate has been the length of DPT needed for an accurate diagnosis. Nowadays, there is no evidence that support the use of extended-day DPT over single-day DPT. It has been

**Abbreviations:** BAT, basophil activation test; BL, betalactam; DPT, drug provocation test; IR, immediate reaction; LTT, lymphocyte transformation test; NIR, non-immediate reaction; sIgE, specific immunoglobulin E; ST, skin test.

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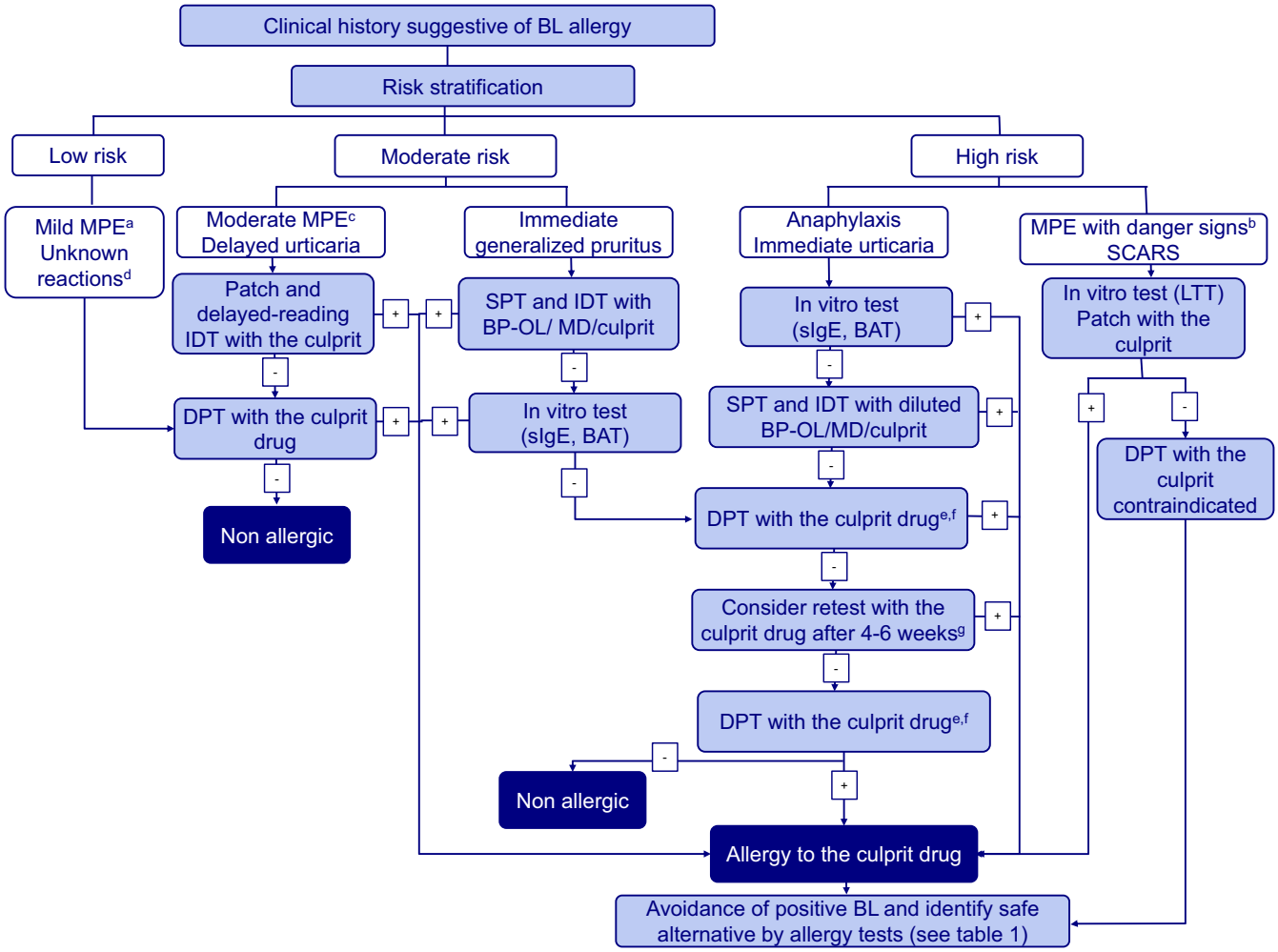


**FIGURE 1** Algorithm for diagnosis approach of patients reporting clinical history suggestive of BL allergy. BP-OL: Benzylpenicilloyl-octa-L-lysine. IDT: Intradermal test. MD: Minor determinant. MPE: Maculopapular exanthema. SCARS: Severe cutaneous allergic reactions. SPT: Skin prick test. [a]Non urticarial exanthema, involving <50% of the body surface, with no danger signs[b], onset >6 h after the drug administration, resolving in <7 days, not requiring hospitalization or systemic treatment other than antihistamines.[1,8] [b]Danger signs: intense facial involvement, atypical target lesions, bullous lesions, dark red erythema, extensive pustulosis, painful skin, mucosal involvement, generalized lymphadenopathy, liver impairment, renal impairment, >38.5°C, alterations in blood cell counts, hypocomplementemia, and pneumonitis.[1,8] [c]Involving >50% of body surface, with no systemic symptoms, resolving in >7 days, requiring topical/systemic steroids.[1,8] [d]Patient cannot remember what happened during index reaction. [e]Contraindicated in near fatal anaphylaxis.[1,8] [f]If amoxicillin-clavulanic acid is the culprit and the patient reacts in DPT to it, tolerance to amoxicillin should be assessed. [g]In patients with strong suspicion of allergic reactions to BLs, specially for severe IRs, consider to perform retest 4–6 weeks after the initial negative study.

proposed prolonged DPT only for NIRs reaching at least the maximum single therapeutic/unit dose and with a minimum 48 h washout period between doses. Additionally, the duration of a full treatment (7–10 days) is not recommended.[8]

In patients with strong suspicion of immediate allergic reactions to penicillins who display negative results on the allergological work-up, a risk of resensitisation should be considered before considering the patient as non-allergic. Retest should be considered to be performed 4–6 weeks later, specially for severe IRs.[20]

In those patients confirmed as allergic, for selecting alternative BLs it is important to take into account the role of side chain[1,2] (Table 1).

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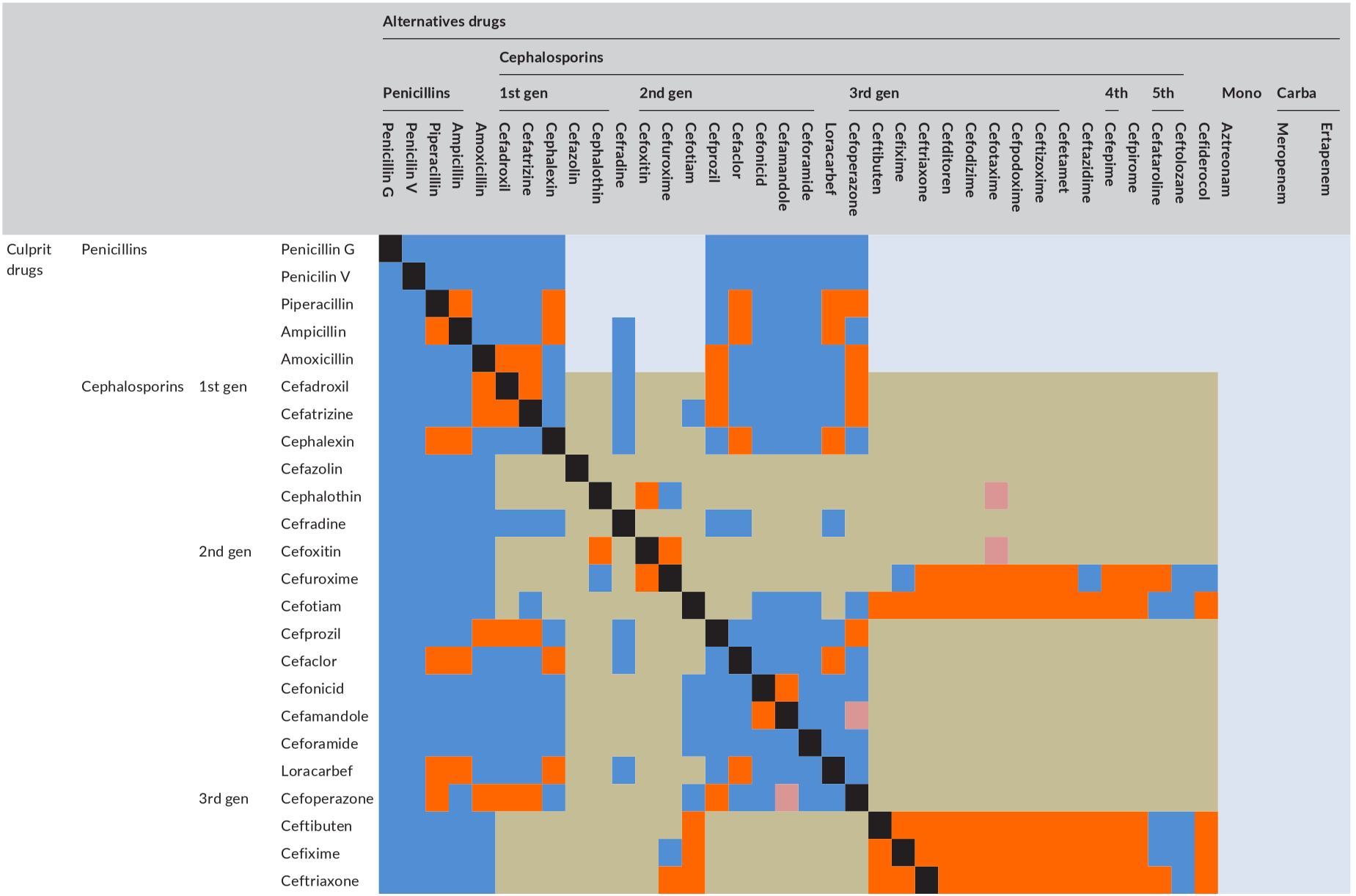
## CONFLICT OF INTEREST STATEMENT

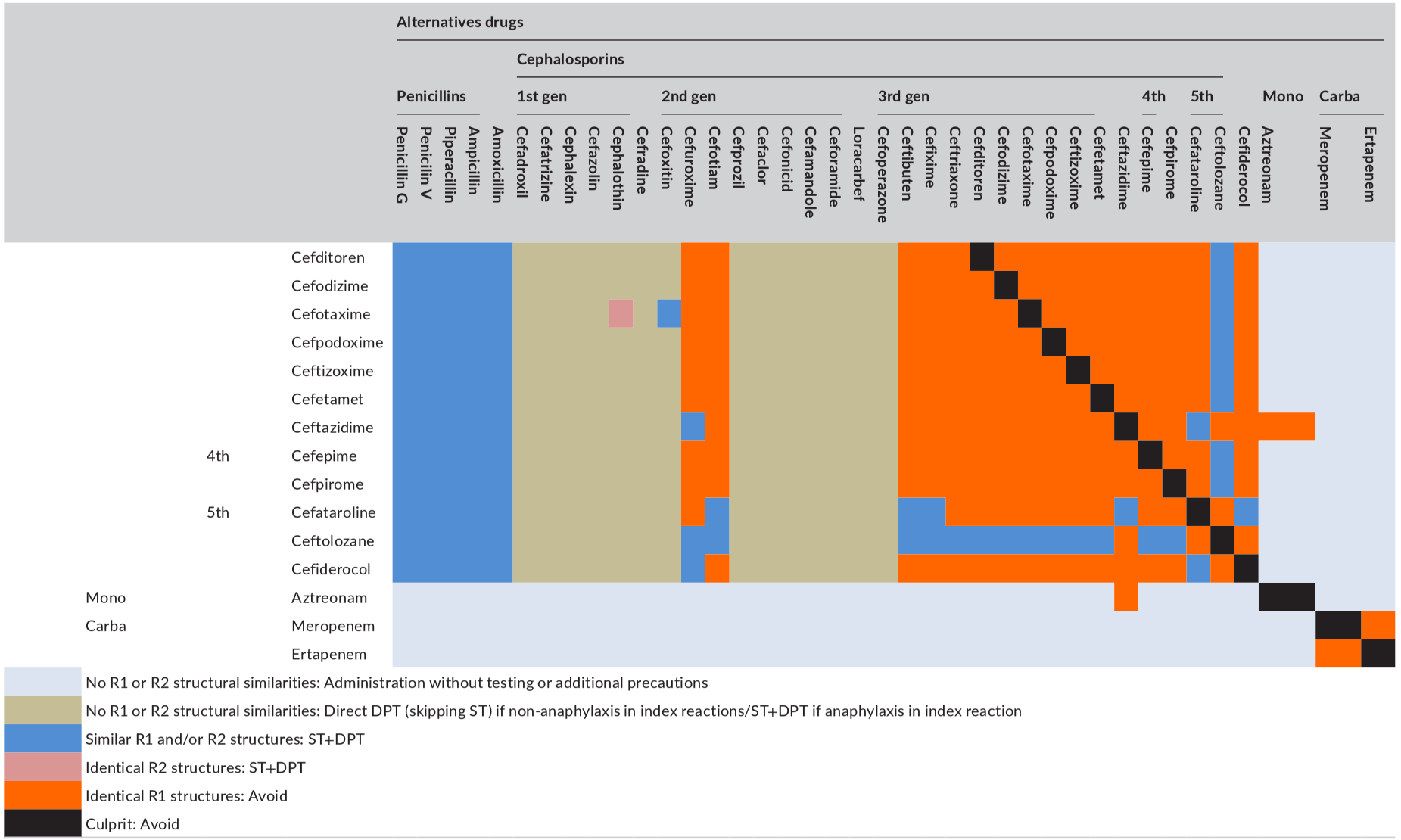
The authors declare no conflicts of interest.

**TABLE 1** Allergological approach for selecting safe alternative drugs in allergic patients to BLs, based on the similarities or identities in the structures of the R side chain and the recommendations provided by the EAACI position papers on betalactam allergy diagnosis and drug provocation testing[1] and on the "Drug allergy 2022: a practice parameter update".[2]




*(Continues)*

**TABLE 1** (Continued)




*Note*: The betalactamase inhibitors are not included in the table as based on their structures, it is assumed that the risk for cross-reactivity to BL antibiotics would be rare.

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## REFERENCES

1. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper. *Allergy*. 2020;75(6):1300-1315.
2. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol*. 2022;150(6):1333-1393.
3. Sousa-Pinto B, Tarrio I, Blumenthal KG, et al. Accuracy of penicillin allergy diagnostic tests: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2021;147(1):296-308.
4. Ariza A, Mayorga C, Bogas G, et al. Detection of serum-specific IgE by Fluoro-enzyme immunoassay for diagnosing type I hypersensitivity reactions to Penicillins. *Int J Mol Sci*. 2022;23(13):6992.
5. Bennett MR, Mathioudakis AG, Wu J, et al. Performance characteristics of basophil activation tests for diagnosing penicillin allergy: a meta-analysis. *J Allergy Clin Immunol Pract*. 2024;12(3):714-723.
6. Mayorga C, Çelik GE, Pascal M, et al. Flow-based basophil activation test in immediate drug hypersensitivity. An EAACI task force position paper. *Allergy*. 2024;79(3):580-600.
7. Céspedes JA, Fernández-Santamaría R, Ariza A, et al. Diagnosis of immediate reactions to amoxicillin: comparison of basophil activation markersCD63andCD203cin a prospective study. *Allergy*. 2023;78(10):2745-2755.
8. Barbaud A, Garvey LH, Torres M, et al. EAACI/ENDA position paper on drug provocation testing. *Allergy*. 2024;79(3):565-579.
9. Srisuwatchari W, Phinyo P, Chiriac AM, Saokaew S, Kulalert P. The safety of the direct drug provocation test in Beta-lactam hypersensitivity in children: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract*. 2023;11(2):506-518.
10. Moral L, Toral T, Muñoz C, et al. Direct oral challenge for immediate and non-immediate beta-lactam allergy in children: a real-world multicenter study. *Pediatr Allergy Immunol*. 2024;35(3):e14096.
11. Trubiano JA, Vogrin S, Copaescu A, et al. Direct oral penicillin challenge for penicillin allergy delabeling as a health services intervention: a multicenter cohort study. *Allergy*. 2022;77(3):1038-1042.
12. Brillant-Marquis F, Proulx É, Ratnarajah K, et al. Safety of direct drug provocation for the evaluation of penicillin allergy in low-risk adults. *J Allergy Clin Immunol Pract*. 2024;12(2):451-457.
13. Li PH, Thong BY, Pawankar R, et al. APAAACI clinical pathway on direct provocation testing for penicillin allergy delabeling. *Asia Pac Allergy*. 2023;13(4):142-147.
14. Savic L, Ardern-Jones M, Avery A, et al. BSACI guideline for the set-up of penicillin allergy de-labelling services by non-allergists working in a hospital setting. *Clin Exp Allergy*. 2022;52(10):1135-1141.
15. Sabato V, Gaeta F, Valluzzi RL, Van Gasse A, Ebo DG, Romano A. Urticaria: the 1-1-1 criterion for optimized risk stratification in beta-lactam allergy Delabeling. *J Allergy Clin Immunol Pract*. 2021;9(10):3697-3704.
16. Trubiano JA, Vogrin S, Chua KYL, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Int Med*. 2020;180(5):745-752.
17. Copaescu AM, James VS, Chua KYL, Rose MT, De Luca J, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med*. 2023;183(9):944-952.
18. Copaescu AM, Vogrin S, Shand G, Ben-Shoshan M, Trubiano JA. Validation of the PEN-FAST score in a pediatric population. *JAMA Netw Open*. 2022;5(9):e2233703.
19. Castagna J, Chasset F, Autegarden JE, et al. Assessing delayed penicillin hypersensitivity using the PENFAST+ score. *Front Allergy*. 2023;13(4):1302567.
20. Doña I, Guidolin L, Bogas G, et al. Resensitization in suspected penicillin allergy. *Allergy*. 2023;78(1):214-224.