Editorial

Triage Strategies for Clarifying Reported Betalactam Allergy

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Betalactam antibiotics (BLs) are the first choice of treatment for many bacterial infections,[1,2] but are also the most common elicitors of drug allergy, and a frequent cause of fatal drug anaphylaxis.[3] BL allergy (BLA) may present with all 4 types of hypersensitivity reactions described by Coombs and Gell, whereas immediate anaphylaxis and nonimmediate exanthems are exceedingly most frequent.[4] A vague suspicion of BLA often leads to labeling and subsequent BL avoidance. Approximately 5% to 10% of the general population and up to 19% of inpatients are labeled as BL allergic.[2,5] However, the diagnosis will be confirmed in less than 10% of BLA-labeled patients by allergological tests, including drug provocation tests (DPT), which have a high negative predictive value >95%.[5] Patients report their perceived "penicillin allergy" without having a clear memory or understanding of their reaction, and often this suspicion is transferred uncritically into an allergy label. Most reactions attributed to BLs are in fact manifestations of the infectious disease itself, particularly infection-induced acute urticaria and maculopapular exanthem.[6] BLA-labeled patients with an infection receive a suboptimal antibiotic selection, and have greater treatment costs, a prolonged length of stay, greater readmission rates, and a higher prevalence of antibiotic-resistant organisms as compared with unlabeled patients.[1,2,7] There is a need to identify those >90% of patients with BLA label, in whom the use of BLs can be allowed.

Such a systematic risk stratification approach for health care providers in Australia is published in the current issue of the *Journal of Allergy and Clinical Immunology: In Practice*.[8] Typical clinical manifestations of BLA are classified into 4 color-coded risk groups according to severity as well as to the time interval elapsed after the last reaction (regarded as a risk factor) and were connected to 4 different management recommendations. Color coding adds to the assessment of risk by visualization. Typical BLA clinical manifestations were recorded for the organ skin, respiratory/systemic, hematological, renal, liver, neurological/gastrointestinal, and unknown reactions. Direct delabeling takes place in case of neurological/gastrointestinal symptoms or liver enzyme/renal impairment without failure. Patients with a history of a nonsevere rash in childhood or nonsevere rash/unknown reaction more than 10 years ago were recommended for direct supervised rechallenge. Potentially immune-mediated severe type II-IV reactions, anaphylaxis, and unknown reactions less than 10 years ago were recommended for outpatient allergist consultation, and all others for skin testing followed by oral rechallenge.

The performance of this assessment tool regarding assignment into the right category and management was analyzed by constructing 8 different typical case histories to be correctly classified into the different approaches by a quite limited number of doctors, pharmacists, and specialist nurses (N = 40) as well as hematology/oncology nurses (N = 11).[8] The sensitivity for correct classification into the manifestation groups, immediate hypersensitivity, or nonsignificant exceeded 95% and for delayed hypersensitivity 84%, whereas specificities were >97% for all categories. Management options were attributed correctly less often (sensitivity 79% to 93%) with some recommendations potentially hazardous. Immunology/oncology nurses performed better than doctors for assessment and management. Pharmacists recommended management more often correctly, and there was a trend for better management in senior doctors as compared with junior doctors. Thus, the performance of such a BLA assessment tool depends on the person using it, and training or experience is required for assessment and management.

Delabeling strategies improve antibiotic usage and treatment outcomes. The ideal protocol for verifying true BLA should be easy to perform, safe, and minimize false-positive determinations. Several strategies have been applied:

(1) Routine allergy consultation is still the standard strategy in Europe. Allergy specialists automatically perform a pretest risk assessment when determining the manifestations, chronology, and differential diagnoses from the history.[4] A stepwise approach is then taken with skin tests and *in vitro* tests first, followed by DPT in those patients with negative skin tests.

(2) Skin testing has been used to exclude BLA. A negative immediate skin test to penicillin is sensitive and specific for excluding an immediate BLA. The negative predictive value differs, approaching 100% in the USA in contrast to only 70% in Southern Europe, possibly reflecting different patients and prescribed BLs.[9,10] Skin testing with cephalosporins yields similar results.[5] Systemic reactions to skin tests are infrequent.[10,11] Skin tests may avoid morbidity associated with positive DPT and may identify tolerant alternative BLs. Evaluation of patients with immediate BLA by skin testing before administration of a BL minimizes the risk for a severe reaction at least in the US population.[1,9,11,12] Patients who completed skin testing had 6-fold increased odds of BL use at discharge.[1] On the other hand, for patients with exanthems, skin tests have low sensitivity and specificity.[13] In children

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and adults with nonsevere exanthems mostly associated with other causes than BLA, skin tests are rarely helpful and direct DPT has been recommended.[1,13,14]

(3) Other systematic pretest BLA risk assessment strategies have stratified the clinical manifestations of BLA in the history according to expected risk and the most probable mechanism of hypersensitivity reaction.[1,8,14] Blumenthal et al[1] implemented a computerized guideline for the management of inpatients with penicillin or cephalosporin allergy label. Decisions were based on classifying reactions either into (1) severe type II-IV immunological BLA, (2) type I or unknown BLA as well as (3) mild BLA. Management options were selected accordingly, including BL avoidance, consultation of an allergist and infectious disease specialist, using presumably non−cross-reactive BLs, skin test, and/or direct test dose (usually 1/10 followed by full concentration) procedures. This approach led to a 2-fold increase of BL usage. In a previous analysis of this approach, adverse drug events were reduced from 67% to 21%, as were the costs due to adverse drug reactions and readmissions. In the United Kingdom, a similar algorithm has recently been described to be safe and effective for delabeling in a cohort of 231 patients with penicillin allergy label.[14]

Among all BLA delabeling strategies, allergy specialist consultation with skin tests followed by DPT is the safest, but most time- and resource-consuming approach.[3] In the USA, skin testing before giving BL under supervision carries low to minimal risk, but requires trained personnel and the determination that the patient is eligible for skin testing.[1,11] Regarding the millions of patients involved, additional computerized or systematic assessment tools are required with faster pathways for low-risk patients. Sorting patients' clinical manifestations into different risk groups reduces the need for skin testing or full allergy consultation, implements direct supervised administration with or without test dosing, and thus saves resources.[1,8] Administering non−cross-reactive BLs greatly increases safety, but does not allow delabeling and is best suited for emergency situations and inpatients.[1] Devchand et al[8] proposed a powerful delabeling approach for the community. However, the risk associated with taking the history of the patient and classifying into risk groups correctly as well as that of direct delabeling or BL administration without prior skin test or DPT still has to be analyzed in the daily practice. There is initial evidence that experience and training for decision support might be required to use such a tool correctly. It also has to be noted that, in parallel with delabeling strategies, better education of primary care physicians about the limited clinical pictures of drug hypersensitivity and on the importance of proper drug allergy documentation might be worthwhile and effective in primarily avoiding inaccurate BLA labeling.[4,15]

REFERENCES

1. 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.
2. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, et al. Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. Clin Infect Dis 2016;63:904-10.
3. 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.
4. Brockow K, Ardern-Jones M, Mockenhaupt M, Aberer W, Barbaud A, Caubet JC, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. Allergy 2019;74:14-27.
5. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. Curr Allergy Asthma Rep 2014;14:476.
6. Ponvert C, Weilenmann C, Wassenberg J, Walecki P, Bourgeois ML, de Blic J, et al. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. Allergy 2007;62:42-6.
7. Wu JH, Langford BJ, Schwartz KL, Zvonar R, Raybardhan S, Leung V, et al. Potential negative effects of antimicrobial allergy labelling on patient care: a systematic review. Can J Hosp Pharm 2018;71:29-35.
8. Devchand JA, Urbancic K, Khumra S, Douglas A, 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.
9. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; Joint Council of Allergy, Asthma, and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010; 105:259-73.
10. 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.
11. del Real GA, Rose ME, Ramirez-Atamoros MT, Hammel J, Gordon SM, Arroliga AC, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. Ann Allergy Asthma Immunol 2007;98:355-9.
12. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. J Hosp Med 2013;8:341-5.
13. 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.
14. Mohamed OE, Beck S, Huissoon A, Melchior C, Heslegrave J, Baretto R, et al. A retrospective critical analysis and risk stratification of penicillin allergy delabelling in a UK specialist regional allergy service. J Allergy Clin Immunol Pract 2019;7:251-8.
15. Brockow K, Aberer W, Atanaskovic-Markovic M, Bavbek S, Bircher A, Bilo B, et al. Drug allergy passport and other documentation for patients with drug hypersensitivity—an ENDA/EAACI Drug Allergy Interest Group Position Paper. Allergy 2016;71:1533-9.