

Penicillin Allergy: Mono-, Double-, and Multiple-Drug Hypersensitivity, or Even No Sensitivity?



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Penicillin is the most commonly cited drug in connection with a drug allergy. It is self-reported by approximately 10% of the population¹ and officially recorded for approximately 8% of individuals using health care facilities in the USA.² For the individual and many doctors, proven or even suspected penicillin allergy implies the avoidance of all beta-lactams. Yet, less than 1 in 20 persons will have an acute reaction to the gold standard test for confirming a clinically significant IgE-mediated penicillin allergy, which consists of an oral challenge with a therapeutic dose.³

Several factors may explain this extreme discrepancy: deficient knowledge and understanding on the part of patients and their doctors concerning the mechanisms underlying the clinical signs of allergy, the nonavailability of adequate testing procedures in many regions, the mistaken belief in clinically inconclusive serologic tests,⁴ and even different testing guidelines.⁵ But nonverified or erroneous penicillin allergies, noted even in electronic health records, are being recognized as a significant public health problem.

Salas et al⁶ convincingly report that reactions—immediate or nonimmediate—may appear in the same patient after taking a combination product containing 2 related, but not cross-reactive substances. Three patients presenting with immediate and one presenting with a nonimmediate reaction after taking the combination of amoxicillin (AX) and clavulanic acid (CLV) were evaluated carefully. Skin testing, drug provocation, specific IgE, and basophil activation by flow cytometry were performed in those with immediate reactions, and immunohistochemistry, phenotyping by flow cytometry, dendritic cell maturation, and lymphocyte proliferation assays in the person with nonimmediate reaction. All 4 patients reacted to both substances: the beta-lactam antibiotic AX and the beta-lactamase inhibitor CLV. Although both substances are beta-lactams, no cross-reactivity has been registered between them. This may be due to differences in their chemical structure and the substances produced during their metabolism.⁷ But it remains unclear why some persons treated with the AX-CLV combination develop a selective allergy to CLV while tolerating AX, and vice versa.⁷ Thus, an

accurate diagnosis of patients who experience a reaction after taking AX-CLV is crucial to avoid the use of inappropriate alternative antibiotics, which tend to be more expensive and may have further adverse effects.⁸

This study confirms an established fact: patients reacting selectively to CLV may use all of the other beta-lactams, including AX. This is important because many patients with a so-called penicillin allergy avoid all beta-lactams because of suspected cross-reactivity. Indeed, a certain immunologic cross-reactivity does exist between penicillins, and much less or possibly no clinically significant immunologic cross-reactivity between specific penicillins, cephalosporins, and other non-penicillin beta-lactams, with the possible exception of those specific beta-lactams that share the same side chains.⁹

But why do many patients and doctors avoid all beta-lactams in patients with a penicillin allergy? Potential cross-reactivities must be proven or disproven in each patient. This is frequently not performed, either intentionally or due to the nonavailability of adequate testing facilities. More importantly, IgE immunochemistry vastly overcalls beta-lactam cross-reactivity, which is not observed clinically.¹⁰ The presence of measurable anti-beta-lactam IgE does not mean that therapeutic exposure will cause any clinically significant symptoms.⁴ This fact may be interpreted variously, whereas the European guidelines cite a positive skin test or a positive s-IgE to penicillin as a diagnostic criterion for a penicillin allergy and therefore recommend the avoidance of a drug challenge¹¹; this recommendation is questioned by many allergists.¹² In fact, many American experts postulate that the commercially available serologic tests are unsuitable for clinical use at the present time.⁴

The fact remains that some patients do react to more than one drug, and especially to nonchemically related drugs. Approximately a third of patients reporting at a drug allergy unit mention more than one “drug allergy.”¹³ Multiple-drug hypersensitivity (MDH) was first described as a drug allergy to 2 or more chemically different drugs.¹⁴ It differs from cross-reactivity (due to structural similarities, common metabolic pathways, or pharmacologic mechanisms), flare-up reactions (exacerbation of an existing drug allergy by an early switch of therapy to a novel drug),¹⁵ and the multiple-drug intolerance syndrome.¹⁶ The latter is defined as intolerance to 3 or more neither structurally nor pharmacologically related drugs, with no confirmation after evaluation,¹⁷ and possibly driven by patient anxiety.¹⁸ In documented drug hypersensitivity reactions (DHRs), the prevalence of MDH ranges from 1% to 10%.¹⁹

In summary, the diagnosis of DHRs is challenging and requires a careful approach, regardless of the specific drug involved. This is especially true of a so-called penicillin allergy: patients may react differently, with different consequences. The testing procedures are fairly simple; a beta-lactam allergy can be safely

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managed by 7 steps.² Allergists should adhere to the known protocols. More importantly, international guidelines should be harmonized or even unified. The current divergence is not conducive to a standardized approach. Salas et al⁶ have described their critical approach in 4 patients. The allergy community needs common guidelines for the evaluation of all patients with a suspected penicillin allergy.

REFERENCES

1. Solensky R. Penicillin allergy as a public health measure. *J Allergy Clin Immunol* 2014;133:797-8.
2. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014;14:476.
3. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013;1:258-63.
4. Macy E, Goldberg B, Poon KY. Use of commercial anti-penicillin IgE fluorometric enzyme immunoassays to diagnose penicillin allergy. *Ann Allergy Asthma Immunol* 2010;105:136-41.
5. Torres MJ, Romano A, Celik G, Demoly P, Khan DA, Macy E, et al. Approach to the diagnosis of drug hypersensitivity reactions: similarities and differences between Europe and North America. *Clin Transl Allergy* 2017;7:7.
6. Salas M, Laguna JJ, Dona I, et al. Patients taking amoxicillin-clavulanic can become simultaneously sensitized to both drugs. *J Allergy Clin Immunol Pract* 2017;5:694-702.
7. 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.
8. 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.
9. Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. *Ann Allergy Asthma Immunol* 2014;112:404-12.
10. Liu XD, Gao N, Qiao HL. Cephalosporin and penicillin cross-reactivity in patients allergic to penicillins. *Int J Clin Pharmacol Ther* 2011;49:206-16.
11. 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.
12. Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test to penicillin or positive specific IgE to penicillin does not predict penicillin allergy. *J Allergy Clin Immunol Pract* 2017;5:676-83.
13. Chiriac AM, Demoly P. Multiple drug hypersensitivity syndrome. *Curr Opin Allergy Clin Immunol* 2013;13:323-9.
14. Sullivan T, Remedios C, Ong M, Gilliam L. Studies of the multiple drug allergy syndrome. *J Allergy Clin Immunol* 1989;83:270.
15. Pichler WJ, Daubner B, Kawabata T. Drug hypersensitivity: flare-up reactions, cross-reactivity and multiple drug hypersensitivity. *J Dermatol* 2011;38:216-21.
16. Patriarca G, Venuti A, Schiavino D, Romano A, Fais G, Di Rienzo V. The syndrome caused by multiple drug intolerance [in Italian]. *Recenti Prog Med* 1980;68:21-33.
17. Schiavino D, Nucera E, Roncallo C, Pollastrini E, De Pasquale T, Lombardo C, et al. Multiple-drug intolerance syndrome: clinical findings and usefulness of challenge tests. *Ann Allergy Asthma Immunol* 2007;99:136-42.
18. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol* 2012;108:88-93.
19. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy* 2014;69:420-37.

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