

Oral amoxicillin-associated anaphylaxis, 1 year after negative penicillin testing and oral amoxicillin challenge



Nicolas Urriola, MBBS, BMedSci^a, Lee Paganini, BHSc^a, Sean Riminton, MBChB, PhD, FRACP, FRCPA^{a,b}, and Sandhya Limaye, MBBS (Hons), PhD, FRACP, FRCPA^{a,b}

Clinical Implications

- A case demonstrating resensitization to amoxicillin induced by intradermal testing and oral challenge, resulting in anaphylaxis on subsequent exposure, is presented. Resensitization is thus identified as a rare but potentially significant hazard of β -lactam allergy testing.

TO THE EDITOR:

Penicillin class antibiotic skin testing strategies are designed to reduce the risk of anaphylaxis on re-exposure to penicillin, identify candidates suitable for safe future use, and minimize the significant morbidity associated with an unconfirmed penicillin allergy.¹ Although subsequent courses of antibiotics can resensitize skin test-negative individuals in rare cases, the testing and challenge procedure itself has never been documented to induce resensitization. Here we describe a very rare case with resensitization likely provoked by the allergy testing procedure, resulting in life-threatening anaphylaxis on the first clinical oral amoxicillin re-exposure 1 year later.

A 58-year-old woman was referred to an allergy service for the investigation of possible amoxicillin allergy. Ten years earlier, she experienced orofacial angioedema and rash on day 8 of a course of oral amoxicillin prescribed for a respiratory tract infection. She had avoided all β -lactam antibiotics since. Skin prick and intradermal tests were negative (Table 1). The patient received a single-dose oral drug challenge of 250 mg amoxicillin. There was no clinical reaction and the patient was advised that she was not at a significantly increased risk of immediate hypersensitivity to amoxicillin with future use.

One year later, she presented with throat constriction, orofacial angioedema, and generalized urticaria within 30 minutes of taking amoxicillin 500 mg prescribed for presumed diverticulitis. The clinical diagnosis of anaphylaxis was made, and she was treated with IM adrenaline, IV hydrocortisone, cetirizine, and ranitidine with good response. Anaphylaxis was confirmed by the detection of elevated serum mast-cell tryptase of 19.2 μ g/L (0–11 μ g/L), which later returned to normal (8.6 μ g/L). Notably, this was her first exposure to any penicillin class antibiotic since skin testing and oral challenge.

Within 1 month of anaphylaxis, the patient returned for further testing. Specific IgE testing was positive to amoxicilloyl at 1.35 kUA/L (<0.35 kUA/L) and negative to ampicillin, penicillin G, and penicillin V (ImmunoCAP, Phadia, Sweden). Skin prick and intradermal test results are presented in Table 1. The concentrations used for intradermal testing differed from those

performed 1 year earlier. The clinical features and investigation results allowed a confident diagnosis of anaphylaxis secondary to amoxicillin allergy.

We suspect that the patient had an IgE-mediated hypersensitivity to amoxicillin at the time of the index reaction 10 years earlier, although specific IgE testing procedures were not performed at the time. Time-dependent decay of the allergic response explains the negative skin tests and oral drug challenge on later testing. Re-emergence of clinical reactivity on first subsequent exposure, together with detectable specific IgE to amoxicillin, is explained by resensitization provoked by intradermal injection or oral challenge.

DISCUSSION

Resensitization to penicillin after negative skin tests appears to be a variable but infrequent phenomenon,^{2,3} with higher rates reported if patients received an oral challenge.⁴ Documented cases of immunological reactivity after delabeling of an allergic state are largely confined to cutaneous reactions (whether IgE- or cell-mediated) although more serious reactions have been described.⁵

Hershkovich et al³ studied the phenomenon of penicillin class antibiotic resensitization by repeating skin tests and oral drug challenge at a 1- to 5-month interval in children with negative results. Two patients (2%) demonstrated sensitization and/or allergy on retesting, one to penicillin and the other to amoxicillin. Another study,⁵ also in a pediatric population, estimated the prevalence of resensitization after delabeling at around 2%, although resensitization may have occurred via subsequent antibiotic courses rather than the testing procedure itself.

In adult patients, resensitization after initial negative skin tests is rare. A study of 53 adults with a history of IgE-mediated penicillin allergy and negative skin tests demonstrated a 0% resensitization rate after 3 subsequent courses of oral penicillin with evidence of negative skin tests before each course. The authors concluded that adult patients are not at significantly increased risk of resensitization and that negative skin tests can be used to predict safe future use.⁶

Similarly, Macy et al⁷ concluded that penicillin use after negative skin testing is safe with resensitization occurring rarely. Penicillin use was reviewed in 1246 skin test-negative individuals over a mean follow-up period of 4.26 years. A total of 4.8% of patients reacted to penicillin on first exposure. There were no serious reactions, and only one of 33 patients who reacted and was retested was skin test positive.

In contrast, our patient experienced anaphylaxis on first exposure after negative skin tests and oral challenge. Specific IgE and intradermal tests confirmed resensitization. Although testing dilutions differed between the 2 occasions and amoxicillin dose differed between drug challenge and subsequent reaction, it is unlikely that a 250 mg oral amoxicillin dose would fail to elicit a clinical reaction within 1 hour if clinically significant sensitization were present. The more likely explanation is that the challenge dose elicited resensitization with significant consequences occurring 1 year later.

TABLE I. Comparison of specific IgE testing and challenge results at testing and after anaphylaxis

Test	2013	2014
Specific IgE—Penicillin (ImmunoCAP)	Not tested	Negative <0.35 kUA/L
Specific IgE—Amoxicilloyl (ImmunoCAP)	Not tested	Positive 1.35 kUA/L*
Skin prick tests	Negative	Negative
• PPL† 0.04 mg/mL		
• MDM† 0.5 mg/mL		
• Amoxicillin 100 mg/mL		
Intradermal tests	Negative	Not tested
• PPL† 1/1000 of above		
• MDM† 1/1000 of above		
• Amoxicillin 0.2 mg/mL		
Intradermal tests	Not tested	Negative
• PPL† 0.04 mg/mL		
• MDM† 0.5 mg/mL		
• Ampicillin 10 mg/mL		
• Amoxicillin 1 mg/mL		
Intradermal tests	Not tested	Positive 6 × 6 mm wheal 8 × 8 mm flare*
• Amoxicillin 10 mg/mL		
Amoxicillin indication	Challenge	Therapy
Amoxicillin dose	250 mg	500 mg
Reaction	Nil	Not done

MDM, Minor determinant mixture; PPL, benzylpenicilloyl-poly-L-lysine.

*Positive results indicate sensitization to amoxicillin.

†PPL and MDM manufactured by Diater Laboratories (Madrid, Spain).

To our knowledge, this is the first report of resensitization to amoxicillin provoked by intradermal testing and/or oral challenge, resulting in anaphylaxis in an adult patient. This case demonstrates that adverse reactions are possible after all antibiotic exposures and highlights the important concept that all antibiotic use is associated with predictable rates of adverse reactions.⁸ It is also one of a very small number of documented cases of oral amoxicillin-associated anaphylaxis.^{9,10} Anaphylaxis is thought to occur with approximately one in every 39,000 parenteral penicillin exposures,¹¹ but no good data exist for the anaphylaxis rate with oral amoxicillin. The phenomenon we document of resensitization induced by skin testing or oral challenge is an extremely rare but potential hazard of penicillin

allergy testing. The morbidity associated with an unconfirmed penicillin allergy is vastly higher.¹

^aDepartment of Immunology, Concord Hospital, Sydney, NSW, Australia^bConcord Clinical School, University of Sydney, Sydney, NSW, Australia

No funding was received for this work.

Conflicts of interest: N. Urriola is employed by NSW Health. The rest of the authors declare that they have no relevant conflicts.

Received for publication December 1, 2015; revised January 18, 2016; accepted for publication January 29, 2016.

Available online March 26, 2016.

Corresponding author: Sandhya Limaye, MBBS (Hons), PhD, FRACP, FRCPA, Department of Immunology, Level 6W, Concord Hospital, Hospital Road Concord, Sydney, NSW 2139, Australia. E-mail: sandhya.limaye@sydney.edu.au. 2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.01.014>

REFERENCES

- Macy E, Contreras MS. 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.
- Bittner A, Greenberger P. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. *Allergy Asthma Proc* 2004;25:161-4.
- Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R. Beta lactam allergy and resensitization in children with suspected beta lactam allergy. *Clin Exp Allergy* 2009;9:726-30.
- Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 2008;100:37-43.
- 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.
- Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Int Med* 2002;162:822-6.
- Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol* 2003;111:1111-5.
- Macy E, Poon K-Y. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009;122:778.e1-7.
- Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. *J Antimicrob Chemother* 2007;60:1172-9.
- Zisa G, Riccobono F, Calamari AM, D'Antonio CD, Galimberti M. A case of protracted hypotension as unique symptom of a biphasic anaphylaxis to amoxicillin. *Eur Ann Allergy Clin Immunol* 2009;41:60-1.
- Galvao TF, Silva MT, Serruya SJ, Newman LM, Klausner JD, Pereira MG, et al. Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. *PLoS One* 2013;8:e56463.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.