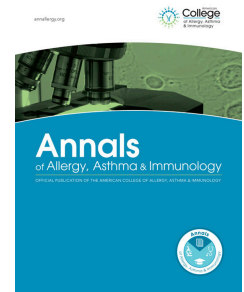


# Accepted Manuscript

Anaphylaxis to amoxicillin-clavulanate, differentiating the components

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Drug hypersensitivity skin testing (ST) has been standardized only when referring to penicillin. However, this method remains a common practice for other drugs and while being a practical tool, oral provocation tests (OPT) are the gold standard in diagnosis of drug hypersensitivity and should be used when available.<sup>1</sup>  $\beta$ -lactams remain the most frequently reported cause of adverse drug reactions.<sup>2</sup> Isolated adverse drug reactions to clavulanate, a  $\beta$ -lactamase inhibitor added to amoxicillin to form amoxicillin-clavulanate, remain rarer but have been reported.<sup>3,4</sup> ST with amoxicillin-clavulanate does not differentiate between the two components, amoxicillin and clavulanate. This case report demonstrates an approach to the diagnostic workup in a patient with a previous anaphylactic reaction to amoxicillin-clavulanate that required differentiation between the two components, amoxicillin and clavulanate.

A 62-year-old male heart transplant candidate, due to complicated coronary artery disease, presented with one episode of lip and facial angioedema, shortness of breath and flushing of his upper extremity after completing a ten day course of amoxicillin-clavulanate (875 mg/125 mg) for sinusitis; with onset of symptoms six to eight hours after the final dose. The patient presented to an emergency room and was given diphenhydramine and systemic steroids both intravenously with resolution of his symptoms after six hours; he was subsequently discharged home. Four months later and with no new exposures to any component of this medication, he came to the Allergy Clinic. While the presentation was not strictly consistent with the timeframe of an IgE-mediated reaction, interrogation, examination, and clinical history did not identify a possible cause for the patient's symptoms other amoxicillin-clavulanate. With that in mind, we began the assessment of a probable allergy to this medication. Skin tests (prick and intradermal) to penicillin G (10,000 U/mL), penicilloate, benzylpenicilloyl polylysine and amoxicillin (2 mg/ml) were negative. We then conducted a one-step OPT with 250mg of amoxicillin. After a 30 minute

observation period without any symptoms, the OPT was deemed negative and allergy to amoxicillin was ruled out. He was instructed to continue to avoid amoxicillin in the combination with clavulanate.

Approximately four months after penicillin ST and the OPT with amoxicillin, the patient had negative ST (prick and intradermal) to published non-irritant concentrations of amoxicillin-clavulanate (20 mg/ml) and ampicillin-sulbactam (20 mg/ml).<sup>5</sup> False negative ST to non-irritant concentrations of amoxicillin and clavulanate have been reported.<sup>4</sup> Since clavulanate without amoxicillin was not available for ST or OPT, we performed a two-step OPT to amoxicillin-clavulanate starting at 1/10 of the dose, waited for 30 minutes with no reaction and then gave the full dose (875 mg). This OPT protocol was consistent with published practice parameters. The practice parameters recommend to make the OPT less than four steps due to the fact that anything greater could, theoretically, modify reactions of effector cells, essentially turning the OPT into a desensitization.<sup>5</sup> The OPT was positive. After having no symptoms during the first step, the patient developed urticaria on his upper back left upper extremity and chest (Figure 1) and experienced bilateral hand flushing within one hour of the full dose (875 mg). These symptoms resolved over the course of two hours after the administration of IM diphenhydramine 50 mg, fexofenadine 180 mg PO, and montelukast 10 mg PO. The patient was therefore diagnosed with IgE-mediated potential to clavulanate and was counseled to avoid all forms of  $\beta$ -lactamase inhibitors and use equally efficacious alternatives.

While IgE-mediated hypersensitivity reactions to penicillin are more common, IgE-mediated hypersensitivity reactions to  $\beta$ -lactamase inhibitors, including clavulanate, sulbactam, and tazobactam in isolation, are rarer but have been reported. This case depicts a clavulanate IgE-mediated reaction in the setting of previously negative ST. Clavulanate and other  $\beta$ -lactamase inhibitors have traditionally been

thought to have low immunogenic capability, but one study found out that seven out of 199 patients with negative ST to different penicillin determinants, tolerated drug provocation testing to benzylpenicillin and amoxicillin but reacted immediately to amoxicillin-clavulanate and were considered allergic to clavulanate.<sup>3</sup> The aforementioned study was performed with patients from one allergy clinic's population located in the south of Spain. Different studies in more diverse populations could help assess the actual prevalence of  $\beta$ -lactamase inhibitor allergy and could even prove helpful to decide whether evaluation for  $\beta$ -lactamase inhibitor allergy should be warranted in cases such as this one in which a reaction occurred while taking a combined medication (i.e. amoxicillin-clavulanate and ampicillin-sulbactam).

While ST to clavulanate in isolation was not available at our institution, ST to clavulanate has been previously performed elsewhere. In one study a total of 9 patients were evaluated after having a reaction to amoxicillin-clavulanate and after ruling out other possible culprits through OPT. The patients initially had negative skin prick testing with clavulanate at 10 mg/mL and negative intradermal testing at 0.1 mg/mL, but seven of the nine patients had positive intradermal testing at 1 mg/mL, 8 had positive intradermal tests for amoxicillin-clavulanate, and an OPT to amoxicillin-clavulanate was performed in one of the patients with a positive result<sup>4</sup>. Interestingly, our patient had negative skin prick testing to non-irritant concentrations of amoxicillin-clavulanate (20 mg/ml) and ampicillin-sulbactam (20 mg/ml), two times the dose of clavulanate when compared with the aforementioned study. Instead of escalating the dose for skin testing and since OPT is regarded as the gold standard for diagnosing drug allergies<sup>1</sup>, we favored OPT with amoxicillin-clavulanate after a negative OPT with amoxicillin alone.

Our findings reinforce both performing due diligence when evaluating an adverse drug reaction and the need for more research to establish the prevalence of  $\beta$ -lactamase inhibitor allergies. Currently, penicillin allergy skin testing is the only standardized drug allergy diagnostic test. It is therefore known that ST with established concentrations of penicillin determinants looking for immediate reactions approaches a negative predictive value of nearly 100% and a positive predictive value between 40 to 100%<sup>1</sup>.

An algorithm similar to the one we used in the assessment of our patient was used in a study that evaluated 268 patients. In this study, a total of 11 cases were found to be selective responders to clavulanate after ST or DPT while being tolerant to penicillin G and V as well as amoxicillin alone<sup>6</sup>. The authors of this study had clavulanate alone available for skin testing and determined their patients as selective responders to clavulanate with positive ST; they performed DPT in four of these patients and confirmed an allergy to clavulanate after positivity of the test. Since isolated  $\beta$ -lactamase inhibitors are not available to all allergists for skin testing, no standardization regarding ST exists. In addition to this, published studies evaluating skin tests for clavulanate fail to provide compelling evidence that these tests are helpful during the work up of patients such as ours. Even in our patient, skin tests with non-irritant concentrations were negative but the positivity of the oral provocation test suggests this was a false negative. For this reason, in patients in whom  $\beta$ -lactam allergy has been discarded and evaluation for  $\beta$ -lactamase inhibitor allergy is warranted, an oral provocation test might be an appropriate approach and skin testing could probably be performed in order to prepare for a more significant reaction during OPT or even defer the provocation test if this test was to be positive.

Other methods such as Basophil Activation Test (BAT) to clavulanate have been shown to have high positive predictive value (96%), sensitivity (55%), and specificity (89%). This suggests the BAT could be a

good complement in the work up of these patients provided its availability and keeping in mind DPT is still the gold standard for drug allergy testing<sup>7</sup>.

Finally, to our knowledge, there are no studies that assess cross-reactivity between the different  $\beta$ -lactamase inhibitors and this could be an interesting topic to evaluate. Perhaps an extended evaluation for each  $\beta$ -lactamase inhibitor would prove beneficial in specific situations in which a patient with confirmed allergy to a  $\beta$ -lactamase inhibitor is in need of one of these combined medications; this hypothetical patient might benefit from tests with remaining  $\beta$ -lactamase inhibitors to which no allergy has been yet proven.

In summary, allergy to  $\beta$ -lactams is a relatively common scenario regarding drug allergies and these antibiotics are frequently given alongside  $\beta$ -lactamase inhibitors which have been reported to have some immunogenicity albeit in a smaller degree. In cases in which clinical history suggests that a combined medication could be the trigger for an IgE-mediated reaction and the use of  $\beta$ -lactams may become a necessity in the future (e.g. a transplant patient), an assessment for  $\beta$ -lactamase inhibitor allergy may be helpful after allergy to  $\beta$ -lactams has been ruled out. A positive result to  $\beta$ -lactamase inhibitors but not to  $\beta$ -lactams would allow the patients to receive this frequently prescribed group of medications so long as they do not contain the  $\beta$ -lactamase inhibitor.

## References

1. Solenksy R, Khan DA, Bernstein IL, et al. Drug Allergy: An Updated Practice Parameter. *Annals of Allergy, Asthma & Immunology*. 2010; 105: 273
2. Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy and Asthma Proceedings*. 2014;35(6):489-494.
3. Torres MJ, Ariza A, Mayorga C, et al. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. *The Journal of allergy and clinical immunology*. 2010;125(2):502-505.e502.
4. Sanchez-Morillas L, Perez-Ezquerro PR, Reano-Martos M, Laguna-Martinez JJ, Sanz ML, Martinez LM. Selective allergic reactions to clavulanic acid: a report of 9 cases. *The Journal of allergy and clinical immunology*. 2010;126(1):177-179.
5. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; 68: 702-712.
6. Blanca-Lopez N, Perez-Alzate D, Ruano F, et al. Selective immediate responders to amoxicillin and clavulanic acid tolerate penicillin derivative administration after confirming the diagnosis. *Allergy* 2015; 70:1013-1019.
7. Salas M, Fernandez-Santamaria R, Mayorga C, et al. Use of the basophil activation test may reduce the need for drug provocation in amoxicillin-clavulanic allergy. *J Allergy Clin Immunol Pract* 2018; 6(3):1010-1018;e2

Figure 1. Urticaria on upper back and left upper extremity/chest during an open oral challenge to amoxicillin-clavulanate

ACCEPTED MANUSCRIPT

