

## Caution Against Temporary Tolerance and Negative Skin Testing During the Anergic Period Following Systemic Reactions

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The “anergic” or refractory period is defined as a period of around 4-6 weeks following a systemic allergic reaction when skin testing results are negative. It is thought to be due to depletion of mast cell mediators after intense degranulation [1]. This phenomenon has been classically described in the context of insect venom allergy, although the precise duration and tolerance upon re-exposure to the culprit allergen within this period is unknown. We report a case of accidental re-exposure to amoxicillin-clavulanate (AC), with negative skin test results during the anergic period up to 8 weeks following confirmed intraoperative anaphylaxis.

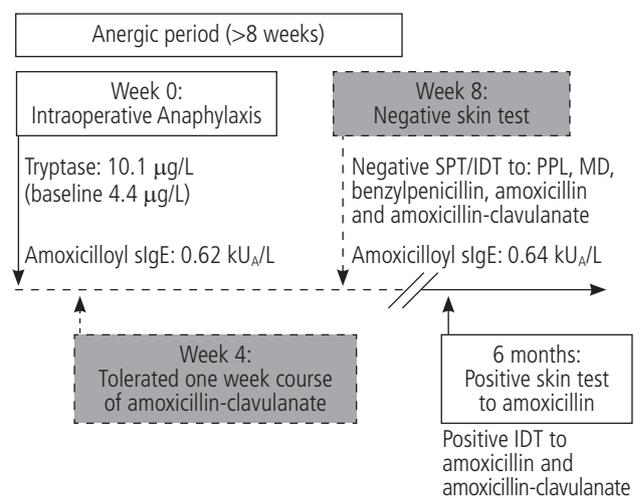
A 59-year-old man experienced intraoperative anaphylaxis following induction for planned radiofrequency ablation of hepatocellular carcinoma under general anesthesia. He had no prior history of drug allergy. Chlorhexidine solution was used for skin preparation, and induction with fentanyl, propofol, and cisatracurium was uneventful. Fifteen minutes later, 1.2 g of intravenous AC was given. Within minutes, the patient became hypotensive and airway pressure increased, thus necessitating resuscitation with repeated doses of inotropes and bronchodilators. The operation was cancelled, and a high serum tryptase level was observed 1 hour after the event (significantly raised at 10.1 µg/L [baseline, 4.4 µg/L]). Given the timing of drug administration, anaphylaxis to AC was considered most likely and the patient was referred to our Allergy Clinic for further evaluation, with an appointment scheduled for 8 weeks later.

The patient was re-admitted 4 weeks later (ie, before the appointment) for transarterial chemoembolization of his hepatocellular carcinoma under local anesthesia. After an uneventful procedure, he was mistakenly prescribed a course of oral AC 1 g twice daily for 1 week despite suspected previous anaphylaxis to the drug. He completed the 1-week course of AC without experiencing a reaction.

Eight weeks after the anaphylaxis episode, the patient underwent a work-up at our Allergy Clinic to investigate intraoperative anaphylaxis. The histamine control was positive at 5 mm. Skin prick tests (SPTs) and intradermal

tests (IDTs) were performed with all potential culprits according to the European Academy of Allergy and Clinical Immunology (EAACI) recommendations. These included fentanyl, propofol, cisatracurium, latex, chlorhexidine, penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, amoxicillin, and AC [2]. The results of the SPTs and IDTs were unequivocally negative. In view of the uninformative skin test results, serum specific IgE (sIgE; ImmunoCAP, Phadia) to latex, chlorhexidine, penicilloyl G, penicilloyl V, and amoxicilloyl was determined. Amoxicilloyl sIgE was positive at 0.64 kU<sub>A</sub>/L, whereas the results for penicilloyl G, penicilloyl V, latex, and chlorhexidine sIgE were all negative. To exclude possible de novo sensitization by the recent oral AC exposure at week 4, the acute serum sample taken during the index anaphylactic reaction was retrieved, and amoxicilloyl sIgE was found to be positive (0.62 kU<sub>A</sub>/L) upon retrospective testing. The patient declined drug provocation testing and was diagnosed with likely IgE-mediated amoxicillin allergy. Repeat skin tests performed at 6 months after the initial episode confirmed the diagnosis. The IDT results became positive with both amoxicillin and AC (while persistently negative for all other drugs). The clinical course and the results of our investigation are summarized in the Figure.

Although the anergic period following anaphylaxis has been well reported, few studies have investigated its exact duration [3-6]. Refractoriness to skin testing has been attributed to the depletion of mast cell mediators following the systemic allergic reaction, although the time required for mast cell repletion remains unknown. The arbitrary recommendation of waiting 4-6 weeks to avoid false-negative results is largely based on expert opinion only. In this case, SPT and IDT remained negative even at 8 weeks after the event, and the IDT result only became positive upon repeat testing at 6 months (we were unable to offer earlier testing



IDT indicates intradermal test; MD, minor determinant; PPL, penicilloyl-poly-L-lysine; sIgE, specific IgE; SPT, skin prick test.

Figure. Summary of the patient's clinical course and results of the investigation.

owing to reduced services during the COVID-19 pandemic). In addition, a positive SPT result to histamine does not seem to accurately reflect mast cell repletion, as demonstrated in this case by the positive histamine control at week 8. Before further studies regarding the optimal duration for testing become available, we recommend repeating *in vivo* tests up to >8 weeks after the reaction in cases where clinical suspicion remains.

Our report is the first to describe tolerance to a full-course culprit drug rechallenge during the anergic period. We postulate that this state of temporary tolerance to AC in the present case was due to depletion of mast cell mediators during the anergic period, which is mechanistically similar according to traditional acute drug desensitization [7].

This case also highlights the complementary role of sIgE in suspected drug allergy. Despite low and variable sensitivity to  $\beta$ -lactam allergy, sIgE may be useful, especially when *in vivo* tests cannot be performed [8]. The positive amoxicilloyl sIgE results allowed us to determine with greater confidence whether the sensitizing event was prior to the index event, rather than to the patient's accidental exposure to AC at week 4 (ie, asymptomatic desensitization). Given that the amoxicilloyl sIgE was already positive in the acute serum sample during anaphylaxis (with persistent levels at week 8), this finding seems more indicative of a prior sensitization event. Moreover, the timing of drug administration also pointed to AC as being the most clinically likely culprit, since all other agents were administered much earlier prior to onset of anaphylaxis. According to EAACI recommendations, we also advocate that sIgE should be considered following skin testing in the work-up of  $\beta$ -lactam allergies to avoid unnecessary and potentially hazardous drug provocation testing [8].

Our study was subject to a series of limitations. Because the patient declined any further drug provocation testing, we were unable to confidently exclude drug allergy to all the other agents introduced during surgery. In addition, there may be cofactors in the intraoperative event that were not reproduced during the work-up at week 8. However, taking into consideration the timing of drug administration and the absence of sIgE to any other agents tested, amoxicillin remained the most likely culprit. *De novo* sensitization and asymptomatic sensitization to AC during the exposure 4 weeks after the event were also considered and cannot be definitively ruled out. However, neither seems likely, because sIgE to amoxicilloyl was already positive in the blood sample taken at the time of the index reaction. Mast cell depletion during the event, as well as persistent depletion 8 weeks later, could explain the similar levels of sIgE in these 2 samples.

In conclusion, our report is the first to demonstrate tolerance of a culprit drug rechallenge during the anergic period following anaphylaxis and that refractoriness can last up to 8 weeks with negative skin test results. We caution allergists to be wary of a possible prolonged anergic period and to remember that tolerance to a potential culprit during the anergic period does not exclude allergy. All possible culprits should be retested after at least >8 weeks (and perhaps even longer) regardless of prior tolerance during the anergic period. The optimal cut-off for this period urgently warrants further investigation.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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