Caution against Temporary Tolerance and Negative Skin Testing During Anergic Period Following Systemic Reactions

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The “anergic” or refractory periodis defined as a period of negative skin testing around 4-6 weeks following a systemic allergic reaction, 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, but the precise duration and tolerance upon culprit allergen re-exposure within this period is unknown. We report a case of accidental re-exposure to amoxicillin-clavulanate (AC) with negative skin tests during the anergic period up to 8weeks following confirmed intra-operative anaphylaxis.

A 59-year old man suffered from intra-operative anaphylaxis following induction for planned radiofrequency ablation for hepatocellular carcinoma (HCC) under general anesthesia. He had no prior history of drug allergy. Chlorhexidine solution was used for skin preparation and induction was performed uneventfully with fentanyl, propofol and cisatracurium. Fifteen minutes later, 1.2g of intravenous AC was given. Within minutes, the patient developed raised airway pressure and hypotension which required resuscitation with repeated doses of inotropes and bronchodilators. The operation was cancelled and an acute serum tryptase was checked1-hour post-event. The acute tryptase level was significantly raised at 10.1 µg/L, with a baseline tryptase of 4.4 µg/L. Given the timing of drug administration, anaphylaxis to AC was

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deemed most likely and the patient was referred to our Allergy Clinic for further evaluation with an appointment scheduled 8weeks later.

Prior to his Allergy Clinic appointment, the patient was re-admitted 4 weeks later for transarterial chemoembolization for his HCC under local anesthesia. After an uneventful procedure, he was mistakenly prescribed a course of oral AC 1g twice daily for 1 week despite suspected previous anaphylaxis to AC. Fortunately, he completed the one-week course of AC without any reaction.

At week 8 post-anaphylaxis, the patient was seen at our Allergy Clinic for workup of intra-operative anaphylaxis. Histamine control was positive at 5mm. Skin prick tests (SPT) and intradermal tests (IDT) were performed with all possible agents including fentanyl, propofol, cistracurium, latex, chlorhexidine, penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, amoxicillin and AC - as per European Academy of Allergy and Clinical Immunology [EAACI] recommendations[2]. All SPT and IDT were unequivocally negative. In view of uninformative skin tests, serum specific-IgE (sIgE; by ImmunoCAP, Phadia) to latex, chlorhexidine, penicilloyl G, penicilloyl V and amoxicilloylwere checked. Amoxicilloyl sIgE was positive at 0.64 kUA/L, while penicilloyl G, penicilloyl V, latex and chlorhexidine sIgE were all negative. To exclude possible *de novo* sensitization by his 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 kUA/L)upon retrospective testing. The patient declined drug provocation testing and he was diagnosed with likely IgE-mediated amoxicillin allergy. Repeat skin tests performed at 6months post-anaphylaxis confirmed the diagnosis with

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conversion to positive IDT with both amoxicillin and AC (while persistently negative results for all other drugs). Summary of his clinical course and investigation results are shown in Figure 1.

Although the anergic period following anaphylaxis has been well reported, there have been few studies investigating on the exact duration of this phenomenon [3-6].The refractoriness to skin testing has been attributed to the depletion of mast cell mediators following the systemic allergic reaction but the time required for mast cell repletion is 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-week post-anaphylaxis and IDT only converted positive upon repeat testing at 6 months (unfortunately, we were unable to offer earlier testing due to the cut-down of our services during the COVID-19 pandemic).In addition, SPT positivity 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 therefore recommend repeating any *in vivo* tests up to >8 weeks post-reaction if any clinical suspicion remains.

Furthermore, we are first to describe the tolerance to a full course culprit drug re-challenge during the anergic period. We postulate that this state of temporary tolerance to AC in our patient was possible due to depletion of mast cell mediators during the anergic period, which is mechanistically similar as per traditional acute drug desensitization [7].

This case also highlights the complementary role of sIgE in the suspected drug allergy. Despite a low and variable sensitivity to for beta-lactam allergy, sIgE may be useful specially when *in vivo*

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tests cannot be performed[8]. The positive amoxilloyl sIgE results allowed us to more confidently differentiate whether the sensitizing event was prior to the index event, rather than during the patient's accidental exposure to AC at week 4(i.e. asymptomatic desensitization). Given that the amoxicilloyl sIgE was already positive in the acute serum sample during anaphylaxis (with persistent levels at week 8)this was more in favor of a prior sensitization event. Moreover, AC was also clinically the most likely culprit from the timing of drug administration as all other agents were administered much earlier prior to onset of anaphylaxis. In accordance to EAACI recommendations, we also advocate that sIgE should be considered following skin testing in the workup-up of beta-lactam allergies in order to avoid unnecessary and potentially hazardous drug provocation testing[8].

There were a few limitations to this study. Because the patient declined any further drug provocation testing, we were not able to confidently exclude drug allergy to all the other agents introduced intra-operatively. In addition, there may be possible cofactors in the intra-operative event that were unaccounted for that were not reproduced during his workup at week 8. However, taking in 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, or asymptomatic sensitization to AC during his exposure at 4 weeks post-event was also considered and cannot be definitively ruled out, but unlikely because sIgE to amoxicilloyl was already positive in the blood sample taken during the time of the index reaction. Mast cell depletion during the time of event as well as persistent depletion 8 weeks later could explain the similar levels of sIgE in these two samples.

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In conclusion, our report is first to demonstrate tolerance of a culprit drug re-challenge during the anergic period following anaphylaxis and that refractoriness can last up to 8 weeks with negative skin tests. We caution Allergists to be wary of possible prolonged anergic period and that tolerance to a possible culprit during the anergic period cannot exclude allergy. All possible culprits should be re-tested at least >8 weeks (and perhaps even longer) regardless of prior tolerance during the anergic period, and the optimal cut-off duration of this period urgently warrants further investigation.

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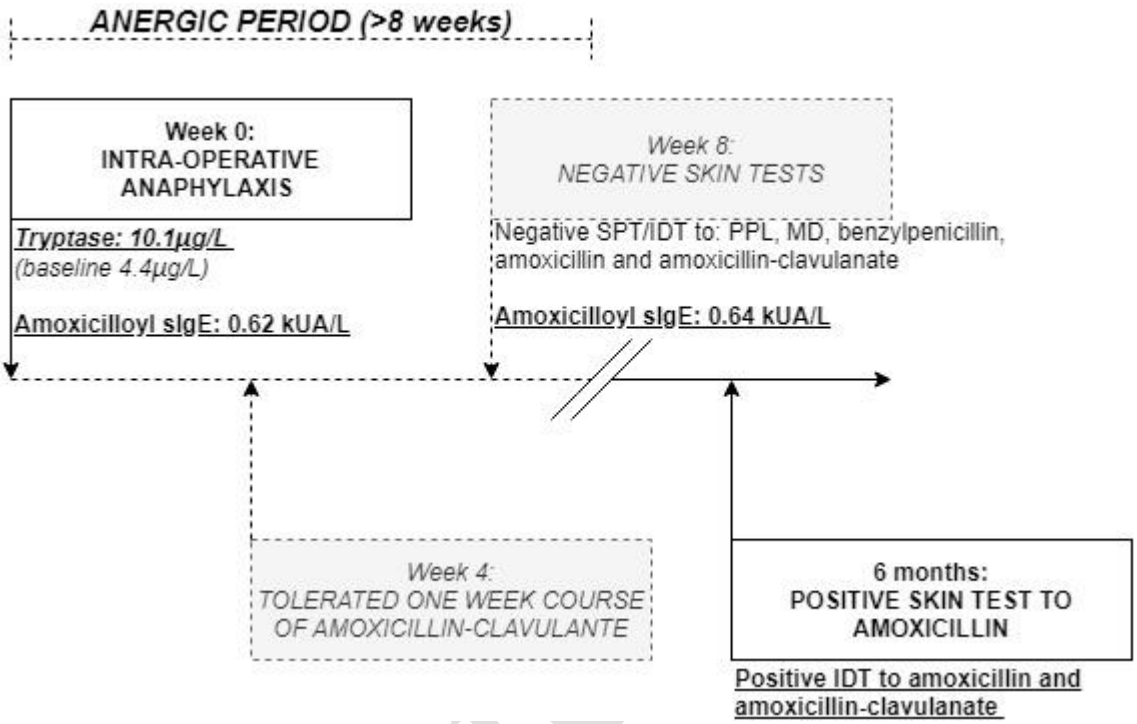
Figure 1.Summary of the patient's clinical course and investigation results.



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

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