

## Clinical Communications

### Fatal anaphylaxis from a second amoxicillin/clavulanic acid provocation after a prior negative provocation

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#### Clinical Implications

- This is a case report of fatal anaphylaxis due to clavulanic acid resensitization after negative prior provocation test result. Caution should be taken before delabeling amoxicillin/clavulanic acid in patients with aspirin-exacerbated respiratory disease during an acute illness.

#### TO THE EDITOR:

Unconfirmed penicillin allergy in hospitalized patients is associated with longer hospital stays and increased rates of serious drug-resistant infections. Routine penicillin allergy testing is therefore promoted in patients with self-reported penicillin allergy.<sup>1</sup> However, resensitization is a concern because some patients with a history of anaphylaxis are reported to become resensitized after an initial negative diagnostic test result. Although clinical resensitization to penicillin has been reported,<sup>2,3</sup> clavulanic acid, a beta-lactamase inhibitor in a combined tablet, has rarely been reported for its role in causing a severe reaction by resensitization.<sup>4,5</sup>

We report a case of fatal anaphylaxis due to clavulanic acid after negative prior provocation in a 35-year-old man with a previous diagnosis of aspirin-exacerbated respiratory disease (AERD). AERD was confirmed by diagnoses of chronic rhinosinusitis with nasal polyposis and asthma as well as a history of ibuprofen hypersensitivity with a positive aspirin provocation test result. He had no previous underlying medical comorbidities, including cardiac diseases, psychiatric diseases, and mast cell disorders. He reported a history of amoxicillin/clavulanic acid allergy, manifesting as generalized pruritic rashes without systemic symptoms shortly after taking the first dose, 15 years before the fatal anaphylaxis episode. He also reported a history of hypersensitivity to other drugs, including clarithromycin and levofloxacin, although he was unable to recall the details of these events.

Multiple episodes of acute bacterial rhinosinusitis led to antibiotic selection problems due to his multiple drug hypersensitivity. He was therefore evaluated for antibiotic allergy. Skin tests with penicillin G sodium (20,000 IU/mL), ampicillin (20 mg/mL), amoxicillin/clavulanic (20 mg/mL), and cloxacillin (20 mg/mL) showed negative results. We then performed an amoxicillin/clavulanic acid provocation test. After 2 hours of close observation, the result was negative (cumulative dose = 1520/216.6 mg). Allergological diagnostic test results are summarized in Table I. The documentation of amoxicillin/clavulanic allergy was then delabeled. He reported

tolerance of 3 to 4 courses of over-the-counter amoxicillin 2000 mg/d to treat his upper respiratory tract infections between visits.

Twenty months later, he again developed bacterial sinusitis not improved by 4 days of amoxicillin (2000 mg/d). Physical examination revealed purulent discharge per anterior nares. Lung auscultation was normal. We decided to switch from amoxicillin to amoxicillin/clavulanic acid. We did not perform skin testing before the first dose of amoxicillin/clavulanic acid because the patient was taking antihistamines. However, we were concerned about the possibility of resensitization to clavulanic acid because the patient had not been exposed to clavulanic acid since the last negative provocation test result. To date, there are no data to confirm that clavulanic acid has a low rate of resensitization similar to penicillin, and the patient also had asthma, which is a risk factor for severe anaphylaxis if the reaction occurred. We, therefore, administered amoxicillin/clavulanic acid by in-hospital graded challenge. We began the first dose of amoxicillin/clavulanic acid at 300/21.45 mg. Shortly after the first dose, he suddenly developed chest pain and dyspnea with generalized skin erythema. He was administered 0.5 mg epinephrine with 2 separate doses 5 minutes apart. At 6 minutes, he developed sudden loss of consciousness and cardiovascular collapse. Cardiopulmonary resuscitation was immediately initiated. The electrocardiogram revealed ventricular fibrillation, alternating with asystole. After 45 minutes of cardiopulmonary resuscitation, he was placed on extracorporeal membrane oxygenation and was transferred to the intensive care unit. Serum tryptase level at 2 hours after the onset of reaction was 12.4 µg/L. He was diagnosed with severe anaphylaxis due to amoxicillin/clavulanic acid ingestion. He ultimately died because of ventilator-associated pneumonia, acute respiratory distress syndrome, septic shock, and multiple organ failure. The time frame of the event is summarized in Figure 1.

To our knowledge, this is the first fatal anaphylaxis case due to a second amoxicillin/clavulanic acid provocation test in a patient after a first negative provocation test result. We used 1520/216.6 mg of amoxicillin/clavulanic acid in the first provocation, enough to confirm the negative result. This reaction was most likely compatible with clavulanic acid resensitization because our patient took a 4-day course of amoxicillin before undergoing amoxicillin/clavulanic acid challenge. He took the last dose of amoxicillin (1000 mg) at 9 AM, 4 hours before the amoxicillin/clavulanic acid challenge. Therefore, it is unlikely that amoxicillin was a culprit of such a severe reaction.

Retesting after first negative allergy investigation is a controversial issue.<sup>6</sup> The US practice parameter 2010<sup>7</sup> stated that retesting penicillin skin tests routinely is not indicated in patients with a history of nonsevere reactions who have tolerated 1 or more oral penicillin courses. In contrast, retesting in patients with a history of severe immediate reactions to beta-lactams and who display negative results in the first evaluation, including drug provocation test, is weakly recommended from the European perspective. Our case had a remote benign rash with a subsequent negative challenge. Therefore, we did not perform retesting.

**TABLE 1.** Allergological diagnostic testing results

| First allergy testing (July 2016)             | Second allergy testing (March 2018)                                      |
|-----------------------------------------------|--------------------------------------------------------------------------|
| <b>Skin test (SPT and IDT)*</b>               | <b>Skin test</b> , not done because the patient was taking antihistamine |
| Penicillin G sodium (20,000 IU/mL): negative  |                                                                          |
| Ampicillin (20 mg/mL): negative               |                                                                          |
| AMX/CL (20 mg/mL): negative                   |                                                                          |
| Cloxacillin (20 mg/mL): negative              |                                                                          |
| Negative control†: negative                   |                                                                          |
| Positive control†: positive (5 × 5 mm)        |                                                                          |
| <b>AMX/CL provocation (30-min intervals)</b>  | <b>AMX/CL provocation</b>                                                |
| Dose 1: 160/22.8 mg                           | Dose 1: 300/21.45 mg                                                     |
| Dose 2: 400/57 mg                             |                                                                          |
| Dose 3: 960/136.8 mg                          |                                                                          |
| Negative provocation after 2 h of observation | Positive provocation after 5 min from first dose                         |

AMX, Amoxicillin; CL, clavulanic acid; IDT, intradermal test; SPT, skin prick test.

\*We did not use penicilloyl-polylysine because of unavailability of the agent.

†Normal saline and histamine (10 mg/mL) were used as negative and positive controls, respectively.

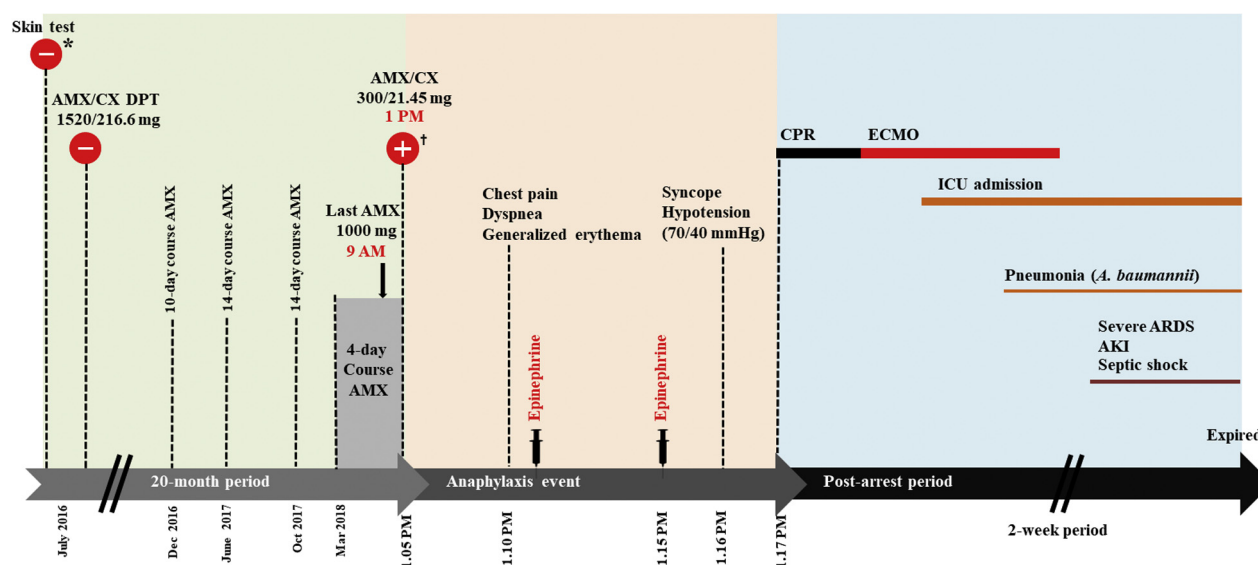


**FIGURE 1.** The event timeline. *AKI*, Acute kidney injury; *AM*, amoxicillin; *ARDS*, acute respiratory distress syndrome; *CPR*, cardiopulmonary resuscitation; *CX*, clavulanic acid; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit. \*Negative result/reaction. †Positive result/reaction.

Although penicillin resensitization is rare, there are no data to confirm that clavulanic acid has a low rate of resensitization similar to penicillin. The aim of penicillin delabeling is to allow the patient to safely take the drug when indicated. This means they should be able to use the delabeled agents during an acute bacterial infection. Acute bacterial sinusitis might play a role as a cofactor increasing the severity of reaction. We agree that penicillin delabeling is safe and cost-effective in most patients.<sup>8</sup> However, our patient's condition was complicated; specifically, he had AERD and was likely to be infected with upper respiratory tract pathogens, further complicated by a brittle asthmatic status. We report this occurrence to emphasize the need for caution in prescribing an antibiotic after its delabeling in a patient with AERD. We suggested expanding the importance of retesting, not only in

cases with a severe immediate reaction but also in patients with significant comorbidities who need frequent antibiotic use. Physicians should also be aware of the potential for clavulanic acid resensitization (in the absence of amoxicillin resensitization) in combined drugs.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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