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CASE REPORT OPEN ACCESS

# A case of persistent IgE sensitisation almost two decades following ampicillin anaphylaxis

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**Abstract**
*Background:* Although most immunoglobulin E (IgE)-mediated penicillin allergy wanes with time, sensitisation may occasionally persist for many years. Previous reports on the loss of penicillin-specific IgE sensitisation were based on non-anaphylaxis cases and, although uncommon, persistent sensitisation may still be possible in the minority of cases.
*Objective:* This case highlights that irrespective of the elapsed duration since the index reaction, it is important to remain vigilant when approaching patients with a history of severe reactions.
*Material and Methods:* We described a case of persistent IgE sensitisation almost two decades following ampicillin anaphylaxis.
*Results:* A 78-year-old male with a history of perioperative penicillin anaphylaxis in 2003 was referred for allergy workup in 2022 before his knee joint replacement surgery. The patient had strictly avoided all beta-lactams since the index reaction. However, his penicillin-specific sensitisation persisted, evidenced by positive skin tests (with generalised urticaria after intradermal testing) and basophil activation tests.
*Conclusion:* To our knowledge, this was the first case of positive BAT tested around two decades following the index reaction. This case illustrates that a cautious approach may still be warranted in patients with a history of severe reaction to penicillin regardless of the duration since the reported index reaction.


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## Introduction

The natural history of Immunoglobulin E (IgE)-mediated penicillin allergy has been extensively studied, and it is well reported that sensitisation wanes with time. A retrospective study demonstrated that the prevalence of positive penicillin skin tests after a documented reaction was lower among patients tested after 10 years or more than those tested after 7–12 months (22% vs. 73%).[1] Another prospective study also demonstrated that 81% of the patients had persistent positive skin tests at 1 year but dropped to 67% at 5 years, indicating a loss of penicillin-specific IgE over time.[2] In fact, the duration since the reported index reaction is associated with lower risk of genuine penicillin allergy and often used as a parameter for risk stratification.[3–6] However, we report a case which illustrates that a cautious approach may still be warranted in patients with a history of severe reaction to penicillin regardless of the duration since the reported index reaction.

## Case Report

A 78-year-old male, with a history of perioperative anaphylaxis in 2003, was referred to our clinic for allergy workup before his knee joint replacement surgery. According to patient's case record, he presented with right psoas abscess and was admitted for emergent surgical drainage. He had no known history of any drug allergy. During induction, he developed hypotension and bronchospasm after 5 min following administration of ampicillin and rocuronium, followed by a generalised rash. Resuscitation with intravenous adrenaline was required. He was subsequently prescribed thiopental, midazolam, alfentanil, and suxamethonium. He was stabilised and operated with post-operative intensive care monitoring. Acute tryptase (ImmunoCAP; Phadia Laboratory Systems, Sweden) was significantly elevated at 17.7 µg/L. Baseline tryptase level was 6.3 µg/L. He was labelled with ampicillin allergy upon discharge, and since then had strictly avoided all beta-lactams. No allergy testing services were available at the time. He adhered to avoidance of all beta-lactams and thereafter did not experience any further episodes of adverse or allergic drug reactions. He underwent total knee replacement under general anaesthesia in July 2022, which was uneventful. Suxamethonium and cisatracurium were used during the procedure. He did not receive rocuronium again.

The patient attended our clinic in 2022 and consented to drug allergy workup. Skin tests were performed with latex, rocuronium, and chlorhexidine, which were all negative. Penicillin skin testing with benzylpenicilloylpolylysine (PPL, 0.04 mg/mL), benzylpenilloate (0.5 mg/mL), benzylpenicillin (6 mg/mL), amoxicillin (20 mg/mL), and ampicillin (20 mg/mL) was performed, with a significantly positive intradermal skin testing to PPL (wheal size: 13 × 11 mm). In addition, the patient also developed generalised itchiness and urticarial eruptions over his body and limbs shortly after intradermal skin test, which resolved with oral antihistamines. *In vitro* auxiliary tests, including specific IgE and basophil activation tests, were also performed. Specific IgE (ImmunoCAP; Phadia Laboratory Systems) demonstrated graded 2 positivity towards penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl, while negative for chlorhexidine and latex (Table 1). Basophil activation test (BAT) also demonstrated reactivity to PPL (Figure 1). Overall, these findings supported the diagnosis of penicillin allergy, and the patient was counselled accordingly.

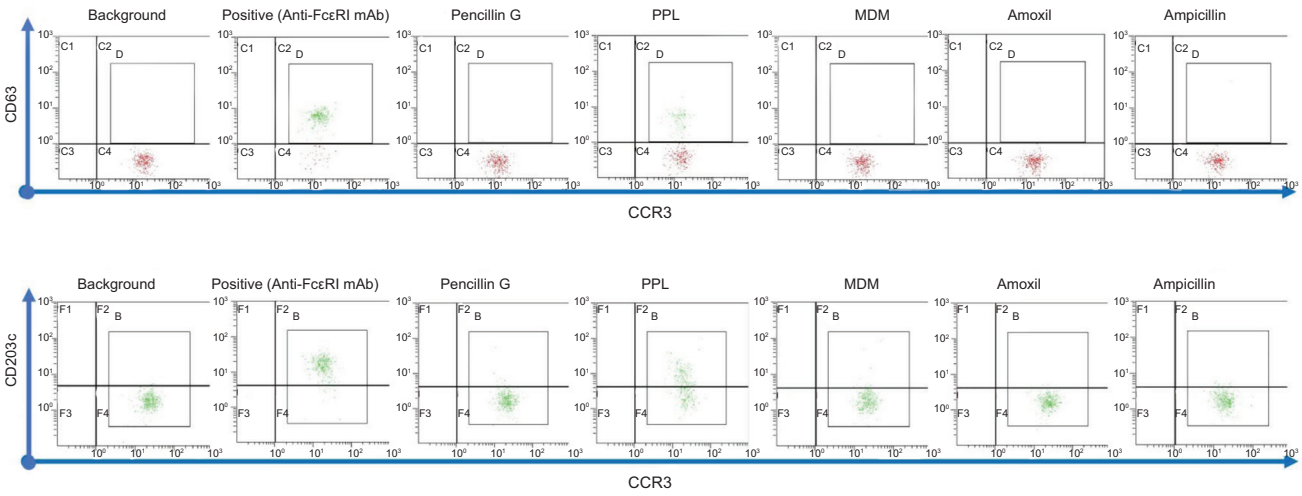
## Discussion

We confirmed that the patient had strictly avoided all beta-lactams since the index reaction in 2003; however, his penicillin-specific sensitisation persisted. He remained clinically allergic to penicillin, demonstrated by a generalised urticarial eruption even after exposure to minimal amounts of penicillin during skin testing. Although most IgE-mediated penicillin allergy wanes with time, sensitisation may occasionally persist for many years (or even decades) such as in this case report. Irrespective of the elapsed duration since the index reaction, it is important to remain vigilant when approaching patients with a history of severe reactions. As IgE antibodies generally decrease with time, obtaining a positive skin tests 10 years after the reaction is extremely rare. However, previous literature on the evolution of sensitivity to penicillin in anaphylaxis cases is limited, and, although uncommon, persistent sensitisation may still be possible in the minority of cases.[1,2,7] This phenomenon is reminiscent of other persistent IgE-mediated allergies, such as certain food allergies, which also persist throughout life despite allergen avoidance.[8,9] The exact underlying mechanisms or unidentified environmental exposures driving this persistent sensitisation in individuals remain to be elucidated. Regardless of this, a positive skin test with a concordant history of immediate-type allergy is significant and suggests persistent penicillin allergy. Generally, *in vitro* tests have lower sensitivity than skin tests, with the sensitivity of BAT in beta-lactam allergy workup reported to be around 50%.[10–12] Similarly, the sensitivity of these assays also decreases with duration since the index reaction. In a study comprising patients with proven neuromuscular blocking agent anaphylaxis, the sensitivity of BAT could be increased from 36.1% to 85.7% when only allergies with an onset of less than 3 years were included.[13] Therefore, yielding a positive BAT decades after the index event is rare.

To our knowledge, this was the first reported positive BAT tested around two decades following the index

**Table 1** Specific IgE results.

| Allergen | Specific IgE level (kUa/L) |
|---|---|
| Latex | <0.1, negative (grade 0) |
| Penicilloyl G | 1.05, positive (grade 2) |
| Penicilloyl V | 0.93, positive (grade 2) |
| Ampicilloyl | 0.93, positive (grade 2) |
| Amoxicilloyl | 0.86, positive (grade 2) |
| Chlorhexidine | 0.14, negative (grade 0) |




| | CD63 % | CD63 SI (%) | CD203c % | CD203c SI (MFI) |
|---|---|---|---|---|
| Negative | 0.3 | | 2.7 | |
| Anti-FcƐRI mAb (Positive control) | 88.5 | 269.2 | 96.2 | 8.4 |
| Penicillin G | 0.7 | 2 | 3.6 | 1.1 |
| PPL | 28.2 | 85.5 | 49.0 | 3.3 |
| MDM | 0.3 | 1 | 3.8 | 1.3 |
| Amoxil | 0.7 | 2 | 4.3 | 1.1 |
| Ampicillin | 0.3 | 1 | 5.9 | 1.2 |

**Figure 1** Basophil activation test results. Basophil activation test is considered positive if CD63 > 5% and SI > 2, or CD203c > 10.9% and SI > 2.9. FcεRI: high-affinity IgE receptor; mAb: monoclonal antibody; PPL: benzylpenicilloylpolylysine; MDM: minor determinant mixture; SI: stimulation index; MFI: mean fluorescence intensity.

reaction. Although specific IgE for penicillin was known to suffer from suboptimal sensitivity, our patient also had positive specific IgE to penicilloyl, ampicilloyl, and amoxicilloyl despite negative skin tests towards benzylpenilloate, benzylpenicillin, ampicillin, and amoxicillin. Our findings also support the complementary use of *in vitro* tests to enhance diagnostic yield, especially in unusual cases with a history of severe reactions. Furthermore, the sensitisation patterns in beta-lactam allergies also vary among different populations. Although fewer patients have been reported to be monosensitised to PPL in Europe, monosensitisation to PPL was found in 20.4% of Chinese.[14] Hence, as illustrated in our case, it is essential to include both PPL and benzylpenicilloate in beta-lactam antibiotic skin tests for certain populations, such as Chinese.

## Conclusion

To conclude, we reported an unusual case with persistent penicillin sensitisation and allergy despite decades of avoidance. We therefore advocate that proper assessment prior to re-exposure is still warranted for patients with a history of anaphylaxis, irrespective of the time elapsed. Moreover, complementary use of *in vitro* tests may be considered to enhance the diagnostic yield.

## Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

## Author Contributions

E.Y.L.A. coordinated the patient's care, researched the data and drafted the manuscript. V.C., A.K.C.K., K.L., J.C.Y.W. and H.H.Y.Y. coordinated the patient's care and researched the data. P.H.L. coordinated the patient's care and critically reviewed and edited the manuscript. All authors contributed to the final version of the manuscript.

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