Delayed positive skin tests in patients with immediate hypersensitivity reactions to beta-lactams

Rik Schrijvers, Bárbara Kong Cardoso, Jean Luc Bourrain, Pascal Demoly, Anca Mirela Chiriac

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Authors:

Rik Schrijvers M.D. PhD*[1], Bárbara Kong Cardoso M.D.*[2], Jean Luc Bourrain M.D.[3], Pascal Demoly M.D. Ph.D. [3,4], Anca M Chiriac M.D. Ph.D.[3,4]

Author's affiliation:

[1] KU Leuven department of microbiology and clinical immunology, allergy and clinical immunology research group, KU Leuven, Leuven, Belgium

[2] Department of Immunoallergology, Hospital São Bernardo – Centro Hospitalar de Setúbal, Portugal

[3] Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Univ Montpellier, France;

[4] UMR-S 1136 INSERM-Sorbonne Université, Equipe EPAR - IPLESP, Paris, France

Corresponding author:

Dr Anca Mirela CHIRIAC

a-chiriac@chu-montpellier.fr

0033 467 33 61 07

Allergy Unit

Arnaud de Villeneuve Hospital

University Hospital of Montpellier

371, Avenue du Doyen Gaston Giraud

34295 Montpellier Cedex 5, Montpellier, France

*These authors have contributed equally to this work

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Clinical implications

Skin tests for presumed IgE-mediated reactions to beta-lactams may be negative on immediate reading, but rarely demonstrate positivity on delayed reading with wheal-and-flare. Clinicians should be aware of this possible presentation.

The allergy work-up of a presumed immediate drug hypersensitivity reaction (DHR) is well established for beta-lactams (BL)[1]. Patients undergo skin tests (ST) (prick (SPT) and intradermal (IDT) tests), followed by an immediate reading. In case of negative results and in the absence of contraindications, a drug provocation test (DPT) is performed, often on the same day.

We describe three cases of immediate DHR to BL in which ST were negative on immediate reading, yet all developed a late wheal-and-flare reaction, that contra-indicated DPT (**Table 1**).

Case 1, 64-year-old female, presented with palm and sole pruritus, malaise and dyspnea 30 minutes after taking amoxicillin/clavulanic acid (AxC), 500/62.5mg for a dental infection. She returned to her dentist where she was treated with prednisolone 80mg. The treatment was ineffective and the reaction worsened (vomiting, loss of consciousness, systolic pressure 60mmHg). Adrenaline was administered, and she was transferred to the emergency department. Tryptase measurements at the time of the event and baseline were 9.8 and 6.2 μg/mL, respectively. She had no atopy but suffered from SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) syndrome and hypothyroidism treated with infliximab and L-thyroxine, respectively. She took 1g of paracetamol 9h before the event. Intake of amoxicillin 4 months earlier was uneventful. ST to penicillin G (Pen G), AxC, ampicillin (Amp) 4 weeks later were all negative on immediate reading. When the patient returned for the DPT, she

mentioned a late reaction at the prior ST had occurred. IDTs were repeated and revealed again negative immediate reading. However, 4h and 6h later a dose-dependent wheal for IDT to AxC and Amp was observed, fading over the following days (**Figure 1-** Case1). The patient was considered allergic to AxC and Amp. A paracetamol DPT was negative.

Case 2, 26-year-old male was on noradrenaline because of circulatory instability after a trauma. He received suxamethonium, ethomidate, midazolam, sufentanyl to induce general anaesthesia. After achieving circulatory stability, he was rushed to emergency orthopedic surgery (where propofol, sufentanyl, paracetamol were administered). Two hours after the beginning of the procedure and 30 minutes after the (presumably) second injection of AxC (2g; the patient seemed to have received AxC and gentamycin while in the emergency unit, but this information could not be undoubtedly confirmed) he experienced rapidly increasing circulatory instability, demanding increasing doses of noradrenalin and then adrenalin syringe-pump. After cardio-circulatory recovery, the patient developed urticaria. Tryptase and histamine levels 30 minutes after the onset were 4.8 μg/mL and 36.9 nmol/L (normal <10 nmol/L), respectively. Baseline tryptase was <1 μg/L. The patient had a history of allergic rhinoconjunctivitis, took no maintenance treatment and previously underwent general anesthesia uneventfully. He didn't recall prior penicillin use. ST with PenG, AxC, Amp 6 weeks later were negative on immediate reading. When the patient returned for the DPT, he described a late reaction on the previous ST that lasted for several days. IDTs were repeated demonstrating negative immediate reading, yet wheal-and-flare at PenG, AxC, and Amp 24h later, lasting for several days, with an accompanying lymphangitis on day 3 (**Figure 1-** Case2). Further allergy work-up was negative. The patient was considered allergic to penicillins. He tolerated cefuroxime and ceftriaxone.

Case 3, 49-year-old male, presented 1 hour and 30 minutes after the start of renal stent placement with isolated generalized erythema while in the post-operative care unit. The patient had received propofol, sufentanil, mivacurium, betamethasone, cefazolin, ketoralac, paracetamol, and desflurane. Baseline tryptase level was 10.6 µg/L, no acute measurement was performed. The patient suffered from Crohn's disease but received no maintenance treatment. ST performed 10 weeks later were negative on immediate reading. A few hours later, a reaction was observed at the cefazolin ST. The IDT for cefazolin was repeated, together with other BL ST, and negative on immediate reading yet an itchy wheal-and-flare appeared at the cefazolin ST appeared 3h30 and again waned 8h30 later (**Figure 1-**Case3). The patient was considered allergic to cefazoline, a DPT for cefuroxime was negative.

An immediate IgE-mediated reaction on ST is expressed by a wheal-and-flare reaction caused by mast cell degranulation. The release of histamine, the major mediator in this reaction, begins within 5 minutes after allergen exposure and peaks at 30 minutes. Histamine and other mediators can trigger the release of substance P by axonal reflexes and additionally expand histamine release from the cutaneous mast cells [2]. Any IgE-mediated reaction consists of an immediate and a late-phase reaction (LPR). It is the former that is used in clinical practice as a reference for ST reading.

The IgE-mediated LPR in ST is a reaction that begins several hours after the exposure of the allergen via SPT or IDT (peaking at 6-12h and resolving in approximately 24-48h). Generally, this reaction occurs when the immediate reading of the IDT reveals a large wheal-and-flare reaction, as shown for respiratory allergens [3,4].

Several mechanisms have been put forward to explain the LPR, involving other mediators than histamine (such as TNF-alpha, IL-6[5]) that orchestrate the recruitment of a mixed cellular infiltrate[6], a prolonged stimulation of mast cells, and altered expression of adhesion molecules on vascular

endothelium at the reaction site[4]. Late-onset presumed IgE-mediated reactions (urticaria, anaphylaxis) have been described[7] mostly after bee-stings. The authors suggested a stimulation of IgE antibodies with persisting venom antigen. In asthmatics, intradermal administration of allergens was able to elicit a late phase asthmatic reaction without an early, IgE-mediated response, and was attributed as T-cell-mediated[6,8,9]. Here, skin reaction was absent both on immediate and LPR[9].

In our work, case 1 and 2 suffered from an immediate DHR with ST positivity only on delayed reading suggesting a mitigated early phase ST response. In case 3, concordant late-onset index reaction and ST were observed, possibly alluding to a reaction to a metabolite. Of note, none of the index reactions were reminiscent of a type IV reaction. The peculiarity of the cases is that no immediate phase reaction preceded the alleged LPR and, to our knowledge, there is no previous report of this in beta-lactam allergy.

We did not perform confirmatory DPTs for ethical reasons and our observations do not provide a definite mechanistic explanation. Delayed ST positivity in the evaluation of a presumed IgE-mediated DHR is rare. We do not envision that this approach changes the recommendation of the use of ST, immediately followed by DPT in case of negative ST on immediate reading. However, if ST performed for a possible immediate DHR results in a delayed reaction, this should be taken into consideration despite the atypical presentation, before exposing patients to a potentially high risk DPT.

References:

1. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68:702–712.

2. Chiriac AM, Bousquet J, Demoly P. In Vivo Methods for the Study and Diagnosis of Allergy. In: Elsevier Inc, editor. Middleton's Allergy: Principles and Practice: 8th ed. 2013. p. 1119–32.

3. Yates AB, deShazo RD. Delayed Hypersensitivity Skin Testing. Immunology and Allergy Clinics of North America. 2001;21:383–97.

4. Barata LT, Ying S, Meng Q, Barkans J, Rajakulasingam K, Durham SR, et al. IL-4- and IL-5-positive T lymphocytes, eosinophils, and mast cells in allergen-induced late-phase cutaneous reactions in atopic subjects. J Allergy Clin Immunol. 1998;101:222–30.

5. Nagai H, Abe T, Yamaguchi I, Mito K, Tsunematsu M, Kimata M, et al. Role of mast cells in the onset of IgE-mediated late-phase cutaneous response in mice. J Allergy Clin Immunol. 2000;106:S91-98.

6. Galli SJ, Tsai M. IgE and mast cells in allergic disease. Nature Medicine. 2012;18:693–704.

7. Asai Y, Uhara H, Miyazaki A, Saiki M, Okuyama R. Late Onset of Acute Urticaria after Bee Stings. Case Rep Dermatol. 2016;8:341–3.

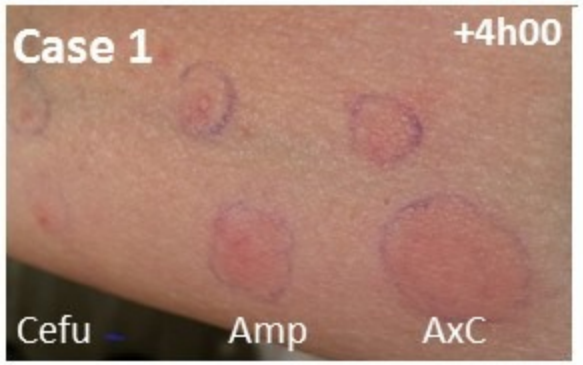
8. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med. 2001;344:30–7.

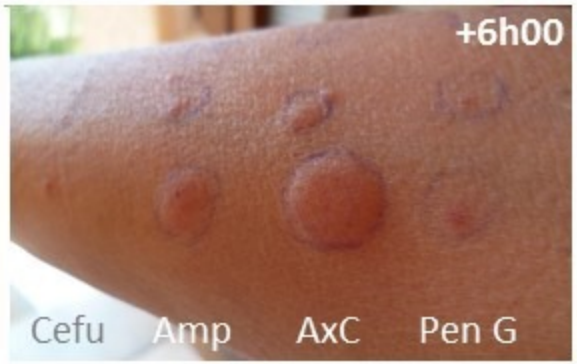
9. Haselden BM, Kay AB, Larché M. Immunoglobulin E-independent major histocompatibility complex-restricted T cell peptide epitope-induced late asthmatic reactions. J Exp Med. 1999;189:1885–94.

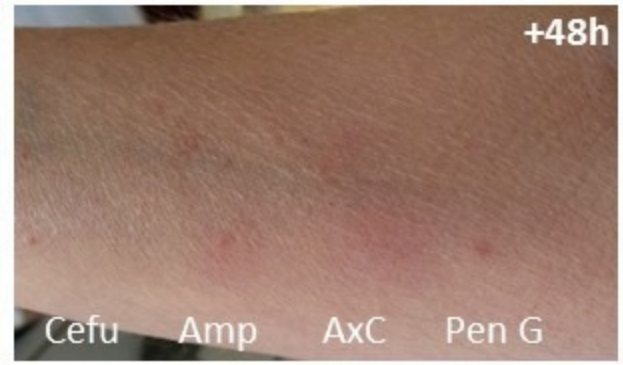
Table 1 - Characterization of Clinical Cases (on separate file)

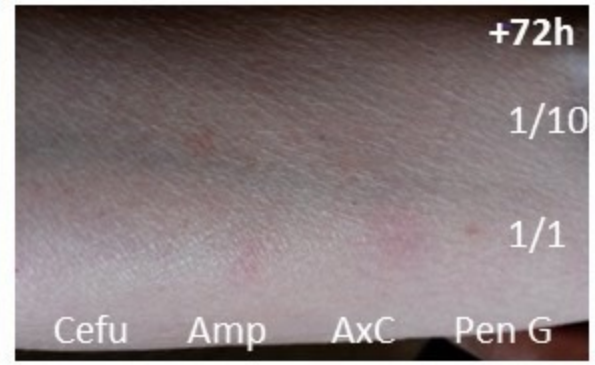
Figure 1 - Skin Test positive results in the 3 cases

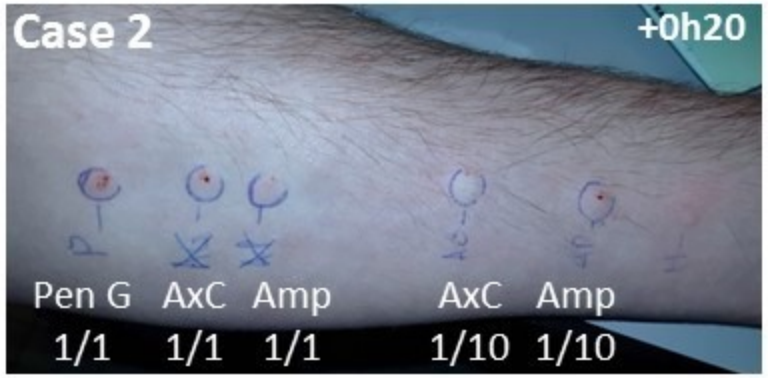
Legend: Skin test results in the 3 cases, on different time points, using the indicated drugs (penicillin G, Pen G; ampicilline, Amp; amoxicilline, Ax; amoxicillin clavulanic acid, AxC; cefuroxim, Cefu; cefazoline, Cefa) demonstrate late skin test positivity with a wheal-and-flare-like reaction for Amp and AxC in case 1; Pen G, AxC, Amp in case 2; and Cefa in case 3. The outer right picture in case 2 demonstrates an accompanying lymphangitis on day 3. ST were performed according to ENDA/DAIG recommendations[1] (maximal concentration (1/1) for Cefu 2 mg/mL; Amp 25 mg/mL; Ax 25 mg/mL; AxC 25 mg/mL of Ax; Pen G 10,000 IU/mL), except for benzyl penicilloyl-polylysine (PPL, e.g. PRE-PEN, ALK Abello, USA) and minor determinant mixture (MDM) associated with increased ST sensitivity for diagnosing penicillin allergy, that are not available in France and Cefa IDT at 30 mg/ml in case 3, being negative in 20 controls. Co-sensitization to clavulanic acid was deemed unlikely but testing for clavulanic acid alone is not available in France.

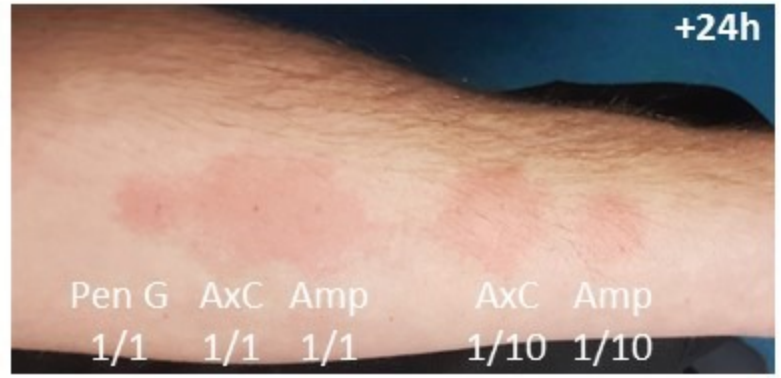

Case 1
+4h00
Cefu
Amp
AxC

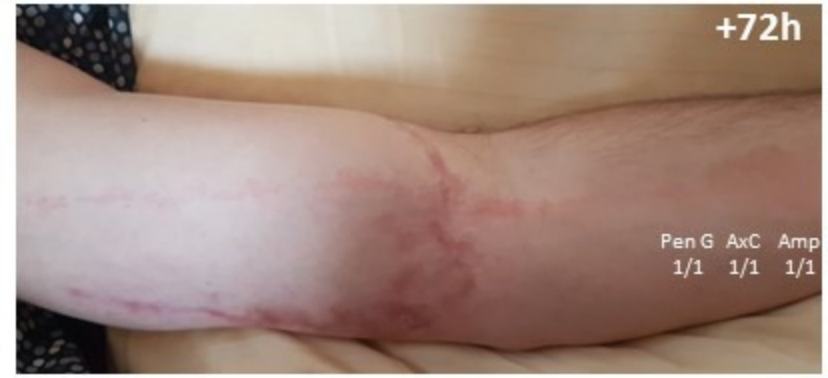

+6h00
Cefu
Amp
AxC
Pen G

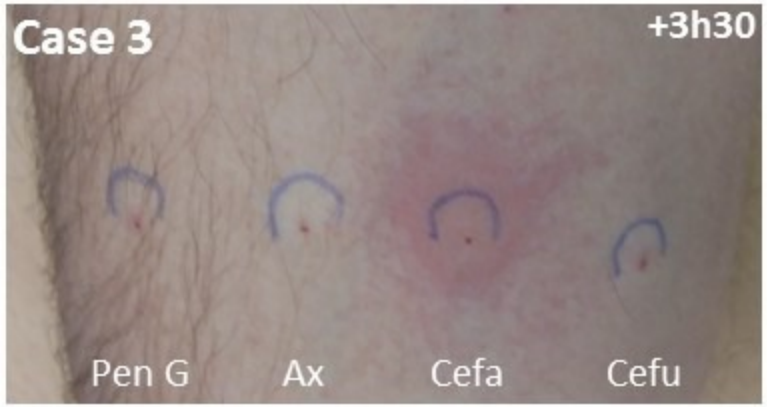

+48h
Cefu
Amp
AxC
Pen G

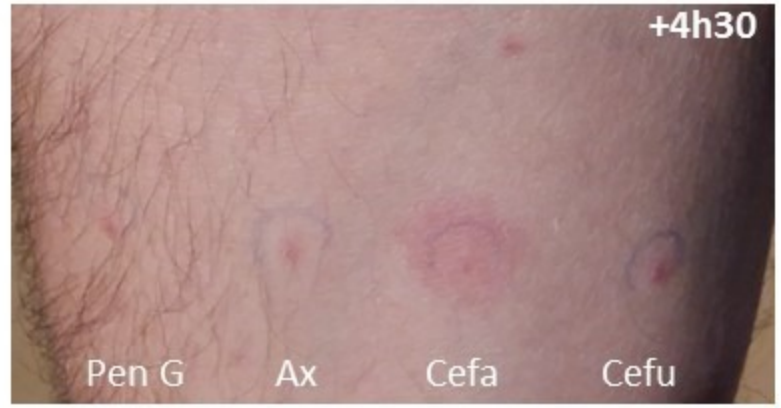

+72h
1/10
1/1
Cefu
Amp
AxC
Pen G

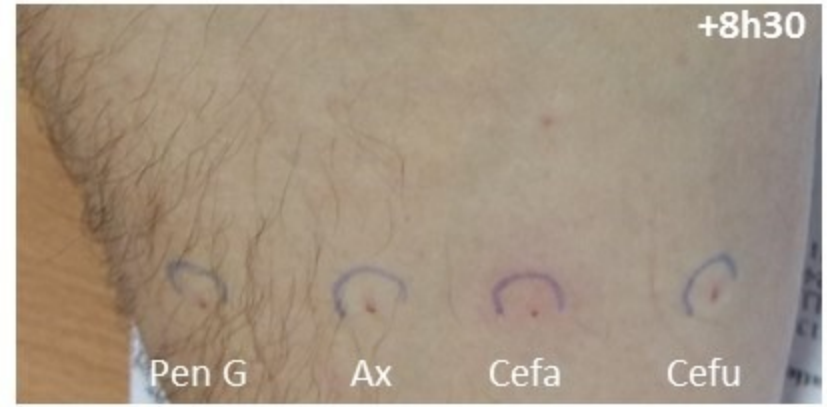

Case 2
+0h20
Pen G
AxC
Amp
AxC
Amp
1/1
1/1
1/1
1/10
1/10


+24h
Pen G
AxC
Amp
AxC
Amp
1/1
1/1
1/1
1/10
1/10


+72h
Pen G
AxC
Amp
1/1
1/1
1/1


Case 3
+3h30
Pen G
Ax
Cefa
Cefu


+4h30
Pen G
Ax
Cefa
Cefu


+8h30
Pen G
Ax
Cefa
Cefu

Case	Age, sex	Index reaction	Culprit (admi-nistration route)	Reaction interval	Reaction duration	Reaction treatment	Test interval	ST positivity*	Duration of ST positivity (start-end)	Tryptase acute (µg/L)	Tryptase baseline (µg/L)	Maintenance treatment(s)
#1	64, F	Anaphylaxis	AxC (po)	30 min	Short (Minutes – hours)	CS, adrenaline	4 we	Amp, AxC	4h – 4d	9.8	6.2	Infliximab, L-thyroxine
#2	26, M	Anaphylaxis	AxC (IV)	30 min after 2nd dose£	Short (Minutes – hours)	Nor-adrenaline	6 we	Amp, AxC, Pen G	24h – 5d	4.8	<1	None
#3	49, M	Generalized erythema	Cefa (IV)	1h30	Short (30 min)	CS, anti-H2	10 we	Cefa	3h30-8h30	ND	10.6	None

Table 1 - Characterization of Clinical Cases

Legend:

Abbreviations: ST, skin tests; AxC, amoxicillin clavulanic acid; Cefa, cefazoline; CS, corticosteroids; IV, intravenous; ND, not determined; po, per os; we, weeks;
* Skin test results were independently confirmed. £ It remains uncertain whether a 'first' dose was actually given (discordant recordings in emergency mobile unit, emergency department, and surgery unit concerning a first dose early before the event). Alternatively, a reaction after a first dose was missed due to co-administration of noradrenaline, or a delayed presentation of anaphylaxis with concordant late skin test positivity occurred, with unknown mechanism.