



# Immediate flare-up–like reaction of skin tests to betalactams with lymphangitis during drug provocation test

Maria de Filippo, Omar Ali Al Ali, Jean Luc Bourrain, Pascal Demoly, Anca Mirela Chiriac

## ► To cite this version:

Maria de Filippo, Omar Ali Al Ali, Jean Luc Bourrain, Pascal Demoly, Anca Mirela Chiriac. Immediate flare-up–like reaction of skin tests to betalactams with lymphangitis during drug provocation test. *Journal of Allergy and Clinical Immunology: In Practice*, 2021, 9 (2), pp.1021-1023.e1. 10.1016/j.jaip.2020.09.016 . hal-03338248

**HAL Id: hal-03338248**

**<https://hal.umontpellier.fr/hal-03338248>**

Submitted on 13 Feb 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

**Immediate flare-up-like reaction of skin tests to betalactams with lymphangitis during drug provocation test**

**DE FILIPPO Maria<sup>1,2\*</sup>M.D, AL ALI Omar<sup>1\*</sup> M.D, BOURRAIN Jean Luc<sup>1</sup> M.D, DEMOLY Pascal<sup>1,3</sup> MD-PhD, CHIRIAC Anca Mirela<sup>1,3</sup> MD-PhD**

<sup>1</sup> Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France;

<sup>2</sup> Department of Pediatrics, Policlinico San Matteo Pavia, Istituto di Ricovero e Cura a Carattere Scientifico, Italy;

<sup>3</sup> Equipe EPAR - IPLESP, UMR 1136 INSERM - Sorbonne Université, Paris, France

\* The authors contributed ex aequo.

Words: 1242

*\* Post publication corresponding author:*

Dr Anca Mirela CHIRIAC, a-chiriac@chu-montpellier.fr

Allergy Unit, Arnaud de Villeneuve Hospital, University Hospital of Montpellier

Address: 371, Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, Montpellier, France

Phone: +33 467336107

Conflict of interest: none

Beta-lactam (BL) antibiotics are the most common cause of drug-induced hypersensitivity reactions (DHR).

#### Clinical Implications:

We present two clinical cases of patients with suspected immediate BL DHR who underwent drug allergy work-up according to standardized diagnostic procedures, including skin tests (ST: prick, SPT and intradermal tests, IDT) and drug provocation tests (DPT)<sup>1</sup>. ST became positive after the first DPT dose. The patients gave their consent to the diagnostic allergy work-up and use of their de-identified data for research purposes.

A 68-year-old man placed on the liver transplantation waitlist for cirrhosis due to hepatitis C viral infection in August 2017 was admitted to the hospital for cholangitis. The patient was empirically treated with piperacilline/tazobactam (piperacillin 4g/t.i.d) intravenously. He had previously tolerated this drug. About 45 minutes after the first dose, he developed pruritus and urticaria on the neck and trunk without other associated symptoms. He rapidly recovered with cetirizine (10 mg) by oral route. In December 2018 the patient reported a similar episode, treated with intravenous dexchlorpheniramine. In June 2019, the patient underwent ST with several penicillin and cephalosporin reagents. Histamine was used as a positive control. As SPT and IDT at the highest recommended concentrations were negative when read after 15 minutes and 20 minutes respectively (according to current recommendations), we proceeded to DPT (the first dose was given 60 minutes after the IDT reading). Single-blind challenge with intravenous piperacilline/tazobactam was performed, with 30 minutes increments, starting with 5%<sup>2</sup> (200 mg) of the therapeutic dose (4000 mg) that elicited his initial reaction. A few minutes before the administration of the second dose the patient reported itching on the arms and scalp, in the absence of objective clinical signs. Therefore, we decided to interrupt the test and monitor the patient for 15 minutes. A few minutes later the patient presented a localized itchy erythema at the site of the ST corresponding to pure IDT to piperacillin/ tazobactam and piperacillin, with ascending lymphangitic infiltration (Figure 1). No wheal was observed. The ST was nonetheless considered positive, the DPT was interrupted and cetirizine (10 mg) was administered. Two hours after the administration of the first dose of the drug, the patient presented localized urticaria on the arms and the abdomen, with resolution in 90 minutes (see Figure E1 in the Online Repository).

A 62-year-old male patient, mentioned an episode of potential DHR in October 2012, with generalized urticaria, preceded by pruritus of palms and soles. This reaction started five minutes after the ingestion of 1000 mg amoxicillin for sinusitis, and during a meal containing shrimps. The allergy work-up was performed six weeks after the initial reaction. Skin tests (read at 20 min for IDT) were negative at the maximum recommended concentrations. As the patient had a history of immediate reaction, DPT with amoxicillin was started immediately after reading the skin tests. The began with 1 mg of amoxicillin (this was the first dose of the empirical DPT protocols that have been used in our unit till 2016). Thirty minutes after the first dose of amoxicillin, the patient presented a positive ST (> 3mm increase in the diameter compared to the injected wheal, surrounded by erythema) in IDT only at the site of amoxicillin injection, with a linear shape form and ascending lymphangitis 7.5 cm upward from the injection site (Figure 2). All the other ST were negative. The DPT was stopped immediately, he was treated with cetirizine (10 mg) and monitored for 90 minutes. No other symptoms appeared.

When negative immediate-reading ST occur in patients with a clinical history compatible with an immediate reaction (i.e., potentially IgE-mediated), a DPT is usually performed, in absence of contra-indications<sup>1</sup>. In the two cases we present, the first dose of the oral DPT was followed by ST positivity, associated in Case 1 with a systemic reaction (dose administered, 5% of initial eliciting dose). The peculiarity of the second case is that the patient developed a positive ST at 60 minutes, as opposed to 20 minutes following their performance and 30 minutes after the start of DPT without systemic symptoms (dose administered 0.1% of the initial eliciting dose). The absence of any systemic reaction in Case 2 may be due to the low initial dose.

ST reversal in these patients is likely due to a flare-up phenomenon. Flare-up reactions refer to the reactivation of previous positive ST or the switch from negative to positive ST, usually after a systemic challenge. This phenomenon is classically described in delayed-type allergy<sup>3</sup>. To the best of our knowledge, such rapid flare-up reactions have not been described for BL (published cases include delayed reactions)<sup>3,4</sup>, but case reports suggestive of a flare-up-like reactivity suggesting IgE-mediated allergy have been described for other drugs (e.g., ibuprofen<sup>5</sup>, paracetamol<sup>6</sup>).

In the two cases we present we observed localized superficial inflammation processes that induced linear in superficial lymphangitis from the site of the IDT of piperacillin and piperacillin/tazobactam (Case 1) and amoxicillin (Case 2), extending toward the arm. Lymphangitis is an inflammation of one or more lymphatic channels mostly induced by infections (mostly bacterial infections) occurring at the distal site of vessels. Many other causes could induce linear supralymphatic eruptions with superficial lymphangitis and some of these are viral and fungal

109 infections, insect or spider bites, and iatrogenic etiologies like vaccinations, purified protein  
110 derivative placement<sup>7</sup>. In a case series reported by Kano et al, three different cases which focus on  
111 the theme of superficial lymphangitis were discussed and the idea of the effect of contact allergens  
112 as a co-factor in this pathology was put forward. In their report, ST were negative for the alleged  
113 contact allergens and this is why they were merely considered as co-factors<sup>8</sup>. In our cases, the drugs  
114 are not contact allergens in the clinical history but injecting them by IDT may render them similar  
115 to a contact allergen. Most described cases of allergic lymphangitis concern delayed  
116 hypersensitivity reactions. Because dendritic cells are known to migrate from the sites of allergen  
117 exposure to draining lymph nodes during the inflammatory response, this hypothesis could explain  
118 why the linear lesions begin within the sites of IDTs and extend proximally to the draining lymph  
119 nodes, in delayed DHR. The two cases we presented revealed acute superficial lymphangitis, which  
120 raises the hypothesis of a local immunologic reaction to an allergen along lymphatic vessels,  
121 establishing a linear lesion overlying the skin. The promptness in onset and resolution of the lesions  
122 supports the assumption of this local reaction being elicited by mast cell mediator release, as  
123 connective tissue mast cells are located by nerve endings and alongside the blood and lymphatic  
124 vasculature<sup>9</sup>. Late-phase IgE-associated inflammatory responses to allergens cannot be excluded,  
125 considering that the reaction occurred later than classically observed in ST for immediate type  
126 reactions.

127 Although in Case 1, the reactive IDTs did not match the recommended positivity criteria (no wheal  
128 was detected, only surrounding erythema), in Case 2, the IDT became positive according to  
129 recommended reading criteria. In our experience, in more than 4000 patients tested for a suspicion  
130 of DHR to BL, these are the only two cases of their kind.

131 As clinicians working in the drug allergy field and operating with iatrogenic procedures (especially  
132 with BL antibiotics), we should be aware of rare cases. In these examples, monitoring the site of a  
133 negative ST (despite clinical histories of immediate reactions) even after reading the ST result  
134 within recommended lapses of time and when starting DPT prevented us from exposing our patients  
135 to higher doses of allergens and potentially a more severe reaction.

136

137 Funding: none

138

139

140

141

142

143

## BIBLIOGRAPHY

1. Romano A, Atanaskovic-Markovic M, Barbaud A, Bircher AJ, Brockow K, Caubet JC et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams - an EAACI position paper [published online ahead of print, 2019 Nov 21]. *Allergy*. 2019;10.1111/all.14122. doi:10.1111/all.14122
2. Chiriac AM, Rerkpattanapipat T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. *Allergy*. 2017;72(4):552-561.
3. Tramontana M, Hansel K, Bianchi L, Agostinelli D, Stingeni L. Flare-up of previously negative patch test and intradermal test with amoxicillin after oral provocation. *Contact Dermatitis*. 2018;79(4):250-251.
4. Reig Rincón de Arellano I, Villalón García AL, Cimarra Alvarez-Lovell M, Robledo Echarren T, Martínez-Cócerca MC. Flare up to betalactams. *Allergol Immunopathol (Madr)*. 2005;33(5):282-284. doi:10.1157/13080932
5. González de Olano D, González Mancebo E, Gandolfo Cano M, Menéndez Baltanás A, Trujillo Trujillo MJ. Flare-up-Like phenomenon in a skin prick test after oral challenge with ibuprofen. *J Investig Allergol Clin Immunol*. 2007;17(6):414-415.
6. Rodríguez-Fernández A, Sánchez-Domínguez M, Noguerado-Mellado B, Rojas-Pérez-Ezquerria P. Flare-Up Phenomenon of Intradermal Test with Anaphylactic Reaction to Paracetamol (Acetaminophen). *Recent Pat Inflamm Allergy Drug Discov*. 2019;13(1):69-72.
7. Cohen BE, Nagler AR, Pomeranz MK. Nonbacterial Causes of Lymphangitis with Streaking. *J Am Board Fam Med*. 2016;29(6):808-812.
8. Kano Y, Inaoka M, Shiohara T. Superficial lymphangitis with interface dermatitis occurring shortly after a minor injury: possible involvement of a bacterial infection and contact allergens. *Dermatology*. 2001;203(3):217-20.
9. Pal S, Nath S, Meininger CJ, Gashev AA. Emerging Roles of Mast Cells in the Regulation of Lymphatic Immuno-Physiology. *Front Immunol*. 2020;11:1234.

## Figure Legends

**FIGURE 1:** The following reagents were tested at the maximal non-irritant concentrations ("pure"): penicillin G (10 000 UI/ml, PG), amoxicillin/clavulanic acid (20 mg/ml for amoxicillin, Ag), ampicillin (20 mg/ml, Ap), piperacillin (20 mg/ml), piperacillin/tazobactam (20 mg/ml for piperacillin), cefuroxime (20 mg/ml, Z), ceftriaxone (20 mg/ml, C4).

**FIGURE 2:** Positive skin test to amoxicillin (20 mg/ml); the injected wheal is circled at the time of the performance of IDT; the increased wheal, erythema and lymphangitis occurred after 1 mg amoxicillin by oral route.

**FIGURE 1**



**FIGURE 2**

