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# Piperacillin-tazobactam anaphylaxis: a rare cause of occupational disease

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**Key words**

*anaphylaxis; beta-lactams; drug hypersensitivity; occupational diseases; piperacillin*

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***Summary***

*Piperacillin is a beta-lactam antibiotic of penicillin family. Some penicillins were reported as occupational diseases cause, but piperacillin anaphylaxis with occupational sensitization is rare. We describe the case of a female nurse with recurrent anaphylaxis in last few months without apparent cause, only in work environment. Latex allergy was excluded after negative latex glove provocation. Later during diagnostic workup, the patient reported a similar reaction minutes after piperacillin preparation. She denied any previous antibiotic therapeutic exposure. Skin prick tests (SPT) to beta-lactams were positive to piperacillin, penicillin G and major and minor determinants. SPT to cefuroxime was negative but intradermic test was positive. The patient has indication for beta-lactams eviction and for adrenaline auto-injector kit. No further reactions occurred after patient's transfer to another department with minimum possible exposure. Allergic risk prevention is essential and must be rapidly implemented to avoid incapacitating occupational diseases development.*

## Introduction

Anaphylaxis is a rapid-onset, multisystem hypersensitivity reaction with potentially fatal outcome (1). Clinically, anaphylaxis most frequent manifestations are cutaneous; however, respiratory, cardiovascular, gastrointestinal, and other symptoms may also occur (1). Drug-induced anaphylaxis (DIA) hypersensitivity mechanism is mainly an IgE-mediated response, but others have been characterized (1). Penicillin was in the past DIA most frequent cause, but was recently surpassed by amoxicillin (1). Healthcare professionals (HCP) are exposed to a large number of substances that act as allergens and/or irritants (2). These allergenic substances were known to cause contact dermatitis, but nowadays a wide spectrum of clinical manifestations like asthma, rhinitis, conjunctivitis and anaphylaxis is also included (2).

Piperacillin is an extended-spectrum beta-lactam antibiotic of the ureidopenicillin family, commonly used in combination with tazobactam, a beta-lactamase inhibitor. Some penicillins have been reported to cause occupational diseases (3-7), but only one case of piperacillin anaphylaxis with occupational sensitization has been described, and the diagnosis was only supported by serum IgE antibody detection (8). The authors describe the first case report of piperacillin anaphylaxis with occupational sensitization and diagnosis confirmed by skin tests.

## Case report

A 28 year-old female nurse, with previous rhinitis history, was referenced to our outpatient clinic due to, in the last few months, recurrent episodes of generalized pruritus and cuta-

neous erythema, face swelling, chest urticarial papules, cough, dyspnea, wheezing and sometimes abdominal pain without apparent cause. The patient worked in the internal medicine ward for 5 years, and episodes were only work-environment related, excluding similar home episodes. These clinical manifestations usually resolved minutes after hydrocortisone intravenous administration. As other allergic diseases, the patient reported hand contact dermatitis with latex gloves. Patch testing previously performed in the dermatology department found a methylchloroisothiazolinone sensitization. The patient used only nitrile gloves, although latex gloves were used in the ward. In the first appointment the patient denied any association between the manifestations and food, drugs or latex exposure. She also denied previous surgeries, food or drug allergy and any previous antibiotic therapeutic exposure. Her parents also confirmed this last fact. Skin prick tests (SPT) identified sensitization to aeroallergens. Due to patient's occupation and work-environment involvement, a detailed latex allergy investigation was performed, including a latex glove provocation procedure that was negative. Due to diagnosis absence, the patient was instructed to register all possible triggers, and an adrenaline auto-injector kit was prescribed. Two months later, a similar reaction occurred minutes after piperacillin-tazobactam preparation in work context. The patient reconfirmed that she was never treated with any antibiotic and had no accidental administration of this or other drug. Beta-lactams SPT, including piperacillin-tazobactam, were positive to piperacillin-tazobactam (2.5 mg/mL), penicillin G and major and minor determinants. SPT to cefuroxime was negative, but intradermic test was positive (2.5 mg/mL). Available beta-lactams specific IgE determinations were all negative: amoxicillin, ampicillin, penicillin G and penicillin V. The patient has now indication for beta-lactams eviction. After the diagnosis the patient was transferred to the nuclear medicine department to minimize beta-lactams exposure risk and since then no further reactions occurred.

**Discussion**

Patient's clinical manifestations can be classified as moderate anaphylaxis (9), and as occupational anaphylaxis as the triggers and conditions are only work-environment related (10). This case illustrates how a detailed history is essential in drug allergy workup (11), although drug provocation test (DPT) is the diagnostic "gold standard" due to its finest sensitivity (12). In this patient DPT was not performed, but occupational anaphylaxis diagnosis can be established based in the temporal relationship between piperacillin handling and manifestations, the piperacillin positive SPT (13) and the absence of exposure other than preparation handling. For immediate IgE-mediated hypersensitivity reactions, the presence of drug-specific IgE is usually taken as sufficient diagnostic evidence (11,13). Specific IgE *in vitro* assays are available, although most are not adequately validated (11). We used a validated and indicated *in vivo* methodology (14) and this may be a strength of our study compared to the previously published similar case (8). There is clinically significant cross-reactivity between penicillins, and much less or possibly no clinically significant cross-reactivity between specific penicillins, cephalosporins, and other non-penicillin beta-lactams (15). Piperacillin shares the beta-lactam ring with ampicillin, amoxicillin and cloxacillin (16) and so these antibiotics must be avoided in this patient. The sensitization found to cefuroxime may represent a co-sensitization also due to exposure, or might be associated to beta-lactams cross-reactivity. The clinical relevance of cefuroxime sensitization should be evaluated by DPT. Carbapenems and monobactams are also safely used in individuals with confirmed penicillin allergy (15) and may constitute another alternative.

In this case, sensitization was probably due to occupational nontherapeutic exposure to antibiotics. It can occur by various routes, and contact with spilled drugs and powder or foam inhalation are the most common (4). Cutaneous sensitization is often fast, in weeks or months (2), and was probably enhanced in this patient by a damaged skin barrier leading to local and systemic immune responses (17). Clearly identified risk factors for drug-induced anaphylaxis, like female sex or concurrent medications, do not include professional exposure (1), although some studies point out that HCP seem to have an increased risk of penicillin allergy (18,19). Lifelong avoidance of the drug and cross-reactive drugs is recommended when drug-induced anaphylaxis has occurred (13).

Piperacillin is provided as a powder, and should be dissolved prior to administration. This antibiotic preparation generates more aerosolization than other intravenous antibiotics (8). This patient had anaphylaxis without direct drug contact, suggesting that piperacillin inhalation may be another major route of sensitization or symptoms trigger.

One possible limitation of this case report is the relative uncertainty about sensitization route, although both patient and parents denied recent and frequent therapeutic exposures, as well as in remote past. This question was several times reconfirmed and this is a strength compared to the previously published report where occupational sensitization was assumed only based in occupational exposure (8).

Technical prevention is based on risk elimination, possibly replacing products or substances responsible for allergic manifestations to non-sensitizing agents (2). Allergic risk prevention is essential, and must be rapidly implemented to prevent incapacitating occupational diseases. The authors describe the case report of a health care professional that developed beta-lactams allergy in the context of occupational exposure.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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