## Immunoglobulin E–Mediated Severe Anaphylaxis to Paclitaxel

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Key words: Paclitaxel hypersensitivity reactions. Macrogolglycerol ricinoleate. Skin tests. Dot-blot assay.

Palabras clave: Reacciones de Hipersensibilidad a paclitaxel. Ricinoleato de macrogolglicero. Prueba cutánea. Dot-blot.

Immediate hypersensitivity reactions to taxanes have been related to nonspecific mediator release from mast cells. While the excipient macrogolglycerol ricinoleate has been implicated in complement or mast cell activation, an immunoglobulin (Ig) E-mediated mechanism has never been demonstrated.

We report the case of a 49-year-old woman with a history of isocyanate-induced occupational asthma who presented with an enlarged supraclavicular lymph node identified as a poorly differentiated adenocarcinoma. The patient was started on carboplatin and paclitaxel and tolerated the first cycle well. During the second cycle, however, a few seconds after starting paclitaxel infusion, she presented dizziness, flushing, dyspnea, desaturation, hypotension, and collapse requiring orotracheal intubation. Carboplatin was not administered. Intravenous premedication with granisetron, ranitidine, methylprednisolone, and dexchlorpheniramine was used. The paclitaxel administered was Paclitaxel Teva (Teva Genéricos Española S.L., Madrid, Spain), which contains macrogolglycerol ricinoleate.

The allergy study performed 1 month later in the intensive care unit included skin tests consisting of prick and intradermal (ID) tests with Paclitaxel Teva (6 mg/mL/0.0001-1 mg/mL), carboplatin (10mg/mL/0.001-1 mg/mL), ranitidine (10mg/mL/0.01mg/mL), granisetron (1 mg/mL/0.01 mg/mL), methylprednisolone (20 mg/mL/2 mg/mL), and a latex skin prick test. The results were positive only for Paclitaxel Teva (ID, 0.0001 mg/mL). Fifteen control patients with cancer and previous adverse reactions to paclitaxel had negative skin tests. Controlled challenge tests were negative for ranitidine, granisetron, methylprednisolone, and dexchlorfeniramine.

Paclitaxel and macrogolglycerol ricinoleate (in powder and petrolatum, respectively) were supplied separately by Teva Genéricos Española S.L. Serum specific-IgE analysis of the 2 products was performed using an IgE dot-blot assay (Bio-Rad, Hercules, California, USA) according to the manufacturer's instructions, with 53 mg of paclitaxel reconstituted in 500 µL of dimethyl sulfoxide (Sigma-Aldrich, Madrid, Spain) and unmodified macrogolglycerol ricinoleate. A polyvinylidene fluoride transfer membrane was used. Serum was applied with a blocking buffer (phosphate buffered saline containing 1% bovine serum albumin and 0.05% Tween, 1:1 v/v). The antibody was a mouse anti-human IgE (Fc) HRP (Southern Biotech) and the Western Lightning Plus-ECL system (PerkinElmer Life and Analytical Sciences, Shelton, Connecticut, USA) was used as substrate. The results were positive for paclitaxel and negative for macrogolglycerol ricinoleate (Figure).

The patient was changed to an alternative chemotherapy regimen with cisplatin and gemcitabine, with good tolerance and complete response. Taxanes have been avoided. As a challenge test was not carried out with macrogolglycerol ricinoleate, the patient was instructed to avoid drugs containing this excipient (a list was supplied).

Paclitaxel-related immediate hypersensitivity reactions occur in up to 30% of patients, with this percentage decreasing to under 10% with the administration of antihistamine and corticosteroid premedication [1-3]. Most reactions occur within the first few minutes of infusion, usually after the first or second dose, indicating that prior sensitization is not necessary. For this reason these reactions are thought to be non-IgE mediated [1-4]. Macrogolglycerol ricinoleate has also been implicated in anaphylactic reactions on the basis that it can induce complement activation, giving rise to anaphylotoxins that trigger mast cells and basophils for a secretory response [5].

The use of premedication and/or the slowing of infusion rates are effective but not always successful [6]. A safe and effective standardized protocol for rapid drug desensitization

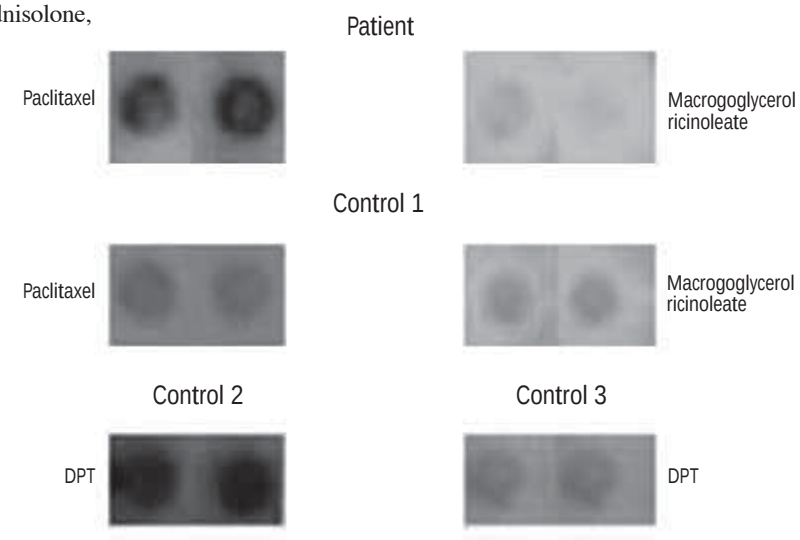


Figure. Immunoglobulin E dot-blot assay. The patient's serum was positive to paclitaxel and negative to macrogolglycerol ricinoleate. Serum from a nonallergic patient was used as a negative control (control 1). Other controls were performed using *Dermatophagoides pteronyssinus* (Dpt) extract, the serum from a patient allergic to Dpt (control 2, positive), and the serum from a nonallergic patient (control 3, negative).

has been reported [2,3]. Both IgE-mediated and non-IgE–mediated immediate hypersensitivity reactions of any severity are amenable to rapid desensitization.

We have presented an exceptional case of an IgE-mediated reaction to paclitaxel, the first such case to be reported to the best of our knowledge. The reaction, which was severe and produced with a minimum dose, occurred with the second exposure (the first cycle was well tolerated). These data suggest a type I hypersensitivity reaction, although most paclitaxel-induced immediate hypersensitivity reactions reported have the same characteristics and an IgE-mediated mechanism has never been demonstrated.

In our patient we proved this IgE-mediated mechanism using skin and in vitro tests. Although skin tests are assumed to be negative in taxane-induced immediate hypersensitivity reactions, there are few reports of skin test results following such reactions [7].

Our patient has a background of atopy, which has been identified as a risk factor for the development of hypersensitivity reactions to chemotherapeutic drugs [3].

Lastly, we recommend performing skin tests in patients with immediate hypersensitivity reactions to taxanes, especially in the case of very severe reactions, if a previous dose has been tolerated and in patients with a history of atopy since an IgE-mediated mechanism is also possible.

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## Nonirritating Concentration for Skin Testing With Cephalosporins

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Key words: ß-Lactams. Cephalosporins. Diagnostic skin tests. Nonirritating concentration.

Palabras clave: Betalactámicos. Cefalosporinas. Pruebas cutáneas diagnósticas. Concentración no irritativa.

Although diagnostic skin tests with cephalosporins are still considered experimental because of unknown hapten determinants, skin testing is a useful tool in evaluating immediate and delayed reactions to these ß-lactams [1]. Skin testing with drugs should be performed using the highest concentration of drug that does not elicit an irritant skin test response in an adequate number of healthy control individuals. While there is agreement on nonirritating concentrations for penicillin tests, the same cannot be said for cephalosporins.

Empedrad et al [2] recommend performing skin prick and intradermal tests using a concentration of 10 mg/mL for cefotaxime, cefuroxime, ceftazidime, and ceftriaxone and of 33 mg/mL for cefazolin. The concentration recommended for prick and intradermal tests by Torres et al [3] and later by Blanca et al [4] for cephalosporins in general was 1 to 2 mg/mL and 2 mg/mL, respectively.

The aim of the present study was to ascertain if 20 mg/mL can be considered a nonirritating concentration for intradermal skin tests for cephalosporins.

We have been performing diagnostic skin prick and intradermal tests for ß-lactams at our center since 1988 with benzylpenicilloyl-poly-L-lysine (PPL) ($5 \times 10^{-5}$mMol/L), minor determinants mixture (MDM) ($2 \times 10^{-2}$mMol/L), benzylpenicillin (10 000 IU/mL), amoxicillin-clavulanic acid (20 mg/mL), and cefuroxime (20 mg/mL). We also use this concentration of 20 mg/mL for all other cephalosporins

and ß-lactams that are occasionally tested when they are suspected to be the cause of an adverse reaction. Before using these concentrations in routine testing, we tested 10 healthy controls, beginning with the full-strength concentration and continuing with 10-fold dilutions until we found the non-irritating concentration.

All the reagents were freshly prepared immediately before testing. Positive and negative controls were performed with histamine (10 mg/mL) for prick tests and normal saline for intradermal tests following procedures described in the literature [5].

We reviewed the information recorded in our database between January 2000 and June 2009 and report relevant findings (Table).

Table Skin Tests with Cephalosporins at a Concentration of 20 mg/mL

| | | |
|---|---|---|
| Nonirritating | | |
| 215 patients | Cefuroxime | Second-generation cephalosporin |
| 31 patients | Ceftriaxone | Third-generation cephalosporin |
| 24 patients | Cefotaxime | Third-generation cephalosporin |
| 24 patients | Ceftazidime | Third-generation cephalosporin |
| 5 patients | Cefazolin | First-generation cephalosporin |
| Irritating | | |
| 7 control subjects | Cefepime | Fourth-generation cephalosporin |

In our experience, all the cephalosporins tested, with the exception of cefepime (together with the ß-lactam aztreonam), can be used at a concentration of 20mg/mL in skin tests. These 2 ß-lactams are the only ß-lactams in Italy that contain L-arginine in lyophilized powder form, and in neither case is the concentration specified in the product information. We found that a concentration of 20 mg/mL of both cefepime and aztreonam was irritating for all the controls, perhaps because of the presence of L-arginine. The final concentration used for testing was 2 mg/mL, a concentration still used at our center.

Our review of the database showed that skin prick and intradermal tests at a concentration of 20 mg/mL were not irritating for some cephalosporins. The use of such a concentration would increase the sensitivity of the tests and help to diagnose patients who would otherwise yield negative results.

At the current stage of our investigation we can say that some cephalosporins are not irritating at a concentration of 20 mg/mL, but this probably does not apply to all members of the family. We intend to continue with our research in this area, although for less common cephalosporins we will need to combine results from several centers.

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## Specific Immunoglobulin E as a Valuable Parameter to Minimize the Risk of Anaphylactic Reactions During in Vitro Fertilization

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Key words: Anaphylaxis. Insemination. Bovine serum albumin. Epithelium sensitization.

Palabras clave: Anafilaxis. Inseminación artificial. Seroalbúmina bovina. Sensibilización a epitelios.

Anaphylaxis is an umbrella term for an acute reaction involving a severe, life-threatening and generalized or systemic hypersensitivity reaction. The term *allergic anaphylaxis* should be used when the reaction is mediated by an immunological mechanism; i.e., one that is immunoglobulin (Ig) E-, IgG- and/or immune complex/complement-related. An anaphylactic reaction mediated by IgE antibodies may be referred to as IgE-mediated allergic anaphylaxis, and anaphylaxis from any

 

nonimmunological source should be referred to as nonallergic anaphylaxis [1]. These reactions may occur after ingestion, skin contact, injection, or inhalation of causative substances.

Anaphylaxis is a nonreportable disease, and its morbidity and mortality are probably underestimated [2]. There are certainly no exhaustive data regarding the incidence of anaphylaxis, and estimates are disparate. The discrepancies could be due to underreporting, and differences in the case definition of anaphylaxis, evaluation tools used to analyze populations, and/or the causative agents involved. Taking into account the last parameter, the need to define new or rare causative agents of anaphylaxis and thorough investigation of their etiopathologies is essential.

In this regard, bovine serum albumin (BSA) is a well-known cause of anaphylaxis, and its relationship with allergy to animal epithelia is an emergent concept.

To the best of our knowledge, only 6 cases of severe anaphylactic reactions due to BSA after standard intrauterine insemination or in vitro fertilization (IVF) have been reported [3-8]. The anaphylactic reactions are extensively described and the identification of BSA as a causative agent of anaphylaxis is unquestionable. These studies have demonstrated IgE-mediated hypersensitivity to BSA and polyvalent atopic sensitization to animal dander. They reported that the reaction to BSA could be caused by cross-reactivity with serum albumins contained in heterologous allergenic sources.

Although information is scarce, the indisputable demonstration of BSA as the trigger of anaphylactic reactions and its relationship to prior animal epithelium sensitization makes it necessary to define this protein as an important risk factor and to quantify the risk of anaphylactic reactions in women undergoing IVF or artificial insemination (AI).

Gaig et al [9] estimated the prevalence of allergy to animal epithelia in the Spanish female population to be 2%. Studies by our group have revealed that 10% of all individuals sensitized to animal (cat and dog) dander exhibit specific IgE reactivity to BSA (personal data). This means that 2 out of every 1000 women that undergo IVF or AI are theoretically at risk of developing anaphylactic reactions due to BSA. Considering the data published by Marqueta et al [10], where a total of 53000 cases of IVF and AI were registered in 2004, more than 100 women per year are at risk of anaphylactic reactions due to BSA in Spain.

It is likely that the same reasoning can be applied to other countries, thus significantly increasing the total number of women at risk of developing anaphylaxis during IVF or AI. Thus, a history of anaphylaxis and/or atopic diseases is the most consistent determinant risk factor, where the investigation of mammal epithelia and serum albumin sensitizations is unavoidable. Sensitization to different mammalian serum albumins contained in animal epithelia, and the high level of cross-reactivity demonstrated between them, explains the development of anaphylaxis to BSA in such cases.

Considering that prevention is a major issue in anaphylaxis, and that molecular diagnosis is an accurate technique for minimizing the risk of allergic reactions due to BSA during IVF or AI, an exhaustive and accurate preoperative history of allergy with specific IgE testing against animal dander and serum albumins is highly recommended, especially in women who have a history of allergy to animal epithelia.

This is a prime example of a clinical situation in which in vitro measurement of IgE can be helpful to evaluate sensitization versus the risk of anaphylaxis.

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## Cinitapride-Induced Exanthema

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Key words: Allergy. Cinitapride. Hypersensitivity. Orthopramides. Exanthema.

Palabras clave: Alergia. Cinitaprida. Hipersensibilidad. Ortopramidas. Exantema.

Cinitapride is an orthopramide (Figure) with prokinetic activity in the gastrointestinal tract and high procholinergic activity. It also exhibits serotoninergic activity secondary to blockade of presynaptic serotonin receptors and low antidopaminergic activity [1]. It has low toxicity and high therapeutic levels in patients with gastroesophageal reflux disease. In the last few years it has been widely used as a substitute for cisapride, after potentially serious arrhythmias were observed [2].

We present the case of a 76-year-old man referred to our department by the gastroenterology service with a diagnosis of gastroesophageal reflux disease, for which domperidone (Motilium, Laboratorios Esteve, Spain) and cinitapride (Cidine, Almirall Prodes, Spain) were prescribed. After 10 days taking both drugs simultaneously, he complained of itching and rash in the scrotal region, groins, and popliteal fossa, with edema and erythema on the penis. He stopped using the drugs and was admitted to the emergency room of our hospital, where he was treated with topical corticosteroids. The symptoms resolved completely in 7 days.

The patient denied personal or familial atopy. He was sent to our allergy department where he underwent prick tests with cinitapride (0.2 mg/mL saline solution), domperidone (2 mg/mL saline solution), and other orthopramides, such as clebopride (0.1 mg/mL saline solution), and metoclopramide (2 mg/mL saline solution). The results were negative.

Patch tests performed in 10% pet with cinitapride, domperidone, clebopride, and metoclopramide gave negative results at 48, 72, and 96 hours. The patient therefore gave his consent for a challenge test. A single-blind placebo-controlled drug challenge performed with 10 mg domperidone was negative, and the patient was prescribed a tablet every 8 hours for 5 days, which he tolerated. He was later given 1 cinitapride pill in our department (1 mg) and was prescribed this agent every 8 hours for 5 days. Five days later the patient came to our department with rash and itching on the neck, groins, and scrotal region, and papuloerythematous lesions on the palate. He was administered oral antihistamines, and symptoms disappeared after a few days.

There are few reports of hypersensitivity reactions to prokinetic drugs, and even fewer of immunoglobulin (Ig) E–mediated allergy: 1 case of IgE-mediated allergy to metoclopramide [3], 1 case of metoclopramide-induced nonthrombocytopenic purpuric rash [4], and 1 case of anaphylaxis after ingesting cisapride, with the excipient mannitol as the cause of the reaction [5].

This is the first report of hypersensitivity to cinitapride. Although the patient can tolerate other orthopramides, we were unable to determine the mechanism involved in this case of delayed hypersensitivity.

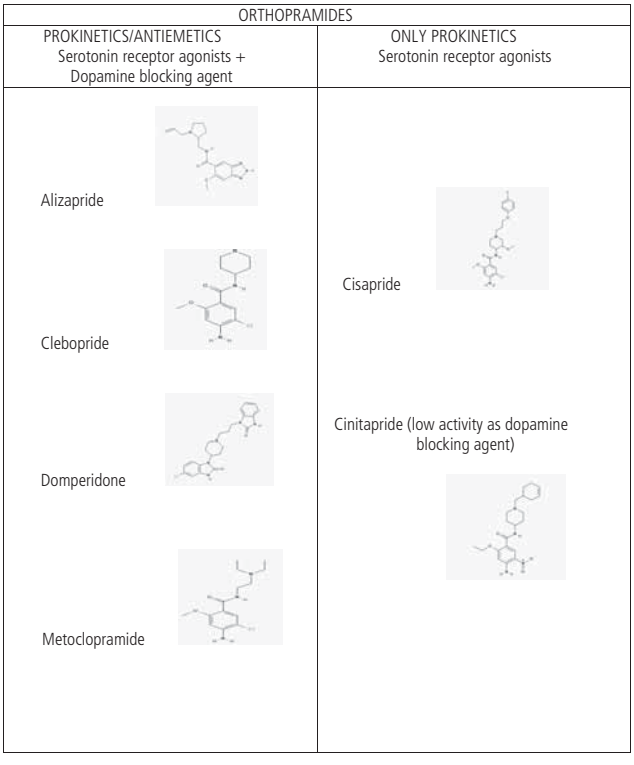


Figure. Classification of the orthopramides.

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## ß-Lactam Hypersensitivity: From Guidelines to Daily Practice

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Key words: ß-Lactam hypersensitivity. Skin tests. Specific IgE. Drug provocation test.

Palabras clave: Hipersensibilidad de betalactámicos. Pruebas cutáneas. IgE específica. Prueba de provocación con fármacos.

ß-lactams are a leading cause of allergic drug reactions. Several clinical entities have been described and are commonly classified as immediate reactions and nonimmediate reactions, the former occurring within the first hour of drug intake and the latter more than 1 hour after intake [1,2]. The diagnostic approach to ß-lactam allergy should include a detailed clinical history, skin tests, and provocation tests according to the guidelines of the European Network on Drug Allergy (ENDA) [3,4].

The aim of this study was to analyze the value of the diagnostic algorithm proposed by ENDA when approaching hypersensitivity reactions to ß-lactams in daily practice.

The study population comprised patients who presented at our allergy outpatient clinic from January 2006 to December 2008 with suspected hypersensitivity reactions to ß-lactams based on a detailed clinical history. Each patient underwent determination of specific immunoglobulin (Ig) E (ImmunoCAP, Phadia, Uppsala, Sweden) to available ß-lactams (penicillin G, ampicillin, amoxicillin, cefaclor) and skin tests to penicilloyl polylysine, minor determinant mix (Diater, Madrid, Spain), penicillin G, amoxicillin, cefuroxime, and the suspected culprit ß-lactam. Histamine (10 mg/mL) was used as a positive control for prick tests and 0.9% saline solution as a negative control for prick and intradermal tests. Skin prick tests were carried out first and, if negative, intradermal tests were performed with an immediate reading (20 min) and a late reading (72 h). If these were negative, a provocation test was carried out with the culprit drug. Open challenge was performed under hospital surveillance (at least 6 h) and was considered positive if a similar clinical reaction occurred.

We included 110 patients (75% women, mean [SD] age 47 [17] years), of whom 43% reported urticaria, 23% maculopapular exanthema, 13% anaphylaxis, and 7% other symptoms. In 14% of cases, patients were unable to define the symptoms. Most patients (64%) reported a nonimmediate reaction and only 36% reported an immediate reaction. The median (interquartile range [IQR]) delay between the reaction and the investigation was 24 months (12-108 mo).

ß-Lactam allergy was confirmed in 48 patients (44%): 56% reported cutaneous symptoms, 19% anaphylaxis, and 19% had no firsthand recall of the reaction. The diagnosis was established by positive results for specific IgE (19%, n=9), skin testing (71%; n=34), or drug provocation testing (10%, n=5) (Table).

Among the 9 patients with positive IgE results to ß-lactams, 5 reported an immediate reaction and 4 a nonimmediate reaction (all from 1 to 6 h after intake), and the median (IQR) delay between the reaction and the test was 12 months (3-24 mo).

Of the 34 patients with positive skin test results, 23 (68%) were to penicillins only, 1 (3%) to cephalosporins only, and 10 (29%) had positive results to both. Twenty had a history of immediate reactions and they all had a positive intradermal test result at 20 minutes. Fourteen patients had a history of nonimmediate reactions: 12 reported symptoms between 1 and 6 hours after drug intake and had a positive intradermal test result at 20 minutes; 2 reported symptoms between 6 and 72 hours after drug intake and had a positive intradermal test result at the late reading.

The risk of a positive challenge after negative skin tests was 7% (n=5): 1 patient reported an immediate reaction and experienced anaphylaxis on challenge that was promptly resolved with standard procedures; 4 reported a nonimmediate reaction and had maculopapular exanthema when provoked (median exposure of 72 h).

In a significant proportion of the population, allergy to ß-lactams was confirmed, mostly as IgE-mediated hypersensitivity (by positive specific IgE or an immediate positive intradermal test result). There was a good correlation between a history of immediate reaction and diagnosis of IgE-mediated hypersensitivity. On the other hand, even though most patients reported nonimmediate reactions to ß-lactams, only 2 positive intradermal reactions occurred at the late reading and 4 nonimmediate reactions occurred with the drug provocation test. Analysis of the chronology of nonimmediate reactions revealed that those occurring within 6 hours of exposure had a higher prevalence of IgE-mediated hypersensitivity. Patch testing could provide greater insight into the mechanism of drug hypersensitivity involved.

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Table. Results of Diagnostic Procedures in Patients With Confirmed Allergy to ß-Lactams[a]

| Patients (n=48) | Culprit Drug | Adverse Reaction | | | | Specific IgE, >0.1 $kU_A/L$ | Skin Tests | | | DPT | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IR | NIR | | | | Prick | ID | | | |
| | | <1 h | 1-6 h | 6-72 h | >72 h | | | 20 min | 72 h | I | NIR |
| 1 | BP | | UA | | | – | – | BP+, C+ | – | NA | NA |
| 2 | AP | | UA | | | BP+ | – | C+ | – | NA | NA |
| 3 | AP | A | | | | BP+, AP+ | – | C+ | – | NA | NA |
| 4 | AP | UA | | | | – | – | BP+, C+ | – | NA | NA |
| 5 | AP, C | UA | | | | – | – | BP+, C+ | – | NA | NA |
| 6 | AP | | UA | | | – | – | BP+, C+ | – | NA | NA |
| 7 | BP | UA | | | | – | – | BP+, C+ | – | NA | NA |
| 8 | AP | | UA | | | – | – | BP+, C+ | – | NA | NA |
| 9 | BP | UDS | | | | – | – | BP+, C+ | – | NA | NA |
| 10 | BP | A | | | | – | – | BP+, C+ | – | NA | NA |
| 11 | AP | UA | | | | – | – | BP+, C+ | – | NA | NA |
| 12 | AP | | | MPE | | – | – | – | BP+, C+ | NA | NA |
| 13 | AP, C | A | | | | – | – | BP–, AP– | – | AP+ | |
| 14 | AP | | | MPE | | – | – | BP–, AP– | – | AP– | AP+ |
| 15 | C | A | | | | – | – | BP–, AP–, C+ | – | AP– | – |
| 16 | AP | | UA | | | – | – | BP–, AP+, C– | – | C– | – |
| 17 | BP | UA | | | | – | – | BP+, AP– | – | AP– | – |
| 18 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |
| 19 | AP | UA | | | | – | – | BP+, C– | – | C– | – |
| 20 | AP | | UA | | | – | – | BP–, AP+, C– | – | C– | – |
| 21 | AP | UA | | | | BP+ | – | C– | – | C– | – |
| 22 | AP | UA | | | | – | – | BP–, AP+, C– | – | C– | – |
| 23 | AP | UA | | | | – | – | BP–, AP+, C– | – | C– | – |
| 24 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |
| 25 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |
| 26 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |
| 27 | AP | | | MPE | | – | – | BP–, AP– | – | AP– | AP+ |
| 28 | AP | | UA | | | – | – | BP+, C– | – | C– | – |
| 29 | AP | | | MPE | | – | – | – | BP+, C– | C– | – |
| 30 | AP | | UA | | | – | – | BP–, AP+, C– | – | C– | – |
| 31 | AP | | UA | | | – | – | BP+, C– | – | C– | – |
| 32 | BP | A | | | | – | – | BP+, C– | – | C– | – |
| 33 | AP | | UA | | | BP+, AP+ | – | C– | – | C– | – |
| 34 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |
| 35 | AP | | UA | | | – | – | BP–, AP–, C– | – | AP–, C– | AP+ |
| 36 | AP | A | | | | BP–, AP+ | – | BP–, C– | – | C– | – |
| 37 | AP | | UDS | | | – | – | BP+, C– | – | C– | – |
| 38 | BP | A | | | | – | – | BP+, C– | – | C– | – |
| 39 | AP | A | | | | BP+, AP+ | – | C– | – | C– | – |
| 40 | BP | | UA | | | – | – | BP+, C– | – | C– | – |
| 41 | AP | A | | | | BP+, AP+ | – | C– | – | C– | – |
| 42 | AP | | UA | | | – | – | BP+, C– | – | C– | – |
| 43 | AP | | | MPE | | – | – | BP–, AP– | – | AP– | AP+ |
| 44 | AP | UA | | | | – | – | BP–, AP+, C– | – | C– | – |
| 45 | AP | | UA | | | – | – | BP+, C– | – | C– | – |
| 46 | AP | | UA | | | BP+ | – | C– | – | C– | – |
| 47 | BP | | UA | | | BP+ | – | C– | – | C– | – |
| 48 | BP | UDS | | | | – | – | BP+, C– | – | C– | – |

Abbreviations: A, anaphylaxis; AP, aminopenicillins (amoxicillin; amoxicillin-clavulanate; ampicillin); BP, benzylpenicillins (penicillin G/V, minor determinant mixture/penicilloyl-polylysine); C, cephalosporins; DPT, drug provocation test; IR, immediate reaction; ID, intradermal test; Ig, immunoglobulin; MPE, maculopapular exanthema; NA, not applicable; NIR, nonimmediate reaction; UA, urticaria/angioedema; UDS, unable to define symptoms.

[a]Highest concentrations used (mean of each component): amoxicillin-clavulanate, 20 mg/mL; benzylpenicillin, 25 000 IU/mL; cephalosporin, 2 mg/mL; minor determinant mixture, 1.5 mmol/L; penicilloyl polylysine, $1.07 \times 10^{-2}$ mmol/L.