

ANTIBIOTIC ALLERGY

S. CAIMMI¹, D. CAIMMI², E. LOMBARDI³, G. CRISAFULLI⁴, F. FRANCESCHINI⁵, G. RICCI⁶,
G.L. MARSEGLIA²

¹*Pediatric Unit, "Maggiore" Hospital, Crema, Department of Pediatrics, University of Pavia, Italy;*

²*Department of Pediatrics, "San Matteo" Foundation IRCCS, University of Pavia, Pavia, Italy;*

³*Unit of Respiratory Medicine, Department of Pediatrics, University of Florence, Anna Meyer University Hospital for Children, Florence, Italy;*

⁴*Allergy Unit, Department of Pediatrics, University of Messina, Messina, Italy.*

⁵*Pediatric Unit, "Ospedali Riuniti", University Hospital, Ancona, Italy;*

⁶*Department of Pediatrics, University of Bologna, Bologna, Italy.*

Antibiotics are commonly injected during the perioperative period and are responsible of 15% of the anaphylactic reactions. Anaphylaxis triggered by antibiotics primarily involves penicillin and cephalosporin. The management of patients with histories of allergic reactions to antibiotics is a common situation in clinical practice. The confirmation or invalidation of the allergic nature of the reported reaction is not based on in vitro tests, but on a rigorous allergological work-up based on detailed analysis of clinical history, skin tests and drug provocation test. Considering a possible cross-reactivity between penicillins, once an immediate penicillin allergy has been diagnosed, skin testing with the alternative molecule (cephalosporin, carbapenem, aztreonam) is mandatory and, if negative, the relevant drug should be given in an appropriate setting at increasing doses.

The goal of antibiotic therapy is to achieve the best possible clinical outcomes while consuming the least amount of hospital resources. Antibiotics may be prescribed both for treating acute events and for prophylaxis even in a perioperative environment. An increased number of patients report reactions to certain molecules. Ten to 20% of patients of all ages, in facts, report symptoms suggesting a hypersensitivity reaction to one or several anti-infectious drugs, betalactams being involved in 80% of cases in the pediatric population (1). Even though most reactions reported in children do not result from drug hypersensitivity, when children report a history of anaphylaxis and immediate urticaria and angioedema, the risk of hypersensitivity is high (1). Moreover, when antibiotics are injected during the perioperative period as prophylaxis or treatment, they appear to be responsible for 15% of the allergic reactions. Anaphylaxis triggered by antibiotics primarily involves penicillins and cephalosporins (70%), which share the betalactam ring, and it may occur at first exposure to the

allergen.

Beta-lactam antibiotics (BLs) are frequently responsible for drug allergy. They comprise more than 50 different molecules grouped into two major families, namely penicillins and cephalosporins (2). Benzylpenicillin (BP) was the first reported BL involved, followed over the years by different penicillins and cephalosporins, with amoxicillin now being the drug which most frequently induce reactions (3). The term "allergy", though, is often applied incorrectly by both patients and doctors to any adverse reaction that occurs during treatment with penicillins, and many "adverse effects" are clearly intolerances (4).

CLASSIFICATION OF ALLERGIC REACTIONS TO ANTIBIOTICS

Allergic reactions to drugs are induced by different immunologic mechanisms that are mainly -IgE-dependent or T cell-mediated reactions (5). The European Network

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Correspondence address: Silvia Caimmi, MD
Pediatrics Unit, "Maggiore" Hospital, Crema, Department of
Pediatrics, University of Pavia, Italy;
Largo Ugo Dossena, 2 26013 Crema, Italy
Phone: +39.335.8068953
Fax: +39.0382.33912
E mail: sissi_del_78@hotmail.com

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for Drug Allergy (ENDA) has devised various diagnostic algorithms for the evaluation of immediate and non-immediate reactions (6). Nevertheless, specifically, hypersensitivity reactions can lead to any of the 4 immunologic effectors mechanisms described by Coombs and Gell (3).

Type I (immediate) reactions occur less than 1 hour after drug administration and are mediated by drug-specific IgE antibodies, with the typical clinical manifestations being urticaria and anaphylaxis. Immediate reactions are generally induced by therapeutic doses, although they may occur with much lower amounts, such as micrograms, picograms, or even less (3). In the lymph nodes, BLs, free or conjugated, are taken up by dendritic cells, processed, and presented to T and B cells. Within the context of a TH2 response, specific IgE antibodies to the hapten-carrier complex are produced (3). On further re-exposure, the penicillin-protein complex is recognized by IgE antibodies, with a subsequent release of inflammatory mediators such as histamine, prostaglandin D2, sulfidoleukotrienes, tryptase, and many cytokines (3). This release of mediators is responsible for the clinical outcome.

Type II (cytotoxic) and type III (immunocomplex) reactions are mediated by drug-specific, complement-fixing IgG or IgM antibodies and most hematologic reactions concern hemolytic anemia. In such reactions, at least two mechanisms may occur: those reactions in which BLs bind to cell membrane proteins and those in which immunocomplexes are formed in serum and later adsorbed to red blood cells, resulting in hemolysis (3). Most cases induced by BLs depend on the presence of BL-dependent antibodies (mainly IgG), which react with BLs that bind firmly to cell membranes inducing extravascular red cell destruction (3).

Type IV reactions are known as delayed or non-immediate hypersensitivity reactions and are induced by various T-cell subsets. These reactions occur within an interval of 24 to 48 hours after drug intake and their most frequent clinical expression consists in a maculopapular exanthema (3). In the classification by Coombs and Gell, four additional sub-classifications have been proposed (type IVa–d) to better explain the different mechanisms. BLs are involved in all the 4 type IV reactions: BLs can cause macrophage activation (type IVa [TH1] reaction), eosinophil-rich exanthemas (type IVb), bullous skin diseases (type IVc), as well as neutrophilic inflammation, such as in the acute generalized exanthematous pustulosis (AGEP) (type IVd) (3). In this type of reaction, a predominance of CD4+ T cells has been found in the perivascular dermis, while similar levels of CD4+ and CD8+ T cells have been reported in the dermo-epidermal layer and epidermis. These cells are activated and express

high levels of the skin homing-receptor, cutaneous lymphocyte antigen, and produce cytotoxic markers, such as perforin and granzyme B. The cytokine and chemokine pattern is mainly Th1 (IFN- γ and TNF α), although it has been reported that IL-5 may be involved in maculopapular or measles-like exanthemas.

In drug hypersensitivity, an additional level of complexity derives from the p-i concept (pharmacological interaction with immune receptors) as drugs may act more like superantigens. The p-i concept postulates a bypassing of the development of a normal immune response, as a direct, pharmacological stimulation of memory and effector T cells is implied. It could appear at the first encounter with the drug, as no sensitization is required. Those T cells which happen to be stimulated by drugs are assumed to actually have a peptide specificity to which they were primed; however, which peptides are recognized is unknown (7). It is unclear whether the drug-induced stimulation of peptide-specific T cells may result in a different clinical picture and a lot of other questions are open.

CLINICAL PATTERNS

Reactions to antibiotics that manifest as rashes can be difficult to assess. Maculopapular rashes that are not pruritic occur in patients taking ampicillin and emerge during antibiotic treatment (8). These rashes are very unlikely to be IgE mediated and are most likely idiopathic. Therefore, they are not a contraindication for the future use of the drug. The most well-known example of this is the rash that develops among patients with acute Epstein-Barr virus infection after they receive amoxicillin: these patients are not allergic to amoxicillin (8).

When a real immediate reaction occurs, it usually appears within a period ranging from minutes to no longer than 1 hour after BLs administration by any route (3). The two main entities usually recognized are urticaria, with or without angioedema, and anaphylaxis. Urticaria is defined as rapidly evolving transient itchy wheals occurring at different sites of the body, which may represent the first stage of an anaphylactic reaction (6). Anaphylaxis is defined as a serious allergic reaction with a rapid onset that may cause death consisting of generalized pruritus, erythema, and angioedema; difficulty breathing; upper or lower airway obstruction; and, in more severe cases, cardiovascular collapse leading to anaphylactic shock (3). In the onset of the reaction, differentiating urticaria from anaphylaxis may sometimes be difficult, since urticaria can be one of the initial symptoms of anaphylaxis.

The identification of a non-immediate reaction to antibiotics is sometimes difficult, because of the heterogeneity of the clinical manifestations that can be

quite similar to the symptoms of infectious or autoimmune diseases. Non-immediate reactions include the accelerated and delayed reactions: these reactions usually appear from 24 to 48 hours after drug administration, even though symptoms may be seen within 1 hour after the intake of the drug (3). The most frequent entity is maculopapular exanthema, followed by urticaria. Rare reactions include fixed drug eruption and contact dermatitis, while less common and yet more severe manifestations include acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), and bullous eruptions such as erythema multiform, Stevens-Johnson syndrome, and toxic epidermal necrolysis (3).

Beta-lactam antibiotics

BL allergy is over-reported: in facts, many patients who have a history compatible with allergy have negative skin tests to the suspected antibiotic (9). The reasons for the discrepancy between the higher rate of suspected allergy by history versus the confirmed allergy rate as defined by a history compatible with BL allergy and positive skin tests is probably due to multiple factors including non-allergic adverse events, rash as part of the natural history of the disease for which antibiotics were prescribed, and loss of the specific IgE conferring the allergy years after the exposure (9).

BLs include a large number of antibiotics that are usually the first choice for the treatment of different diseases mainly in childhood. Depending on their chemical structure (Fig.1), BLs are classified into 2 major classes, penicillins and cephalosporins, and 4 minor classes, monobactams, carbapenems, oxacephems, and clavams (3). The basic structure of all BLs consists of a 4-member BL ring that, in penicillins, is connected with a 5-member thiazolidine ring and, in cephalosporins, with a 6-member dihydrothiazine ring. The former has 1 side chain (R1), and the latter has 2 (R1 and R2), with substitution at the R1 and R2 side chains resulting in various antibiotics with different chemical structures (3).

The role of the side-chain structures as antigenic determinants is now widely accepted, particularly in hypersensitivity reactions to amoxicillin and cephalosporins, while the role of R2 side-chains as allergenic determinants has mainly been shown in vitro (6).

Vancomycin

Anaphylaxis with vancomycin remains rare: angioedema, dyspnea, and hypotension can occur. Intradermal reactions with vancomycin should be performed below a concentration of 10 µg/mL. Documented cases of IgE-mediated allergy from

vancomycin remain anecdotal. Anaphylaxis with vancomycin should be distinguished from red man syndrome, a clinical entity resulting from non-specific histamine release and observed within 5-10 min after start of infusion when the drug is rapidly injected. The red man syndrome typically consists of pruritus, burning sensation, and an erythematous eruption that spreads over face, neck, and upper torso. Teicoplanine can also cause red man syndrome. (10)

Quinolones

Quinolones constitute the third most important group of antibiotics involved in perioperative anaphylaxis. Unlike penicillin, there are no validated skin testing reagents, as these drugs can induce direct histamine release. This class of antibiotics is increasingly popular with the rise of drug-resistant bacteria and because many have an oral formulation. Anaphylactic reactions have a reported incidence of 0.46-1.2/100 000 patients, and toxic epidermal necrolysis (TEN) has been documented in case reports.

Macrolides

Macrolides are characterized by their basic structure which is made up of a lactonic cycle with 2 oxidic chains. They are classified according to the number of carbon atoms in the cycle: 14 membered (i.e. erythromycin, roxithromycin, dirithromycin, clarithromycin), 15 membered (azithromycin) and 16 membered macrolides (i.e. spiramycin, josamycin, midecamycin). Epidemiological studies show that macrolides are amongst the safest antibiotics. An immediate IgE dependent hypersensitivity has been shown with erythromycin in some cases, serious reactions such as anaphylaxis and Stevens-Johnson syndrome have also been reported, but are rare. The mechanism is unknown and the skin tests are negative in most other cases. It would appear that allergies to macrolides are unlikely to be as class allergies. Avoidance is the treatment of choice. Few cases of successful desensitization have been reported (11).

DIAGNOSIS OF HYPERSENSITIVITY TO ANTIBIOTICS

The suspicions of antibiotic allergies are extremely frequent, while true demonstrated allergies are less frequent. Nevertheless, a simple avoidance of the suspected drug could be risky; therefore, it is important to reach a firm diagnosis.

First, diagnosis of allergy or intolerance to other drugs (i.e. antipyretics, analgesics, and non-steroid anti-inflammatory drugs -NSAIDs-) and intolerance to excipients must be ruled out by means of clinical

history, careful examination of the information sheets of the suspected drugs, and challenge in patients reporting recurrent reactions to several anti-infectious drugs (1). Carefully collecting the patient's history, physicians should verify that symptoms are compatible and have occurred within 1 h of drug-intake (6). The allergologist should fulfill the ENDA questionnaire that allows a standardized evaluation of the case. Afterwards, the diagnosis is based on immediate and late-reading skin tests and provocation tests, in the absence of contra-indications.

Skin tests - Skin testing is the basic diagnostic tool. In both the ENDA document and the American practice parameters, skin testing were standardized for BLs, but not for other antibiotics (Table 1). For the procedure, it is recommended to perform prick testing first, and if results are negative, the intradermal test should be performed (3). Results of skin testing with immediate readings are often negative in non-immediate reactions like many forms of exanthemas. However, this does not rule out a delayed, mainly T-cell-based reaction. Intradermal and/or patch tests with a late reading at 24 to 48 hours have usually been recommended for the diagnosis of non-immediate reactions to BLs. Intradermal testing is done in the same way as for immediate reactions. Readings are taken at 48 and 72 hours, and any infiltrated papule with a diameter greater than 3 mm is considered as a positive result. The specificity of skin testing with BLs is between 97% and 99% whereas the sensitivity is around 50%.

Patch tests can be performed with all types of antibiotics. Readings should be taken 15 minutes after removal of the strips and again 24 and 48 hours later. Nevertheless, patch tests are not standardized and have a good specificity, but a low sensitivity.

In patients with a positive skin test, a systemic reaction may occur, mainly when they have a history of anaphylaxis. Considering these observations, certain precautions should be taken during BL skin testing to prevent systemic reactions: ready-to-use emergency material, consideration of contraindications (beta-blockers), starting with low and then gradually increasing

concentrations, and strict supervision in the hospital during and after (at least 1 h) skin testing (3).

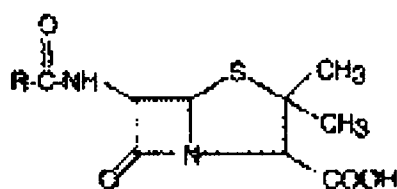
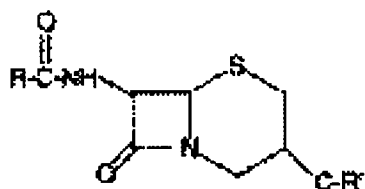
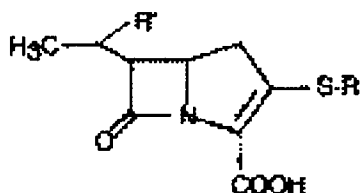
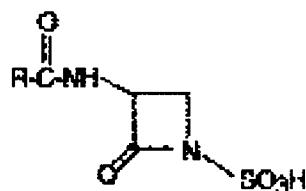
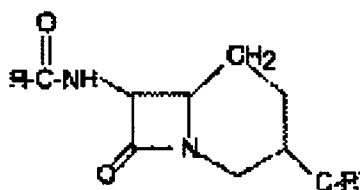
In vitro tests - Two main methods have been used to detect specific IgE antibodies to BLs: detection of these antibodies in serum by immunoassays and detection on the basis of basophil activation on contact with the hapten, either by quantification of mediator release (histamine or leukotrienes) or basophil activation marker expression (6). Nevertheless, cases with a history of an immediate reaction to BLs, displaying negative results with skin tests and positive results using serum-specific IgE assays, have been reported. It is therefore advisable to perform serum-specific IgE assays in addition to skin tests in order to improve the sensitivity of the allergologic work-up.

Several tests have been developed based on the capacity of basophils to be activated and release different mediators (12). The basophil activation test (BAT) is a useful tool in the in-vitro diagnosis of immediate hypersensitivity reactions to drugs, whether these are caused by IgE-dependent mechanisms or other mechanisms leading to the release of histamine and other mediators of immediate hypersensitivity reactions. Several cellular markers exist which are capable of providing information on the activation processes of effectors cells in immediate reactions following their in-vitro stimulation with either allergens or drugs. Currently, those most frequently used are CD63 and CD203c. The results obtained in terms of sensitivity and specificity with this technique are encouraging and allow a diagnosis to be made in a not negligible number of cases, thus avoiding the use of challenge tests. The combination of the results from BAT and immunoassay increaseds sensitivity to 65.7% or even to 85% when the results of skin tests were also included, without changing the specificity (12).

Drug provocation tests - The sensitivity of allergologic tests is not 100%; in selected cases, therefore, drug provocation tests (DPTs) are necessary (13). DPTs are widely considered to be the "gold standard" to establish or exclude the diagnosis of hypersensitivity to a certain drug,

Table 1. Maximum drug concentration recommended for Skin Prick Tests and Intradermal Tests

Hapten	Dose	Unit
Benzylpenicillin	10 000-25 000	IU/mL
Amoxicillin	20-25	mg/mL
Ampicillin	20-25	mg/mL
Cephalosporin	2	mg/mL

**Penicillins****Cephalosporins****Carbapenems****Monobactams****Carbacephems****Fig. 1. Structures of beta-lactam antibiotics.**

as they not only reproduce hypersensitivity symptoms, but also any other adverse clinical manifestation, irrespective

of the mechanism.

A DPT is indicated to exclude hypersensitivity in non-suggestive histories of drug hypersensitivity and in patients with non-specific symptoms, such as vagal symptoms under local anesthesia, and to establish a firm diagnosis in suggestive histories of drug hypersensitivity (13). Moreover, DPT is needed to provide safe alternatives and to exclude cross-reactivity of related drugs in proven hypersensitivity.

Patients who display negative results with DPTs should be re-tested 2 to 4 weeks later, considering a possibility of resensitization, mainly if immediate reactions have occurred (13). A lower starting dose should be used in patients with severe reactions and the cumulative dose should be adapted for children or persons with kidney or liver disease. DPTs with Benzyl penicillin can be performed not only in order to establish the responsibility of this drug, but also to distinguish those patients with selective reactions from those who react to the whole penicillin group. DPTs are also useful to assess cross-reactivity between different BLs (3). DPTs can be considered for those patients who have tested negative for the skin tests and in vitro tests, who have no risk factors, and for whom diagnosis is mandatory. Drugs are administered at increasing doses, with a minimum interval of 30 minutes between each administration if good tolerance is established at the previous dose, until the full therapeutic dose is reached (3).

Though not well established, the negative predictive value is important for both the patient and the physician (14). The patient has to know whether a reaction can occur after taking a drug, which was tested negatively (14). It is now well known that adverse drug reactions and especially drug allergy/ hypersensitivity are sources of anxiety and lead to an avoidance of the drug (14). On the other hand, the physician has to know whether she or he can safely prescribe a drug with previous negative allergy work-up (14).

RESENSITIZATION AFTER ALLERGOLOGIC TESTS

Observations that in patients with clear anaphylactic reactions; the results of skin tests were not always positive and that positivity was in part caused by the time interval between drug occurrence and the time of evaluation led to the suspicion that time interval was critical in the evaluation (3).

In some studies, resensitization has been observed in patients retested about 1 month after a negative allergologic test, including DPT, followed by full therapeutic courses, with a frequency ranging from 0.9% to 27.9% (6). This phenomenon appears to occur mainly

in subjects who have experienced immediate reactions to BLs (6). If we just consider patients with immediate reactions, the rate of conversion to skin test positivity could be higher. Therefore, it would be advisable to retest 2-4 weeks after the first work-up those patients who have suffered from immediate reactions and who have displayed negative results.

ASSESSMENT OF CROSS-REACTIVITY

Cross-reactivity between penicillins and cephalosporins seems to be low (10%) and is attributed to the common beta-lactam ring.

Penicillins and cephalosporins have similar chemical configurations. Cephalosporins and penicillins differ in that the 5-membered thiazolidine ring of penicillin is replaced with a 6-membered dihydrothiazine ring in the cephalosporins. However, after degradation, penicillin forms a stable penicilloate ring, with preservation of the thiazolidine ring, whereas cephalosporins undergo rapid fragmentation of the rings (8).

The rates of reactions among penicillin-allergic patients (with history or skin test confirmation) appear to differ according to cephalosporin generation and only IgE-mediated reactions are likely to become more severe with time and to result in anaphylaxis (8). Nevertheless, it has to be considered that the cross-reactivity rates between penicillin and most second-generation and third-generation cephalosporins appear very low and may actually be lower than the cross-reactivity rate between penicillins and other classes of antibiotics (8).

All first generation cephalosporins have the potential for cross-reactivity, probably because their structural features are more similar to those of penicillin, while most second and third generation cephalosporins are highly unlikely to be associated with cross-reactivity, due to differences in their chemical structure (6). It is difficult to determine the role of skin testing in the assessment of cross-reactivity. Although it is accepted that a positive cephalosporin skin test in patients allergic to penicillins indicates cross-reactivity, controversy exists about whether a negative cephalosporin skin test in these patients will predict good tolerance to the cephalosporins concerned (6). Moreover, cross-reactivity is not a bilateral phenomenon, with subjects primarily sensitized to penicillins equally recognizing cephalosporins or vice versa.

DESENSITIZATION FOR DRUG HYPERSENSITIVITY

The term desensitization has traditionally been used for type I allergic reactions only; other terms, such as

tolerance induction, have been applied for non-allergic hypersensitivity reactions (15). Drug desensitization is a high-risk procedure used only in patients who seem not to have different alternatives. Desensitization protocols have been developed and are used in patients with allergic reactions to antibiotics (mainly penicillin), insulin, sulfonamides, chemotherapeutic and biologic agents, and many other drugs (15).

Such procedure is defined as the induction of a temporary state of tolerance of a compound responsible for a hypersensitivity reaction, that can only be maintained by continuous administration of the medication. It should be noticed that, if the drug concerned is discontinued, the tolerance state is lost within a period of time that can vary from a few hours to a few days (15). Desensitization is performed by administering increasing doses of the medication concerned over a short period of time (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated (15). Drug desensitization must be clearly differentiated from a DPT which is simply a diagnostic tool. Moreover, in this last procedure, the physician usually starts with low doses to avoid severe reactions, but dose increments are rapid and not aimed at inducing tolerance (15).

CONCLUSIONS

Antibiotics are commonly injected during the perioperative period as prophylaxis or treatment and are responsible of 15% of the anaphylactic reactions. Penicillins and cephalosporins are mainly involved. The management of patients with history of allergic reactions to antibiotics is a common situation in clinical practice. Severe and life-threatening reactions to these medications are rare and only few children reporting reactions to antibiotics are really allergic to these drugs. Acute urticaria and angioedema are caused primarily by infections (especially benign viral illnesses), independently of the treatment. Skin reactions may also result from interactions between antibiotics and infectious agents, such as Epstein-Barr virus and influenza virus, with subjects generally tolerating subsequent exposure to the drugs concerned.

In patients reporting reactions to antibiotics, especially to betalactams, the confirmation or invalidation of the allergic nature of the reactions is not based on *in vitro* tests, but on a rigorous allergologic work-up based on detailed analysis of clinical history and, if necessary, skin and challenge tests.

Skin tests with betalactams are safe, especially in children, but, since few cases of anaphylaxis have been reported in adults, they must be performed in a hospital with a critical care unit. In patients reporting anaphylactic

reactions, all classes of betalactams are contra-indicated because there is a high risk of cross-sensitization to several betalactams in the same and different classes.

Considering a possible cross-reactivity between penicillins, once an immediate penicillin allergy has been diagnosed, skin testing with the alternative betalactams (cephalosporin, carbapenem, aztreonam) is mandatory and, if negative, the relevant drug should be given in an appropriate setting at increasing doses.

REFERENCES

1. Ponvert C, Scheinmann P. Antibiotic allergy and pseudo-allergy in child. *Rev Fr Allergol* 2003;43:385-92.
2. Rozieres A, Hennino A, Rodet K, Gutowski MC, Gunera-Saad N, Berard F, Cozon G, Bienvenu J, Nicolas JF. Detection and quantification of drug-specific T cells in penicillin allergy. *Allergy* 2009;64:534-42.
3. Torres MJ, Blanca M. The complex clinical picture of β -lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. *Med Clin N Am* 2010;94:805-20.
4. Pegler S, Healy B. In patients allergic to penicillin, consider second and third generation cephalosporins for life threatening infections. *BMJ* 2007;335:991.
5. Thong B, Blanca M. Advances in the understanding of hypersensitivity reactions to drugs. *Curr Opin Allergy Clin Immunol* 2009;9:291-2.
6. Blanca M, Romano A, Torres M, Fernández J, Mayorga C, Demoly P, Bousquet PJ, Merk HF, Sanz ML, Ott H, Atanaskovic-Markovic M. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009;64:183-93.
7. Pichler WR. Drug hypersensitivity reactions: classification and relationship to T-cell activation. *Drug hypersensitivity*. Basel, Karger 2007:168-89.
8. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendations for prescribing cephalosporin antibiotic for penicillin-allergic patients. *Pediatrics* 2005;115:1048-57.
9. Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R. Beta lactam allergy and resensitization in children with suspected beta lactam allergy. *Clin Exp Allergy* 2009;39:726-30.
10. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007;62:471-87.
11. Araujo L, Demoly P. Macrolides allergy. *Curr Pharm Des* 2008;14:2840-62.
12. Sanz ML, Gamboa PM, Mayorga C. Basophil activation tests in the evaluation of immediate drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2009;9:298-304.
13. Bousquet PJ, Gaeta F, Bousquet-Rouanet L, Lefrant JY, Demoly P, Romano A. Provocation test in diagnosing drug hypersensitivity. *Curr Pharm Des* 2008;14:2792-802.
14. Demoly P, Romano A, Botelho C, Bousquet-Rouanet L, Gaeta F, Silva R, Rumi G, Rodrigues Cernadas J, Bousquet PJ. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010;65:327-32.
15. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, Campi P, Sanz ML, Castells M, Demoly P, Pichler WJ for the European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* 2010;65:1357-66.