APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Drug allergy evaluation for betalactam hypersensitivity: Cross-reactivity with cephalosporines, carbapenems and negative predictive value

Mona Al-Ahmad,[1,2] Tito Rodriguez-Bouza[2]

Abstract

Background: There are no studies on cross-reactivity of betalactams among patients allergic to penicillin, or on the negative predictive value (NPV) of penicillin allergy evaluation from Arabian Gulf countries

Objective: We aimed to assess the role and NPV of drug provocation test (DPT) for betalactam hypersensitivity reactions in patients referred for allergy evaluation in Kuwait

Methods: Skin test (ST) was performed for all patients with a history of betalactam hypersensitivity, other than anaphylaxis. Patients with a negative ST were challenged with a DPT containing phenoxymethyl penicillin or the culprit drug. Patients with anaphylaxis or who tested positive to betalactams were then challenged with a DPT containing cefuroxime, meropenem or ceftriaxone. Patients who tested negative were contacted by phone to evaluate subsequent betalactam intake

Results: A total of 214 patients were tested for betalactam hypersensitivity. We had 91(42.5%) positive cases. Among positives, there were 78 (85.7%) patients with an initial reaction to penicillin and 13 (14.3%) who reacted to cephalosporin. DPT with alternative betalactam was performed in fifty who tested positive for betalactam hypersensitivity and 45 (90%) tolerated alternative antibiotics. Phone calls to 113 (59.8%) patients with negative betalactam testing showed that among 40(35.4%) patients who were successfully contacted; 17 (15%) took betalactams and 23 (20%) did not. Among the 17 patients who took betalactams, our calculated NPV for penicillin testing range from 88.2 to 100%, as the 2 patients who reported a reaction refused confirmatory retesting.

Conclusion: Carbapenems and cephalosporines can be safely given to penicillin allergic patients by means of skin testing and if negative, proceeding with a graded challenge. Our calculated NPV for penicillin testing is similar to other studies

Keywords: Penicillins, hypersensitivity, Kuwait, Carbapenems, Cephalosporins, drug hypersensitivity, skin tests, anaphylaxis, urticaria

From:
[1] Microbiology Department, Faculty of Medicine, Kuwait University
[2] Drug Allergy Unit, Department of Allergy, Al-Rashed Allergy Center, Kuwait
* Both authors contributed equally to this work.

Corresponding author:
Mona Al-Ahmad
Microbiology Department, Faculty of Medicine, Kuwait University
P.O. Box 24923, Safat 13110, Kuwait
E-mail: Alahmadm@hsc.edu.kw

Introduction

Betalactam antibiotics, including penicillin, remain the most common cause of drug-induced hypersensitivity reactions.[1] Approximately 10% of patients in the US self-report to be allergic to penicillin,[2-5] but over 90% of them tolerate penicillin when tested[6,7] Betalactam allergy is a common concern among allergists,[6-13] and it is mandatory to have a full drug allergy workup in these patients.[8,14-16] Compared with non-allergic patients, those wrongly labeled as allergic to penicillin average 0.59 days in the hospital and present increased rates of increased *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*.[17]

Both the American Academy of Allergy Asthma and Immunology (AAAAI) and the European Network for Drug Allergy (ENDA) have published guidelines for the management

of hypersensitivity to drugs or betalactams,[8,14] but unfortunately there are few studies from Arabian Gulf Countries to assess possible regional differences.[13]

According to the AAAAI guidelines, drug provocation tests (DPT) are intended for patients who, *"after a full evaluation, are unlikely to be allergic to the given drug"*,[8] while in the ENDA guidelines,[14,15,18] the DPT is considered the gold standard for diagnosing drug hypersensitivity reactions (*"DPT is still needed to confirm the diagnosis and has to be performed in patients with a suspected drug allergy"*).[14] The ENDA guidelines consider DPTs *"useful to assess cross-reactivity between different betalactams"*, and it recommend skin testing followed by a DPT if a penicillin-allergic patient is in need of an alternative betalactam.

The aims of this study are to evaluate the use of alternative betalactams such as carbapenems and cephalosporins in penicillin-allergic patients and to clarify the negative predictive value of full allergy evaluations in an Arabian Gulf country, Kuwait.

Patients and Methods

Al-Rashed Allergy Center is a tertiary public allergy center in the country of Kuwait. Drug allergy cases are referred to our center from all hospitals in Kuwait. Research ethics approval was obtained from the Faculty of Medicine.

An allergy workup was performed on all patients referred to our clinic due to possible hypersensitivity reaction to penicillins from January 2009 to April 2016. Due to cultural reasons, patients with anaphylaxis usually refuse drug testing, and safety is an important feature in Kuwait healthcare environment, so anaphylaxis patients were not included into the full penicillin allergy evaluation due to the increased risk of reactions during skin testing[19]

The skin prick test (SPT) and intradermal testing (IDT) were performed with undiluted major determinants, benzylpenicilloyl-polylysine (PPL) (Diater, Madrid, Spain), undiluted minor determinants (MDM) (Diater, Madrid, Spain), 10,000 U/ml Penicillin G (Sandoz Gmb H, Kundl-Astria/Autriche Sanduz), 25 mg/ml Ampicillin (Ampicillin Sodium equivalent to 500 mg Ampicillin activity, Bristol-Myers Squibb, U.S.A), and 25 mg/ml Amoxicillin (Hymox Forte in powder form, Biocheme Spimaco, Saudi Arabia). A concentration of 2 mg/ml was used for the skin testing of all cephalosporins. The positive and negative controls were 10 mg/ml histamine phosphate and saline solution, respectively.

All patients presenting with negative skin testing (ST) followed a single-blinded oral drug provocation test (DPT). For patients recruited before 2013, DPT was performed with 300 mg of phenoxymethyl penicillin in the form of a potassium salt tablet (Ospen, Biocheme Spimaco, Saudi Arabia). For patients recruited after 2013, our unit decided to challenge patients with the culprit drug to increase the sensitivity of testing.

A prospective study from January 2009 to April 2016 was performed on all patients presenting with anaphylaxis as the initial reaction or testing positive to betalactams including ST and DPT to cefuroxime and meropenem or ceftriaxone. The decision was made to provide the patient with one oral and one parenteral broad-spectrum betalactam alternative, available for future treatment. For skin testing, a concentration of 1 mg/ml was used for meropenem (AstraZeneca, UK) and 2 mg/ml for cefuroxime (Glaxo, Italy) or ceftriaxone (Sandoz, Austria). In patients presenting with negative ST, a DPT with 1 g intravenous meropenem (AstraZeneca, UK) and 500 mg of cefuroxime orally (Glaxo, UK) or ceftriaxone IV at a dose of 2 g (Sandoz, Austria) was used. The DPT starts with a 1/10 dilution, followed by the remaining 9/10 dilution. Patients are instructed to withhold systemic antihistamines for at least 5 days prior to the SPT and systemic corticosteroids for at least 5 weeks prior to DPT. All DPT tests were performed at least 5 weeks after a positive testing. All patients signed an informed consent before testing with notification about the estimated risk from testing. The skin test was read 20 minutes after the application and the results were considered positive if there is a wheal accompanied by erythema 3mm larger than a negative control or a wheal 3 mm larger than the injected papule in IDT.[20] The drug provocation test was performed in a ward by a trained physician with continuous monitoring of vital signs and full access to resuscitation support.[16] DPT was considered negative if there were no signs of a hypersensitivity reaction, defined by the occurrence of cutaneous (urticaria, angioedema, pruritus), respiratory (chest tightness, dyspnea, cough, wheezing, rhinitis), gastrointestinal (nausea, vomit, abdominal cramping, diarrhea), cardiovascular (hypo/hypertension, syncope, tachycardia, chest pain), or neurological (dizziness, disorientation) symptoms or throat tightness after 2 hours of observation. Upon discharge, all patients had full access to the hospital to report any delayed drug reactions. Patients with the following manifestations were excluded from drug evaluation: bullous exanthemas, DRESS, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis and toxic epidermal necrolysis.[8,14] Patients who were unlikely to receive new betalactam treatment due to severe comorbidities were also excluded. A total of 100 patients presenting to our center for drug allergy evaluation were challenged with a single dose of placebo during a single-blinded situation and monitored for 30 minutes.

A follow-up interview was conducted for the patients who tested negative for betalactam, excluding the ones tested in the prior six months. Patients were contacted by a phone call, up to three times, to inquire about the following:

- Have you taken any drug from the penicillin family since your negative testing at our clinic? No specific names of available betalactams were given to patients.
- If there was no betalactam intake: Why?
- If there was betalactam intake: Did you have any reaction after intake? Patients reporting any reaction were invited to repeat testing at our clinic.

Results

A total of 214 patients were tested for betalactams; the average age was 38.5 years and the F:M ratio was 139:25. Ninety-one (42.5%) patients tested positive to betalactams, and among them, 78 (85.7%) had an initial reaction to penicillin and 13 (14.3%) to cephalosporin (**Figure 1**). Among patients presenting with initial reaction to penicillin, 39 (50%) presented with anaphylaxis as initial reaction and 39 (50%) with urticaria. Among urticaria patients, 29 were deemed positive after ST and

10 after DPT. Testing for alternative betalactams was performed in 28 (71.8%) among the anaphylaxis group and in 22 (56.4%) among the urticaria group.

Out of the 78 patients initially reacting to penicillin, 50 (64.1%) were skin tested, and of those with negative ST, DPT with alternative betalactam was performed. The negative results were as follows: 26 patients received meropenem and cefuroxime, 17 received meropenem alone, 2 received ceftriaxone alone. Five patients presented with positive results as summarized in **table 1**. Unfortunately, out of the 78 patients who reacted to penicillin, 28 rejected testing, did not complete the full investigation or could not be contacted for testing with the alternative betalactam. (**Figure 1**)

One patient from the control group presented with delayed angioedema on the lips after placebo. Among the 100 patients challenged with placebo, only one presented a reaction that was considered positive.

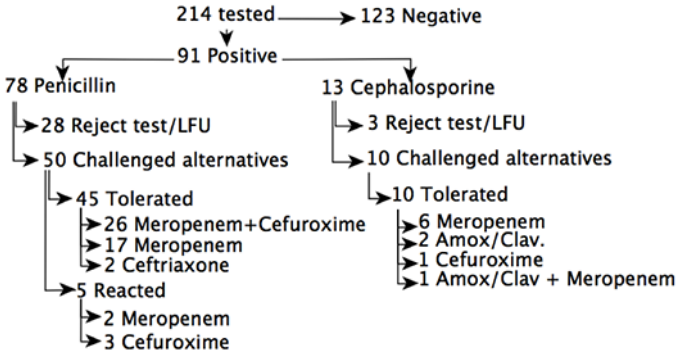

Figure 1. Diagram showing the flow of patients who were evaluated for penicillin and then challenged with alternatives

LFU: lost to follow up

Table 1. Patients with positive testing to the alternatives antibiotics

	Initial reaction			Reaction on testing	
Number of patient/ Sex/ Age in years	**Drug**	**Time**	**Symptoms**	**Drug**	**Symptoms**
#1 ♀/55	Amoxicillin	1 year ago	Immediate reaction: erythema, SOB, cough	Cefuroxime (DPT)	Immediate reaction: erythema, SOB, cough, throat tightness
#2 ♀/44	Penicillin	22 years ago	Immediate reaction: throat tightness, dizziness, tachycardia	Meropenem (IDT)	Positive IDT
#3 ♀/9*	Amoxicillin	2years ago	Immediate urticaria	Amoxicillin (DPT)	Immediate urticaria
				Cefuroxime (DPT)	Immediate urticarial
#4 ♀/33*	Amoxicillin/ clavulanic	6 months ago	Immediate urticaria, dyspnea on 2 occasions	Cefuroxime (IDT)	Positive IDT
#5 ♀/77	Amoxicillin/ clavulanic	1-3years ago	Delayed urticaria and facial angioedema on several occasions	Meropenem (DPT)	Delayed urticaria and facial angioedema

* This patient tolerated later DPT with meropenem

It was found that 5/50 (10%) of the group of patients challenged with alternative betalactams reacted positively with the test compared with only 1/100 (1%) of the control group. This difference was statistically significant, with chi-square=7.031, P=0.008.

Among the 13 patients who tested positive for cephalosporin, 9 (69.2%) presented with anaphylaxis as initial reaction while 4 (30.8%) presented with urticaria. A total of 10 patients were tested for alternative betalactams and all deemed negative with the following results: 6 tolerated DPT with meropenem, 2 with amoxicillin/clavulanic acid, and one with amoxicillin/clavulanic acid and meropenem. One patient who reacted to ceftriaxone in the past tolerated cefuroxime. 3 (23%) rejected testing, did not complete the full investigation or could not be contacted for testing with the alternative betalactam. (**Figure 1**)

We followed the first 113 patients who tested negative to betalactams by phone. Ten patients were not included due to testing in the prior six months. Two patients reported a reaction following betalactam intake: one patient denied cooperation including data regarding his reaction to betalactams while another presented with urticarial reaction alone. Both rejected the option of retesting. Out of the 40 patients contacted, we found

Table 2. Outcomes of contacting patients with Negative Penicillin allergy evaluation (N=113) by a phone call

	N= 113	% of total	% of contacted
Unable to contact*	73	64.6%	-
Took penicillin:			
Reaction	2	1.8%	5%
No reaction	15	13.3%	37.5%
Did not take penicillin			
Afraid	13	11.5%	32.5%
No need/unsure	10	8.8%	20%

N: total number of patients with negative Penicillin allergy evaluation who were contacted a phone call

*Includes: Wrong patient information/not cooperative/not picked up calls.

out that 15 (37.5%) took the medicine without having any reaction, and 23 (52.5%) did not take any betalactam or were unsure about it. Among the 23 patients who did not take any betalactam, 10 (43.4%) patients did not need treatment with betalactams, and 13 (56.5%) did not use betalactams due to either the patient's or treating physician's fear of another allergic reaction (**Table 2**).

Discussion

To our knowledge, this is the first study evaluating the both the patterns of cross-reactivity to alternative betalactams in patients with confirmed penicillin allergies and the NPV for penicillin testing among patients from an Arabian Gulf Country.

Based on the AAAAI practice parameter,[8] patients with a history of penicillin allergy or positive ST should receive carbapenems via graded challenge. On the other hand, ENDA guidelines[14] recommend that alternative betalactam ST is mandatory for patients with a penicillin allergy. If an alternative ST is negative, a full challenge with increasing doses is required. Our patients were challenged on a graded therapeutic dose of the culprit betalactam.

In previous studies, less than 1% of patients with a prior positive ST to penicillin had a positive ST to carbapenems, and all patients with negative ST to carbapenems tolerated the tested dose of carbapenem.[21-26] In our study, we found a 4.6% cross -reactivity between penicillin and meropenem. This number is higher than prior studies,[21-27] but our data must be taken with caution as it is the result of only two patients, one of whom presenting with a delayed reaction to DPT.

According to the AAAAI guidelines, ST prior to administration of carbapenems is not advised. In our study, only one patient reacted to meropenem despite negative skin testing, and the reaction was mild.

Rates of cross-reactivity to cephalosporins in confirmed penicillin-allergic patients have decreased since the 1980s from 20% to 2% or less, likely due to the decrease in use of first-generation cephalosporins, which share similar structures with penicillin.[8,14]

The AAAAI practice parameter[8] states that patients with history of Ig-E mediated reaction to penicillin *"may receive cephalosporins with minimal concern about an immediate reaction if ST results for penicillin major and minor determinants are negative."* If penicillin ST is positive, cephalosporin ST is recommended, followed by graded challenge or rapid induction of tolerance. However, the ENDA[14] guidelines state that ST with alternative betalactam is mandatory, and if negative, it is advised to challenge with the relevant drug at increasing doses, addressing also that the cross-reactivity seems very rare for delayed reactions. All our patients with a history of allergy to cephalosporin tolerated the challenge with other betalactam agents. Our local center practice is in accordance with the ENDA guidelines.

There is evidence supporting the avoidance of cephalosporin with similar side chains to the culprit penicillin, specifically in the case of amoxicillin and ampicillin,[28-30] and fatalities have been reported with cephalothin, which shares a similar side chain with penicillin.[31] However, cephalosporin with different side chains can still present cross-reactivity, probably due to common composition shared by both.[8,14]

One of our patients, who tolerated meropenem, reacted to cefuroxime DPT despite a negative ST testing to penicillin (both major and minor determinants). According to the AAAAI guidelines, it is recommended to safely administer cephalosporin with dissimilar side chains in cases of negative minor and major determinants in prior testing, but the reaction presented by our patient was mild.

There are few published studies on the NPV of penicillin testing and none on the follow-up of patients with negative tests. The NPV of a full penicillin evaluation (SPT, IDT, and DPT) in both adults and children is relatively high (92.9-100%).[32-34] This should reassure doctors to prescribe betalactams even in patients with negative allergic workups.

Our calculated NPV ranged from 88.2 to 100% because two patients who reported to have presented a reaction to betalactams after negative allergy workup rejected further testing in our center, so they could not be confirmed or discarded as allergic betalactams. Our data are similar to previously reported studies.[32-34] (**Table 3**) We did not re-challenge our patients,[8,14,20,35] and most of the patients received DPT with a 300 mg phenoxymethyl penicillin tablet for the DPT.[13] No patient attended our clinic with a positive reaction after a negative full allergy evaluation.

Among the 40 patients successfully contacted, 23 (57.5%) did not take betalactams, even if strongly indicated, with 13 (32.5%) of them refusing due to fear, either from the patient or the treating physician. This fear to use betalactams despite negative DPT testing is similar to a previous study from Turkey.[33] We noticed that some of the treating doctors even repeated the test themselves with non-standardized techniques, even though this practice should be strongly avoided.[16]

We are aware of some limitations in our study. This is a relatively small study population, and we evaluated patients with only 2 alternative antibiotics, namely meropenem and

Table 3. A comparison between studies evaluating penicillin NPV.

	Total	No reaction	Reaction			NPV
			Positive retest	Negative retest	Lost follow-up or rejected testing	
Al-Rashed	17	15	-	-	2	88.2-100%
Celik(33)	14	13	-	-	1	92.9-100%
Ponvert(34)	93	65	1	6	1	97.8-98.9%
Demoly(32)	118	109	2	4	3	96.6-98.3%

cephalosporins. We also admit that a large portion of our tested population was unfortunately lost to follow up. There is a cultural limitation to follow recommendations regarding drug allergies, which could affect the NPV results. It is possible that patients taking a single antibiotic course were "resensitized" years after testing without exhibiting a reaction, although we would have expected more patients presenting with reactions if this were the case. Further studies are needed, including re-challenge cases, to definitively confirm the patterns of re-sensitization in the Arabian Gulf area.

Acknowledgments

We acknowledge the help of Prof. Ali Sadek, Nurses Hanem Mursi and Nauf Noman in contacting patients by phone.

References

1. Gruchalla RS. 10. Drug allergy. The Journal of allergy and clinical immunology. 2003;111(2 Suppl):S548-59.
2. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Archives of internal medicine. 2001; 161:15-21.
3. Kerr JR. Penicillin allergy: a study of incidence as reported by patients. The British journal of clinical practice. 1994;48:5-7.
4. Kagy L, Blaiss MS. Anaphylaxis in children. Pediatric annals. 1998;27: 727-34.
5. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. Ann Allergy Asthma Immunol. 2000; 85:195-9.
6. Gadde J, Spence M, Wheeler B, Adkinson NF, Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. Jama. 1993;270: 2456-63.
7. Manuyakorn W, Singvijarn P, Benjaponpitak S, Kamchaisatian W, Rerkpattanapipat T, Sasisakulporn C, et al. Skin testing with beta-lactam antibiotics for diagnosis of beta-lactam hypersensitivity in children. Asian Pac J Allergy Immunol. 2016;34:242-7.
8. Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Joint Council of Allergy A. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105:259-73.
9. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34:1597-601.
10. Branellec A, Thomas M, Fain O, Kettaneh A, Stirnemann J, Letellier E. [Frequency of self-reported penicillin allergy in the area of Seine-Saint -Denis (France)]. Rev Med Interne. 2008;29:271-6.
11. Sagar PS, Katelaris CH. Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. Asia Pac Allergy. 2013;3: 115-9.
12. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. Ann Allergy Asthma Immunol. 2006;9:681-7.
13. Al-Ahmad M, Rodriguez Bouza T, Arifhodzic N. Penicillin allergy evaluation: experience from a drug allergy clinic in an Arabian Gulf Country, Kuwait. Asia Pac Allergy. 2014;4:106-12.
14. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64:183-93.
15. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, et al. Diagnosis of nonimmediate reactions to beta-lactam antibiotics. Allergy. 2004;59:1153-60.
16. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014;69:420-37.
17. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. The Journal of allergy and clinical immunology. 2014;133:790-6.
18. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58:854-63.
19. Co Minh HB, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. J Allergy Clin Immunol. 2006;117:466-8.
20. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003;58:961-72.
21. Romano A, Viola M, Gueant-Rodriguez RM, Gaeta F, Pettinato R, Gueant JL. Imipenem in patients with immediate hypersensitivity to penicillins. N Engl J Med. 2006;354:2835-7.
22. Romano A, Viola M, Gueant-Rodriguez RM, Gaeta F, Valluzzi R, Gueant JL. Brief communication: tolerability of meropenem in patients with IgE -mediated hypersensitivity to penicillins. Ann Intern Med. 2007;146:266-9.
23. Wall GC, Nayima VA, Neumeister KM. Assessment of hypersensitivity reactions in patients receiving carbapenem antibiotics who report a history of penicillin allergy. Journal of chemotherapy. 2014;26:150-3.
24. Atanaskovic-Markovic M, Gaeta F, Gavrovic-Jankulovic M, Velickovic TC, Valluzzi RL, Romano A. Tolerability of imipenem in children with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2009; 124:167-9.
25. Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. Allergy. 2008;63:237-40.
26. Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2015;135:972-6.
27. Kula B, Djordjevic G, Robinson JL. A systematic review: can one prescribe carbapenems to patients with IgE-mediated allergy to penicillins or cephalosporins? Clin Infect Dis. 2014;59:1113-22.
28. Miranda A, Blanca M, Vega JM, Moreno F, Carmona MJ, Garcia JJ, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol. 1996;98:671-7.
29. Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med. 2004;141:16-22.
30. Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Munoz D, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. Allergy. 1994;49:108-13.
31. Spruill FG, Minette LJ, Sturner WQ. Two surgical deaths associated with cephalothin. JAMA. 1974;229:440-1.
32. Demoly P, Romano A, Botelho C, Bousquet-Rouanet L, Gaeta F, Silva R, et al. Determining the negative predictive value of provocation tests with beta-lactams. Allergy. 2010;65:327-32.
33. Celik GE, Aydin O, Dogu F, Cipe F, Boyvat A, Ikinciogullari A, et al. Diagnosis of immediate hypersensitivity to beta-lactam antibiotics can be made safely with current approaches. Int Arch Allergy Immunol. 2012;157:311-7.
34. Ponvert C, Weilenmann C, Wassenberg J, Walecki P, Bourgeois ML, de Blic J, et al. Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. Allergy. 2007;62:42-6.
35. Garcia Nunez I, Barasona Villarejo MJ, Algaba Marmol MA, Moreno Aguilar C, Guerra Pasadas F. Diagnosis of patients with immediate hypersensitivity to beta-lactams using retest. J Investig Allergol Clin Immunol. 2012;22:41-7.