Allergy to β-Lactam Antibiotics in Children

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ABSTRACT. *Background.* **Skin tests with soluble β-lactams can be used to diagnose immediate and delayed hypersensitivity (HS) reactions to β-lactam antibiotics. Very few studies have been performed with children with suspected β-lactam allergy. In these studies, immediate HS to β-lactams was diagnosed by skin tests in 4.9% to 40% of children. The diagnostic and predictive values of immediate responses in skin tests are good, because very few children with negative skin test results have positive oral challenge (OC) test results. Delayed responses in skin tests (intradermal and patch tests) have been reported in adult patients and children suffering with urticaria, angioedema, and maculopapular rashes during treatments with β-lactam antibiotics. However, the diagnostic and predictive values of late responses are unknown. Semi-late responses in skin tests with β-lactams have never been studied in adults or children.**

Objectives. **The aims of this study were to confirm or rule out the diagnosis of allergy to β-lactams in children with histories of adverse reactions to these antibiotics, to determine whether allergic children were sensitized to one or several classes of β-lactams, and to evaluate the frequency and diagnostic value of immediate, accelerated, and delayed responses in skin tests with β-lactam antibiotics in children.**

Methods. **We studied 325 children with suspected β-lactam allergy. Skin tests (prick and intradermal) were performed with soluble forms of the suspected (or very similar) β-lactams and with one or several β-lactams from other classes. The reaction was assessed after 20 minutes (immediate), 8 hours (accelerated), and 48 to 72 hours (delayed). OCs with the suspected β-lactams were performed in patients with negative skin test results, except those with severe serum sickness-like reactions and potentially harmful toxidermias.**

Results. **Skin tests and OCs led to the diagnosis of β-lactam allergy in 24 (7.4%) and 15 (4.6%) of the children, respectively. Thus, only 12% of the children were diagnosed as allergic to β-lactams by means of skin tests and OC. HS to β-lactams was suspected from clinical history in 30 (9.2%) children reporting serum sickness-like reactions and potentially harmful toxidermias. In a few children, we diagnosed food allergy and intolerance to excipients or nonsteroidal antiinflammatory drugs. No cause was found in the other children.**

Based on skin tests and OC, the prevalences of immunoglobulin E-dependent and of semi-late or delayed sensitizations to β-lactam assessed were similar (6.8% vs 5.2%, respectively). Most immunoglobulin E-dependent sensitizations were diagnosed by means of skin tests (86.4%). In contrast, most semi-late and delayed sensitizations were diagnosed by OC (70.6%). The likelihood of β-lactam allergy was significantly higher for anaphylaxis (42.9% vs 8.3% in other reactions) and immediate reactions (25% vs 10% in accelerated and delayed reactions).

Of the children diagnosed as allergic to β-lactam by means of skin tests, OC, and clinical history, 11.7% were sensitized to several classes of β-lactams. The risk was significantly higher in children with anaphylaxis (26.7% vs 7.5% of the children with other reactions) and in children reporting immediate reactions (33.3% vs 8.5% of the children with accelerated and delayed reactions).

Finally, age, sex, personal history of atopy, number of reactions to β-lactams, and number of reactions to other drugs were not significant risk factors for β-lactam allergy.

Conclusion. **The skin tests were safe, and the immediate reaction to skin tests successfully diagnosed allergy to β-lactam antibiotics in children reporting reactions suggestive of immediate HS. In contrast, most accelerated and delayed reactions were diagnosed by OC. Thus, our results suggest that the diagnostic and predictive values of skin tests for nonimmediate HS to β-lactams in children are low. They also strongly suggest that most reactions reported in children are attributable to infectious diseases or interactions between drugs and infectious agents rather than to β-lactam HS.** *Pediatrics* **1999; 104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e45; *β-lactams, allergy, skin tests, oral challenge, child.***

ABBREVIATIONS. ID, intradermal; PPL, benzyl-penicilloyl polylysine; MDM, minor determinant mixture; HS, hypersensitivity; MPR, maculopapular rash; OC, oral challenge; SSLR, serum sickness-like reaction; EM, erythema multiforme; SJS, Stevens–Johnson syndrome; GEP, generalized exanthematous pustulosis; DTH, delayed-type hypersensitivity.

Between 1% and 10% of patients treated with β-lactam antibiotics report reactions suggestive of allergy to these drugs.[1–4] Immediate responses to prick tests and intradermal (ID) tests with benzyl-penicilloyl polylysine (PPL) and minor determinant mixture (MDM) have good diagnostic and predictive values in patients with reactions suggestive of immediate hypersensitivity (HS) to penicillins.[2,5–7] However, skin tests with PPL and MDM may fail to detect specific sensitization to individual β-lactams.[8–12] In contrast, skin tests using soluble β-lactams diagnose a significant number of immediate sensitizations to penicillins and β-lactams.[5,12–18]

Delayed responses to individual β-lactams in skin tests (ID and patch tests) have been reported in adult

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patients and children with delayed reactions to β-lactam antibiotics, such as urticaria and angioedema, maculopapular rash (MPR), and unidentified rashes.[19–26] Accelerated responses in skin tests with β-lactams have never been studied in patients with suspected β-lactam allergy.

Other tests, such as radioallergosorbent test, have low specificity and sensitivity.[11,13,22,27–31] Moreover, it has been shown that >50% of patients with positive radioallergosorbent test results have negative test results after 1 year.[32–34]

We studied immediate, accelerated, and delayed responses to skin tests with soluble β-lactams and oral challenge (OC) in children reporting reactions suggestive of allergy to β-lactam antibiotics. Our goals were to confirm or rule out allergy to β-lactams and to determine whether the children were sensitized to one or several classes of these drugs. We also evaluated the frequency and diagnostic value of accelerated and delayed responses to skin tests with β-lactam antibiotics in children.

METHODS

Patients

This study included 325 children (169 boys and 156 girls), 8 months to 17.8 years of age (mean: 5.25 years). Of the children, 146 (44.9%) had a personal history of atopy. The mean time between the most recent reaction and the tests was 18.5 months (1 month to 15 years). Patients took no antihistamines or oral corticosteroids for 2 to 4 weeks before skin tests and OC.

Reactions to β-lactams were classified as described by Levine.[35] A total of 469 reactions were reported, with 117 children (36%) reporting ≥2 reactions to treatment with a particular β-latam (n = 10; 3.1%) or several β-lactams (n = 107; 32.9%). Amoxicillin alone or associated with clavulanic acid was most frequently reported to cause adverse reactions (60%), followed by first generation cephalosporins (cephadroxil, cefaclor, cephatrizine, and cephalexine: 29.6%). Other suspected β-lactams were cefixime, cefpodoxime, penicillins V and M, cefuroxime, and ampicillin. Children reporting several reactions were classified based on the most severe and/or most rapid reaction (Table 1). Of the children, 75 (23.1%) had tolerated treatment with other classes of β-lactams since his or her most recent reaction.

Of the children, 138 (42.5%) also reported one or several reactions (primarily urticaria, angioedema, and unidentified rashes) to other drugs. Macrolides and sulfonamides were the primary drugs involved.

Skin Tests

Skin tests were performed with the soluble form of the suspected (or very similar) β-lactams and one or several β-lactams from other classes, at various concentrations (250–25 000 IU/mL for benzylpenicillin and 0.25–25 mg/mL for other β-lactams), as described by Vervloet and Pradal.[36] The stock solution was prepared by reconstituting the freeze-dried β-lactam with 0.9% NaCl. Solutions of the required concentrations were obtained by serial dilutions of the stock solution with 0.9% NaCl. For children reporting reactions to a combination of amoxicillin and clavulanic acid, skin tests were performed with amoxicillin only.

Increasing concentrations of the reagents were tested initially by the prick method. If prick test results were negative, 0.02 mL of the solutions were serially injected intradermally. A weal ≥3 mm (prick) or 5 mm (ID) in diameter, present 15 to 20 minutes after the application, was defined as an immediate positive response if there was also a negative response to control solution (0.9% saline) and a positive response to histamine (prick: 1 mg/mL; ID: 0.1 mg/mL). Accelerated and delayed responses to ID injections were recorded after 8 hours (accelerated) and 48 to 72 hours (delayed) and were classified as positive if weals ≥5 mm in diameter were present.

The soluble β-lactams used were benzylpenicillin (Penicillin G; Panpharma Laboratories, Fougeres, France), oxacillin (Bristopen; Bristol-Myers Squibb, New York, NY), amoxicillin (Clamoxyl; Beecham, Philadelphia, PA), ampicillin (Totapen; Bristol-Myers Squibb), ticarcillin (Ticarpen; Beecham), cephaloridin (Ceporine; Glaxo Wellcome, Greenford, UK), cephalotin (Keflin; Lilly, Indianapolis, IN), cefazolin (Cefazolin; Panpharma, Fougènes, France), cephamandole (Kefandol; Lilly), cefotaxime (Claforan; Roussel, Frankfurt, Germany), ceftazidime (Fortum, Glaxo Wellcome), and ceftriaxone (Rocephine; Roche, Burlington, NC).

OCs

OCs with the suspected β-lactams were performed for children with negative skin test results, except those reporting serum sickness-like reaction (SSLR) and potentially harmful toxidermias. Thus, 271 children underwent OC with the suspected β-lactams, either at the hospital for 24 to 48 hours (immediate and accelerated reactions; n = 96) or at home (delayed reactions; n = 175). In the hospital, children received a first dose of 0.5 mg of the drug. The dose was increased gradually until the appropriate cumulative dose per day for age and weight was reached. At home, daily therapeutic doses were prescribed for 5 to 7 days. Children were advised to stop treatment and to take oral antihistamines and/or corticosteroids if they experienced a reaction.

OCs also were performed with a β-lactam from a class other than the class suspected of causing the reaction in 39 children with positive skin test results or OC for the suspected β-lactams and negative test results with β-lactams from other classes and in children with SSLR and potentially harmful toxidermias.

OCs were classified as positive if an adverse reaction of an allergic nature (eg, urticaria and/or angioedema, MPR, erythema multiforme [EM]) occurred during the treatment or within 24 to 48 hours of the end of the treatment.

Statistical Analysis

Differences were assessed by the χ^2 test. A P value $< .05$ was considered to be significant.

RESULTS

Skin Tests

Immediate assessments of prick tests were always negative, and most immediate responses were recorded intradermally at concentrations of 2500 IU/mL for benzylpenicillin and of 2.5 mg/mL for the

TABLE 1. Clinical Data for Children With Suspected β-Lactam Allergy According to Nature, Severity, and Time of Onset of Adverse Reactions*

Reaction (Nature and Severity)	Time of Onset			Total
	Immediate	Accelerated	Delayed	
Anaphylaxis	14	9	12	35 (10.8%)
Urticaria and/or angioedema	20	81	74	175 (53.8%)
Severe SSLR			16	16 (4.9%)
Maculopapular rashes			10	10 (3%)
EM, SJS, GEP, and erythroderma		3	11	14 (4.3%)
Unidentified rashes	2	35	38	75 (23%)
Total	36 (11%)	128 (39.4%)	161 (49.6%)	325 (100%)

* Children reporting several reactions were classified on the basis of the most severe and/or most rapid reaction.

other β-lactams. Accelerated and delayed responses with aminopenicillins and cephalosporins were observed intradermally at concentrations of 25 mg/mL. In 2 children with accelerated and delayed responses to ID injections, prick tests (25 mg/mL) became positive at the 8th and the 48th to 72nd hours, respectively.

Skin test results were positive with one class or several classes of β-lactams in 22 children (6.8%), either immediately (19 cases: 5.9%) or at accelerated and delayed assessments (3 cases: 0.9%). Two other children had negative skin test results, but reported the development of an accelerated benign urticaria, probably attributable to inadvertent subcutaneous injection of the reagent. These 2 children were diagnosed as allergic to the suspected β-lactams. Skin test results were negative in all the children reporting MPR, SSLR, and potentially harmful toxidermia. Thus, 24 children (7.4%) were diagnosed as allergic to one β-lactam or several β-lactams by means of skin tests (Table 2). There was no significant difference between the children tested within 1 year of their most recent reaction (16/178: 9%) and those tested later (8/147: 5.5%).

Oral Challenge

OC test results with the suspected β-lactams were positive for 17 of 271 children (6.3%; Table 3; cases 25–41). Immediate or accelerated reactions were recorded in 7 hospitalized children. Delayed reactions were detected by a physician in 10 children with OC performed at home. All the reactions were mild and easily controlled with antihistamines and/or corticosteroids. The frequency of positive OC was not significantly different between the children tested within 1 year of their most recent reaction and the children tested later.

OC test results with β-lactams other than those suspected were negative, except in 1 child with a severe SSLR to amoxicillin, associated with clavulanic acid, reporting delayed urticaria in response to OC with cefixime (case 42).

In 3 children, OC test results were positive for amoxicillin associated with clavulanic acid, but negative with amoxicillin alone, suggesting an allergy to clavulanic acid (cases 27, 31, and 40). Three other children with positive OC test results for pediatric suspensions of β-lactams tolerated OC with tablets or capsules of the same β-lactams (cases 34, 35, and 41). These children are probably intolerant to the excipients present in the pediatric suspension, because they also reported reactions to unrelated drugs containing the same excipients. Thus, OC allowed the diagnosis of β-lactam allergy in 15 children (4.6%).

TABLE 2. Case Histories of 24 Children With Positive Skin Test Results to β-Lactams (n = 22) or Cutaneous Reactions Induced by Skin Tests (n = 2)

Cases	Clinical Symptoms (Drugs)	Chronology	Positive Skin Test Results	Negative OC Test Results
Anaphylaxis				
1	Urticaria + respiratory distress (amoxicillin)	Immediate	Penicillin G, amoxicillin, cefazolin, cefotaxime	ND
2	Shock with laryngeal edema (cefatrizine)	Immediate	Amoxicillin, cefazolin	Cefixime
3	Shock (cefaclor)	Immediate	Amoxicillin, cefazolin	Cefpodoxime
4	Shock (cefatrizine)	Immediate	Cefazolin, cefotaxime	Amoxicillin
5	Urticaria + laryngeal edema (cefatrizine)	Immediate	Cefazolin	Amoxicillin
6	Urticaria + laryngeal edema (cefatrizine)	Immediate	Cefazolin	Amoxicillin
7	Urticaria + laryngeal edema (cefatrizine)	Immediate	Cefazolin	ND*
8	Severe faintness + angioedema (cefatrizine)	Immediate	Cefazolin, cefotaxime	Amoxicillin
9	Urticaria + laryngeal edema (cefixime)	Delayed	Cefotaxime	Amoxicillin
10	Urticaria + laryngeal edema (amoxicillin)	Delayed	Amoxicillin, cefotaxime	ND
11	Urticaria + laryngeal edema (cefaclor)	Delayed	Cefazolin	ND*
12	Angioedema + respiratory distress (amoxicillin + clavulanic acid)	Delayed	Amoxicillin†	Cefixime
Mild to moderate urticaria or angioedema				
13	Angioedema (amoxicillin)	Accelerated	Amoxicillin, cefotaxime	ND
14	Urticaria (cefpodoxime)	Accelerated	Cefotaxime	Amoxicillin
15	Angioedema (cefixime)	Accelerated	Cefotaxime	Amoxicillin
16	Angioedema (amoxicillin)	Accelerated	Amoxicillin	ND*
17	Urticaria (cefixime)	Accelerated	Cefotaxime	Amoxicillin
18	Urticaria + angioedema (cefadroxil)	Accelerated	Cefazolin‡	Amoxicillin
19	Urticaria + angioedema (cefatrizine)	Accelerated	Cefazolin‡	Amoxicillin and cefpodoxime
20	Urticaria + angioedema (amoxicillin)	Accelerated and delayed	Amoxicillin†	ND*
21	Urticaria + angioedema (amoxicillin)	Delayed	Amoxicillin†	ND*
22	Urticaria (cefadroxil)	Delayed	Cephalotin	Oracillin, amoxicillin
Other reactions				
23	Unidentified rash (cefaclor)	Delayed	Amoxicillin, cefazolin	ND
24	Unidentified rash (amoxicillin)	Delayed	Amoxicillin, cefotaxime	ND

ND indicates not done.
* No reaction with nonsuspected betalactams since the (most recent) reaction.
† Immediate response negative, only accelerated and delayed skin tests positive.
‡ Negative skin test results, but accelerated urticaria following skin tests.

TABLE 3. Oral Challenge in 18 Children With Negative Skin Test Results to β-Lactams

Cases	Clinical Symptoms (Drugs)	Chronology	OC Positive With (Chronology)	Oral Challenge Negative With
Anaphylaxis				
25	Angioedema + palmoplantar pruritus (amoxicillin)	Immediate	Amoxicillin (immediate urticaria and angioedema)	Cefixime
	MPR (cephatrizine)	Delayed		
26	Urticaria + laryngeal edema (amoxicillin)	Accelerated	Amoxicillin (immediate urticaria and angioedema)	ND (treatments tolerated with cephalosporins)
27	Laryngeal edema (amoxicillin)	Accelerated	Amoxicillin-clavulanic acid (immediate angioedema)	Amoxicillin
	Urticaria + angioedema (amoxicillin-clavulanic acid)	Delayed		
Mild to moderate urticaria or angioedema				
28	Urticaria (amoxicillin)	Accelerated	Amoxicillin (delayed urticaria)	Cefixime
	Urticaria (cefatrizine)	Accelerated		
29	Urticaria (amoxicillin)	Delayed	Amoxicillin (delayed urticaria)	Cefixime
30	Urticaria (cefixime)	Delayed	Cefixime (accelerated urticaria)	Cefaclor, cefpodoxime
	Unidentified rash (cefaclor)	Delayed		
31	Urticaria (amoxicillin-clavulanic acid)	Accelerated	Amoxicillin-clavulanic acid (accelerated urticaria)	Amoxicillin
32	Angioedema (cefaclor)	Accelerated	Amoxicillin (delayed angioedema)	Cefixime
	Angioedema (amoxicillin)	Accelerated		
33	Urticaria + angioedema (amoxicillin)	Delayed	Amoxicillin (delayed urticaria)	ND (treatments tolerated with cefuroxime)
34	Urticaria + angioedema (amoxicillin-clavulanic acid)	Accelerated	Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid tablets
	Urticaria + angioedema (cephadroxil)	Accelerated	Suspension (accelerated urticaria and angioedema)	
35	Angioedema (amoxicillin-clavulanic acid)	Accelerated	Amoxicillin-clavulanic acid and cefpodoxime suspensions (delayed angioedema)	Amoxicillin-clavulanic acid tablets
	Angioedema (cefixime)	Accelerated		
	Angioedema (cefpodoxime)	Accelerated		
Other reactions				
36	Unidentified rash (amoxicillin suspension)	Accelerated	Amoxicillin tablets (accelerated morbilliform rash)	Cefixime
37	Unidentified rash (amoxicillin-clavulanic acid)	Delayed	Amoxicillin (accelerated morbilliform rash)	ND (treatments tolerated with cephalosporins)
38	Unidentified rash (amoxicillin)	Accelerated	Amoxicillin (delayed urticaria)	Cefpodoxime
	Unidentified rash (cefaclor)	Accelerated		
39	Unidentified rash (amoxicillin)	Accelerated	Amoxicillin (delayed urticaria and angioedema)	Cefpodoxime
40	Unidentified rashes (amoxicillin-clavulanic acid)	Accelerated	Amoxicillin-clavulanic acid (delayed urticaria)	Amoxicillin
41	Unidentified rash (cephadroxyl)	Delayed	Cefadroxyl suspension (delayed morbilliform rash)	Cephadroxyl tablets
42	SSLR (amoxicillin-clavulanic acid)	Delayed	Cefixime (delayed urticaria)	ND

ND indicates not done.

Clinical History

Based on clinical history, SSLR was diagnosed in 16 children; 6 reacted to amoxicillin only, 8 to cephalosporins only, and 2 to amoxicillin and cephalosporins (including case 42). A total of 14 other children were diagnosed as having severe EM, Stevens–Johnson syndrome (SJS), generalized exanthematous pustulosis (GEP), or erythroderma associated with treatments with amoxicillin only (5 children), amoxicillin associated with clavulanic acid (6 children), or other β-lactams (3 children).

Final Diagnosis

Based on skin tests, OC, and clinical history, 68 (20.9%) children (31 boys and 37 girls), from 4 months to 16 years of age (mean: 5.5 years), were diagnosed as allergic to one β-lactam or several β-lactam antibiotics (Table 4). A total of 57 (83.8%) reacted to penicillins or cephalosporins only, 3 (4.4%) to clavulanic acid, and 8 (11.8%) to both penicillins and cephalosporins (Table 5). In 11 other children, we diagnosed intolerance to excipients (3 cases) (Table 3), food allergy (5 cases), and aspirin intolerance (3 cases; Table 6). The cause of the original reaction was not identified for the other children.

Potential Risk Factors for HS to β-lactam Antibiotics

Based on skin tests and OC, HS to β-lactams was diagnosed in 39 children (21 boys and 18 girls; mean age: 6.8 years). There was no significant difference in the age and sex of children with positive and negative skin and OC test results. Skin and OC test results were positive in 18 of 146 (12.3%) children with a personal history of atopy and in 21 of 179 (11.7%) children with no personal history of atopy (P = not significant). Responses to skin tests and OC were

TABLE 4. Diagnosis of Allergy to β-Lactam Antibiotics in 68 Children, *n* (%)

Symptoms	Diagnostic Method			Total
	Responses to Skin Tests	Oral Challenge	Clinical History	
Severe anaphylaxis	12 (34.3%)	3 (8.6%)		15/35 (42.9%)
Urticaria and/or angioedema	10* (5.7%)	6 (3.4%)		16/175 (9.1%)
SSLR		1†	16	16/16
Toxidermias			14	14/14
Unidentified rashes	2 (2.7%)	5 (6.7%)		7/75 (9.4%)
Total	24/325 (7.4%)	15/325 (4.6%)	29/325 (8.9%)	68/325 (20.9%)

* Including 2 children with negative skin test results but accelerated urticaria after skin testing.
† One child diagnosed as allergic on the basis of clinical history (severe SSLR to amoxicillin + clavulanic acid) and with positive OC test results with cefixime.

TABLE 5. Sensitization to β-Lactams Diagnosed by Skin Tests, OC, and Clinical History in 68 Children

Clinical Symptoms	Penicillins or Cephalosporins	Penicillins and Cephalosporins	Clavulanic Acid	Total
Anaphylaxis	10	4	1	15
Urticaria and angioedema	14	1	1	16
Other reactions	33	3*	1	37
Total	57	8	3	68

* Including 1 child diagnosed as allergic on the basis of clinical history (severe SSLR to amoxicillin and clavulanic acid) and with a positive OC with cefixime.

TABLE 6. Case Histories of 8 Children With Negative Skin and OC Test Results With Betalactam Antibiotics

Case	Personal Atopy	Reactions: Nature and Chronology (suspected drug)	Diagnosis
43	Yes, allergy to cow's milk and eggs	Accelerated urticaria (cefiximine) Delayed urticaria + laryngeal edema (amoxicillin)	Probable coincident ingestion of eggs or cow's milk
44	Yes, allergy to cow's milk	Immediate shock (amoxicillin) associated with clavulanic acid)	Coincident ingestion of cow's milk (proven)
45	Yes, peanut allergy	Accelerated urticaria + angioedema (amoxicillin)	Coincident ingestion of peanut (proven)
46	Yes	Delayed urticaria + angioedema (amoxicillin)	Coincident ingestion of egg (proven)
47	Unknown before tests with foods	Delayed laryngeal edema (amoxicillin)	Leguminous allergy (positive skin tests and OC)
48	Yes	Accelerated urticaria and angioedema (amoxicillin and cefatrizine)	Aspirin intolerance (proven by OC)
49	No	Accelerated urticaria and angioedema (amoxicillin)	Aspirin intolerance (proven by OC)
50	No	Delayed urticaria and angioedema (cefadroxil)	Aspirin intolerance (proven by OC)

also similar for children reporting one reaction only and those reporting several reactions to β-lactams, and there was no significant difference between the children reporting reactions to other drugs and those reporting reactions to β-lactams only.

Based on the type of clinical reaction in children with positive skin or OC test results, skin tests led to the diagnosis of HS to one or several β-lactams in 12 of 15 (80%) children reporting anaphylaxis (cases 1–12), in 10 of 16 (62.5%) children with urticaria and angioedema (cases 13–22), and in 2 of 7 (28.6%) children reporting unidentified rashes (cases 23–24). OC led to the diagnosis of HS to β-lactams in 3 (20%; cases 25–27), 6 (37.5%; cases 28–33), and 5 (71.4%; cases 36–40) of the allergic children reporting anaphylaxis, urticaria and angioedema, and unidentified rashes, respectively. The OC test result was also positive with a cephalosporin (cefixime) in 1 child reporting a severe SSLR to amoxicillin associated with clavulanic acid (case 42). The differences between children reporting anaphylaxis, urticaria, and angioedema, and those reporting other reactions were highly significant ($P < .001$).

Positive immediate responses to skin tests were recorded in 11 of 35 (31.4%) children reporting anaphylaxis (cases 1–11), 6 of 175 (3.4%) children with mild to moderate urticaria or angioedema (cases 13–17 and 22), and 2 of 75 (2.7%) children reporting unidentified rashes (cases 23–24). OC led to the diagnosis of immediate HS in 3 (8.6%) of the children with anaphylactic reactions (cases 25–27). Thus, based on skin and OC tests, immediate HS to β-lactam antibiotics was diagnosed in 22 (56.4%) allergic children, including 14 of 15 (93.3%), 6 of 16 (37.5%), and 2 of 7 (28.6%) children with anaphylaxis, urticaria and angioedema, and other reactions, respectively. The differences between children reporting anaphylaxis and those reporting other reactions were significant ($P \leq .01$).

Accelerated and delayed responses to skin tests were recorded in 1 (2.8%) of the children with anaphylaxis (case 12) and in 4 (2.2%) of the children with

mild to moderate urticaria and angioedema (cases 18–21). OC led to the diagnosis of semi-late and delayed HS in 6 (3.4%) of the children with mild to moderate urticaria and angioedema (cases 28–33) and 6 (6.6%) of the children with SSLR and unidentified rashes (cases 36–40 and 42). Thus, based on skin and OC tests, semi-late and delayed HS to β-lactams was detected in 17 (43.6%) children allergic to β-lactams, including 1 (6.7%), 10 (62.2%), and 6 (75%) of the children reporting anaphylaxis, urticaria and angioedema, and other reactions, respectively. The differences between children reporting anaphylaxis and those reporting other reactions were highly significant ($P < .001$).

Of the 15 (26.7%) allergic children reporting anaphylaxis, 4 were sensitized to both penicillins and cephalosporins, versus 4 of the 53 (7.5%) allergic children who reported other reactions ($P < .001$) (Table 5).

Based on the chronology of the clinical reactions in children with positive skin or OC test results, skin tests led to the diagnosis of HS to one or several β-lactams in 8 of 9 (88.9%) children reporting immediate reactions (cases 1–8), in 8 of 17 (47%) children with accelerated reactions (cases 13–20), and in 8 of 12 (66.7%) children with delayed reactions (cases 9–12 and 21–24). OC test results were positive in 1 (11.1%; case 25), 9 (52.9%; cases 26–28, 31, 32, 36, 38–40) and 4 (33.3%; cases 29, 30, 33, 37) of the allergic children reporting immediate, accelerated, and delayed reactions, respectively. The differences between children reporting immediate reactions and those reporting accelerated and delayed reactions were highly significant ($P < .001$).

Positive immediate responses to skin tests were recorded in 8 of 36 (22.2%; cases 1–8), 5 of 128 (3.9%; cases 13–17), and 6 of 161 (3.7%; cases 9–11 and 22–24) children reporting immediate, accelerated, and delayed reactions, respectively. OC led to the diagnosis of immediate HS in 1 (2.8%) of the children with immediate reactions (case 25) and in 2 (1.6%) of the children reporting accelerated reactions (cases 26–27). Thus, based on skin and OC test results, immediate HS to β-lactams was diagnosed in 9 of 9 (100%), 7 of 17 (41.2%), and 6 of 13 (46.1%) allergic children with immediate, accelerated, and delayed reactions, respectively. The differences between children who reported immediate reactions and those who reported accelerated and delayed reactions were significant ($P \leq .01$).

Accelerated and delayed responses in skin tests were recorded in 3 (2.4%; cases 18–20) and 2 (1.2%; cases 12 and 21) of the children reporting accelerated and delayed reactions, respectively. OC led to the diagnosis of semi-late and delayed HS in 7 (5.5%) of the children with accelerated reactions (cases 28, 31, 32, 36, and 38–40) and 5 (3.1%) of the children with delayed reactions (cases 29, 30, 33, 37, and 42). Thus, based on skin and OC test results, semi-late and delayed HS to β-lactams was detected in 0, 10 (58.8%), and 7 (53.8%) allergic children with immediate, accelerated, and delayed reactions, respectively. The difference between the children reporting immediate reactions and those reporting accelerated and delayed reactions was highly significant ($P < .001$).

Of the 9 allergic children reporting immediate reactions, 3 (33.3%) were sensitized to both penicillins and cephalosporins, versus 5 of the 59 (8.5%) allergic children who reported other reactions ($P < .001$).

DISCUSSION

In this article, we report the largest series of children with suspected β-lactam allergy. Our results are similar to those of Mendelson et al[37] but conflict with those of Pichichero et al,[17] who reported positive skin or OC test results in 23.5% of children. These differences in results probably stem from differences in the selection of children.

β-lactam allergy may not have been diagnosed in some children in our study. Previous results show that ≤9% of children with negative skin and OC test results relapse during subsequent treatment with the suspected β-lactams.[17,27,37] The allergic immune response in some patients with negative skin test results is also boosted by OC or inadvertent contact with β-lactams.[17,38] However, preliminary results from an ongoing prospective unpublished study have shown that only a few children with negative skin and OC test results relapse during subsequent treatment with the suspected β-lactams.

Skin Tests

Skin tests were performed with soluble β-lactams at concentrations ≤25 000 IU/mL for benzylpenicillin and ≤25 mg/mL for other β-lactams. Some reports have suggested that β-lactams at concentrations >1 mg/mL are irritant.[39] However, most children in our study had negative skin test results, including those with positive OC test results. Thus, concentrations of 2.5 mg/mL and 25 mg/mL gave no false-positive responses in the skin tests.

Only 0.6% of the children in our study reported mild accelerated urticaria induced by skin tests, consistent with previous studies showing that skin tests with penicillin derivatives and soluble β-lactams are well tolerated.[27,28] However, anaphylactic reactions have been reported in some adult patients[7] but not in children.

Immediate responses to skin tests were recorded in 5.9% of children, consistent with previous studies showing a positive immediate response in skin tests with penicillin derivatives and soluble β-lactams in 3% to 40% of patients.[6,8,17,23,27,28,40,41] The frequency of positive immediate responses in skin tests was significantly higher in children reporting severe anaphylaxis and immediate reactions than in children reporting other reactions, consistent with the results of previous studies performed with adults[7,8,13,42] and children.[27,28]

Delayed responses in skin tests have been reported in 0.6% to 17% of patients with suspected β-lactam allergy, especially in patients with MPR and accelerated or delayed urticaria or angioedema during treatment with ampicillin or amoxicillin.[19,21–26] In these patients, immunohistological skin test studies showed a typical delayed-type hypersensitivity (DTH) reaction.[43–45] We found positive accelerated

and delayed responses in skin tests in 0.9% of children, consistent with previous works suggesting that DTH reactions to β-lactams are rare.[21]

Discordance Between Skin and OC Tests

OC allowed the diagnosis of β-lactam allergy in 4.6% of the children in our study. Our results are consistent with previous studies showing that ≤17% of patients with negative skin test results have positive OC test results.[17,27,28,41] There may be several reasons for differences in skin and OC test results.

First, we did not perform skin tests with PPL and MDM. Previous studies have shown that most patients who have positive skin test results with PPL and/or MDM also have immediate responses in skin tests with soluble penicillins and that a few allergic patients have immediate responses to PPL and/or MDM only,[11,13] especially children.[17,23] Only 2 children with negative skin test results and immediate responses in OC with amoxicillin (cases 25 and 26) could have been diagnosed as having immediate HS to penicillins by skin tests with PPL and MDM. Our results are very similar to those of Pichichero and Pichichero,[17] who diagnosed immediate HS to β-lactams based on OC in 8.6% of allergic children skin-tested with PPL, MDM, and soluble β-lactams.

Second, patch tests were not performed, because most patients with positive patch tests also have delayed responses in ID tests, and ID tests identify DTH to β-lactams in more patients than do patch tests.[22,24] Thus, very few of the children with negative skin test results and positive OC test results could have been diagnosed as allergic by patch tests.

Third, the interval between the most recent reaction and skin testing may be long. In most studies, the frequency of positive immediate responses in skin tests decreases as this interval increases with a negativation rate of 10% to 15% per year.[21,46–48] However, we found that the frequency of positive skin test results was similar for children tested within 1 year of their most recent reaction and children tested later, consistent with previous studies in children, showing no significant time-dependent decrease in the frequency of positive skin test results.[17,37]

Fourth, negative skin test results with positive OC test results may result from antigenic differences in the reagents used for skin tests and the drugs responsible for the reaction. This may account for negative skin test results in patients reacting to oral β-lactams with no corresponding soluble form, such as cefaclor, cefatrizine, and cefixime, as reported herein for some children. This notion is supported by recent results showing in vitro reactivity with cefaclor in children with severe allergy to this β-lactam, but negative in vitro and OC test results with a very closely related β-lactam.[49]

Fifth, accelerated and delayed reactions may be attributable to an allergy to metabolites of β-lactams rather than to the native drugs themselves, as shown with SSLR to cefaclor and sulfonamide-induced or anticonvulsive drug-induced toxidermias.[50–52] This may explain why most children with negative skin test results and positive OC test results reported accelerated or delayed urticaria, angioedema, and unidentified rashes in response to treatment with β-lactams.

Sixth, negative skin test results with positive OC test results also may result from allergy or intolerance to substances not used in skin tests such as clavulanic acid and excipients. In 3 children, allergy to clavulanic acid was suggested strongly by positive OC test results with amoxicillin associated with clavulanic acid and negative OC test results with amoxicillin alone. In 3 other children, we diagnosed intolerance to excipients, although the parents did not agree to double-blind, placebo-controlled OC. These children reacted with pediatric suspensions of the suspected β-lactams but tolerated OC with tablets or capsules of the same β-lactams. They also reported reactions to other drugs containing the same excipients and tolerated these drugs if the suspected excipients were absent. Previous reports have shown that few patients have immediate[53] or delayed HS[20] to clavulanic acid and that some patients who report reactions to β-lactams are actually intolerant to excipients rather than to β-lactams.[27,28]

Etiology in Children With Negative Test Results

Skin and OC test results were negative in most children in this study, suggesting that most of the reactions reported were not attributable to immediate, semi-late, and tuberculin-type DTH to β-lactam antibiotics.

SSLR and potentially harmful types of toxidermia may result from lymphocyte-mediated cytotoxicity rather than from tuberculin-type DTH.[50,54–57] Lymphocyte-mediated cytotoxicity cannot be assessed by ID or patch tests. Thus, our results are consistent with those reporting negative responses in ID and patch tests in children with bullous or pustular eruptions caused by β-lactams.[22,58] We did not perform OC with the suspected β-lactams in children reporting SSLR and potentially harmful types of toxidermia to avoid triggering a severe reaction. All the children reporting severe SSLR, EM, SJS, GEP, or erythroderma were considered to be allergic to the suspected β-lactams. However, negative skin and OC test results with β-lactams have been reported for 10 children with mild to moderately severe SSLR and EM.[17] Thus, a significant number of cases of SSLR and potentially harmful types of toxidermia in our study may result from infectious diseases rather than from allergy to β-lactam antibiotics (see below).

Most of the reactions reported probably were caused by infectious diseases. Acute urticaria and angioedema are caused primarily by infections (especially benign viral illnesses) independent of treatment.[59] Various infectious agents, such as mycoplasmas and viruses, cause urticaria morbilliform and unidentified rashes in children,[60] and MPR, SJS, and toxic epidermal necrolysis may result from the destruction of infected epidermal cells by cytotoxic T lymphocytes.[61] Skin reactions also may result from interactions between infectious agents and antibiotics, as described in Epstein–Barr virus, influenza virus, and human immunodeficiency virus infections.[62,63] Subjects generally tolerate subsequent exposure to the drugs concerned,[64] consistent with

our observations that OC test results were seldom positive in children with negative skin test results.

Potential Risk Factors for β-lactam Allergy

The frequency of positive skin and OC tests was significantly higher in children reporting anaphylaxis and immediate reactions, consistent with previous reports showing that severe immediate and accelerated reactions are often attributable to immunoglobulin E-dependent HS to β-lactams.[7]

A total of 20.5% of children with positive responses in skin tests or OC were sensitized to several β-lactams from various classes. This crossreactivity between the various classes of β-lactam antibiotics was first suspected from clinical histories and skin tests[10,46,65–67] and then confirmed by immunologic studies performed in vitro.[66,68] The frequency of positive skin or OC test results to penicillins and cephalosporins was significantly higher in children with β-lactam-induced anaphylaxis than in allergic children reporting other reactions, suggesting that anaphylaxis is a major risk factor for sensitization to crossreactive allergenic determinants of β-lactam antibiotics.

Atopy may be a risk factor for β-lactam allergy (particularly for anaphylaxis) in adults[5,69,70] and children.[28] However, responses to skin and OC tests were similar for children with and without a personal history of atopy in our study, as previously reported in adults[1,70,71] and children.[17,27] Our results are also consistent with previous reports showing that age and sex are not significant risk factors for allergy to β-lactams in children.[17,27]

The frequency of positive skin and OC test results was slightly higher in children with several reactions to β-lactam antibiotics than in those children with only one reaction, but this difference was not significant. Therefore, the number of reactions associated with β-lactam treatments is probably not a risk factor for β-lactam allergy, consistent with the results of Pichichero and Pichichero,[17] who found no difference in the frequency of previous β-lactam treatments in skin test-positive versus skin test-negative children.

Nearly half the children reported reactions to other drugs, a higher proportion than in other studies.[72–74] Of the children, 3 were probably intolerant to excipients, and 5 were allergic to foods. Our results agree with those of previous studies suggesting that recurrent reactions to several drugs may be attributable to intolerance to excipients, coincident allergy, or pseudo-allergy to foods.[27] Finally, the frequency of positive skin and OC test results with β-lactams was similar for children reporting reactions to unrelated drugs and children reacting to β-lactams only. This is consistent with previous results suggesting that penicillin allergy and non-β-lactam allergy develop independently.[73]

CONCLUSION

We have shown that only a few of the children reporting reactions suggestive of allergy to β-lactams were really allergic to these antibiotics. We also showed that skin tests with β-lactam antibiotics are safe and have a high diagnostic value in children who report reactions suggestive of immediate HS, especially those with anaphylactic reactions. Anaphylaxis was a major risk factor for sensitization to crossreactive antigenic determinants of various classes of β-lactams. Accelerated and delayed responses in skin tests were seldom positive, and most children with nonimmediate HS to β-lactams were diagnosed using OC tests. Finally, most of the reactions reported by children were probably attributable to infectious diseases or to interactions between drugs and infectious agents rather than to HS to β-lactams.

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REFERENCES

1. Adkinson NF. Risk factors for drug allergy. *J Allergy Clin Immunol*. 1984;74:567–572
2. Lin RY. A perspective on penicillin allergy. *Arch Intern Med*. 1992;152:930–937
3. Markowitz M, Kaplan E. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet*. 1991;337:1308–1310
4. Norby SR. Problems in evaluation in adverse reactions to beta-lactam antibiotics. *Rev Infect Dis*. 1986;8:358. Supplement
5. Levine BB, Kotzlov DM. Prediction of penicillin allergy by immunological tests. *J Allergy*. 1969;43:231–244
6. Saxon A, Gilden N, Beall N, et al. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med*. 1987;107:204–215
7. Sogn DD, Evans R, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Disease Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med*. 1992;152:1025–1032
8. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin test reagents. *J Allergy Clin Immunol*. 1982;69:238–244
9. Blanca M, Vega JM, Garcia J, et al. Allergy to penicillin with good tolerance to other penicillins: study of the incidence in subjects allergic to beta-lactams. *Clin Exp Allergy*. 1990;20:475–481
10. Silviu-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side chain penicillin determinants. *J Allergy Clin Immunol*. 1993;91:694–701
11. Romano A, Blanca M, Mayorga C, et al. Immediate hypersensitivity to penicillins: studies on Italian patients. *Allergy*. 1997;52:89–93
12. Vega JM, Blanca M, Garcia JJ, et al. Immediate allergic reactions to amoxicillin. *Allergy*. 1994;49:317–322
13. Audicana M, Bernaola G, Urrutia I, et al. Allergic reactions to beta-lactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporins. *Allergy*. 1994;49:108–113
14. Blaiss MS, De Shazo RD. Drug allergy. *Pediatr Clin North Am*. 1988;35:1131–1147
15. Torres MJ, Blanca M, Garcia J, et al. Evaluation of a large cohort of subjects allergic to penicillins. *J Allergy Clin Immunol*. 1995;95:285
16. Weber EA. Cefazolin specific side chain hypersensitivity. *J Allergy Clin Immunol*. 1996;98:849–850
17. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr*. 1998;132:137–143
18. Ferrer M, Verdegay FJG, Lopez-Paeza JL, et al. Diagnostic efficiency of cutaneous tests with penicillin metabolites, amoxicillin and ampicillin in the diagnosis of allergy due to aminopenicillins. *Allergy*. 1998;53:97
19. Aihara M, Ikezawa Z. Evaluation of the skin test reactions in patients with delayed-type rash induced by penicillins and cephalosporins. *J Dermatol*. 1987;14:440–448
20. Jaques D, Claeys M, Bonzon M, et al. Delayed hypersensitivity related to clavulanic acid: usefulness of lymphocyte transformation tests. *J Allergy Clin Immunol*. 1995;95:284
21. Prieto A, Herrero T, Aranzabal A, et al. Systemic cell-mediated hypersensitivity to beta-lactam antibiotics: cross-reactivity study by skin tests. *J Allergy Clin Immunol*. 1995;95:286

22. Romano A, Di Fonzo M, Papa G, et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy*. 1995;50:113–118
23. Romano A, Quaratino D, Papa G, et al. Aminopenicillin allergy. *Arch Dis Child*. 1997;76:513–517
24. Barbaud A, Reichert-Penetrat S, Trechot P, et al. The use of skin testing in the investigation of cutaneous adverse drug reactions. *Br J Dermatol*. 1998;139:49–58
25. Terrados S, Blanca M, Garcia J, et al. Non-immediate reactions to beta-lactams: prevalence and role of the different penicillins. *Allergy*. 1995;50:563–567
26. Warrington RJ, Silviu-Dan F, Magro C. Accelerated cell-mediated immune reactions in penicillin allergy. *J Allergy Clin Immunol*. 1993;92: 626–628
27. Juchet A, Rancé F, Brémont F, Dutau G. Exploration de l'allergie aux bêtalactamines chez 45 enfants. *Rev Fr Allergol*. 1994;34:369–375
28. Ponvert C, Mazeyrat R, Scheinmann P, et al. Exploration allergologique des réactions aux bêtalactamines chez l'enfant: résultats d'une étude de 50 enfants, comportant des tests cutanés à lecture immédiate, des RAST, et des tests de réintroduction par voie orale. *Rev Fr Allergol*. 1996;36: 162–175
29. Sanz ML, Garcia BE, Prieto I, et al. Specific IgE determination in the diagnosis of beta-lactam allergy. *Invest Allergol Clin Immunol*. 1996;6: 89–93
30. Worral GJ, Hull C, Briffet E. Radioallergosorbent testing for penicillin allergy in family practice. *Can Med Assoc J*. 1994;150:37–41
31. Adkinson NF, Mardiney M, Wheeler B. Natural history of IgE-dependent drug sensitivities. *J Allergy Clin Immunol*. 1986;78:75–79
32. Blanca M, Vega JM, Garcia J, et al. New aspects of allergic reactions to beta-lactams: cross-reactions and unique specificities. *Clin Exp Allergy*. 1994;24:407–415
33. Chandra RK, Jodlekar SA, Tomas E. Penicillin allergy. *Arch Dis Child*. 1980;55:857–860
34. Kraft D, Roth A, Mischer P, et al. Specific and total serum IgE measurements in the diagnosis of penicillin allergy: a long-term follow-up study. *Clin Allergy*. 1977;7:21–28
35. Levine BB. Immunological mechanisms of penicillin allergy: a haptenic model system for the study of allergic diseases in man. *N Engl J Med*. 1966;275:1115–1125
36. Vervloet D, Pradal M, eds. *Drug Allergy*. HS-M Ewert AB, Sundyborg, Sweden: Pharmacia; 1992: 55–59
37. Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine selective penicillin allergy testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol*. 1984;73:76–81
38. Blanca M, Garcia T, Vega JM, et al. Anaphylaxis to penicillins after nontherapeutic exposure: an immunological investigation. *Clin Exp Allergy*. 1996;335–340
39. Adkinson NF, Thompson WL, Maddrey WC, Lichtenstein LM. Routine use of penicillin skin testing in an inpatient service. *N Engl J Med*. 1971;285:22–24
40. Erffmeyer JE. Reactions to antibiotics. *Immunol Allergy Clin North Am*. 1992;12:633–648
41. Macy E, Richter PK, Falkoff R, Zeiger R. Skin testing with penicilloate and penilloate prepared with an improved method: amoxicillin oral challenge in patients with negative skin test responses to penicillin reagents. *J Allergy Clin Immunol*. 1997;100:586–591
42. Levine BB, Redmond AP, Fellner MJ, et al. Penicillin allergy and the heterogeneous immune responses of man to benzylpenicillin. *J Clin Invest*. 1966;45:1895–1906
43. Barbaud A, Béné C, Schmutz JL, et al. Role of delayed cellular hypersensitivity and adhesion molecules in amoxicillin-induced morbilliform rashes. *Arch Dermatol*. 1997;133:481–486
44. Fernandez-Rivas M. Heterogeneous isolated late skin test responses to aminopenicillins. *J Allergy Clin Immunol*. 1997;99:428. Supplement
45. Garcia-Ortiz JC, Bellido J. Delayed hypersensitivity to amoxicillin. *Allergy*. 1997;37:126. Supplement
46. Sullivan TJ, Wedner HJ, Shatz GS, et al. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol*. 1981;68:171–180
47. Green GR, Rosenblum AH, Sweet C. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. *J Allergy Clin Immunol*. 1977;60:339–345
48. Shepherd GM. Allergy to beta-lactam antibiotics. *Immunol Allergy Clin North Am*. 1991;11:611–633
49. Kearns GL, Wheeler JG, Rieder MJ, Reid J. Serum sickness-like reactions to cefaclor: lack of in vitro cross-reactivity with loracarbacef. *Clin Pharmacol Ther*. 1998;63:686–693
50. Kearns GL, Wheeler JG, Childress SH, Letzig LG. Serum sickness-like reactions to cephaclor: role of hepatic metabolism and individual susceptibility. *Pediatr Pharmacol Ther*. 1994;125:805–811
51. Hertl M, Bohlen H, Jugert F, et al. Predominance of epidermal $CD8^+$ T lymphocytes in bullous cutaneous reactions caused by betalactam antibiotics. *J Invest Dermatol*. 1993;101:794–799
52. Wolkenstein P, Charue D, Laurent P, et al. Metabolic predisposition to cutaneous adverse drug reactions: role in toxic epidermal necrolysis caused by sulfonamides and anticonvulsivants. *Arch Dermatol*. 1995;131: 544–551
53. Fernandez-Rivas M, Perez-Carral C, Cuevas M, et al. Selective allergic reactions to clavulanic acid. *J Allergy Clin Immunol*. 1995;95:748–750
54. Hebert AA, Sigman ES, Levy M. Serum sickness-like reactions from cephaclor in children. *J Am Acad Dermatol*. 1991;25:805–808
55. Blanca M. Allergic reactions to penicillins: a changing world. *Allergy*. 1995;50:777–782
56. Vial T, Pont J, Pham E, et al. Cefaclor-associated serum sickness-like disease: eight cases and review of the litterature. *Ann Pharmacother*. 1992;26:910–914
57. Hertl M, Merk HF. Lymphocyte activation in cutaneous drug reactions. *J Invest Dermatol*. 1995;105:95–98. Supplement
58. Prieto A, Lopez-Saez P, Olalde S, et al. Recurrent pustular eruption induced by amoxicillin. *J Allergy Clin Immunol*. 1996;97:348
59. Mortureux P, Léauté-Labréze C, Legrain-Liferman V, et al. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol*. 1998;134:319–323
60. Cherry JD. Cutaneous manifestations of systemic infections. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. Philadelphia, PA: WB Saunders & Co; 1987:786–817
61. Chosidow O, Bourgeault I, Roujeau JC. Drug rashes: what are the targets of cell-mediated cytotoxicity? *Arch Dermatol*. 1994;130:627–629
62. Haverkos HV, Amsel Z, Drotman P. Adverse drug-virus interactions. *Rev Infect Dis*. 1991;13:697–704
63. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. *J Am Med Assoc*. 1986;256:3358–3363
64. Carr A, Cooper DA, Penny R. Allergic manifestations of human immunodeficiency virus (HIV) infection. *J Clin Immunol*. 1991;11:55–64
65. Anderson JA. Cross-reactivity to cephalosporins in patients allergic to penicillins. *Pediatr Infect Dis*. 1986;5:557–561
66. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol*. 1989;83:381–385
67. Saxon A, Adelman DC, Patel A, et al. Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol*. 1988;82:213–227
68. Moreno F, Blanca M, Mayorga C, et al. Studies of the specificities of IgE antibodies found in sera from subjects with allergic reactions to penicillins. *Int Arch Allergy Immunol*. 1995;108:74–81
69. Hunter DA, Hunter WJ. Penicillin allergies. *Am J Hosp Pharm*. 1994;51: 1963–1964
70. Kern RA, Winberley NA. Penicillin reactions: their nature, growing importance, recognition, management and prevention. *Am J Med Sci*. 1953;226:357–362
71. Rytel MN, Klioa FM, Arlander TR, Miller LF. Detection of penicillin hypersensitivity with penicilloyl-polylysine. *J Am Med Assoc*. 1963;186: 894–898
72. Kamada M, Twarog FJ, Leung DYM. A comparison of multiple versus single antibiotic sensitivity in pediatric patients. *Allergy Proc*. 1991;12: 347–350
73. Khoury L, Warrington R. The multiple drug allergy syndrome: a matched-control retrospective study in patients allergic to penicillins. *J Allergy Clin Immunol*. 1996;98:462–464
74. Sullivan TJ, Ong RC, Gilliam LK. Studies of the multiple drug allergy syndrome. *J Allergy Clin Immunol*. 1989;83:270

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