

ORIGINAL ARTICLE

Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests

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Keywords

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Abstract

Studies based on skin and challenge tests have shown that 12–60% of children with suspected betalactam hypersensitivity were allergic to betalactams. Responses in skin and challenge tests were studied in 1865 children with suspected betalactam allergy (i) to confirm or rule out the suspected diagnosis; (ii) to evaluate diagnostic value of immediate and non-immediate responses in skin and challenge tests; (iii) to determine frequency of betalactam allergy in those children, and (iv) to determine potential risk factors for betalactam allergy. The work-up was completed in 1431 children, of whom 227 (15.9%) were diagnosed allergic to betalactams. Betalactam hypersensitivity was diagnosed in 50 of the 162 (30.9%) children reporting immediate reactions and in 177 of the 1087 (16.7%) children reporting non-immediate reactions ($p < 0.001$). The likelihood of betalactam hypersensitivity was also significantly higher in children reporting anaphylaxis, serum sickness-like reactions, and (potentially) severe skin reactions such as acute generalized exanthematic pustulosis, Stevens–Johnson syndrome, and drug reaction with systemic symptoms than in other children ($p < 0.001$). Skin tests diagnosed 86% of immediate and 31.6% of non-immediate sensitizations. Cross-reactivity and/or cosensitization among betalactams was diagnosed in 76% and 14.7% of the children with immediate and non-immediate hypersensitivity, respectively. The number of children diagnosed allergic to betalactams decreased with time between the reaction and the work-up, probably because the majority of children with severe and worrying reactions were referred for allergological work-up more promptly than the other children. Sex, age, and atopy were not risk factors for betalactam hypersensitivity. In conclusion, we confirm in numerous children that (i) only a few children with suspected betalactam hypersensitivity are allergic to betalactams; (ii) the likelihood of betalactam allergy increases with earliness and/or severity of the reactions; (iii) although non-immediate-reading skin tests (intradermal and patch tests) may diagnose non-immediate sensitizations in children with non-immediate reactions to betalactams (maculopapular rashes and potentially severe skin reactions especially), the diagnostic value of non-immediate-reading skin tests is far lower than the diagnostic value of immediate-reading skin tests, most non-immediate sensitizations to betalactams being diagnosed by means of challenge tests; (iv) cross-reactivity and/or cosensitizations among betalactams are much more frequent in children reporting immediate and/or anaphylactic reactions than in the other children; (v) age, sex and personal atopy are not significant risk factors for betalactam hypersensitivity; and (vi) the number of children with diagnosed allergy to betalactams (of the immediate-type hypersensitivity especially) decreases with time between the reaction and allergological work-up. Finally, based on our experience, we also propose a practical diagnostic approach in children with suspected betalactam hypersensitivity.

Background

Studies based on skin and challenge tests have shown that 12–60% (mean: 10–15%) of the children with suspected betalactam hypersensitivity were truly allergic to betalactams and that the risk of hypersensitivity to betalactams was significantly higher in the children reporting immediate and/or severe reactions than in the other children (1–4).

Objectives

We present the results of a retrospective study aiming (i) to confirm or rule out a suspected diagnosis of betalactam allergy in children; (ii) to evaluate the diagnostic value and tolerance of immediate and non-immediate responses in skin and challenge tests with betalactams; (iii) to determine the frequency of betalactam allergy in those children; (iv) to identify potential risk factors for betalactam allergy; and (v) to determine the influence of time elapsed since the (most recent) reaction on responses in skin and challenge tests, in a very large number of children with suspected betalactam allergy. Based on our experience, including in children prospectively followed after a negative allergological work-up (5), we also aimed to propose a practical diagnostic approach.

Methods

Patients

Between December 1990 and July 2009, 1865 children were explored for suspected betalactam hypersensitivity. Preliminary results have been published for 325 of those children (3). The reactions were classified as immediate when they occurred within the first hour of drug administration and non-immediate when they occurred more than 1 h after the administration (6). The children reporting several reactions to a single or several betalactam(s) were classified based on their most rapid and/or most severe reaction.

Skin tests

As previously reported (3), pricks, intradermal (ID), and patch tests were performed with the soluble forms of the suspected (or very similar) betalactams and other betalactams from the same and other classes. Briefly, the betalactams used were benzyl-penicillin (Penicillin G[®]; Diamant, Paris-la Défense, France), oxacillin (Bristopen[®]; Bristol, New York, NY, USA), amoxicillin (Clamoxyl[®]; Beecham, Philadelphia, PA, USA), ampicillin (Totapen[®]; Bristol), piperacillin (Piperacillin[®]; Beecham), ticarcillin (Ticarcillin[®]; Beecham), cephaloridin (Ceporine[®]; Glaxo-Wellcome, Greenford, UK), cefalotin (Keflin[®]; Lilly, Indianapolis, IN, USA), cefazolin (Cefazoline[®]; Panpharma, Fougères, France), cephamandole (Kefandol[®]; Lilly), cefuroxime (Zinnat[®]; Glaxo-Wellcome), cefotaxime (Claforan[®]; Roussel, Frankfurt, Germany), ceftazidime (Fortum[®]; Glaxo-Wellcome), ceftriaxone (Rocephine[®]; Roche, Burlington, NC, USA), imipenen (Tienam[®]; Merck-Sharp, Whitehouse Station, NJ, USA), and aztreonam

(Azactam[®]; Sanofi-Aventis, Paris, France). Pure powders of penicillin V (Oracillin[®]; Schwartz-Pharma, Boulogne-Billancourt, France), cefaclor (Alfatil[®]; Lilly), cefadroxil (Oracefal[®]; UPSA, Rueil-Malmaison, France), and cefixime (Oroken[®]; Aventis, Paris, France), kindly provided by the laboratories, were also used for pricks and patch tests. Betalactams were serially diluted with 0.9% sterile NaCl. The concentrations used were 250–25 000 IU/ml for penicillin G and 0.25–25 mg/ml for the other betalactams for pricks and ID tests and 250 000 IU/ml for penicillin G and 250 mg/ml for the other betalactams for patch tests.

Pricks and ID tests were performed in all the children. Patch tests were performed in 286 selected children reporting non-immediate reactions, using plastic Haye's test chambers (Destaing Lab, Grasse, France). Non-suspected betalactams were randomly tested in the children to control specificity of the responses in skin tests (pricks, ID, and patch tests).

Responses in skin tests were assessed at 15–20 min (immediate, pricks, and ID), 6–8 h (semi-late, ID), 48–72 h (late, ID, and patch tests), and 6–7 days (hyper-late, ID, and patch tests), according to the ENDA/EAACI guidelines (7). Briefly, a weal ≥ 3 mm (prick) or 5 mm (ID) in diameter, present 15–20 min 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). Semi-late, late, and hyper-late responses to ID injections were classified as positive if weals ≥ 5 mm in diameter were present. Patch tests were considered as positive when erythema and weals (+), erythema, wheals and vesicles (++), erythema, coalescent vesicles and/or bullae (+++) were present.

Challenge tests

Challenge tests with the suspected betalactams were performed in children with negative skin test results, except those with severe reactions to useless betalactams (first-generation cephalosporins especially). In those children, challenge tests were performed with alternative betalactams. Challenge tests were performed either in the hospital for 24 h–3 days when the suspected allergic reactions were immediate or had occurred within 2–3 days of the start of treatment or at home (mild to moderately severe other reactions), as previously reported (3). In children with positive responses in skin or challenge tests, challenge tests were performed with other betalactams from the same and other classes, except for the children with known tolerance to these betalactams since their allergic reaction.

In the hospital, children received a first dose of 1–10 mg of the drug. The dose was increased gradually until the appropriate cumulative dose for age and weight was reached. On the second and third days of the challenge test, the children were administered one-half of the therapeutic dose at 9 am and 12 h. At home, daily therapeutic doses were prescribed for 3–10 days, according to the chronology of the suspected allergic reaction. Children were advised to stop treatment, to take oral antihistamines and/or corticosteroids and to consult a physician if they experienced a reaction.

Challenge tests were considered as positive if an objective adverse reaction of an allergic nature [e.g. urticaria and/or angioedema, maculopapular rash, and erythema multiforme (EM)] occurred during the treatment or within 24–48 h at the end of the treatment.

The study was approved by the hospital ethics committee and prior informed consent was obtained from the parents before skin and challenge tests were performed in the children.

Statistical analysis

Differences between groups of children were assessed by the chi-squared test. A *p* value <0.05 was considered to be significant.

Results

Challenge tests with the suspected or alternative betalactams were not performed in 424 children with negative (*n* = 414) or positive (*n* = 10) skin test results, either because the parents refused the challenge test (*n* = 324) or because the children reported a severe reaction to useless betalactams and had tolerated other betalactams since their (most recent) reaction (*n* = 99) or because the children died from a severe illness (*n* = 1). The demographic and clinical characteristics of these children did not differ from those of the children who completed the allergological work-up.

Thus, skin and challenge tests were performed in 1431 children (639 F and 792 M, mean age = 5.5 years, range: 4 months–18 years) reporting 1571 reactions to a single or several betalactams. Amoxicillin alone or associated with clavulanic acid was the most frequently suspected betalactam (*n* = 1019, 64.9%), followed by third-generation cephalosporins (*n* = 338, 21.5%) and other betalactams (*n* = 214, 13.6%). The clinical characteristics of the children are indicated in Table 1, according to the type of the reaction. The reactions were immediate in 162 (11.3%) and non-immediate in 1269 (88.7%) children. The mean time between the (most

recent) reaction and the allergological work-up was 18.7 months (range: 0.5 month–15 years). The children with severe or worrying reactions (anaphylaxis, urticaria/angioedema, SSLR, potentially severe skin reactions, and immediate reactions) were referred more rapidly than the children with maculopapular rash (MPR) and unidentified rashes and non-immediate reactions (Tables 2 and 3: *p* < 0.0001 and *p* = 0.0002, respectively). Six hundred and 21 children (43.4%) had a personal history of atopy.

Based on their clinical history and responses in skin or challenge tests, 227 of those 1431 children (15.9%) were diagnosed allergic to betalactams (Table 1). Immediate-type and non-immediate-type hypersensitivities to betalactams were diagnosed in 50 (3.5%) and 177 (12.4%) children, respectively. The likelihood of betalactam hypersensitivity was significantly higher in the children reporting immediate (50/162, 30.9%) than in the children reporting non-immediate (177/1269, 13.9%) reactions (*p* < 0.001) and in the children reporting anaphylaxis, serum sickness-like reaction (SSLR) and potentially harmful skin reactions vs urticaria/angioedema, MPR, and unidentified rashes (*p* < 0.0001). Selective hypersensitivity to clavulanic acid was diagnosed in 37 of the 87 (42.5%) children diagnosed allergic to amoxicillin associ-

Table 2 Time elapsed between the (most recent) reaction and the allergological work-up, according to the type/severity of the reaction, in 1431 children studied for suspected betalactam allergy. The difference between the two groups of children is highly significant (*p* < 0.0001)

Reaction (type/severity)	≤1 year, <i>n</i>	>1 year, <i>n</i>	Total
Anaphylaxis	77	23	100
Urticaria/angioedema	655	358	1013
MPR/unidentified rashes	103	161	264
SSLR/severe skin reactions	34	20	54
Total	869	562	1431

MPR, maculopapular rash; SSLR, serum sickness-like reaction.

Table 1 Clinical characteristics of 1431 children with suspected betalactam hypersensitivity, and results of allergological investigations in the 227 children diagnosed allergic to betalactams

Reactions Reported (<i>n</i>)	Confirmed allergy : <i>n</i> (%), by means of	Positive skin tests <i>n</i> (%/diagnosed)	Positive challenge tests <i>n</i> (%/diagnosed)	Convincing clinical history <i>n</i> (%/diagnosed)	Cross-reactivity/cosensitization <i>n</i> (%/diagnosed)
Anaphylaxis (100)	50/100 (50)	37/50 (74)	13/50 (26)		22/50 (44)
Urticaria/oedema (1013)	126/1013 (12.4)	51/126 (40.5)	75/126 (59.5)		34/126 (27)
MPR and other rashes (264)	28/264 (10.6)	9/28 (32.1)	19/28 (67.9)		5/28 (17.8)
SSLR (23)	11/23 (47.8)	3/11 (27.3)	4/11 (36.4)	4/11 (36.4)	3/11 (27.3)
Harmful skin reaction					
AGEP (3)	3/3 (100)	1/3 (33.3)	ND	2/3 (66.6)	0
EM (21)	4/21 (19)	1/4 (25)	ND	3/4 (75)	0
SJS (6)	4/6 (66.6)		ND	4/4 (100)	0
DRESS (1)	1/1	1/1	ND		1
Total (1431)	227/1431 (15.9)	103/227 (45.4)	111/227 (48.9)	13/227 (5.7)	65/227 (28.2)

AGEP, acute generalized exanthematic pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; EM, erythema multiforme; MPR, maculopapular rash; ND, not done; SJS, Stevens–Johnson syndrome; SSLR, serum sickness-like reaction.

Table 3 Time elapsed between the (most recent) reaction and the allergological work-up, according to the chronology of the reaction, in 1431 children studied for suspected betalactam allergy. The difference between the two groups of children is highly significant ($p = 0.0002$)

Reaction (chronology)	≤1 year, n	>1 year, n	Total
Immediate	120	42	162
Non-immediate	749	520	1269
Total	869	562	1431

ated with clavulanic acid, based on negative responses in skin and challenge tests with amoxicillin and positive responses in challenge tests with amoxicillin-associated with clavulanic acid.

By means of skin and/or challenge tests, we also diagnosed allergic or non-allergic hypersensitivity to other drugs (e.g. non-opioid analgesics, antipyretics, and non-steroidal anti-inflammatory drugs), foods or additives in 34 (2.4%) children. No cause was found in the other children.

Immediate and non-immediate responses in skin tests diagnosed 86% (43/50) and 33.8% (60/177) of immediate and non-immediate sensitizations to betalactams.

In the 43 children diagnosed as having immediate-type hypersensitivity by means of skin tests, positive responses were observed in prick tests in two children (4.6%) and in ID tests at the concentrations of 0.25 in one (2.3%) and 2.5–25 mg/ml in 40 (93%) of the children, respectively. Non-immediate responses in ID tests were observed only at the higher concentrations used (25 000 IU/ml for penicillin G and 2.5–25 mg for the other betalactams). Isolated hyper-late responses in ID and/or patch tests were observed in six children who had reported non-immediate urticaria/angioedema ($n = 3$), SSLR ($n = 1$), EM ($n = 1$), and acute generalized exanthematic pustulosis (AGEP, $n = 1$). Of 10 betalactam-allergic children tested simultaneously by means of ID and patch tests, four responded to ID and patch tests, two to ID only, and four to patch tests only.

Adverse reactions were observed in six children (2.6%), including one immediate reaction (urticaria and asthma) and five non-immediate mild to moderate reactions (e.g. urticaria).

In the children with a negative allergological work-up and/or skin tested with non-suspected and non-potentially cross-reactive betalactams, false-positive responses were observed in immediate-reading ID tests with the highest concentrations of penicillin G in 2/841 children (0.24%), cefazolin in 1/862 children (0.1%), cefotaxime in 11/325 children (3.4%), and imipenem in 1/10 children (10%). False-positive late and/or hyper-late responses were also observed in patch tests with penicillin G in 3/270 children (1.1%), ampicillin in 2/265 children (0.75%), amoxicillin in 1/280 children (0.36%), and cefazolin in 2/256 children (0.8%).

One hundred and eleven of the 1431 children reacted to 130 challenge tests with the suspected and/or other betalactams. Forty-two reactions were induced by challenge tests performed in the hospital. Thirty-six of these reactions (85.7%) occurred in the hospital, and 6 (14.3%) occurred

once the children were back home. Eighty-eight reactions were reported to challenge tests performed at home. The mean time between the beginning of those challenge tests and the reactions was 3.8 days (range: 3 h–10 days). All the reactions were mild to moderately severe and resolved rapidly with oral antihistamines and/or corticosteroids, except for one urticaria with asthma exacerbation and two severe SSLR.

Cross-reactivity and/or co-sensitization with other betalactams in the same and/or other classes was diagnosed in 64 (28.2%) of the allergic children, either by means of skin tests ($n = 48$, 75%) or by means of challenge tests or clinical history ($n = 16$, 25%). Cross-reactivity/co-sensitization was diagnosed in 38/50 (76%) children with immediate and in 26/177 (14.7%) children with non-immediate-type sensitization to betalactams ($p < 0.001$). Most cross-reactivities or co-sensitizations in immediate- and non-immediate-type hypersensitivities were diagnosed between betalactams in the same class and/or with side-chain homology (e.g. aminopenicillins themselves and/or penicillins and/or first-generation cephalosporins: data not shown). However, 12 of the 64 (18.7%) children diagnosed allergic to second- and/or third-generation cephalosporins also reacted with penicillins, including aminopenicillins (data not shown).

Of the 227 allergic children, 125 (55%) were boys and 102 (45%) were girls ($p = \text{NS}$). Eighty-six (38%) of the allergic children and 535 (44.6%) of the non-allergic children had a personal history of atopy ($p = \text{NS}$). Mean age at the time of allergological work-up was 6 years (range: 4 months–17 years) in children diagnosed allergic to betalactams, and 5.4 years (range: 0.5 months–18 years) in the non-allergic children ($p = \text{NS}$). Betalactam hypersensitivity was diagnosed in 152 of the 869 children (17.5%) tested within 1 year of their (most recent) reaction and 75 of the 562 children (13.3%) tested later ($p = 0.036$). Immediate-type hypersensitivity to betalactams was diagnosed in 43 (28.9%) of the children tested within 1 year of their (most recent) reaction and in 7 (9.3%) of the children tested later ($p < 0.01$). Non-immediate-type hypersensitivity was diagnosed in 109 (71.7%) of the children tested within 1 year and in 68 (90.7%) of the children tested later ($p < 0.05$). The respective responses in skin and challenge tests and clinical history, in children diagnosed as having immediate- and non-immediate-type hypersensitivities to betalactams according to the time elapsed since their (most recent) reaction is indicated in Table 4. The differences between children tested within and later than 1 year are not significant ($p = 0.25$ for immediate-type hypersensitivity and $p = 0.56$ for non-immediate-type hypersensitivity, respectively).

Discussion

To our knowledge, we report the largest study carried out in children with suspected betalactam hypersensitivity.

Skin tests were not performed with penicilloyl-polylysine (PPL) and minor determinant mixture (MDM). Although these tests may help to diagnosis in up to 15% of the patients with immediate-type hypersensitivity to penicillins (8), we (preliminary results: not published) and other authors have

Table 4 Diagnosis of betalactam hypersensitivity by means of skin and challenge tests, and clinical history, according to the time elapsed between the (most recent) reaction and the allergological work-up. The differences are not significant ($p = 0.25$ for immediate-type hypersensitivity, and $p = 0.56$ for non-immediate-type hypersensitivity)

Type of hypersensitivity and diagnostic tests	≤1 year, n	>1 year, n	Total
Immediate-type			
Skin tests	36	7	43
Challenge test	7	0	7
Sub-total	43	7	50
Non-immediate-type			
Skin tests	40	20	60
Challenge test	62	42	104
Clinical history	7	6	13
Sub-total	109	68	177
Total	152	75	227

shown that the contribution of skin testing with PPL and/or minor determinants of penicillins in diagnosing immediate-type and non-immediate type hypersensitivities to betalactams is very limited (9, 10). However, skin tests with benzylpenicillin, which can partially compensate for skin tests with PPL and MDM (11), were performed in all the children with suspected penicillin allergy.

Although, for several betalactams, we used higher than usually recommended concentrations (12), only a few false-positive responses were observed in the children with a negative allergological work-up and/or skin tested with non-suspected and non-potentially cross-reactive betalactams. Most of these reactions were observed in immediate-reading ID tests to cefotaxime and imipenem.

In the children reporting suspected allergic reactions to amoxicillin associated with clavulanic acid, skin tests were performed with amoxicillin alone because we (preliminary results: not published) and other authors have shown that skin tests performed with amoxicillin associated with clavulanic acid were not reliable (13, 14), and because, until recently, no commercial preparation of clavulanic acid alone was available. However, it has recently been reported that skin tests performed with clavulanic acid alone may be sensitive and specific (15).

Although systemic reactions, including anaphylaxis, have been reported in 8–11% of patients skin tested with betalactams (16, 17), only 2.6% of the allergic children (0.6% of the 1431 children) in our study reported mild to moderate reactions to skin testing, probably attributable to inadvertent subcutaneous injection of the reagents. This result is consistent with other studies showing that skin tests with betalactams are safe, especially in children (1–4).

Consistent with other studies (1–4), 15.9% of the children in our study were diagnosed allergic to betalactams. Most allergic children had reported immediate and/or severe reactions (anaphylaxis, SSLR, potentially harmful skin reaction), confirming that the likelihood of betalactam hypersensitivity increases with the earliness and the severity of the reaction (1–4).

Selective hypersensitivity to clavulanic acid was diagnosed in 42.5% of the children diagnosed allergic to amoxicillin associated with clavulanic acid. The prevalence of clavulanic acid allergy is unknown, but up to 30% of the patients reacting to amoxicillin associated with clavulanic acid have been diagnosed allergic to clavulanic acid based on negative responses in *in vivo* and/or *in vitro* tests with amoxicillin and positive responses with amoxicillin associated with clavulanic acid (3, 10, 13).

In our study, 86% of immediate-type hypersensitivities to betalactams were diagnosed on immediate responses in skin tests and 68.4% of non-immediate-type hypersensitivities by means of challenge tests, highlighting the diagnostic value of skin tests for immediate-type hypersensitivity and of challenge tests for non-immediate-type sensitizations to betalactams (1, 3, 4, 8, 12, 17, 18).

Non-immediate responses in skin tests have been reported in patients with non-immediate-type hypersensitivity to betalactams (3, 18–21). Our results in the 10 children diagnosed as having non-immediate-type hypersensitivity to betalactams by means of ID and patch tests suggest that patch tests should be performed in children reporting non-immediate reactions to betalactams (SSLR and potentially harmful skin reaction especially), as previously reported (21, 22). Our results in six children with isolated hyper-late responses in ID and/or patch tests also confirm that skin tests should be read at days 6–7 in the patients reporting non-immediate reactions and with negative responses in skin tests at days 2–3 (20).

According to the European guidelines (23), challenge tests are contraindicated in patients reporting anaphylaxis and potentially harmful skin reactions. However, SSLR, EM, and Stevens–Johnson syndrome (SJS) in children result mainly from (viral) infections (24). In our study, more than half of the children reporting SSLR, EM, and SJS, and with negative responses in skin tests, tolerated a complete course of the suspected betalactams, consistent with previous results (2). These results suggest that challenge tests with the suspected betalactams, if essential only (future necessity), might be performed in children with SSLR, EM, and SJS and negative responses in skin tests.

Theoretically, challenge tests should be performed in the hospital, under medical supervision. However, as shown in other studies, the diagnosis of non-immediate hypersensitivity to betalactams in children is mainly based on prolonged challenge tests (2, 3, 12, 18). In the present study, a few children only reacted to challenge tests performed at home, and most reactions were mild to moderately severe. Thus, we confirm that prolonged challenge tests may be performed at home in the children with negative responses in skin tests and reporting mild to moderately severe non-immediate reactions to useful/essential betalactams.

Consistent with other studies (1, 19, 25, 26), respectively, 76% and 14.7% of the children diagnosed as having immediate- and non-immediate-type hypersensitivities to betalactams in our study reacted to other betalactams in the same and/or other classes. Most cross-reactivities or co-sensitizations in immediate- and non-immediate-type hypersensitivities were diagnosed between betalactams in the same class and/or with

side-chain homology. However, 18.7% of the children diagnosed allergic to second- and/or third-generation cephalosporins also reacted with penicillins, including aminopenicillins, suggesting that cross-reactivity between or co-sensitization to cephalosporins and penicillins may be more frequent than previously reported, as shown recently (26–28) and that penicillins should be tested (skin tests and, if negative, challenge tests) in the children reporting suspected allergic reactions to cephalosporins.

As shown previously (2, 3, 12), personal atopy, age, and sex were not significant risk factors for betalactam allergy in children. Two-thirds of the children diagnosed allergic to betalactams in our study have been explored within the first year of their most recent reaction. This may result from several causes:

- 1 A time-trend decrease in *in vivo* and *in vitro* reactivities (of immediate-type especially) (25, 29–32), which may lead to resensitization by challenge tests, including well-tolerated challenge tests and allergic reactions during subsequent treatments with betalactams (2, 33–36). However, in our study, all the seven children diagnosed as having immediate-type hypersensitivity to betalactams later than 1 year after their (most recent) reaction had positive responses in skin tests. Moreover, we and other authors (5, 37) have shown that 97–99% of the children with negative responses in skin and challenge tests did not develop subsequent sensitization and allergy to betalactams;
- 2 The fact that a majority of children with severe or worrying reactions, which result from betalactam hypersensitivity more frequently than less worrying reactions, are referred for allergological work-up more promptly than the children with mild to moderately severe and non-immediate reactions, as shown in our study.

Conclusion

To our knowledge, we report the largest study carried out in children with suspected betalactam hypersensitivity. Few children were truly allergic, and the likelihood of betalactam allergy increased with the earliness and/or the severity of the reactions. Cross-reactivity and/or co-sensitization among betalactams was more frequent in children reporting anaphylaxis and/or immediate reactions than in the other children. Skin tests with betalactams were safe, and immediate-reading skin tests had a good diagnostic value in children with immediate-type hypersensitivity to betalactams. Although the diagnostic value of non-immediate-reading skin tests was low, ID and/or patch tests diagnosed non-immediate-type hypersensitivity in numerous children with betalactam-induced urticaria/angioedema, SSLR, and potentially harmful skin reaction. Age, sex, and personal history of atopy were not significant risk factors.

Based on our large experience and on a review of the literature, we suggest a practical diagnostic approach in children with suspected betalactam hypersensitivity:

- 1 In anaphylaxis and immediate reactions, we suggest that all classes of betalactams should be withdrawn until skin tests (pricks and ID), and, possibly, *in vitro* tests (29, 38), with the suspected betalactam(s) and other betalactams

from the same and other classes and challenge test (if necessary), have been performed. Ideally, the allergological work-up should be performed 4–6 weeks after the reaction (7) and, in any case, as soon as possible because there is a high annual rate of negativization of diagnostic tests for immediate-type betalactam allergy (25, 29–32).

- 2 In non-immediate mild to moderately severe urticaria and/or angioedema, the allergological work-up, based on skin tests (pricks, ID, and/or patch tests) and challenge tests in the children with negative skin test results, is also recommended. The risk of betalactam hypersensitivity is low, and cross-reactivity to several (classes of) betalactams is infrequent. Thus, betalactams from other classes than that suspected are not contraindicated.
- 3 As a rule, whether skin tests are positive or negative, the suspected betalactams are contraindicated in patients with SSLR, EM, and SJS, with no contraindication for other (classes of) betalactams. However, SSLR, EM, and SJS in children are mainly because of (viral) infections, and our results suggest that an allergological work-up based on non-immediate-reading ID and patch tests can be performed in children with SSLR, EM, and SJS and that challenge tests might be proposed in the children with negative skin test results and reporting reactions to essential (future necessity) betalactams.
- 4 Non-immediate-reading ID and patch tests may also be useful in children with AGEF, TEN, and drug rash with eosinophilia and systemic symptoms, especially when several drugs are suspected. However, challenge tests with the suspected drugs are contraindicated in children with negative responses in skin tests because there is a high risk of severe relapse (23). Although the risk of cross-sensitization is low, betalactams from the same class are contraindicated, but not betalactams in other classes. Recent advances with *in vitro* tests for non-immediate-type drug-induced hypersensitivity have been published (39, 40), but deserve confirmation.
- 5 In the other cases, such as unidentified mild rashes and MPR, skin tests are probably useless. The diagnosis of betalactam hypersensitivity is often ruled out based on tolerance of the challenge test with the suspected drug. However, an allergological work-up is needed in the rare children relapsing during challenge test (41).
- 6 Finally, prolonged challenge test (full therapeutic dose $\times$ several days) may be performed at home in the children reporting mild to moderately severe non-immediate reactions to betalactams, provided that the children have been prescribed an emergency treatment (oral antihistamines and/or corticosteroids).

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Conflict of interest

The authors do not declare any competing interests.

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