

ORIGINAL ARTICLE

Beta-lactam hypersensitivity in children with cystic fibrosis: a study in a specialized pediatric center for cystic fibrosis and drug allergy

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Keywords

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Abstract

Background: Beta-lactam hypersensitivity (HS) is suspected in 5–12% of the children, but proven in only 10–15% of those children, based on skin and challenge tests results. In contrast, 30–60% of patients with cystic fibrosis (CF) are diagnosed allergic to beta-lactams, based mainly on the clinical history of the patients.

Objectives: To confirm or rule out a suspected beta-lactam HS in CF children and to determine the prevalences of suspected and confirmed beta-lactam HS in those children.

Patients and methods: Children with CF and suspected beta-lactam HS were explored by means of skin and challenge tests with the suspected and alternate beta-lactams. The results in CF children were compared with those reported in the literature in non-CF children.

Results: Eight of the 701 CF children followed in our center between 1990 and 2011 (1.14%), and 11 other children from other centers were explored for suspected beta-lactam HS. Beta-lactam HS was diagnosed in nine of these children (47.3%). Based on the results in the children followed in our center, the prevalence of beta-lactam HS was 0.71% (5/701) in CF children vs. a mean estimated prevalence of 1–1.5% in the general pediatric population.

Conclusion: Our results contrast with those of most previous studies. Although half of the CF children with suspected beta-lactam HS were truly allergic to beta-lactams, the general prevalence of beta-lactam HS in CF children was very low. This may result from tolerance induced by frequent and/or prolonged treatments with beta-lactams.

Drug hypersensitivity (HS), to beta-lactams especially, is suspected in 5–12% of children (1–4), but studies based on skin and challenge tests have shown that only 12–60% (mean: 10–15%) of those children, that is, 0.5–1.8% of the children in the general population, are truly allergic to beta-lactams (5–8). In contrast, beta-lactam HS is suspected/diagnosed in 29–62% (mean = 30%) of patients with cystic fibrosis (CF) (9–14), but solely based on the clinical history of the patients, probably leading to overdiagnosis. Indeed, recent studies based on skin, *in vitro*, and challenge tests have shown that only 0–4% of patients with CF were truly allergic to beta-lactams (15, 16).

Objectives

We aimed to confirm or rule out a suspected diagnosis of beta-lactam HS in CF children, and to determine the prevalences of

suspected and confirmed beta-lactam HS in those children. We also aimed to compare these prevalences with the prevalences reported in the literature in non-CF children.

Methods

Patients

We reviewed retrospectively the files of the children followed for CF between 1990 and 2011 in our specialized unit for CF (CRCM: Centre de ressources & de compétences pour la mucoviscidose) and for drug allergy exploration in children (Pulmonology & Allergy pediatric unit). During this period, 701 CF children were followed in the CRCM, and 19 CF children (eight followed in our CRCM and 11 in other centers) were explored for suspected beta-lactam HS. The reactions were classified as immediate when they occurred within the first

hour of drug administration and non-immediate when they occurred later (17).

Skin tests

As previously reported (8), pricks, intradermal (ID), and patch tests were performed with the soluble forms of the suspected (or very similar) beta-lactams and other beta-lactams from the same and other classes. Beta-lactams were serially diluted with 0.9% sterile NaCl. The concentrations used were 250–25,000 IU/ml for penicillin G, 0.25–25 mg/ml for the other beta-lactams for pricks and ID tests, 250,000 IU/ml for penicillin G, and 250 mg/ml for the other beta-lactams for patch tests. Pricks and ID tests were performed in all the children. Patch tests were performed in selected children reporting non-immediate reactions, using plastic Haye's test chambers (Destaing Lab, Grasse, France).

Responses in skin tests were assessed at 15–20 min (immediate, pricks, and ID), 6–8 h (semilate, ID), 48–72 h (late, ID, and patch tests), and 6–7 days (hyperlate, ID, and patch tests), according to the ENDA/EAACI guidelines (18). Briefly, a wheal ($\pm$ surrounding erythema) ≥ 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). Semilate, late, and hyperlate responses to ID injections were classified as positive if indurated erythema/papules ≥ 5 mm in diameter were present. Patch tests were considered as positive when erythema and papules (+), erythema and vesicles (++), erythema, coalescent vesicles, and/or bullae (+++) were present.

Challenge tests

Challenges with the suspected betalactams were performed several days or weeks after skin testing in children with negative skin test results. Challenges were performed either in the hospital for 24 hours–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 (8). In children with positive responses in skin or challenge tests, challenges 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.

Challenges were considered as positive if an objective adverse reaction of an allergic nature, such as anaphylaxis, urticaria and/or angioedema, maculopapular rash, erythema multiforme, etc., occurred during the treatment or within 24–48 hours of the end of the treatment (8).

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

Statistical analysis

The differences for quantitative data were assessed by the Student's *t*-test, and the differences for qualitative data were

assessed by the chi-square test or by the Fisher's exact test when the number of cases was low. A *p* value < 0.05 was considered significant.

Results

Clinical and demographic characteristics of the children

The 19 CF children (mean age = 11.2 yrs, range: 1.4–18.6 yrs; ratio M/F = 0.58) reported 39 reactions to ceftazidime (*n* = 13, 33.3%), amoxicillin alone or associated with clavulanic acid (*n* = 7, 17.9%), ureido/carboxypenicillins (*n* = 8, 20.5%), aztreonam (*n* = 5, 12.8%), and other beta-lactams (*n* = 7, 17.9%). When it was known (*n* = 32/39), these drugs had been administered for secondary infections by *Pseudomonas aeruginosa* (*n* = 19, 59.3%), *Staphylococcus aureus* *meti S* (*n* = 10, 31.25%), *Achromobacter xylosoxidans* (*n* = 1, 3.1%), *H. influenza* (*n* = 1, 3.1%), or *E Coli* (*n* = 1, 3.1%). The drugs had been administered orally and intravenously (IV) in 9/39 (23%) and 30/39 (77%) cases, respectively. Twenty-eight reactions (71.8%) were urticaria/angioedema, and 11 reactions (28.2%) were grade 3–4 anaphylaxis. Nineteen reactions (48.7%) were immediate and 20 (51.3%) non immediate. The mean time between the (most recent) reaction and the allergological work-up was 4.4 months (range: 0.5 month–5 years).

Results of allergological work-up

HS to a single or several beta-lactam(s) was diagnosed in nine of the CF children (47.3%), including five of the children followed in our CRCM and four children followed in other centers, by means of positive responses in skin (*n* = 5, 55.5%) and challenge (*n* = 3, 33.3%) tests, and clinical history (relapsing anaphylaxis to aztreonam, including when the drug was administered using a “desensitization” protocol; *n* = 1, 11.1%). Those children had reported 23 reactions to tazocillin (piperacillin-tazobactam, *n* = 4), ceftazidime (*n* = 8), aztreonam (*n* = 5), ticarcillin/temocillin (*n* = 2), amoxicillin (*n* = 2), oxacillin (*n* = 1) and piperacillin (*n* = 1). The reactions were pruritic rashes or urticaria/angioedema (*n* = 14, 60.9%) and anaphylaxis (*n* = 9, 39.1%). Thirteen reactions (56.5%) were immediate and 10 (43.5%) were non immediate (Table 1). Mean age at the time of allergological work-up was 12.9 yrs (range: 1.4–18.7 yrs) in children diagnosed allergic to beta-lactams and 9.6 yrs (range: 1.7–16.9 yrs) in the non-allergic children (*p* = 0.1780). Beta-lactam HS was diagnosed in seven of the 17 children (41.17%) tested within 1 yr of their (most recent) reaction, and two of the 2 children tested later (*P* ≤ 0.5). The mean numbers of IV treatments with beta-lactams in CF children allergic (*m* = 11.4, range: 0–40) and non-allergic to beta-lactams (*m* = 3, range: 0–16) were not significantly different (*p* = 0.19).

We do not know the numbers of CF children followed in other centers. Thus, we can determine the prevalence of suspected and confirmed beta-lactam HS only in CF children followed in our CRCM. Five of those 8 children with CF and suspected beta-lactam HS (62.5%) were diagnosed allergic to beta-lactams. Based on these data, we can estimate that the

Table 1 Characteristics of the CF children with proven betalactam hypersensitivity, based on skin and challenge tests results, and clinical history

Patient (n°)	Sex	Age	Suspected BL	Reactions (type & chronology)	Skin test results	Challenge test results
1	M	14.3 y	Tazocillin	Giant urticaria (< 30 mn)	Tazocillin : +(immediate reading) Piperacillin : + (immediate reading) Aztreonam : + (immediate reading)	ND ND ND
2	M	17 y	Oxacillin Tazocillin	Urticaria (< 30 mn) Urticaria (< 30 mn)	Oxacillin : + (semi-late & late readings) Tazocillin : 0 (all readings)	ND
6	F	17 m	Amoxicillin/CA Amoxicillin	Urticaria/angioedema (D7) Urticaria (D6)	Amoxicillin : 0 (all readings)	Amoxicillin : MPR (D7)
7	F	15.4 y	Ceftazidime Ceftazidime Tazocillin	Pruritus/laryngeal edema (30 mn) Pruritus/laryngeal edema (30 mn) Pruritic rash (D4)	Ceftazidime : 0 (all readings) Tazocillin : 0 (all readings)	Ceftazidime : + (4 h) Ceftriaxone : + (3 h) Tazocillin : + (D3-4) Amoxicillin : tolerated
8	M	13 y	Ceftazidime Tazocillin Piperacillin Aztreonam	Urticaria (< 30 mn) Urticaria/asthma/ hypotension (< 30 mn) Urticaria,/asthma/ hypotension (< 30 mn) Urticaria/asthma/ hypotension (< 30 mn)	Ceftazidime, 0 (all readings) Tazocillin, 0 (all readings) Piperacillin, 0 (all readings) Aztreonam, 0 (all readings)	Ceftazidime : + (immediate) Tazocillin, piperacillin and aztreonam : + (immediate, including using desensitization)
9	F	8 y	Ticarcillin	Anaphylactic shock (< 30 mn)	Ticarcillin : + (immediate reading) Imipenem : + (immediate reading)	ND ND
11	F	15 y	Ceftazidime Aztreonam Temocillin	Urticaria (1 h) Urticaria (1 h) Urticaria (1 h)	Ceftazidime : 0 (all readings) Aztreonam : + (immediate reading) Ticarcillin : 0 (all readings)	Ceftazidime : tolerated Aztreonam : ND Temocillin/ticarcillin : ND
12	M	13.5 y	Ceftazidime Ceftazidime Ceftazidime	Pruritus (D4) Pruritus (90 mn) Pruritus (D2)	Ceftazidime : 0 (all readings) Ceftriaxone : + (immediate reading)	Ceftazidime : tolerated
19	F	18.7 y	Ceftazidime Aztreonam Aztreonam Aztreonam	Larynx edema/ tachycardia (8 h) Pruritus/larynx edema/hypotension (8 h) Rash/hypotension (desensitization: D3) Generalized and larynx edema (desensitization : 6 h)	Ceftazidime : 0 (all readings) Aztreonam : 0 (all readings)	Ceftazidime : tolerated Ticarcillin : tolerated Aztreonam : ND (highly suggestive clinical history)

BL, betalactam; CA, clavulanic acid; CF, cystic fibrosis; D, day; F, female; h, hours; M, male; m, months; mn, minute; MPR, maculopapular rash; ND, not done/not determined; y, years).

prevalence of suspected beta-lactam HS is 8/701 (1.14%) and that the prevalence of confirmed beta-lactam HS is 5/701 (0.71%) in the CF children (Table 2).

Discussion

High doses of beta-lactams, IV ureido/carboxypenicilins and ceftazidime especially, are widely administered to treat respiratory infections in CF patients. Thus, suspected beta-lactam HS restrict therapeutic options in those patients,

leading to the choice of other anti-infectious drugs, often less effective and sometimes more dangerous.

Our results contrast with those of other studies showing that anti-infectious drug HS, to beta-lactams especially, is suspected in 29–62% (mean = 30%) of patients with CF (9–14) vs. 5–12% of the children in the general pediatric population (1–4). In the retrospective study by Wills et al. (10), in 53 CF children and adolescents, the prevalence of anti-infectious drug HS was 33%, the most frequently suspected antibiotic being piperacillin. The most allergenic route of administration was the IV

Table 2 Prevalences of suspected and proven beta-lactam allergy in cystic fibrosis (CF) children

	CF children (n = 19)	
	CRCM Necker-EM	Children in other centers
Suspected allergy		
n	8	11
Prevalence	1.14% (8/701)	Unknown
Proven allergy in children with suspected allergy		
n	5	4
Prevalence	62.5% (5/8)	36.4% (4/11)
Proven allergy in all the children		
n	5	4
Prevalence	0.71% (5/701)	Unknown

route, and the risk of reaction increased with the number of IV courses of antibiotherapy. As in the retrospective Pleasants' study (9), in 111 adults, most frequent reactions were febrile non-immediate reactions. In Burrows' retrospective study (11), in 150 adolescents and adults, the prevalence of beta-lactam HS was 36%, and the risk of HS increased with the age of the patients and the number of treatments. The most important prevalence of beta-lactam HS (62%) was reported by Koch et al. (14), in 121 children chronically infected by *Pseudomonas aeruginosa* and frequently treated with beta-lactams (mean number of courses: 23). These results strongly suggested that the high prevalence of (suspected) allergy to anti-infectious drugs in patients with CF resulted from their frequent exposition to these drugs. Indeed, it has been shown that repeated IV administration of antigens/allergens was highly immunogenic/allergenic (19, 20). However, in these studies, diagnosis of beta-lactam HS was solely based on clinical history, probably leading to overdiagnosis. Indeed, more recent studies based on skin, *in vitro*, and challenge tests have shown that only 0–4% of patients with CF were truly allergic to beta-lactams (15, 16).

Our results show that:

- 1 Only a very few CF children needed to be explored for suspected beta-lactam HS by means of skin and challenge tests (1.14% in the CRCM vs. 5–12% of the children in the general population). Several factors may explain this result: (i) A high degree of cooperation between pulmonologists and allergists, leading to an extensive allergological work-up only in the children with a highly suggestive clinical history of beta-lactam allergy. In the other children, with not or less suggestive reactions such as non-immediate benign urticaria or non-urticarial rashes and isolated non-immediate fever, skin tests were not performed and diagnosis was often ruled out directly on the tolerance of challenge tests performed with the suspected beta-lactams; (ii) although it has been claimed that frequent exposure to drugs may lead to sensitization and allergic HS (10, 11, 14), repeated or chronic exposure to antigens/allergens may also lead to immunological tolerance, depending on the genetic background, the age and nutritional status of the subjects, the conditions of allergen exposure, and other environmental factors (19, 20); and (iii) as shown in non-CF children, most allergic-like reactions to beta-lactams more likely

result from the infectious diseases (viral infections especially) for which the antibiotics have been prescribed and/or from microbial death than from drug HS (6–8). Furthermore, viral infections/reactivations may be promoted by various drugs, including beta-lactams, either because of the immunoregulatory properties of the drugs or by direct activation of viral replication (21–23).

- 2 Numerous children with CF and suspected beta-lactam HS were diagnosed allergic to beta-lactams (47.3% of the whole group and 62.5% of the children of the CRCM). Indeed, the CF children with suspected beta-lactam HS were highly selected, based on their clinical history. Most of those children reported urticaria/angioedema and anaphylaxis, and most reactions were immediate. It has been shown that the risk of HS to beta-lactams was significantly higher in the children reporting immediate and/or severe reactions than in the other children (5–8). Moreover, in those children, development of beta-lactam HS may have been promoted by «danger signals» related to chronic infection, inflammation, and fever (24). Finally, all but two children with CF and suspected beta-lactam HS were explored within 1 yr of their (most recent) reaction. This may also explain the high prevalence of beta-lactam HS in those children. Indeed, numerous studies have shown that the patients with beta-lactam HS loosed their reactivity, of the immediate-type especially, with time (6, 8, 25–28).
- 3 Few CF children are truly allergic to beta-lactams (0.7% for the children of the CRCM) vs. 1–1.8% of the other children. Our results contrast even more with those of previous studies reporting a mean prevalence of 30% of beta-lactam HS in patients with CF (9–14), but firmly agree with those of Møller et al. (15). In their study, 16 of 84 patients with CF developed skin reactions during intensive carbenicillin therapy. All the patients had negative responses in skin and *in vitro* tests (specific IgM, IgG, and IgE determinations, and leukocyte histamine-release test) with carbenicillin and tolerated prolonged oral challenges with phenoxymethylpenicillin. Our results are also consistent with those of Caimmi et al. (16). In this study, also performed in a highly specialized center, 23/171 (13.45%) patients with CF reported a highly suggestive clinical history of beta-lactam HS. Based on skin tests, challenge tests, and clinical history, only seven of these patients (30.4%), representing 4% of the patients with CF, were diagnosed allergic to beta-lactams. Based on these studies and our own results, the prevalence of beta-lactam HS in CF children appears quite similar to, if not lower than the prevalence found in non-CF children (1–1.8%).

Limitations to our study are as follows:

- 1 Our study was retrospective. Several children from other centers with CF and beta-lactam HS may have been missed (not sent for allergological work-up, and/or treated with other anti-infective drugs or treated with the suspected drugs using a “desensitization” protocol).
- 2 Drug allergy is more frequent in adults than in children (28), either due to the age of the patients and/or to a larger exposure to drugs (29). In Burrows' study (11), only 14% of the 54 patients with CF and (suspected) beta-lactam HS

were children and adolescents. Thus, it should be interesting to follow the CF children until adulthood to determine the (possible) onset of new beta-lactam hypersensitivities. However, in Wills et al. study (10), a similar prevalence of beta-lactam HS (33%) was reported as well in children as in adults with CF.

- 3 In most studies previously reported, piperacillin was the most frequent beta-lactam suspected to induce HS in patients with CF. However, in the CF children in our study, pseudomonal colonizations and infections were treated with other beta-lactams, ceftazidime especially, which does not cross-react immunologically with piperacillin (7, 30). Thus, it is difficult to compare the results of studies performed in patients treated with different beta-lactams.
- 4 Only children with a highly suggestive clinical history (immediate and/or potentially severe reactions) were explored by means of skin and challenge tests. In the children with non-suggestive or less suggestive reactions diagnosis was often ruled out on the tolerance of first-line challenges performed with the suspected beta-lactams. This was especially the case in children reporting late-onset (10–15 days) febrile reactions, in whom shorter treatments with the suspected drugs were tolerated. The mechanisms responsible for these febrile delayed reactions are unknown, and these children were not diagnosed allergic to beta-lactams in our study.

Conclusion

To our knowledge, we report the largest study concerning the prevalence of suspected and diagnosed beta-lactam HS in children with CF. We show that the frequency of proven beta-lactam HS is high in CF children with suspected beta-lactam HS. This probably results from a rigorous selection of the children with a highly suggestive clinical history. Such a selection is not observed in the general pediatric population, referred to allergological centers by their general practitioners or pediatricians. In contrast, the global prevalences of suspected and confirmed beta-lactam HS are lower in CF children than in children without CF. This unexpected result, as compared to the classical data in the literature, should be confirmed by prospective studies also based on skin and challenge tests, and not only on the clinical history of the patients.

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Conflict of interest

The authors declare they have no competing interests in relation with this article.

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