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The diagnosis of hypersensitivity to antibiotics is rarely confirmed by allergy work-up in cystic fibrosis patients

Running Title: Antibiotic hypersensitivity in cystic fibrosis

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Highlights:

- The prevalence of antibiotic hypersensitivity in CF patients is comparable to that observed in the general population
- Only a small proportion of suspected antibiotic hypersensitivities is confirmed by the allergology work up and/or the drug challenge
- β -lactams are the most frequently involved antibiotics in these reactions, but attention must be paid to other molecules, especially cotrimoxazole.

Keywords: cystic fibrosis – antibiotic – hypersensitivity – allergy work-up

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Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance receptor; CI = confidence interval; CTX = cotrimoxazole; FDE = Fixed Drug Eruption; FEV1 = forced expiratory volume in 1 second; HSR = hypersensitivity reaction; IDT = intradermal test; IV = intravenous; sIgE = specific IgE; SCAR = severe cutaneous adverse drug reaction; SPT = skin prick-test.

Conflicts of interest: None of the study authors declared any conflicts of interest.

Abstract

Background: Cystic fibrosis (CF) patients receive many antibiotic treatments for recurrent respiratory infections and frequently report antibiotic hypersensitivity reactions (HSRs).

Methods: In this retrospective study, medical records of CF patients were reviewed to clarify the clinical features, the culprit antibiotics and the prevalence of antibiotic HSRs in the CF population.

Results: From 601 CF patients, 95 suspected antibiotic HSRs occurred in 60 patients (prevalence of 10.0%). β -lactams were the most common inducers but cotrimoxazole was also frequently involved. 76 of 95 suspected HSRs were assessed by allergy work-up including skin tests (43/76 reactions) and/or drug reintroduction as a full course of the culprit antibiotic (73/76 reactions). From the 43 suspected HSRs that were skin tested, only 3 had positive skin tests and were not subjected to drug readministration. All the other 73 suspected HSRs received a full course of the culprit antibiotic: HSR symptoms recurred in 10/73 cases and therefore were considered as confirmed antibiotic HSRs; for the remaining 63 suspected HSRs that did not relapse after drug readministration, the diagnosis of antibiotic HSRs was excluded. In summary, 13/76 suspected HSRs were confirmed as antibiotic HSRs.

Conclusion: The prevalence of suspected and confirmed antibiotic HSRs in CF patients appears similar to that reported in the general population. Of note, most of the antibiotic Suspected HSRs are not confirmed after allergology work-up. A complete allergy work-up appears therefore crucial to make a correct diagnosis and to avoid unnecessary contra-indication of major antibiotics.

Keywords: allergy work-up; antibiotics; cystic fibrosis; hypersensitivity.

Introduction

Drug hypersensitivity reactions (HSRs) are frequent adverse drug reactions defined as reactions “that clinically resemble allergy”¹. Among them, distinction must be made between allergic and non-allergic HSRs². In allergic HSRs, the drug acts as a hapten and leads to the activation of a specific adaptive immune response: production of drug-specific immunoglobulin (Ig)E leading to major activation of mast cells and basophils (IgE-mediated allergy), production of drug-specific IgG/IgM or proliferation and activation of drug-specific T cells (non-IgE-mediated allergy)^{2,3}. In contrast, in non-allergic HSRs, the adaptive immunity can be activated by a direct interaction of the drug with an immune receptor (*pharmacological interaction with immune receptors* [*p-i*] concept³), or by pharmacological off target activity on a non-immunological receptor (such as the MRGPRX2⁴) or an enzyme (such as the cyclooxygenase)⁵. Distinction is important because drug-specific mechanisms (allergic HSRs) induce a higher risk of more severe reactions with time and, in most cases, lead to strict avoidance of the culprit drug, whereas patients with non-allergic HS can usually receive the drug with some precautions⁶. Thus a complete allergy work-up, including skin tests, *in vitro* tests and drug challenge must be carried out when a HSR occurs¹.

In patients with cystic fibrosis (CF), antibiotics are used to treat infectious respiratory exacerbations or to eradicate pathogens, which chronically infect their airways. Notably, airway infection by *Pseudomonas aeruginosa*, occurring in 44.6% of CF patients in 2017⁷, is considered as an important step in the disease. The frequent resistance of *P. aeruginosa*⁸ requires the use of broad spectrum antibiotics, limiting the therapeutic arsenal to a few molecules. Thus, a diagnosis of allergy to one of these antibiotics may be detrimental for CF patients. Unnecessary antibiotic exclusion without confirmed diagnosis of HSR may lead to suboptimal treatment and increased socio-economic impact^{9–11}.

While some studies have reported a higher prevalence of antibiotic HSRs in the CF population (up to 60%)^{12–16}, others have suggested the same prevalence as in the general population (less than 20%)^{17–19}. However, most of these studies limited their observation to β -lactams and did not include the results of the allergy work-up necessary to confirm HSR diagnosis and to discriminate as far as possible allergic from non-allergic HSRs. In this context, the aim of our study was to analyze the suspected antibiotic HSRs in a cohort of both child and adult CF patients in order to define the clinical features, the antibiotics involved, the percentage of confirmed HSRs and the role of positive skin tests in the allergy work-up of these reactions.

Patients and methods

We conducted a retrospective study in the CF reference and competence center data base in Lyon, France. The cohort was obtained using the words “intolerance”, “hypersensitivity” and “allergy” in the search algorithm of our medical file system. The collected data were analyzed anonymously. The study was approved by the ethics committee of Lyon University Health Center and the National Commission for Data Protection and Liberties (2018/08/24).

Selection of CF patients. In order to estimate the prevalence of Suspected HSRs in the CF population, all CF patients followed in the center between January 2012 and August 2018, who had a history of suspected HSR during an antibiotic treatment, were included in the study. Each reaction was considered individually, even if several occurred in the same CF patient. We then excluded any suspicion of HSR, except those with positive skin test, which were assessed with neither a provocation test, nor a full course reintroduction of the culprit antibiotic.

Antibiotic HSR. Following international consensus¹, a reaction that looked like an allergy was named “suspected HSR”. For HSR diagnosis confirmation, clinical signs of HSR after the reexposition to the culprit antibiotic were needed: that corresponded to positive skin tests (prick-test [SPT] and/or intradermal test [IDT] with reading at 30 minutes for immediate reactions and IDT and/or patch-test with reading at 48-72 hours for nonimmediate reactions) or recurrence of the symptoms during an antibiotic full course. In cases of both negative skin test and absence of HSR symptoms during the antibiotic reintroduction, the diagnosis of HSR was excluded.

Immediate and non-immediate reactions. A reaction was considered as “immediate” if a clinical reaction congruent with a HSR occurred within six hours after starting the antibiotic course and as “non-immediate” if it occurred later^{1,20,21}.

Data on suspicion of HSRs. For every reaction, we collected: (i) the offending antibiotic name and its class, route of administration [oral or intravenous (IV)], (ii) the delay of onset of the HSR after the treatment initiation, (iii) the clinical symptoms: type of skin symptoms [pruritus, urticaria, exanthema, fixed drug eruption (FDE)], systemic involvement (gastrointestinal, respiratory, cardiovascular or neurologic symptoms), duration of skin symptoms. For immediate reactions, the Ring and Messmer grade 1 to 4²² was collected to evaluate severity.

For each suspected HSR, we collected age, anthropometrical parameters (body weight, height and body mass index [BMI], expressed for children as Z-score for age and height using the World Health Organization references, available on www.who.int), forced expiratory volume in 1 second (FEV1) expressed as Z-score²³ and as a percent predicted using the Zapletal reference equation²⁴, the bacteriologic and Aspergillus status of the patient. We also collected BMI and mean FEV1 one year before the HSR onset. We documented if the patient, when the reaction occurred, had an exocrine pancreatic insufficiency, diabetes and/or CF liver disease, if he was treated with systemic corticosteroids and had already reacted during another drug course. We reported the number of oral and intravenous antibiotic courses over the previous year.

For each patient, we also collected gender, type of *CFTR* (cystic fibrosis transmembrane conductance receptor) mutation, and atopic history.

Allergy work-up. We collected the results of SPT, IDT and patch-tests when available, and antibiotic reintroduction. Skin tests were performed using known non-irritating concentrations for the following β -lactams²⁵: amoxicillin (SPT and IDT: 20 mg/ml; patch-tests: 5%), cephalosporins (2 mg/ml; 5%), cloxacillin (20 mg/ml; 5%). Major and minor determinants were also used for SPT and IDT (minor determinant mixture at 2.10^{-2} mM and penicilloyl-poly-L-lysine at 5.10^{-5} mM). For other β -lactams and non- β -lactam antibiotics, the concentrations were used according to medical literature or the current practices of our center: meropenem (1 mg/ml), imipenem (0.5 mg/ml), piperacillin-tazobactam (4.5 mg/ml), cotrimoxazole (8 mg/ml), azithromycin (0.01 mg/ml), ciprofloxacin (0.02 mg/ml), vancomycin (0.005 mg/ml), doxycycline (0.1 mg/ml). For linezolid (commercial concentration: 2 mg/ml), and teicoplanin (125 mg/ml), the 1/1000 dilution was used. For antibiotic reintroduction, we considered a classical reintroduction test (one antibiotic intake or antibiotic course for three days maximum)²⁰ and, when negative, complete reintroduction, in terms of length of treatment and dosage of antibiotic.

Other definitions. Exocrine pancreatic insufficiency was considered if the patient received pancreatic enzyme supplements, CF liver disease if he received ursodeoxycholic acid and diabetes if he received insulin therapy.

Chronic bacterial colonization was defined by positive cytobacteriological testing of expectorated sputum to the same germ three times over the previous six months. Allergic bronchopulmonary aspergillosis (ABPA) was considered according to Agarwal et al definition²⁶.

Statistical analysis. Statistical descriptions were performed using the R software (version 3.3.2, <http://www.R-project.org>). The characteristics of CF patients and reactions were described using absolute and relative frequencies for categorical variables, and mean ($\pm$ standard derivation) for quantitative variables.

Non-parametric Wilcoxon tests were performed to compare quantitative outcomes among the different subgroups. For influence of qualitative outcomes, Fisher's exact tests were performed.

Results

Figure 1 summarizes the diagnosis flowchart for suspicions of antibiotic HSR in our cohort.

CF cohort inclusion. Between January 2012 and August 2018, 601 patients were followed in the pediatric and adult CF centers in Lyon. Among them, 60 underwent 95 suspicions of antibiotic HSR, giving a prevalence of 10.0% and a frequency of 15.8 suspected reactions for 100 CF patients (Figure 1). Focusing on HSR confirmation, we included 49 CF patients (with 76 suspected HSRs) who received a complete allergology work-up and/or the reintroduction of a full course of the culprit antibiotics. Nineteen suspected HSRs were excluded from the study since they were skin test negative but were not subjected to drug readministration; one excluded reaction was a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, a severe cutaneous adverse drug reaction (SCAR) that usually contra-indicates the drug reintroduction; the 18 other reactions were non-severe: 3 fixed drug eruptions, 2 acute urticaria and 13 non-specific eruptions.

CF cohort description. Clinical features of the patients for the 76 reactions are reported in Table 1. Briefly, there were more females than males (ratio females/males = 1.13) and as many pediatric (< 18 years old) patients (n = 36, 47.4%) as adult ($\geq$ 18 years old) patients (n = 40, 52.6%); most of them carried at least one Δ F508 mutation (85.7%). Patients with a suspected HSR had a BMI slightly over the expected value in the CF population; all of them had at least one CF-related complication, e.g. exocrine pancreatic insufficiency.

Suspected antibiotic HSR. Features of Suspected HSRs are reported in Table 2. Based on the chronology between drug administration and reported clinical signs when available, 29/76 suspected HSRs (38.2%) were immediate and 8/76 (10.5%) non-immediate. The most frequent type of reaction was urticaria (38/76, 50.0%). Others were isolated pruritus, exanthema and fixed drug eruption. Extra-cutaneous symptoms occurred in 16/76 suspected HSRs (21.1%) and concerned only the immediate reactions. They included dyspnea, abdominal pain, emesis, confusion, fever and hypotension. Concerning the severity of the reactions, 12 immediate reactions were grade 2 or more in the Ring and Messmer classification (15.8% of the suspected HSRs); no nonimmediate suspected HSR were SCARs.

Allergy assessment. Skin tests were performed for 43/76 reactions: SPTs and IDTs were performed for all of them (43/43). Three were positive at immediate reading (one SPT and one IDT in two adults and one IDT in one child)(3/76; 3.9% of suspected HSRs). Patch-tests were performed for only 8 of them (8/43) and all were negative.

For the remaining 40/43 reactions with negative skin tests and the 33/76 reactions that did not receive skin tests, a full course of the involved antibiotic was completed with the following results (Figure 1): (i) recurrence of the reaction in 10 cases, confirming the diagnosis of antibiotic HSR (10/76; 13.1% of the suspected HSRs); (ii) absence of reaction in 63/76 cases (82.9%), excluding the diagnosis of HSR.

Among the 10 recurrences of HSR symptoms, 3 occurred in children and 7 in adults. The symptoms were immediate in 7/10 cases [anaphylaxis with epinephrine injection in two cases (one child and one adult), acute urticaria without other symptoms in 5 cases] and delayed presenting as non-severe fixed drug eruption in 3 cases.

In summary, among 76 suspicions of antibiotic HSR, only 13 were confirmed HSRs (17.1% of suspected HSRs), including three with positive immediate skin tests (3.9% of suspected HSRs). In contrast, 63/76 suspected HSRs (82.9%) were not confirmed.

Antibiotic involvement. Table 2 reports the antibiotics involved in suspected HSR. As expected, the most frequently ones were β -lactams, involved in 64.5% of the suspected HSRs. Cotrimoxazole (CTX) was also frequently associated, in 18.4% of Suspected HSRs. Of note, suspicions of HSRs occurred during IV treatment in 67.1% of the cases.

Table 3 reports the antibiotics involved in the 13 confirmed HSRs. β -lactams were involved in 9 cases, based on 2 positive skin tests, 3 recurrences of fixed drug eruption and 4 isolated urticaria during reintroduction. Cotrimoxazole was associated with 3 HSRs, because of 2 anaphylaxis that led to epinephrine injection and one isolated urticaria during reintroduction. Vancomycin induced one HSR with a positive skin test and without criteria for Red-Man syndrome diagnosis.

Predictive risk factors of HSR. We then sought to define predictive clinical features for future HSRs. To this end, we compared the clinical features of patients with a final diagnosis of HSR and those for whom the diagnosis of HSR was excluded (Table 4). We did not find any significant difference either in CF-related clinical features (type of mutation, FEV1, BMI at reaction and one year before, CF complications), or in the clinical presentation of the reactions and antibiotic

features. Moreover, the age criteria (child/adult) was not a predictive feature for the HSR diagnosis.

Discussion

We conducted a retrospective study in 601 CF patients. In this population, the prevalence of suspected antibiotic HSR was 10.0% but the diagnosis of HSR was confirmed in only 17.1% of the cases. As expected, β -lactams were the antibiotics most frequently involved in suspected HSR (64.5%) but CTX was also often involved (18.4%). Of note, three reactions were associated with positive immediate skin tests.

Comparison of HSR prevalence in different populations. Many studies have reported a higher prevalence of antibiotic HSRs in CF patients than in the general population (up to 60%^{17,18,27} versus 15.3%²⁸). Of note, these previous studies called HSRs all the reactions that looked like an allergy, regardless of the results of antibiotic challenge or reintroduction. In our cohort of 601 CF patients, the prevalence of suspicions of antibiotic HSR was 10.0%. Among these reactions, 17.1% were confirmed HSRs and only 3.9% had a positive skin test. All these features are close to those reported in the general population^{28,29}. This result is similar to previous studies considering complete allergy work-up in CF population^{17–19}. Other studies did not report results of allergy assessment and then proposed unnecessary antibiotic avoidance. The small proportion of confirmed HSRs and positive skin test HSRs among the suspected reactions reinforces the message that allergy assessment in those reacted patients is necessary^{1,20,30}.

Reaction labelling. In the present study, the definitions of suspected and confirmed HSRs were based on the most recent international guidelines¹. Notably, a reaction that resembles allergy was a suspected HSR, and the diagnosis confirmation was based on a positive drug provocation test or positive skin test¹, meaning that the symptoms were reproducible². Here, we confirmed the diagnosis of HSR with a full antibiotic course as reintroduction for two reasons: (i) many suspected HSRs were managed with a direct antibiotic reintroduction rather than a drug provocation test, in a pragmatic approach, except for severe suspected HSRs; (ii) several days of treatment may be needed for the diagnosis of nonimmediate HSRs. Of note, all those reintroductions were performed during a hospitalization for infectious CF decompensation.

In accordance with this approach, drug reintroduction was not performed in one case of DRESS syndrome, despite the patch-test negativity, and the patient was excluded from the analysis. The DRESS syndrome is classified as a SCAR, whose symptoms may be life-threatening. The reactivation of the Human Herpes Virus-6 (HHV-6) may be also associated, and

is one of DRESS diagnosis criteria for some groups³¹. Anyhow, in some severe cases, despite the absence of a definitive HS diagnosis, drug avoidance is required.

Allergy assessment. In our study, 33/76 suspected HSRs were not assessed by skin tests, but directly with drug reintroduction. More and more studies highlight this option of directly carrying out drug challenge/reintroduction without skin tests, notably when the reactions were not severe, e.g. isolated urticaria or skin exanthema^{32–36}. Our results confirm this finding, especially since CF patients have no higher risk of HSRs, despite the repetition of antibiotic exposures. Thus, low-risk patients may have a direct drug reintroduction, but the low-risk status must be clear established³⁶. In our patients drug reintroduction was done at a full antibiotic course because (i) the suspected HSR reaction was mild/moderate and restricted to skin; (ii) the patients were hospitalized for the treatment of a lung infection, and (iii) the benefit/risk ratio was in favor of the drug readministration.

We propose that CF patients could receive a full antibiotic course as reintroduction in order to definitively confirm or exclude the diagnosis of HSR²⁰, in the absence of contra-indication such as severe suspected HSRs (DRESS or other SCARs). The complete reintroduction should be performed in a hospital setting, after skin tests and, when possible, after a gradual reintroduction challenge, in order to prevent severe immediate reactions that could occur after the first antibiotic intake in the event of allergic HSR.

Interestingly, in our patients, the full course reintroductions of the culprit antibiotics were performed during infectious exacerbation, that is unusual. Indeed, drug provocation tests should be performed over a few days at most and in the absence of any cofactor that could promote HSR¹. However, CF patients receive longer antibiotic courses than the general population (2 to 3 weeks of treatment) and some HSRs occur after several days or weeks of treatment³⁷; CF patients also accumulate more antibiotic molecules in their organisms, which could promote nonallergic HSR. Moreover, these patients are frequently exposed to many cofactors, such as viral infections, polypharmacy, stress. Thus, it seems important for the clinician to be informed whether the CF patient, under the real conditions of treatment, will react during the antibiotic course, in order to adjust the patient's drug management.

CTX-induced HS. Most of the reactions occurred during β -lactam treatment, as previously described²⁰. As a new finding, in our study, 18.4% of Suspected HSRs were induced by CTX,

whereas the prevalence of CTX-induced suspected HSRs is 2 to 9% in the general population^{20,38}. This reflects another population with a high prevalence of CTX-induced reactions: the HIV-infected population. In this population, the prevalence of CTX-induced suspected HSRs reaches up to 60%³⁹. This high prevalence is thought to be linked to changes in the oxidative metabolism of HIV-infected cells leading to increased sensitivity to CTX metabolite sulfonamide hydroxylamine⁴⁰ and direct cellular toxicity of CTX nitroso metabolites⁴¹. Similar redox imbalance has been highlighted in *CFTR* defective cells. This redox imbalance is worsened by the lower absorption of fat-soluble antioxidant vitamins by CF patients⁴². Thus, a metabolism mechanism might explain the higher frequency of CTX-induced HSRs in CF compared to the general population.

Study limitations. The main limitation of our study is its retrospective nature, leading to lack of important data. Thus, the delay between the index reaction and the allergy assessment was variable and could impact the results of skin tests and drug reintroduction, since the natural history of drug hypersensitivities is not well known. Thus, prospective studies are needed to overcome these limitations.

Conclusion

A complete allergy assessment is necessary for effective allergy delabeling in CF patients who experienced a suspected antibiotic HSR. Of note, β -lactams provided most of the HSRs, but CTX was also frequently involved. A link with the *CFTR* defect, inducing an oxidative stress, is a possible explanation and should be explored.

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Table 1. Cystic fibrosis patient features at time of antibiotic hypersensitivity

Table 1A: CF patient general features (N = 49)

Gender, n (%)	
- Male	23 (46.9%)
- Female	26 (53.1%)
Mutation, n (%)	
- Homozygous $\Delta F508/\Delta F508$	23 (46.9%)
- Heterozygous $\Delta F508$ /other	19 (38.8%)
- Other mutations	7 (14.3%)

Table 1B: CF patient features at suspected HSR (N = 76)

Reaction occurred during, n (%)	
- Childhood (< 18 years)	36 (47.4%)
- Adulthood (≥ 18 years)	40 (52.6%)
BMI at the reaction in children (mean Z-score $\pm$ sd)	-0.92 $\pm$ 1.12
BMI at the reaction in adults (mean $\pm$ sd)	20.0 $\pm$ 2.18
BMI a year earlier in children (mean Z-score $\pm$ sd)	-1.06 $\pm$ 1.07
BMI a year earlier in adults (mean $\pm$ sd)	20.0 $\pm$ 2.39
<i>CF complications, n (%)</i>	
Exocrine pancreatic insufficiency	76 (100%)
Diabetes	24 (31.6%)
Cystic fibrosis liver disease	17 (22.4%)
Chronic <i>Staphylococcus aureus</i> colonization	17 (22.4%)
Chronic <i>Pseudomonas aeruginosa</i> colonization	37 (48.7%)

sd: standard deviation; BMI: body mass index; CF: cystic fibrosis; HS: hypersensitivity; NR: non-reported

Table 2. Clinical description of suspicion of hypersensitivity reactions in cystic fibrosis patients.
Data are expressed in number (% of suspected HSRs, from 76 reactions).

Symptoms and signs of suspected HSRs, n (% of total reactions)

- Urticaria	38 (50.0%)
- Pruritus	6 (8.0%)
- Exanthema	1 (1.3%)
- Fixed drug eruption	3 (3.9%)
- Missing data	28 (36.9%)
- Systemic symptoms (dyspnea, abdominal pain, emesis, subjective and objective confusion, fever, hypotension)	16 (21.1%)

Delay from antibiotic initiation, n (% of total reactions)

- < 6 hours	14 (18.4%)
- < 24 hours	5 (6.6%)
- 1 to 9 days	21 (27.6%)
- > 10 days	10 (13.1%)
- Missing data	26 (34.3%)

Type and severity of suspected HSRs[†], n (% of total reactions)

- Immediate	29 (38.2%)
○ Grade 1 [‡]	17 (58.6%)
○ Grade 2 [‡]	8 (27.6%)
○ Grade 3 [‡]	4 (13.8%)
○ Epinephrine injection	2 (6.9%)
- Non-immediate	8 (10.5%)
- Missing data	39 (51.3%)

Involved antibiotics, n (% of suspected HSRs)

- B-lactams	49 (64.5%)
- Cotrimoxazole	14 (18.4%)
- Azithromycin	1 (1.3%)

- Ciprofloxacin	6 (8.0%)
- Vancomycin	2 (2.6%)
- Linezolid	1 (1.3%)
- Doxycycline	1 (1.3%)
- Teicoplanin	1 (1.3%)
- Pristinamycin	1 (1.3%)

†based on time since the last medication and clinical description

‡according to Ring and Messmer classification ²²

HSR: hypersensitivity reaction

Table 3. Antibiotics involved in hypersensitivity in cystic fibrosis patients. Data are expressed in number (%).

	Confirmed HSRs	HSRs with positive skin test
	n (%)	n (%)
B-lactams	9 (69.2%)	2 (66.7%)
Cotrimoxazole	3 (23.1%)	
Vancomycin	1 (7.7%)	1 (33.3%)
Total	13	3

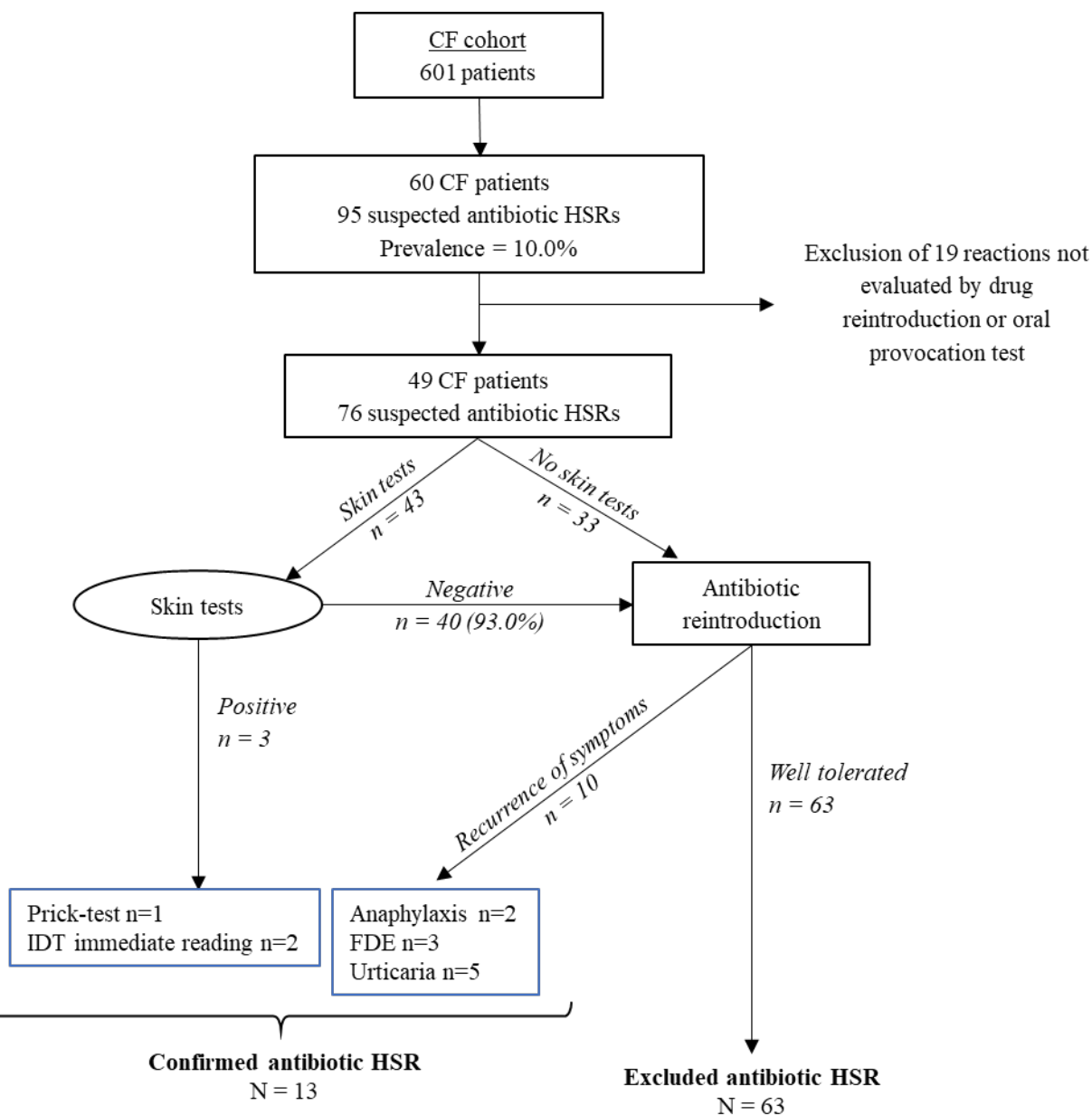
HSR: hypersensitivity reaction

Table 4. Comparison of clinical data of CF patients, regarding the diagnosis or the exclusion of HSR. Data are expressed in mean (standard deviation) or number (% of population).

Diagnosis	Confirmed HSRs n = 13	Excluded HSRs n = 63	p-value
<i>General clinical features</i>			
Age (years)	20.2 (10.9)	17.2 (9.1)	0.30 [‡]
- Child (< 18 years)	4 (30.8%)	32 (50.8%)	0.23 [†]
- Adult (≥ 18 years)	9 (69.2%)	31 (49.2%)	
Gender			1 [†]
- Male	9 (69.2%)	29 (46.0%)	
- Female	5 (38.5%)	34 (54.0%)	
<i>CF-related clinical features</i>			
Mutation			0.32 [†]
- Homozygous ΔF508/ΔF508	5 (38.5%)	31 (49.2%)	
- Heterozygous ΔF508/other	6 (46.1%)	24 (38.1%)	
- Other mutations	2 (15.4%)	8 (12.7%)	
FEV1 (Z-score)	-3.3 (2.1)	-3.6 (1.7)	0.87 [‡]
Mean FEV1 over past year (Z-score)	-2.9 (1.8)	-3.4 (1.7)	0.50 [‡]
BMI (Z-score, < 18 years)	-0.60 (0.9)	-0.99 (1.2)	0.36 [‡]
BMI one year before (Z-score, < 18 years)	-0.73 (0.5)	-1.15 (1.16)	0.45 [‡]
BMI (adults > 18 years)	19.0 (3.2)	18.3 (5.4)	0.07 [‡]
BMI one year before (adults > 18 years)	19.2 (3.3)	19.6 (2.4)	0.12 [‡]
Nb of antibiotic courses over previous year	1.3 (1.0)	4.0 (2.3)	0.17 [‡]
ABPA	0	2 (3.2%)	1 [†]
Chronical colonization of airways	7 (53.8%)	33 (52.4%)	0.68 [†]
Corticosteroid treatment	6 (46.1%)	13 (20.6%)	0.51 [†]
Diabetes	5 (38.5%)	20 (31.7%)	1 [†]
CF liver disease	2 (15.4%)	14 (22.2%)	0.49 [†]
<i>Antibiotic course features</i>			
Mode of administration			0.35 [†]
- IV	11 (84.6%)	41 (65.1%)	

- Oral	2 (15.4%)	22 (34.9%)	
Continuous course	3 (23.1%)	6 (9.5%)	0.35 [†]
<i>Clinical features of HSRs</i>			
Skin symptoms	13 (100.0%)	63 (100.0%)	1 [†]
Systemic involvement	1 (10.0%)	14 (22.2%)	0.68 [†]

[†]Fisher's exact test; [‡]non-parametric Wilcoxon test. FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; BMI: body mass index; Nb: number; ABPA: Allergic bronchopulmonary aspergillosis; IV: intravenous; HSR: hypersensitivity reaction



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Figure 1. Diagnosis flowchart of antibiotic hypersensitivity reactions in cystic fibrosis patients. HSR = hypersensitivity reaction.