



Beta-lactam allergy in adults with cystic fibrosis

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Abstract

Background: Allergic reactions to one or more beta-lactam antibiotic can pose a management problem in patients with cystic fibrosis (CF), and may limit antibiotic choice.

Method: The aim of this study was to assess the prevalence of allergy to anti-pseudomonal beta-lactam antibiotics in an adult CF centre and to assess variables, which may contribute to the development of allergic reactions. A questionnaire-based interview and a review of medical records were performed.

Results: Of the 150 patients, 54 (36%) had allergic reactions to one or more beta-lactam antibiotics and 20 (19%) had allergic reactions to multiple beta-lactam antibiotics. The proportion of patients allergic to specific beta-lactam antibiotics varied from 10% to 26%. Rates of reactions were highest for penicillins and cephalosporins, intermediate for carbapenems and lowest for aztreonam. Of all reactions, 40% occurred within 24 h of the commencement of an individual antibiotic course. Patients with one or more beta-lactam allergic reactions had received greater cumulative exposure ($p < 0.0001$), were older ($p = 0.016$) and had lower lung function ($p = 0.037$) than patients without a history of beta-lactam allergy. Cystic Fibrosis transmembrane regulator (CFTR) status, gender, peripheral blood eosinophil count and total IgE concentrations were not different in patients with allergic reactions.

Conclusions: This study demonstrates that the prevalence of allergic reactions to beta-lactam antibiotics is high in adults with CF. Increasing age; cumulative exposure and decreasing FEV₁ were associated with the development of allergy.

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1. Introduction

Cystic fibrosis (CF) is the most common lethal recessively inherited disease of Caucasians. Most of the morbidity and mortality is related to chronic suppurative lung disease [1]. The prevalence of *Pseudomonas aeruginosa* (*P. aeruginosa*) increases with age and approaches 80% in adults with CF [2]. The current recommended treatment for pulmonary exacerbations of *P. aeruginosa* includes the combination of intravenous beta-lactam antibiotic and an aminoglycoside for

10 to 21 days [3,4]. Anti-pseudomonal beta-lactam antibiotics available in Australia are licensed only for intravenous use. These antibiotics from four classes include penicillins (ticarcillin and piperacillin), cephalosporins (cefpirome, cefepime and ceftazidime), carbapenems (imipenem and meropenem) and a monobactam (aztreonam). Since the mid-1990's, ticarcillin has only been available in combination with clavulanic acid (Timentin®). Piperacillin is available in two preparations, piperacillin alone (Pipril®) and in combination with tazobactam (Tazodin®). Imipenem has only been available in combination with cilastatin (Primaxin®).

Beta-lactam antibiotic allergy has been variably reported from less than one percent up to eight percent of patients in the general population [5]. Several reports including three cohort studies, describe a higher prevalence of allergic

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reactions to beta-lactam antibiotics in patients with CF ($\geq 29\%$) [6–13]. The highest reported prevalence was reported in Danish patients where over 60% of patients had an allergic reaction to one or more beta-lactam antibiotics [11]. These reactions manifest with a variety of symptoms including anaphylaxis, pruritis, rash and drug fever.

Several components of the immune system may be involved including B- and T-lymphocytes, mast cells and basophils in allergic reactions. Complement activation and antibody response may be involved especially IgG, IgE and IgM [14]. A recent review has highlighted the lack of published information regarding antibiotic allergy in patients with CF, in particular the role of specific CFTR mutations, cumulative exposure, and previous allergy to related antibiotics in the development of allergic reactions [15].

The primary aim of this study was to determine the prevalence of allergy to beta-lactam antibiotics in adults with CF in the current era. The study also assessed patient recall of allergy episodes and variables which may have contributed to the development of antibiotic allergy. The hypothesis tested was that allergy to beta-lactam antibiotics results from cumulative exposure in CF patients.

2. Methods

2.1. Setting and patient selection

The Prince Charles Hospital (TPCH) provides care for 200 patients with CF with some patients receiving shared care with regional hospitals in Queensland (3.5 million km²), Northern NSW and Northern Territory. Adults attending the Adult CF Centre in April 2004 including post lung transplant patients were studied. Some patients received intravenous therapy solely at TPCH and Royal Children's Hospital (RCH), and some had previously been managed elsewhere.

2.2. Study design

The retrospective study comprised of two components: 1) a structured questionnaire-based telephone interview; and 2) data collection from the medical record. The interview collected demographic information and data about exposure to beta-lactam antibiotics, hospitals attended, history of home intravenous therapy, and beta-lactam related allergic reactions. Further information was sought from patients with a previous allergic reaction including timing, symptoms and location of reactions, previous exposure and treatment of reactions.

A review of medical records at TPCH for the 150 patients was performed using a structured approach to collect the following data: antibiotic exposure, documentation, symptoms and timing of reactions and clinical information, including IgE concentrations, peripheral blood eosinophil count, and FEV₁% predicted. The most recent results available within 12 months of April 2004 were recorded. In most cases, these were collected during clinical stability at

an outpatients review (annual assessment) except when logistical issues precluded this and then blood was collected at the end of treatment of an infective exacerbation. Skin testing was infrequently performed and was not analysed further. The records of patients who had attended RCH as children were also examined using the same structured approach. In view of the size of the catchment area of the centre, some patients had received some care in hospitals other than TPCH or RCH. Total cumulative exposure was calculated for patients who attended only TPCH and RCH and data was collected up to the time of lung transplantation. All of the data from the medical record review was collected using a consistent structured approach by JAB at TPCH and RCH. Reactions that occurred at hospitals other than TPCH or RCH could not be verified in medical records. When the patient could provide clear details of the time and place of a reaction and the drug involved and symptoms were typical of an allergic reaction, data was documented as for verified reactions. Reactions were classified as life threatening or non-life threatening.

The classification of allergic reactions according to time interval between last dose administration and their onset was proposed by Levine: immediate reactions that occur within 1 h, accelerated reactions that occur from one to 24 h and delayed reactions from 24 to 72 h or more [16]. Non-immediate reactions are those occurring more than 1 h after drug administration. A simplified classification has been adopted by the European Network of Drug Allergy (<http://www.eaaci.net>) in immediate and non-immediate reactions [17]. Immediate reactions occur within the first hour after drug administration and non-immediate reactions are those occurring after 1 h of drug administration. However, documentation in the medical record did not always include the exact timing of many reactions with respect to administration, making such classification difficult. This necessitated the adoption of a modified classification system for the purposes of this study. "Early" reactions were classified as occurring <24 h after the commencement of a specific course and "delayed" reactions after 24 h.

2.3. Statistical analysis

Descriptive statistical test analysis was performed using the Number Cruncher Statistical Software (NCSS®). Patients were divided into two groups (no allergic reactions or $\geq$ one previous reaction). Statistical tests included chi-square (or Fisher's exact test (where numbers ≤ 6)), *t*-tests and Mann-Whitney *U* tests where appropriate. A *p* value of <0.05 was considered statistically significant. The logistic regression analysis was chosen to describe the relationship between outcome (allergy or no allergy) and the variables collected during the study. The model was built using NONMEM version 5 and the G77 Fortran compiler. Variables were added manually to the model in a forward sequential manner. Parameters that allowed for interaction between the variables were also added until the full model was obtained. The

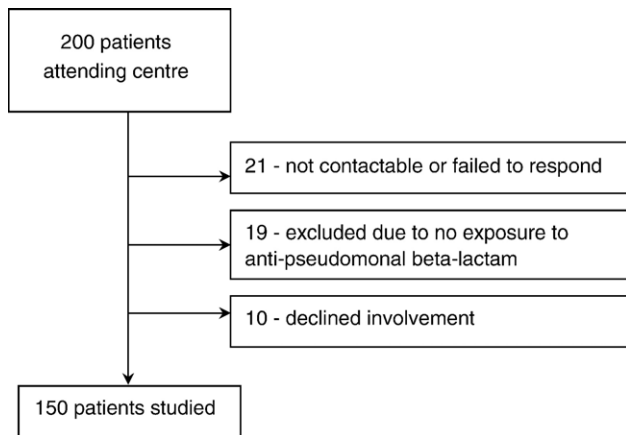


Fig. 1. Patient recruitment at the Adult CF Centre, TPCCH.

likelihood ratio test was used to discriminate between competing models with a change in >3.84 units (corresponding to a $p < 0.05$ according to a chi-squared distribution) considered significant.

The study was approved by TPCCH and RCH Human Research and Ethics committees and the University of Queensland Ethics committee. All patients provided written consent before accessing their patient information.

3. Results

The available cystic fibrosis patient population in the Queensland area was 200 patients. One hundred and fifty (150) patients participated in the study (Fig. 1) (April–November 2004). The median age of the study group was 26 years (range 17–57) and 43% were female. Nineteen patients (13%) had received a lung transplant. Total lifetime cumulative antibiotic exposure was available for 73 of 150 (49%) patients.

3.1. Prevalence of allergic reactions

A total of 54 of the 150 (36%) patients experienced at least one allergic reaction to an anti-pseudomonal beta-lactam antibiotic. No patients experienced an allergic reaction to intravenously administered aminoglycosides. Subsequent administration without incident (allergic phenomenon) of aminoglycosides (usually tobramycin) with a different beta-lactam antibiotic excluded an initial aminoglycoside reaction in all cases. The 54 patients had a total of 93 allergic reactions (0.6 reactions per patient in the overall population and 1.7 reactions per patient with allergy). Of the patients with beta-lactam allergy, 63% ($n=34$) had allergic reaction to one beta-lactam drug class, 20% ($n=11$) to two beta-lactam classes, 11% ($n=6$) to three beta-lactam classes and 6% ($n=3$) to all four beta-lactam classes. Most patients (14 of 20) with two or more allergies were allergic to both penicillins and cephalosporins. However, six patients were allergic to combinations other than penicillins and cepha-

losporins. The rates of cross-sensitivity to different combinations of antibiotics in patients exposed are summarised in Table 1. The percentage of patients with allergies to the differing combinations ranged from 4.9% to 12.0%. The majority of reactions (72%) occurred while patients were under the care of TPCCH, with 11 (of 93) having reactions while receiving home intravenous therapy. Only 13 of 93 (14%) reactions occurred in patients less than 18 years.

For the patients who had data on cumulative exposure ($n=73$), the patients received a total of 1321 courses or a mean ($\pm$ SD) number of courses per patient of 18.1 ± 15.4 . This equates to a total of 14,349 days of therapy or a mean ($\pm$ SD) number of days per patient of 196 ± 139 days. Of these, 42 of the 1321 (3.2%) courses were complicated by allergic reaction (or one reaction every 342 treatment days). Details of patients exposed and specifics of allergy profiles are given in Table 2. Ticarcillin and ceftazidime are currently first line anti-pseudomonal beta-lactams in our centre and these drugs have high rates of allergy.

3.2. Profile of allergic phenomenon

Of the 93 reactions, 37 (40%) were “early” reactions and 56 (60%) were “delayed”. Two reactions were considered life-threatening (anaphylaxis) and required adrenaline (ticarcillin and ceftazidime). Almost half of the reactions that manifested after 24 h occurred more than seven days into a course. Aztreonam was the only antibiotic which did not have any acute reactions recorded and there were no delayed reactions found with piperacillin.

A variety of allergy related symptoms was experienced by the 54 patients (Fig. 2). Pruritis and rash were most common followed by a wide range of other symptoms. Dyspnoea, cutaneous tingling and angioedema manifested more commonly in reactions occurring within 24 h and fever and flushing in reactions occurring after 24 h from

Table 1
Allergy to combinations of beta-lactam antibiotics

Antibiotic combinations	Patients allergic to both antibiotics (#)	Patients exposed to both antibiotics (#)	Patients exposed to both with allergic reactions to both antibiotics (%)
Ticarcillin	11	120	9.2
Ceftazidime			
Ticarcillin	6	71	8.5
Meropenem			
Ticarcillin	2	41	4.9
Imipenem			
Ceftazidime	9	75	12.0
Meropenem			
Ceftazidime	4	51	7.8
Aztreonam			
Meropenem	4	41	9.8
Aztreonam			
Imipenem	2	28	7.1
Aztreonam			
Ticarcillin	3	51	5.8
Aztreonam			

Table 2
Allergy profiles for specific beta-lactam antibiotics

Class	Antibiotic	Patients exposed (#)	Patients exposed/population (%)	Allergic patients (#)	Allergic patients/patients exposed (%)	Time of allergy (course)*
Penicillins	Ticarcillin	132	88	29	22	7 (4,10)
	Piperacillin	23	15	6	26	3
Cephalosporins	Ceftazidime	137	91	31	23	3 (2,18)
	Cefepime	12	8	3	25	0
	Cefpirome	5	3	0	0	0
Carbapenems	Imipenem	40	26	6	15	2
	Meropenem	78	52	13	17	3 (2,3)
Monobactams	Aztreonam	51	34	5	10	8

*Number of courses of specific antibiotics given prior to development of allergic reaction based on 73 patients where cumulative exposure was available. Reported results are medians (25th, 75th percentiles). If patients numbers ≤ 6 , median is reported.

commencement of a course. The “other” category of symptoms included haemorrhagic cystitis (eight episodes), hepatitis (two episodes) and isolated reports of shakiness, loss of peripheral vision, anxiety and dizziness. Each episode of haemorrhagic cystitis was related to ticarcillin.

3.3. Patient knowledge and documentation in medical record

Forty-five of 54 (83%) patients with one or more allergy were able to accurately recall all reactions that were subsequently documented in the medical record. Of the total cohort, three patients (2%) experienced an allergic reaction, that was documented and verified in the medical record, but were unable to recall it. Eleven patients (7.3%) reported allergic episodes, which were unable to be substantiated in the medical record, despite the record being available and thoroughly assessed. All of these patients were re-exposed subsequently to the “reported” antibiotic without incident and the “reported” reaction was discounted.

Accurate details of prior antibiotic allergy were documented in the current medical record (including inpatient and outpatient) in 86% of patients. Only 50% had symptom details of allergy and 20% had a date documented on the front of the latest volume of the record.

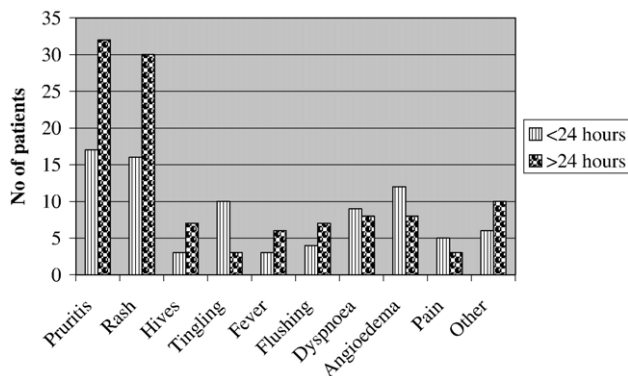


Fig. 2. Symptoms of allergy in early and delayed reactions*. *Multiple symptoms may have manifested for individual reactions.

3.4. Risk factors for allergic reactions

The age of the patients was significantly greater in patients with a history of allergic reactions than patients without an allergic history ($p < 0.05$) (Table 3). The current FEV₁% predicted was also significantly lower in patients with a history of beta-lactam allergy than those without such a history ($p < 0.05$). Gender, CFTR status, IgE concentration and peripheral blood eosinophil count were not different in allergic patients. A higher proportion of patients over 25 years had allergies compared with younger patients (Table 3). Patients with allergy were exposed to significantly more courses of antibiotics than those without allergies ($p = 0.00005$). A higher proportion of patients with lifetime exposure > 20 courses had allergies to at least one antibiotic

Table 3
Clinical features in relation to allergy status

Variable	No allergies (n=96)	One or more allergies (n=54)	p value
Age of patients [n=150]*	24.5 (19, 30)	28 (23,33)	$p = 0.016^{\#}$
Age ≥ 25 years [n=150] $\S$	50% [n=96]	70% [n=54]	$p = 0.015^{\#}$
Cumulative courses [n=73] $\S$	6 (2, 20) [n=49]	29 (17, 47) [n=24]	$p = 0.00005^{\#}$
> 20 courses of antibiotics [n=73]*	29% [n=49]	63% [n=24]	$p = 0.019^{\#}$
Gender (F/M) [n=150] $\S$	40% / 60% [n=96]	50% / 50% [n=54]	NS $^{\#}$
CFTR mutations [n=126] $\S$			NS $^{\#}$
Δ F508/ Δ F508	47%	58%	
Δ F508/other	39%	31%	
Other/other	14%	11%	
FEV ₁ % predicted [n=150]*	59 (40, 79) [n=96]	50 (33, 67) [n=54]	$p = 0.037^{\#}$
IgE concentration μ g/L [n=122]*	132 (51, 456) [n=74]	126 (35, 215) [n=48]	NS $^{\#}$
Eosinophil count $\times 10^9$ /L [n=149]*	0.18 (0.01, 0.33) [n=95]	0.21 (0.11, 0.34) [n=54]	NS $^{\#}$

$\S$ Categorical data presented as percentages.

*Continuous data expressed as median (25th–75th percentile).

$^{\#}$ Wilcoxon signed rank test, $^{\#}$ chi-square test.

NS — Not significant.

(63%) than those with no allergies (29%). In addition, a higher proportion of those with total exposure >20 courses had allergy to two or more antibiotics (71%) than those with less than 2 allergies (27%) (data not shown). The only statistically significant univariate logistic regression models that could be supported by the allergy data were cumulative exposure (Δ likelihood=6.138) and FEV₁% (Δ likelihood=5.031). The final logit was described by $-0.797 + 0.483 \times (\text{cumulative exposure}/20)$ and $0.358 + -1.65 \times (\text{FEV}_1\%/100)$. Joining these two variables using interaction model (addition or multiplicative) did not significantly improve the cumulative exposure model, i.e. Δ likelihood <3.84 ($p > 0.05$).

4. Discussion

Studies of antibiotic allergy in patients with CF are urgently required as evidenced by the imbalance between three review articles [8,15,18] and three cohort studies of allergy in patients with CF [9–11]. A recent review highlighted the need for studies of determinants of allergy in CF patients [15]. The prevalence of allergy to intravenous antipseudomonal beta-lactam antibiotics in this study was 36% in adults with CF comparable with two other studies (29% and 33%) [9,10] but lower than one study (61%) [11]. This difference was evident despite increased age of patients in the current study [11]. The increased prevalence of allergic reactions reported by Koch et al. may relate to increased cumulative exposure in patients who are routinely admitted for parenteral therapy. Notably the single study which involved only paediatric patients reported similar rates of beta-lactam allergy as seen in the current report of adult patients [10].

The greater usage of the immunogenic, piperacillin, reported in the earlier studies may have also contributed to the prevalence of allergy. The percentage of the patient group exposed to piperacillin was highest in Koch's study (95%) [11] and lower in Pleasants, Wills [9,10] and the current study (34%, 25% and 15% respectively) [9–11]. Previously, piperacillin tended to be associated with a higher allergy risk (36% to 51%) in contrast with the current study (26%), highlighting potential differences in the modern era of antibiotic prescribing compared with earlier studies.

The previous studies in CF patients have consistently reported the prevalence of allergic reactions to penicillins to be higher than to cephalosporins [9–11]. Our study reports similar rates of allergic reactions for these two drug classes. This may result from the reduction in piperacillin administration; the increasing use of other beta-lactams and increased lifetime exposure to both classes with increased survival. In all studies, including our study, the prevalence of reactions to carbapenems and monobactams is less than other antibiotic classes [9–11]. It is unclear if this relates to these agents being less immunogenic or whether total exposure to these agents is less as they are generally second line agents and reserved for management of advanced lung disease.

Almost 30% of reactions to ticarcillin manifested as haemorrhagic cystitis which has features of an immunological reaction involving the IgG and IgM [19,20].

Thirty-seven percent of patients with beta-lactam allergy reacted to multiple antibiotics. This may result from cross-sensitivity to related compounds (i.e. IgE antibodies to a common chemical component) or result from separate immune response to unrelated molecules. As ceftazidime and aztreonam share common side chain structures, cross sensitivity has been suggested to be a common clinical problem [21]. However, only 7.8% of patients exposed to both antibiotics were allergic to aztreonam and ceftazidime. Rates of allergy to combinations of penicillins and carbapenems (4.9% and 8.5%) were no higher than any other combinations (5.8% to 12.0%), as has been recently suggested in the literature [22,23]. Aztreonam was successfully administered to many patients with other beta-lactam allergies as previously reported [11,24–26]. Further study of the mechanisms of allergic reactions is required to improve understanding of cross-sensitivity. A higher proportion of early reactions were found in the current study compared with previous studies. Koch et al. reported that 28% of all reactions were immediate (definition not provided) [11]. Forty percent of reactions in the current study occurred within 24 h of initial dose of an antibiotic course. The high rate of late reactions with piperacillin reported by Koch et al. may contribute to this difference.

This study has demonstrated that knowledge of the timing and features of a reaction do not necessarily provide information about the mechanism of the allergy (Fig. 3). Many later reactions occurring during the delayed periods had similar features to early reactions, making it difficult to distinguish IgE from non-IgE mediated reactions. This distinction is important as only IgE mediated reactions are thought to be suitable for desensitization procedures [24].

4.1. Patient knowledge

We are not aware of any studies reporting the patient recall of antibiotic-induced allergy in CF. This study demonstrated that patients with CF were generally reliable sources of information about their allergy history. Reassuringly the false negative reporting of allergy was very low. The importance of accurate documentation in the medical record of details of allergic reactions is crucial to reduce the risk of future adverse events [15].

4.2. Predictors of allergic phenomenon

In the current study, increasing age, cumulative exposure and decreasing FEV₁% predicted were correlated with the presence of at least one beta-lactam allergy. Cumulative exposure and FEV₁% predicted but not age was predictive of beta-lactam allergy by univariate analysis. Of note the addition of FEV₁% predicted to cumulative exposure did not improve the prediction model. In a review of the topic, Moss

observed that reactions occurred mainly in older patients with CF [8]. However, age may merely be a marker of cumulative exposure rather than an independent variable [17,20]. The lower FEV₁ in those patients with allergy is expected as lung function decreases with increasing age and results in increasing antibiotic exposure.

The total courses of antibiotics patients were exposed to were significantly higher in patients with at least one allergy compared to those without allergy. A higher proportion of patients with a cumulative exposure greater than 20 courses had experienced at least one allergy compared with those without allergy. Wills et al. also reported an association between the number of reactions and the number of antibiotic courses [10]. Six of seven patients who received 20 or more intravenous courses had at least three antibiotic reactions which were more than those with less than 20 courses (one of 23 patients). This is supported by the high prevalence of allergy in patients with high antibiotic exposure in the Danish patients [11].

Our data suggest that nonspecific markers of atopy including blood eosinophil count and IgE concentrations are not related to the development of allergic reactions. Similarly, gender and specific CFTR mutations are not related to the occurrence of allergy. However, the factors which contribute to the development of allergic reactions to beta-lactam antibiotics are likely to be complex. Interestingly, 14 of 49 (29%) of patients who had not developed any allergic reactions had a cumulative exposure of greater than 20 courses (nine over 30 courses and one patient over 80 courses). This suggests that there must be additional factors which influence the risk of an allergic reaction to beta-lactams.

4.3. Limitations of the study

There are a number of limitations when considering our findings. Thirty-one of the population (16%) declined involvement or were not contactable. Patients with milder disease who are less frequently reviewed at the centre may have not participated, which could lead to an over-estimation of the allergy rate. As this was a retrospective study, details of the timing and symptoms of reactions were not always precise and analysis was based on the number of patients where data were available. A prospective birth cohort study would be required to circumvent this limitation.

Access to all medical records for all patients to calculate total cumulative lifetime exposure was impractical in this study. Despite this limitation the cohort whose cumulative exposure was available had similar clinical characteristics to the whole cohort. The reliance on patient recall of antibiotic exposure and allergy where data could not be verified in the medical record (i.e. those patients managed at hospitals in addition to RCH and TPCH) may have led to inaccuracies in classification of individual patients (nature and timing of event), particularly when exposure or allergy occurred many years previously. The patient's self-reported antibiotic exposure and allergies were also used to guide the process finding

relevant information in the medical records. It is possible that some data may have been missed despite efforts to collect complete information. In the future the development of complete electronic medical records may allow for more accurate recording of adverse events in patients with CF.

Notably, the symptoms of drug allergy were protean and in some cases were non-specific (e.g. anxiety, flushing, pain). These symptoms may present allergic phenomenon, however, may be a result of other clinical events. Cautious re-exposure of beta-lactam in this situation may better define whether a true allergy has occurred and under close medical supervision may be appropriate in some cases.

In conclusion, allergic reactions to anti-pseudomonal beta-lactam antibiotics are common in patients with CF. Penicillin and cephalosporins appear to have a similar risk of allergy and many patients are allergic to multiple antibiotics. High cumulative exposure and lower FEV₁ were associated with the development of beta-lactam allergy and the increasing survival of patients with CF and aggressive protocols for treatment of *P. aeruginosa* are likely to result in many patients having limited antibiotic choice due to allergic reactions.

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