

ORIGINAL ARTICLE

Antibiotic hypersensitivity in cystic fibrosis – Low frequency of anaphylaxis over 16 000 courses

Aleksandra Kowalik¹ | Isabelle de Monestrol^{1,2} | Kimmo Sorjonen³ |
Knut Brockow⁴ | Theo Gülen^{5,6,7} 

¹Stockholm Cystic Fibrosis Centre, Karolinska University Hospital Huddinge, Stockholm, Sweden

²Department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska Institutet, Stockholm, Sweden

³Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

⁴Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

⁵Department of Respiratory Medicine and Allergy, Karolinska University Hospital Huddinge, Stockholm, Sweden

⁶Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

⁷Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Correspondence

Theo Gülen, Department of Respiratory Medicine and Allergy, K85, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden.

Email: theo.gulen@sl.se; theo.gulen@ki.se

Funding information

Erica Lederhausen Memorial Foundation, Sweden, Grant/Award Number: n/a; Konsul TH C Bergh Foundation, Sweden

Aims: Drug hypersensitivity reactions (DHR) to antibiotics are common and a substantial issue in managing patients with cystic fibrosis (CF). This study aimed to assess the prevalence and clinical features as well as risk factors of DHR to antibiotics in CF.

Method: A 20-year retrospective study was conducted among 226 CF patients (100 children and 126 adults) attending our centre. The Swedish Registry for Cystic Fibrosis and electronic medical records enabled us to ascertain the number and routes of antibiotic courses. All suspected DHR were evaluated.

Results: The patients had a total of 16 910 antibiotic courses, of which 6832 (40%) were intravenously administered. Of 226 enrolled CF patients, 70 (31%) developed overall 131 DHR to antibiotics. The prevalence of DHR increased with advancing age ($P < .001$). Beta-lactams elicited 71% of all DHR and piperacillin was the most common single culprit (30% of intravenous and 24% of all DHR). Reactions were mild to moderate and mostly limited to skin; no severe cutaneous adverse reactions were observed. Additionally, anaphylaxis was rare, constituting 2.3% (3/131) of all DHR. Patients with DHR were exposed to significantly more courses of antibiotics than those without DHR (median 124 vs. 46, retrospectively, $P < .001$).

Conclusions: DHR to antibiotics, particularly to beta-lactams, are increased in CF patients, and associated with a higher number of cumulative exposures because of recurrent infections. However, severe cutaneous or systemic DHR, such as anaphylaxis, appear to be rare.

KEYWORDS

anaphylaxis, antibiotic reactions, beta-lactams, cystic fibrosis, drug hypersensitivity, piperacillin

The authors confirm that the Principal Investigator for this paper is Theo Gülen and that he had direct clinical responsibility for patients.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

1 | INTRODUCTION

Drug hypersensitivity reactions (DHR) to antibiotics are a substantial problem. Annually, on the basis of 6614 cases, 142 505 visits were estimated to US emergency departments because of drug-related adverse events to antibiotics,¹ most of them to beta-lactams. In contrast to predictable adverse drug events due to their pharmacological side effects, DHR mostly consist of either immediate pruritus, urticaria, vomiting, dyspnoea, hypotension and anaphylaxis or non-immediate exanthems of different severities. Although DHR, particularly to beta-lactam antibiotics, are self-reported both in adults and children with a prevalence of approximately 10% in the general population,² in only about 10% of these cases can this suspicion be confirmed by allergy diagnostics.^{2,3} Females have higher allergy incidence rates for antibiotics and there is a steady increase in antibiotic allergy prevalence with ageing.⁴

Cystic fibrosis (CF) is a rare, inherited disease with recurrent pulmonary exacerbations. Therefore, these patients frequently require 10 or 14-day courses of antibiotics for suppression of chronic infection with organisms such as *Pseudomonas aeruginosa* (*Pa*). The intravenous treatment consists of two medications: often beta-lactams (ceftazidime, piperacillin, meropenem or aztreonam) in combination with aminoglycosides (most often tobramycin) or colistimethate sodium.⁵

DHR to parenteral antibiotics have been reported to occur in up to 20–60% of antibiotic courses in CF patients.^{6–10} More recently, studies have suggested lower prevalence, because not all patients with assumed DHR were confirmed by allergy testing and/or drug challenge.^{11–13} However, allergy evaluation is not routinely applied in CF patients with suspected DHR due to the high number of patients cared for in cystic fibrosis centres and patients needing immediate treatment not allowing allergy testing first.³ Therefore, there is a risk for mislabelling predictable adverse drug events as DHR¹⁴ and performing desensitizations in these patients¹⁵ if reactions are not recorded properly and assessed by allergists. In the current study, we had the opportunity to assess the prevalence of DHR to antibiotics in the largest studied cohort of both CF patients and cumulative antibiotic exposures. The cohort was well-characterized due to continuous electronic file records as well as assessment of the recorded reactions by two independent allergists. Further, we evaluated the risk factors and clinical features of reported DHR.

2 | METHODS

2.1 | Study population and study design

The Swedish CF Registry was established in 1992 and contains annually updated data on broad characteristics of the CF patients in Sweden. Please see the following link for the exact data recorded in the Registry: [Variabellista_cfregistret.xlsx](https://www.variabellista.cfregistret.xlsx) (live.com). The CF Registry has enrolled 733 patients as of 31 December 2018. Of these, 258 attending the Stockholm CF Center (SCFC) between 1 January

What is already known about this subject

- Patients with cystic fibrosis (CF) have an increased risk for antibiotic hypersensitivity, particularly to beta-lactams.
- However, there has been considerable variation in the reported prevalence of drug reactions.

What this study adds

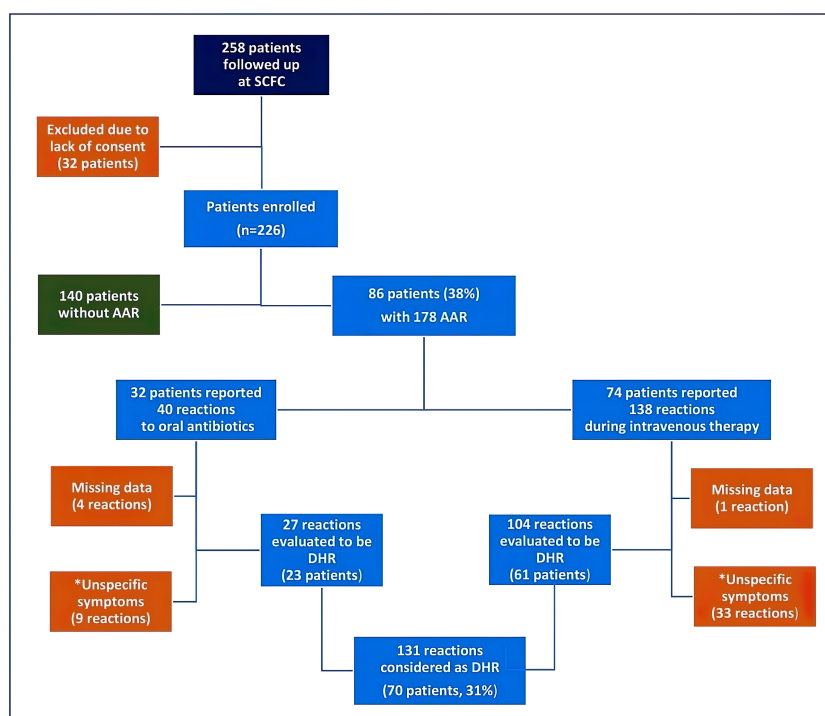
- The risk is highly associated with the number of cumulative exposures to antibiotics and increasing age.
- However, the reactions are mostly mild and limited to skin, as anaphylaxis is infrequent.

1999 to 31 December 2018 were identified and invited to participate in a 20-year retrospective study. Of these, 226 CF patients gave their written consent and were enrolled in the study (Figure 1). The study was approved by the Regional Ethic Committee of Stockholm (Dnr: 2019–00109).

Adverse antibiotic reactions (AAR) were defined as all reported unexpected events that occurred during antibiotic courses, which required a subsequent medical intervention, or such combination of symptoms requiring administration of antihistamines and/or corticosteroids and/or adrenaline and discontinuation or change of antibiotic treatment. A DHR was diagnosed if symptoms were typical of an immediate or delayed-type hypersensitivity, such as urticaria, anaphylaxis or exanthem as described.¹⁶ Excluded reactions consisted of unspecific symptoms such as isolated fever, headache, malaise, joint pain without swelling. In certain cases, it was difficult to distinguish AAR from DHR. Therefore, we evaluated on a case-by-case basis. For instance, facial tingling was included when described as itchy sensation/numbness under the skin or in the mouth and lips. However, tingling in fingers and feet mimicking paraesthesia was not included as it may be an adverse reaction in patients exposed to colistimethate. Moreover, isolated fever that occurred mostly during the first 2–3 days of courses was also excluded, hypothetically considered more likely to be an expression of Jarish Herxheimer reaction rather than drug-induced fever, which most often occurs towards the end of the course.¹⁷ Thus, DHR was limited to type I and type IV-mediated reactions in this study.

The data were collected both from the CF patient registry and medical records. The following data were retrieved from the CF Registry for this study: demographics, presence and duration of *Pa*-colonization as of 31 December 2018 (defined according to modified Leeds criteria and/or significantly raised anti-pseudomonas antibodies as defined by the European Cystic Fibrosis Society Patient Registry),¹⁸

FIGURE 1 Flowchart for patient selection process. Of note, although there are 70 patients with DHR, 14 patients reacted with both intravenous and oral antibiotic courses. *Symptoms, such as isolated fever, headache, malaise, joint pain without swelling were classified as unspecific. SCFC, Stockholm Cystic Fibrosis Center; DHR, drug hypersensitivity reactions; AAR, antibiotic adverse reactions



and number of antibiotic courses (in total and per year both for oral and intravenous administrations) as of 31 December 2018. In addition, data regarding AAR were collected from the medical records at the time of chart review (31 December 2018). Afterwards, all AAR data was retrospectively evaluated by two experienced allergists (A.K. and T.G.) and patients with possible DHR were identified. Moreover, DHR, with regard to parenteral antibiotic courses, were documented in detail including the date of onset relative to the day of the antibiotic treatment course, the onset of the reaction in relation to administration of the infusion, type of symptoms, treatment of the reaction, and change or discontinuation of antibiotic treatment. Oral antibiotic treatments were included whenever sufficient documentation was available.

A more detailed review of the medical records was performed for individuals with possible antibiotic-induced anaphylaxis by two experienced allergists (A.K. and T.G.) to ensure that anaphylaxis diagnosis was supported by clinical findings and fulfilled the current criteria for anaphylaxis.^{19,20} The information included details of anaphylaxis history, presence of atopy, additional reactions to antibiotics, and administered therapy during the anaphylactic episode.

Further, reactions that occurred during intravenous treatment were classified according to the time interval between the first drug administration and their onset,³ as “immediate” (when they occurred within the first hour) or “nonimmediate” (when occurred after the first hour). Also, we used a modified classification for nonimmediate reactions by subdividing these reactions into “early” (accelerated) (when occurring >1 to ≤24 hours after the commencement of a specific course) and “late” when reactions occurred after 24 hours.²¹

2.2 | Statistical analysis

For all statistical analyses, we used R 4.0.2 (The R Project for Statistical Computing, www.r-project.org). Categorical variables were summarized using frequencies and percentages, while continuous variables were presented as median and range. Because the distribution of these data was not normal, group differences were analysed using the Mann–Whitney *U*-test for continuous variables and Chi-square test for categorical variables. All tests were performed using a level of significance of $P < .05$. The logistic regression analyses were performed to assess the association between a history of DHR and potential risk factors.

3 | RESULTS

3.1 | Patient characteristics

The overall follow-up time for the study subjects was 3993 patient-years, and the average total number of antibiotic courses per subject/year was 5.4 ± 2.1 in the current study. Moreover, the patients in the cohort had a total of 16 910 antibiotic courses, of which 6832 (40%) were intravenously administered. For further characteristics of the enrolled patients, see Table 1. As of 31 December 2018, there were almost as many children (<18 years) as adults in the cohort, 100 and 126, respectively. Overall, male subjects (54%) predominated.

TABLE 1 Population demographics and characteristics of the study subjects

Characteristics	Male n = 122 (54%)	Female n = 104 (46%)	Total n = 226
^a Average age at the end of the study, mean ± SD, range, quartiles (y)	24.4 ± 17.1 (0.5–76.5) 10.3; 21.0; 35.3	22.3 ± 15.2 (0.7–61.1) 10.0; 18.0; 31.6	23.4 ± 16.3 (0.5–76.5) 10.2; 19.8; 33.6
^a Average number of follow-up years per subject at the end of the study, mean ± SD, range, quartiles (y)	17.0 ± 14.2 (0.3–54.1) 5.3; 12.7; 26.0	18.4 ± 14.6 (0.2–58.2) 6.8; 13.6; 28.4	17.7 ± 14.4 (0.2–58.2) 6.5; 13.5; 26.7
Average total number of antibiotic courses per year per subject, mean ± SD, range, quartiles	5 ± 2.3 (0–10.6) 3.7; 5.1; 6.5	5.8 ± 1.8 (0.9–9.6) 4.4; 5.8; 7.2)	5.4 ± 2.1 (0–10.6) 4; 5.6; 6.8
Average total number of oral antibiotic courses per year per subject, mean ± SD, range, quartiles	3.7 ± 2.1 (0–9.2) 2; 3.4; 5.3	4.1 ± 2.1 (0–9.2) 2.6; 4; 5.5	3.9 ± 2.1 (0–9.2) 2.1; 3.7; 5.5
Average total number of parenteral antibiotic courses per year per subject, mean ± SD, range, quartiles	1.6 ± 1.6 (0–8.3) 0.3; 1.2; 2.7	2 ± 1.6 (0–7.7) 0.8; 2; 2.8	1.8 ± 1.6 (0–8.3) 0.4; 1.5; 2.8
^a Average number of total drug hypersensitivity per subject at the end of the study, mean ± SD, range, quartiles	0.4 ± 0.9 (0–6) 0; 0; 6	0.8 ± 1.4 (0–8) 0; 0; 1	0.6 ± 1.2 (0–8) 0; 0; 1
Average number of drug hypersensitivity reactions per course of oral antibiotic per subject, mean ± SD, range, quartiles	0 ± 0.01 (0–0.03) 0; 0; 0	0 ± 0.02 (0–0.11) 0; 0; 0	0 ± 0.01 (0–0.1) 0; 0; 0
Average number of drug hypersensitivity reactions per course of parenteral antibiotic per subject, mean ± SD, range, quartiles	0.02 ± 0.1 (0–1) 0; 0; 0.01	± 0.03 (0–0.2) 0; 0; 0.01	0.02 ± 0.1 (0–1) 0; 0; 0.01

^aAs of 31 December 2018.

3.2 | Prevalence of drug hypersensitivity reactions

Among 226 enrolled patients, 86 with AAR were identified, of whom 70 CF patients were deemed to have DHR after re-evaluation by the allergists (Figure 1). Thus, the overall frequency of DHR was 31% in the current study, and 70 patients experienced a total of 131 DHR (Figure 1). However, when considering the total antibiotic courses administered in the cohort, the frequency of DHR was only 0.77% (131/16 910) during the whole period.

3.3 | Clinical features of hypersensitivity reactions

The most common clinical features of the DHR were cutaneous manifestations (98%) with the highest frequency of pruritus 30% (52 DHR), followed by exanthema 23% and urticaria 18% (Figure 2A). Tingling was reported in 16 reactions (9%) most of which were classified under colistimethate treatment (11 reactions), followed by meropenem (4 reactions) and piperacillin (1 reaction). No severe skin reactions were observed in our cohort.

Symptoms from non-cutaneous organs were rare and included gastrointestinal (GI) manifestations (nausea, vomiting, diarrhoea) (8.4%), respiratory symptoms (dyspnoea, coughing) (5.3%) and cardiovascular symptoms (tachycardia, dizziness, hypotension) (3.1%) (Figure 2B). Three of 131 reactions (2.3%) were potentially life-threatening and were labelled as anaphylaxis. All three patients were adults (>18 years) and two of them were females. Symptoms of anaphylaxis presented with cutaneous and cardiovascular symptoms (hypotension) in two patients, whereas one patient had cutaneous and respiratory symptoms with fall in oxygen saturation (89%).

3.4 | Time of onset of drug hypersensitivity reactions

Time of onset was recorded only for intravenous courses and available for 99 of 104 reactions. There were 29 (of which three were anaphylaxis) immediate reactions (28%), occurring in most cases at the beginning of infusion of the first dose and 20 early reactions (19%)

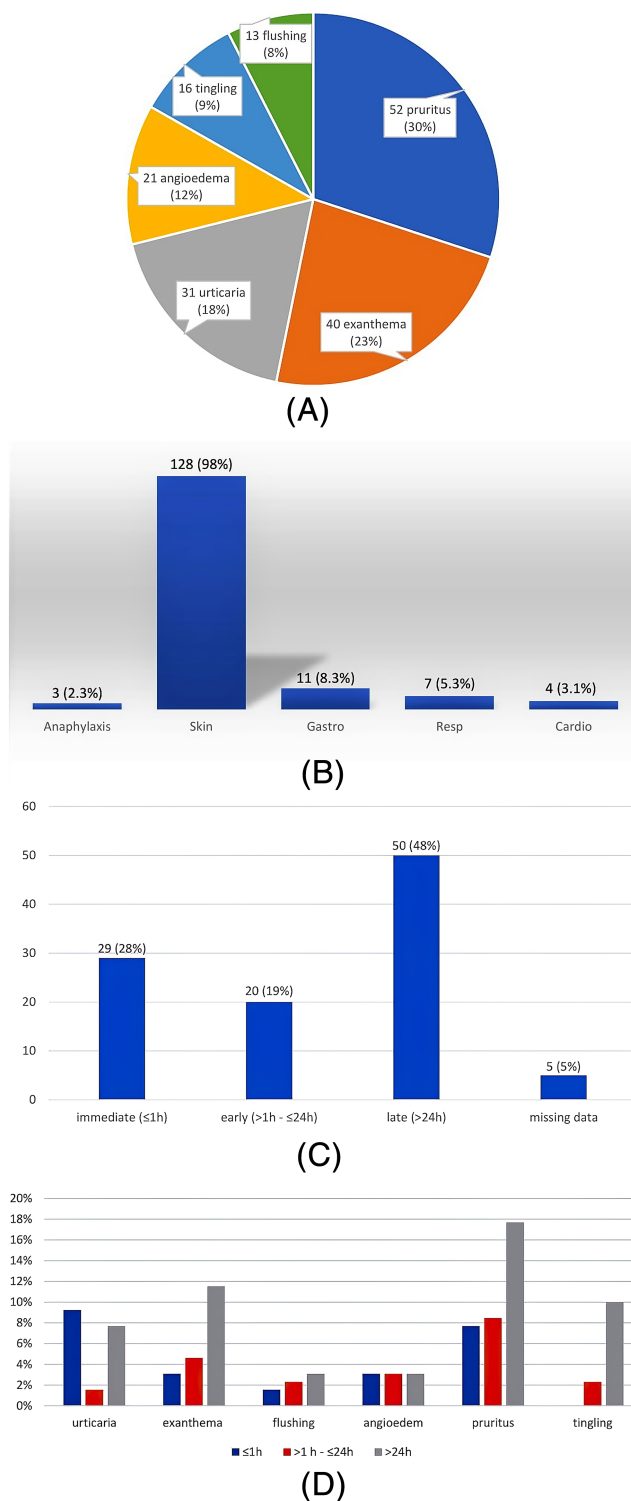


FIGURE 2 Clinical features of drug hypersensitivity reactions to antibiotics in cystic fibrosis patients: (A) Clinical manifestations of 128 cutaneous hypersensitivity reactions. Multiple skin-symptoms may be present during a single reaction. (B) Distribution of organ systems involved in 131 drug hypersensitivity reactions. Of note, multiple organs may be involved in certain reactions. Abbreviations: Gastro, gastrointestinal; Resp, respiratory; Cardio, cardiovascular. (C) Time for onset of 104 drug hypersensitivity reactions during intravenous treatment. Time is calculated from onset of infusion and classified as immediate, if started in ≤ 1 h (included three cases with anaphylaxis) or non-immediate, if started >1 h: early >1 h– ≤ 24 h or late > 24 h. Each bar represents a separate sub-group, shown as number and percent, n (%). (D) Time of onset of cutaneous symptoms during intravenous courses

which occurred later than 1 hour but before 24 hours after the first dose given (Figure 2C). The remaining 50 DHR (48%) were late, presenting on Day 2 or later (range 2–10 days). Some cutaneous reactions, such as urticaria, flushing and angioedema presented both as early and late reactions, whereas exanthema, pruritis and tingling were more common after 24 hours (Figure 2D).

3.5 | Culprit antibiotics eliciting drug hypersensitivity reactions

All culprit antibiotics causing hypersensitivity reactions ($n = 131$) are illustrated in Figure 3A. Most, 79% (104 of 131), DHR occurred during parenteral administered antibiotics, in 61 patients. The number of DHR during oral antibiotic courses were 27, which occurred in 23 patients. Moreover, 20% (14 of 70 patients) reacted to both oral and intravenous antibiotics, and 43% (30 of 70 patients) reacted to multiple antibiotics (≥ 2) (Figure 3B).

Piperacillin was responsible for the highest number of reactions (31 DHR), corresponding to 24% of all DHR and 30% of the intravenous DHR, followed by ceftazidime (22 DHR, 17% and 21%, respectively), colistimethate (18 DHR, 14% and 17%, respectively) and

meropenem (17 DHR, 13% and 16%, respectively) (Figure 3A). Notably, beta-lactams as a class were responsible for 71% (93 DHR) of overall and 81% (84 DHR) of all parenteral courses. Regarding oral antibiotic courses, cotrimoxazole was the most common drug eliciting DHR (13 reactions and 48% of all oral antibiotics), followed by amoxicillin (four reactions, 15% of oral antibiotics) and ciprofloxacin (three reactions, 11% of oral antibiotics). All 27 DHR presented with cutaneous symptoms; mostly exanthema (12 DHR), followed by angioedema (9 DHR), urticaria (5 DHR), pruritis (5 DHR) and flushing (4 DHR). Notably, certain reactions exhibited multiple skin symptoms. Time for onset was available only for 14 DHR, all nonimmediate, occurring usually after some days. No anaphylaxis was observed during oral antibiotic courses.

3.6 | Risk factor analysis

The odds for DHR were found to be 5.8 times higher with intravenous antibiotics compared to oral courses. Further, comparisons between patients with and without history of DHR are shown in Table 2. Overall, higher cumulative number of antibiotics courses, increasing age as well as longer period of time with *Pa*-colonization were identified as

Distribution of all involved antibiotics

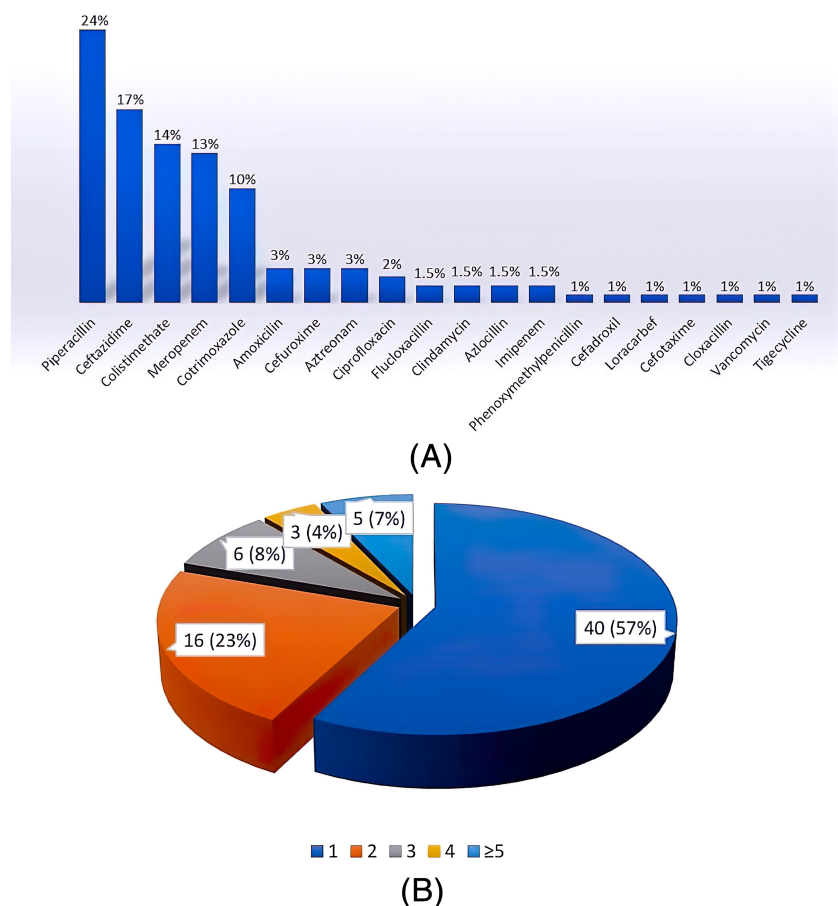


FIGURE 3 Illustration of antibiotics causing drug hypersensitivity. (A) Distribution of all culprit antibiotics eliciting drug hypersensitivity reactions ($n = 131$) during all courses in patients with cystic fibrosis. (B) Pie chart showing the distribution of 70 patients who reacted to one or several antibiotics. Each slice of the pie is labelled with the number and percent, n (%)

TABLE 2 Clinical features of CF patients who reacted with antibiotics compared to non-reacting patients

Characteristics	All	No DHR	DHR	P-value
Age, median (range)	19.8 (0.5–76.5)	14.4 (0.5–76.5)	29.5 (4.7–61.1)	<0.001 ^a
Age_at_diagnosis, median (range)	0.7 (0–62.2)	1 (0–62.2)	0.4 (0–35.4)	0.111 ^a
Gender, n (%)				0.095 ^b
Female, n (%)	104 (46)	66 (42.3)	38 (54.3)	
Male, n (%)	122 (54)	90 (57.7)	32 (45.7)	
CFTR genotype				0.534 ^b
F508del/F508del, n (%)	97 (42.9)	68 (43.6)	29 (41.4)	
F508del/other, n (%)	84 (37.2)	60 (38.5)	24 (34.3)	
Other/other, n (%)	45 (19.9)	28 (17.9)	17 (24.3)	
Total number of antibiotic courses, median (range)	63 (0–338)	46 (0–338)	124 (9–272)	<0.001 ^a
Total number of intravenous antibiotic courses, median (range)	17 (0–264)	8 (0–264)	59.5 (0–177)	<0.001 ^a
Total number of oral antibiotic courses, median (range)	38 (0–219)	34 (0–219)	60 (0–160)	<0.001 ^a
Years of <i>Pa</i> -colonization, median (range)	16.7 (0.2–46.2)	11.5 (0.2–46.2)	20.8 (0.7–41.1)	<0.001 ^a

DHR, drug hypersensitivity reactions; *Pa* – *P. aeruginosa*.

P-values were analysed using the ^aMann–Whitney *U*-test and ^bChi-square test.

risk factors in univariate analyses. In contrast, the status of the cystic fibrosis transmembrane conductance regulator (CFTR) and gender were not significantly different between patients with DHR and those without. Moreover, when we performed logistic regression analyses, we found the cumulative numbers of intravenous antibiotic courses to be the most significant predictor for the development of DHR. This is because both age as of 31 December 2018 and time with *Pa*-colonization had quite strong associations with number of intravenous antibiotic courses ($r = 0.50$, $P < .001$ and $r = 0.68$, $P < .001$, respectively). Compared with the univariate effect, the logistic effect of standardized age on history of DHR decreased from $\beta = 0.91$ ($P < .001$) to $\beta = 0.36$ ($P = .08$) when adjusting for number of intravenous antibiotic courses. The corresponding values for time with *Pa*-colonization was a decrease from $\beta = 0.84$ ($P = .001$) to $\beta = 0.47$ ($P = .14$). This suggests that number of intravenous antibiotic courses accounted for approximately 60% and 44% of the associations between history of DHR and age and time with *Pa*-colonization, respectively.

4 | DISCUSSION

Hypersensitivity reactions to antibiotics in CF patients generate a significant clinical problem, as they appear to be more frequent than in the general population. Here, we conducted a 20-year retrospective study at a single tertiary care centre evaluating the prevalence and clinical manifestations of hypersensitivity reactions to antibiotics by screening 16 910 courses in 226 CF patients. To the best of our knowledge, this is the largest studied cohort of CF patients so far.

We found an overall prevalence of DHR of 31% in the current study. This appears to be higher when compared to a population-based study reporting an overall rate of antibiotic allergy to be 15.3%.⁴ However, the number of courses was higher in CF patients

and that was significantly associated with the development of DHR. Interestingly, however, the reaction rate per antibiotic course was 0.77% (1 in 129 courses) in the cohort. This does not appear fundamentally different from a population-based study showing the rate of DHR to oral penicillin of 0.60% and parenteral penicillin courses of 0.77%.²² Notably, most reactions were mild and limited to skin, as severe cutaneous and immediate systemic allergic reactions, i.e., anaphylaxis, were infrequent in this cohort.

Nevertheless, the prevalence of DHR was in line with the previous cohort studies analysing antibiotic hypersensitivity in CF patients: 29% in Pleasants et al.,⁷ 34% in Wills et al.⁸ and 36% in Burrows et al.,⁹ but lower than Roehmel et al. (60%)¹⁰ and Koch et al. (62%).⁶ The great variation in reports might be due to the criteria applied for hypersensitivity and design of study. For instance, the study by Koch et al. included only patients with chronic *Pa*-infection, which were about half of all patients⁶ and the study by Roehmel et al. enrolled only patients who had at least four intravenous antibiotic courses,¹⁰ which might have led to selection bias. Further, some studies included both children and adults, whereas others included mostly adult patients. In our study, we had almost as many children ($n = 100$) as adults ($n = 126$). In addition, most previous studies described DHR to intravenous beta-lactams; however, in the present study, we analysed DHR to all kinds of antibiotics used both in intravenous and oral courses.

The majority of DHR in the current study were limited to the skin and the severity of reactions were mild to moderate. Notably, none of the patients in our cohort had a severe cutaneous adverse reaction including Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Although these reactions have been described in CF patients,^{23,24} they appear to be as uncommon as in the normal population. Likewise, severe immediate DHR were rare, as anaphylaxis

was only present in three DHR (2.3%). By contrast, the previous studies by Koch et al.⁶ and Roehmel et al.¹⁰ reported much higher anaphylaxis rates of 5.6% and 15%, respectively. Nevertheless, our overall observation, in line with other studies, supports the notion that anaphylactic reactions are rare in CF,^{7,9} since we observed only three anaphylactic reactions in 16 910 documented antibiotic courses. Moreover, anaphylactic reactions in our study were caused by piperacillin, meropenem and colistimethate. To the best of our knowledge, colistimethate has not been previously reported in anaphylactic reactions in CF patients, as most previous studies only analysed DHR to beta-lactams. Interestingly, no anaphylaxis was observed during oral antibiotic courses. Although patients with anaphylaxis experienced DHR to other antibiotics as well, no additional anaphylaxis was reported. Moreover, when we compared the anaphylaxis rate to the population studies, the results were of interest. The reaction rate of anaphylaxis was 0.017% (1 in 5637 of total courses) in the cohort, which appears to be higher than in the normal population. For instance, a large population-based study reported 1 oral penicillin-associated anaphylaxis in 255 320 courses and 1 parenteral penicillin-associated anaphylaxis in 123 792 courses.²² Likewise, oral and parenteral cephalosporin-associated anaphylaxis in the general population were reported to be 1 in 180 381 and 1 in 60 953 courses, respectively.²⁵ Thus, we can suggest that the rate of antibiotic-induced anaphylaxis is increased in CF.

Furthermore, 79% of all DHR occurred during parenteral antibiotic courses (104/6832 vs. 27/10 078 oral antibiotic courses; $P < .001$) indicating that this route of exposure or higher drug dosage may be associated with an increased risk for DHR.²⁶ Another factor which might contribute is that these reactions were documented more accurately. Among the culprit antibiotics, piperacillin was the most common causing 30% of intravenous and 24% of all DHR as in line with the previous reports.⁷⁻⁹ This was followed by ceftazidime, colistimethate and meropenem. Of note, beta-lactams were responsible for 71% (93 DHR) overall and 81% (84 DHR) of the parenteral courses, which is in line with another study (79%)¹⁰ and may reflect the frequency of beta-lactam use in the respective centres.^{9,27} Moreover, 43% of patients experienced DHR to more than two antibiotics (Figure 3B), which is similar to data in the literature.¹⁰ Notably, the most common oral antibiotic eliciting DHR was cotrimoxazole (48% of oral antibiotic DHR).

About half of the DHR with intravenous courses were observed during the first 24 hours, as 28% occurred during the first hour and 19% within 1–24 hours. However, 48% of all DHR were delayed, presenting on Day 2 or later, which was somewhat lower than previous studies.^{8,9} Notably, all anaphylactic reactions occurred immediately, i.e., within the first hour of infusion, suggesting a possible IgE-mediated mechanism. Milder DHR, such as urticaria, flushing and angioedema presented both as early and as late reactions. Conversely, pruritus, exanthema and tingling were more common on the second day or later during treatment, typical for a delayed type hypersensitivity (Figure 2D). Hence, this data suggests that the start of parenteral antibiotic treatment in CF patients should preferably be initiated at hospital to make sure safety aspects, whereas later dosages can be given on an outpatient basis.

Previous studies have shown inconsistent results regarding potential risk factors for DHR in patients with CF. In the current study, we found a higher prevalence of DHR with increasing age, a longer period of time with *Pa*-colonization and a higher number of cumulative exposures to antibiotics. However, multivariate logistic regression analyses indicated that a big portion of the univariate associations between history of DHR and age and time with *Pa*-colonization could be accounted for by number of intravenous antibiotic courses. Thus, a higher number of cumulative exposures to antibiotics appears to be the most significant risk factor for developing DHR. Moreover, no associations between CFTR genotype, gender and the risk of DHR were found.

The main strength of this single-centre study was that we had the opportunity to assess the prevalence of DHR in the largest studied cohort of CF patients by screening 16 910 antibiotic courses. The cohort was well characterized due to continuous electronic file records as well as retrospective assessment of the recorded reactions by two independent allergists. Thus, the risk for data to be missed due to recall bias was clearly reduced in comparison to other studies. Conversely, its major limitation was the retrospective nature of the study. Details of the timing and symptoms of DHR to oral antibiotic courses were not always accurately documented as often reported by patients.

In addition, lack of confirmatory allergy testing should also be mentioned as a limitation in this study. However, considering the high number of patients affected, it is not always possible in clinical practice to systematically perform allergy work-up and/or drug provocation tests to confirm the diagnosis. In the present study, two allergists independently re-evaluated the reported reactions and assessed their likelihood of being a true DHR. Non-specific manifestations were excluded from the analysis, such as anxiety, flushing, pain, fever, if they rather presented an infectious, toxic or somatoform reaction. Although DHR in individual cases cannot be fully ruled out without allergy tests, the prevalence reported in this study should be more accurate than that from previous studies, in which not all reported reactions were reviewed by allergists.

In conclusion, our study demonstrates that patients with CF have an increased risk for DHR, which is highly associated with the number of cumulative exposures to antibiotics. However, the severity of most reactions was mild and limited to skin, as anaphylaxis was rare. Considering a substantial increase in the life expectancy and growing number of adult patients, there is apparently an unmet need to improve care of CF patients. Although not generally feasible in the clinical routine, systematic allergy work-up to confirm DHR with a compatible history may therefore be instrumental to avoid overdiagnosis and to achieve further improvement in the management of CF patients.

ACKNOWLEDGEMENTS

We would like to thank to Berit Widén for her help in recruiting the study patients.

A.K. received a scholarship from Erica Lederhausen Memorial Foundation, Sweden for this study. T.G. was supported by grants from the Konsul TH C Bergh Foundation, Sweden.

COMPETING INTERESTS

The authors declare that they have no conflicts of interest related to this study.

CONTRIBUTORS

A.K. collected the data and took active part in designing the study, analysing and interpreting the data as well as drafting and revising the manuscript. I.d.M. took active part in the design of the study, analysis and interpretation of the data and revising of the manuscript. K.S. analysed the data and took an active role in interpretation of the data. K.B. interpreted the data and revised the manuscript critically. T.G. conceptualized and designed the study; analysed and interpreted the data; wrote and revised the manuscript; and supervised the project. All authors approved the final submitted manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Theo Gülen  <https://orcid.org/0000-0002-1683-8882>

REFERENCES

- Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008; 15(47):735-743. doi:10.1086/591126
- Brockow K. Triage strategies for clarifying reported betalactam allergy. *J Allergy Clin Immunol Pract*. 2019;7(3):1066-1067. doi:10.1016/j.jaip.2018.08.009
- Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420-437. doi:10.1111/all.12350
- Macy E, Poon K-YT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009;122(778):e1-e7.
- Sanders DB, Solomon GM, Beckett VV, et al. Standardized Treatment of Pulmonary Exacerbations (STOP) study: observations at the initiation of intravenous antibiotics for cystic fibrosis pulmonary exacerbations. *J Cyst Fibros*. 2017;16(5):592-599. doi:10.1016/j.jcf.2017.04.005
- Koch C, Hjelt K, Pedersen SS, et al. Retrospective clinical study of hypersensitivity reactions to aztreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple treatment courses. *Rev Infect Dis*. 1991;13(Suppl 7):S608-S611. doi:10.1093/clinids/13.Supplement_7.S608
- Pleasant RA, Walker TR, Samuelson WM. Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest*. 1994;106(4):1124-1128. doi:10.1378/chest.106.4.1124
- Wills R, Henry RL, Francis JL. Antibiotic hypersensitivity reactions in cystic fibrosis. *J Paediatr Child Health*. 1998;34(4):325-329. doi:10.1046/j.1440-1754.1998.00197.x
- Burrows JA, Nissen LM, Kirkpatrick CM, Bell SC. Beta-lactam allergy in adults with cystic fibrosis. *J Cyst Fibros*. 2007;6(4):297-303. doi:10.1016/j.jcf.2006.11.001
- Roehmel JF, Schwarz C, Mehl A, Stock P, Staab D. Hypersensitivity to antibiotics in patients with cystic fibrosis. *J Cyst Fibros*. 2014;13(2):205-211. doi:10.1016/j.jcf.2013.10.002
- Matar R, Le Bourgeois M, Scheinmann P, de Blic J, Ponvert C. Beta-lactam hypersensitivity in children with cystic fibrosis: a study in a specialized pediatric center for cystic fibrosis and drug allergy. *Pediatr Allergy Immunol*. 2014;25(1):88-93. doi:10.1111/pai.12154
- Caimmi S, Sanfiorenzo C, Caimmi D, Bousquet PJ, Chiron R, Demoly P. Comprehensive allergy work-up is mandatory in cystic fibrosis patients who report a history suggestive of drug allergy to beta-lactam antibiotics. *Clin Transl Allergy*. 2012;2(1):10. doi:10.1186/2045-7022-2-10
- Braun C, Reix P, Durieu I, et al. The diagnosis of hypersensitivity to antibiotics is rarely confirmed by allergy work-up in cystic fibrosis patients. *Pediatr Allergy Immunol*. 2020;31(4):396-404. doi:10.1111/pai.13206
- Stevenson DD, Kowalski ML. An epidemic of over diagnosing drug allergies. *Allergy Asthma Proc*. 2014;35(2):92-94. doi:10.2500/aap.2014.35.1015
- Scherer K, Brockow K, Aberer W, et al. Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group. *Allergy*. 2013;68(7):844-852. doi:10.1111/all.12161
- Brockow K, Ardern-Jones MR, Mockenhaupt M, et al. EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity. *Allergy*. 2019;74(1):14-27. doi:10.1111/all.13562
- Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30(1):57-69. doi:10.1592/phco.30.1.57
- Döring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J*. 2000;16(4):749-767. doi:10.1034/j.1399-3003.2000.16d30.x
- Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020;145(4):1082-1123. doi:10.1016/j.jaci.2020.01.017
- Muraro A, Worm M, Alviani C, et al. EAACI guideline: Anaphylaxis (2021 update). *Allergy*. 2022;77(2):357-377. doi:10.1111/all.15032
- Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med*. 1966;275(20):1115-1125. doi:10.1056/NEJM196611172752009
- Liang EH, Chen LH, Macy E. Adverse reactions associated with penicillins, carbapenems, monobactams, and clindamycin: a retrospective population-based study. *J Allergy Clin Immunol Pract*. 2020;8(4):1302-1313.e2. doi:10.1016/j.jaip.2019.11.035
- Wright MFA, Bush A, Carr SB. Hypersensitivity reactions to intravenous antibiotics in cystic fibrosis. *Paediatr Respir Rev*. 2018;27:9-12. doi:10.1016/j.prrv.2018.01.003
- Tremblay F, Chapdelaine H, Lavoie A, et al. Toxic epidermal necrolysis in a patient with cystic fibrosis. *J Allergy Clin Immunol Pract*. 2016; 4(3):526-528. doi:10.1016/j.jaip.2015.11.021
- Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol*. 2015;135(3):745-52.e5. doi:10.1016/j.jaci.2014.07.062
- Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol*. 1984;74(4):567-572. doi:10.1016/0091-6749(84)90108-8
- Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams—an EAACI position paper. *Allergy*. 2020;75(6):1300-1315. doi:10.1111/all.14122

How to cite this article: Kowalik A, de Monestrol I, Sorjonen K, Brockow K, Gülen T. Antibiotic hypersensitivity in cystic fibrosis – Low frequency of anaphylaxis over 16 000 courses. *Br J Clin Pharmacol*. 2022;88(11):4845-4853. doi:10.1111/bcp.15434