

Clinical Communications

Antibiotic adverse reactions in adult cystic fibrosis patients

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Clinical Implications

- A comprehensive review and classification of documented antibiotic reactions in an adult cystic fibrosis cohort found that adverse antibiotic reactions are common among first-line cystic fibrosis antibiotics and are primarily reactions that could benefit from allergy evaluation or reintroduction.

Cystic fibrosis (CF) is an autosomal-recessive genetic condition characterized by chronic airway infection. High antibiotic utilization is an essential element of successful life-saving care for patients with CF, because frequent and persistent respiratory tract infections remain the major cause of CF morbidity.¹ However, antibiotic reactions occur commonly in patients with CF² and pose a significant barrier to appropriate treatment for CF exacerbations with first-line antibiotics.^{3,4}

A reported 29% to 36% of patients with CF experience reactions to 1 or more beta-lactam (BL) antibiotics,^{3,4} the first-line treatment for the most prevalent pathogens in CF—*Staphylococcus aureus* (70.7%) and *Pseudomonas aeruginosa* (45.7%).¹ Less literature has been published regarding reactions that occur to non-BL antibiotics commonly used for CF exacerbations (trimethoprim-sulfamethoxazole, azithromycin, fluoroquinolones, doxycycline, vancomycin).² Previous investigations focused on reactions to parenteral⁵ or BL antibiotics^{3,4,6} in adult patients, or investigated subsets of CF cohorts.^{5,7} Because oral and inhaled antibiotics as well as non-BL antibiotics are often used in the treatment of CF, a better understanding is needed of the full spectrum and frequency of antibiotic adverse drug reactions (ADRs) in this population. This knowledge could potentially lead to important improvements in CF antibiotic stewardship by helping identify management strategies for patients with CF with documented ADRs.

We performed a comprehensive review of documented reactions to parenteral, oral, and inhaled antibiotics in a full adult CF cohort (n = 115) followed at a tertiary and quaternary academic medical CF center certified by the national CF Foundation. We then classified these documented symptoms into specific ADR types according to standard allergy/immunology classification. This study was approved by the institution's Institutional Review Board (19-27829).

Electronic health records (EHRs) were reviewed retrospectively in July 2019. Our institution's Epic EHR was established in 2012. The EHR was reviewed for patients' demographic characteristics (age, sex, race, ethnicity) and antibiotic reactions documented in the allergy section of each patient's EHR. Pre-specified reaction symptoms and free-text comments were

extracted for all documented antibiotic reactions. Documented reactions to cutaneous antibiotics, nonantibiotic medications, adhesives, environmental allergens, and food allergens were excluded from review. Documented reactions were classified into the following discrete ADR types per definitions in national guidelines.⁸ ADR types were further categorized into groups with similar management strategies: (1) allergy evaluation for potentially IgE-mediated reactions, benign drug rashes, and fever only, (2) avoidance for clear side effects and severe non-IgE-mediated reactions with organ involvement, and (3) reintroduction for intolerances and Red Man syndrome.⁸ Data were summarized using descriptive statistics using STATA 16 (StataCorp LLC, College Station, TX).

In this CF cohort, more than half the patients with CF (60.1%; 70 of 115) had 1 or more documented antibiotic reaction where appropriate management could positively impact their care. A total of 154 antibiotic reactions were documented for the 70 patients with documented antibiotic reactions (Table I). Reactions to BL antibiotics are thought to occur with a higher frequency in the CF population compared with the general population.²⁻⁶ We found that BL antibiotic reactions were the most commonly documented antibiotic ADRs (35.7%; 41 of 115) (Table I). Penicillin antibiotic reactions were reported in 26.1% (30 of 115) of patients compared with reported rates of approximately 10% in the general population,⁸ and cephalosporin antibiotic reactions were reported in 22.6% (26 of 115) of patients compared with reported rates of 1.3% to 1.7% in the general population.⁹

Reviewing reactions to oral and inhaled antibiotics in addition to parenteral antibiotics revealed that a number of reactions were also documented to non-BL antibiotics routinely required for CF management (Table I; see Table E1 in this article's Online Repository at www.jaci-inpractice.org).^{1,2} The most commonly described ADRs were immediate-type hypersensitivity reactions to BL antibiotics (20.8%; 32 of 154), benign drug rashes to BL antibiotics (12.3%; 19 of 154), side effects to aminoglycosides (9.7%; 15 of 154), intolerances to fluoroquinolones (7.1%; 11 of 154), and immediate-type hypersensitivity reactions to sulfonamides (5.2%; 8 of 154) (Table II).

To provide a measure of the utility of reviewing reaction comments extracted from the allergy section of the EHR, we investigated whether providers were interacting with the allergy section of the EHR. All but 3 patients had been seen by a provider and had their allergy list reviewed in the year before chart review.

For optimal antibiotic reaction management, accurate classification of antibiotic reactions into ADR types is necessary so providers can initiate appropriate management.² Indeed, when documented reactions were classified into ADR types, multiple opportunities for improved antibiotic allergy management were identified. Most documented reactions were consistent with immediate-type reactions and benign non-IgE-mediated reactions (57.1%; 88 of 154) (Table II), where allergy evaluation often clarifies the absence of true IgE-mediated hypersensitivity.⁸ Reactions consistent with intolerances, where reintroduction can be considered, were also commonly reported (14.9%; 23 of 154). Indeed, 65% (15 of 23) of the documented intolerance reactions

TABLE I. Antibiotic reactions documented in patients with CF

Antibiotic class	Reactions documented to each antibiotic class, n (%) (n = 154)	No. of patients with reaction documented to each antibiotic class, n (%) (n = 115)
Penicillins*	31 (20.1)	30 (26.1)
Cephalosporins, total	28 (18.2)	26 (22.6)
Third-fifth generation*	19 (12.3)	18 (15.7)
First-second generation*	8 (5.2)	7 (6.1)
Generation not specified	1 (0.6)	1 (0.9)
Aminoglycoside (tobramycin)*	18 (11.7)	17 (14.8)
Fluoroquinolone	18 (11.7)	18 (15.7)
Sulfonamide	14 (9.1)	14 (12.2)
Glycopeptide (vancomycin)†	14 (9.1)	13 (11.3)
Tetracycline	8 (5.2)	8 (7.0)
Macrolide*	8 (5.2)	7 (6.1)
Carbapenem	6 (3.9)	6 (5.2)
Monobactam (aztreonam)	4 (2.6)	4 (3.5)
Oxazolidinone (linezolid)	3 (1.9)	3 (2.6)
Lincosamide (clindamycin)	1 (0.6)	1 (0.9)
Other (metronidazole)	1 (0.6)	1 (0.9)

There were 154 antibiotic reactions documented in 115 patients with CF. The individual antibiotic name is shown in parentheses next to the antibiotic class name for antibiotic classes with only 1 antibiotic in that class.

*The 5 instances where reactions to 2 separate antibiotics were documented within the same class for 1 patient (piperacillin-tazobactam and ticarcillin for penicillin, cephalexin and cefaclor for first-second generation cephalosporin, cefepime and cefuroxime for third-fifth generation cephalosporin, clarithromycin and erythromycin for macrolide, and tobramycin intravenous and tobramycin inhaled for aminoglycoside antibiotics).

†The 1 instance where 2 separate reactions were documented to vancomycin for 1 patient (Red Man syndrome, fixed drug eruption).

TABLE II. Classification of antibiotic reactions into ADR types based on documented symptoms

Antibiotic class	Immediate type (n = 52)	Benign drug rash (n = 32)	Severe non-IgE-mediated (n = 9)	Side effect (n = 22)	Intolerance (n = 23)
Penicillins	17 (33.3)	8 (25.0)	2 (22.2)	0	3 (13.0)
Cephalosporins	12 (23.5)	9 (28.1)	2 (22.2)	0	2 (8.7)
Third-fifth generation	10 (19.6)	6 (18.8)	2 (22.2)	0	0
First-second generation	1 (2.0)	3 (9.4)	0	0	2 (8.7)
Not specified	1 (2.0)	0	0	0	0
Tobramycin	0	0	1 (11.1)	15 (68.2)	1 (4.3)
Fluoroquinolone	2 (3.9)	1 (3.1)	0	3 (13.6)	11 (47.8)
Sulfonamide	8 (15.7)	5 (15.6)	0	0	1 (4.3)
Vancomycin	3 (5.9)	0	1 (11.1)	0	0
Tetracycline	2 (3.9)	2 (6.3)	3 (33.3)	0	1 (4.3)
Macrolide	5 (9.8)	2 (6.3)	0	0	1 (4.3)
Carbapenem	3 (5.9)	3 (9.4)	0	0	0
Aztreonam	0	0	0	4 (18.2)	0
Linezolid	0	1 (3.1)	0	0	2 (8.7)
Clindamycin	0	1 (3.1)	0	0	0
Metronidazole	0	0	0	0	1 (4.3)

The 154 total documented reactions were classified into distinct ADRs. Data are displayed as n (%), with the numerator being the number of reactions per antibiotic class in that ADR and the denominator being the total number of reactions in that ADR. Reactions that could not be categorized (n = 4), pseudoallergic reactions (n = 8), and "fever"-only reactions (n = 4) are not displayed.

had free-text comments, indicating that the culprit antibiotic or antibiotic in the same class had been tolerated. There were only 9 severe non-IgE-mediated reactions necessitating absolute avoidance.

An additional point of interest was the high rate of side effects to tobramycin and inhaled antibiotics, antibiotics that are also central to CF care. Side effects recur with re-exposure to the culprit antibiotic and reintroduction is not recommended.

However, given the importance of inhaled antibiotics in CF care, it may be of benefit in the future to explore strategies to prevent bronchospasm associated with inhaled antibiotics with inhaled beta-agonist and/or anticholinergic co-treatment.

There were limitations to our study. The rates of varying ADR types to each antibiotic class are based on documented reactions, which can be inaccurate. This may explain why various frequencies of ADRs are higher in our report. As such, we stress that

these reaction rates are not sensitization rates that have been determined by allergy testing. Our findings nevertheless provide data regarding the spectrum and frequency of documented antibiotic reactions providers face when trying to prescribe antibiotics for patients with CF. Previously reported reaction rates both in the CF population and in the general population often have not been confirmed with allergy testing and are subject to the same limitations as our study.² We have implemented a CF Antibiotic Allergy Program and are currently reviewing the allergy testing outcomes for patients with CF with documented antibiotic allergies.

In summary, improved classification of potential IgE-mediated, benign non-IgE-mediated, and intolerance reactions by providers would allow for more timely consideration of allergy evaluation and reintroduction in patients with CF when appropriate, thereby liberalizing the use of life-saving antibiotics. With advances in CF care leading to increases in life expectancy and increased need for antibiotics, antibiotic allergy management has emerged as a significant clinical challenge in high-quality CF care.² To our knowledge, this is the first comprehensive review of documented reactions to all antibiotics observed in a cohort of patients with CF followed at an adult CF care center in the United States. This comprehensive review of documented antibiotic reactions in our CF patient population found that patients with CF have a high frequency of antibiotic reactions, not only to BL antibiotics but also to non-BL antibiotics essential to CF patient care. Importantly, most antibiotic reactions were categorized into ADR types that could benefit from allergy evaluation or reintroduction. These findings highlight the need for allergy involvement in high-quality CF care and the need for CF providers to understand the different ADRs and their implications for management. Future studies focusing on the success of allergy involvement at improving antibiotic prescribing practices in a CF population are needed and ongoing at our institution.

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ONLINE REPOSITORY

TABLE E1. Documented reactions to individual antibiotics*

Antibiotic class	Individual antibiotic	Reactions documented to each antibiotic class, n	Reactions documented to individual antibiotic, n
Penicillins			31
	Piperacillin-tazobactam		13
	Penicillin, not specified		8
	Amoxicillin		5
	Amoxicillin-clavulanate		3
	Dicloxacillin		1
	Ticarcillin		1
Third-fifth generation cephalosporins			19
	Ceftazidime		12
	Cefepime		6
	Cefuroxime		1
First-second generation cephalosporins			8
	Cephalexin		3
	Cefaclor		2
	Cefazolin		2
	Cefprozil		1
Cephalosporin, generation not specified			1
Aminoglycoside			18
	Tobramycin		12
	Tobramycin, nebulized		6
Fluoroquinolone			18
	Ciprofloxacin		11
	Levofloxacin		5
	Moxifloxacin		2
Sulfonamide			14
	Sulfa		7
	Trimethoprim-sulfamethoxazole		7
Glycopeptide (vancomycin)			14
Tetracycline			8
	Doxycycline		3
	Minocycline		3
	Tetracycline		2
Macrolide			8
	Clarithromycin		5
	Erythromycin		2
	Azithromycin		1
Carbapenem			6
	Meropenem		4
	Imipenem		2
Monobactam (aztreonam lysine)			4
Oxazolidinone (linezolid)			3
Lincosamide (clindamycin)			1
Other (metronidazole)			1

*This table shows how many reactions were documented for individual antibiotics within each antibiotic class.