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Approach to the evaluation of adverse antibiotic reactions in patients with cystic fibrosis

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ABSTRACT

Background: Adverse drug reactions (ADRs) to antibiotics in patients with cystic fibrosis (CF) are common and often mislabeled as allergies. The labeling of an antibiotic reaction as an allergy can lead to the use of antibiotics that are less efficacious, are more expensive, or have a greater risk of adverse effects.
Objective: To establish a safe approach for the evaluation of ADRs to antibiotics in patients with CF to help clarify future use of these medications.
Methods: Patients with CF whose antibiotic allergies were causing difficulty in their medical management were referred for an allergy evaluation that consisted of a thorough drug allergy history and antibiotic testing if appropriate. If the history was not consistent with a true hypersensitivity reaction (HSR) and test results were negative, the patient underwent a challenge to the offending agent(s) to rule out an HSR. Challenges were only performed if the medication was indicated for future use.
Results: A total of 17 patients (mean age, 32.4 years) underwent a thorough allergy evaluation. A total of 17 antibiotic challenges were performed in 11 patients without a reaction consistent with an HSR or severe delayed reaction. Only 2 medications had a history consist with an HSR, and it was recommended that they undergo a desensitization procedure if the drug was required.
Conclusion: If treatment with appropriate antibiotics becomes difficult in patients with CF because of drug allergies, then referral to an allergist can help safely identify treatment options. Our findings suggest that a thorough evaluation by an allergy specialist can lead to more appropriate treatment options in patients with CF.

Introduction

Antibiotic allergy in patients with cystic fibrosis (CF) has been previously reported to have an incidence of 3 times higher (29%) than the general population.[1,2] Often, any type of reaction to a medication can be listed on the patient's allergy list and is subsequently avoided regardless of the clinical history. The allergy list could be better renamed the adverse drug reaction (ADR) list, given that most drug reactions are not actually true immune-mediated hypersensitivity reactions (HSRs).[3–6]

Type 1 HSRs typically occur rapidly after exposure to an offending agent and induce numerous symptoms that can include urticaria, angioedema, bronchoconstriction, and, in severe cases, hypotension. Because these reactions can be life threatening, patients with type 1 HSRs need to avoid the medication or undergo a drug desensitization procedure. A desensitization procedure is a gradual increase of the offending medication during a several-hour period that induces a temporary state of tolerance.[2,7–9] This is only indicated if the history is consistent with a type 1 HSR.

Also in the differential diagnosis are delayed cell-mediated reactions to medications that typically present days or even weeks after exposure. Most of these reactions are relatively benign maculopapular rashes; however, this group also includes the life-threatening severe cutaneous adverse drug reactions (SCARs), such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). If the history is consistent with a SCAR, then the medication needs to be strictly avoided other than in rare cases where a certain medication is absolutely necessary. Identifying the specific agent that caused these severe delayed reactions can be difficult if multiple medications are given at the same time and the

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reaction develops. Fortunately, these reactions are relatively rare and often can be identified by clinical history.

In the CF population, the most significant contributor to morbidity and mortality is related to chronic suppurative lung disease.[10] Because of the development of resistant strains of bacteria, the choice of antibiotics often becomes limited, particularly in the adult CF population.[11] Colonization of multidrug-resistant strains of bacteria often correlate with worsened clinical outcomes for patients with CF.[12] Several studies have analyzed the prevalence of antibiotic ADRs in patients with CF, but few have pursued a thorough allergy evaluation to classify the type of ADRs or determine whether these patients could in fact successfully receive the antibiotic therapy to which they are purportedly allergic.[1,2] The present study aimed to establish an approach for the evaluation of ADRs to various antibiotics used in the CF population. We also aimed to show that, even in this high-risk patient population, this evaluation, including oral and intravenous (IV) challenge procedures, can be performed safely. The improper diagnosis of antibiotic allergy is a significant hindrance in the treatment of patients with CF and often leads to the use of drugs that are less efficacious, are more expensive, and/or have a greater risk of adverse effects.

Methods

This study was conducted during a 7-year period from January 2009 to December 2015 in patients with CF attending the outpatient CF program at the University of Washington Medical Center with a history of ADRs to antibiotics, limiting the treatment options for CF exacerbations. Although we have a large population of patients with CF, many patients did not require referral given the history was clearly not consistent with an allergic hypersensitivity or the history was consistent with a severe delayed reaction and the drug was strictly avoided.

Baseline evaluation consisted of a complete drug allergy history that entailed both patient recollection and thorough medical record review by an allergy and immunology specialist. If there was a history of SCAR, such as TEN, SJS, or DRESS, no testing or challenges were conducted, and it was recommended that the patient strictly avoid the medication. If the patients had a history more consistent with a known adverse effect, such as tinnitus with an aminoglycoside, then no further testing or challenges were performed, and the patient was advised to take the medication if appropriately monitored for the specific adverse effects. Spirometry (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and FEV_1/FVC ratio) were recorded when patients were not in an acute exacerbation. Sputum organisms within the preceding year were also recorded.

Antibiotic testing occurred a minimum of 6 weeks after a suspected hypersensitivity reaction. Evaluation of possible penicillin sensitivity, including skin prick testing (SPT) and intradermal testing (IDT), was performed per the standardized benzylpenicilloyl polylysine (Pre-Pen) protocol.[2,13] For other antibiotics, patients were skin tested at doses thought to be nonirritating in healthy adults.[14–16] Table 1 details the list of the concentrations used to skin test the patients in this study. If the test results were negative and/or the history was not consistent with a type 1 HSR, SCAR, or other severe and reproducible adverse reaction, then an antibiotic challenge was recommended. Challenge procedures are the gold standard for determination of a true type 1 hypersensitivity reaction. Given the inherent risk of performing a challenge procedure in patients with CF because of their diminished lung function and the possibility of bronchospasm associated with IgE-mediated reactions, only antibiotics that were essential for CF management were challenged. This decision was made after a discussion among pulmonologists, allergists, and the patients took place and was based on factors such as severity of disease and colonized organisms. The ultimate goal was to do no harm, and testing and challenge procedures were only performed if the benefits were thought to significantly outweigh the risks.

Table 1
Concentrations of Antibiotics Used in Skin Prick Testing and Intradermal Testing

Antibiotic	SPT result	IDT 1 result (low)	IDT 2 result (high)
Meropenem	1 mg/mL	0.1 mg/mL	1 mg/dL
Ceftazidime	2 mg/mL	0.2 mg/mL	2 mg/dL
Cefepime	2 mg/mL	0.2 mg/mL	2 mg/dL
Aztreonam	2 mg/mL	0.2 mg/mL	2 mg/dL
Colistin	75 mg/mL	0.25 mg/mL	NA
Penicillin G	10,000 U/mL	NA	10,000 U/mL
Benzylpenicilloyl polylysine	6×10^{-5} M	NA	6×10^{-5} M

Abbreviations: IDT, intradermal testing; NA, not applicable; SPT, skin prick test.

For oral antibiotics, a single therapeutic dose of the antibiotic was administered in our clinic, where acute care is readily available on site. The patients were monitored for a minimum of 1 hour. This challenge procedure rules out an IgE-mediated hypersensitivity. Although delayed reactions can occur, if there is no history of a severe delayed rash then these delayed reactions are often relatively benign.[16] For patients with penicillin allergy and a negative skin test result to penicillin G and benzylpenicilloyl polylysine, a subsequent amoxicillin challenge was performed. For other IV agents, depending on clinical history, IV antibiotic challenge procedures were performed by administering at 30-minute intervals 1/100th of a full dose, followed by 1/10th, followed by the full dose. The IV challenges were conducted in a hospital-based infusion center with vital sign evaluation every 30 minutes. A negative challenge result was determined if the patient had no signs or symptoms of type 1 HSR within 1 hour of full-dose antibiotic administration. Patients were instructed to contact the allergy team if they developed any type of delayed symptoms, such as a rash. Inhaled challenges were conducted in clinic with full dose of the medication, and the patients were monitored for 1 hour after challenge with pre/post spirometry. The goal of the evaluation was to classify drug allergies into the 3 categories: (1) available to use moving forward, (2) strictly avoid moving forward, and (3) can use if desensitized.

Results

Between January 2009 and December 2015, a total of 17 (12 women and 5 men) patients with CF were evaluated in the allergy clinic. Their mean age at evaluation was 34.3 years (range, 22–57 years), with a mean (SD) FEV_1 and FVC of 50% (13.3%) (range, 21%–78%) and 62% (17.3%) (range, 35%–76%), respectively. The mean number of listed antibiotic ADRs per patient was 3.3. The most common reported ADR was β-lactam antibiotics, with 86% of patients reporting a reaction to at least 1 type of β-lactam. The top 2 patient-reported symptoms were rash (both urticarial and nonurticaria) (16.4%) and gastrointestinal symptoms (16.4%), including nausea, vomiting, and diarrhea. Other reactions included myalgia or arthralgia (10.9%), wheezing (9.1%), swelling (9.1%), urticaria (7.3%), flushing (5.5%), and mood changes (5.5%). Less common symptoms include dizziness, chest tightness, palpitations, tendonitis, and skin ulcer. The most common sputum bacteria identified were *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

A total of 11 patients underwent antibiotic skin testing. Of the patients not tested, 4 were advised to have skin testing and/or challenges but were lost to follow-up. Two patients had a reaction in the distant past consisting of a mild delayed maculopapular rash that was clearly not a type 1 HSR and skin testing was deferred. Both patients subsequently tolerated an oral challenge procedure. Of the 11 patients who underwent SPT or IDT, a total of 20 tests