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Original Article

Association between the introduction of a new cystic fibrosis inhaled antibiotic class and change in prevalence of patients receiving multiple inhaled antibiotic classes

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Abstract

Background: In 2010, aztreonam for inhalation solution joined aminoglycosides and colistimethate as a new cystic fibrosis (CF) chronic inhaled antimicrobial therapy. We studied how the introduction of this new inhaled antibiotic class changed the management of US CF patients.
Methods: The use of inhaled aminoglycosides, colistimethate, and aztreonam among patients followed in the CF Foundation Patient Registry was analyzed by age group, lung disease stage, and microbiologic status both annually, and at individual visits between 2009 and 2012.
Results: The overall prevalence of inhaled antibiotic use did not change during the period, but the prevalence of annual and any visit treatment with >1 inhaled antibiotic class more than doubled. Adults, those with advanced lung disease, and those with >1 *Pseudomonas aeruginosa* respiratory culture were more likely to receive >1 antibiotic class.
Conclusions: Inhaled antibiotic management of US CF patients has dramatically changed in association with the introduction of a third inhaled antibiotic class.

Keywords: Cystic fibrosis; Inhaled antibiotics; *Pseudomonas aeruginosa*; Patient registry; Observational research

1. Introduction

Chronic inhaled antipseudomonal antibiotic administration has become the standard of care for the management of cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* airway infections, with the objective of preserving lung function and reducing the risk of pulmonary exacerbations [1,2]. Prior to 2010, inhaled antibiotic management opportunities were essentially limited to two antipseudomonal antibiotic classes: polymyxins (colistimethate) and aminoglycosides (tobramycin, gentamicin, and amikacin), although extemporaneous nebulization of other antibiotics undoubtedly occurred on occasion. In 2010, aztreonam for inhalation solution, a member of the beta-lactam antibiotic class, was approved by the US Food and Drug Administration (FDA) for management of CF patients with *P. aeruginosa*, creating commercial access to a preformulated and tested third inhaled antibiotic class for chronic maintenance of lung health. The most recent CF Foundation (CFF) pulmonary guidelines for chronic medications for maintenance of lung health recommended both inhaled tobramycin and aztreonam for patients with persistent airway *P. aeruginosa*, but did not make a specific statement regarding the incorporation of both medications into management [2].

The CFF Patient Registry (CFFPR), which tracks persons with CF treated at care centers in the US, has annually reported

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the prevalence of use of different inhaled antibiotics among patients aged ≥6 years who have had *P. aeruginosa* detected in their respiratory secretions. Between 2009 and 2012, prevalence of inhaled aztreonam use increased 35% among these patients, from approximately 4% to 39%, while the prevalence of inhaled tobramycin fell only 2%, from 71% to 69%, in the same group [3,4]. These data suggest that introduction of inhaled aztreonam changed the nature of inhaled antibiotic use among CFFPR patients between 2009 and 2012. However, the difference between treatment-naïve patients initiating inhaled anti-pseudomonal antibiotic therapy as opposed to patients already on therapy who receive a second inhaled anti-pseudomonal antibiotic class is difficult to ascertain with these data. A pilot analysis limited to data from our Adult CF program at University Hospitals Case Medical Center in Cleveland has suggested that the proportion of patients receiving rotating inhaled antibiotic classes (e.g., alternating beta-lactam/aminoglycoside) throughout the calendar year doubled between 2009 and 2012 [5]. Therefore, we used the CFFPR to test the hypothesis that the prevalence of patients reported to be receiving more than one inhaled anti-pseudomonal antibiotic class significantly increased nationwide from 2009 to 2012.

2. Methods

This was a descriptive cohort study of individuals followed in the CFFPR at any time between January 1, 2009 and December 31, 2012. The CFFPR employs a standardized data collection form to capture demographic and clinical data, including the use of three classes of inhaled antibiotics: 1) aminoglycosides (tobramycin and other aminoglycosides), 2) polymyxins (colistimethate), and 3) beta-lactams (aztreonam) as chronic pulmonary medications (i.e., not prescribed to treat a pulmonary exacerbation) [4]. Patients were included in the current analysis if they were followed in the CFFPR in any year from 2009 through 2012, had a diagnosis of CF, and were recorded to have received any inhaled antibiotics as chronic pulmonary medications at any visit during the period, irrespective of their age or their microbiologic history. Patients were excluded from analyses beginning in the year of solid organ transplantation. Treatment prevalences were determined among all patients in the CFFPR receiving any chronic inhaled antibiotics, as well as by a priori subgroups of age (<6, 6–12, 13–18, and >18 years of age), lung disease stage categorized by mean forced expiratory volume in 1 s (FEV_1) (<40% predicted, 40%–<70% predicted, 70%–<100% predicted, and ≥100% predicted) for patients with FEV_1 data available, and by microbiologic culture results available during the calendar year. The de-identified dataset included the year of birth for each patient, therefore age was an integer that was calculated by subtracting the year of birth from the cohort year. Mean annual FEV_1% predicted was calculated using the reference equations of Wang [6] for children and Hankinson [7] for males >17 years of age and females >15 years of age.

Two outcomes were studied: 1) the change in the annual prevalence of patients receiving more than one inhaled antibiotic class from 2009 to 2012. This outcome captures individual patient exposure to different inhaled antibiotic classes in a given year. 2) The change in annual prevalence of patients reported to be receiving multiple classes of inhaled antibiotics at *any single visit* between 2009 and 2012. This outcome is an attempt to capture individuals in which different antibiotic classes were given in 'combination', either continuously or by rotation/alternation in a systematic fashion at some point during the year. The second outcome listed above was used to power the study.

Means, standard deviations, and medians were calculated for continuous variables and proportions were calculated for categorical variables. Comparisons between the prevalence of patients receiving treatment with multiple inhaled antibiotics either annually or at a single visit within a year in 2009 and 2012 were conducted using the chi-squared test. A p-value < .05 was considered statistically significant for all analyses. No corrections were made for multiple comparisons. Area-proportional 3-Venn diagrams using ellipses were generated using an online applet at http://www.eulerdiagrams.org/eulerAPE [8]. Because of our large sample size, we anticipated >90% power to detect a 10% absolute increase in the prevalence of multiple inhaled antibiotic class use between 2009 and 2012. Analyses were performed using STATA version 10.0. Patients in the CFFPR (or guardians for minors) gave informed consent permitting their de-identified records to be used for research purposes. The study was reviewed and approved by the institutional review board at the University Hospitals Case Medical Center and Rainbow Babies and Children's Hospital and the Cystic Fibrosis Foundation Patient Registry Committee.

3. Results

Between 2009 and 2012, the number of individuals in the CFFPR who met our inclusion and exclusion criteria increased from 25,080 to 26,487. The prevalence of inhaled antibiotic treatment among all pre-transplant CFFPR patients as well as among subgroups of age, FEV_1% predicted (for those with FEV_1 measures), and *P. aeruginosa* culture status are provided in Table 1. Between 2009 and 2012, the percentage of patients in the CFFPR recorded as receiving any inhaled antibiotics (irrespective of their age or microbiologic status) had a non-significant increase from 51.4% to 52.3% (p = .0577). In contrast, between 2009 and 2012, patients in the CFFPR receiving >1 inhaled antibiotic class annually increased from 7.3% to 17.3% (Table 1) and the prevalence of patients receiving >1 class of inhaled antibiotics at any visit increased from 6.5% to 15.7% (Table 1). Area-proportional Venn diagrams, where the overlap of ellipses identifies patients who received more than one inhaled antibiotic class during the year, allow discrimination of inhaled antibiotic class combinations occurring in 2009 and 2012 (Fig. 1). A sensitivity analysis in which inhaled tobramycin was the only aminoglycoside included did not materially change these results.