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Aerosolized Antibiotics for Patients with Bronchiectasis

To the Editor:

Bronchiectasis is the anatomic distortion of conducting airways that results in chronic infection with cough, sputum production, and recurrent exacerbations of infection (1). The causes of bronchiectasis are many, but patients are commonly classified into those with cystic fibrosis (CF) and those with another diagnosis (i.e., non-CF bronchiectasis [NCFB]) (2). There are several medications approved for use in the treatment of CF bronchiectasis, and it is intuitive that we could translate those therapies to our patients with NCFB (2); however, studies have not demonstrated the same clinical benefit. For example, inhaled antibiotics are the standard of care to suppress chronic *Pseudomonas* infections of the CF airways (3, 4), but clinical trials of aerosolized antibiotics in NCFB have not demonstrated clinical benefit (5–7). Nonetheless, our clinical experience has been that select patients with NCFB have responded well to aerosolized antibiotics.

We reviewed clinical data derived from patients with NCFB seen between 2006 and 2014 to characterize the clinical phenotype of patients successfully treated with aerosolized antibiotics and to define the clinical outcomes that demonstrate benefit. Some of the results of these studies have been previously reported in the form of an abstract (8). This retrospective case series was approved by the Medical University of South Carolina institutional review board. Our inclusion criteria included all patients older than 18 years who had a prior diagnosis of bronchiectasis (excluding CF documented by a normal sweat chloride ± genotyping) confirmed by computed tomography of the chest. We routinely attempt to diagnose the etiology of bronchiectasis. We compared those patients treated with chronic aerosolized antibiotic therapy (study cohort) with those not treated (control cohort). The study cohort was matched with the control cohort by age and sex in a 1:2 fashion. Clinical, radiological, and treatment history was obtained from the electronic health records. If the cause of bronchiectasis was not reported in the reviewed medical record, then it was assumed to be idiopathic in nature. An exacerbation was defined as worsening of respiratory symptoms treated with oral or intravenous antibiotics. The analysis of the data was done using SPSS, version 22 (IBM Corp, Armonk, NY). Comparison between the study and control cohorts were performed using independent *t* test or Pearson's chi-square test. A *P* value less than 0.05 was considered statistically significant.

Data were collated from 91 patients, of whom 31 (34%) were treated with inhaled antibiotics (Table 1), using dosage regimens similar to those prescribed for patients with CF. Six of the 31 patients discontinued therapy because of adverse effects (n = 3), inability to afford therapy (n = 2), or perceived lack of benefit (n = 1). Baseline characteristics (Table 1) were generally well balanced between the two groups. Most patients had *Pseudomonas* present in sputum cultures (more in the study cohort); other pathogens were present (e.g., *Haemophilus*, *Staphylococcus*), but in less than l0% of patients.

Key differences between the groups included (Table 1) a greater number of exacerbations in the year before inhaled antibiotics in the study cohort ($P < 0.0001$), a significantly lower lung function in the study cohort ($P = 0.001$), and a greater presence of nodules ($P = 0.027$) and cysts ($P = 0.05$) on chest computed tomography in the study cohort. Last, the bronchiectasis severity index, a predictive tool that identifies patients at risk of future mortality, hospitalization, and exacerbations (9), was significantly higher (i.e., worse) in the study cohort compared with the control cohort ($P < 0.0001$). In the year after initiation of inhaled antibiotics, there was significant reduction in the number of exacerbations in the study group ($P = 0.003$; Figure 1).

Discussion

We suggest that for patients with NCFB, an important risk factor predicting benefit from inhaled antibiotics is a history of frequent pulmonary exacerbations, and a key clinical endpoint is a reduction in the occurrence of pulmonary exacerbations. We acknowledge that we attribute the reduction in exacerbation frequency in our patients to the addition of the inhaled antibiotics, but there could be other hypotheses that should be tested. Nonetheless, our results are in contrast to clinical trials of aerosolized antibiotics for patients with NCFB, in which no clinical benefit has been demonstrated, including exacerbations (5, 6), yet are consistent with a small study of inhaled gentamicin compared with saline in patients who had more than two prior exacerbations in which there was a significant reduction in pulmonary exacerbations as a secondary endpoint (10).

So why did we not see a clinical benefit in these studies of aerosolized antibiotics for NCFB? It is likely that the subjects recruited into the trials would not all be expected to benefit

Table 1. Key Clinical Factors of Patients in This Study Compared with Those from a Study of Inhaled Antibiotics

Variable	Treated* (*n* = 31)	Untreated (*n* = 60)	Total (*n* = 91)	*P* Value	AZLI 1 (*n* = 134)	AZLI 2 (*n* = 136)
Mean age (SD)	62.6 (16.1)	64.9 (12.7)	64.1 (13.9)	NS	64.2 (12.9)	63.3 (14.2)
Female sex, n (%)	24 (77)	41 (68)	65 (72)	NS	84 (63)	89 (65)
Mean body mass index (SD)	23.1 (4.80)	26.5 (5.31)	25.36 (5.36)	0.004	25.0 (5.1)	23.9 (5.0)
Smoking history, n (%)	15 (48)	27 (45)	42 (46)	NS	63 (47)	44 (32)
Cause of bronchiectasis, n (%)						
ABPA	1 (3)	3 (5)	4 (4)	NS	4 (3)	0 (0)
Aspiration	10 (33)	9 (15)	19 (21)	NS	5 (4)	5 (4)
Ciliary dysfunction	3 (10)	3 (5)	4 (4)	NS	6 (4)	7 (5)
Idiopathic	13 (42)	4 (7)	7 (8)	NS	41 (31)	43 (32)
Immune defect	1 (3)	22 (37)	35 (38)	NS	2 (1)	5 (4)
Post infection	1 (3)	4 (7)	5 (5.5)	NS	47 (35)	47 (35)
Immune defect	1 (3)	8 (13)	9 (10)	NS	1 (<1)	2 (1)
Others	3 (10)	8 (13)	11 (12)	NS	27 (20)	27 (20)
Number of exacerbations in the previous year, n (%)						
0	1 (3)	21 (35)	22 (24)	<0.0001	53 (40)	54 (40)
1	5 (15)	18 (30)	23 (25)	<0.0001	26 (19)	32 (24)
2	9 (20)	14 (23)	23 (25)	<0.0001	27 (20)	20 (15)
⩾3	16 (52)	7 (12)	23 (25)	<0.0001	28 (21)	30 (22)
Mean FVC % predicted (SD)	68 (21.04)	85 (17.15)	79 (20.1)	0.001	Data not available	Data not available
Mean FEV_1 % predicted (SD)	54 (23.76)	74 (20.54)	67 (23.4)	0.001	60.4 (22.6)	63.8 (21.6)
FEV_1 % predicted, n (%)	n = 28	n = 54	n = 82			
⩽50	13 (46)	6 (11)	19 (23)	0.004	52 (39)	37 (27)
>50 to <80	9 (32)	27 (50)	36 (44)	0.004	49 (37)	72 (53)
⩾80	6 (22)	21 (39)	27 (33)	0.004	33 (25)	27 (20)
Radiological features, n (%)						
Cysts	7 (22.5)	5 (9)	12 (13)	0.05	Data not available	Data not available
Cavities	4 (13)	4 (7)	8 (9)	NS	Data not available	Data not available
Nodules	20 (64.5)	24 (41)	44 (48)	0.027	Data not available	Data not available
Pseudomonas infection	27 (87)	28 (54)	45 (54)	<0.0001	217 (82)	219 (80)
History of MAC	16 (52)	25 (48)	41 (49)	NS	30 (11)	20 (7)
History of chronic obstructive pulmonary disease	5 (16)	9 (15)	14 (15)	NS	67 (25)	77 (28)
Chronic macrolide use	20 (65)	26 (43)	46 (50.5)	0.055	57 (21)	76 (28)
Hypertonic saline	24 (74)	31 (52)	55 (60)	0.017	35 (13.2)	22 (8)
Inhaled antibiotics, n						
Tobramycin	23	0				
Aztreonam	3	0				
Amikacin	5	0				
Mean bronchiectasis severity index (SD)	14.5 (3.6)	7.8 (3.9)	10.3 (3.4)	<0.0001	Data not available	Data not available

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; AZLI = aztreonam inhalation solution; MAC = *Mycobacterium avium* complex; NS = not significant.
*Values indicated are prior to inhaled antibiotic treatment.

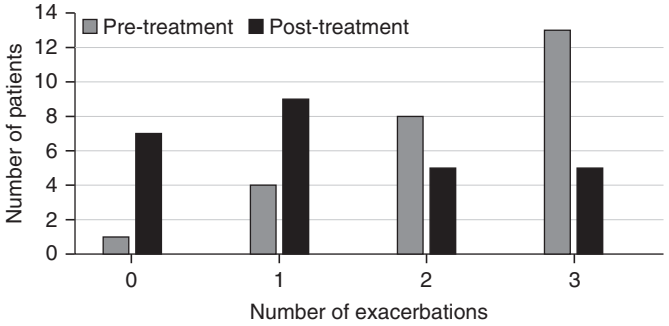

Figure 1. Number of exacerbations before and after initiation of inhaled antibiotics.

from the intervention. When we look at key clinical features of the NCFB participants in an aerosolized antibiotic study (6) (Table 1), we find important differences between our cohorts (treated vs. untreated) and those in the clinical trial. Inclusion criteria for the clinical trial were the presence of bronchiectasis and *Pseudomonas* in sputum cultures, and dosing of antibiotics was similar to that used for patients with CF. Our practice is to consider inhaled antibiotics only after patients have suffered repeated exacerbations despite appropriate use of chronic macrolides, aerosolized hypertonic saline, and airway clearance therapies (11). Although the patients in the clinical trials are similar to our overall population in terms of number of exacerbations, there are striking differences from the treated group; notably, 40% of the patients in the clinical trials had no exacerbations in the previous year compared with only 3% of our study cohort. The patients in the

clinical trials had a higher incidence of chronic obstructive pulmonary disease compared with our study cohort; there was a high rate of chronic obstructive pulmonary disease medications, but low rates of chronic macrolides and hypertonic saline, which are frequently used for the treatment of NCFB (11, 12) and are much lower than used in our study cohort. Hence we suspect that the negative outcome of this particular trial may have been a result of the incorrect inclusion of subjects. Our results could be used to better define and predict patients most likely to benefit from inhaled antibiotics in a clinical trial. ■

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Can Warfarin Be Used in the Treatment of Pulmonary Embolism in Idiopathic Pulmonary Fibrosis?

To the Editor:

There is evidence suggesting that the microenvironment of the fibrotic lung is procoagulant and antifibrinolytic (1). These observations led to the design of a randomized controlled trial in which 145 patients with idiopathic pulmonary fibrosis (IPF) were randomized to receive either oral warfarin, a vitamin K antagonist frequently used as an anticoagulant for venous thromboembolism (VTE), with target international normalized ratio (INR) of 2.0 to 3.0, or placebo (2). The duration of the study was 52 weeks, but it was interrupted after only 28 weeks because an interim analysis showed that a lack of therapeutic benefit in the treatment arm was coupled with a significant increase in mortality. The investigators speculated that the coagulation cascade may exert a protective role during fibrogenesis, and its inhibition may result in fatal outcomes (2).

In the recent revised statement for the treatment of IPF, Raghu and colleagues recommended that clinicians should not use warfarin as anticoagulation in patients with IPF who do not have a known alternative indication for its use (3). It is now well recognized that the diagnosis of IPF is associated with current or past events of thromboembolism (4). Our concern was raised by the recommendation of Raghu and colleagues that patients who have an alternate and/or known indication for anticoagulation, such as venous thromboembolic disease or atrial fibrillation, should follow treatment guidelines for these conditions independent of their underlying IPF (3). According to the guidelines for diagnosis and treatment of acute pulmonary embolism (PE), the immediate use of parenteral heparin should overlap with the initiation of a vitamin K antagonist (i.e., warfarin), or, alternatively, it can be followed by administration of one of the new oral anticoagulants (5). Whenever warfarin was chosen for the treatment of acute PE, the daily dose was adjusted, aiming for an INR level of 2.0 to 3.0, and the duration of the treatment varied depending on the underlying cause and recurrence of the event. Plainly, there are alternatives for the use of warfarin. However, as the recommendation was stated in the IPF document, it leaves the initiative to the treating physician to choose the treatment combination.

In our opinion, it would not be reasonable to allow the administration of warfarin in cases of acute PE in IPF aiming for an INR level of 2.0 to 3.0 because the same drug used with the same INR target has been proved detrimental in IPF. In the document it should have been stressed that it would be preferable if the use of warfarin could be avoided and other alternative agents could be considered. Plainly, a randomized controlled trial for the use of warfarin in patients with IPF with acute PE would be necessary to draw firm conclusions but will never be performed on ethical grounds given the results of the recent study (2).

A growing body of evidence suggests that IPF has many clinical and biological similarities to cancer. A randomized trial of patients with deep vein thrombosis and cancer has shown that the low-molecular-weight heparin (LMWH) dalteparin, given at the dose of 200 U/kg once daily for 4 to 6 weeks, followed by 75% of the initial dose given once daily for up to 6 months, was more effective than warfarin in preventing recurrent VTE, supporting the use of LMWH in this scenario (6). At least 3 to