CHEST

Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis

Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry

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BACKGROUND: Non-cystic fibrosis bronchiectasis ("bronchiectasis") is a chronic inflammatory lung disease often associated with nontuberculous mycobacteria (NTM) infection. Very little data exist to guide bronchiectasis management decisions. We sought to describe patterns of inhaled corticosteroid (ICS) and antibiotic therapy in the United States.

METHODS: We invited 2,000 patients through NTM Info & Research (NTMir) to complete an anonymous electronic survey. We separately queried baseline clinical and laboratory data from the US Bronchiectasis and NTM Research Registry (BRR).

RESULTS: Among 511 NTMir survey responders with bronchiectasis, whose median age was 67 years, 85 (17%) reported asthma and 99 (19%) reported COPD. History of ICS use was reported by 282 (55%), 171 (61%) of whom were treated 1 year or longer, and 150 (53%) were currently taking ICSs. Fewer reported ever taking azithromycin for non-NTM bronchiectasis (203 responders [40%]) or inhaled tobramycin (78 responders [15%]). The median age of 1,912 BRR patients was 69 years; 528 (28%) had asthma and 360 (19%) had COPD. Among 740 patients (42%) without NTM, 314 were taking ICSs at baseline. Among patients without NTM who were taking ICSs, only 178 (57%) had a concurrent diagnosis of COPD or asthma that could explain ICS use. Fewer were taking suppressive macrolides (96 patients [13%]), and of the 70 patients (10%) taking inhaled suppressive antibiotics, 48 (68%) had chronic *Pseudomonas aeruginosa* infection.

CONCLUSIONS: ICS use was common in two national samples of patients with bronchiectasis, with relatively few patients taking suppressive antibiotic therapies. Further research is needed to clarify the safety and effectiveness of these therapies in patients with bronchiectasis.

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KEY WORDS: bronchiectasis; inhaled antibiotics; inhaled corticosteroids; macrolides

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ABBREVIATIONS: aOR = adjusted OR; BRR = Bronchiectasis and NTM Research Registry; ICS = inhaled corticosteroid; LABA = long-acting beta agonists; NTM = nontuberculous mycobacteria; NTMir = NTM Info & Research

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Non-cystic fibrosis bronchiectasis ("bronchiectasis") is a chronic slowly progressive inflammatory pulmonary disease that is characterized by airway inflammation and excess sputum production. The prevalence of this orphan disease increased 8.7% per year between 2000 and 2007, affecting 100,000 to 200,000 patients in the US Medicare population.[1] Associated infections (eg, nontuberculous mycobacteria [NTM], *Pseudomonas aeruginosa*, *Haemophilus influenzae*) worsen inflammation and damage to lungs.[2] The goals of treatment are to improve symptoms, reduce airway inflammation, limit further bronchiectasis progression, and prevent infections. There are no US guidelines for the selection of therapies. The British Thoracic Society published guidelines in 2010 highlighting a lack of evidence for safety and effectiveness of chronic pharmacotherapy.[3] Drugs with anti-inflammatory properties, for example, corticosteroids, have been studied in COPD and other lung diseases, but their safety and effectiveness in bronchiectasis remains unproven.[4] Macrolides (eg, erythromycin, azithromycin) have both antimicrobial and immunomodulatory properties.[5] Historically, inhaled antibiotics are prescribed primarily to control *P aeruginosa* in patients with frequent exacerbations.[3] What is unknown is how many patients with bronchiectasis are taking inhaled corticosteroids (ICSs), macrolide monotherapy, or inhaled antibiotics in the United States or elsewhere. To provide background for a proposed comparative effectiveness and safety study in US patients, we sought to describe the current and past use of ICSs, oral macrolides, and inhaled antibiotics in patients with bronchiectasis and explore patient characteristics associated with each therapy.

Methods

Our first data source was an anonymous electronic 20-question SurveyMonkey survey (e-Appendix 1) developed by several study authors. The survey link was e-mailed by NTM Info & Research (NTMir), a nonprofit NTM patient advocacy organization, to 2,000 patients in December 2013. Responses were collected through January 2014. Patients self-identified as having bronchiectasis. Patients reported whether they had ever taken or were currently taking inhaled tobramycin, oral azithromycin for NTM treatment, oral azithromycin for other infections or exacerbation prevention, oral steroids, or ICSs with or without long-acting beta agonists (LABA). We also asked patients to estimate the cumulative lifetime duration of treatment with azithromycin or ICSs as $<$ 4 weeks, 4 weeks to $<$ 1 year, or 1 year or longer. The survey was anonymous and was conducted as "preparatory to research."

The second data source was the national Bronchiectasis and NTM Research Registry (BRR), managed by the COPD Foundation.[6] The BRR is actively enrolling from 13 sites and includes detailed clinical and microbiological data for $>$ 2,000 patients with bronchiectasis or patients who meet the American Thoracic Society/Infectious Diseases Society of America 2007 case criteria for NTM disease.[7] For this analysis, any patient with a history of or current NTM isolation was classified as having NTM infection ("NTM"), regardless of whether or not they met American Thoracic Society/Infectious Diseases Society of America disease criteria. The BRR collects data from chart review, including patient demographics, current pharmacotherapy, COPD or asthma diagnosis, history of *P. aeruginosa* or *Staphylococcus aureus* isolation, exacerbation in prior 2 years, or hospitalized exacerbation in prior 2 years. BRR data captured current "suppressive" macrolide and inhaled antibiotic therapy, indicating use other than for acute exacerbations. Oral steroids were marked as "continuous" or "intermittent" and combined into a single variable to describe current use. The BRR was approved by each site's institutional review board.

First, we described the characteristics of the survey and registry populations. For both data sets, we reported the proportion of patients taking each class of therapy, stratified by NTM in BRR patients. Next, in patients without NTM in the BRR, we separately compared "current users" of (1) inhaled corticosteroids, (2) macrolides, and (3) inhaled antibiotics to "nonusers" of each group. We performed statistical comparisons using the χ^2 test for categorical variables and the Student *t* test for continuous variables. Finally, in BRR patients without NTM, we conducted separate multivariate logistic regression analysis to evaluate factors associated with current use of each class of drug (compared with nonuse of each). Multivariate models included patient

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characteristics, with $P < .20$ in unadjusted logistic regression analysis. Several variables were categorized for logistic regression models: age (≥ 65 years or < 65 years), exacerbation history (none, nonhospitalized only, or any hospitalized exacerbation in prior 2 years), and FEV_1 % predicted (≥ 80%, 50 to < 80%, and < 50%). All statistical analysis was conducted in SAS, version 9.4 (SAS Institute).

Results

NTMir Survey Responders

The response from the NTMir e-mail included 511 self-identified patients with bronchiectasis (response rate, 26%) (Table 1). There was no information available on nonresponders. The median age of respondents was 67 years; most (420 [93%]) were women. Most (392 [77%]) reported a current diagnosis of NTM infection, and 99 (19%) reported COPD or current *P aeruginosa* infection or colonization.

NTMir Survey Self-Reported Therapy

Overall, 282 patients (55%) reported ICS use in the past or present, including 239 cases (85%) in combination with LABA. Among those who reported the use of ICSs, 171 (61%) reported a cumulative duration of > 1 year total, and 150 (53%) reported current use of ICSs. High rates of current or past antibiotic use were reported, including 203 (40%) taking azithromycin but not for NTM, and 78 (15%) taking inhaled tobramycin. Concurrent ICS and

TABLE 1] Characteristics of NTMir Survey Subjects (n = 511) and Bronchiectasis and NTM Research Registry Patients (n = 1,247 NTM, 776 Without NTM)

Patient Characteristics[a]	NTMir Survey n = 511	Bronchiectasis Research Registry		
		NTM n = 1,247	No NTM n = 776	*P* Value NTM vs no NTM
Age, median, y	67	68	64	< .001
Female sex, No. (%)	420 (93)	1,037 (83)	567 (73)	< .001
Current health, No. (%)				
Very good/good	289 (58)	…	…	
Fair	170 (35)	…	…	
Poor/very poor	34 (7)	…	…	
Genetic condition[b], No. (%)	27 (5)	…	…	
COPD, No. (%)	99 (19)	237 (19)	141 (18)	.64
Asthma, No. (%)	85 (17)	322 (26)	255 (33)	.0007
Current NTM, No. (%)	392 (77)	…	…	
NTM year of diagnosis, median, IQR	2006 (2003-2009)	…	…	
Current *Pseudomonas aeruginosa* infection or colonization, No. (%)	99 (19)	…	…	
P aeruginosa isolation, No. (%)		275 (22)	225 (29)	.0004
Staphylococcus aureus isolation, No. (%)		96 (8)	93 (12)	.001
Current fungal infection (*Aspergillus* or other), No. (%)	45 (9)	…	…	
Gram-negative current infection or colonization, No. (%)	23 (5)	…	…	
Exacerbation in prior 2 y, No. (%)	…	733 (60)	526 (68)	.0002
Hospitalized exacerbation in prior 2 y, No. (%)	…	234 (19)	198 (26)	.0007

BRR = Bronchiectasis and NTM Research Registry; NTM = nontuberculous mycobacteria; NTMir = NTM Info & Research.
[a]Patient characteristics are self-reported in the NTMir survey and abstracted from medical records in the BRR.
[b]Genetic condition: cystic fibrosis, primary ciliary dyskinesia, alpha-1 antitrypsin, other.

macrolide use in the 119 patients without current NTM disease was uncommon (n =3 [3%]).

BRR Patient Characteristics

We included 2,023 BRR patients with bronchiectasis, 776 (38%) of whom had no history of NTM and 1,247 (62%) of whom had NTM. Compared with patients without NTM, those with NTM were older (median age, 68 years vs 64 years; $P < .001$) and more likely to be women (1,037 [83%] compared with 567 [73%]; $P < .001$) (Table 1). Only a COPD diagnosis was similar (18%-19% in each group).

BRR Patient Therapy

Among 1,247 patients with bronchiectasis with NTM, 445 (36%) were taking ICSs. Among 776 patients without NTM with ICS information available, 356 (42%) were taking ICSs; 336 (93%) were also taking a bronchodilator, 66 (17%) were also taking macrolides, and 93 (15%) were also taking inhaled antibiotics. Only 111 (14%) patients without NTM were taking macrolides, and 77 (10%) were taking inhaled antibiotics. Most (57%) did not have COPD or asthma. Individuals taking all three classes of drugs had worse pulmonary function test results (FEV_1, 58%-66% of predicted and FEV_1/FVC ratio, 0.67 compared with FEV_1, 73%-75% of predicted and FEV_1/FVC ratio, 0.70-0.71 if not taking a given drug). Overall, 167 (65%) of 255 patients without NTM with an asthma diagnosis and 77 (55%) of 141 patients with COPD were taking ICSs. Of the 225 patients with *P aeruginosa* isolation, 53 (23.6%) were taking inhaled antibiotics.

Factors Associated With Current ICS Therapy in BRR Patients Without NTM

In univariate analysis, the prevalence of asthma was more than twice as high in patients taking ICSs (46% vs 21% not taking ICSs; $P < .0001$) as was *P aeruginosa* isolation (40% vs 23%; $P < .0001$) (Table 2). The final multivariate model included age category, sex, COPD, asthma, *S aureus, P aeruginosa*, exacerbation history category, and FEV_1 % predicted category. In multivariate analysis (Table 3), asthma (adjusted OR [aOR], 3.1; 95% CI, 1.2-4.3) and *P aeruginosa* isolation (aOR, 1.8; 95% CI, 1.2-2.6) were significantly associated with ICS use.

Factors Associated With Current Macrolide Therapy in BRR Patients Without NTM

Patients taking macrolides were younger (median age, 62.9 years vs 68.8 years among those not taking macrolides; $P = .006$) and had more prior hospitalized exacerbations (36% vs 23%; $P = .006$) and *P aeruginosa* isolation (44% vs 28%; $P = .002$) (Table 2). The final multivariate model consisted of age category, *S aureus, P aeruginosa*, exacerbation history category, and FEV_1 % predicted category (Table 3). In multivariate analysis, *P aeruginosa* isolation (aOR, 2.2; 95% CI, 1.4-3.4) was significantly associated with an increased odds of taking oral macrolides therapy, whereas age > 65 years (a OR, 0.6; 95% CI, 0.4-0.9) was significantly associated with a decreased odds of taking macrolides.

Factors Associated With Current Inhaled Antibiotic Therapy in BRR Patients Without NTM

Patients taking inhaled antibiotics had the highest rates of *P aeruginosa* isolation (69% vs 25% in those not taking inhaled antibiotics; $P < .0001$) and prior exacerbations (87% vs 66%; $P = .0002$) and hospitalized exacerbations (39% vs 24%; $P = .005$) (Table 2). The final multivariate model included sex, asthma, *P aeruginosa*, exacerbation history, and lung function. In multivariate analysis (Table 3), *P aeruginosa* isolation (aOR, 5.9; 95% CI, 3.4-10.5) and prior hospitalization for exacerbation (aOR, 2.6; 95% CI, 1.1-5.9) remained significantly associated with inhaled antibiotic therapy.

Discussion

We observed high rates of ICS use in patients with bronchiectasis despite the lack of evidence to support its use. There was modest use of macrolides and inhaled antibiotics, which was better supported by clinical trial results in patients with bronchiectasis. The use of all three types of pharmacotherapy was associated with a history of *P aeruginosa* isolation.

ICSs, alone or with LABA, are recommended for long-term treatment of severe asthma and in patients with advanced COPD.[8,9] Although the disease mechanisms are different, the use of ICSs in patients with COPD and the inflammatory nature of bronchiectasis has likely led to the use of ICSs for bronchiectasis despite a lack of evidence supporting its use in patients with bronchiectasis. In the BRR, only 57% of patients taking ICSs had either a COPD or asthma diagnosis. Asthma remained significantly associated with ICS use in multivariate analysis, whereas COPD did not. For patients with COPD without bronchiectasis, the benefits of ICSs include fewer exacerbations and improved lung function, although there is an increased risk of serious pneumonia.[10] In a large Danish cohort study, the observed relative risk of serious pneumonia in patients with COPD was 1.69 (95% CI, 1.63-1.75) comparing current ICS users to

TABLE 2] Comparison of Characteristics of Bronchiectasis and NTM Research Registry Patients (N = 776) Without Nontuberculous Mycobacteria Infection Taking vs Not Taking Inhaled Corticosteroids, Oral Macrolides, or Inhaled Antibiotics

Characteristic	Inhaled Steroids n = 356	No Inhaled Steroids n = 420	*P* Value	Oral Macrolides n = 111	No Oral Macrolides n = 665	*P* Value	Inhaled Antibiotics n = 77	No Inhaled Antibiotics n = 699	*P* Value
Age, y	**62.5**	**65**	**.007**	**57**	**65**	**.002**	**59**	**64**	**.05**
Female sex	**247 (69)**	**320 (76)**	**.03**	82 (74)	485 (73)	.84	57 (74)	510 (73)	.84
COPD	**77 (22)**	**64 (15)**	**.02**	21 (19)	120 (18)	.83	15 (19)	126 (18)	.76
Asthma	**167 (47)**	**88 (21)**	**< .0001**	42 (38)	213 (32)	.23	**33 (43)**	**222 (32)**	**.05**
COPD or asthma	**203 (57)**	**132 (31)**	**< .0001**	53 (48)	284 (43)	.52	**42 (55)**	**293 (42)**	**.03**
Pseudomonas aeruginosa isolation	**133 (37)**	**92 (22)**	**< .0001**	**49 (44)**	**176 (26)**	**.0001**	**53 (69)**	**172 (25)**	**< .0001**
Staphylococcus aureus isolation	51 (14)	42 (10)	.06	17 (15)	76 (11)	.24	6 (8)	87 (12)	.23
Exacerbations past 2 y	**263 (74)**	**264 (63)**	**.001**	**87 (78)**	**440 (66)**	**.01**	**67 (87)**	**460 (66)**	**.0002**
Hospitalized exacerbations past 2 y	**112 (31)**	**86 (20)**	**.0005**	**42 (38)**	**156 (23)**	**.001**	**30 (39)**	**168 (24)**	**.005**
FEV_1 (% predicted)[a]	**66**	**75**	**.0003**	**62**	**73**	**.002**	**58**	**73**	**.0001**
FVC (% predicted)[a]	**77**	**85**	**.04**	**76**	**80**	**.02**	**73**	**81**	**.005**
FEV_1/FVC ratio[a]	**0.67**	**0.71**	**.0005**	**0.67**	**0.70**	**.03**	**0.67**	**0.70**	**.03**
Concomitant medications									
Macrolide "suppressive" antibiotics	**66 (19)**	**45 (11)**	**.002**	…	…		**28 (36)**	**83 (12)**	**< .0001**
Inhaled "suppressive" antibiotics	**55 (15)**	**22 (5)**	**< .0001**	**28 (25)**	**49 (7)**	**< .0001**	…	…	
Inhaled steroids	…	…	…	**66 (59)**	**290 (44)**	**.002**	**55 (71)**	**301 (43)**	**< .0001**
Inhaled bronchodilator	**332 (93)**	**202 (48)**	**< .0001**	**90 (81)**	**444 (67)**	**.003**	**72 (94)**	**462 (66)**	**< .0001**
Oral steroids	**83 (23)**	**59 (14)**	**.0009**	**32 (29)**	**110 (17)**	**.002**	**21 (27)**	**121 (17)**	**.03**

Values are No. (%) except for median. Boldface indicates $P < .05$ for comparison.
[a]Prebronchodilator use. Total n = 667 with FVC % predicted; 672 with FEV_1 % predicted and FEV/FVC ratio.

TABLE 3] Multivariate Analysis of Factors Associated With Current Use of Inhaled Corticosteroids, Oral Macrolides, or Inhaled Antibiotics in Bronchiectasis and NTM Research Registry Patients (N = 672 with FEV_1 Results) Without Nontuberculous Mycobacteria Infection

	Inhaled Corticosteroids		Oral Macrolides		Inhaled Antibiotics	
Characteristic	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Age ≥ 65 y	0.85 (0.63-1.15)		**0.61 (0.39-0.94)**	**0.58 (0.37-0.92)**	0.80 (0.48-1.32)	…
Female sex	0.78 (0.55-1.09)	0.85 (0.59-1.23)	1.12 (0.69-1.82)	…	1.23 (0.68-2.22)	…
COPD	1.47 (0.99-2.17)	1.05 (0.68-1.64)	1.06 (0.62-1.82)	…	1.05 (0.55-1.99)	…
Asthma	**3.18 (2.28-4.44)**	**3.07 (2.17-4.33)**	1.27 (0.81-1.97)	…	1.63 (0.98-2.71	1.43 (0.83-2.45)
Pseudomonas aeruginosa isolation	**2.05 (1.45-2.88)**	**1.8 (1.24-2.6)**	**2.44 (1.57-3.78)**	**2.17 (1.36-3.44)**	**7.15 (4.14-12.36)**	**5.94 (3.36-10.51)**
Staphylococcus aureus isolation	1.57 (1.00-2.47)	1.48 (0.92-2.39)	1.47 (0.82-2.62)	1.31 (0.72-2.38)	0.62 (0.26-1.47)	…
Exacerbations prior 2 y						
None (reference)	…	…	…	…	…	…
Nonhospitalized only	1.22 (0.85-1.75)	0.98 (0.67-1.44)	1.35 (0.77-2.34)	1.14 (0.65-2.02)	**2.48 (1.16-5.3)**	1.94 (0.88-4.28)
Any hospitalized	**1.83 (1.20-2.78)**	1.26 (0.8-1.98)	**2.27 (1.27-4.09)**	1.74 (0.94-3.23)	**3.9 (1.79-8.66)**	**2.58 (1.13-5.92)**
Lung function (FEV_1 % predicted[a])						
< 50% (reference)	…	…	…	…	…	…
50% to < 80%	0.72 (0.48-1.07)	0.89 (0.57-1.38)	0.88 (0.52-1.49)	1.2 (0.69-2.09)	**0.62 (0.35-1.11)**	0.92 (0.5-1.72)
≥ 80%	**0.48 (0.31-0.73)**	0.66 (0.41-1.07)	0.49 (0.27-0.89)	0.76 (0.4-1.44)	**0.29 (0.14-0.60)**	0.66 (0.3-1.45)

Boldface indicates $P < .05$. aOR = adjusted OR. $P < .05$.
[a]Prebronchodilator use.

nonusers.[11] Future studies of ICS use in patients with bronchiectasis should distinguish between patients with and those without reactive airway disease and should include comparison groups of LABA alone to determine whether ICS use is beneficial.

Approximately 15% of patients were using macrolides chronically; < 31% received "long-term macrolide treatment" in a report from a five-country European cohort of 1,145 patients with bronchiectasis.[12] Evidence supporting macrolide antibiotic use for 6 to 12 months was observed in three placebo-controlled randomized clinical trials of patients with bronchiectasis published in 2012 and 2013.[13-15] All three studies showed fewer respiratory exacerbations but limited or no improvement in lung function. Given the high rates of NTM found in BRR patients with bronchiectasis, monotherapy with macrolides to prevent exacerbations should be considered only after screening for NTM.[16] Macrolide-resistant NTM is associated with poorer outcomes.[17] Additional trials are needed to evaluate the potential benefit of macrolides regarding prevention of NTM infection as well as to quantify the risks of macrolide resistance developing in NTM. In addition, the rare but serious short-term risks of sudden cardiac arrest should be considered.[18]

Ten percent of BRR patients without NTM (22% of those with *P aeruginosa* isolation) were taking inhaled antibiotics. A similar proportion (8%) overall but a higher proportion (36%) among those with *Pseudomonas* infection in the previously mentioned European cohort had a history of "long-term inhaled antibiotic treatment."[12] There is moderate evidence to support the use of inhaled antibiotics to reduce sputum bacterial load and the risk of exacerbations.[19] Documented risks of inhaled antibiotics include bronchospasm, ototoxicity, and renal failure. According to BTS guidelines, inhaled antibiotics should be considered in patients with *P aeruginosa* colonization who experience 3+ exacerbations per year.[3] Appropriately, prior hospitalized exacerbations and *P aeruginosa* isolation were associated with the use of inhaled antibiotics in our study. Of note, a history of *P aeruginosa* isolation was the only factor independently associated with all three categories of therapy. *P aeruginosa* colonization is associated with worse outcomes in patients with bronchiectasis[12,20-22]; thus physicians may have prescribed ICSs or macrolides to minimize associated inflammation.

Strengths of our study include the use of two national data sources. We captured "suppressive" macrolide use from the BRR and the duration of ICS use in NTMir patients. Limitations include a low NTMir response rate, although NTMir members have a primary diagnosis or history of NTM infection and not all have underlying bronchiectasis. BRR patients are enrolled at specialty clinics and may not represent treatment practices in the community. In addition, we are missing details regarding dose, formulation, and duration of the most recent episode of use to further describe practice patterns in BRR patients. Other factors associated with ICS use, such as symptoms that may drive treatment choice, were not evaluated in this analysis but should be explored.

Conclusions

In conclusion, we observed the high rates of use of ICS despite unproven clinical efficacy and risks of use. Additional evidence is needed so that clinicians and patients can better weigh the risks and benefits and determine the optimal duration of pharmacotherapy for bronchiectasis.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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