Original Research

Association of Chronic Rhinosinusitis and *Pseudomonas Aeruginosa* in Sputum of Patients With Non-Cystic Fibrosis Bronchiectasis

Titas Grabauskas, BA[1] Amanda E. Brunton, MS, MPH[2] Mark L. Metersky, MD[1] Kevin Winthrop, MD[3] Nicole C. Lapinel, MD[4] George M. Solomon, MD[5] Kunal Jakharia, MD[6] Michelle Korah-Sedgwick, MD[7] Alexander Geyer, MD[8]

[1]School of Medicine, University of Connecticut, Farmington, Connecticut, United States

[2]Bronchiectasis and NTM Association, Miami, Florida, United States

[3]Oregon Health and Science University, Portland, Oregon, United States

[4]Pulmonary Critical Care, Northwell Health, New Hyde Park, New York, United States

[5]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, United States

[6]Pulmonary and Critical Care, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

[7]Pulmonary/Critical Care and Allergy/Immunology, Louisiana State University School of Medicine, New Orleans, Louisiana, United States

[8]Division of Pulmonary, Critical Care and Sleep Medicine, Lenox Hill Hospital at Northwell Health, New York, New York, United States

Address correspondence to:
Alexander Geyer, MD
Division of Pulmonary, Critical Care and Sleep Medicine
Lenox Hill Hospital at Northwell Health
New York, NY
Email: ageyer@northwell.edu

Running Head: **CRS and *Pseudomonas Aeruginosa* in Bronchiectasis**

Keywords: bronchiectasis; chronic rhinosinusitis; *Pseudomonas aeruginosa; Haemophilus influenzae*; *Staphylococcus aureus*

Abbreviations: BMI (body mass index); BRR (US Bronchiectasis and Nontuberculous Mycobacteria (NTM) Research Registry); CF(cystic fibrosis); COPD (chronic obstructive pulmonary disease); CRS (chronic rhinosinusitis); FEV1% (forced expiratory volume in the first second%); FVC% (percentage of forced vital capacity); H. influenzae (*Haemophilus influenzae*); NO(nitric oxide); P. aeruginosa (*Pseudomonas aeruginosa*); S. aureus (*Staphylococcus aureus*)

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Abstract

Background: *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus* may chronically infect bronchiectatic airways. Chronic rhinosinusitis (CRS) is common in people with bronchiectasis. Bacterial airway infection and CRS are associated with greater bronchiectasis disease severity. However, the relationship between these pathogens and CRS in people with bronchiectasis is unclear.

Research Question: Is history of CRS associated with sputum positivity for *P. aeruginosa*, *S. aureus*, and/or *H. influenzae* in people with bronchiectasis?

Study Design and Methods: People with bronchiectasis from the US Bronchiectasis and Nontuberculous Mycobacteria (NTM) Research Registry (BRR) with and without physician-reported CRS were compared with respect to demographic and clinical characteristics using cross-sectional study design. Multivariable logistic regression models were used to assess the relationship between CRS and the presence of *P. aeruginosa*, *S. aureus*, and *H. influenzae* in sputum.

Results: Of 1,352 people with bronchiectasis and known CRS status, 222 (16%) had a history of CRS. Those with CRS were more likely to have a sputum culture positive for *P. aeruginosa* (35% CRS vs. 26% non-CRS group; p=0.007), but not *S. aureus* (13% vs. 10%; p=0.21) or *H. influenzae* (6% vs. 7%; p=0.55). After adjusting for patient demographics and clinical characteristics, CRS was associated with *P. aeruginosa* (OR: 1.5; 95% CI: 1.07 to 2.08).

Interpretation: We report an association of history of CRS and sputum culture positivity for *P. aeruginosa* (but not *S. aureus* or *H. influenzae*) in people with bronchiectasis.

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Introduction

Non-cystic fibrosis bronchiectasis (henceforth referred to as bronchiectasis) is a chronic pulmonary condition characterized by permanent bronchial dilatation, mucus plugging and, often, chronic bacterial airway infection. Patients commonly have symptoms of cough, dyspnea, and fatigue.[1] Several factors are linked to bronchiectasis exacerbations and progression, including age, smoking, treatment adherence, comorbid conditions such as chronic rhinosinusitis (CRS)[2] and chronic lower airway infections—particularly those caused by *Pseudomonas aeruginosa*.[1–3]

CRS is defined as prolonged inflammation of the nasal and paranasal sinuses, causing nasal discharge, congestion, facial pain, and olfactory disturbances for at least 12 weeks and accompanied by endoscopic or radiographic evidence of mucosal inflammation.[4] It's reported prevalence among people with bronchiectasis ranges from 7.1%[5] to 62%[6] depending on a study population and the number of centers involved in data collection. In contrast, the estimated prevalence in the general population is between 3.0%[7] and 8.7%[8]. Importantly, CRS has been associated with increased bronchiectasis radiographic disease severity, reduced quality of life, and a shorter time to exacerbation.[6]

Bacterial infection of the lower airways is a key factor associated with the severity of bronchiectasis. For example, a positive pathogenic bacterial sputum culture in people with bronchiectasis was shown to be associated with lower percentage of forced vital capacity (FVC%), forced expiratory volume in the first second (FEV1) %, and longer symptom duration.[9] *P. aeruginosa* is the most commonly isolated pathogen in people with bronchiectasis, with estimates ranging from 21% to 33%.[9,10] *P. aeruginosa* has been associated with worsened bronchiectasis outcomes, including more frequent exacerbations and reduced FEV1 %

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predicted.[11] Other frequently cultured pathogens in people with bronchiectasis include *Haemophilus influenzae* and *Staphylococcus aureus*.[10] Importantly, *H. influenzae* has been associated with higher bronchiectasis severity index and exacerbation frequency.[12]

CRS is associated with bacterial infection of the paranasal sinuses,[13] with *S. aureus* being the most common pathogen in maxillary sinuses of people with CRS.[14] Concordance between upper and lower airway sputum cultures has been observed in people with bronchiectasis.[15] Given the high prevalence of CRS in individuals with bronchiectasis, CRS may act as a reservoir for pathogenic bacteria and thereby increase the risk of lower airway infections.[16,17] Therefore, we aimed to investigate the relationship between a history of CRS and lower airway infection with *P. aeruginosa*, *S. aureus*, and *H. influenzae* in patients enrolled in the U.S. Bronchiectasis and Nontuberculous Mycobacteria (NTM) Registry (BRR). We hypothesized that patients with bronchiectasis and a physician-reported history of CRS would have a higher prevalence of sputum culture positivity for one or more of these three pathogens.

Study Design and Methods

Data Source

The BRR is a centralized database of physician reported adult patients diagnosed with bronchiectasis and/or NTM from 29 sites across the US. Following patient consent, data is abstracted from electronic medical records from the baseline period, defined as the two-year look-back period up to and including the date of consent. Follow-up data is collected annually thereafter. Standardized data collection forms include demographics, medical history and clinical characteristics, respiratory symptoms, microbiology, treatment, and imaging. The data

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coordinating center and each participating site received institutional review board (IRB) approval.[10]

Study Population and Design

People with bronchiectasis and known CRS disease status at baseline were included. Patients with unknown demographics (age, sex, body mass index [BMI]), medical history (smoking history, asthma, chronic obstructive pulmonary disease (COPD), NTM, clinical characteristics (lung function, exacerbation and hospitalization history, imaging, treatment) and microbiology (bacterial and acid-fast bacilli [AFB] cultures) were excluded, as were patients with a diagnosis of cystic fibrosis (CF). This was a cross-sectional study, with all data evaluated from the baseline period only.

Study Variables and Outcomes

Patients were defined as either having or not having a CRS diagnosis, as reported in the BRR. CRS in the BRR is based on physician-reported diagnosis from each participating site. Specifically, the investigators were asked to select all co-existing conditions from the list of 37 possibilities, including rhinosinusitis, that a patient has ever been diagnosed with. Sputum positivity for the study outcomes, *P. aeruginosa*, *S. aureus*, and *H. influenzae*, were defined as at least one positive culture during the baseline period. Covariates included patient age, sex, and several factors known or stipulated to be associated with respiratory *P. aeruginosa* infection such as BMI[18], smoking history[19] (current or former vs. never), asthma, COPD[20], NTM[21], pre-bronchodilator FEV1% predicted[20], history of at least 1 exacerbation during the baseline period[22], history of at least 1 exacerbation- or pulmonary-related hospitalization during the

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baseline period[22], total number of lobes involved on the patient's computed tomography (CT) scan[23], chronic macrolide therapy[24], and inhaled corticosteroid use[25]. NTM diagnosis was defined as those with a physician reported diagnosis meeting the international consensus disease criteria[26,27] plus documentation of at least 1 positive AFB culture during the baseline period.

Statistical Analysis

Descriptive statistics were computed overall and by CRS diagnosis status for the demographics, comorbidities, clinical characteristics, and treatment history of the study population. Chi-square, independent two-sample t-test, and Wilcoxon tests were used to determine the relationship between categorical variables and the mean or median difference between continuous variables, respectively.

We used a multivariable logistic regression model to determine the odds of at least one positive *P. aeruginosa* culture during the baseline period among those with CRS . This process was repeated for *S. aureus* and *H. influenzae*. All models were adjusted for the previously mentioned covariates. All analyses used a significance level of 0.05 ($p<0.05$). No corrections were made for multiplicity. SAS version 9.4 (SAS Institute, Cary, NC, U.S.) was used for all analyses.

Results

Study population

One thousand three hundred and fifty two patients met the study eligibility criteria (Figure 1). Study participants' demographic, clinical and microbiologic characteristics are shown in Table 1.

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Sixteen percent (n=222) of our study population had physician-reported CRS. The CRS group was less likely to be female (73% CRS vs. 80% non-CRS group; p=0.03) and to have a history of nontuberculous mycobacteria (NTM; 34% CRS vs. 49% non-CRS group; p<0.001). Conversely, patients with CRS had higher BMI (23.0 kg/m^2 in CRS vs. 21.9 kg/m^2 non-CRS group; p<0.001), were more likely to have a history of asthma (46% CRS vs. 25% non-CRS group; p<0.001) and primary ciliary dyskinesia (PCD; 7% CRS vs 2% non-CRS group; p<0.001), use inhaled corticosteroids (46% in CRS vs. 37% in non-CRS group; p=0.01;), and be hospitalized for pulmonary-related conditions within two years prior to enrollment in the BRR (35% CRS vs. 23% non-CRS group, p<0.001) (Table 1). Screening our BRR cohort for positive bacterial sputum cultures demonstrated that *P. aeruginosa* as the most common pathogen (n=369; 27.3% of the total cohort), followed by *S. aureus* (n=139; 10.3% of the total cohort) and *H. influenzae* (n=98; 7.2% of the total cohort) (data not shown). Interestingly, the CRS group was more likely to have positive sputum culture for *P. aeruginosa* (35% CRS vs. 26% non-CRS group; p=0.007; Table 1), but not for *H. influenzae* (6% CRS vs. 7% non-CRS group; p=0.55) or *S. aureus* (13% CRS vs. 10% non-CRS group; p=0.21) (Table 1).

History of CRS was associated with positive sputum culture for P. aeruginosa in people with bronchiectasis

To further investigate the clinical factors associated with *P. aeruginosa* infection in people with bronchiectasis, we fit a multivariable logistic regression model using positive sputum culture as the dependent variable. This analysis revealed increased odds of *P. aeruginosa* with CRS (OR: 1.5; 95% CI: 1.07 to 2.08) after adjusting for patient characteristics, including age, BMI, sex, smoking history, asthma, COPD, NTM, FEV1% predicted, exacerbations, hospitalizations, total

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number of lobes involved, chronic macrolide treatment, and inhaled corticosteroid use (Figure 2). History of hospitalizations (OR: 1.4; 95% CI: 1.05 to 1.89), and total number of lobes involved (OR: 1.2; 95% CI: 1.09 to 1.24) were also independently and positively associated with positive sputum culture for *P. aeruginosa* (Figure 2). In contrast, higher FEV1% predicted (OR: 0.98; 95% CI:0.98 to 0.99), current or former smoking status (OR: 0.7; 95% CI:0.54 to 0.92), and history of NTM (OR: 0.5; 95% CI:0.41 to 0.71) were negatively associated with the odds of a positive sputum culture for *P. aeruginosa* (Figure 2).

History of CRS was not associated with positive sputum culture for S. aureus or H. influenzae

We fit similar multivariable logistic regression models, as described above, and found no significant association between CRS and positive sputum cultures for *S. aureus* (OR: 1.4; 95% CI: 0.88–2.24; Figure 3) or *H. influenzae* (OR: 0.7; 95% CI: 0.38–1.30; Figure 4) after adjusting for patient characteristics.

Discussion

Both CRS and bacterial airway infection are common in people with bronchiectasis, but whether CRS is associated with lower airway bacterial infection is not known.[6,28] To address this knowledge gap, we used the BRR data to evaluate the association between history of CRS and the 3 most common bacterial pathogens cultured from sputum of people with bronchiectasis. While *Staphylococci, H. influenza*, and *P. aeruginosa* are frequently cultured from the paranasal sinuses of patients with CRS,[13,14,29,30] the only significant association we found between CRS and positive sputum culture was with *P. aeruginosa*. This association persisted after adjusting for clinical and demographic characteristics.

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A significant concordance between upper and lower airway bacterial cultures in people with bronchiectasis has been previously reported.[15,31] In lung transplant recipients with CF, culturing *P. aeruginosa* from the sinuses before transplantation correlated highly with the growth of the same pathogen in post-transplant bronchoalveolar-lavage fluid.[32] Furthermore, in people with CF and occasional *P. aeruginosa* in sputum, functional endoscopic sinus surgery helped clear the infection from sputum in 31 out of 50 patients.[33] These observations suggest that one potential explanation for our observed association between *P. aeruginosa* and CRS in people with bronchiectasis is that chronic sino-nasal inflammation allows the sinuses to act as a reservoir of infection, from which *P. aeruginosa* can descend into the lower airways.

Another potential explanation for the association of CRS and lower respiratory tract infection with *P. aeruginosa* may involve nitric oxide (NO). The paranasal sinuses are a major source and reservoir of NO in the human respiratory tract.[34] In addition to its well described signaling and vasogenic properties, NO also plays a role in host defense.[35] For example, it has been implicated in *P. aeruginosa* biofilm dispersal.[36] In CRS, however, nasal NO levels are reduced.[37] Therefore, reduced nasal NO in CRS may promote biofilm formation and microbial persistence in the lower airways.[38]

While *S. aureus* and *H. influenzae* were the next most frequently cultured pathogens in the sputum of our BRR cohort, no significant association was observed between history of CRS and positive sputum culture for either pathogen. There are several possible explanations for this. Firstly, the association between CRS and lower airway infection may truly be specific to *P.*

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aeruginosa. This microorganism possesses unique biologic characteristics making it highly suitable for infecting low-oxygen compartments such as poorly ventilated sinuses or mucous-plugged airways.[41–45] Consistently, *P. aeruginosa* has been shown to establish chronic lower airway infections more often than *S. aureus* or *H. influenzae* in people with bronchiectasis[9]. Secondly, the number of subjects with *S. aureus* or *H. influenzae* infections was relatively small (i.e. 28 and 14 out of 222 patients with CRS, respectively), limiting our power to detect the difference between the CRS-positive and -negative patient samples.

In addition to CRS, our study also found that higher frequency of bronchiectasis-related hospitalizations, a greater total number of lobes involved, and lower FEV1% predicted were independently associated with positive sputum culture for *P. aeruginosa*. These findings are in line with prior studies suggesting that *P. aeruginosa* serves as a marker of more severe bronchiectasis[39,40] and highlight the importance of *P. aeruginosa*-focused clinical management in people with bronchiectasis.

Our study has several strengths, including the use of a large, well-characterized cohort of patients recruited from multiple clinical sites for enrollment in the U.S. Bronchiectasis and NTM Registry. Furthermore, clinical and laboratory characteristics were physician-reported, improving data reliability.

Some limitations deserve mention. Reported prevalence of CRS among individuals with bronchiectasis varies widely across studies. Interestingly, larger registry-based studies, such as the Korean Multicenter Bronchiectasis Audit and Research Collaboration[5], as well as multicenter

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studies conducted across four European centers[46], have reported relatively low CRS prevalence estimates (7.1% and 13.1%, respectively). In contrast, smaller single-center studies have reported substantially higher prevalence estimates, with a pooled point estimate of 62% reported in a meta-analysis[6]. These findings suggest that CRS may be underreported in large registry-based datasets or, alternatively, that smaller studies may be subject to selection bias that enriches for patients with CRS. Therefore, it is difficult to assess whether the 16% prevalence of CRS reported in our study population, based on physician-reported CRS history, is an accurate estimate. Despite this caveat, even if under-diagnosis or under-reporting were present, they were likely non-differential which would consequently bias our estimates toward the null. We do acknowledge, however, that if for some reason CRS was preferentially under-reported in *P. aeruginoasa*-colonized patients, a resulting differential misclassification bias could exaggerate the observed association between CRS and *P. aeruginosa*.

Another limitation is that incomplete data on history of CRS, sputum microbiology or clinical characteristics resulted in exclusion of a significant number of patients BRR participants, potentially introducing a selection bias. While we adjusted the model for several important variables, including individual markers of disease severity such as history of exacerbations, residual confounding cannot be excluded. The cross-sectional nature of this study did not permit the evaluation of temporal relationship between CRS and sputum cultures.

Interpretation

Our study demonstrates an association between history of chronic rhinosinusitis and positive sputum culture for *P. aeruginosa*, the most commonly isolated pathogen in people with

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bronchiectasis enrolled in the U.S. Bronchiectasis and NTM Research Registry. Further research is needed to determine the temporal relationship between CRS and bacterial colonization of the upper and lower airways, and whether treatment of CRS can reduce the burden of bacterial infection and clinical outcomes in people with bronchiectasis.

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Ethics statement:
The BRR is a centralized database of patients with bronchiectasis identified at 13 clinical sites throughout the United States. The institutional review board of each participating site approved the study, as did an administrative institutional review board for the data collecting center. For further information, please refer to Aksamit TR, O'Donnell AE, Barker A, et al. Adult Patients With Bronchiectasis. *Chest*. 2017;151(5):982-992. doi:10.1016/j.chest.2016.10.055)

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Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

Take-Home Points

Study Question: Is history of CRS associated with sputum positivity for *P. aeruginosa*, *S. aureus*, and/or *H. influenzae* in people with bronchiectasis

Results: In BRR, history of CRS was associated with positive sputum culture for *P. aeruginosa* (OR: 1.5; 95% CI: 1.07 to 2.08) but not with *S. aureus* (OR: 1.4; 95% CI: 0.88–2.24) or *H. influenzae* (OR: 0.7; 95% CI: 0.38–1.30) after adjusting for clinical and demographic confounders.

Interpretation: There is an association between CRS and lower airway infection with *P. aeruginosa* in people with bronchiectasis.

Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

Table 1: Demographics, clinical and microbiologic characteristics of the study participants from the US Bronchiectasis and NTM Research Registry.

Feature	Overall n=1352	No CRS diagnosis n=1130 (83.6%)	CRS diagnosis n=222 (16.4%)	p-value*
Demographics				
Age (years), median [IQR]	69.0 [61.0-76.0]	70.0 [62.0-76.0]	67.0 [57.0-75.0]	**0.002**
Female, n (%)	1061 (78.5)	899 (79.6)	162 (73.0)	0.029
BMI (kg/m2), median [IQR]	22.1 [19.8-25.5]	21.9 [19.6-25.0]	23.0 [20.2-27.3]	**<0.001**
Current or former smoker, n (%)	553 (40.9)	469 (41.5)	84 (37.8)	0.310
Co-existing conditions/diagnoses				
Asthma, n (%)	391 (28.9)	288 (25.5)	103 (46.4)	**<0.001**
COPD, n (%)	256 (18.9)	223 (19.7)	33 (14.9)	0.090
Rheumatologic disease, n (%)	113 (8.4)	100 (8.8)	13 (5.9)	0.141
IBD, n (%)	33 (2.4)	28 (2.5)	5 (2.3)	0.842
PCD, n (%)	33 (2.4)	17 (1.5)	16 (7.2)	**<0.001**
NTM†, n (%)	627 (46.4)	551 (48.8)	76 (34.2)	**<0.001**
Clinical characteristics				
Pre-bronchodilator FEV1 %predicted, mean (SD)	73.3 (22.9)	72.9 (22.9)	75.3 (22.8)	0.155
≥1 exacerbation in the 2 years prior to enrollment, n (%)	1108 (82.0)	920 (81.4)	188 (84.7)	0.247
≥1 hospitalization in the 2 years prior to enrollment‡, n (%)	335 (24.8)	258 (22.8)	77 (34.7)	**<0.001**
Dyspnea, n (%) *available n=1351*	837 (62.0)	691 (61.2)	146 (65.8)	0.201
Median number of lobes involved [IQR]	3 [2-6]	3 [2-6]	4 [2-5]	0.414
Chest deformity, n (%) *available n=1300*	50 (3.8)	41 (3.8)	9 (4.2)	0.777
Scoliosis, n (%) *available n=1335*	157 (11.8)	131 (11.7)	26 (11.9)	0.955
Pseudomonas aeruginosa isolation, n (%)	369 (27.3)	292 (25.8)	77 (34.7)	**0.007**
Haemophilus influenzae isolation, n (%)	98 (7.2)	84 (7.4)	14 (6.3)	0.554
Staphylococcus aureus isolation, n (%)	139 (10.3)	111 (9.8)	28 (12.6)	0.211

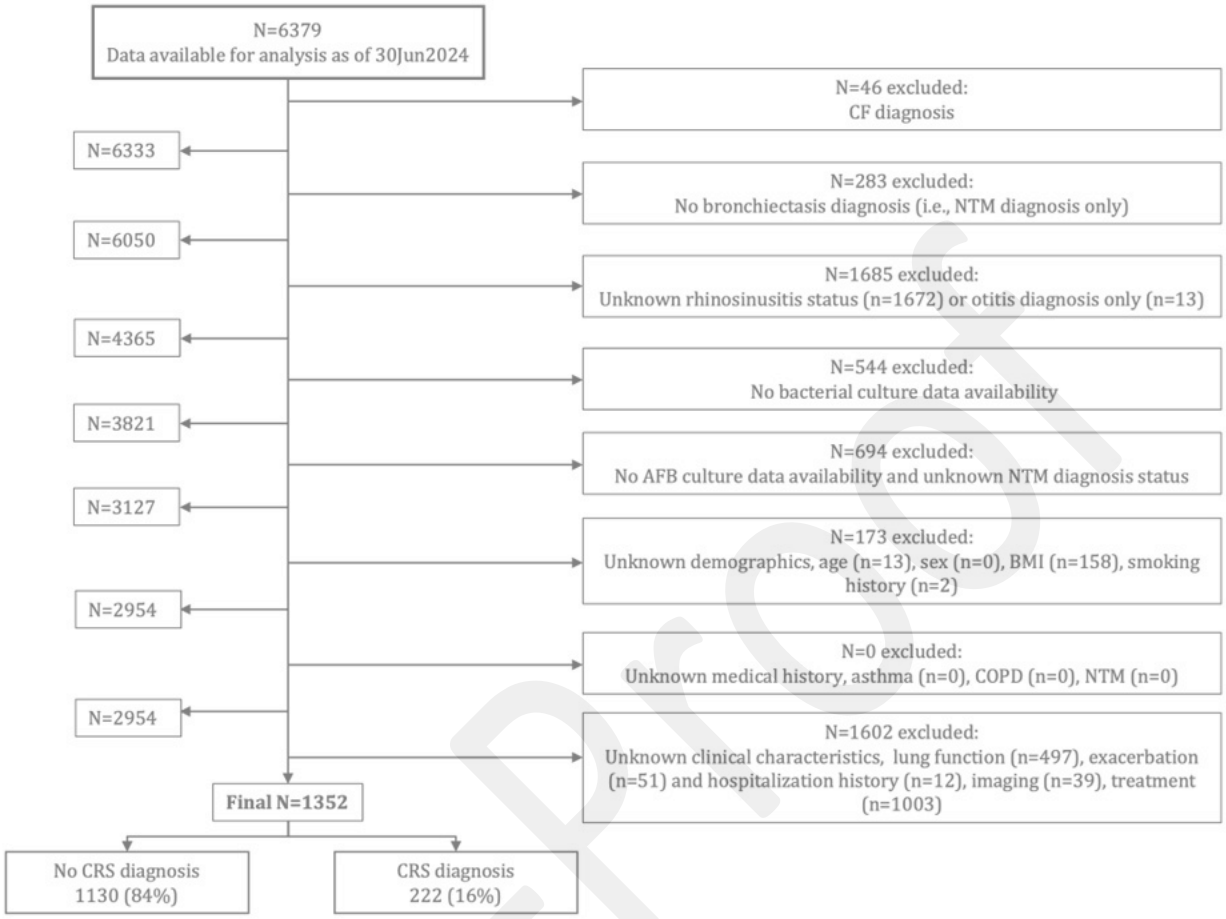
Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

Treatment				
Active NTM treatment, n (%) *data available among those with NTM diagnosis n=341*	169 (49.6)	141 (48.3)	28 (57.1)	0.251
Chronic macrolide therapy, n (%)	187 (13.8)	150 (13.3)	37 (16.7)	0.181
Inhaled corticosteroids, n (%)	524 (38.8)	421 (37.3)	103 (46.4)	**0.011**
Inhaled antibiotics, n (%) *data available n=1167*	204 (17.5)	157 (16.6)	47 (21.4)	0.092

Abbreviations: BE = bronchiectasis, BMI = body mass index, CRS = chronic rhinosinusitus, COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, IBD = inflammatory bowel disease, IQR = interquartile range, NTM = non-tuberculous mycobacteria, PCD = primary ciliary dyskinesia, SD = standard deviation
*Wilcoxon, Independent sample t-test, and chi-square test, as applicable
†Defined as a physician diagnosis meeting NTM guideline criteria and ≥1 positive AFB culture during the baseline period
‡Exacerbation- or pulmonary-related

Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

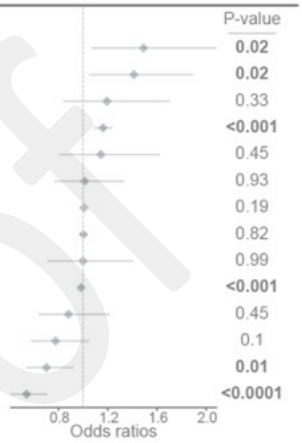
Figure 1: Study cohort flow diagram. CF= cystic fibrosis, NTM = non-tuberculous mycobacteria, AFB = acid-fast bacilli, BMI = body mass index, CRS = chronic rhinosinusitis.



Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

Figure 2: Multivariable logistic regression odds of ≥ 1 positive *Pseudomonas aeruginosa* culture among people with bronchiectasis enrolled in the US Bronchiectasis and NTM Research Registry

Variable	Standard Error	Odd Ratio	Lower 95% CI	Upper 95% CI	P-value
CRS, yes vs. no	**0.170**	**1.49**	**1.067**	**2.082**	**0.02**
≥1 hospitalization during the baseline period vs. none	**0.151**	**1.41**	**1.051**	**1.896**	**0.02**
Chronic macrolide therapy, yes vs. no	0.182	1.19	0.835	1.707	0.33
Total number of lobes involved	**0.032**	**1.16**	**1.092**	**1.236**	**<0.001**
≥1 exacerbation during the baseline period vs. none	0.179	1.14	0.806	1.623	0.45
Inhaled corticosteroid use, yes vs. no	0.14	1.01	0.768	1.332	0.93
Age	0.005	0.99	0.997	1.017	0.19
BMI	0.014	0.98	0.975	1.032	0.82
COPD, yes vs. no	0.174	0.99	0.71	1.405	0.99
Pre-bronchodilator FEV1 %predicted	**0.003**	**0.98**	**0.978**	**0.99**	**<0.001**
Sex, male vs. female	0.165	0.89	0.639	1.217	0.45
Asthma, yes vs. no	0.153	0.78	0.575	1.047	0.1
Current or former smoker vs. never smoker	**0.139**	**0.70**	**0.536**	**0.922**	**0.01**
NTM, yes vs. no	**0.136**	**0.54**	**0.414**	**0.706**	**<0.0001**

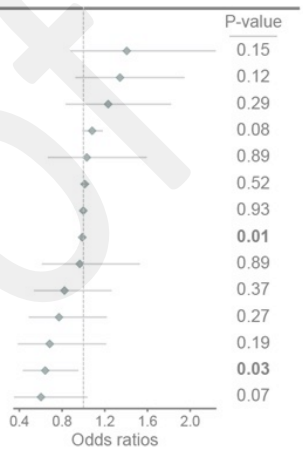


Abbreviations: CRS = chronic rhinosinusitis, BMI = body mass index , COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, NTM = non-tuberculous mycobacteria.

Published online February 23, 2026 https://doi.org/10.15326/jcopdf.2025.0732

Figure 3: Multivariable logistic regression odds of ≥ 1 positive *Staphylococcus aureus* culture among people with bronchiectasis enrolled in the US Bronchiectasis and NTM Research Registry

Variable	Standard Error	Odd Ratio	Lower 95% CI	Upper 95% CI	P-value
CRS, yes vs. no	0.237	1.41	0.883	2.238	0.15
NTM, yes vs. no	0.190	1.34	0.925	1.947	0.12
Inhaled corticosteroid use, yes vs. no	0.199	1.23	0.834	1.821	0.29
Total number of lobes involved	0.045	1.08	0.990	1.181	0.08
≥1 hospitalization during the baseline period vs. none	0.221	1.03	0.668	1.591	0.89
BMI	0.021	1.01	0.973	1.055	0.52
Age	0.007	0.99	0.986	1.013	0.93
Pre-bronchodilator FEV1 %predicted	**0.004**	**0.99**	**0.981**	**0.998**	**0.01**
Sex, male vs. female	0.234	0.97	0.611	1.528	0.89
Asthma, yes vs. no	0.218	0.82	0.537	1.262	0.37
≥1 exacerbation during the baseline period vs. none	0.233	0.77	0.488	1.218	0.27
Chronic macrolide therapy, yes vs. no	0.293	0.68	0.385	1.214	0.19
Current or former smoker vs. never smoker	**0.201**	**0.64**	**0.433**	**0.922**	**0.03**
COPD, yes vs. no	0.277	0.60	0.351	0.952	0.07



Abbreviations: CRS = chronic rhinosinusitis, BMI = body mass index , COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, NTM = non-tuberculous mycobacteria.

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Figure 4: Multivariable logistic regression odds of ≥ 1 positive *Haemophilus influenzae* culture among people with bronchiectasis enrolled in the US Bronchiectasis and NTM Research Registry

Variable	Standard Error	Odd Ratio	Lower 95% CI	Upper 95% CI	P-value
≥1 exacerbation during the baseline period vs. none	**0.352**	**1.03**	**1.130**	**4.489**	**0.02**
Asthma, yes vs. no	0.247	1.18	0.729	1.916	0.49
Chronic macrolide therapy, yes vs. no	0.305	1.12	0.616	2.038	0.71
Pre-bronchodilator FEV1 %predicted	0.005	0.98	0.993	1.013	0.53
BMI	0.024	1.00	0.955	1.049	0.97
Age	**0.007**	**0.97**	**0.960**	**0.989**	**<0.001**
Total number of lobes involved	0.053	0.96	0.866	1.064	0.44
Sex, male vs. female	0.281	0.93	0.535	1.609	0.79
Inhaled corticosteroid use, yes vs. no	0.238	0.89	0.557	1.418	0.62
Current or former smoker vs. never smoker	0.239	0.89	0.554	1.415	0.61
CRS, yes vs. no	0.311	0.71	0.383	1.296	0.26
NTM, yes vs. no	0.231	0.68	0.433	1.071	0.10
≥1 hospitalization during the baseline period vs. none	0.286	2.25	0.365	1.117	0.12
COPD, yes vs. no	0.396	0.49	0.224	1.057	0.07

Abbreviations: CRS = chronic rhinosinusitis, BMI = body mass index , COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, NTM = non-tuberculous mycobacteria.

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