Association between Inhaled Corticosteroid Use and Pulmonary Nontuberculous Mycobacterial Infection

Vincent X Liu, MD MS[1,2] (ORCiD ID 0000-0001-6899-9998), Kevin L Winthrop, MD[3], Yun Lu, MD MPH[1], Husham Sharifi, MD[4.] , Hekmat U Nasiri, MD[2], Stephen J Ruoss, MD[4] (ORCiD ID 0000-0001-7231-3813)

[1]Division of Research, Kaiser Permanente; Oakland, CA
[2]Santa Clara Medical Center, Kaiser Permanente; Santa Clara, CA
[3]Oregon Health and Science University; Portland, OR
[4]Stanford University; Stanford, CA

Corresponding Author
Stephen Ruoss
Stanford University - Medicine
H3149 300 Pasteur Drive Stanford California 94305-5236
United States

Author Contributions: Study conception and design: VXL, KLW, SJR; Analysis and interpretation: VXL, KLW, YL, HS, HUN, SJR; Drafting the manuscript for important intellectual content: VXL, KLW, HS, SJR. SJR is the guarantor of the manuscript, accepting responsibility for the integrity of the work as a whole.

Conflicts of Interest: None of the authors has any conflicts of interest with regard to the manuscript.

Running Title: Inhaled steroids and pulmonary NTM infection

Sources of Funding: The Bill and Jean Lane Center for Nontuberculous Mycobacterial Disease; Dept. of Medicine, Stanford University School of Medicine. VXL was supported by NIGMS K23GM112018.

Keywords: nontuberculous mycobacteria, bronchiectasis, inhaled corticosteroid, COPD, infection

Abstract

Rationale: Nontuberculous mycobacterial (NTM) pulmonary disease prevalence is increasing.

Objectives: To determine the association between the use of inhaled corticosteroids and the likelihood of NTM pulmonary infection among individuals with treated airways disease.

Methods: We conducted a case-control study of airway disease subjects with and without NTM pulmonary infection (based on mycobacterial respiratory cultures) between 2000 and 2010 in Northern California. We quantified the use of inhaled corticosteroids, other airways disease medications, and healthcare utilization within six months of NTM pulmonary infection identification. We used 1:10 case:control matching and conditional logistic regression to evaluate the association between the duration and cumulative dosage of ICS use and NTM pulmonary infection.

Results: We identified 248 cases with NTM pulmonary infection with an estimated rate of 16.4 cases per 10,000 airway disease-treated subjects. The median interval between treated airway disease cohort entry (defined as date of patient filling the third airways disease treatment prescription) and NTM case identification was 1,217 days. Compared with controls, subjects with NTM pulmonary infection were more likely to use airway disease medications including systemic steroids; they were also more likely to utilize healthcare. Any inhaled corticosteroids use between 120 days and two years prior to cohort entry was associated with substantially increased odds of NTM infection. For example, the adjusted odds ratio for NTM infection among inhaled corticosteroids users in a two year interval was 2.51 (95% confidence interval: 1.40-4.49; $p<0.01$). Increasing cumulative inhaled corticosteroids dose was also associated with greater odds of NTM infection.

Conclusions: Inhaled corticosteroids use, and particularly high dose inhaled corticosteroids use, was associated with an increased risk of NTM pulmonary infection.

Nontuberculous mycobacteria (NTM) are environmental organisms that can cause progressive lung disease associated with high morbidity and mortality.[1] Recent epidemiologic studies have reported that the incidence of NTM pulmonary disease is rising globally.[2-5] While precise estimates have been limited by heterogeneity in case definitions and variability in diagnostic reporting, population based assessments estimate the annual prevalence of NTM pulmonary disease to be as high as 47 cases per 100,000 patients in selected North American surveys[6,7], with the highest prevalence rates observed in older patients[2,8].

The clinical impact of NTM pulmonary infection can be substantial, due to relatively poor response rates to current multidrug therapy[1] and the almost universal airways injury and resulting bronchiectasis that accompany NTM pulmonary disease. The resulting chronic and progressive disease can cause significant morbidity and mortality[4,9,10] and can impair quality of life.[11] The impact of NTM infections on healthcare systems is also substantial with disproportionate costs resulting from the need for chronic and complex treatment regimens.[12-14]

The factors predisposing patients to the acquisition of NTM pulmonary disease, or the rising prevalence of disease, remain poorly understood.[8,14] Aspects of exposure environment, intrinsic host response and infection susceptibility, and acquired susceptibility modifiers have been considered as potentially important factors in the increased prevalence. Additionally, recent studies suggest that the use of inhaled corticosteroids (ICS) – an increasingly common therapy for patients with common airway diseases including asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis – is associated with an increased risk of NTM pulmonary disease[5,9,15,16] Corticosteroids can attenuate cellular immunity against intracellular

pathogens, including mycobacteria, raising the potential that inhaled corticosteroids could alter airways immune responses and predispose patients to NTM infection and disease persistence[17]. This potential effect would most likely manifest itself in individuals with chronic airways disease including bronchiectasis, in part due to the increasing use of chronic ICS therapy in this clinical population, even in the absence of data supporting any benefit of this drug class in bronchiectasis.[18,19, 20]

The potential adverse effect of ICS to increase the risk of NTM disease in patients with chronic obstructive disease has been explored in two recent studies in different populations. Andréjak and colleagues found in a nationwide Danish registry that ICS use was associated with increased odds of NTM disease in patients with chronic respiratory disease.[20] And in a case control study in Ontario Canada examining individuals of age greater than 65 with chronic airways disease, Brode and colleagues found that that ICS use was associated with an increased risk of NTM pulmonary disease.[5]

With emerging support for the hypothesis that ICS use can increase the risk of NTM disease in patients with chronic airways disease, we sought to determine whether this potential causative association could be confirmed in a separate and large patient population.

Accordingly, in a large and diverse patient population, we investigated the hypothesis that ICS use increases the risk for pulmonary NTM infection in patients with treated chronic airway disease.

Methods

The population for this case control study was identified from the Kaiser Permanente Northern California integrated healthcare delivery system, which includes 4.1 million persons representing the diverse demographics of a broad geographical region (21 hospitals, 242 medical offices). The Kaiser Permanente system uses a single electronic medical record system for clinical and laboratory data for their entire healthcare system, thus providing access to a robust database for clinical investigation. This study was approved by the Kaiser Permanente Northern California Institutional Review Board.

Identifying Patients with Airways Disease

Figure 1 displays our treated airways disease cohort identification and case-control matching approach. To identify subjects with airways disease, we screened for provider-reported International Classification of Disease, Ninth Revision, Clinical Modification (ICD9) diagnosis codes among adults (aged ≥ 18 years) enrolled in the Kaiser Permanente Northern California integrated healthcare delivery system between January 1, 2000 and December 31, 2010. The use of this database provided access to a large and very broad community-based subject cohort, to avoid biases potentially inherent in smaller or pre-selected subject cohorts. We identified subjects (n = 636,327) with at least one health care provider-reported inpatient or outpatient ICD9 code for asthma (493), chronic obstructive pulmonary disease (491 or 492), and bronchiectasis (494). Given the substantial variability in accuracy of diagnosis of these chronic respiratory diseases, as well as the significant variability in the assignment of ICD

disease codes in bronchiectasis populations[21], we included all these ICD diagnosis codes in our search. From the total identified study population, we specifically excluded subjects (n = 8,427) with any ICD9 diagnosis code of tuberculosis (010 to 018) or cystic fibrosis (277).

Airways Disease Treated Cohort

To further identify a treated cohort of airway disease patients, we evaluated outpatient pharmacy records to select subjects (n = 279,333) who filled at least three prescriptions for airway disease medications within a one-year period surrounding their first assignment of an ICD9 airway disease diagnosis code. Airway disease medications were broadly categorized as: isolated ICS (beclomethasone, budesonide, flunisolide, fluticasone, mometasone, or triamcinolone); mixed ICS, also termed ICS with long-acting beta-agonist (ICS/LABA); and non-ICS medications consisting of short-acting beta-agonists (albuterol or levalbuterol), long-acting beta-agonists (salmeterol or formoterol), anti-cholinergics (ipratroprium or tiotroprium), anti-leukotriene medications (montelukast, zafirlukast, or zileuton), or others (cromolyn or theophylline). In the airways disease treated cohort, we defined the "cohort entry" date for determination of treatment duration as the date the third prescription was filled. This cohort was then used to identify NTM infection cases and controls.

Identifying NTM Infection Cases

From the treated airway disease cohort, we identified subjects with NTM pulmonary infection (n = 549) based on respiratory acid-fast bacilli (AFB) cultures to maximize specificity. We defined confirmed NTM infection cases as either: (1) subjects with any single AFB culture

positive for NTM species from a bronchoscopic specimen; or (2) subjects with at least two positive AFB cultures for NTM from a sputum source within a one-year period. For subjects identified by two positive sputum cultures, the NTM "case index" date was set to the date at which the first positive result was reported and the NTM species was based on the first positive result. We then defined the NTM case duration interval as the number of days between a subject's NTM "case index" date and their treated airway disease "cohort entry" date, including subjects only when their NTM case identification date occurred after their airway disease cohort entry date (n = 310). We excluded subjects with a NTM diagnosis code preceding their case identification index date (n = 6).

Case-Control Matching

For each of the confirmed NTM cases in our primary analysis, we randomly selected 10 controls from the treated airways disease cohort; we excluded individuals with NTM cultures only positive for *M. gordonae* because of the very low likelihood of pathogenicity of this organism. Controls were matched by age (in five-year increments), gender, and airways disease at the "cohort entry" date (hierarchically categorized as bronchiectasis, COPD, and asthma). For each control, we censored their clinical data by the number of days from airways disease cohort entry to replicate their matched case's NTM case duration interval; no matched controls had diagnosis codes for NTM pulmonary disease after beyond the censoring date. We determined the presence of subject comorbidities based on ICD-9 codes prior to 'cohort entry' dates (i.e., diabetes, gastroesophageal reflux disease, interstitial lung disease, rheumatoid arthritis) as well

as the use of other medication based on pharmacy records (i.e., anti-TNF-alpha antagonists, oral corticosteroids, other immunosuppressants, and proton pump inhibitors).

Quantifying Inhaled Corticosteroid Usage

For cases and matched controls, we calculated the daily dose of ICS medication over a 1-year lookback period from the "index date". We used a standardized ICS beclomethasone-equivalency chart to characterize the dosage level of each prescription as high, medium or low.[22] For prescription periods that overlapped, we counted only a single medication dose preferentially taking the most recent prescription. We then quantified the number of days in the lookback period during which an ICS was prescribed, as well as the cumulative dosage of high-, medium- and low-dose ICS use. We used the same procedure to capture the percentage of days using other airway medications, as well as systemic corticosteroids (prednisone, prednisolone, methylprednisolone, and dexamethasone). We considered ICS/LABA medications as contributing to the ICS category. Over the same lookback period, we determined the percentage of days patients spent in outpatient visits, emergency department visits, and hospitalizations.

Statistical Analysis

Descriptive statistics are displayed using mean ± standard deviation or median (interquartile range). Comparisons between groups are based on t-tests, Wilcoxon rank-sum tests, or chi-squared tests. We used conditional logistic regression to evaluate the association between the duration of inhaled corticosteroid use and NTM pulmonary infection in unadjusted and

adjusted analyses. We adjusted for concomitant use of non-ICS medications in the medication-adjusted model and added demographic, comorbidity, and utilization variables in the fully-adjusted model. To evaluate a potential dose-response relationship between ICS and NTM pulmonary infection, we categorized 1-year ICS use in low, medium, and high cumulative dose categories. In sensitivity analyses, we also evaluated look back periods of 120 days and 2 years prior to cohort entry. We used Stata/SE 13.1 to conduct statistical analyses.

Results

Between 2000 and 2010, we identified a total of 549 NTM subjects, based on 2 or more positive AFB sputum sample culturess and/or 1 positive AFB bronchoscopic sample culture. *Mycobacterium avium-intracellulare* was the NTM pathogen identified in 368 (67.0%, Table 1) of positive samples, followed by *M. gordonae* (n = 91; 16.6%), *M. abscessus* (n = 29; 5.3%), and *M. fortuitum* (n = 25; 4.6%). Excluding *M. gordonae* occurrences, this represented 16.4 NTM infection cases per 10,000 airway disease treated subjects.

NTM Case-Control Matching

After restricting the cohort sample to individuals who were treated for airway disease prior to their AFB case positivity, our analytic cohort included 248 non-*M. gordonae* NTM infection cases with a cohort duration of at least 6 months. Median duration of follow-up between treated airway disease cohort entry and AFB case identification was 1,217 days (interquartile range, 525 – 2,139 days). Mean age was 64.2 ± 13.0 years and 63.3% of cases were female

(Table 2). The greatest number of subjects had a clinical provider-assigned diagnosis of asthma (by ICD code) at cohort entry (n = 148; 59.7%), while 73 (29.4%) had a provider-assigned ICD diagnosis of chronic obstructive pulmonary disease. And 30.6% (n = 76) of cases had multiple diagnoses, in particular patients with concomitant diagnoses of asthma and COPD.

Medication Use and Healthcare Utilization Patterns

Compared with controls, NTM cases were more likely to have used ICS prior to cohort entry (Table 2). NTM infection cases were also more likely than control subjects to have used most other medications, including systemic corticosteroids (36.3% versus 14.2%). NTM cases also demonstrated more frequent healthcare utilization based on ambulatory, emergency department, and hospital visits.

Association between ICS Treatment and NTM Infection Cases

Any ICS use within the one year prior to cohort entry was associated with substantially increased odds of NTM infection (Table 3, adjusted odds ratio 2.80; 95% CI: 1.79-4.37; p<0.01). A similar association was present for any ICS use in the 120 days (odds ratio 2.74; 95% CI: 1.83-4.09; p<0.01) or two years (odds ratio 2.51; 95% CI: 1.40-4.49; p<0.01) prior to cohort entry. Increasing cumulative ICS dosage in the year prior to cohort entry (based on tertiles of beclomethasone-equivalent ICS dose) was associated with increasing odds of NTM infection (Figure 2).

Discussion

In this study, we drew from a large and diverse population-based sample of Northern California subjects with treated chronic airway disease to evaluate the association between ICS and NTM pulmonary infection. We found that NTM infection was associated with preceding ICS use and that there was evidence for a dose-response relationship. Each month of high-dose ICS use was independently associated with greatly increased odds of developing NTM pulmonary infection, even after adjusting for other airway disease treatments and healthcare utilization metrics. These data represent an important finding regarding potential factors contributing to the increasing prevalence of respiratory NTM infection and may link the use of ICS with the increasing prevalence.

While the relative absence of standardized public reporting requirements for NTM infections may limit the overall applicability of some data, available infection surveillance data reveal a significant and continued increase in NTM infection prevalence over the last three decades. The prevalence of pulmonary NTM infections in the early 1980s was reported to be as many as 1.8 cases per 100,000 persons, further increasing to 3 to 4 cases per 100,000 persons in the 1990s.[23] Prevalence has continued to increase, with recent studies revealing regional prevalence of over 40 per 100,000.[24] In our study, we noted a substantially higher incidence rate among patients with treated airways disease as compared with the general population.

The causes of increasing NTM disease prevalence are uncertain, but a potentially important factor is the contribution of corticosteroid therapy, and in particular, ICS therapy, to NTM disease pathogenesis. Over the same period of observed marked increase in NTM

infection prevalence, the use of ICS has also increased dramatically. First introduced in Europe in the 1970s, and then in the early 1980s in North America, ICS use has continued to grow substantially, initially with greater penetrance of use in asthma populations, but importantly now with broad use in COPD patients.[18,19] Although it remains uncertain whether the current use of ICS in COPD populations is justified by available data[25,26], ICS use in COPD is very common. Prescription data from North America and Europe reveal ICS use in 40-75% of COPD patients[27,28], and the penetrance of ICS use in COPD appears to be increasing.[29-31] And importantly, while no data exist to support any benefit of ICS deriving to patients with bronchiectasis, the use of ICS in this population is substantial. The recent published data from a national registry study of bronchiectasis patients revealed that over 50% of that bronchiectasis cohort were treated with ICS, even though only a small minority had either an asthma or COPD diagnosis to potentially support the use of ICS in a treatment regimen.[21]

Corticosteroids can alter cellular immune function, critically important in host response and defense against pathogens, and this may contribute substantially to risk of pulmonary infections, including NTM infection. Human histopathological data in COPD patients have demonstrated substantial increased adaptive immune responses in infected peripheral airways[32], and these airways immune responses appear to be significantly attenuated by ICS, even while airways remodeling and mucus impaction are not reduced by ICS.[33] In addition, animal data reveal significant suppression by ICS of multiple cytokine mediators of host responses to intracellular pathogens.[34] Thus, ICS may produce an airways environment that is permissive for infections. This indeed appears to be the case from available background clinical data studying ICS use in COPD. Additionally, and supporting the concerns for adverse effects of

ICS on risk for NTM disease, a recent study of the immune genetic phenotypic responses in NTM disease patients provides direct study corroboration for the central involvement of adaptive cellular immune responses involving the interferon-gamma mediated pathway, an immune response component that is also substantially affected by exogenous corticosteroids.[35]

Prior and substantial studies suggest that the use of ICS therapy in COPD populations is associated with an increased risk for pulmonary infections.[36,37] Similarly, ICS use has been associated with increased risks of tuberculosis infection.[38,39] Brassard et al. reported in a large population-based sample of patients without oral steroid use that high dose ICS use was associated with a roughly twofold increase in the risk of pulmonary tuberculosis infection.

Prior studies have also suggested that ICS use is associated with increases in NTM pulmonary infection.[4,5,9,15,20] Hojo et al. evaluated a cohort of 464 asthma patients in Japan, of whom 14 were found to have NTM infections, and found that patients with NTM infections were more likely to have used fluticasone at higher doses when compared with non-NTM infected asthma patients.[15] In a larger study examining 332 patients with pulmonary NTM and 3,320 general population matched controls in Denmark, Andrejak et al. found that the presence of chronic respiratory disease was associated with an increased likelihood of NTM disease, but also that there was a significantly increased odds of NTM disease among respiratory disease patients who also were exposed to ICS. {Andrejak, 2010 #1389} Additionally, a recent large population-based nested case–control study from Ontario, Canada also reported an increased risk of NTM pulmonary disease in an older cohort (age over 65), offering added support to the hypothesis that chronic treatment with ICS is associated with a dose-dependent increased risk of NTM disease.[5]

Our analysis of a large patient population reveals a significant association between ICS use in patients with chronic airways diseases and an increased risk of NTM infection, and complements and extends the findings of these previously report studies. Indeed, a comparative analysis of our study and the recent report by Brode et al.[5] reveals substantial concordance of the central data of our study and their report. From their similarly structured population-based nested case-control study (although restricted to only studying subjects over age 65), Brode et al. found an adjusted odds ratio (OR) of 1.86 for NTM disease in ICS users compared with non-users (95% CI 1.60–2.15). The adjusted OR in our study was 2.74 (95% CI: 1.83-4.09; p<0.01); and in the report by Andrejak[20], a similar positive association was noted for ICS and risk of NTM disease. And in the reports by Andrejak et al. and Brode et al.[5,20], both also found, as has our study, a significant dose-response association between increasing cumulative ICS dosage and increasing odds of NTM infection (Figure 2). Importantly, our study has extended the observations and conclusions of Brode et al. to include subjects under as well as over age 65, thus avoiding that limitation in their study, while fully supporting the conclusions of infection risk from their study as well as that of Andrejak et al.

The known cellular immune modulatory effects of ICS support a possible causal link between ICS and NTM infection risk, and our data are concordant with other reports of ICS association with infection risk in COPD. The magnitude of the effect revealed in this analysis and the very substantial clinical consequences of NTM pulmonary infection raise the important question of whether the broad and increasing use of ICS for COPD needs to be reconsidered.

There are important limitations in our study. First, while we utilized the ATS-IDSA consensus microbiological criteria to identify patients with NTM infection, we have not

ascertained whether these subjects also met the consensus definition of NTM pulmonary disease. Our case ascertainment method is comparable to that utilized by Brode et al..[5] While we have not investigated the relationship between these microbiologically defined cases and consensus definition of NTM pulmonary disease in this population, prior published work has established that: a) the use of ATS/IDSA consensus microbiological disease criteria are valid as a surveillance tool for identifying pulmonary NTM disease, with a roughly 85% concordance of microbiological disease definition with clinical disease definition[38]; and b) the prognosis of individuals meeting consensus microbiological NTM infection criteria is highly concordant with the prognosis of individuals meeting consensus NTM clinical disease definition[4].

Second, although we followed a rigorous matching protocol, we found notable baseline differences between our cases and controls in medication and healthcare utilization; these differences were also present when we matched by medication and systemic steroids usage at cohort entry. Although we adjusted for these utilization differences in our regression model, we cannot eliminate the potential contribution of residual confounding. This includes the possibility for protopathic bias, i.e., symptoms-based treatment in the absence of clear clinical knowledge of the underlying disease(s); and this potential for protopathic bias could extend to include ICS exposure. Third, although there may be differences in immune system modulation by various ICS, and thus drug-related differences in NTM infection risk dependent on specific ICS used, we have not analyzed these data to answer that question. We have however made dose equivalence adjustments utilizing broadly accepted standard ICS equivalence adjustments, and thus doubt that differences in specific ICS utilized by patients included in this study account for the results we report. Fourth, we chose the case-control study design because of the

relative rare occurrence of NTM pulmonary infection even in our large starting population. However, the case-control approach does not allow us to establish a causal link between ICS use and NTM pulmonary infection. Additional studies, using more robust study designs, are needed to clarify this link. Finally, our inclusion of a broad range of clinical diagnoses of chronic obstructive diseases as designated by ICD-9 codes should be noted. Given the increasingly broad use of ICS in patients with chronic airways diseases, and the variability in assignment of disease diagnosis (and thus ICD code) by clinicians, plus the intrinsic biological and pathological overlaps that exist between specific chronic airways diseases, we chose to more broadly include chronic airways disease diagnoses, including COPD and asthma, in addition to bronchiectasis.[21,40-44] While the approach taken in our analysis might have included some patients in the exposure group who may have no underlying bronchiectasis, if this were the case, it would have the effect of biasing our analysis to the null hypothesis. Thus, our analysis approach allows for a more robust conclusion in consideration of our underlying hypothesis. In addition, past studies of NTM infection risk have clearly identified and included in their analyses subjects without a bronchiectasis diagnosis. In the reports by both Brode et al. and Cowman et al., only a minority of identified NTM disease cases had an established concurrent diagnosis of bronchiectasis.[5,35] Published data do not support an argument that NTM infections only occur in patients with previously identified bronchiectasis, so an a priori restriction of our analysis only to patients with a diagnosis of bronchiectasis would have been clinically unwise and not defensible for a robust investigation of the question.

In summary, our study found that ICS use was associated with a substantial increased risk of NTM pulmonary infection. In the face of uncertainty regarding possible benefits of ICS in COPD, these data argue for a reanalysis of the broad use of ICS in chronic airways diseases.

References

1. McShane PJ, Glassroth J. Pulmonary Disease Due to Nontuberculous Mycobacteria: Current State and New Insights. *Chest.* 2015;148(6):1517-1527.
2. Prevots DR, Shaw PA, Strickland D, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *American journal of respiratory and critical care medicine.* 2010;182(7):970-976.
3. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2009;49(12):e124-129.
4. Winthrop KL, McNelley E, Kendall B, et al. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health disease. *American journal of respiratory and critical care medicine.* 2010;182(7):977-982.
5. Brode SK, Campitelli MA, Kwong JC, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur Respir J.* 2017;50(3).
6. Al Houqani M, Jamieson F, Chedore P, Mehta M, May K, Marras TK. Isolation prevalence of pulmonary nontuberculous mycobacteria in Ontario in 2007. *Can Respir J.* 2011;18(1):19-24.
7. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *American journal of respiratory and critical care medicine.* 2012;185(8):881-886.
8. Henkle E, Hedberg K, Schafer S, Novosad S, Winthrop KL. Population-based Incidence of Pulmonary Nontuberculous Mycobacterial Disease in Oregon 2007 to 2012. *Annals of the American Thoracic Society.* 2015;12(5):642-647.
9. Andrejak C, Thomsen VO, Johansen IS, et al. Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors. *American journal of respiratory and critical care medicine.* 2010;181(5):514-521.
10. Mirsaeidi M, Machado RF, Garcia JG, Schraufnagel DE. Nontuberculous mycobacterial disease mortality in the United States, 1999-2010: a population-based comparative study. *PloS one.* 2014;9(3):e91879.
11. Mehta M, Marras TK. Impaired health-related quality of life in pulmonary nontuberculous mycobacterial disease. *Respir Med.* 2011;105(11):1718-1725.
12. Strollo SE, Adjemian J, Adjemian MK, Prevots DR. The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States. *Annals of the American Thoracic Society.* 2015;12(10):1458-1464.
13. Leber A, Marras TK. The cost of medical management of pulmonary nontuberculous mycobacterial disease in Ontario, Canada. *Eur Respir J.* 2011;37(5):1158-1165.
14. Thomson R, Donnan E, Unwin S. Nontuberculous Mycobacterial Lung Disease. Time to Get a Grip! *Annals of the American Thoracic Society.* 2015;12(10):1425-1427.

15. Hojo M, Iikura M, Hirano S, Sugiyama H, Kobayashi N, Kudo K. Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy. *Respirology.* 2012;17(1):185-190.

16. Dirac MA, Horan KL, Doody DR, et al. Environment or host?: A case-control study of risk factors for Mycobacterium avium complex lung disease. *American journal of respiratory and critical care medicine.* 2012;186(7):684-691.

17. Marras TK. Host susceptibility or environmental exposure in Mycobacterium avium complex lung disease: it takes two to tango. *American journal of respiratory and critical care medicine.* 2012;186(7):585-586.

18. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *The New England journal of medicine.* 2007;356(8):775-789.

19. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *American journal of respiratory and critical care medicine.* 2008;177(1):19-26.

20. Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax.* 2013;68(3):256-262.

21. Henkle E, Aksamit TR, Barker AF, et al. Pharmacotherapy for Non-Cystic Fibrosis Bronchiectasis: Results From an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *Chest.* 2017.

22. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother.* 2009;43(3):519-527.

23. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *American journal of respiratory and critical care medicine.* 2007;175(4):367-416.

24. Marras TK, Mendelson D, Marchand-Austin A, May K, Jamieson FB. Pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998-2010. *Emerging infectious diseases.* 2013;19(11):1889-1891.

25. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2012(9):CD006829.

26. Ernst P, Saad N, Suissa S. Inhaled corticosteroids in COPD: the clinical evidence. *Eur Respir J.* 2015;45(2):525-537.

27. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *The New England journal of medicine.* 1999;340(25):1941-1947.

28. Van Andel AE, Reisner C, Menjoge SS, Witek TJ. Analysis of inhaled corticosteroid and oral theophylline use among patients with stable COPD from 1987 to 1995. *Chest.* 1999;115(3):703-707.

29. Bourbeau J, Sebaldt RJ, Day A, et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. *Can Respir J.* 2008;15(1):13-19.

30. Mehuys E, Boussery K, Adriaens E, et al. COPD management in primary care: an observational, community pharmacy-based study. *Ann Pharmacother.* 2010;44(2):257-266.

31. Smith CJ, Gribbin J, Challen KB, Hubbard RB. The impact of the 2004 NICE guideline and 2003 General Medical Services contract on COPD in primary care in the UK. *QJM : monthly journal of the Association of Physicians.* 2008;101(2):145-153.

32. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *The New England journal of medicine.* 2004;350(26):2645-2653.

33. Hogg JC, Chu FS, Tan WC, et al. Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *American journal of respiratory and critical care medicine.* 2007;176(5):454-459.

34. Patterson CM, Morrison RL, D'Souza A, Teng XS, Happel KI. Inhaled fluticasone propionate impairs pulmonary clearance of Klebsiella pneumoniae in mice. *Respir Res.* 2012;13:40.

35. Cowman SA, Jacob J, Hansell DM, et al. Whole-Blood Gene Expression in Pulmonary Nontuberculous Mycobacterial Infection. *Am J Respir Cell Mol Biol.* 2018;58(4):510-518.

36. Yawn BP, Li Y, Tian H, Zhang J, Arcona S, Kahler KH. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. *Int J Chron Obstruct Pulmon Dis.* 2013;8:295-304.

37. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax.* 2013;68(11):1029-1036.

38. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *American journal of respiratory and critical care medicine.* 2011;183(5):675-678.

39. Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax.* 2013;68(12):1105-1113.

40. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax.* 2009;64(8):728-735.

41. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a Comorbidity of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *PloS one.* 2016;11(3):e0150532.

42. De la Rosa D, Martinez-Garcia MA, Giron RM, et al. Clinical impact of chronic obstructive pulmonary disease on non-cystic fibrosis bronchiectasis. A study on 1,790 patients from the Spanish Bronchiectasis Historical Registry. *PloS one.* 2017;12(5):e0177931.

43. Mao B, Lu HW, Li MH, et al. The existence of bronchiectasis predicts worse prognosis in patients with COPD. *Sci Rep.* 2015;5:10961.

44. Novosad SA, Barker AF. Chronic obstructive pulmonary disease and bronchiectasis. *Curr Opin Pulm Med.* 2013;19(2):133-139.

Table 1. Nontuberculous mycobacteria identified in respiratory sample mycobacterial cultures from all airway disease treated patients.

Mycobacterial species	No. (% of total)
Avium-intracellulare	368 (67.0)
Gordonae	91 (16.6)
Abscessus	29 (5.3)
Fortuitum	25 (4.6)
Chelonae	19 (3.5)
Kansasii	19 (3.5)
Szulgai	6 (1.1)
Xenopi	4 (0.7)
Simiae-avium	4 (0.7)
Terrae	3 (0.6)
Lentiflavium	2 (0.4)
Scrofulaceum	2 (0.4)
Aurum	1 (0.2)
Mucogenicum	1 (0.2)
Flavescens	1 (0.2)
Asiaticum	1 (0.2)
Interjectum	1 (0.2)
Gastri	1 (0.2)

(Note: *M gordonae* isolates were excluded as a possible cause of NTM pulmonary infection.)

Table 2. Baseline characteristics of NTM pulmonary infection cases and matched controls.

	NTM Cases	Controls
No.	248	2,480
Age	64.1 ± 13.1	64.2 ± 13.1
Female	157 (63.3%)	1,570 (63.3)
Entry diagnosis		
Asthma	148 (59.7)	1,480 (59.7)
Bronchiectasis	27 (10.9)	270 (10.9)
Chronic obstructive pulmonary disease	73 (29.4)	730 (29.4)
Race		
White	180 (72.9)	1,727 (70.1)
Comorbid diagnoses		
Diabetes mellitus	26 (10.5)	359 (14.5)
Gastroesophageal disease	32 (12.9)	350 (14.1)
Interstitial lung disease	14 (5.7)	86 (3.5)
Rheumatoid arthritis	10 (4.0)	31 (1.3)
Healthcare utilization, in past year		
Ambulatory visit	246 (99.2)	2,320 (93.6)
Emergency department	95 (38.3)	616 (24.8)
Hospitalization	113 (45.6)	661 (26.7)
Airways disease medication use, in past 120d		
Inhaled corticosteroid	187 (75.4)	1,111 (44.8)
Mixed ICS + LABA	42 (16.9)	161 (6.5)
SABA	108 (43.6)	725 (29.2)
LABA	39 (15.7)	201 (8.1)
Anticholinergic	104 (41.9)	437 (17.6)
Leukotriene antagonist	29 (11.3)	96 (3.9)
Oral corticosteroid	90 (36.3)	353 (14.2)
Other drug exposure in past year		
TNF-α-antagonist	2 (0.8)	2 (0.1)
Other immunosuppressant	11 (4.4)	54 (2.2)
Proton pump inhibitor	48 (19.4)	414 (16.7)

Data are means ± standard deviation, and frequency (percentage)
Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; SABA: short-acting beta-agonist

Table 3. Association of inhaled corticosteroid use with risk (odds ratios, OR) of NTM pulmonary infection, stratified by the period of ICS use prior to cohort entry and the diagnosis at cohort entry.

		Odds ratios (95% confidence interval for NTM infection with ICS use		
Any ICS use	No.	Unadjusted OR	Medication-adjusted OR	Fully-adjusted OR
Within prior 120 days	*2,728*	3.88 (2.87-5.26)	2.86 (2.02-4.05)	2.74 (1.83-4.09)
Within past 1 year	*2,321*	4.14 (2.80-6.13)	3.04 (1.97-4.68)	2.80 (1.79-4.37)
Within past 2 years	*1,829*	4.49 (2.62-7.70)	2.82 (1.59-5.00)	2.51 (1.40-4.49)

The medication-adjusted model adjusts for prior use of airway treatment medications, oral corticosteroids, immunosuppressant medications, and proton pump inhibitors over the same period.
The fully-adjusted model includes medications as well as age, gender, entry diagnosis, comorbid conditions (diabetes, GERD, interstitial lung disease, rheumatoid arthritis), and healthcare utilization over the same period.
Abbreviations: ICS: inhaled corticosteroid; OR: odds ratio

Figure 1. Cohort identification and case-control matching for primary analysis.

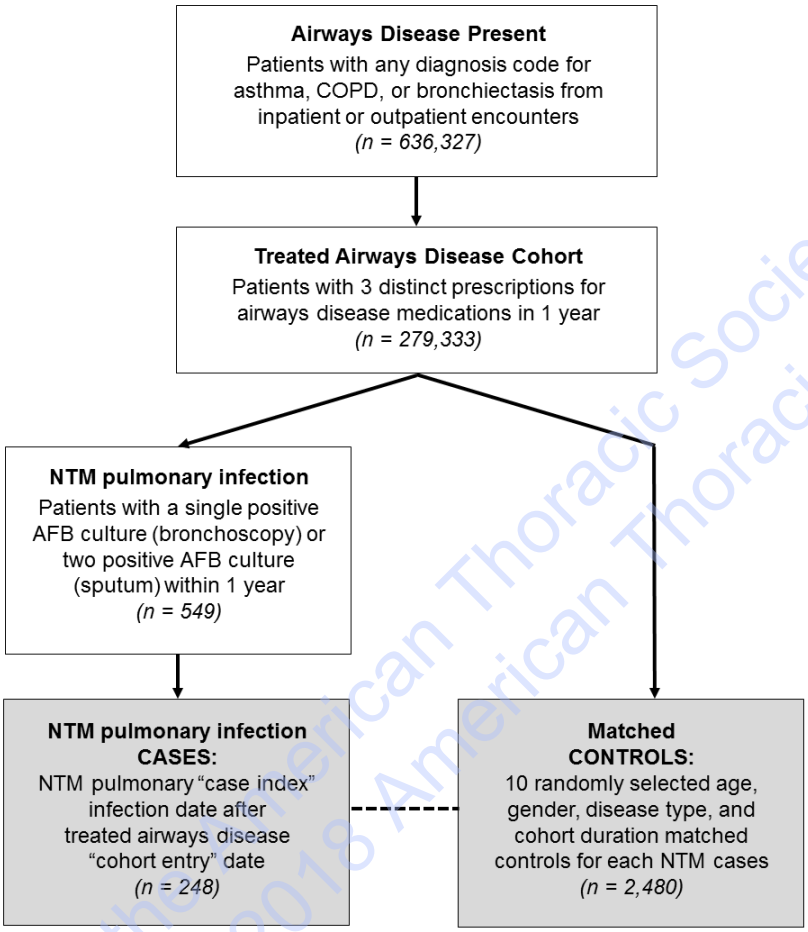

Figure 2. Adjusted odds ratios and 95% confidence intervals for NTM pulmonary infection based on tertiles of cumulative dosage of beclomethasone-equivalence inhaled corticosteroid use in the 1 year prior to cohort entry. The reference group is patients without inhaled corticosteroid use in the year prior to cohort entry.