Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis

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Principal Investigator:
Kevin L. Winthrop, MD, MPH
Oregon Health & Science University

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name
Title

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List of Abbreviations

BRR	Bronchiectasis Research Registry
BRRC	Bronchiectasis Research Registry Consortium
BTS	British Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
CF	Cystic Fibrosis
CMS	Centers for Medicare and Medicaid
ICS	Inhaled Corticosteroids
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MAC	Mycobacterium Avium Complex
NTM	Nontuberculous Mycobacteria
OHSU	Oregon Health & Science University
PHI	Protected Health Information
PI	Principal Investigator
PPV	Positive Predictive Value
QT	QT interval (a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle)
UAB	University of Alabama at Birmingham
VPN	Virtual Private Network

Protocol Summary

Title: Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis

Population: Medicare patients with non-cystic fibrosis (non-CF) bronchiectasis.

Study Duration: 3 years

Objectives:

Primary:

- Among a national cohort of non-CF bronchiectasis patients, we will compare the relative safety of inhaled corticosteroids (ICS) and macrolide therapy with regards to acquisition of pulmonary nontuberculous mycobacterial (NTM) disease and prevention of hospitalized respiratory infection.

Secondary:

- Secondary safety outcomes include sudden cardiac arrest, hearing loss, bone loss, and other opportunistic infections.
- Secondary effectiveness outcomes of importance as identified by preliminary patient input will include all-cause death, all-cause hospitalization, and hemoptysis.

1 KEY ROLES

Individuals: **Principal Investigator:** Kevin L. Winthrop, MD, MPH

Co-investigator: Emily Henkle, PhD, MPH

Co-investigator: Jeffrey Curtis, MD, MS, MPH
Co-investigator: Charles Daley, MD
Co-investigator: David Griffith, MD
Co-investigator: Elisha Malanga
Study Statistician: Lang Chen, MD

Institutions: Oregon Health & Science University

University of Alabama at Birmingham

National Jewish Health

University of Texas Healthcare Northeast

COPD Foundation

NTM Info & Research

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

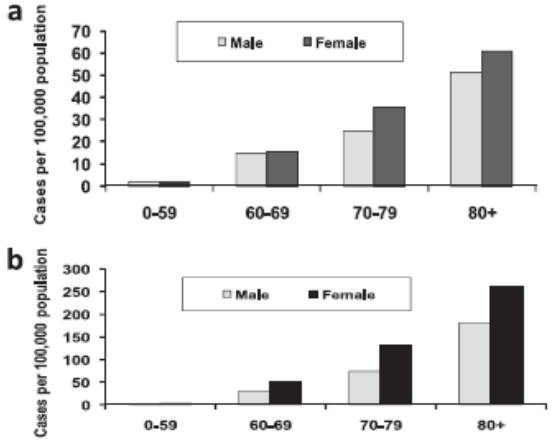
2.1.1. Non-cystic fibrosis bronchiectasis: Non-cystic fibrosis (CF) bronchiectasis is a rare lung disease of increasing incidence, causing chronic morbidity and disability in an estimated 100,000 Americans over age 65.[1,2] Patients with bronchiectasis suffer chronic productive cough, debilitating weakness and fatigue, dyspnea, hemoptysis, and are at high risk for recurrent pneumonia and death due to lung infections. Mortality is 3-4% per year, and 1-year mortality after hospitalization for pneumonia increases to 13%.[3-6] The effect upon quality of life is marked, and chronic disability can greatly diminish individual participation in social, occupational, and recreational settings. The quotes below taken directly from our pilot survey of non-CF bronchiectasis patients highlight patient concerns about their bronchiectasis diagnosis:

(1) "My biggest concern is that it increases my risk of repeated infection. And there is nothing I can do to reverse the damage."
(2) "One of the most frustrating symptoms of my bronchiectasis in the past two years is that my hemoptysis episodes have gone from about 2 or 3 a year to over 15 a year. It is a 'symptom' that is so unpredictable."
(3) "Dismay of lack of understanding by medical practice, lack of understanding about degree of seriousness."
(4) "The chance of [nontuberculous mycobacteria] recurrence is on my mind even when [feeling] well now"

While the etiology of this chronic inflammatory disease is multi-factorial, it is characterized by airway inflammation and excess mucous production. This in turn leads to a vicious cycle of colonization and infection with microbial organisms that promote inflammation, drive progression of airway damage, and cause frequent exacerbations.[7] Exacerbations are a regular complication characterized by increased respiratory symptoms and decreased lung function and often result in hospitalization. Important pathogens in this setting include nontuberculous mycobacteria (NTM) such as *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus*, as well as bacterial organisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae*.[4] While strategies exist to manage colonizing bacteria such as pseudomonas, chronic NTM disease eventually occurs in a substantial proportion of bronchiectasis patients resulting in long-term disability and the need for chronic, often life-long, therapy with multiple antibiotics.[4,6]

2.1.2 Pulmonary NTM disease (Criterion 1): NTM are ubiquitous environmental organisms found in water distribution systems and soil that cause chronic, debilitating pulmonary disease primarily in those over age 40.[8,9] Patients typically suffer from chronic cough, wheezing, dyspnea, fatigue, night sweats, weight loss, depression, social anxiety, hemoptysis, and other symptoms. Pulmonary NTM disease is also a rare disease that is increasing in the U.S, with an estimated 50,000 prevalent cases identified in patients over age 65 from 1997 through 2007 during a review of Medicare databases.[10-12] NTM incidence estimates range from 15.5-26.7/100,000 in those over 50 years of age.[12-14] Disease disproportionately affects females, incidence increases with age (see Figure 1), and occurs more frequently with chronic underlying lung disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis where lung architectural distortion puts them at high risk for collecting pathogens from the environment like NTM.[12,14] An increasingly predominant clinical presentation is generally a slender, older female ("Lady Windermere"), with interstitial nodular infiltrate, bronchiectasis in the right middle lobe or lingula, or bronchiolitis ("tree in bud") on high resolution CT scan (see Figure 2).[9,15,16] NTM infection is destructive and its associated inflammation drives both the development and progression of airway damage and dilatation. NTM can both cause bronchiectasis, as well as secondarily infect those already with the disorder. In our prior study in Oregon, as well as a Danish case-control study, NTM was strongly associated with non-CF bronchiectasis.[14,17] An estimated 2-10% of non-CF bronchiectasis patients will be infected with NTM at any given time and in one retrospective study, 30% were diagnosed with NTM disease over a 7-year period.[18-21] NTM therapy is prolonged and difficult. It typically includes the use of 3 or 4 concurrent antibiotics as part of an azithromycin- or clarithromycin-based regimen for 18-24 months with a low chance of cure.[9] Many patients fail therapy and over half will have either recrudescent NTM disease or new NTM infection from the environment after completing such therapy. Surgical resection is sometimes necessary, and antibiotic therapy is often difficult to tolerate. Given the morbidity of NTM disease and its treatment, and its close relationship with bronchiectasis, prevention of NTM disease is of great importance among these high risk individuals.

Figure 1. Average Pulmonary NTM Prevalence by Age and Sex in Two U.S. Healthcare Organizations



(*A*) Average annual prevalence by age and sex. Group Health and Kaiser Permanente Southern California combined, 2004–2006. (*B*) Cumulative incidence by age and sex. Group Health and Kaiser Permanente Southern California combined, 2004–2006.

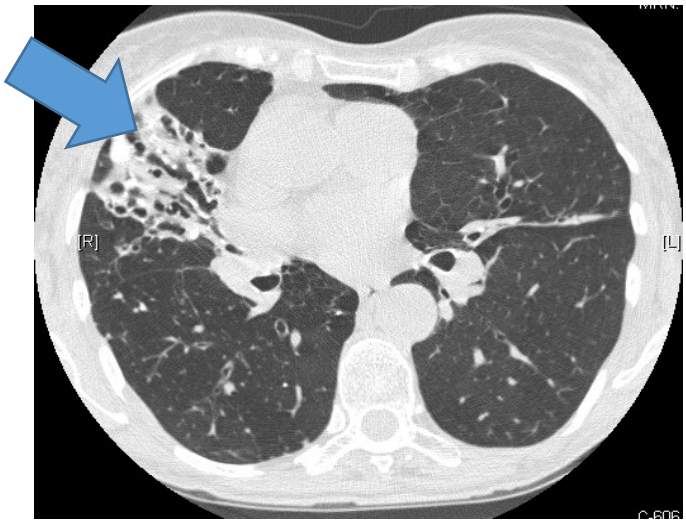


Figure 2. Computed tomography (CT) scan of patient with chronic *M. avium* complex disease in the right middle lobe in which bronchiectasis and inflammatory infiltrate are evident (arrow)

2.1.3. Non-CF Bronchiectasis Treatment: At present, pharmacologic strategies are commonly employed to treat non-CF bronchiectasis, yet very little effectiveness or safety data exist to guide patient-centered decision making. The goals of treatment are to improve symptoms, reduce airway inflammation, limit further bronchiectasis progression, and prevent chronic lung infection and acute symptomatic infectious exacerbations. We believe that some of the therapies frequently employed in this setting, however, might actually harm patients increasing the risk of hospitalization due to respiratory infections, and importantly, increasing the risk of pulmonary NTM disease. There are no published U.S. guidelines for non-CF bronchiectasis treatment, but in 2010 the British Thoracic Society (BTS) produced guidelines summarizing current therapies.[22] These therapies include oral or inhaled corticosteroids, oral or inhaled antibiotics, and techniques to promote airway hygiene/mucous clearance (Table 1).

Most of these therapies have received little research attention within non-CF bronchiectasis and the proposed benefits/risks of their use have been extrapolated from other settings of chronic lung disease like COPD or CF. However, the pathophysiology and natural history of non-CF bronchiectasis is distinct from these and other lung diseases, and therapies that benefit one do not necessarily benefit the other. For example, DNAse, which improves mucus clearance and outcomes in CF bronchiectasis patients, actually caused worsened lung function in non-CF bronchiectasis patients.[23,24] This underscores the importance of evaluating therapies within the setting of non-CF bronchiectasis, rather than extrapolating from studies performed in other chronic lung disease conditions.

Table 1. Pharmacotherapies used in bronchiectasis

Anti-inflammatory		Bronchodilators		Antibiotics	Mucous clearance
Inhaled steroids	beclomethasone budesonide flunisolide fluticasone mometasone triamcinolone	**Short acting**	albuterol levabuterol pirbuterol	azithromycin clarithromycin erythromycin inhaled tobramycin inhaled colistin inhaled gentamycin inhaled aztreonam	inhaled hypertonic saline
		Long acting	formoterol tiotropium salmeterol		
Combined steroid/ bronchodilator	ipratratropium/ albuterol budesonide/ formoterol fluticasone/ salmeterol				
Oral steroids	prednisone				

2.1.4. Oral and Inhaled corticosteroids (ICS): There is no evidence that long-term use of corticosteroids benefit patients with non-CF bronchiectasis, and their potential risks have been poorly studied in this setting. Yet, use of corticosteroids among such patients is common. Corticosteroids are prescribed short-term to treat bronchiectasis exacerbations, but are also frequently prescribed chronically in an attempt to limit inflammation and slow bronchiectasis progression. There is evidence that ICS therapy reduces exacerbations and slows the decline of quality of life in patients with advanced COPD.[25] However, the BTS guidelines and a more recent U.S. review of therapies suggest there is a lack of evidence to support the chronic use of oral or ICS in bronchiectasis.[20,22] To date, no large clinical trials have looked at ICS use in non-CF bronchiectasis. Several small randomized trials in patients with multiple exacerbations in the prior year have suggested an improvement in symptoms in patients receiving ICS for 6-12 months, but no difference in other outcomes when compared to placebo.[26-28]

To our knowledge, there are no long term studies specifically evaluating the risks of oral steroids or ICS in non-CF bronchiectasis patients. Such therapy increases the risk of opportunistic infections due to mycobacteria, fungus, and other pathogens.[29] Further, we and others have identified both oral steroids and ICS as likely risk factors for acquiring pulmonary NTM disease. In Oregon we identified high rates (16%) of oral corticosteroid use among patients with pulmonary NTM, and a later case-control study suggested a nearly 8 fold higher risk for NTM in users of oral corticosteroids.[14,17] In addition, there is data in other types of chronic lung disease suggesting that oral steroid or ICS use increases the risk of infection, particularly pneumonia,[30] an outcome for which non-CF bronchiectasis patients are already at increased risk. In COPD patients a population-based study identified a RR of 1.69 (95% CI 1.63-1.75) for serious pneumonia in current ICS users.[31] A recent meta-analysis concluded that budesonide and fluticasone, with or without long-acting bronchodilators, are associated with increased risk of serious adverse pneumonia events in COPD patients but not an increased risk of death.[32] Although subject to some controversy, inhaled corticosteroids have been also been associated with bone loss in asthmatic and COPD patients, similar to oral corticosteroids.[33]

2.1.5. Antibiotic strategies: There is limited evidence that long-term use of antibiotics benefit patients with non-CF bronchiectasis, and the risks of such therapy are poorly defined.
Antibiotics are used with the twin goals of reducing bacterial load in the airways, which in turn reduces airway inflammation, and exerting an immunomodulatory role independent of bacterial load reduction.[34] Macrolides (erythromycin, azithromycin) are oral antibiotics that exhibit immunomodulatory effects that may have clinical benefits for a variety of diseases associated with airway inflammation including non-CF bronchiectasis patients.[35] Two small randomized clinical trials evaluated long term (6 months to 1 year) azithromycin and a third evaluated long term erythromycin use in non-CF bronchiectasis patients. While macrolide-treated groups experienced fewer respiratory exacerbations, defined as increasing symptoms (requiring treatment in two studies), there was limited or no improvement in overall lung function.[36-38] One additional advantage of azithromycin (but not erythromycin) is its antimicrobial activity against NTM such that its long-term use theoretically could be protective against NTM. Only one study, to our knowledge, has evaluated this idea, and it was conducted in the CF setting. Investigators using case-control methods found CF patients who developed NTM were less likely to be using macrolides in the prior year.[39] A potential danger of macrolide monotherapy, however, is the development of macrolide resistance in those already infected with NTM.[40] Accordingly, macrolide monotherapy is not to be used in the treatment of pulmonary NTM disease (similar to tuberculosis where multiple drugs are used to diminish the evolution of drug resistance).[9] Further, macrolide resistance in other important organisms can occur (e.g. *S. pneumonia*) and the two macrolide RCTs in non-CF bronchiectasis patients routinely tested for it during the trial found higher rates of macrolide-resistant non-NTM pathogens in the macrolide treatment groups.[36,37] One of these studies excluded patients with NTM and neither reported any data on NTM isolates or resistance.

Aerosolized antibiotics, including tobramycin (and less commonly aztreonam, colistin, and gentamycin) are frequently prescribed in the CF setting primarily for those colonized with *Pseudomonas* and potentially could be useful in non-CF bronchiectasis. A small trial evaluated inhaled tobramycin versus placebo in 30 non-CF bronchiectatics for 6 months and found it was associated with a reduction in hospital stays, but there was no difference in exacerbation frequency or quality of life measures.[41] While these trials highlight a potential benefit of oral or inhaled antibiotics for non-CF bronchiectasis patients, they are small and of inadequate duration to provide the essential information regarding benefits and risks of longer courses of treatment.

In general, the relative risks of antibiotic therapy compared to benefits are not clear. Azithromycin use has been linked to sudden cardiac death in population-based studies[42], and it is known to cause QT prolongation with potential for causing other cardiac arrhythmias, particularly when used with other drugs that also cause QT prolongation.[43] Further, as previously mentioned, a significant risk of long-term azithromycin use would be the selection of macrolide-resistant NTM in patients colonized with NTM. NTM patients with *M. avium* resistant to macrolides who remained culture positive after subsequent therapy had a 1–year mortality rate of 34%.[40] Accordingly, it is recommended that CF and non-CF bronchiectasis patients be

screened for NTM prior to adopting long-term macrolide strategies.[22,40] Inhaled tobramycin, an aminoglycoside antibiotic, is associated with an increased risk of bronchospasm, dyspnea, wheezing, and chest pain compared to placebo, which may precipitate discontinuation of the drug and impair quality of life.[44] Potentially other more serious side effects of inhaled aminoglycoside use include permanent ototoxicity and renal failure, effects seen with parenteral use but which have received very limited study to date with inhaled use.[45]

2.2 Scientific Rationale

Non-CF bronchiectasis is a rare chronic disease for which little data exist to inform patients and physicians regarding treatment decisions. We believe findings from our study will assist patients and their physicians in choosing safer therapies that diminish their risks of negative outcomes identified as of high importance to them, including the development of complicated opportunistic infections such as NTM infection, hospitalized respiratory infections, all-cause hospitalization, death, and others. We hypothesize that antibiotic therapy protects against these outcomes, and that the relative risks of ICS do not support the widespread use of such therapy among non-CF bronchiectasis patients today.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

This is a minimal risk study. There is a small risk of breach of confidentiality.

2.3.2 Known Potential Benefits

Medicare patients will not benefit directly from the study since they will remain anonymous. However, subjects may benefit in the future since the project may provide information on relative risks and benefits of common therapies which will impact decision-making around treatment for non-CF bronchiectasis patients.

3 OBJECTIVES AND SPECIFIC AIMS

We propose to evaluate the benefits and harms of the most common therapies prescribed for non-CF bronchiectasis using a large cohort of bronchiectasis patients identified within Centers for Medicare and Medicaid Services (CMS) data, with linkage to a national non-CF bronchiectasis registry to validate outcomes lacking prior validation. Our patient co-investigators and stakeholders have identified the two most common therapies used in this disease, ICS and suppressive macrolide antibiotics, and they have identified the potential benefits and risks of these therapies of greatest importance to them. Together, we hypothesize that ICS use leads to increases in hospitalized pulmonary infections, death, and opportunistic infection due to NTM, while macrolide use does not. Our proposed study evaluates the relationship of ICS and macrolide use and the relative risk of these and other patient-identified outcomes. We will work with patients and clinical stakeholders to interpret and disseminate results from the study.

Specific Aim 1*:* Among a national cohort of non-CF bronchiectasis patients, we will compare the relative safety of ICS and macrolide therapy with regards to acquisition of pulmonary NTM disease. Secondary safety outcomes include sudden cardiac arrest, hearing loss, bone loss, and other opportunistic infections.

- Our primary hypothesis is that ICS, compared to macrolide therapy, is associated with an increase in the relative risk of NTM disease

Specific aim 2*:* Among a national cohort of non-CF bronchiectasis patients, we will compare the effectiveness of ICS and macrolide therapy with regards to prevention of hospitalized respiratory infection. Secondary effectiveness outcomes of importance as identified by preliminary patient input will include all-cause death, all-cause hospitalization, and hemoptysis.

- Our primary hypothesis is that ICS, compared to macrolide therapy, is associated with an increase in the relative risk of hospitalized respiratory infection

4 STUDY DESIGN

The study is a retrospective cohort design conducted using Medicare data from 2006-2014. Among a national cohort of non-CF bronchiectasis patients, we will evaluate and compare the clinical effectiveness and safety of long-term ICS and macrolide antimicrobial therapies. The proposed specific aims were generated based on our initial assessment of patient priorities (prevention of NTM infection, hospitalized respiratory infection, all-cause death, all-cause hospitalization, and hemoptysis) and operationally defined based on our prior work with CMS and other large administrative databases. Analyses will be conducted within a primary cohort of non-CF bronchiectasis patients. In some cases, outcomes could be considered both "effectiveness" and "safety" outcomes (e.g. prevention or acquisition of NTM disease) and hence there is overlap in the concepts of effectiveness and safety within the protocol. Our analytic approach is similar and discussed jointly in Section 7.

5 STUDY POPULATION

5.1 Selection of the Study Population

Complete national 2006-2014 Medicare data from Part A, B and D will be obtained from CMS. We will use ICD-9 code 494.0 (bronchiectasis without acute exacerbation) to identify patients with bronchiectasis within Medicare. This code has been used to evaluate trends in bronchiectasis diagnosis and hospitalization in Medicare patients in previously published studies, although its validity has not been determined to our knowledge.[1,46] Accordingly, we conducted a pilot validation study at three geographically varied sites (medical centers in Portland, OR, Tyler, TX, and Denver, CO) in which we randomly selected across the three sites a total of 290 electronically identified outpatients over age 18 with 494.0 diagnoses. Using chest CT scan as a gold standard, we found the positive predictive value (PPV) of a single 494.0 code for bronchiectasis to be 90.3% (95% CI 86.4-93.2%). In addition, 100 inpatient records with a primary or secondary discharge diagnostic code for bronchiectasis (494.0) were reviewed at OHSU, with an observed PPV of 95.8% (95% CI 89.8-98.4). The vast majority of reviewed patients in this validation exercise were Medicare patients, and we believe it is likely that this code has similar validity at other medical centers caring for Medicare patients. However, we acknowledge that it is possible the PPV may differ by medical system.

5.2 Inclusion/Exclusion Criteria

In order to potentially further increase the PPV for identifying bronchiectasis patients in our cohort study, we will define bronchiectasis patients as those patients with any pulmonologist - recorded 494.0 ICD-9CM.

From this identified bronchiectasis cohort, we will exclude patients with cystic fibrosis (ICD-9 codes 277.00-277.09), HIV infection (042), and a history of organ transplant (V42.0, V42.1, V42.6, V42.7, V42.8). Rationale for exclusion includes the fact that such patients are fundamentally different than non-CF bronchiectasis patients who lack these factors with regard to their risk for infection, hospitalization, and many of the outcomes under study in this protocol.

6 RESEARCH METHODS

6.1 Study Outcome Measures

Table 2 lists the validated operational algorithms used to identify key outcomes already identified in the literature or by patient ranking. Primary outcome events will be the date of NTM infection (Aim 1) and hospitalized respiratory infection (Aim 2). Secondary outcomes will include all-cause mortality, all-cause hospitalization, hemoptysis, and hip fracture included as a result of patient input. Secondary safety outcomes of concern include the potential adverse events of cardiovascular events (arrhythmia, myocardial infarction), hearing loss, and opportunistic infection.

Table 2. Proposed outcomes and operational definitions

Diagnosis	Algorithm/ ICD-9-CM Principle Diagnostic Codes	Validation Studies
Pulmonary Events		
Non-tuberculosis mycobacteria (NTM) infection	031 (inpatient or outpatient)	Winthrop 2011[47], Winthrop 2013[48]
Hospitalized respiratory infection	480-487.0 (inpatient)	Jackson 2003[49], Grijalva 2008[50]
Hemoptysis	786.3 (inpatient)	Not validated (see section 6.3.8)
Other Safety/Effectiveness Events		
All-cause hospitalizations	-	-
Death	-	-
Opportunistic infection (other than NTM)	See Appendix A	See Appendix A
Arrhythmia	427.x (principal diagnosis)	Tamariz 2012[51]
Myocardial infarction	410.X1	Kiyota 2004[52]
Hip fracture	820.0x, 820.20, 820.21, 820.22, 820.8 821.0x,	Narongroeknawin 2012[53]
Sensorineural hearing loss	389.1 [except 389.13, .15, .16 and .17], 389.2 [except 389.21]	not validated

6.2 Therapy Exposure Rules and Definitions

In this protocol, we borrow from established methodology and our experience conducting prior pharmacovigilance studies using Medicare and other administrative databases evaluating the comparative effectiveness and safety of immunosuppressive therapies used in other inflammatory diseases.[54-57] Table 3 lists key terminology and definitions, further described below.

Table 3. Terms and operational definitions

Term	Definition
Cohort inception date	Date of first treatment with ICS or macrolide
Baseline period	12 months prior to cohort inception OR later treatment episode start date
Clean period	12 months prior to cohort inception OR later treatment episode start date
New use	Absence of prescription for medication group in question during clean period
Treatment episode	≥28 day supply of either an ICS or macrolide regimen, through 30 days after switch or no refill of prescription
Treatment episode start date	First date of prescription for ≥28 day supply of either an ICS or macrolide regimen
Discontinuation date	Sum of days supply + 30-day grace period

Similar to these studies, we will allow patients who have a qualifying treatment episode (defined below) of chronic ICS or chronic macrolides to enter the study cohort on the date of first receipt of that therapy **("cohort inception date").** Only new users will be included in the analysis, with **"new use"** as defined as an absence of prescriptions for the specific medication group in question during a "**clean period**" of 12 months prior to inception date. National Drug Codes, obtained from First Databank by UAB, will be used to identify drugs of interest.

As described in Table 1, ICS include beclomethasone, budenoside, flunisolide, fluticasone, mometasone, triamcinolone, ipratratropium/ albuterol, budesonide/formoterol, or fluticasone/salmeterol. We will lump these therapies and analyze them according to effective steroid dose. Antibiotics of interest include the macrolides (oral azithromycin, clarithromycin, and erythromycin). A qualifying "**treatment episode"** will be defined as ≥28 day supply of either an ICS or macrolide regimen, with the first date of prescription receipt defined as the **"treatment episode start date."** A treatment episode ends when the patient (1) switches to a new regimen that meets a different operational definition or (2) does not refill the prescription or another within the same exposure category (i.e. ICS or macrolides) within 30 days after the end of the drug supply. The pharmacy variable "days-supply" will be used to estimate the intended duration of each prescription. The "**discontinuation date"** is defined as the sum of (days supply + 30-day grace period). Patients may re-enter the cohort as new users. Patients who leave the drug exposure cohort can subsequently contribute new episodes of medication use if selection criteria (including "clean period") were re-fulfilled and can potentially contribute episodes to more than one exposure group.

For patients who switch therapies within their exposure group prior to the discontinuation date, they will be considered to have continuous exposure. This is very unlikely for macrolides, however, as almost all patients will have used azithromycin (erythromycin and clarithromycin use in suppressive fashion is rare) and are unlikely to switch to other macrolides. Although also unlikely, a patient starting erythromycin might switch to azithromycin prior to the discontinuation date. In this case, the patient will be considered to have continued macrolide exposure (i.e. the same treatment episode). Rules around ICS exposure and product switches within that

exposure group will be handled similarly, and exposure measured as effective steroid dosage (see Section C20).

6.3 Attribution of Events to Exposure Groups

Exposure time will begin at the "**treatment episode start date**". The follow up will end at the earliest date of death, first outcome occurrence, end of study period, lost coverage, or treatment switch or discontinuation. Since patients rarely start or switch therapies at random, and they may, in fact, change or stop therapies based upon prodromal symptoms (e.g. chest pain consistent with angina), the length of the at-risk period will continue through the "**discontinuation date"** (30 days beyond the exhaustion of the drug supply). Events occurring in this at-risk period will be attributed to the exposure, however for NTM infection outcome we will perform sensitivity analyses using a longer window of "at risk" time, specifically of 90 days after the exhaustion of drug supply. We believe this is appropriate given the length of time it can sometimes take to diagnose NTM disease (e.g. cultures take 4-6 weeks to grow after collection). For all outcomes under study, except hospitalized respiratory infection, patients must have no evidence (inpatient or outpatient ICD-9 code) of the condition of interest during the 12 month clean-period in order to be included within that specific analysis. For example, only patients without evidence of NTM by ICD-9 code within the baseline period will be included into the analyses of NTM incidence.

Because this study is an evaluation of "real world" effectiveness and safety, we expect that some patients who start one exposure will at some point add the alternate exposure. Our data suggests that concurrent use is uncommon and <10% of ICS users are taking macrolides at the same time. For example, a patient who starts ICS might add macrolides after 3 months of ICS therapy. From that time on, they are exposed to both until one therapy is discontinued. For such patients, in our primary analysis we will right censor patients prescribed both ICS and antibiotics at the time of the patient meeting a qualifying comparison treatment episode. In sensitivity analyses, however, we will not right censor them at this time, but rather analyze such patients in a third category of combined ICS and antibiotic use until one or both therapies are discontinued.

6.4 Control of Confounding

We will collect **baseline clinical and demographic data during the 12 month baseline period prior to treatment episode start date**. These covariates are listed in Table 4 and are summarized here, and are adapted from our previous experience with RA and other inflammatory disease cohorts within Medicare. Descriptive analyses will be performed for all variables in Table 4 for the full bronchiectasis cohort and the "new user" treated cohort. Demographics include age, sex, median household income (census block group with linkage of zip code), nursing home/community residence, rural/urban residence, and state of residence (to

generate geographic region of residence: Midwest, Northeast, South, and West). We will collect the number of prior hospitalizations (with or without infection) and physician and pulmonologist office visits. Patients using oral corticosteroids for at least 90 days continuously prior to index date will be categorized as baseline systemic corticosteroid users (yes or no). For all baseline systemic corticosteroid users, we will calculate a mean outpatient prescribed daily dose of prednisone equivalents in the 6 months prior to index date: less than 5 mg/d (low dose), 5 to less than 10 mg/d (medium dose), and 10 mg/d or more (high dose).[57] The total number of antibiotic prescriptions during the baseline period will be obtained, including those typically used to treat acute respiratory infection (erythromycin, azithromycin, clarithromycin, inhaled tobramycin, levofloxacin, moxifloxacin, ciprofloxacin, amoxicilin, amoxicilin/clavulanate, or doxycycline). The Charlson comorbidity index will be calculated at the date of cohort inception.[58,59] Comorbidities will include the following: COPD, asthma, lung cancer, alpha-1 antitrypsin deficiency, interstitial lung disease, pulmonary fibrosis, primary immune deficiencies (including common variable immune deficiency), primary ciliary diskinesia, allergic bronchopulmonary aspergillosis, silicosis, and rheumatoid arthritis. Pre-existing NTM disease within the baseline period will be identified using ICD-9 codes for NTM (031) or any prescription for ethambutol (an antibiotic specific to tuberculosis or NTM therapy), and pre-existing *Pseudomonas* disease identified using ICD-9 codes (041.7, 482.1, 008.42).

Table 4. Baseline demographic and clinical covariates for use in propensity score calculation within the Medicare bronchiectasis cohort

Variable	Proposed Definition	Notes
Age	Log continuous variable	
Sex	Male or female	
Median household income	Census block group with linkage of zip code	
Nursing home residence	Nursing home or community	
Rural/urban	Rural or urban	
Region of residence	Geographic region of residence: Midwest, Northeast, South, West	
Cohort calendar year	2006-2014	
Number of physician office visits	Continuous variable	
Any hospitalization (incl. infections)	Continuous variable	
Hospitalization for non-infections	Continuous variable:	
Number of unique medication classes	Continuous variable or categorical based on the distribution	
Total number of antibiotic prescriptions	erythromycin, azithromycin, clarithromycin, inhaled tobramycin, levofloxacin, moxifloxacin, ciprofloxacin, amoxicilin, amoxicilin/clavulanate, or doxycycline 12 months prior to index date	
Total number of acute exacerbations	Number of antibiotic prescriptions (see above) for >7 but <28 days	*Added 7/25/16*
Oral corticosteroid use	Yes/no	
Mean oral corticosteroid dose	mean outpatient prescribed daily dose of prednisone equivalents in the 6 months prior to index date: less than 5 mg/d (low dose), 5 to less than 10 mg/d (medium dose), and 10 mg/d or more (high dose)	Ref: Winthrop KL, et al. JAMA 2013;309:887-95
Oxygen tank prescription	Yes/no	*Added 7/25/16*

Frequency of encounters	Number of dates with an outpatient physician encounter resulting in a diagnosis in the 12 months prior to the start of follow-up exclusive of emergency department encounters	Ref: Hoangmai H et al. Pham JAMA. 2005;294(4):473-481
Frequency of pulmonologist encounters	Number of dates with an outpatient pulmonologist encounter resulting in a diagnosis in the 12 months prior to the start of follow-up exclusive of emergency department encounters	
Charlson comorbidity score	'001', '002', '003', '004', '005', '008', '009', '032.81', '034', '035', '036.0', '036.1', '036.42', '038', '040', '040.81', '041', '049.0', '056.71', '077.9', '091.81', '093.2','094.2', '094.81', '095.2', '098.5', '098.82', '098.84', '130', '131.03', '289.5', '289.59', '320', '323', '324', '372.0', '376.03', '381.5', '382', '383.0', '383.1', '383.9', '391.1', '397.9', '421', '421.9', '422.92', '461', '462', '463', '464.0', '465', '466', '472', '473','475', '478.21', '478.22', '478.24', '481', '482', '483', '485', '486', '510', '513', '526.4','528.3', '540.1', '566', '567', '569.5', '569.61', '572', '574', '575', '576.1', '590', '597','599.0', '601', '608.4', '611.0', '614.3', '614.4', '681', '682', '686.1', '686.8', '686.9','711.0', '711.9', '728.86', '728.86', '730.0', '730.1', '730.2', '785.4', '790.7', '958.3','98.12', '98.32', '996.6', '998.5'	*Ref: Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol 1992;45:613–*19.*
COPD/emphysema	491.xx - chronic bronchitis, 492.xx - emphysema, 493.2 - chronic obstructive asthma, 496.xx - chronic airway obstruction, not elsewhere classified	Ref: Cooke, C et al. BMC Health Serv Res. 2011 Feb 16;11:37. doi: 10.1186/1472-6963-11-37.
NTM infection	031 or ethambutol prescription	
Pseudomonas infection	041.7, 482.1, 008.42	
Asthma	2 inpatient or 1 inpatient 493	Ref: Gershon AS. Can Respir J. 2009 Nov-Dec;16(6):183-8
Lung cancer	>1 162.x (not 162.0), 231.2	Ref: Ramsey SD et al. J Manag Care Pharm. 2009 Oct;15(8):659-68.
Alpha-1 antitrypsin deficiency	273.4	
Interstitial lung disease	>2 inpatient or outpatient ICD-9 codes (515, 516.3, 516.8, and 518.89) given > 7 days apart	Ref: Herrinton et al. PharmEpi Drug Saf. 2013;22:394-402
Primary immune deficiency	279.x, excluding lymphoma/leukemia, HIV	Ref: Resnick. J Clin Immunol. Jan 2013; 33(1): 40–48.
Primary ciliary dyskinesia	759.3	
Allergic bronchopulmonary aspergillosis	518.6	
Silicosis	502	
Rheumatoid arthritis	1+ inpatient or outpatient visit coded 714.xx AND a biologic or non-biologic DMARD	Ref: Curtis J et al. Arthritis Rheum. 2007;57(2):343-6
Abbrev: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification ; PPV, positive predictive value; Ref, reference		

6.5 Statistical Analysis

6.5.1 Crude incidence calculation: In separate outcome-specific models, we will calculate crude incidence using incident events divided by total exposed person-years for each exposed group (ICS or macrolides). Exposed person-time will be calculated as the sum of the number of days between each treatment episode start date and censoring-date (time of event, death, end of exposure risk period [i.e. discontinuation date], or end of study time-period, whichever comes first). Estimated rates per 100 person-years of follow-up and 95% confidence intervals will be calculated.

6.5.2 Propensity score generation and primary analysis using multivariable Cox modeling: We will use propensity score methods to ensure ICS and macrolide exposure groups are similar in patient characteristics in an effort to minimize potential sources of confounding, including confounding by indication. For each patient, we will calculate a propensity score (PS) in a logistic regression model using the full set of baseline demographic and comorbidity data including proxy measures for underlying bronchiectasis severity such as frequency of hospitalizations, pulmonary visits, respiratory antibiotic use, prednisone use, and others (Table 4). This model will be used to estimate the probability a patient receives therapy with ICS, and a propensity score (PS score) for this outcome will be generated and given to each patient. PS scores will be reviewed for overlapping distributions between the primary comparison groups (ICS and macrolide exposure) and the goodness of fit will be evaluated using the C statistic.[54] The PS score will be grouped into deciles and non-overlapping tails between exposure groupswill be trimmed so that only overlapping exposure cohorts will be compared.[60] In our primary analysis, we will use Cox proportional hazard regression models to compare incidence of outcomes between new users of ICS and macrolides.[61] Since patients could contribute ≥1 episode of new use (with an updated set of covariates), we will use the Huber-White “sandwich” variance estimator and calculate robust standard errors for all estimates.[62] We will recalculate the propensity score whenever the patient begins a new qualifying episode of the same treatment within the same analysis. The final disease specific-outcome models for cohort analyses will include the exposure group, propensity score decile, and baseline oral prednisone use (yes/no), as well as an indicator variable for inhaled antibiotic use (y/n) after cohort inception. Although inhaled antibiotics are seldom used (inhaled tobramycin is commercially available for this purpose), it could be an important confounder so that we will control for it in this fashion. All analyses will be done in SAS (SAS Institute Inc., Cary, N.C.).

6.6 Sample Size Considerations

We define *a priori* that a 25% increase (hazard ratio of 1.25) is a clinically meaningful increase in the risk of a given outcome (hospitalization, death, etc.). We expect to identify approximately 100,000 bronchiectasis patients in the Medicare data.[1] Based upon our preliminary patient survey data, we anticipate a minimum of 40% will be treated with ICS and 15% with macrolides each year resulting in an annual cohort of 55,000 treated patients. If we identify 10,000 new

users of ICS and 4000 of macrolides, and conservatively assume 5% of patients on antibiotics are develop NTM infection, or a similar number are hospitalized each year for pneumonia (see preliminary data), we have 82% power to detect a HR of 1.25 comparing ICS to macrolides for either of these outcomes. The test statistic used is the two sided Z test with pooled variance and the significance level of the test was targeted at 0.05. Given that other outcomes under study are more frequent or of a similar frequency, we expect to be well powered to conduct the other primary and secondary analyses.

6.7 Sensitivity Analyses

We do not have any planned subgroup or formal heterogeneity of treatment effects analyses. A number of sensitivity analyses will be conducted.

6.7.1. Alternative models: First, we will explore including additional variables individually within the models, beyond PS decile, baseline oral prednisone, and inhaled antibiotics. Other factors that will be considered are age, sex, COPD, asthma, and pseudomonas colonization. Although these factors are currently being controlled within the PS score, they are potentially strong risk factors and we will perform these sensitivity analyses to ensure they are adequately controlled for in this fashion.

6.7.2. Macrolide only exposure: Second, although it is unlikely that a large number of patients will be using erythromycin, for the outcome of NTM disease we will conduct a secondary analysis limiting macrolide users to those starting azithromycin or clarithromycin, as erythromycin lacks antimicrobial activity against NTM.

6.7.3. Dose response to steroids: Third, within the ICS category, there could be differential risk based upon the contained steroid dosage. Using methods described previously, we will convert all ICS to fluticasone equivalent doses (fluticasone 50 mcg, budesonide 80 mcg, beclomethasone 100 mcg, triamincinolone, flunisolide 200 mcg).[31] Treatment episodes will then be categorized as high (1000 mcg/day or more), medium (500-999 mcg/day), or low (<500 mcg/day).

6.7.4. Dual use of ICS and macrolides: Fourth, we will look at the effects of concomitant exposure to ICS and antibiotics. Although preliminary data suggests a small percentage of patients using concomitantly (<10%), we will look at this subgroup individually. For this analysis, patients will be censored at the start of a concomitant qualifying therapy and reclassified into a third exposure group labeled “dual ICS/macrolides.” They will be evaluated separately and censored according to the same rules as for the primary analysis.

6.7.5. Inhaled antibiotics: Finally, our patient partners have expressed an interest in lesser-used inhaled antibiotics (tobramycin and aztreonam). We will explore the incidence of events in new

users of these therapies, although given they are used less frequently we will likely lack statistical power to make formal comparisons with either ICS or macrolide users.

6.8 Missing Data

Missing data constitute a very minor problem in the Medicare data system. Medicare data covers adults age 65 and older and people under age 65 with certain disabilities and captures the entirety of beneficiaries' healthcare encounters. For example, no beneficiary has missing demographic information (gender, race, birth date, zip code). No claim record has a missing claim date, all carrier and outpatient records have at least one non-missing diagnosis code, no carrier line record has a missing diagnosis code, only a few inpatient claims have a missing primary discharge diagnosis, and dispensing files have no missing values for product, quantity dispensed or days of supply. We use SAS programs to determine the missing counts for each variable in each data file, in each year, used in our analyses as part of our standard operating procedures. We do not exclude beneficiaries because of missing or invalid data. If such data cannot be corrected, we exclude the affected claim (very often, there is a replicate claim containing valid data). Therefore the use of these data minimizes problems of misclassification bias due to missing data on the primary outcomes, exposures, and confounders. The BRR (described below) has excellent completeness, with less than 5% missing data for any given variable and most at 1% or less.

6.9 Validation Registry Linkage Substudy

We plan to use the BRR as a validation cohort for previously unvalidated claims-based algorithms for secondary outcomes as described below. The project will submit a finder file including subjects from participating BRRC sites to ResDAC containing the date of birth, sex, and social security number (SSN) to create a crosswalk to link BRR and Medicare data. Alternatively, if sites are unable to access full SSN data, we will perform probabilistic linkage using date of birth, sex, and physician visit dates or other dates that can be matched to claims dates and associated physicians. The BRR, which collects detailed clinical, laboratory, microbiology, and radiology data from the medical record, will primarily be used to validate the claims-based algorithms for outcomes lacking prior validation: hemoptysis and pseudomonas colonization. The gold standard for hemoptysis is clinical documentation of episodes requiring bronchial embolization or surgery. For pseudomonas, the gold standard will be a positive culture result, present in about 25% of BRR patients. In each case we will calculate the positive predictive value (PPV) and 95% CI for the ICD-9 codes as defined in Table 3. If needed, we can explore additional algorithms including requiring two codes or in combination with pharmacy data if the PPV is determined to be too low. In addition, we can confirm that patients were treated with the medications and determine how many pseudomonas and NTM infections were missed by administrative data. This cohort will not only be valuable to validate exposures and outcomes within our study, but will serve future studies in the validation of various algorithms for

these and other exposures/outcomes.

7 PRIVACY, CONFIDENTIALITY, AND DATA SECURITY

7.1 Human Subjects Considerations

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

7.2 Protection Against Risk

8.3.1 Data storage: The release of personal information is highly unlikely as data safeguards will be maintained throughout the study. To protect against the risk of loss of confidentiality we will use a secure system of file storage. The finder file to ResDAC containing identifiers including social security numbers will be used for creating a one-time data crosswalk to link BRR and Medicare data. After the crosswalk is completed the finder file will be destroyed. Any analytic data files, which will contain health information, will be coded and tracked by study identification number so that study staff will not have access to both identifiers and health information. Any paper or electronic data linking study identification numbers, identifiers and health information will be kept secured and accessible only by authorized local personnel working on the study. All staff is required to sign pledges promising to maintain study subject confidentiality.

8.3.2 Medicare data storage: Raw Medicare data will be stored and processed at UAB on a dedicated, layered-security system, which can be accessed only by designated project staff under the direct supervision of the site PI. Since the system is behind multiple firewalls, is monitored regularly, and is accessible only to key personnel, the risk of unlawful penetration is not a significant data safeguard concern. All applications are run on the server, thereby eliminating the need to house data on individual desktop or laptop computers that are generally more of a security risk. Administrative access to databases and corresponding data will be limited to the analyst team using Remote Desktop Protocols and/or Virtual Private Network (VPN) technologies. Furthermore, all databases will reside behind industry-strength firewalls.

Password protection will be used in additional places on the server for all transactions that allow entry and editing of data, provide access to sensitive subject data or administrative privileges. Passwords will be managed to require all users to change their password within 90 days and strict rules will be implemented to require strong passwords. Additionally, beneficiary contact information will be encrypted and write-protected to maintain data integrity. Data access will be limited to investigators and key study personnel. Prior to receiving PHI access, researchers must demonstrate completion of HIPAA training and abide by security procedures.

Administrative access to databases and corresponding data will be limited to the analyst team using Remote Desktop and/or Virtual Private Network (VPN) technologies. Furthermore, all databases will reside behind industry-strength firewalls. Individuals, such as analysts and statisticians, have access to the data for their specific projects. Other members of the research team who do not require access to the raw CMS data do not have access to the data.

All output containing individual identifiable information is treated as confidential data. This information is never transferred electronically via email or other protocols. Shredders are used on any printed material containing individual identifiers. Printed tabular material will not contain cell sizes less than 11. At the conclusion of this study, a CMS “Certification of Destruction” certifying the proper destruction of all data obtained will be sent to CMS.

8.3.3 BRR data: All electronic data for the Bronchiectasis Research Registry is housed at DatStat, a secure coordinating center. Datstat maintain highest levels of research and human subject/HIPAA privacy protections as well as 21 CFR Part 11. On the DatStat platform, all communication between the client browser and the web server is protected using SSL encryption. SLL Encryption will also be used for transmitting data to and from any external software systems and databases. Additional measures to ensure the security of the data include: restricting access to users with valid IDs and passwords and using a hardware firewall to restrict access to the web server and database. In accordance with DatStat standard operating procedures, system security logs and event logs are monitored daily to detect unauthorized attempts to access the system. DatStat’s follows internal Standard Operating Procedures and industry standard guidelines for securing data and services running its application. These guidelines and standard operating procedures include, securing servers with complex, hard to guess passwords, processes to lock down and secure servers by changing administrator account credentials, managing port security at the firewall level, and restricting logical and physical access to servers to only essential personnel.

All data transferred to DatStat’s collocated datacenter are stored, processed, and analyzed within the datacenter. At DatStat’s colocation facility, all access to the datacenter is controlled through locked doors which require an escort, and pre-authorized by another internal employee listed on the account. The DatStat office space remains locked after working hours. Access to computer data files is controlled by passwords released only to the personnel who use such files. In addition, data files with personal identifiers (and sensitive information per designation by a study’s Steering Committee) are encrypted. Physical access to servers and data backup is restricted to a minimal number of IT professionals. Such access is provided only with strong passwords that regularly expire, minimizing the chance that passwords distributed inadvertently and/or unknowingly could cause inappropriate data access. Access to data stored on the server is available only to designated users who log in with specified usernames and passwords. Users are logged out after a period of time. A listing of the named users with a description of their access privileges is available within the applications.

7.3 Data Safety and Monitoring

Not applicable given the nature of this administrative data only project.

8 INFORMED CONSENT PROCESS

8.1 Informed Consent Process

The research project will be reviewed by the Institutional Review Board (IRB) at both project sites, Oregon Health & Science University (OHSU) and University of Alabama at Birmingham (UAB).

The research proposed will use national Medicare administrative data to examine Medicare beneficiaries with non-CF bronchiectasis. These patients do not actively participate, nor do they submit any information not already present in their claims data. Therefore a Waiver of Authorization and waiver of informed consent will be submitted to the IRBs at OHSU and UAB prior to obtaining protected health information (PHI). The research cannot be conducted without access to and use of PHI or without a waiver, and it is not practical to obtain Authorizations for Release of PHI from hundreds of thousands of patients. All data will be transferred from Medicare to UAB and OHSU under a data use agreement (similar to prior agreements already in place) which describes exactly how the data will be used and protected.

Similarly, the project proposes to link pre-existing BRR and Medicare data for the validation study. Dr. Winthrop is a BRRC Investigator who is authorized to use the BRR data and his team will handle the linkage. Patients do not actively participate, nor do they submit any information not already present in claims or registry data. Therefore, a Waiver of Authorization and waiver of informed consent will be submitted to the IRB at OHSU prior to obtaining protected health information (PHI). The research cannot be conducted without access to and use of PHI or without a waiver, and it is not practical to obtain Authorizations for Release of PHI from the registry patients who enrolled across multiple sites.

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SUPPLEMENTS/APPENDICES

Appendix A. Opportunistic Infection Outcomes and Definitions

Diagnosis	Algorithm/ ICD-9-CM Principle Diagnostic Codes	Notes
Tuberculosis	Any ICD-9 code (010-018) AND pharmacy records indicating prescription for PZA prescribed on same day within +/- 90 days of first code date	Veteran's Affairs (VA) hospital ICD-9 data compared with medical record review: TB, PPV 0.73 (95%CI, 0.54-0.92); Ref: Schneeweiss et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. Journal of clinical epidemiology 2007;60:397-409 KNPC validation work: TB code, sensitivity = 100%, but PPV 0.54. Any code plus INH/RIF, sensitivity 0.79 and PPV 0.85
Histoplasmosis	Any ICD-9 code (115) WITH cumulative supply of >30 days of any of the following three drugs: fluconazole, itraconazole, or voriconazole given within +/- 90 days of first code date	VA project with spec 0.91, and PPV 0.50;
Blastomycosis	Any ICD-9 116 WITH cumulative supply of >30 days of any of the following three drugs: fluconazole, itraconazole, or voriconazole given within +/- 90 days of first code date	VA project with ppv 100%;
Coccidioidomycosis	Any ICD-9 (114) WITH cumulative supply of >30 days of any of the following three drugs: fluconazole, itraconazole, or voriconazole given within +/- 90 days of first code date	KNPC suggests Code alone, sensitivity 0.59, PPV 0.59-0.72; one code + RX increases PPV to 0.91 VA project w/ PPV 0.67, specificity 0.92
Cryptococcosis	Any ICD-9 (117.5, 321.0) WITH cumulative supply of >30 days of any of the following three drugs: fluconazole, itraconazole, or voriconazole given within +/- 90 days of first code date	VA ICD-9 as above PPV 100% [0.45-1.0]; Ref: Schneeweiss JCE 2007 (full ref above) KNPC suggests Code alone, sensitivity 0.54, PPV .78; code plus pharmacy data ppv 0.80 VA project with spec 0.67, PPV 0.67
Endemic Mycosis (non-specific outcome of all endemic fungi above)	ICD-9 484.7 WITH cumulative supply of >30 days of any of the following three drugs: fluconazole, itraconazole, or voriconazole given within +/- 90 days of first code date	VA ICD-9 as above: TB, PPV 0.73 (95%CI, 0.54-0.92); all OIs combined (TB, NTM, aspergillus, cryptococcus) PPV 0.73 (0.61-0.85) ; Ref: Schneeweiss JCE 2007 (full ref above)
Nocardiosis/actinomycosis	Any ICD-9 (039)	from VA project: ppv 0.38
Listeriosis	Any ICD-9 (027.0)	from VA project ppv 1.00
Toxoplasmosis	Any ICD-9 (130)	from VA project ppv 0.67
Pneumocystsis	Any ICD-9 (136.3)	from VA project ppv 0.53
Legionellosis	Any ICD-9 (482.84)	from VA project ppv 1.00
Salmonellosis	Any ICD-9 (003	from VA project ppv 0.88
Aspergillosis	Any ICD-9 (117.3, 484.6) WITH any outpatient RX for voriconazole, itraconazole, posaconazole given within +/- 90 days of first code date.	ICD-9 alone in VA system, PPV .67 [0.4-0.94]) ; Ref: Schneeweiss JCE 2007 (full ref above) Change DC, PPV = 0.71 (.44-.90) in UAB discharge codes of transplant patients (unpublished data); VA project (code plus meds) with specificity 0.95, PPV 0.70 Ref: JW Baddley Abstract #2093; ACR 2013
Zoster	Any ICD-9 code 053 (outpatient or inpatient code) WITH any outpatient RX acyclovir, famvir, or valacyclovir given +/- 90 days of first code date.	a. Outpatient code PPV = 0.94 in managed care setting in age > 60 Ref: Jumaan et al. J Infect Dis 2005;191:2002-7 Inpatient codes in either first or second position without pharmacy data had high PPV for simply having zoster during the time of hospital stay PPV =0.85). Similar high PPV for both inpatient (0.94) and outpatient codes (0.83) of any position seen in Kaiser NW data Ref: Mullooly J et al. Epidemiol Infect. 2005;133:245-53