

Application of diagnostic criteria for non-tuberculous mycobacterial disease to a case series of mycobacterial-positive isolates

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ABSTRACT

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have provided guidelines to assist in the accurate diagnosis of lung disease caused by nontuberculous mycobacteria (NTM). These microbiologic, radiographic, and clinical criteria are considered equally important and all must be met to make the diagnosis of NTM lung disease. To assess the significance of the three criteria, each was evaluated for its contribution to the diagnosis of NTM lung disease in a case series. Laboratory reports of any specimen positive for NTM isolation were collected between January 1, 2006 and December 31, 2010 at a university medical center. Medical records were reviewed in detail using a standardized form. The total number of patients with a culture from any site positive for NTM was 297 while the number from respiratory specimens during the same period was 232 (78%). Samples from two of these patients also yielded *M. tuberculosis* complex and were excluded. While 128 of the remaining 230 patients (55.7%) in the cohort met the microbiologic criterion for diagnosis of NTM lung disease, 151 (65.6%) and 189 (78.3%) met the radiologic and clinical criteria respectively. Only 78 patients (33.9%) met all three criteria provided by the ATS/IDSA for diagnosis of NTM lung disease. This evaluation reaffirms that defining NTM lung disease using either one or two of the criteria provided by the 2007 ATS/IDSA guidelines may significantly overestimate the number of cases of NTM lung disease. Based on the experience of defining NTM lung disease in this case series, recommendations for modification of the ATS/IDSA guidelines are provided which include expansion of both radiologic patterns and the list of symptoms associated with NTM lung disease.

1. Introduction

Nontuberculous mycobacteria (NTM; also known as atypical mycobacteria and mycobacteria other than tuberculosis) are a classification group of all *Mycobacteria* species, over one hundred in number, excluding *Mycobacterium leprae* and those in the *M. tuberculosis* complex. These microbes are ubiquitous in environments and can be isolated from natural waters, potable water, water aerosols (showerheads, hot tubs, and pedicure spas), soils, domestic and wild animals, foods, and biofilms (especially those of water distribution systems) [1,2]. NTM are typically opportunistic pathogens and several species are associated

with human disease which can be classified into four clinical presentations: chronic lung disease, lymphadenitis, cutaneous disease, and disseminated disease [3]. The most common presentation of NTM infection is chronic lung disease which typically occurs among those with pre-existing disease and the immunocompromised [4,5].

A single isolation of NTM from the respiratory tract does not necessarily indicate NTM lung disease but can reflect either colonization or specimen contamination. Accordingly, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have provided guidelines to assist in the accurate diagnosis of NTM lung disease [6]. The ATS/IDSA guidelines provide microbiologic,

Abbreviations: ATS, American Thoracic Society; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria; VATS, video assisted thoracoscopic surgery

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radiographic, and clinical criteria which are considered equally important; all three must be met to make a diagnosis of NTM lung disease. The microbiologic criterion includes positive culture results from a) at least two separate expectorated sputum samples, b) a bronchial wash/lavage, or c) a transbronchial/other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or stain positive). The radiographic criterion requires a) an observation of nodular or cavitary opacities on a chest X-ray or b) a CT scan that shows multifocal bronchiectasis with multiple small nodules. More recently, the radiographic criterion has been interpreted to demand one of two different radiographic manifestations: fibrocavitary or nodular bronchiectatic disease [7,8]. Fibrocavitary presentation of NTM lung disease demonstrates cavitary lesions predominantly in the upper lobes while nodular bronchiectatic disease presents as multifocal bronchiectasis, clusters of small nodules, and branching linear structures that commonly involve the right middle lobe and the lingular segment of the left upper lobe [9,10]. The clinical criterion demands pulmonary symptoms and appropriate exclusion of other diagnoses, especially pulmonary tuberculosis.

Using the ATS/IDSA guidelines, the three criteria required for the diagnosis of NTM pulmonary disease were applied to a case series of mycobacterial-positive isolates collected at a university medical center. To determine the significance of the three diagnostic criteria, each was evaluated for its contribution to the diagnosis of lung disease by NTM in the case series.

2. Methods

Laboratory reports of any specimen positive for NTM isolation between January 1, 2006 and December 31, 2010 at the University of North Carolina Medical Center, Chapel Hill, NC were collected. NTM isolate origins were classified as: pulmonary, sterile site, dermal, catheter, other, and unknown. The date(s) and anatomic site(s) of isolation and the species of mycobacteria were recorded. For patients with more than one isolate during the study period, the initial three were described.

The protocol for the collection of all data was approved by the University of North Carolina School of Medicine Committee on the Protection of the Rights of Human Subjects. Medical records were reviewed in detail by a board-certified pulmonologist. A standardized computer form was used to report available data on all patients with at least one NTM isolate. Data included demographic information (age, gender, and race). Smoking status (current, ex-smoker, and never smoker) was quantified. The dates and features of interpretations of chest X-rays and CT scans of the chest obtained during the study period (up to 3 of each) were collected. Medication use and the presence of both pulmonary symptoms (cough, phlegm, shortness of breath, hemoptysis, and chest pain) and systemic symptoms (fatigue, fever, night sweats, weight loss, rash/dermal lesions, and pain other than chest pain) were recorded. Co-morbidity was reported including respiratory

(asthma, chronic obstructive pulmonary disease, pneumonia, cystic fibrosis, sarcoidosis, and other pulmonary diagnoses), cardiovascular (coronary artery disease, heart failure, and mitral valve prolapse), gastrointestinal (gastroesophageal reflux, malabsorption, gastrectomy, hepatitis, and cirrhosis), renal (kidney failure), and human immunodeficiency virus (HIV)-related disease. In addition, diagnoses of diabetes, connective tissue disease (rheumatoid arthritis, lupus, scleroderma, and mixed connective tissue disease), scoliosis, kyphosis, pectus excavatum, and neoplasms were noted. Regarding scoliosis, kyphosis, pectus excavatum, mention of the conditions in either the clinic records or radiology reports was accepted as diagnostic evidence.

3. Results

A total of 297 patients at the university medical center had mycobacteria isolated from clinical specimens between January 1, 2006 and December 31, 2010. Demographic information on the patient cohort is provided (Table 1). Of the 297 patients, 232 (78%) grew mycobacteria from at least one respiratory specimen. Two patients grew *Mycobacterium tuberculosis*, leaving 230 patients with NTM in the study cohort. Patients with respiratory cultures positive for NTM included 196 (84%) with sputum samples, 29 (13%) with bronchoalveolar lavage samples, and 5 with lung biopsies (2%) obtained via video assisted thoroscopic surgery (VATS). Relative to patients with any positive NTM culture, those with positive pulmonary cultures were older since the former included cutaneous and lymph node infections which were observed predominantly among children and young adults (Table 1). Males and females were observed in approximately equal numbers among those with any positive culture and positive pulmonary cultures (Table 1). In this group of patients with positive pulmonary specimens, the number of sputum cultures positive for NTM ranged from 0 to 11.

While 128 of the 230 patients (55.7%) in the cohort met the microbiologic criterion for diagnosis of pulmonary disease, 151 (65.6%) and 189 (78.3%) met the radiologic and clinical criteria respectively. Ninety-two (40.0%) met both the microbiologic and radiologic criteria and 78 (33.9%) met all three criteria provided by the ATS/IDSA for diagnosis of pulmonary mycobacteria disease (Fig. 1).

Mycobacterium avium complex (MAC) accounted for mycobacterial isolates cultured from 119 of the 230 patients with pulmonary specimens (Table 2). Forty-six of these were from patients who had only one positive sputum. Two patients provided sputum specimens which grew MAC and this was followed by sputum cultures which grew *M. fortuitum*. Two patients had MAC in a sputum sample and then MAC in a lavage sample and two other patients had MAC in sputum followed by MAC in blood cultures. *M. gordonae* was isolated from 40 sputum samples and six of these patients provided two specimens positive for this species. Three sputum isolates were positive for *M. gordonae* but later sputum samples revealed MAC. One sputum was positive for *M. gordonae* but the patient had follow-up bronchoscopy with lavage which grew MAC. Twenty-one sputum specimens provided *M. abscessus*. One

Table 1
Characteristics of patients with a positive NTM culture, positive pulmonary culture, and positive pulmonary culture(s) meeting ATS/IDSA criteria for lung disease.

	Number of patients with NTM isolate (%)	Number of patients with NTM pulmonary isolate (%)	Number of patients with NTM pulmonary isolate meeting ATS/IDSA criteria for infection (%)
Total number	297	230	78
Age	49.0 ± 22.1 years	52.2 ± 21.6 years	54.6 ± 17.6
Female	150 (51%)	118 (51%)	48 (62%)
Race	192 (65%) White	156 (68%) White	60 (77%) White
	63 (21%) Black	48 (21%) Black	12 (15%) Black
	10 (3%) Asian	6 (3%) Asian	1 (1%) Asian
	32 (11%) Other	20 (9%) Other	5 (6%) Other
Smoking	59 (20%) current smokers	48 (21%) current smokers	9 (12%) current smokers
	68 (23%) ex-smokers	61 (27%) ex-smokers	25 (32%) ex-smokers
	170 (57%) never smokers	121 (53%) never smokers	44 (56%) never smokers

*232 patients with pulmonary isolates, 2 co-infections with *M. tuberculosis* complex, 230 patients included in final analysis of pulmonary isolates.

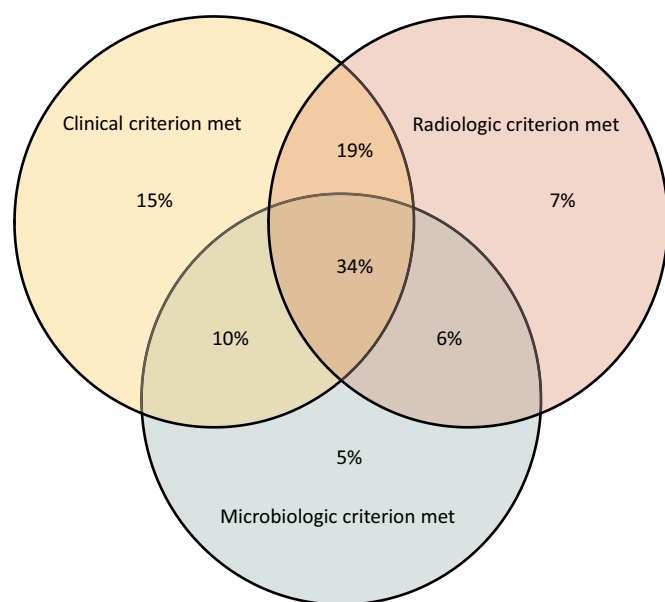


Fig. 1. Venn diagram demonstrating percentage of the cohort meeting the microbiologic, radiologic, and clinical criteria provided by the ATS/IDSA for diagnosis of pulmonary mycobacteria disease.

Table 2

NTM isolated from patients with a positive culture, positive pulmonary culture, and positive pulmonary culture(s) meeting ATS/IDSA criteria for lung disease.

	Number of patients with NTM isolate (%)	Number of patients with NTM pulmonary isolate (%)	Number of patients with NTM pulmonary isolate meeting ATS/IDSA criteria for infection (%)
Total	297	230	78
MAC	152 (51%)	119 (52%)	50 (64%)
<i>M. gordonae</i>	45 (15%)	40 (17%)	6 (8%)
<i>M. abscessus</i>	25 (8%)	21 (9%)	10 (13%)
<i>M. fortuitum</i>	17 (6%)	13 (6%)	2 (3%)
<i>M. mucogenicum</i>	16 (5%)	13 (6%)	4 (5%)
<i>M. chelonae</i>	10 (3%)	2 (<1%)	1 (1%)
<i>M. immunogenum</i>	10 (3%)	2 (<1%)	0
<i>M. massiliense</i>	7 (2%)	5 (2%)	3 (4%)
<i>M. kansasii</i>	1 (<1%)	1 (<1%)	1 (1%)
<i>M. lentiflavum</i>	1 (<1%)	1 (<1%)	0
<i>M. peregrinum</i>	1 (<1%)	1 (<1%)	0
<i>M. porcinum</i>	1 (<1%)	1 (<1%)	0
<i>M. saskatchewanense</i>	1 (<1%)	1 (<1%)	0
<i>M. scrofulaceum</i>	1 (<1%)	1 (<1%)	0
<i>M. terrae</i>	1 (<1%)	1 (<1%)	1 (1%)
Two mycobacteria	6 (2%)	6 (3%)	0
Not known	2 (<1%)	2 (<1%)	0

patient provided a sputum sample which grew *M. abscessus* and then had a lavage sample which also was positive for *M. abscessus*. Another patient grew *M. abscessus* from a sputum sample but later repeated sputum specimens grew MAC. There were 13 sputum isolates positive for *M. fortuitum*. Ten of these were single sputum samples only. Two of these patients had a positive second and/or third sputum and a lavage sample which grew *M. fortuitum*. Yet another patient had *M. fortuitum* isolated from the first sputum specimen while *M. terrae* grew from later samples. Isolates from sputum samples which never provided a positive repeat sample included *M. lentiflavum*, *M. peregrinum*, *M. porcinum*, *M. saskatchewanense*, and *M. scrofulaceum*. There were two sputum mycobacterial isolates which could not be speciated but a second sputum sample from the one of the patients grew *M. mucogenicum*. A large number of sputum cultures grew microorganisms other than the NTM

Table 3

Radiographic procedure among those patients with a positive pulmonary isolate.

Radiographic procedure	Meets ATS/IDSA radiologic criterion for infection	
	Yes	No
Chest X-ray	18	20
CT scan of the chest	145	81

reported. Finally, there were 29 lavage samples reported as positive for NTM. These included 20 for MAC, 6 for *M. abscessus*, and 3 for *M. gordonae*. Two lung biopsies, two samples of resected tissue, and an excised nodule were all positive for MAC.

In the cohort of 230 patients with positive pulmonary isolates, 38 had chest X-rays and 226 had CT scans of the chest during the initial evaluation. The total number of procedures exceeded 230 since several patients had a chest X-ray immediately followed by a CT scan of the chest. In this same cohort, 151 had chest X-rays and/or CT scans of the chest considered to meet the radiologic criterion provided by the ATS/IDSA for NTM lung disease. Almost all those patients considered to meet the recommendations for diagnosis of pulmonary disease had a CT scan of the chest (145 of 151) (Table 3). Bronchiectasis and bilateral small nodules were abnormal radiographic patterns observed on a few chest X-rays among those patients with positive pulmonary isolates meeting the ATS/IDSA radiographic criterion for lung infection (Table 4A). However, the most common abnormal radiographic pattern noted on the chest X-rays among those patients with positive pulmonary isolates was unilateral infiltrate/density/consolidation and this did not meet the ATS/IDSA criterion. Among those patients with positive pulmonary isolates meeting ATS/IDSA radiographic criterion for lung infection, the most common abnormal patterns observed on CT scan of the included small nodules, “tree-in-bud”, bronchiectasis, “ground glass opacity”, and cavity (Table 4B). A significant number of patients who did meet the ATS/IDSA microbiologic criterion for diagnosis of NTM lung disease did not meet the radiographic criterion (Fig. 1 and Table 5A). Similarly, a significant number of patients who met the radiographic criterion did not meet the microbiologic criterion (Fig. 1 and Table 5A).

In the cohort of 230 patients with a positive pulmonary isolate, 180 reported one or more pulmonary symptoms (cough, phlegm, hemoptysis, shortness of breath, and chest pain). The frequencies of individual symptoms are provided (Table 6). Of the 50 patients with no respiratory symptoms, 10 had systemic symptoms (fevers, night sweats, and weight loss). Asymptomatic individuals met both the microbiologic and radiologic criteria for pulmonary disease recommended by the ATS/IDSA (Fig. 1 and Table 5B and C respectively). Of the 78 patients who met the microbiologic and radiologic criteria and had pulmonary symptoms, all had other possible diagnoses excluded.

Regarding co-morbidity, bronchiectasis and history of pneumonia were reported in either the records or radiology reports by approximately 1 of 4 patients with positive pulmonary isolates (Table 7). Chronic obstructive pulmonary disease, cystic fibrosis, and asthma were also commonly reported among those with a positive pulmonary

Table 4A

Abnormal radiographic pattern observed on chest X-rays among those patients with a positive pulmonary isolate.

Abnormal radiographic patterns observed on chest X-rays	Number of patients
Unilateral infiltrate/density/consolidation	12
Bronchiectasis	11
Bilateral small nodules	7
Diffuse interstitial opacities	5
Bilateral opacity	1
Ground glass opacity (lobar)	1
Linear density	1

Table 4B

Abnormal radiographic pattern observed on CT scans among those patients with a positive pulmonary isolate.

Abnormal radiographic patterns observed on CT scans of the chest	
Nodules ± “tree-in-bud” ± bronchiectasis ± “ground glass opacity”	122
Nodules ± bronchiectasis ± situs inversus	2
Cavity ± bronchiectasis ± “ground glass opacity” ± fibrosis	21
Infiltrate/opacity/consolidation	41
Emphysema	8
Interstitial lung infiltrate ± “honeycombing”	5
Combined pulmonary fibrosis and emphysema	1
Solitary nodule	4
Lung mass(es)	4
Atelectasis	4
Granuloma(s)	1
Adenopathy and calcified lymph nodes	5
Pleural effusion(s)	7

Table 5A

Comparison of the ATS/IDSA microbiologic and radiologic criteria for lung infection among those patients with positive pulmonary culture.

	Microbiologic criterion met	
	Yes	No
Yes	92	59
Radiologic criterion met		
No	36	43

Table 5B

Comparison of the ATS/IDSA microbiologic and clinical criteria for lung infection among those patients with positive pulmonary culture.

	Microbiologic criterion met	
	Yes	No
Yes	102	78
Clinical criterion met		
No	26	24

Table 5C

Comparison of the ATS/IDSA radiologic and clinical criteria for lung infection among those patients with positive pulmonary culture.

	Radiologic criterion met	
	Yes	No
Yes	122	58
Clinical criterion met		
No	29	21

Table 6

Pulmonary symptoms.

	Positive isolate (n = 297)	Positive pulmonary isolate (n = 230)
Cough	184 (62%)	167 (73%)
Phlegm	134 (45%)	127 (55%)
Shortness of breath	89 (30%)	80 (35%)
Hemoptysis	24 (8%)	21 (9%)
Chest pain	21 (7%)	18 (8%)

isolate. Regarding non-respiratory co-morbidity, HIV-related disease was most frequently reported followed by diabetes. In the cohort of 230 positive pulmonary isolates, 159 had either chronic lung diseases (bronchiectasis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, and sarcoidosis) or HIV-related disease. While gastroesophageal reflux was observed frequently among those with pulmonary isolates, other gastrointestinal diseases (i.e. malabsorption,

Table 7

Co-morbidity and use of medications.

	Positive isolate (n = 297)	Positive pulmonary isolate (n = 230)
Bronchiectasis	64 (22%)	64 (28%)
History of pneumonia	53 (18%)	57 (25%)
Chronic obstructive pulmonary disease	41 (14%)	37 (16%)
Cystic fibrosis	32 (11%)	32 (14%)
Asthma	27 (9%)	25 (11%)
Sarcoidosis	2 (1%)	5 (2%)
HIV	53 (18%)	32 (14%)
Diabetes	29 (10%)	21 (9%)
Gastroesophageal reflux	27 (9%)	23 (10%)
Organ transplant	15 (5%)	9 (4%)
Corticosteroids	33 (11%)	25 (11%)
Biologic drugs	6 (2%)	5 (2%)

gastrectomy, hepatitis B, hepatitis C, and cirrhosis) were infrequently reported (<1, <1, 2, 3, and 2% respectively) (Table 7). Neoplastic disease and renal insufficiency were noted by 17 and 6% respectively in the same group. Cardiac co-morbidity included coronary artery disease (8%), heart failure (4%), and mitral valve prolapse (<1%). Connective tissue disease (rheumatoid arthritis, lupus, scleroderma, and mixed connective tissue disease) was uncommon in the cohort with a pulmonary isolate (3, 3, <1, and <1% respectively). Finally, 7%, 3%, and <1% of patients with a pulmonary isolate were diagnosed to also have scoliosis, kyphosis, and pectus excavatum respectively. Corticosteroid use was common among those with positive isolates and positive pulmonary isolates while monoclonal antibody biologic drugs were not (Table 7).

4. Discussion

In this case series, patients with pulmonary cultures positive for NTM represented 77% of all patients with isolates approximating results of prior studies but contrasting one recent investigation in France which showed that pulmonary isolates included only 54% of a cohort [6,11]. The mean age of patients with positive pulmonary isolates (i.e. 52 years) and that among those patients meeting the ATS/IDSA criteria for NTM lung disease (i.e. 55 years) were comparable to what has previously been reported [6,11]. Among those patients with pulmonary isolates, there was an equal number of males and females but in the cohort meeting the criteria for NTM lung infection, females predominated.

Applying the ATS/IDSA criteria, only about 1 out of 3 patients with a pulmonary isolate was diagnosed to have NTM lung disease. In our cohort, many cases who did meet the microbiologic criterion for lung disease did not meet the criteria for radiologic evidence and pulmonary symptoms of NTM lung disease. This investigation approximates other studies which observed that fifty-three of 212 (25%) and thirty-one of 132 patients (23.5%) with pulmonary isolates met the diagnostic criteria provided by the ATS/IDSA for NTM lung disease [12,13]. This is also comparable to the percentage of isolates (28%) among non-cystic fibrosis patients diagnosed with bronchiectasis meeting the same ATS/IDSA for NTM lung disease [14]. It similarly approaches the results of older studies which showed 25–33% pulmonary isolates meeting the 1997 ATS criteria for diagnosis of NTM lung disease [15–17]. Accordingly, this evaluation may reaffirm that defining NTM lung disease using either one or two of the criteria provided by the 2007 ATS/IDSA guidelines will significantly overestimate the number of cases of NTM lung disease [4,18,19]. It may not be possible to assume that patients undergoing sputum and/or bronchoscopic assessment are likely to have radiographic findings and pulmonary symptoms allowing a diagnosis of NTM lung disease; a lack of access to radiographic and clinical information precludes appropriate evaluation for NTM lung disease.

Conversely, the results of this investigation may demonstrate the limitations of the ATS/IDSA criteria for NTM lung disease. That is, a number of patients who really have disease may be asymptomatic on presentation and are detected due to incidental findings on imaging that lead to microbiologic sampling. Accordingly, the number of true cases of NTM lung disease may be underestimated by applying the 2007 ATS/IDSA criteria.

While prior investigations have demonstrated that MAC, *M. kansasii*, and *M. fortuitum* are the most frequent NTM isolated from pulmonary samples, MAC, *M. gordonae*, *M. abscessus*, *M. fortuitum*, and *M. mucogenicum* were most frequently isolated in pulmonary samples in this case series while MAC and *M. abscessus* were the NTM associated with the greatest number of lung infections [6,19]. While its participation in NTM lung disease has been contested, the number of pulmonary isolates of *M. gordonae* in this case series is comparable to a recent survey of the global distribution of NTM which observed this species to be second only to MAC in prevalence [20].

Almost every patient in this cohort with a positive pulmonary isolate for NTM had a CT scan of the chest. This provides additional evidence that the CT scan is most frequently employed to meet the radiographic criterion included in the diagnosis of NTM lung disease [21]. CT imaging is significantly more sensitive than the chest X-ray and is currently the standard in the evaluation of suspected NTM lung disease [6]. Comparable to other investigation, the most common CT findings of NTM lung disease in this study included small nodules, a “tree-in-bud” pattern, bronchiectasis, and “ground glass opacity” [22–24]. The classic fibrocavitary appearance was observed infrequently comparable to other studies in which cavities have been reported in as few as 13% of patients fulfilling ATS criteria for NTM infection [8]. There are radiographic patterns of possible NTM lung injury observed on both the chest X-ray and the CT scan of the chest which currently are not included in the radiographic criterion recommended by the ATS/IDSA guidelines. There were numerous patients in this study who presented with radiological descriptions of infiltrates, air space disease, ground glass opacity, consolidation, and solitary nodules. Such infiltrates, ground-glass opacities, and consolidation were also observed frequently in mycobacterial infections in other studies [22–29]; these findings may occur with higher incidence among patients infected with the human immunodeficiency virus infection and with interstitial lung disease [25,30]. While consolidation has been observed with cases of bronchiectasis, it can also be observed in a segmental, subsegmental, or lobar distribution without evidence of bronchiectasis [31–33]. Infiltrates, opacity, and/or consolidation can be associated with the development of cavitary lung disease (e.g. abscesses and aspiration-related lung diseases) and specifically could precede the cavitary form of NTM lung disease [34,35]. In contrast, solitary nodule was infrequent in our cohort but NTM infections can manifest in such nodules [25,36]. Based on observations in this study, infiltrates, opacities, consolidation, and solitary nodules should be considered as potential evidence supporting the radiographic criterion for NTM lung disease.

In this case series of patients with pulmonary NTM isolates, it was somewhat surprising that pulmonary symptoms could not be found among some who otherwise met all criteria for the diagnosis of NTM lung disease. It is anticipated that the absence of pulmonary symptoms may reflect the retrospective approach used (e.g. a lack of documentation) rather than a true asymptomatic state. In other studies, the ATS/IDSA criteria have been modified to suggest ‘possible disease’ in those patients meeting microbiologic criteria with abnormal CT scans but without data regarding pulmonary symptoms [37]. However, there is a consensus that the microbiologic, radiologic, and clinical criteria should be considered equally important. The results of this case series suggest that the requirement for pulmonary symptoms provided by the ATS/IDSA for the diagnosis of NTM lung disease might include non-respiratory symptoms such as fevers, chills, and night sweats.

The current clinical criterion for the diagnosis of NTM lung disease also requires appropriate exclusion of other diagnoses. This demands an

integration of the microbiologic, radiographic, and the presence of pulmonary symptoms and then determination of any potential relationships with alternative diagnoses. Accordingly, the criteria for diagnosis of NTM lung disease provided by the ATS/IDSA must be approached sequentially by first addressing the microbiologic and radiologic criteria and the presence of pulmonary symptoms followed by excluding other diagnoses. It may be more efficient to reorganize the criteria for diagnosis of NTM lung disease to include four distinct requirements: 1) microbiologic, 2) radiographic, 3) pulmonary symptoms, and 4) exclusion of other diagnoses.

The co-morbidities reported in this study support previous recognized associations of NTM lung disease with underlying lung disease (i.e. chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis) and human immunodeficiency virus-related disease [6]. An increased prevalence of NTM lung disease with pneumoconiosis and pulmonary alveolar proteinosis was not observed because of the small number of patients with such disease. NTM has a high prevalence among individuals diagnosed with cystic fibrosis in the United States, with one in five affected and was a major co-morbidity among the patients in our cohort [38]. While pre-existing lung diseases are the main risk factors for NTM lung disease, there were patients who met the ATS/IDSA criteria but had no underlying lung disease (possibly 5% to 33%) [12,39,40]. Contrary to prior studies, few classic cases of NTM lung disease were observed among those with an unusual body habitus such as scoliosis, kyphosis, and pectus excavatum [41]. While 7%, 3%, and <1% of patients with a pulmonary isolate in this investigation were considered to also have scoliosis, kyphosis, and pectus excavatum respectively, these structural variations can be observed in approximately the same prevalence, or greater, in the general population [42–44].

There are limitations of this study with the major one being a retrospective approach. Data was absent for very few patients but clinic notes may not have accurately documented respiratory symptoms. In addition, this study was conducted at a single university medical center and subsequently has a small population size. Small numbers limited analyses for associations between a specific mycobacteria, radiologic findings, and pulmonary symptoms. Finally, CT images used in this study were not high resolution because the study was retrospective.

We conclude that a small number of patients (33.9%) with pulmonary NTM isolates can be diagnosed to have NTM lung disease using the ATS/IDSA guidelines. Significant percentages of cases failed to meet each of the microbiologic, radiologic, and clinical criteria. Defining NTM lung disease using either one or two of the criteria provided by the 2007 ATS/IDSA guidelines may significantly overestimate the number of cases of NTM lung disease.

Adherence to the ATS/IDSA guidelines has previously been demonstrated to be incomplete and current medical practice for diagnosis of NTM lung disease can disregard them at times in favor of personal clinical experience [13]. This impacts diagnosis, as well as treatment and prognosis, of patients with NTM lung disease. The reluctance to use the ATS/IDSA guidelines could possibly reflect the difficulty of meeting specific criteria.

Future guidelines might consider modification of the radiographic and clinical criteria to accept 1) infiltrates, opacities, consolidation, and solitary nodules on chest X-rays and CT scans and 2) systemic symptoms of fevers, chills, and night sweats as support for the diagnosis of NTM lung disease.

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Ethical statement

The protocol for the collection of all data was approved by the

University of North Carolina School of Medicine Committee on the Protection of the Rights of Human Subjects.

Declaration of Competing Interest

None declared.

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