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Nontuberculous Mycobacterial Lung Infections in Ontario, Canada: Clinical and Microbiological Characteristics

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Abstract *Study Objectives* The aim of this study was to determine gender and clinical phenotype frequencies in pulmonary nontuberculous mycobacterial (NTM) infection and the frequency of disease in NTM isolates. *Design* The study is a retrospective observational cohort study of two overlapping cohorts: population cohort and clinical cohort. *Setting* The study was conducted at the University Health Network and Ontario Mycobacteriology Laboratory in Toronto, Ontario, Canada. *Patients or Participants* The population cohort consisted of all patients with one or more pulmonary NTM isolates in Ontario in 2003. The clinical cohort consisted of all patients with one or more pulmonary NTM isolates at our hospital in 2002–2003. *Interventions* The study entailed the review of laboratory records and demographics (both cohorts) and detailed clinical records (clinical cohort). *Measurements and Results* In the population cohort ($N = 1651$), females comprised 48% overall and 51% with microbiological disease criteria. In the clinical cohort ($N = 552$), females comprised 48% overall and 55% with NTM disease. In the population cohort, 45% fulfilled microbiological disease criteria, and in the clinical cohort 46% of patients had disease. Patients with MAC isolates fulfilled microbiological disease criteria in 51% of population cohort cases and all disease criteria in 52% of clinical cohort cases. Women more commonly fulfilled microbiological disease criteria in the population cohort (51 vs. 45%, $P = 0.02$) and all disease criteria in the clinical cohort (53 vs. 40%, $P = 0.03$). Among clinical cohort patients, 26% (13 women, 44 men) had fibrocavitation, while 62% (101 women, 37 men) had nodular bronchiectasis. *Conclusions* Women comprised a small majority with disease. Nodular bronchiectasis in women was most common, but significant proportions of each gender with each radiographic type were observed. NTM isolation, particularly MAC, was frequently associated with disease.

Keywords Epidemiology · Mycobacterial infections · Atypical · Mycobacteria · Atypical · Sex

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Introduction

Pulmonary nontuberculous mycobacterial (NTM) infection is an increasingly common [1] and challenging clinical problem. Isolation of pulmonary NTM does not necessarily indicate advanced infection or "disease," since NTM may be present in respiratory tract secretions without obvious illness ("colonization") or may sometimes contaminate clinical specimens [2]. Disease is usually defined by the

presence of repeated isolation, clinical illness, and consistent radiographic changes [2]. Treatment is generally considered only when there is disease, and it usually comprises prolonged multidrug therapy. In the setting of colonization, treatment is often withheld because of its potential toxicities and the uncertain potential for progression.

Historically, pulmonary NTM disease has been described in two settings: with underlying lung disease, classically emphysema, with predominantly upper-lobe cavitary/"fibrocavitary" NTM disease in middle-aged men; or without underlying lung disease, with predominantly middle lobe/lingula "nodular bronchiectasis" in elderly women. It was stated that the former group (middle-aged men) previously comprised the majority of patients with pulmonary NTM, with a recent emergence of the latter group (elderly women) [2]. The American Thoracic Society (ATS) guidelines regarding NTM disease state that there is currently a postmenopausal female patient predominance for *Mycobacterium avium* complex (MAC) lung disease [2], referencing two studies, both of which excluded patients with predisposing lung disease [3, 4]. The selection bias in these two studies precludes their use in understanding the relative frequency of the two patient types. The relative frequency by gender and clinical disease type in pulmonary NTM is unknown. We performed a mixed population-based and selected retrospective cohort study of pulmonary NTM in Ontario, Canada, to determine the gender and clinical characteristics of unselected patients with pulmonary NTM infection.

Study Population and Methods

We retrospectively identified all patients with pulmonary NTM isolates in Ontario, Canada, during 2002 and 2003, from the records of the TB and Mycobacteriology Laboratory of the Public Health Laboratory in Toronto (PHL TB laboratory), where more than 95% of NTM isolates in Ontario (2003 population of 12.2 million) are identified. Specimen culture was performed using the BACTEC MGIT 960 system (Becton Dickinson Microbiology Systems, Sparks, MD, USA). Specimens were processed and analyzed as described by Hanna et al. [5]. NTM cultures were speciated by DNA probes (AccuProbe, Gen-Probe, San Diego, CA, USA) for *M. avium* complex (MAC) and *M. gordonae*, and by HPLC for other species [6]. Identification of species within MAC was not performed.

We studied two overlapping cohorts, each a subset of all patients (Fig. 1). The population cohort comprised essentially every person in Ontario with one or more pulmonary NTM isolates in 2003. For population cohort patients, we had data regarding microbiology, age, and gender only. The clinical cohort comprised all patients with one or more pulmonary NTM isolates in 2002–2003 and a record at our hospital (University Health Network, Toronto) with enough detail to permit classification according to the presence of NTM disease. For clinical cohort patients, the patient record was used to classify patients according to ATS criteria for NTM disease ($\geq$2 sputum cultures or $\geq$1 bronchoscopy culture positive and consistent radiographic findings or clinical symptoms) [2]. In addition, smoking, prior lung disease, malignancy, immune suppression, and type of NTM imaging abnormalities were reviewed for clinical cohort patients. Clinical cohort patients with disease were classified by dominant radiographic abnormality, i.e., nodular bronchiectasis (centrilobular nodules and/or bronchiectasis) versus fibrocavitation (cavitation). Clinical records were reviewed in duplicate and original images were reviewed if written reports were inadequate for classification. Complete microbiological data were available for all patients (both cohorts) from the laboratory. We excluded patients with only *M. gordonae* isolation because it is a common contaminant [7] and rarely causes disease [2]. There is significant overlap between the two cohorts (Fig. 1). We used this design for a true population-based assessment of age and gender distribution (population cohort) and to identify NTM disease and clinical phenotype (clinical cohort). To increase the size of the clinical cohort, a 2-year study period was used.

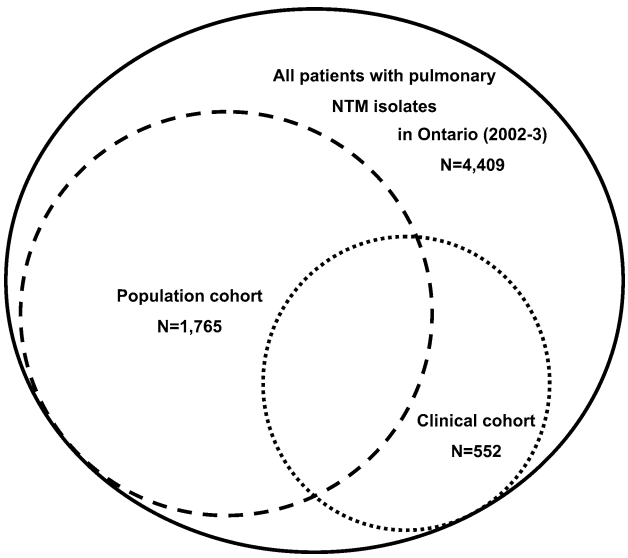

Fig. 1 Venn diagram representing the study cohorts: *Solid line* bounds all patients with at least one pulmonary NTM isolate in the province of Ontario in 2002 or 2003; *Dashed line* bounds the "population cohort": all patients with at least one pulmonary NTM isolate in the province of Ontario in 2003. *Dotted line* bounds the "clinical cohort": all patients with at least one pulmonary NTM isolate in the province of Ontario in 2002 or 2003 and a record at our clinical institution with adequate detail to classify according to NTM disease

Gender and age distributions of the cohorts were compared by inspection or proportions and medians (quartiles), respectively. No statistical comparisons were made because the cohorts overlapped. Additional clinical characteristics in the clinical cohort were also reviewed. Comparisons between groups within a cohort were performed using Yates-corrected χ^2 tests, or Wilcoxon rank-sum tests for age comparisons. Data were managed using Microsoft® Access 2000 (Redmond, WA, USA) and statistical analyses was performed with SAS® version 8.02 (SAS Institute, Cary, NC, USA) and Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA). This study was approved by our institutional review board.

Results

Population Cohort

Gender and age were available for 1651 (94%) and 1654 (94%), respectively, of the 1765 patients in the population cohort. Females comprised 48% (793/1651), and the median (quartiles) age was 67 (51–77) years for all patients. Women were slightly older [68 (43–78) vs. 66 (48–77) years, $P = 0.01$]. Overall, 46% (813/1765) met the ATS microbiological criteria. Women more commonly met the microbiological criteria (51 vs. 45%, $P = 0.02$). Patients who fulfilled microbiological criteria had a higher median age [69 (55–78) vs. 65 (57–76) years, $P < 0.0001$]. Selected characteristics are presented in Table 1. The age distribution of the entire cohort and of patients who met microbiological criteria is presented in Fig. 2. MAC was isolated in 58% of people, *M. xenopi* in 27%, and other species in less than 10%. ATS microbiological criteria were fulfilled more frequently with MAC than with *M. xenopi* [52% (532/1033) vs. 40% (189/475), $P < 0.0001$].

Characteristics of population cohort patients with the most common NTM species are summarized in Table 2. Patients with MAC tended to be oldest [69 (52–78) years], and patients with *M. fortuitum* tended to be youngest [63 (45–74) years]. Patients with MAC most often fulfilled the ATS microbiological criteria, while patients with *M. fortuitum* least often did so (51 vs. 28%, $P < 0.0001$). Women were overrepresented among patients who fulfilled the ATS microbiological criteria, except with *M. xenopi*, where men comprised the majority overall and were slightly more likely to meet the ATS microbiological criteria than were women.

Clinical Cohort

The clinical cohort comprised 552 patients (48% female). The median age was 67 (53.5–77) years for all patients, without significant difference between genders. Patient characteristics are presented in Table 1, age distributions of the entire cohort and patients with disease are presented in Fig. 2, and the ATS diagnostic criteria are presented in Table 3. The ATS disease criteria were fulfilled in 46%, with women more frequently fulfilling the criteria than men (52 vs. 41%, $P = 0.01$). MAC was isolated in 62% of patients, *M. xenopi* in 27%, and other species in less than 10%. The ATS disease criteria were more frequently fulfilled with MAC than with *M. xenopi* (52 vs. 36%, $P = 0.001$). Women with MAC met the ATS disease criteria more often than men (57 vs. 46%, $P = 0.04$), but this was not apparent with *M. xenopi* (38% of women vs. 34% of men fulfilled disease criteria, $P = 0.71$).

Among patients with NTM disease, the median age was 68 (56–78) years, 55% were female, 56% had underlying lung disease, and most had smoked (55% prior and 13% current, Table 4). Overt immune deficiency was present in 15%. Nodular bronchiectasis was identified in 62% (138/221), and fibrocavitation was identified in 26% (57/221). There was no difference in age between men and women with NTM disease. However, fewer women had underlying lung disease (41 vs. 75%, $P < 0.001$), a history of smoking (50 vs. 87%, $P < 0.001$), or overt immune suppression (9 vs. 23%, $P = 0.02$). Nodular bronchiectasis (versus fibrocavitation) was dominant in women [80% (101/127) vs. 10% (13/127)], but was less common in men [39% (37/94) vs. 47% (44/94), P value by gender <0.001]. Among the 91 patients with NTM disease without underlying lung disease or predisposing conditions, 67 (74%) were women and 24 (26%) were men.

Patients with MAC tended to be slightly older [68 (56–78) vs. 64 (52–78) years, $P = 0.34$], female [59% (104/177) vs. 46% (25/54), $P = 0.06$], and less likely to have underlying structural lung disease [51% (73/143) vs. 68% (32/47), $P = 0.06$] than patients with *M. xenopi* (Table 5). Nodular bronchiectasis (versus fibrocavitation) was seen most often in MAC disease [71% (115/162) vs. 18% (29/162)] compared with *M. xenopi* disease [34% (16/47) vs. 43% (20/47), P value by species <0.001].

Population Versus Clinical Cohort

There are no important differences regarding gender (48% females in both), age (median = 67 years in both), and proportions of MAC and *M. xenopi* between the population and clinical cohorts. The population cohort had a smaller proportion of patients who fulfilled the ATS microbiological criteria than the clinical cohort (46 vs. 63%) and a smaller proportion with one or more acid-fast-positive specimens (17 vs. 28%). There is a fairly even division between men and women within all

Table 1 Comparative characteristics of subgroups of patients with pulmonary NTM isolates in Ontario, 2002–2003

	Population cohort[a]		Clinical cohort[b]	
	Entire cohort ($N = 1765$)	Meeting ATS microbiological criteria[c] ($N = 813$)	Entire cohort ($N = 552$)	Meeting ATS disease criteria[d] ($N = 255$)
Female gender	48% (793/1651)	51% (401/785)	48% (267/552)	55% (139/255)
Age (years) [median (quartiles)]	67 (51, 77)	69 (55, 78)	67 (53.5, 77)	68 (56, 78)
ATS criteria				
Microbiological[c]	46% (813/1,765)	100%	63% (349/552)	100%
Disease[d]	Unknown	Unknown	46% (255/552)	100%
NTM species				
MAC	58% (1033/1765)	65% (532/813)	62% (340/552)	69% (177/255)
M. xenopi	27% (475/1765)	23% (189/813)	27% (150/552)	21% (54/255)
Number positive cultures [median (quartiles)]	1 (1, 2)	2 (1, 3)	2 (1, 3)	3 (2, 6)
People with ≥1 positive acid-fast smear	17% (305/1765)	31% (251/813)	25% (137/552)	45% (114/255)

ATS American Thoracic Society, *MAC Mycobacterium avium* complex, *NTM* nontuberculous mycobacteria

[a] Population cohort consists of patients who had at least one pulmonary NTM isolate in 2003 in the province of Ontario

[b] Clinical cohort consists of patients who had at least one pulmonary NTM isolate in 2002–2003 in the province of Ontario and a record at our clinical institution (University Health Network—UHN) that was adequately detailed to allow classification according to the ATS NTM disease criteria

[c] At least two positive sputum cultures or ≥1 bronchoscopy culture positive, or a positive biopsy with a single positive sputum culture

[d] At least 2 sputum cultures or ≥1 bronchoscopy culture positive and consistent radiographic findings or clinical symptoms

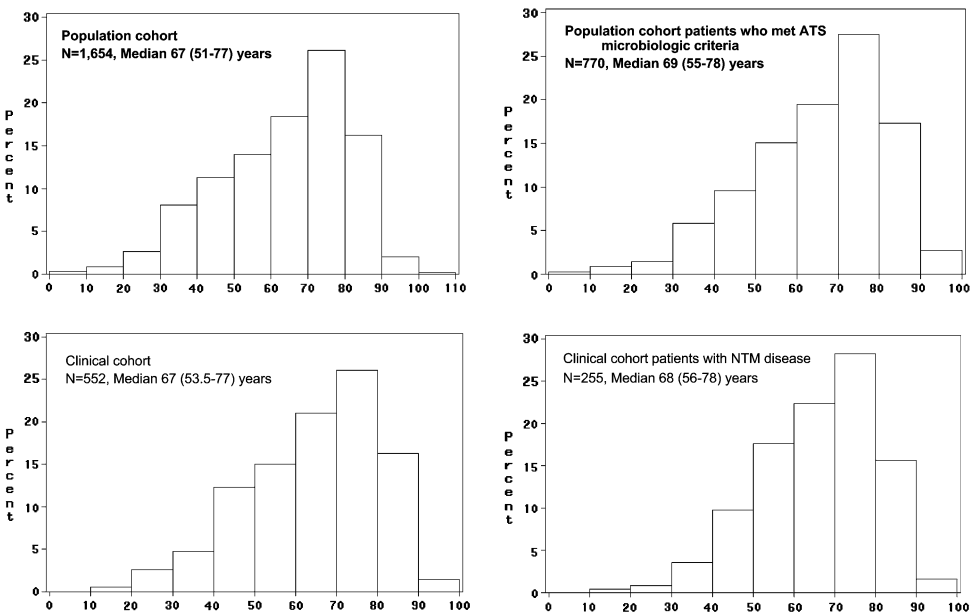

Fig. 2 Age distribution histograms: The majority of patients are older than 65 years of age in all groups. Age was known for 1654 of 1765 patients in the population cohort

groups, except in clinical cohort patients with NTM disease (55% female compared with 48–51% female in other groups).

There are many important similarities between the population and clinical cohorts. First, the median age is similar in all groups, ranging from 67 to 69 years, with a similar spread. Second, patients who fulfilled the microbiological criteria tended to be older. Third, there are higher proportions of patients with MAC in subgroups fulfilling the NTM diagnostic criteria. In the population cohort, 51% with MAC versus 39% with *M. xenopi* fulfilled the microbiological criteria ($P < 0.0001$). Similarly, in the clinical cohort, 52% with MAC versus 36% with *M. xenopi* fulfilled disease criteria ($P < 0.001$).

Table 2 Age, gender, and microbiological characteristics of patients with pulmonary NTM isolates in Ontario, 2003

Characteristic	All species ($N = 1765$)	MAC ($N = 1033$)	*M. xenopi* ($N = 475$)	*M. fortuitum* ($N = 117$)
Age [median (quartiles)]				
All	67 (51, 77)	69 (52, 78)	66 (52, 76)	63 (45, 74)
Microbiological criteria met	69 (55, 78)	69.5 (56, 79)	67.5 (55, 76)	65 (48, 74)
Microbiological criteria not met	65 (47, 76)	68 (46, 77)	65 (47, 76)	61 (43, 75)
P value for difference*	<0.0001	0.001	0.07	0.55
Female/Male				
Overall	48%/52%	52%/48%	42%/58%	38%/62%
Microbiological criteria met	51%/49%	55%/45%	40%/60%	50%/50%
Microbiological criteria not met	45%/55%	48%/52%	43%/57%	32%/68%
P value for difference**	0.026	0.039	0.64	0.13
Number positive cultures [median (quartiles)]	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 1)
Patients with ≥1 AFB-positive specimen	17%	23%	11%	8%
Patients meeting microbiological criteria	46%	51%	40%	28%

Microbiological criteria refer to the American Thoracic Society guidelines for determining the presence of pulmonary NTM disease

* Wilcoxon rank-sum test assessing difference in age depending on fulfillment of microbiological disease criteria

** Yates-corrected χ^2 test compares gender by fulfillment of microbiological criteria

Table 3 ATS diagnostic criteria for pulmonary NTM disease in clinical cohort patients

Criterion	Total ($N = 552$)	Women ($N = 267$)	Men ($N = 285$)	*P*
Clinical	68% (213/313)	76% (127/168)	59% (86/145)	0.003
Radiologic	69% (355/516)	75% (185/247)	63% (170/269)	0.006
Microbiological	63% (349/552)	66% (176/267)	61% (173/285)	0.24
Disease[b]	46% (255/552)	52% (139/267)	41% (116/285)	0.01

ATS American Thoracic Society, *NTM* nontuberculous mycobacteria

Clinical cohort consists of patients who had at least one pulmonary NTM isolate in 2002–2003 in the province of Ontario and also had a record at our clinical institution (University Health Network—UHN)

[b] At least 2 sputum cultures or ≥1 bronchoscopy culture positive and consistent radiographic findings or clinical symptoms

Discussion

In our large population-based assessment of age and gender in pulmonary NTM isolates (population cohort), pulmonary NTM isolates occurred in the elderly, with a slight majority of men. In our clinical cohort, we also observed a slight male majority overall, but females comprised a slight majority with NTM disease. The gender distribution with respect to pulmonary NTM infection is controversial. Studies that have suggested an overwhelming female predominance in NTM disease have generally been restricted to patients without underlying lung disease or immune suppression [3, 4, 8]. Given the geographic heterogeneity in NTM disease, it is worth considering international literature divided by region. From North American population-based studies, one can calculate a weighted mean of 37% female for patients with all NTM species and 38% female when restricted to MAC [9–12]. Because women more often have nodular bronchiectasis [more difficult to detect on chest X-ray (CXR) than cavitary disease], we also consider only the most recent North American study during which CT scanning would have been more widely utilized (1993–1996) [12]. This study similarly observed that 37% of patients were female. Interestingly, North American studies from single institutions (from 1960 to 2003) had different results, with 47% females overall, and 64% were females specifically for MAC [3, 13–18]. Finally, a truly population-based study for the state of Oregon in 2005–2006 used microbiological criteria exclusively for the diagnosis of NTM disease [19]. Patients were classified as having disease if they fulfilled the ATS microbiological criterion for disease, and although this methodology has not been extensively validated, the results bear striking similarity to our own. The gender ratio for any pulmonary NTM isolate was not presented, but of patients who fulfilled microbiological criteria, women comprised a small majority (58%) in Oregon, compared with 51% in our population cohort. The gender ratio among all patients in North America with pulmonary NTM disease is not clear from published literature.

Table 4 Clinical cohort patients who met ATS disease criteria described by gender

Characteristic	Clinical cohort[a] patients by gender			
	All ($N = 255$)	Female ($N = 139$)	Male ($N = 116$)	P value*
Age	68 (56, 78)	68 (57, 77)	69 (54, 78)	0.94
Prior lung disease[b]	56% (118/209)	41% (47/114)	75% (71/95)	<0.001
COPD	39% (83/215)	24% (27/114)	55% (56/101)	<0.001
Prior TB	17% (29/170)	19% (18/97)	15% (11/73)	0.69
Lung cancer	5% (9/182)	5% (5/101)	5% (4/81)	1
Smoking				<0.001**
Never	32% (45/141)	49% (39/79)	13% (6/62)	
Previous	55% (78/141)	44% (35/79)	72% (43/62)	
Current	13% (18/141)	6% (5/79)	15% (13/62)	
Asthma	15% (26/175)	20% (20/98)	8% (6/77)	0.03
GERD	11% (19/173)	11% (11/96)	10% (8/77)	0.98
Any cancer	19% (35/183)	20% (20/102)	19% (15/81)	1
Immune deficient	15% (31/204)	9% (11/116)	23% (20/88)	0.02
HIV	4% (8/204)	0% (0/116)	9% (8/88)	
Lung transplant	5% (11/204)	3% (3/116)	9% (8/8)	
Stem cell transplant	1% (2/204)	1% (1/116)	1% (1/88)	
Other	5% (10/204)	6% (7/116)	3% (3/88)	
Radiologic classification[c]				<0.001
Nodular bronchiectasis	62% (138/221)	80% (101/127)	39% (37/94)	
Fibrocavitation	26% (57/221)	10% (13/127)	47% (44/94)	
Neither	12% (26/221)	10% (13/127)	14% (13/94)	

ATS American Thoracic Society, *COPD* chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease

ATS disease criteria are two or more sputum cultures or one or more bronchoscopy culture positive and consistent radiographic findings or clinical symptoms

[a] Clinical cohort consists of patients who had at least one pulmonary NTM isolate in 2002–2003 in the province of Ontario and a record at our clinical institution (University Health Network—UHN)

[b] Likely causes of structural lung disease, including COPD, prior TB, lung cancer, or other clinically important abnormalities

[c] Nodular bronchiectasis is defined as the presence of centrilobular nodules and/or bronchiectasis, without dominant cavitation. Fibrocavitation is defined as the presence of dominant cavitation. Most cases that were neither nodular bronchiectatic nor fibrocavitary were discrete nodular (noncentrilobular) and/or infiltrative

* P value for comparison according to gender

** Never versus ever smoked

A Welsh population-based study conducted before 1985 included all NTM species and reported 9% females [20], while recent studies from Greece and the Netherlands (from 1999 to 2006) report 30% females [21, 22]. Studies that focused on non-MAC single species (especially *M. kansasii* and *M. xenopi*) [23–27] generally reported a far lower female proportion. A sentinel-site study from France, including all common NTM species, reported a proportion of 45% female overall, with 60% of patients with MAC disease being female [28]. The recent European literature therefore also varies by study design and presents a slightly lower a fraction of female patients with NTM disease than the North American literature.

Population-based studies from East Asia have reported an average of 10% females overall [29, 30], and the one study that reported on MAC separately found a 40% female rate in this subgroup [29]. Two single-institution studies from East Asia have reported on gender ratios in patients with all NTM (53% female) [31, 32] and with MAC (70% female) [31, 33], the latter results driven overwhelmingly by one large study [33]. Therefore, East Asian studies have also presented discrepant results, with females in the minority in population-based studies and in the majority in single-institution studies. One population-based study in each of Australia and New Zealand reported gender frequency among patients with all NTM species, and 34% [34] and 81% [35], respectively, were females.

In general, it appears that in single-institution studies there is generally a higher proportion of females than in population-based studies. Furthermore, females appeared

Table 5 Clinical cohort patients who met ATS disease criteria described by NTM species

Characteristic	NTM species			
	Any ($N = 255$)	MAC ($N = 177$)	*M. xenopi* ($N = 54$)	*P* value*
Age	68 (56, 78)	68 (56, 78)	64 (52, 78)	0.34
Females	55% (139/255)	59% (104/177)	46% (25/54)	0.06
Prior lung disease[a]	56% (118/209)	51% (73/143)	68% (32/47)	0.06
COPD	39% (83/215)	34% (50/147)	52% (25/48)	0.04
Prior TB	17% (29/170)	15% (18/118)	19% (7/37)	0.79
Lung cancer	5% (9/182)	5% (6/125)	5% (2/40)	1
Smoking				0.30**
Never	32% (45/141)	36% (34/94)	24% (8/33)	
Previous	55% (78/141)	51% (48/94)	64% (21/33)	
Current	13% (18/141)	13% (12/94)	14% (4/33)	
Asthma	15% (26/175)	12% (15/121)	24% (9/38)	0.15
GERD	11% (19/173)	12% (14/119)	5% (2/38)	0.53
Any cancer	19% (35/183)	18% (23/125)	24% (10/41)	0.54
Immune deficient	15% (31/204)	15% (21/143)	11% (5/45)	0.72
HIV	4% (8/204)	4% (6/143)	4% (2/45)	
Lung transplant	5% (11/204)	5% (7/143)	0% (0/45)	
Stem cell transplant	1% (2/204)	1% (2/143)	0% (0/45)	
Other	5% (10/204)	4% (6/143)	7% (3/45)	
Radiologic classification[b]				<0.001
Nodular bronchiectasis	62% (138/221)	71% (115/162)	34% (16/47)	
Fibrocavitation	26% (57/221)	18% (29/162)	43% (20/47)	
Neither	12% (26/221)	11% (18/162)	23% (11/47)	

ATS American Thoracic Society, *NTM* nontuberculous mycobacteria, *MAC Mycobacterium avium* complex, *COPD* chronic obstructive pulmonary disease, *GERD* gastroesophageal reflux disease

Clinical cohort consists of patients who had at least one pulmonary NTM isolate in 2002–2003 in the province of Ontario and a record at our clinical institution (University Health Network—UHN)

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[a] Likely causes of structural lung disease, including COPD, prior TB, lung cancer, or other clinically important abnormalities

[b] Nodular bronchiectasis is defined as the presence of centrilobular nodules and/or bronchiectasis, without dominant cavitation. Fibrocavitation is defined as the presence of dominant cavitation. Most cases that were neither nodular bronchiectatic nor fibrocavitary were discrete nodular (noncentrilobular) and/or infiltrative

* *P* value for comparison according to species (MAC vs. *M. xenopi*)

** Never versus ever smoked

to be in the minority in most studies but represented a greater proportion or a majority in subgroups with MAC. We hypothesize that clinical institution-based studies may have access to more detailed clinical data and may more accurately classify patients according to the presence of significant disease by removing less sick patients. This is consistent with our own observations that males comprise the majority with NTM isolates (but are more often "colonized"), while women are more likely to experience NTM "disease" and may comprise the majority with disease, especially in the case of MAC. This hypothesis is consistent with skin test data showing that men were more likely to have been sensitized to MAC [36]. Also, women appear to comprise the vast majority of patients with idiopathic pulmonary NTM (without underlying lung disease or identifiable predisposition). The precise fraction of men and women among patients with idiopathic pulmonary NTM is not clear. Reports have ranged from as high as 94% women in a specialty NTM clinic [4] to as low as 74% in our institution-based clinical cohort.

Eighty-eight percent of patients could be classified according to radiologic nodular bronchiectasis or fibrocavitation. The majority (62%) had nodular bronchiectasis and 73% of these patients were women. A minority (26%) had fibrocavitation and 77% of these patients were men. Although women generally had nodular bronchiectasis and

men generally had fibrocavitation, 10% of women had fibrocavitation and 39% of men had nodular bronchiectasis. In a prior series on pulmonary NTM disease, 6/29 patients (21%) were found to have pulmonary MAC disease of predominantly the right middle lobe (RML) and lingula in the absence of prior lung disease or other predisposition [37]. All six patients were women, were 45-72 years old, and likely had nodular bronchiectasis. In the present study, 32% had predominantly RML/lingula disease without prior lung disease or predispositions, supporting the notion that patients with idiopathic pulmonary NTM with RML/lingula disease make up a sizable proportion of NTM patients. We further observed that 14% of patients with idiopathic RML/lingula NTM disease were men, which has not previously been described. This should alert clinicians to the presence of this small but distinct group.

Aside that for *M. kansasii*, there are limited population-based data regarding radiologic type of NTM lung disease. In a population-based study in Manitoba, Canada, 10 non-HIV patients with pulmonary NTM disease not due to *M. kansasii* were identified over a 3-year period, wherein 20% (2/10) had radiographic cavities [38]. In a population-based study done in 1960 in British Columbia, Canada, among 16 patients with Runyon group 2–4 (presumed non-*M. kansasii*), 25% had cavities [39]. A single-institution study done in Orange County, California, USA, between 1971 and 1981, reviewed 15 MAC patients, 14 with cavities [16]. In a health maintenance organization study performed in the northwest U.S. from 1975 to 1986, 29 MAC patients were identified and 38% (11/29) had cavities [17]. Although there was no description of a nodular bronchiectatic phenotype, 21% (6/29) had isolated middle lobe/lingula disease. In a study conducted at two hospitals in Philadelphia between 1978 and 1987, among 21 non-HIV infected patients with MAC without identifiable predispositions, 24% had cavities [3]. The limited North American literature suggests that the minority of patients with pulmonary NTM disease have a cavitary type, but there are very few data that classify patients with respect to the presence of nodular bronchiectasis.

In a hospital-based comprehensive review of all 53 patients with NTM disease in a region in the Netherlands, fibrocavitation (53%, 28/53) was more common than nodular bronchiectasis [22]. However, radiologic assessments were generally limited to CXR (CT was done infrequently), so accurate assessment of the fractions of nodular bronchiectasis and fibrocavitation could not be made. The authors wondered if their sample was biased in that the cases of nodular bronchiectasis that typically may be milder are less likely referred to hospitals and therefore are more often missed in their study. Population-based studies of *M. xenopi* have suggested relatively high rates of CXR cavitation, including 48% (12/25) in the Netherlands [26] and 74% (17/24) in Croatia [27]. In a consecutive series of patients with MAC disease from England and Wales in the 1960 s, 35% (23/65) had cavities on CXR [40]. A sentinel-site study from France, which included all common NTM species, reported cavitation in 12% (25/207), nodules in 25% (52/207), "infiltrates" in 36% (72/207), and "nonspecific" findings in 34% (70/207) among patients with disease due to species other than *M. kansasii* [28]. The European literature suggests that the majority of patients with pulmonary NTM disease probably do not have cavitary disease, but the studies are heterogeneous.

In Taiwan, among 11 consecutive patients with disease not due to *M. kansasii*, CXR revealed cavitation in two patients (18%) [31]. In a consecutive series of 195 patients at a single institution in South Korea, 52% had nodular bronchiectasis, 42% had upper-lobe cavities, and 6% had unclassifiable abnormalities [32]. In a similarly designed series of 273 patients in Japan, 60% had nodular bronchiectasis and 40% had cavitary-type disease [33]. East Asian studies therefore report a majority of nodular bronchiectasis in pulmonary NTM. A population-based study in North Australia between 1989 and 1997 reported that most pulmonary NTM cases were due to MAC, that 72% presented with cavities on chest radiograph, and that the radiographic abnormalities involved the upper lobes in 86% and middle lobe/lingula in 32% of the patients [34], consistent with older studies from other parts of the world.

Overall, most studies of the radiographic presentation of pulmonary NTM disease are not population-based and lack both adequate radiographic review and extensive use of CT scanning. However, available data are generally consistent with our results: a minority of patients present with cavitation, and a large proportion of the remainder have nodular bronchiectasis.

We postulate that some of the differences in gender distribution and radiographic presentation could be due to geographic and temporal differences in the frequency of COPD and TB. An increasing rate of COPD in women with respect to men could be contributing to a change of COPD from a male- to female-predominant disease. Populations with higher rates of TB and COPD might also be expected to have a higher proportion of upper-lobe cavitary NTM disease. These simplistic hypotheses are speculative and could likely explain only a small fraction of the differences observed between regions and studies. The differences that have been observed are undoubtedly related to variability in study design and regional health care priorities, in addition to true population differences. Finally, these hypotheses do not explain why females with nodular bronchiectasis appear to comprise the largest proportion of pulmonary NTM patients. The classically described tall, lean body morphotype, with high rates of scoliosis, pectus excavatum, and mitral valve prolapse, and high prevalence

of cystic fibrosis transmembrane conductance regulator gene mutation imply some sort of genetic defect that may be expressed more commonly in females [8].

The frequency with which pulmonary NTM isolates are associated with disease is not well known but varies by species. A systematic review found 20–30% of MAC and *M. xenopi* isolates were associated with disease [41]. In the present study, we observed a significant difference in "pathogenicity" between MAC and *M. xenopi*. In the population cohort, 52% with MAC versus 40% with *M. xenopi* fulfilled the ATS microbiologic criteria ($P < 0.0001$). Similarly, in the clinical cohort, 52% with MAC versus 36% with *M. xenopi* fulfilled the ATS disease criteria ($P = 0.001$). Furthermore, MAC tended to be associated with underlying lung disease less often than with *M. xenopi* (51 vs. 68%, $P = 0.06$). MAC intrinsically may be more pathogenic than *M. xenopi*, the latter being an organism more commonly associated with underlying lung disease, especially emphysema [42]. Furthermore, the very high frequency of patients with MAC isolates who fulfilled the disease criteria should alert clinicians to the likelihood that the pathogenicity of these organisms is far greater than previously appreciated.

Our study has some important limitations. First, the retrospective design limited analyses to routinely collected clinical data. Incomplete data in the clinical cohort may over- or underestimate the frequency of NTM disease. Inferences from the clinical cohort may not be generalizable to the population cohort. The population and clinical cohorts appeared to be similar in several respects (age, gender, and species distributions), so we believe that the clinical cohort data lead to valid approximations of the relative frequency of patient phenotypes and differences in phenotypes between species. However, clinical cohort patients tended to have more positive cultures, suggesting that they may comprise a group biased for more severe infection, so the fraction of patients with disease (46% in the clinical cohort) is probably smaller in the population cohort. One might correct for this factor by focusing on patients who meet the microbiologic criteria. In the clinical cohort, 73% of the patients who fulfilled the microbiologic criteria had disease. In the population cohort, 46% fulfilled the microbiologic criteria. Assuming that 73% of the people who meet the microbiologic criteria have disease, then NTM disease is expected to be present in 34% of all patients with NTM isolates in our population cohort, which is greater than estimates from previous aggregate data.

Another limitation of this study might be the relatively imprecise species identification available for MAC isolates. The *M. avium* complex contains several recognized species, and potentially there could be important differences between species. However, we think that our results remain useful for several reasons. There are relatively few data supporting major differences between different MAC species. In a study of NTM isolation at a large cancer center between 1999 and 2003, *M. avium* and *M. intracellulare* from mostly pulmonary sources were compared [43]. There were 62 patients with *M. avium* and 65 with *M. intracellulare*. Women tended to have *M. intracellulare* more often, and this species was more often associated with disease. Other studies have not identified important differences [44, 45]. Recently identified MAC species have not been studied adequately to understand whether they are associated with important differences, and it appears that they may be relatively uncommon in our experience. Regarding recently identified species within the MAC, of 11 pulmonary *M. chimaera* isolates from a number of Italian hospitals, it was reported that the species was associated with disease in 64% of patients (7/11) [46]. This rate of disease is impossible to interpret given the nonrandom selection of patients (sampling appeared to be one of convenience rather than systematic). Regardless, the result is not obviously different from our own results, where we observed that among all subjects with MAC isolates, 52% had significant disease (the numbers are not significantly different given the small sample size of the *M. chimaera* study). In addition, many clinical laboratories continue to identify NTM as MAC, so our data are likely useful to clinicians who receive these results. The DNA probe (AccuProbe) methodology was shown to identify some NTM organisms as MAC and subsequently classified as a distinct species, *M. saskatchewanense* [47]. The significance of this nonspecificity of the AccuProbe, and its relevance to our study, is not clear. Since the PHL TB laboratory recently introduced an identification method that distinguishes MAC isolates as either *M. avium* or *M. intracellulare*, fewer than 5% could not be classified, and although we have not studied a random sample of our MAC isolates, the specimens that have been typed in detail have been described as *M. avium* subspecies *hominissuis*. We therefore suspect that misclassification of species is probably not a major concern and that the data regarding MAC in the present study remain highly informative.

Conclusions

In Ontario, women comprise only a slight majority of the patients with pulmonary NTM disease, and men comprise a very slight majority of the patients with pulmonary NTM isolates. Patients with nodular bronchiectasis are the largest recognizable group, made up predominantly but not exclusively of women. We observed a high rate of disease among patients with NTM isolates, especially among patients with MAC isolates. Compared with *M. xenopi*, MAC appears to be more commonly associated with

disease and nodular bronchiectasis but less commonly with underlying lung damage. Pulmonary NTM disease in Ontario is heterogeneous, both by gender and by radiographic type. Our results are consistent with aggregated data from Asia and with many data from the USA and Europe.

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