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Management of Nontuberculous Mycobacterial Infection in The Elderly

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Abstract

The incidence of nontuberculous mycobacteria (NTM) has increased over the last decades. Elderly people are more susceptible to NTM and experience increased morbidities. NTM incidence is expected to rise due to an increasing elderly population at least up to 2050. Given the importance of NTM infection in the elderly, an increasing interest exists in studying NTM characteristics in aged population. In this review, we summarize the characteristics of NTM infection among elderly patients. We focus on epidemiology, clinical presentation, and treatment options of NTM in this age group. We highlight the differences in the diagnosis and treatment between rapid and slow growing mycobacterial infections. The current recommendation for treatment of NTM is discussed. We debate if *in vitro* susceptibility testing has a role in treatment of NTM. Drug-drug interaction between antibiotics used to treat NTM and other medications, particularly warfarin, is another important issue that we discuss. Finally, we review the prognosis of NTM disease in elderly patients.

Keywords

Nontuberculous mycobacterium; NTM; Elderly; Treatment

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Conflict of interests

The authors have no conflicts of interests to declare related to this manuscript.

Case report

A 70 year-old woman was referred to our Bronchiectasis Clinic for chronic cough. Her past medical history was significant for 30 pack-year smoking and measles without pneumonia in childhood. She stated that for the last nine months she had a productive cough and chest pain. The cough had gradually progressed along with yellow, brown or blood tinged sputum. She first noticed hemoptysis 8 months prior and the last hemoptysis episode was a few weeks ago, but never expectorated gross blood. She received a course of levofloxacin with some temporary improvement in symptoms.

The chest pain was localized to midsternum and described as stabbing, burning, and heavy pressure feeling. It improved with sleep and worsened by singing, smoke exposure, coughing, eating oily food, sitting and standing. While she noted awakening due to coughing, she did not note a relation to position.

She had no dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fever, chills, night sweats, weight loss as well as history of environmental or drug allergies asthma, tuberculosis (TB), diabetes, gastroesophageal reflux disease, seizure, HIV risks (including drugs, multiple sexual partners and transfusions) and exposure to TB patient, silica or significant asbestos. She worked in office jobs in the past.

Past medical history included measles, a throat abscess at age 12, tonsillectomy at age 13 and hemorrhagic gastritis 8 years ago. She had kidney stones that were removed. Family history was significant for emphysema and chronic bronchitis. She was taking low dose aspirin for Heart disease prevention and naproxen for joints pain.

Review of systems uncovered lightheadedness with palpitation, early satiety, and posterior neck pain.

On physical examination, the patient was a well-appearing, white woman in no distress. Her weight was 70.9 kg. Her vital signs included pulse 105/minute, blood pressure 122/78 mm Hg, and temperature 36.9C. Her oxygen saturation was 94% at room. The lungs had crackles at the bases but these improved with repeated breathing. She also had scant wheezing in the right anterior lower chest. The point of maximum impulse of the heart was not palpated. S1 and S2 were normal. She had a midsystolic click and I–II/VI systolic murmur. There was no gallop. The rest of physical examination was within normal range of limits.

The chest images showed many nodules, right middle lobe bronchiectasis, upper and lower lung circular opacities, suggesting bronchial and bronchiolar cuffing and lucencies that indicated cystic bronchiectasis. She also had mild scoliosis. (Images 1 and 2). Laboratory tests showed normal CBC and differentiation, total serum levels of immunoglobulins (Ig) E, A and G, blood chemistries and lipid profile. ECG was within normal limits.

Three sequential sputum specimens were sent for AFB smear, culture and drug susceptibility testing. Two days later, AFB smears reported positive and PCR test showed negative for *M. tuberculous* complex. From two sputum cultures *Mycobacterium avium was* isolated later. *In vitro* antibiotics susceptibility testing showed the *M. avium* isolate was sensitive to

clarithromycin, ciprofloxacin, moxifloxacin, rifabutin, rifamycin, clofazimine and ethambutol, but resistant to cycloserine and amikacin, and intermediate to streptomycin and kanamycin.

Given clinical symptoms, chest x-ray and CT-scan results, and two positive sputum specimens for *M. avium*, pulmonary nontuberculous mycobacteria (NTM) was diagnosed and treatment was started with clarithromycin 500 milligram (mg) twice per day, rifampicin 600 mg once a day and ethambutol 1200 mg once a day. Her cough and chest pain were gradually improved. The sputum cultures for AFB were obtained monthly until sputum conversion. Her sputum cultures converted negative within 4 months after initiating antibiotics therapy. She was categorized as cured when completed 12 months treatment after sputum conversion. She was closely observed and no evidence of relapse was detected up to 2 years follow up.

Introduction

Nontuberculous mycobacteria have been recognized as human pathogens since the 1950, and to date, over 150 species of *Mycobacterium* have been identified [1–3]. Table 1 shows the most common NTM that cause infection in the elderly. They represent a diverse group of environmental organisms that can be isolated from water sources, soil, animals, and food [4, 5]. Human NTM infection is mainly acquired from environmental exposures [6, 7], although potential human-to-human transmission was recently suggested. [8] The NTM incidence has been increasing in the last decades. HIV was responsible for this increase from 1980s to 1990s. Afterward, the increase has mainly been in women without any of the classic risk factors. Although the exact cause is unclear, it may be a result of the improved methods of NTM detection, as well as growth of the elderly population. [9–12]

Similar to the rest of the world, both the United States (US) and Europe are facing with an aging population and it is estimated that the number of people aged 65 and older in the US will increase to 88.5 million in 2050. It is almost twice the elderly population in 2010 (40.2 million). [13, 14]

Elderly people are more susceptible to NTM and most likely to need health and long term caring services. The average age for NTM infection is reported between 50 and 70 years old [15]. It was shown that age is an important prognostic factor for NTM disease. [16] Elderly HIV population is another concern [17, 18]. Given approximately 34 million people live with HIV infection in the world (2,300,000 of those in Europe) [19], HIV associated NTM will become to an important health concern in the coming years.

Despite the importance of NTM infection in the elderly, there is limited information on the characteristics of diseases caused by these pathogens. The aim of this study was to briefly review the epidemiology and clinical characteristics of NTM diseases among elderly patients.

Methods

A literature search was performed for articles published between 2000 and 2013 using the search terms ‘nontuberculous mycobacteria’ and ‘elderly’, ‘epidemiology’, ‘treatment’, ‘symptoms’, ‘prevention’ and ‘diagnosis’. PubMed, Cinahl, Embase and the Cochrane Library were reviewed. Titles of interest were further reviewed by abstract. Reference lists of relevant studies were hand-searched for additional studies.

Studies included in this review met the following criteria:

- Study populations included patients with NTM.
- Articles were full reports, case reports or reviews.
- Articles were in English.
- Articles were published in peer-reviewed journals.

1. What is the prevalence of NTM among elderly?

Although the incidence of pulmonary infection by NTM has been noted to be increasing, a formal epidemiological evaluation of this disease has been deficient until recently [20]. According to a laboratory assessment from 1993 to 1996 performed by the Centers for Disease Control and Prevention, the rate of positive NTM cultures was 7.5–8.2 cases per 100,000 persons. However, a recent survey showed a positive culture rate of 17.7 per 100,000 in non-HIV patients in the U.S. [21–23]. Moreover, the rate of pulmonary disease with *Mycobacterium avium* complex (MAC) has been reported to be 0.2 cases per 100,000 in Europe, while investigators in the United Kingdom estimated the incidence of NTM respiratory disease 2.0 per 100,000 [21, 24–26].

Over the last 18 years, a study revealed that NTM isolates have increased in the Scottish Borders region and, interestingly, these cases have occurred predominantly among elderly [11]. In line with these results, a study performed in the US demonstrated that the prevalence of pulmonary NTM disease was highest in people aged over 50 years (15.5 cases per 100,000 persons) [27]. A report from Australia showed an increased number of NTM infection from 1999 to 2005 especially in elderly women [28]. Lai *et al.* showed the incidence of NTM increased in Taiwan from 2000 to 2008 [29]. (Table 2)

Al-Houqani *et al.* demonstrated in a population-based study in Ontario, Canada that MAC lung disease increased substantially with age; from 1 in 100,000 in people <50 years old to 48 in100,000 in people over 79 years old [30].

MAC is a ubiquitous bacterium causing disease for human as well as animals in Europe, US and many regions of the world [31, 32]. It is a well-known pathogen for causing a pulmonary disease in elderly women known as Lady Windermere syndrome that presents with isolated middle lobe or lingular bronchiectasis [33]. *Mycobacterium kansasii* followed by *M. fortuitum*, *M. scrofulaceum*, *M. chelonae* and *M. xenopi* are reported as most common isolated pathogens after MAC [24, 31, 34]. *Mycobacterium gordonae* is frequently isolated from elderly patients with pulmonary symptoms and is considered as contamination [20].

However, it could be considered as a potential opportunistic pathogen in a patient with severe immunodeficiency and advance AIDS [35].

2. What are the risk factors for NTM in elderly?

NTM pulmonary infection typically occurs in two different groups of patients. The first group of patients usually are white middle-aged or elderly men who have classic mycobacterial risk factors such as smoking, alcohol abuse, structural lung diseases, and other comorbid conditions. The second group are mainly elderly nonsmoking women without any of these risk factors. [36, 37]. Patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchiectasis, previous TB, pneumoconiosis and alveolar proteinosis are more at risk of NTM disease [38–40]. Considerably, structural lung disease has higher prevalence in elderly [41].

Genetic abnormalities in the cell immunity pathway like interleukin-12/interferon-γ synthesis, cystic fibrosis transmembrane conductance regulator (CFTR) mutations, human leukocyte antigen (HLA) alleles, polymorphisms of solute carrier 11A1, and the vitamin D receptor cause increased vulnerability to systemic NTM disease [42–45]. Impaired IFN-gamma pathway such as IFN-γ deficiency may also play a role for increasing susceptibility to NTM [46–48].

In HIV patients, disseminated NTM infection typically happens just after the CD4 T-lymphocyte cell counts drop lower than 50/μl, suggesting that T-cell activities or cytokines are necessary for mycobacterial resistance [49–51].

Lady Windermere syndrome is a typical example of NTM presentation in patients without any classical risk factors. It presents with right middle lobe and/or lingua involvement. It is proposed that this syndrome may be associated with a fastidious habit of voluntary cough suppression that causes secretions accumulation, which is ideal for growth of the organisms [33, 42]. Patient is commonly older age white female with no history of smoking and also without any previous lung diseases [52, 53]. Certain physical phenotypes seem to be more common among them, including a tall slender body habitus, scoliosis, pectus excavatum and mitral valve prolapsed [54–56]. It is suggested that leptin deficiency may play a role in susceptibility to NTM in thin elderly women [57]. This unique body morphology resemble those seen in inherited connective tissue disorders like Marfan’s syndrome [58]. Preceding reports assumed structural abnormalities of the chest might predispose elderly patients to MAC lung infections [55, 59]. Figure 1 shows the risk factors for NTM diseases in the elderly.

3. Is the NTM presentation different in the elderly in comparison to the adults?

Among the elderly, NTM can lead to both asymptomatic infection and symptomatic involvement. The most common clinical manifestation of NTM disease in this group of patients is lung disease, with MAC being the most frequent infection in both US and Europe [60]. Conversely to the older patients, children the clinical presentation of an NTM infection typically consists of a chronic unilateral cervical lymphadenopathy with spontaneous drainage and fistula [20, 61]. Nearly all patients have chronic or recurring cough. Other symptoms include sputum production, dyspnea, chest pain, hemoptysis, fatigue, fever and

weight loss. Diagnosis is often hampered by symptoms caused by coexisting lung diseases [20, 62]. For instance, NTM diagnosis may be missed in a patient with non-CF bronchiectasis who chronically experiences all mentioned symptoms [63]. Physical examination is nonspecific as well and may reveal underlying pulmonary pathology, such as COPD and bronchiectasis. On auscultation, findings might consist of rhonchi, crackles and wheezes [2]. In HIV patients, NTM accompany by symptoms such as fever, night sweats and weight loss [51]. However, fever may be undetectable in some of elderly patients with pulmonary infection [64].

Clinically, pulmonary NTM can be categorized into either primary infection with no pre-existing lung disease or secondary to underlying lung diseases. Hypersensitivity pneumonitis (HP) and a nodular bronchiectatic pattern on CT scan (as seen in Lady Windermere syndrome) are the primary clinical presentations related to NTM infection [65, 66].

HP that is allergic reaction to MAC rather than an infection is generally related to aerosols of water including household water, pools, hot-tubs (hot-tub lung) and metalworking fluids [67, 68]. This is usually a disease of younger people [69, 70]. Older patients with Lady Windermere syndrome commonly present with the characteristic nodular-bronchiectatic changes and tree-in-bud appearance in high resolution computed tomography [69]. The nodular-bronchiectatic pattern has commonly been accompanied with MAC, although other species, including *M. abscessus* in the US and *M. xenopi* and *M. malmoense* in Europe, are also commonly related to this form of disease [71].

Studies show convincing evidence of NTM association with underlying lung diseases. It has been reported that NTM are associated with at least 10% of all adult patients with bronchiectasis [39]. The symptoms are nonspecific including chronic cough with or without sputum. Cavitation may occur in later stages of the disease. As we described earlier, NTM are commonly observed in the elderly women with scoliosis, pectus excavatum, and mitral valve prolapse without severe cardiopulmonary disease or significant smoking history [72]. A lean body habitus besides other musculoskeletal or soft tissue abnormalities and a high incidence of CFTR gene mutations have now been reported with this pattern of disease [73]. Progression can be very slow happening over months and years and may not occur at all [52].

4. How is NTM diagnosed in the elderly?

Methods for isolation/detection—NTM is a group of environmental pathogens that humans encounter on a daily basis. Isolation of NTM from one sputum sample in the setting of underlying lung disease such as bronchiectasis may represent ‘colonization’ of the respiratory tract rather than infection [70, 74, 75]. The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) have established guidelines to aid physicians in making the diagnosis of NTM. These guidelines indicate that in order to diagnose pulmonary NTM disease, clinical, radiological, and microbiological evidence of the disease should be met [5]. Table 3 shows criteria for diagnosing NTM according to ATS/IDSA guidelines.

While useful in TB, neither IFN-γ release assay (IGRA) nor tuberculin skin test is useful to diagnose NTM. In fact, the main benefit of skin testing or IGRA is to rule out tuberculosis. Worth mentioning, *M. kansasii*, *M. szulgai* and *M. marinum* infections may cause false positive IGRA result due to cross reaction with ESAT-6 and CFP-10 antigens [76, 77].

Acid-fast microscopy (Insensitive): This method is the simplest, cheapest and fastest way of identifying patients with mycobacterial infections [78]. The specificity of AFB staining for detecting acid-fast bacilli is high, however, the overall sensitivity of the microscopy test is only 22–65% [10, 79]. Currently, there are different methods of acid-fast stains that Kinyoun and Ziehl-Neelsen stains are the most commonly used [80].

Fluorescence in situ hybridization (FISH) (Insensitive): The acid-fast stain is unable to differentiate between *M. tuberculosis* (MTB) complex organism and NTM. However, a molecular biology approach using FISH could be helpful [81, 82]. This method is limited by poor function to identify the presence of the relatively common isolated species including *M. flavescens*, *M. fortuitum*, and *M. xenopi* [81].

Mycobacterial culture (Gold standard for isolation): Acid-fast microscopy is the first important method to diagnose mycobacterial infections, but it should be followed by culture for confirmation of presence of NTM and species identification. In addition, culture is required to perform drug susceptibility testing and genotyping [10, 83]. Many species of NTM need a couple of weeks to grow on solid media and are called slow growing mycobacteria (SGM). Instead, the rapidly growing Mycobacteria (RGM) grow in a short time, approximately a week [84]. Therefore, knowing the growth time of isolate may help the clinician to narrow the differential diagnosis of the possible pathogen [20]. For example, MAC as the most common NTM disease is known as a SGM. To increase probability of NTM isolation, it is recommended to incubate both liquid and solid media at 35 and 30°C [85].

Methods for identification

Nucleic acid hybridization methods: The AccuProbe (Gen-Probe Inc., San Diego, CA) nucleic acid hybridization kits allows for rapid identification of the MTB complex, the *M. avium* complex, *M. kansasii* and *M. gordonae*. This assay offers rapid identification within 2 hours as soon as sufficient colonies are achieved following growth in culture [86]. It was shown that the test has very high sensitivity and specificity (more than 95%) to differentiate mycobacteria species [87].

High-performance liquid chromatography (HPLC): HPLC for mycolic acids of the cell wall has been approved to be a rapid (less than 2 hours) and inexpensive method to recognize a wide range of mycobacteria species either from sputum or culture [88]. However, the assay needs highly trained staff due to the visual interpretation of the chromatographic patterns, high-cost instruments, expertise in instrument maintenance and standardized growth conditions including the need for a large biomass when using Ultraviolet-HPLC [89]. This test is not available in diagnostic laboratories.

Polymerase chain reaction (PCR) and Restriction fragment length polymorphism (RFLP): This rapid tool usually is performed on AFB isolates that grow either in liquid or on solid media. Since it is amplified by PCR, the assay involves less biomass than either the AccuProbe or HPLC [90]. Due to the interspecies genetic variability, there is a risk of misidentification with this test [10]. Consequently, to conquer this problem, two new diagnostic algorithms are established [91, 92].

5. How to treat NTM in elderly patients?

Antibiotic therapy for NTM disease involves multiple medications. Consequently, the risk of drug toxicities is relatively high, especially in elderly subjects [93]. For instance, elderly patients with MAC disease commonly complain of gastrointestinal symptoms from the long-standing use of clarithromycin and azithromycin [94]. Therefore, a few elemental questions should be addressed for decision-making on NTM treatment. Does the patient have any clinical symptoms? Will the patient benefit from multidrug therapy? Can the patient be examined regularly to assess the evidence of disease establishment and progression? Will therapy be more unbearable than the disease, particularly for elderly patients with trivial symptoms?

A decision to treat NTM is mainly based on clinical and radiological characteristics, underlying diseases and NTM species. Subsequently, antibiotic therapy is planned by the species identified, the pattern and the extent of lung involvement and possibly drug susceptibility testing. It was shown that not offering a treatment to the patient who met NTM diagnosis, or poor therapeutic response for any reason including inappropriate antibiotic therapy may conclude extensive pleural thickening, atelectasis, advance bronchiectasis and cavitation [95–97].

The treatment of pulmonary NTM disease, as outlined in the latest ATS/IDSA guideline, includes seven essential concepts [20]. The first six instructions are generalizations linking to treatment of infection caused by slowly growing NTM. The seventh concept gives a perspective about differences in management of infections caused by rapidly growing NTM. (Table 4) In addition, it has been shown that if pulmonary NTM disease has caused localized lung involvement, a combined surgical/medical management may worth considering [2].

There is increasing evidence that following the results of *in vitro* antimicrobial susceptibility tests may increase NTM clinical response [98–100]. The authors believe antibiotic susceptibility testing has a significant role in the selection of the most effective therapy for NTM. The disagreement reported between *in vitro* susceptibility and clinical response in some circumstances may drive from unstandardized laboratory methods [101]. Clinical and Laboratory Standards Institute (CLSI) recently established recommendations for drug susceptibility testing for NTM with standardized methods and antimicrobial breakpoints [102]. However, limited data are available about drug susceptibility guided NTM therapy.

ATS/IDSA guidelines suggest to perform macrolide susceptibility test routinely for all MAC isolates. These guidelines also recommend *M. Kansasii* isolates should be tested for rifamycins. Routine drug susceptibility test for RGM should be requested as well. *M. abscessus*, *M. chelonae* and *M. fortuitum* should be tested for amikacin, imipenem,

doxycycline, fluoroquinolones, trimethoprim-sulfamethoxazole, cefepim, clarithromycin, linezolid, tigacyclin and tobramycin [20]. We suggest susceptibility test for all patients who remain culture-positive after 6 months of antibiotic therapy.

Ideally, sputum culture should be requested monthly during antibiotic therapy until sputum converting to negative in two consequence months. At that point, sputum culture should be monitored every 3 months until the end of the treatment. If any new pulmonary symptom occurs, an extra sputum culture should be requested.

There are little data regarding genotyping of NTM. It should be considered that NTM genotyping may be helpful in a patient with recurrent presence of positive culture during treatment. To meet the cure definition, combined antibiotic therapy should be continued for 12 months after sputum conversion.

6. What are the risks of drug interactions induced by NTM medications in the elderly?

Drug-drug interaction is an important issue in elderly. Macrolides, rifamycins and fluoroquinolones are vastly used for NTM treatment particularly SGM. They usually cause interaction with metabolisms of other drugs via interacting with cytochrome P-450 (CYP) [103]. CYP isoenzymes are a group of enzymes located in the endoplasmic reticulum of hepatocytes [104]. Macrolides inhibit oxidation of several drugs via CYP. Some of those include, but are not limited to, alprazolam, midazolam, clozapine, carbamazepine, simvastatin, lovastatin, warfarin and cyclosporine [103]. A patient who takes warfarin and macrolide concomitantly is in risk for increasing international normalized ratio (INR). Therefore, monitoring INR carefully is advised [105]. The risk of over anticoagulation in patients prescribed azithromycin on a warfarin regimen is controversial. Recent studies showed the addition of azithromycin to a stable warfarin regimen resulted in a significant change in the INR and warfarin dosage alteration [106]. Macrolides, particularly clarithromycin, may have interaction with direct thrombin inhibitors and factor Xa inhibitors, new oral anticoagulants. Clarithromycin increases anticoagulant effect of rivaroxaban and dabigatran [107]. Therefore, caution is needed in patient concurrently receiving clarithromycin with this group of drugs.

Rifamycin group drugs (rifampin, rifabutin and rifapentine) are strong inducer of CYP enzyme. They may lower efficacy of several drugs if use concomitantly. However, rifapentine causes less drug interaction. Concomitant administration of warfarin may decrease its serum level and cause INR goes to under therapeutic level. The drug interaction with rifampin has been recently reviewed [108].

Quinolones are another group of inhibitors of CYP enzyme. They inhibit metabolism of nonsteroidal antiinflamatory drugs and theophylline. It should be considered that quinolones absorption is inhibited with concomitant use of aluminum and magnesium antacids, calcium supplements and dairy products [109]. Medication list of any NTM patient should be reviewed before starting antibiotics. Consulting with a clinical pharmacist is well worth in patients on multiple medications.

7. What is the prognosis of NTM in elderly?

NTM-related mortality is increasing. There is a strong association between age and NTM mortality [110, 111]. The mortality rate from limited NTM infections (lung, skin and so on) is low, but mortality rate due to disseminated NTM infection is reported to be about 30% to 40% [16, 112]. Indeed, the mortality was found to be higher in patients older than 65 years. Besides male gender and high levels of comorbidities, advanced age was assumed to be a strong predictor of five-year mortality [16]. Additionally, according to the British Thoracic Society studies, *M. xenopi* was reported with the highest mortality rate [113]. The impact of pulmonary NTM on pulmonary remodeling (fibrosis, pulmonary hypertension and airway diseases) is unclear and should be investigated.

Conclusions

The incidence of NTM infections is growing, probably due to a combination of factors including advancing age. They are being recognized with improvements in laboratory methodology, liquid culture techniques and advance molecular methods. Because of the ubiquitous nature of NTM as environmental pathogens, it is vital to differentiate between clinical disease and colonization. There is a considerable variation in treatment management that should be deliberated before starting the treatment. While the US and European populations are aging and NTM diseases are rising in elderly population with a high mortality rate, we would hope to see an increasing focus on research in NTM infection, and multicenter trials. Creation of regional referral institutions can improve management of this challenging group of diseases.

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Abbreviations

TB	Tuberculosis
Ig	Immunoglobulins
NTM	Nontuberculous mycobacteria
US	United States
MAC	*Mycobacterium avium* complex
COPD	Chronic obstructive pulmonary disease
CF	Cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
HLA	human leukocyte antigen
HP	Hypersensitivity pneumonitis
ATS	American Thoracic Society

IDSA	Infectious Diseases Society of America
IGRA	IFN-γ release assay
FISH	Fluorescence in situ hybridization
MTB	*M. tuberculosis*
SGM	Slow growing mycobacteria
RGM	Rapidly growing Mycobacteria
HPLC	High-performance liquid chromatography
PCR	Polymerase chain reaction
RFLP	Restriction fragment length polymorphism
CLSI	Clinical and Laboratory Standards Institute
CYP	Cytochrome P-450
INR	International normalized ratio

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Learning points

- The Epidemiology of NTM infection has been changing in the last decades. The incidence of NTM is increasing and the increase has mainly been in elderly women without any of the classic risk factors.
- Because of the ubiquitous nature of NTM as environmental pathogens, it is vital to differentiate between clinical disease and colonization.
- Acid-fast microscopy is the first important method to diagnose mycobacterial infections, but it should be followed by culture for confirmation of presence of NTM and species identification.
- A decision to treat NTM is mainly based on clinical and radiological characteristics, underlying diseases and NTM species.
- Antibiotic therapy for NTM disease involves multiple medications. The treatment of pulmonary NTM disease, as outlined in the latest ATS/IDSA guideline, concludes seven essential concepts.
- Drug-drug interaction is an important issue in elderly. Consulting with a clinical pharmacist is well worth in patients on multiple medications.

Highlights

- Elderly women are the most susceptible group to NTM.
- Lung disease is the most common clinical manifestation of NTM in the elderly.
- Acid-fast microscopy and culture are the most important methods to diagnose NTM.
- Clinical data and NTM species should be evaluated before starting treatment.
- Drug-drug interaction is an important issue in the elderly.

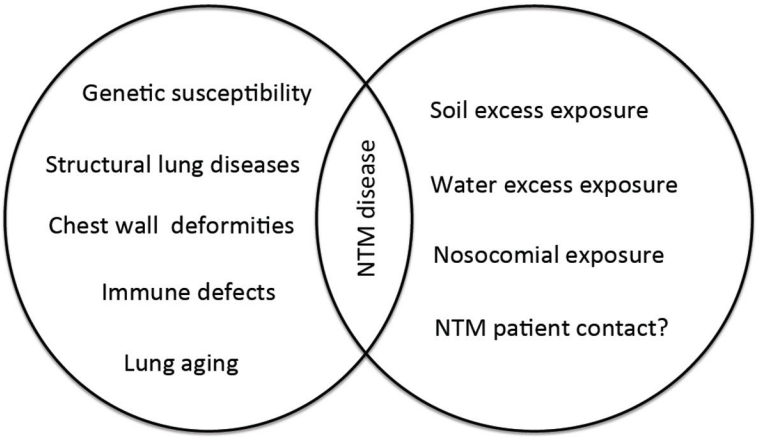

Figure 1.

Illustration of risk factors for NTM disease. Immune defects include HIV/AIDS, immunosuppressant such as TNF-a inhibitors, chemotherapy agents and radiotherapy.

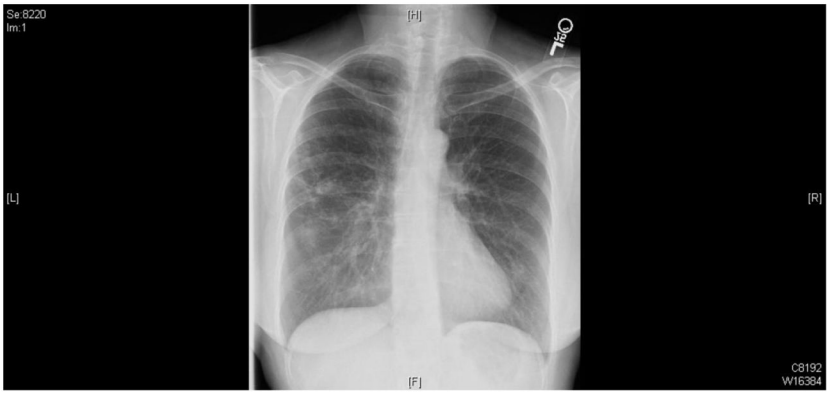

Image 1.

The chest X-ray shows diffuse interstitial fibrotic-type opacities throughout both lungs. There are ill-defined somewhat nodular appearing densities with a hint of cavitation in them on the right side, particularly in the apical segment of the lower lobe. Mild scoliosis is notable.

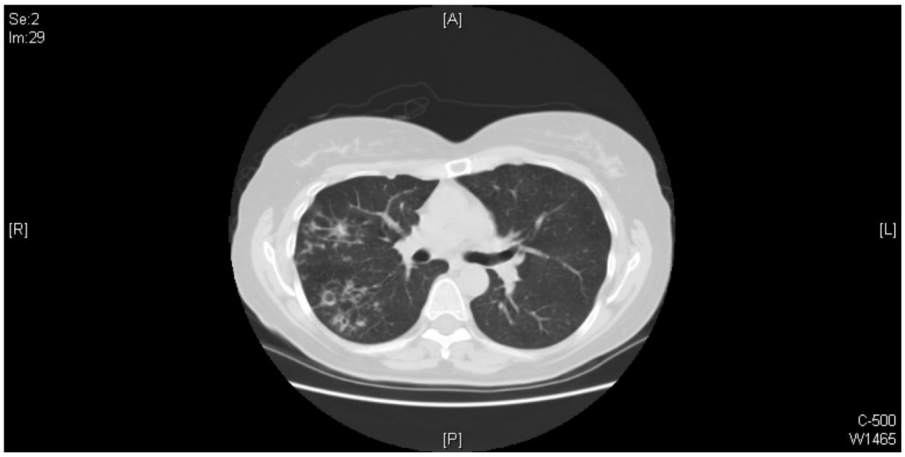

Image 3.

The representative image of chest CT scan shows that multiple small airways opacities are scattered in the right upper lobe, superior right lower lobe, and right middle lobe. Small areas of bronchiectasis are present in the right upper lobe. The largest area of cystic bronchiectasis/small cavity formation measures approximately 1 centimeter and it is present in the posterior right upper lobe.

Table 1

Most common NTM causing infections in elderly

Slow-Growing Mycobacteria (SGM)	Rapid-Growing Mycobacteria (RGM)
M. avium complex	*M. abscessus*
M. Kansasii	*M. chelonae*
M. xenopi	*M. fortuitum*
M. simiae	*M. marinum*
M. malmoense	
M. szulgai	

Table 2

Major studies reporting the prevalence of NTM pulmonary disease

Lead author	Year	Country	Prevalence*
Marras[4]	1999–2000	USA	16.6
Winthrop[27]	2005–2006	USA	8.6
Winthrop[60]	2000–2008	USA	4.1
Prevots[23]	2004–2006	USA	5.5
Moore[26]	1995–2006	England, Wales, and Northern Ireland	2.9
Lai[29]	2000–2008	Taiwan	7.9
Thomson[28]	1999–2005	Australia	3.3

*Nontuberculous mycobacteria infection prevalence rate per 100.000 population

Table 3

Summary of the American Thoracic Society diagnostic criteria for pulmonary nontuberculous mycobacterial infection

General
• ymptoms of a pulmonary disease and • Exclusion of other lung diseases
Chest Images
• Chest radiograph: cavitary or nodular opacifications or • High resolution computed tomographic scan (HRCT): multifocal bronchiectasis with multiple small nodules
Laboratory
• Positive culture results from at least two separate specimens or • Positive culture from at least one bronchial wash or BAL or • Transbronchial (TLBC) or other lung biopsy with granulomatous inflammation changes or • AFB plus one or more sputum, bronchial wash or BAL culture which are positive for NTM
Expert consultation is suggested when NTM isolates are either infrequently encountered or usually indicated environmental contamination
Patients who are believed to have NTM lung disease but not meet the diagnostic criteria should be followed until the diagnosis is established or excluded
Making the diagnosis of NTM lung disease does not demand the institution of therapy, which is a decision upon potential risks and benefits of therapy for every individual patient

Table 4

Seven concepts on treatment of pulmonary NTM diseases

NTM classification	Therapy	
Slowly growing NTM (SGM)	**1**	**Macrolide** regimens suggested for the majority of infections
	2	Ethambutol included as an enhancing drug
	3	**Rifamycin** added as a third medication
	4	Parenteral aminoglycoside can be added (1 to 3 months) for cavitary disease or severe infection
	5	Dosing interval: unclear whether daily or intermittent is feasible, but the intermittent may be effective and has decreased cost and toxicity.
	6	Treatment duration: initial aim is 12-month therapy beyond sputum conversion to smear negative. Re-assessment of infection status at the end of this period of therapy is essential
Rapidly growing NTM(RGM)	**7**	Different regimens compared with those for slow growing NTM disease. Initial therapy may extend by several months of parenteral therapy with cefoxitin-amikacin or imipenem-amikacin. Long-term oral suppressive therapy may be necessary. Expert consultation is recommended.