Lady Windermere syndrome

Ann Marie Kumfer MD, Hawa Edriss MD

Abstract

Non-tuberculosis Mycobacterium spp *(NTM) pulmonary disease is increasing in incidence and is a common cause of undiagnosed lung disease in older patients. NTM pulmonary disease occurring in patients without preexisting lung disease was only recently described by Prince in 1988. In 1992, Reich and Johnson presented a case series of six women describing a predilection of* Mycobacterium spp *pulmonary disease for the middle lobe, and its homolog, the lingula, in elderly women without preexisting pulmonary disease. Later high resolution computed tomography studies (HRCT) showed that the characteristic image findings in these cases were nodules and bronchiectasis most commonly occurring in the middle lobe and lingula. This subtype of disease is now usually referred to as nodular bronchiectasis, and some researchers have doubted whether there really is a predilection for the middle lobe. Although Reich and Johnson hypothesized that cough suppression in "polite" women was the mechanism of disease, there are no large studies which support this idea. Mutations in the cystic fibrosis transmembrane receptor, unique skeletal phenotypes, and impaired function of the modulators of granuloma formation are the most common characteristics found in patients with nodular bronchiectasis. These patients usually respond well to clarithromycin-based multi-drug regimens, but surgery is sometimes required to resect the infected regions of the lung.*

Keywords: Lady Windermere Syndrome, nodular bronchiectasis, *M. avium,* non-tuberculous *Mycobacterial spp* (NTM).

Introduction

Non-tuberculous *Mycobacterium spp* (NTM) are increasingly recognized as important pathogens in human diseases.[1] This group includes mycobacterial pathogens other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae.* The incidence of NTM infections is increasing, and a recent study reported an 8.2% increase in prevalence per year between 1997 and 2007.[2] These mycobacterial species are a ubiquitous part of the normal flora in the soil and water.[1,3] They have been isolated in the plumbing of patients with NTM infections and in the water supply of some hospitals in the United States and worldwide.[4-8] The route of infection is through the inhalation of aerosols,[9] but recent studies have shown that person-to-person spread of disease is possible in patients with cystic fibrosis.[10] *Mycobacterium spp* have a relatively impermeable cell wall and can form biofilms contributing to the difficulty in eradicating them with antibiotics or disinfectants.[11] Non-tuberculous *Mycobacterium* infections can involve lymph nodes, bone and soft tissue, and most commonly the lungs.[1] *M. avium* and *M. intracellular* (*Mycobacterium avium* complex [MAC]) are important NTM pathogens which cause disease in patients with impaired host defenses and preexisting lung disease.[12,13] However, MAC can

Corresponding author: **Hawa Edriss**
Contact Information: Hawa.edriss@ttuhsc.edu
DOI: 10.12746/swrccc.v5i20.402

also cause pulmonary disease in patients without these risk factors.

There are three common subtypes of MAC pulmonary disease in non-immunocompromised individuals: 1) fibrocavitary disease resembling tuberculosis commonly found in elderly, male smokers with preexisting pulmonary disease, 2) nodular bronchiectasis most commonly found in elderly, post-menopausal females, and 3) hypersensitivity-like disease known as "hot tub lung" that has both inflammatory and infectious components.[1,14,15] This review focuses on nodular bronchiectasis since this pulmonary disease may account for up to 59% of MAC disease seen in pulmonary practices.[16]

Bronchiectasis

Bronchiectasis is a result of inflammatory damage to the cartilage in small to medium airways that leads to irreversible airway damage and dilation.[17-19] Common symptoms include a chronic cough with sputum production, fatigue, and hemoptysis.[19,20] Patients with adult-onset bronchiectasis are often middle age to elderly women.[20,21] Cystic fibrosis is a common cause of bronchiectasis which ususally presents in childhood, but adult-onset bronchiectasis can be associated with cystic fibrosis transmembrane conductance regulator (CFTR) mutations and cystic fibrosis.[22,23] Non-cystic fibrosis bronchiectasis in adults often has no obvious cause or is a sequalae of infections but can occur in patients with immunodeficiency, chronic obstructive pulmonary disease, connective tissue disease, allergic bronchopulmonary aspergillosis (ABPA), and ciliary dyskinesia.[21,24] Lady Windermere syndrome (LWS), a unique subtype of *M. avium* pulmonary disease, is associated with bronchiectasis, but it is unknown whether bronchiectasis precedes *M. avium* infection or is a result of infection.[25] Airway involvement in bronchiectasis is usually diffuse, but some diseases are associated with more focal distributions of bronchiectasis in the lung. Bronchiectasis in cystic fibrosis usually involves the upper lobes, ABPA the central airways, and LWS and tuberculosis the middle lobes.[18,22,26] It has been proposed that the middle lobe predilection is due to obstruction of the long, right middle lobe bronchus by the lymphadenopathy associated with mycobacterial infections.[26]

Lady Windermere Syndrome

In 1987, Prince noted a new clinical syndrome characterized by *M. avium* pulmonary disease in elderly, non-immunocompromised women. *M. avium* pulmonary infection was previously associated with pre-existing pulmonary disease or HIV. These patients usually presented with cough and sputum production. Seventy-one percent of patients had nodules.[15] In 1992, Reich and Johnson reported a case series on six elderly female patients with MAC pulmonary disease isolated in the middle lobe/lingula. These women had no hilar adenopathy or cavitary disease. Reich and Johnson hypothesized that voluntary cough suppression in elderly women led to retained secretions in the narrow, dependent right middle lobe bronchus. They coined the term LWS after the Victorian character with fastidious manners in the play *Lady Windermere's Fan* by Oscar Wilde (first performed in 1892). The paper stated that the defining features of LWS were "(1) initial involvement of the periphery of the lingula or of its counterpart, the middle lobe; (2) absence of clinically evident predisposing pulmonary disease; and (3) exclusivity of the features to female patients."[27]

Studies in patients with nodular bronchiectasis have shown that most patients are females around age 60.[15,27,28] Most patients diagnosed in the United States are Caucasians or Asian.[16,29,30] The majority of patients do not have a significant smoking history.[29,31] These individuals usually have nodular bronchiectasis with diffuse pulmonary involvement of 3-4 lobes; the right middle lobe and lingula are most commonly involved.[16,29,32] Bronchiectasis in the middle lobe and lingula is highly suggestive of MAC disease.[32,33] However, isolated middle lobe and lingular disease is a rare manifestation of nodular bronchiectasis even on early high resolution computed tomography (HRCT) scans.[16] In the Reich and Johnson study only 6/29 patients originally examined had middle lobe and lingular involvement. It is possible that these patients had more diffuse disease that was not seen on the older imaging modalities; most of their patients in this

Table 1. Case series with Lady Windermere syndrome

Ref # number of cases, mean age, gender	Skeletal phenotype	X-ray/HRCT	Treatment	Response
2,7 6 65 yr 100% F	NR	CXR showing LL and RML infiltrates No adenopathy	1-lingulectomy 4-combination of anti-tuberculosis drugs 2-no treatment	Good response to treatment
31 13 57 yr 100% F	12/13 slender, variable history of scoliosis, MVP, PE	No specific information besides RML and lingular involvement	All underwent resection of the RML and/or lingula due to non-response to medications	All tolerated procedure well 15% reactivation requiring antibiotic therapy
28 134 59 yr 96% F	Slender with mean BMI of 21.5	Focal fibronodular BR in the RML and LL	All underwent early thoracoscopic lobectomy or segmentectomy	7% operative morbidity usually air leaks No mortality 12% had a second procedure
34 9 60 yr 100% F	NR		Lobectomy, segmentectomy, wedge resection after failing chemotherapy	100% had negative sputum culture after surgery and post-operative chemotherapy
35 27 63 yr 67% F	NR	RML and lingular (92.5%) Tree-in-bud centrilobular nodules (88.8%) BR (92.5%)	NR	NR

Abbreviations: CXR-Chest x-ray, LL-left lingular lobe, RML-right middle lobe, INH-isoniazid, RMP-rifampin, EMB-ethambutol, SM-streptomycin, BR-bronchiectasis, NR-not reported, PE-pectus excavatum, MVP-mitral valve prolapse

series did not have a CT scan. Baseline characteristics of patients with nodular bronchiectasis do not vary significantly from those with isolated middle lobe/lingular disease as seen in Tables 1 and 2. We found no studies comparing treatment response in those with diffuse versus isolated disease.

Pathogenesis

While most MAC infections occur in patients who are immunocompromised or have underlying pulmonary disease,[12,36] LWS/nodular bronchiectasis is a unique form of MAC infection that predominately occurs in elderly women without pre-existing pulmonary disease or overt immunodeficiency.[15,27] Reich and Johnson, who named this syndrome, attributed the middle lobe/lingula predilection to cough suppression.[27] The bronchi in the middle lobe have small diameters and lack collateral ventilation making clearance of secretions difficult without expectoration.[37-39] This idea is supported by a case series which showed that voluntary cough suppression could lead to cylindrical bronchiectasis.[40] However, evidence for cough suppression prior to developing LWS is limited to case reports.[41,42] Reich and Johnson had no data that their patients with middle lobe disease had a history

Table 2. Case series with nodular bronchiectasis

Ref # number of cases, mean age, gender	Skeletal phenotype	CXR/HRCT	Treatment	Outcome
15 21 66 yr 81% F	NR	71% with discrete pulmonary nodules most commonly RUL	15- combination of anti-tuberculosis drugs 3-lobectomy 3-no treatment	52%- remission or stable disease 14%- death from progressive disease 24%- relapse with one case requiring lobectomy
16 31 63 yr 94% F	NR	Only 23% had initial RML and LL involvement, Avg # lobe involved- 3.3, nodules (40%), BR (17%)	Most patients started on a macrolide-based regimen with CLR, EMB, and RMP	After 12 months, 50% failed therapy, 86% remained symptomatic
29 63 60 yr 95% F	Tall low BMI, scoliosis (51%), PE (11%), MVP (9%)	Diffuse BR RML (90%) LL (73%) Diffuse nodules	NR	NR

Abbreviations: RAL-Right anterior lobe, INH-isoniazid, RMP-rifampin, RML-right middle lobe, LL-left lingular lobe, CLR- clarithromycin, EMB-ethambutol, BR-bronchiectasis, BMI-body mass index, PE-pectus excavatum, MVP-mitral valve prolapse, NR- not reported

of cough suppression. Rubin criticized this proposed mechanism stating that patients with neuromuscular diseases with poor cough are not more susceptible to LWS.[43] Additionally, a survey showed that 68% of patients with pulmonary NTM did not report reluctance to cough in public.[29]

There are several well-established risk factors for this infection. These include host anatomic factors, host immune factors, genetic factors, and environmental factors.[44] Important anatomic factors include skeletal abnormalities, low BMI, and mitral valve prolapse. Multiple studies have shown that skeletal abnormalities are more common in patients with MAC pulmonary disease. Iseman reported that 70% of these patients have scoliosis or pectus excavatum.[45] Other studies have also reported an increased incidence of scoliosis and pectus excavatum, occurring in up to 51% of patients with pulmonary NTM.[29,46] Mitral valve prolapse also occurs frequently in these patients. Many studies have shown that most women with LWS have a low-normal BMI and a slender body habitus with decreased subcutaneous fat.[29,46-48] Decreased subcutaneous fat is associated with an increased adiponectin/leptin ratio; increased adiponectin/leptin ratios inhibit the Th-1 response, an important adaptive immune response to *M. avium* infection.[47,49,50] Lady Windermere syndrome also occurs predominately in post-menopausal patients.[15,37] Low estrogen levels in slender, post-menopausal women may increase susceptibility to MAC disease.[47] Nutritional deficiencies may also contribute to the development of LWS since malnutrition is associated with increased risk of *M. tuberculosis* infection and with worse outcomes in NTM infections.[51,52]

Several genetic factors and subtle immune phenotypes are more common in patients with LWS than in the general population. Most notably, 36.5% of patients with pulmonary NTM had one CFTR mutations compared to 15.6% of individuals in the control population.[29] Another study found that in patients

presenting to a pulmonary clinic with bronchiectasis and MAC pulmonary disease 47.6% had a mutation in the CFTR gene.[23] Cystic fibrosis is a known cause of diffuse bronchiectasis and impaired mucus clearance.[21,53] While it is not clear whether the bronchiectasis associated with LWS precedes or is a result of MAC disease,[25] one possible explanation might involve mutations in CFTR which cause diffuse bronchiectasis and damaged airways susceptible to MAC pulmonary disease. Laboratory studies show that *M. avium* binding is mediated through fibronectin, a glycoprotein exposed on damaged epithelium.[54,55] It seems possible that prior epithelial damage is required to establish MAC infections. Supporting this mechanism is the fact that LWS/ nodular bronchiectasis is much more common in Caucasian populations,[2,30] which have a higher rate of CFTR mutations than black or Hispanic populations.[56] However, this does not explain the high incidence of LWS in Asian populations.[2] Studies on conditions with impaired mucus clearance, such as chronic bronchitis, have shown that smoking can induce acquired mutations in CFTR.[57] It is possible that either age-related acquired mutations or cumulative pulmonary damage from insidious lung disease caused by a less functional CFTR protein could explain the predilection for older individuals. However, most patients with LWS have never smoked, and this eliminates one possible explanation for chronic occult lung disease.[31] Another factor not explained by the CFTR mutation theory is why LWS shows a middle lobe predilection since cystic fibrosis usually causes upper lobe bronchiectasis.[18,22] However, CFTR mutations leading to diffuse bronchiectasis do help explain the multilobular lung involvement commonly seen in image studies of patients with nodular bronchiectasis.[29,35,58]

Some studies on individuals with LWS have noted subtle immune defects that can increase susceptibility to LWS. The immune response to *M. avium* infection is mediated through a Th-1, cell-mediated pathway. Important cytokines in the cell-mediated response and in granuloma formation are IL-12, INF-γ, and TNF-α.[59] Studies measuring cytokine production in peripheral blood monocytes and whole blood after stimulation have shown decreased INF-γ and TNF-α in patients with MAC pulmonary disease compared to healthy controls.[46,60-62] However, other studies have shown no difference in stimulated INF-γ production in NTM infections.[29,63] Seventy-seven percent of individuals with interferon-γ receptor deficiencies had environmental mycobacterium disease, most commonly *M. avium.*[64] However, another study in LWS patients did not find a significant association with interferon receptor deficiency.[16] A recent study showed that elderly individuals' peripheral blood cells have decreased heme oxygenase-1 expression after *M. avium* stimulation.[65] Heme oxygenase-1 is an important modulator in granuloma formation; decreased expression in elderly individuals may lead to poor granuloma formation and a higher disease burden.[66] This could help explain the predilection on LWS for older individuals.

Some authors have noted the phenotype of patients with LWS with a slender body habitus with skeletal abnormalities and mitral valve prolapse is similar to the phenotype seen in Marfan syndrome.[45,47] These authors proposed that perhaps patients with LWS have a defect in fibrillin postulated to increase the expression in TGF-β, a cytokine involved in the pathogenesis of *M. avium.*[29,47] Supporting this hypothesis, TGF-β expression was increased in the blood of those with NTM pulmonary following stimulation with *M. intracellulare.*[67]

In summary, there are several phenotypic, genetic, and immune factors associated with LWS. Environmental exposure may also increase risk of *M. avium* disease since *M. avium* is a ubiquitous bacterium found in the soil and water.[3] Increased soil exposure was associated with increased risk of *M. avium* infection while aerosol generating activities were not.[68,69] NTM most commonly occurs in the southeast region of the United States.[2] The risk for LWS likely involves several factors which allow an environmental bacterium to cause disease in individuals without pre-existing lung disease or overt immunosuppression.

Diagnosis

According to the 2007 ATS guidelines, the minimum diagnostic work-up for NTM lung disease in those with clinical symptoms includes: 1) a chest

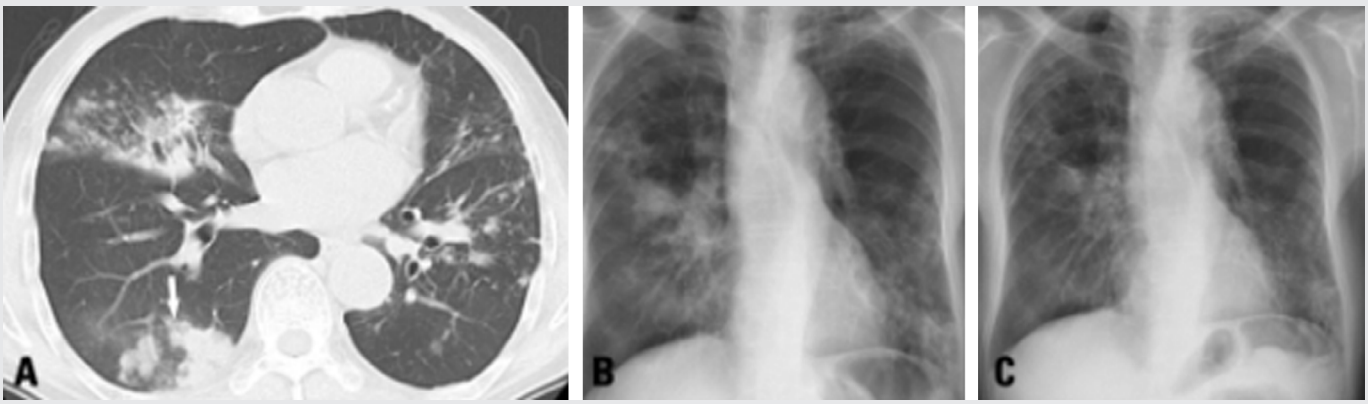

Figure. A 72-year-old man with NB-MAC with consolidations treated with anti-MAC therapy. (**A**) Axial CT shows multifocal cylindrical bronchiectasis and centrilobular nodules with volume loss in both lungs. (**B**) Plain radiograph obtained on the same day as Figure A shows multifocal consolidations and small nodular opacities in right lung and left lower lung zone. (**C**) Plain radiography 2 months later shows a decrease in the consolidations and nodules of both lungs.

From Texas Tech University Health Sciences Center Library in Lubbock, TX - OPEN*i* (beta) – search term-nodular bronchiectasis-accessed 3/10/2017.

x-ray for those with cavitary disease or HRCT for those with nodular bronchiectasis (Figure), 2) three sputum samples with acid-fast bacteria staining and cultures on solid and liquid media, and 3) exclusion of *M. tuberculosis* or other diseases with a similar presentation.[1] Culture on both liquid and solid media increases the sensitivity of NTM detection by 15%.[70] To be diagnostic, sputum culture should be positive on two separate occasions to rule out contamination; bronchial washings require one positive culture.[1] In LWS, HRCT scans usually show diffuse bronchiectasis with "tree and bud" opacities and small peripheral nodules involving the middle lobe; the chest X-ray is often normal.[1,33,71] The middle lobe is most frequently involved.[1,29] One study found that the presence of bronchiectasis with multiple small nodules on CT scan had a sensitivity and specificity of 80% and 87%, respectively, at predicting a positive MAC culture.[72] Isolated middle lobe or lingular disease with nodules and bronchiectasis is highly suggestive of LWS even if MAC cultures are negative.[33]

This diagnosis can be difficult because of the lower bacterial burden in nodular bronchiectasis compared to cavitary disease;[1,32,70] one study demonstrated only 38% of patients with nodular bronchiectasis have positive sputum cultures.[73] Another study found that 45% of patients need to undergo bronchoscopy due to a negative sputum cultures or an inability to provide adequate samples.[16] Studies show that in patients with MAC pulmonary disease, cultures from bronchial lavages have a greater sensitivity than sputum cultures; positive cultures were present in 93.8% and 50% of bronchial washings compared to 64.3% and 23.1% of sputum samples, respectively.[74,75] In suspected cases of LWS with three negative sputum samples, bronchoscopy with bronchial washings may be needed to confirm the diagnosis. Recently, polymerase chain reaction (PCR) and serodiagnostic tests have been utilized for rapid diagnosis. An enzyme immunoassay (EIA) test that detects serum anti-glycopeptidolipid (GPL) core IgA antibody has sensitivity and specificity ranging from 70.1%-81.3% and 88.3%-93.9%.[76,77] Recent studies show that real-time PCR is 71.1%-100% sensitive for detecting *M. avium* in a sputum sample depending on the assay.[78-80] In addition, real-time PCR takes only two hours to confirm a diagnosis

compared to eight days needed to detect *M. avium* in liquid culture and can provide early detection of antibiotic resistance of an *M. avium* isolate to clarithromycin at known alleles.[80,81] Positron emission tomography using 18F-fluorodeoxyglucose is a promising tool for diagnosing disease severity and response to treatment that merits more investigation.[82,83]

Treatment

Mycobacterium avium complex pulmonary disease is difficult to eradicate. Mycobacteria have relatively impermeable cell walls and can form biofilms which make eradication of these bacteria with antibiotics or disinfectants difficult.[11,84] Nodular bronchiectasis may not require treatment. One study showed that only 48% of patients presenting with nodular bronchiectasis required treatment due to disease progression.[73] The 2007 American Thoracic Society (ATS) NTM guidelines recommend treating MAC pulmonary disease with bronchiectasis with intermittent therapy three-times-weekly including clarithromycin 1,000 mg or azithromycin 500 mg as the backbone of the treatment regimen. These guidelines suggest adding ethambutol 25 mg/kg and rifampin 600 mg to the triweekly regimen to prevent macrolide resistance. This regimen should be continued for 12 months after negative sputum cultures.[1] A meta-analysis of MAC treatment showed that regimens containing macrolides had better pooled success proportions.[85] A recent study comparing daily to intermittent therapy (three times weekly) found that patients with intermittent dosing were less likely to modify their drug regimen. Studies testing three times weekly therapy in noncavitary MAC pulmonary disease showed sputum conversion rates of 71-84%.[86-88] Studies with intermittent dosing also showed a non-significant trend toward better symptomatic relief, radiological improvement, and sputum conversion.[87] A large trial of three-times weekly dosing showed that no patients in this study developed macrolide resistance on this regimen.[88]

Little information is available to guide treatment options for patients failing intermittent therapy. The guidelines suggest adding streptomycin based on a study showing higher sputum clearance of MAC.[1,89] There are no official guidelines on the use of fluoroquinolones in MAC pulmonary disease. Daily therapy and surgical intervention are promising treatment modalities for patients who fail intermittent therapy or who have cavitary disease. A recent study of patients who had failed 12 months of intermittent therapy showed that 30% of sputum specimens (6/20) converted when switched to daily therapy with azithromycin (250-500 mg), rifampin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg).[90] Treatment of patients with MAC pulmonary disease and macrolide resistance has low success rates with antibiotic therapy, and surgery is a possible treatment in these patients.[91,92] Two surgical studies using lobectomy and segmentectomy for isolated disease or disease not responding to several months of antibiotics showed that 92%-100% of patients underwent sputum conversion after surgery.[28,34] There was no operative mortality in these studies. Thus, surgery appears to be a relatively safe option for patients failing antibiotic therapy who have sufficient cardiopulmonary reserve.

Conclusions

Three types of NTM lung disease occur in non-immunocompromised patients: 1) fibrocavitary disease most commonly found in elderly men with preexisting pulmonary disease, 2) nodular bronchiectasis most commonly found in elderly, post-menopausal women, and 3) hypersensitivity-like disease known as “hot tub lung.” Nodular bronchiectasis was first described by Prince who noted nodular disease occurring predominately in elderly women without preexisting disease. Reich and Johnson noted a middle lobe/lingular predilection in a case series of six patients. They named this disease caused by MAC occurring in the middle lobe/lingula of women LWS and suggested that cough suppression in well-mannered women was the likely mechanism for this infection. Although nodular bronchiectasis often shows a predilection for the middle lobe, diffuse nodules and bronchiectasis are usually present.[16,29] Lady Windermere Syndrome with disease isolated to the middle lobe and lingula occurs rarely. This disease can occur in men although it is much more common in women.[28,93] Most studies do not support cough suppression as an important factor

in disease pathogenesis. Skeletal abnormalities and CFTR mutations are prevalent in patients with nodular bronchiectasis; subtle immune deficiencies affecting the Th-1 immune response and granuloma formation may also have a role in disease pathogenesis. This disease can be diagnosed with HRCT scans and positive cultures in patients with clinical symptoms. Newer tests, such as PCR, can expedite diagnosis. A large proportion of patients with nodular bronchiectasis do not require treatment. Those who do usually respond well to a three-drug regimen of clarithromycin, ethambutol, and rifampin; those who do not respond to antibiotics may require surgery. Since NTM lung disease is increasing in incidence and is a common cause of undiagnosed geriatric lung disease, it is important to know the clinical presentation and treatment of LWS/nodular bronchiectasis.[94-96]

Article citation: Kumfer AM, Edriss H. Lady Windermere Syndrome. The Southwest Respiratory and Critical Care Chronicles 2017;5(20):22-32.
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX
Submitted: 3/10/2017
Accepted: 5/28/2017
Reviewer: Richard Winn MD
Conflicts of interest: none

References

1. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175:367-416.
2. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med 2012;185:881-6.
3. Falkinham JO. Environmental sources of nontuberculous mycobacteria. Clin Chest Med 2015;36:35-41.
4. Falkinham JO. Nontuberculous mycobacteria from household plumbing of patients with nontuberculous mycobacteria disease. Emerg Infect Dis 2011;17:419-24.
5. Khosravi AD, Hashemi Shahraki A, Hashemzadeh M, Sheini Mehrabzadeh R, Teimoori A. Prevalence of non-tuberculous Mycobacteria in hospital waters of major cities of Khuzestan Province, Iran. Front Cell Infect Microbiol 2016;6:42.
6. Ovrutsky AR, Chan ED, Kartalija M, et al. Cooccurrence of free-living amoebae and nontuberculous Mycobacteria in hospital water networks, and preferential growth of Mycobacterium avium in Acanthamoeba lenticulata. Appl Environ Microbiol 2013;79:3185-92.
7. Fernandez-Rendon E, Cerna-Cortes JF, Ramirez-Medina MA, et al. Mycobacterium mucogenicum and other nontuberculous mycobacteria in potable water of a trauma hospital: a potential source for human infection. J Hosp Infect 2012;80:74-6.
8. Nishiuchi Y, Maekura R, Kitada S, et al. The recovery of Mycobacterium avium-intracellulare complex (MAC) from the residential bathrooms of patients with pulmonary MAC. Clin Infect Dis 2007;45:347-51.
9. Parker BC, Ford MA, Gruft H, Falkinham JO. Epidemiology of infection by nontuberculous mycobacteria. IV. Preferential aerosolization of Mycobacterium intracellulare from natural waters. Am Rev Respir Dis 1983;128:652-6.
10. Bryant JM, Grogono DM, Greaves D, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet 2013;381:1551-60.
11. Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. J Thorac Dis 2014;6:210-20.
12. Kiehn TE, Edwards FF, Brannon P, et al. Infections caused by Mycobacterium avium complex in immunocompromised patients: diagnosis by blood culture and fecal examination, antimicrobial susceptibility tests, and morphological and seroagglutination characteristics. J Clin Microbiol 1985;21:168-73.
13. Hill UG, Floto RA, Haworth CS. Non-tuberculous mycobacteria in cystic fibrosis. J R Soc Med 2012;105 Suppl 2:S14-8.
14. Kwon YS, Koh WJ. Diagnosis and treatment of nontuberculous mycobacterial lung disease. J Korean Med Sci 2016;31:649-59.
15. Prince DS, Peterson DD, Steiner RM, et al. Infection with Mycobacterium avium complex in patients without predisposing conditions. N Engl J Med 1989;321:863-8.
16. Huang JH, Kao PN, Adi V, Ruoss SJ. Mycobacterium avium-intracellulare pulmonary infection in HIV-negative patients without preexisting lung disease: diagnostic and management limitations. Chest 1999;115:1033-40.
17. Pasteur MC, Bilton D, Hill AT, Group BTSBn-CG. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65 Suppl 1:i1-58.
18. Javidan-Nejad C, Bhalla S. Bronchiectasis. Radiol Clin North Am 2009;47:289-306.
19. Barker AF. Bronchiectasis. N Engl J Med 2002;346:1383-93.

20. Altenburg J, Wortel K, van der Werf TS, Boersma WG. Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital. Neth J Med 2015;73:147-54.

21. Pasteur MC, Helliwell SM, Houghton SJ, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000;162:1277-84.

22. Mason AC, Nakielna BE. Newly diagnosed cystic fibrosis in adults: pattern and distribution of bronchiectasis in 12 cases. Clin Radiol 1999;54:507-12.

23. Ziedalski TM, Kao PN, Henig NR, Jacobs SS, Ruoss SJ. Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection. Chest 2006;130:995-1002.

24. Gao YH, Guan WJ, Liu SX, et al. Aetiology of bronchiectasis in adults: A systematic literature review. Respirology 2016;21:1376-83.

25. Bonaiti G, Pesci A, Marruchella A, Lapadula G, Gori A, Aliberti S. Nontuberculous Mycobacteria in noncystic fibrosis bronchiectasis. Biomed Res Int 2015;2015:197950.

26. King PT. The pathophysiology of bronchiectasis. Int J Chron Obstruct Pulmon Dis 2009;4:411-9.

27. Reich JM, Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest 1992; 101:1605-9.

28. Yu JA, Pomerantz M, Bishop A, Weyant MJ, Mitchell JD. Lady Windermere revisited: treatment with thoracoscopic lobectomy/segmentectomy for right middle lobe and lingular bronchiectasis associated with non-tuberculous mycobacterial disease. Eur J Cardiothorac Surg 2011;40:671-5.

29. Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 2008;178:1066-74.

30. Yeager H. The Lady Windermere syndrome: is there a racial as well as a gender bias? Chest 2008;134:889-90.

31. Pomerantz M, Denton JR, Huitt GA, Brown JM, Powell LA, Iseman MD. Resection of the right middle lobe and lingula for mycobacterial infection. Ann Thorac Surg 1996;62:990-3.

32. Lynch DA, Simone PM, Fox MA, Bucher BL, Heinig MJ. CT features of pulmonary Mycobacterium avium complex infection. J Comput Assist Tomogr 1995;19:353-60.

33. Levin DL. Radiology of pulmonary Mycobacterium avium-intracellulare complex. Clin Chest Med 2002;23:603-12.

34. Watanabe M, Hasegawa N, Ishizaka A, et al. Early pulmonary resection for Mycobacterium avium complex lung disease treated with macrolides and quinolones. Ann Thorac Surg 2006;81:2026-30.

35. Polverosi R, Guarise A, Balestro E, Carloni A, Dalpiaz G, Feragalli B. High-resolution CT of nontuberculous Mycobacteria pulmonary infection in immunocompetent, non-HIV-positive patients. Radiol Med 2010;115:191-204.

36. Sexton P, Harrison AC. Susceptibility to nontuberculous mycobacterial lung disease. Eur Respir J 2008;31:1322-33.

37. Reich JM. Pathogenesis of Lady Windermere syndrome. Scand J Infect Dis 2012;44:1-2.

38. Inners CR, Terry PB, Traystman RJ, Menkes HA. Collateral ventilation and the middle lobe syndrome. Am Rev Respir Dis 1978;118:305-10.

39. Gudbjartsson T, Gudmundsson G. Middle lobe syndrome: a review of clinicopathological features, diagnosis and treatment. Respiration 2012;84:80-6.

40. Wells A, Rahman A, Woodhead M, et al. The clinical-features of voluntary cough suppression associated with chronic pulmonary suppuration (atussis nervosa)-a controlled evaluation. American Review of Respiratory Disease; 1993: a461-a.

41. Dhillon SS, Watanakunakorn C. Lady Windermere syndrome: middle lobe bronchiectasis and Mycobacterium avium complex infection due to voluntary cough suppression. Clin Infect Dis 2000;30:572-5.

42. Tryfon S, Angelis N, Klein L, et al. Lady Windermere syndrome after cardiac surgery procedure: a case of Mycobacterium avium complex pneumonia. Ann Thorac Surg 2010;89:1296-9.

43. Rubin BK. Did Lady Windermere have cystic fibrosis? Chest 2006;130:937-8.

44. Honda JR, Knight V, Chan ED. Pathogenesis and risk factors for nontuberculous mycobacterial lung disease. Clin Chest Med 2015;36:1-11.

45. Iseman MD, Buschman DL, Ackerson LM. Pectus excavatum and scoliosis. Thoracic anomalies associated with pulmonary disease caused by Mycobacterium avium complex. Am Rev Respir Dis 1991;144:914-6.

46. Kartalija M, Ovrutsky AR, Bryan CL, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. Am J Respir Crit Care Med 2013;187:197-205.

47. Chan ED, Iseman MD. Slender, older women appear to be more susceptible to nontuberculous mycobacterial lung disease. Gend Med 2010;7:5-18.

48. Lee SJ, Ryu YJ, Lee JH, Chang JH, Shim SS. The impact of low subcutaneous fat in patients with nontuberculous mycobacterial lung disease. Lung 2014;192:395-401.

49. Park KG, Park KS, Kim MJ, et al. Relationship between serum adiponectin and leptin concentrations and body fat distribution. Diabetes Res Clin Pract 2004;63:135-42.

50. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716-24.

51. Portillo K, Morera J. Nutritional status and eating disorders: neglected risks factor for nontuberculous mycobacterial lung disease? Med Hypotheses 2012;78:39-41.

52. Morimoto K, Yoshiyama T, Kurashima A, et al. Nutritional indicators are correlated with the radiological severity score in patients with Mycobacterium avium complex pulmonary disease: a cross-sectional study. Intern Med 2014;53:397-401.

53. Livraghi A, Randell SH. Cystic fibrosis and other respiratory diseases of impaired mucus clearance. Toxicol Pathol 2007;35:116-29.

54. Middleton AM, Chadwick MV, Nicholson AG, et al. Inhibition of adherence of Mycobacterium avium complex and Mycobacterium tuberculosis to fibronectin on the respiratory mucosa. Respir Med 2004;98:1203-6.

55. Middleton AM, Chadwick MV, Nicholson AG, et al. The role of Mycobacterium avium complex fibronectin attachment protein in adherence to the human respiratory mucosa. Mol Microbiol 2000;38:381-91.

56. Hamosh A, FitzSimmons SC, Macek M, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998;132:255-9.

57. Raju SV, Solomon GM, Dransfield MT, Rowe SM. Acquired Cystic Fibrosis Transmembrane Conductance Regulator Dysfunction in Chronic Bronchitis and Other Diseases of Mucus Clearance. Clin Chest Med 2016;37:147-58.

58. Girodon E, Cazeneuve C, Lebargy F, et al. CFTR gene mutations in adults with disseminated bronchiectasis. Eur J Hum Genet 1997;5:149-55.

59. Lake MA, Ambrose LR, Lipman MC, Lowe DM. "Why me, why now?" Using clinical immunology and epidemiology to explain who gets nontuberculous mycobacterial infection. BMC Med 2016;14:54.

60. Safdar A, White DA, Stover D, Armstrong D, Murray HW. Profound interferon gamma deficiency in patients with chronic pulmonary nontuberculous mycobacteriosis. Am J Med 2002;113:756-9.

61. Kwon YS, Kim EJ, Lee SH, et al. Decreased cytokine production in patients with nontuberculous mycobacterial lung disease. Lung 2007;185:337-41.

62. Greinert U, Schlaak M, Rüsch-Gerdes S, Flad HD, Ernst M. Low in vitro production of interferon-gamma and tumor necrosis factor-alpha in HIV-seronegative patients with pulmonary disease caused by nontuberculous mycobacteria. J Clin Immunol 2000;20:445-52.

63. Lim A, Allison C, Price P, Waterer G. Susceptibility to pulmonary disease due to Mycobacterium avium-intracellulare complex may reflect low IL-17 and high IL-10 responses rather than Th1 deficiency. Clin Immunol 2010;137:296-302.

64. Dorman SE, Picard C, Lammas D, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet 2004;364:2113-21.

65. Surolia R, Karki S, Wang Z, et al. Attenuated heme oxygenase-1 responses predispose the elderly to pulmonary nontuberculous mycobacterial infections. Am J Physiol Lung Cell Mol Physiol 2016;311:L928-L40.

66. Regev D, Surolia R, Karki S, et al. Heme oxygenase-1 promotes granuloma development and protects against dissemination of mycobacteria. Lab Invest 2012;92:1541-52.

67. Ovrutsky AR, Merkel PA, Schonteich E, et al. Patients with non-tuberculous mycobacterial lung disease have elevated transforming growth factor-beta following ex vivo stimulation of blood with live Mycobacterium intracellulare. Scand J Infect Dis 2013;45:711-4.

68. Maekawa K, Ito Y, Hirai T, et al. Environmental risk factors for pulmonary Mycobacterium avium-intracellulare complex disease. Chest 2011;140:723-9.

69. Dirac MA, Horan KL, Doody DR, et al. Environment or host?: A case-control study of risk factors for Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2012;186:684-91.

70. van Ingen J. Microbiological diagnosis of nontuberculous mycobacterial pulmonary disease. Clin Chest Med 2015;36:43-54.

71. Ochiai S, Kido Y, Tanoue S, et al. [Evaluation of CT appearance of Mycobacterium avium complex infection–comparison with bronchiectasia]. Kekkaku 2000;75:341-7.

72. Swensen SJ, Hartman TE, Williams DE. Computed tomographic diagnosis of Mycobacterium avium-intracellulare complex in patients with bronchiectasis. Chest 1994;105:49-52.

73. Lee G, Lee KS, Moon JW, et al. Nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Natural course on serial computed tomographic scans. Ann Am Thorac Soc 2013;10:299-306.

74. Sugihara E, Hirota N, Niizeki T, et al. Usefulness of bronchial lavage for the diagnosis of pulmonary disease caused by Mycobacterium avium-intracellulare complex (MAC) infection. J Infect Chemother 2003;9:328-32.

75. Tanaka E, Amitani R, Niimi A, Suzuki K, Murayama T, Kuze F. Yield of computed tomography and bronchoscopy for the diagnosis of Mycobacterium avium complex pulmonary disease. Am J Respir Crit Care Med 1997;155:2041-6.

76. Higashi Y, Nakamura S, Tomono H, et al. [Serodiagnosis of the mycobacterium avium complex by using iga antibodies for the glycopeptidolipid core antigen]. Kekkaku 2016;91:27-32.

77. Kitada S, Levin A, Hiserote M, et al. Serodiagnosis of Mycobacterium avium complex pulmonary disease in the USA. Eur Respir J 2013;42:454-60.

78. Tran AC, Halse TA, Escuyer VE, Musser KA. Detection of Mycobacterium avium complex DNA directly in clinical respiratory specimens: opportunities for improved turnaround time and cost savings. Diagn Microbiol Infect Dis 2014;79:43-8.

79. Shrestha NK, Tuohy MJ, Hall GS, Reischl U, Gordon SM, Procop GW. Detection and differentiation of Mycobacterium tuberculosis and nontuberculous mycobacterial isolates by real-time PCR. J Clin Microbiol 2003;41:5121-6.

80. Bainomugisa A, Wampande E, Muchwa C, et al. Use of real time polymerase chain reaction for detection of M. tuberculosis, M. avium and M. kansasii from clinical specimens. BMC Infect Dis 2015;15:181.

81. Hirama T, Shiono A, Egashira H, et al. PCR-Based rapid identification system using bridged nucleic acids for detection of clarithromycin-resistant Mycobacterium avium-M. intracellulare complex isolates. J Clin Microbiol 2016;54:699-704.

82. Treglia G, Taralli S, Calcagni ML, Maggi F, Giordano A, Bonomo L. Is there a role for fluorine 18 fluorodeoxyglucose-positron emission tomography and positron emission tomography/computed tomography in evaluating patients with mycobacteriosis? A systematic review. J Comput Assist Tomogr 2011;35:387-93.

83. Demura Y, Tsuchida T, Uesaka D, et al. Usefulness of 18F-fluorodeoxyglucose positron emission tomography for diagnosing disease activity and monitoring therapeutic response in patients with pulmonary mycobacteriosis. Eur J Nucl Med Mol Imaging 2009;36:632-9.

84. Yamazaki Y, Danelishvili L, Wu M, et al. The ability to form biofilm influences Mycobacterium avium invasion and translocation of bronchial epithelial cells. Cell Microbiol 2006;8:806-14.

85. Xu HB, Jiang RH, Li L. Treatment outcomes for Mycobacterium avium complex: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis 2014;33:347-58.

86. Lam PK, Griffith DE, Aksamit TR, et al. Factors related to response to intermittent treatment of Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2006;173:1283-9.

87. Jeong BH, Jeon K, Park HY, et al. Intermittent antibiotic therapy for nodular bronchiectatic Mycobacterium avium complex lung disease. Am J Respir Crit Care Med 2015;191:96-103.

88. Wallace RJ, Brown-Elliott BA, McNulty S, et al. Macrolide/azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. Chest 2014;146:276-82.

89. Kobashi Y, Matsushima T, Oka M. A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary Mycobacterium avium complex disease. Respir Med 2007;101:130-8.

90. Koh WJ, Jeong BH, Jeon K, et al. Response to switch from intermittent therapy to daily therapy for refractory nodular bronchiectatic Mycobacterium avium complex lung disease. Antimicrob Agents Chemother 2015;59:4994-6.

91. Moon SM, Park HY, Kim SY, et al. Clinical characteristics, treatment outcomes, and resistance mutations associated with macrolide-resistant Mycobacterium avium complex lung disease. Antimicrob Agents Chemother 2016;60:6758-65.

92. Kadota T, Matsui H, Hirose T, et al. Analysis of drug treatment outcome in clarithromycin-resistant Mycobacterium avium complex lung disease. BMC Infect Dis 2016;16:31.

93. Figueira Gonçalves JM, Rodríguez González J. Lady Windermere Syndrome: does it occur only in women? Arch Bronconeumol 2016;52:538-9.

94. Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop KL. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. Clin Infect Dis 2009;49:e124-9.

95. Marras TK, Chedore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997 2003. Thorax 2007;62:661-6.

96. Kennedy TP, Weber DJ. Nontuberculous mycobacteria. An underappreciated cause of geriatric lung disease. Am J Respir Crit Care Med 1994;149:1654-8.