REVIEW ARTICLE
Iran J Allergy Asthma Immunol
April 2018; 17(2):100-109.

What Immunological Defects Predispose to Non-tuberculosis Mycobacterial Infections?

Esmaeil Mortaz[1,2,3], Milad Moloudizargari[1], Mohammad Varahram[4], Mehrnaz Movassaghi[3], Johan Garssen[2,5], Mehdi Kazempour Dizagie[4], Mehdi Mirsaeidi[6], and Ian M. Adcock[7]

[1] Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands
[3] Clinical Tuberculosis and Epidemiology Research Center, National Research Institute for Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Nutricia Research Centre for Specialized Nutrition, Utrecht, The Netherlands
[6] Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Miami, Coral Gables, Florida, USA
[7] Cell and Molecular Biology Group, Airways Disease Section, National Heart and Lung Institute, Imperial College London, London, UK

Received: 11 August 2017; Received in revised form: 18 September 2017; Accepted: 15 November 2017

ABSTRACT

Nontuberculous mycobacteria (NTM) are categorized as one of the large and diverse groups of environmental organisms which are abundant in water and soil. NTM cause a variety of diseases in humans that mainly affect the lung. A predisposition to pulmonary NTM is evident in patients with parenchymal structural diseases including bronchiectasis, emphysema, tuberculosis (TB), cystic fibrosis (CF), rheumatologic lung diseases and other chronic diseases with pulmonary manifestations. Lung infections are not the only consequences of being infected by NTM as they can also infect skin and soft tissue and may also cause lymphadenitis (predominantly in young children) and disseminated disease in human immunodeficiency virus (HIV)-infected patients or those with severely compromised immune system. NTM are also found in many subjects without any known risk factors. Although the recent advances in imaging and microbiologic techniques including gene sequencing have provided a better view of the problems caused by NTM and has enhanced our understanding of the disease, many uncertainties regarding the immunologic response to NTM still exist. There is also limited data on the immunogenetics of NTM infection. Here, the authors reviewed the main immunogenetic defects as well as other immunological conditions which are associated with an increased the risk of NTM infections.

Keywords: Immunodeficiency; Interferon; Interleukin-12; Lung disease; Non-tuberculous mycobacteria

Corresponding Author: Mohammad Varahram, MD, PhD; Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: (+98 21) 2610 9505, Fax: (+98 21) 2610 9484, E-mail: mo.varahram@gmail.com

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

INTRODUCTION

For a long time, nontuberculous mycobacteria (NTM) were considered as environmental organisms of limited clinical relevance. Population-based data regarding the incidence of lung diseases caused by NTM was scarce with voluntary-reported rates of 0.7 to 1.8 cases annually per 100,000 people worldwide.[1] However, in the past decade, the prevalence of NTM in the aged population has been shown to be significant being even higher than that of tuberculosis (TB) in the US.[2-4]

The general healthcare community recognized the importance and significance of disseminated *Mycobacterium* (*M.) avium* and *M. intracellulare* as major NTM infections during the human immunodeficiency virus (HIV) pandemic and the expansion of iatrogenic immunosuppression confirmed their infectious role.[5] The risk of NTM infection is increased in subjects with an abnormal immune system. For instance, a powerful anti- interferon (IFN)-γ activity within plasma was attributed to the existence of high affinity IFN-γ neutralizing autoantibodies in a patient with severe *M. cheloneae* infection.[6] Other studies have linked the presence of anti-IFN-γ antibodies to disease progression.[7,8] This indicates the clinical importance of immune dysregulation, which could lead to NTM infection.

Reports of the clinical significance of NTM isolates from lung specimens are variable. The highest rates reported are in the United States[2-4] and the most scarce epidemiologic data are available from Asian countries.[9] This may reflect the presence of many undiagnosed cases and the lack of documented data in countries with less sophisticated and organized healthcare systems. For instance, in South Korea, approximately 25% of patients from whom NTM, mainly *M. avium* complex and *M. abscessus*, were isolated showed clinical NTM lung infections with variable severities. These infections ranged from upper lobe cavitary manifestations to less severe clinical forms.[9] In eastern China, NTM comprised 60% of all smear positive clinical isolates with *M. intercellulare* being the most prevalent species of clinical importance.[2] A meta-analyses conducted in Iran, reported the prevalence of NTM to be 10.2% among culture positive tuberculosis cases with *M. simiae*, *M. intracellulare*, and *M. fortuitum*, being the most prevalent species.[10] Another study by the same team showed that 30% of multi-drug resistant TB patients had NTM and showed pulmonary signs of NTM infection.[11] The major underlying causes and risk factors among the studied patients included malignancies, organ transplantation and infection with HIV which all indicated the presence of direct or/and indirect immunosuppression.[11]

The environmental prevalence of NTM in the suburbs of Tehran is linked to the species isolated from clinical specimens with the most prevalent species being *M. farcinogens* and *M. fortuitum.*[12] These regional differences in both the prevalence of NTM infections and the major strains contributing to disease manifestations may reflect the importance of NTM infections in each geographical region. This provides opportunities for designing appropriate management measures to control the clinical burden of the disease. The present paper is a general overview of the major immunogenetic defects as well as other immunological conditions contributing to an increased risk of NTM infections.

NTM Infection in Immunocompromised Patients

The most prominent human factors that predispose humans to NTM can be classified into two main categories: pre-existing structural lung disease and patients with one or more of a variety of genetic defects in cell-mediated immune pathways.[13] The second group of factors all cause an immunocompromising state giving rise to a defective immune response against NTM. These factors include interleukin (IL)-12/IFN-γ axis abnormalities, association with certain HLAs, autosomal and X-linked mutations and polymorphisms of several genes whose function is important in macrophage function.[13,14] We summarize here some of the most important of these immunological factors.

Primary and Secondary Immunodeficiency Patients

NTM is more prevalent in primary and secondary immune deficiency disorders (Figure 1). Mendelian susceptibility to *M. tuberculosis* (MSMD) is a primary immunodeficiency in which patients bear mutations in critical cytokine pathways such as IL-12B, the IL-12 receptor (IL-12R) β1 or the IFN-γ receptors (IFN-γR)1[15-17] and IFN-γR2 predisposing them to NTM infection.[18]

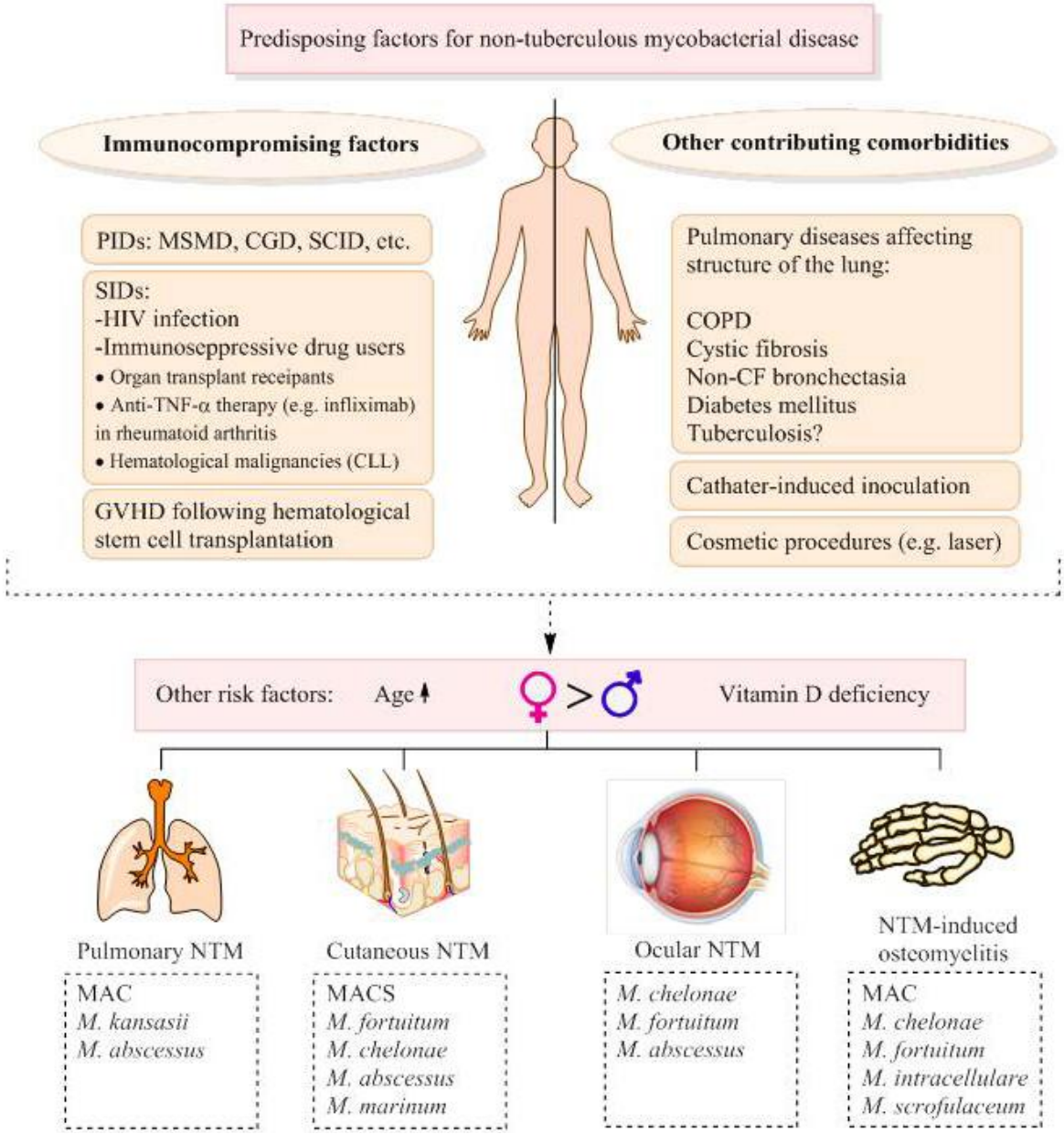

Figure 1. Important predisposing factors of nontuberculous mycobacteria (NTM). Primary and secondary immunodeficiencies, immunosuppressive agents and graft versus host disease following hematopoietic stem cell transplantation predispose individuals to NTM infections. Moreover, chronic obstructive pulmonary disease, cystic fibrosis, non-CF bronchectasia, diabetes mellitus and concurrent infection with mycobacterium tuberculosis are risk factors for NTM. NTM infection has a range of manifestations including pulmonary, cutaneous, ocular, disseminated disease (mainly in HIV positive patients) and NTM-induced osteomyelitis. Cosmetic procedures are also a risk factor for NTM. The major species responsible for infection at each site are shown.

NTM, Non-tuberculous Mycobacteria; PID, Primary Immunodeficiency; MSMD, Mendelian Susceptibility for Mycobacterial Disease; CGD, Chronic Granulomatous Disease; SCID, Severe Combined Immunodeficiency; SID, Secondary Immunodeficiency; HIV, Human Immunodeficiency Virus; CLL, Chronic Lymphocytic Leukemia; GVHD, Graft Versus Host Disease; COPD, Chronic Obstructive Pulmonary Disease; CF, Cystic Fibrosis.

Mutations in the transcription factor STAT1[19-21] results in a failure to respond to signals from type I (IFNα/β), type II (IFN-γ) and type III (IFNλ1/ 2/3) interferons resulting in an enhanced risk of mycobacterial and viral infections. A similar effect is seen in subjects with a deficiency in tyrosine kinase 2 (TYK2), a janus kinase widely active in cytokine signaling. Tyk2 depletion prevents signaling from the IL-12-IL-12Rβ1 complex resulting in defective control of mycobacterial infection.[22] Production of IL-12 in response to IFN-γ is hindered by mutations in interferon regulatory factor (IRF)-8[23] and mutations in interferon stimulated gene (ISG)-15 confers susceptibility to NTM.[24] NTM susceptibility is also caused by a deficiency in nuclear factor-κB essential modulator (NEMO). This implicates NF-κB and, by extrapolation, its upstream drivers tumour necrosis factor (TNF) and/or signaling via Toll-like receptors (TLRs) in NTM infection.[25,26] An increase in local and/or systemic complications following vaccination with bacillus Calmette-Guérin (BCG) is seen in some primary immunodeficiencies such as chronic granulomatous disease (CGD).[27] A defect in mononuclear phagocytes is the simplest explanation for NTM susceptibility although several other factors such as natural killer (NK) cell deficiency and impaired cytokine release have also been evoked.[28-30] A significant risk of NTM infection is found with autosomal dominant deficiency of the transcription factor GATA-2.[31]

Patients with immunodeficiencies that profoundly affect the number or function of T cells are at risk of NTM infection as well as by many other intracellular pathogens. This includes severe combined immune deficiency (SCID)[32] and isolated CD4+ T cell deficiency[33] which is associated with both pulmonary and disseminated NTM infection. HIV infection, especially in patients with CD4+ T cell counts of less than 50/μl of blood, is associated with the considerable proportion of NTM infections seen in secondary immunodeficiencies.[34] Based on the type and severity of immunosuppression, the symptoms and manifestation of NTM pulmonary disease vary among immunosuppressed patients. *Mycobacterium avium* complex (MAC) are the most common species isolated from NTM patients in the US.[35] They are also the most common cause for the disseminated NTM disease in patients with systemic immunosuppression (e.g. HIV infection) and severe CD4 cell depletion.[35] Historically, 43% of AIDS patients had disseminated NTM infections, defined as NTM isolation from either blood or mesenteric lymph nodes on autopsy, in the pre-anti-retroviral therapy (ART) era.[36]

NTM affects the respiratory system irrespective of whether it is due to primary or secondary infection. Pulmonary disease in the form of a single NTM manifestation, is rare in HIV patients, and is present in only 2.5% of 200 patients with disseminated MAC infection. Recently, Amran et al. reported the presence of elevated levels of cytomegalovirus (CMV) antibodies in plasma from patients with stable pulmonary NTM disease. Higher levels of CMV antibodies in NTM patients may be an indication of frequent episodes of CMV reactivation. This suggests that NTM patients may have CMV end-organ disease but they often experience non-specific symptoms (fever, malaise, etc) consistent with CMV reactivation.[37]

Haematological Malignancies

There is evidence of an increased prevalence of NTM infection in patients with hematological malignancies. The mean prevalence of NTM infection is 1.2% in patients with hematological malignancies whilst it ranged from 0.3% to 3.8% in patients with myeloma and chronic lymphoid leukemia respectively.[38] In addition, the incidence of NTM infection among hematopoietic stem cell recipients ranges from 0.4% to 4.9%.[39-42] These rates are far higher than the prevalence rate in the normal population[34-46] and suggest that NTM may be an opportunistic infection in patients with hematological malignancies.

Anti-TNF-α Therapy

A dramatic increase in the number of NTM reports has been associated with anti–TNF-α therapy.[47] The majority of patients with anti–TNF-α–related NTM were elderly women suffering from rheumatoid arthritis (RA). Several factors may explain these findings. Firstly, RA is the most prevalent autoimmune inflammatory disease for which anti–TNF-α therapies have been used.[48] Approximately 0.5%–1.0% of the US population suffer from RA[49,50] and almost 40% of these are on anti-TNF-α therapy.[48] Secondly, about 10% of RA patients suffer from rheumatoid lung disease which causes bronchiolitis and bronchiectasis which are known risk factors for NTM disease.[51] Moreover,

pulmonary NTM disease and RA are more common among women older than 50 irrespective of anti–TNF-α therapy.[1] Finally, a high percentage of patients receiving anti–TNF-α therapy may have serious co-morbid conditions that increase the risk of NTM infection.[52]

The risk of pulmonary and disseminated TB is increased using TNF-α inhibitors[53,54] and consequently this may also increase the risk for NTM disease following TB-induced remodeling.[55-57] Despite aggressive anti-mycobacterial treatment, pulmonary NTM disease progressed in TB patients whilst they were receiving anti–TNF-α therapy.[58] Although this can lead to serious sickness and even death, the safety of continuing anti–TNF-α therapy during anti-mycobacterial therapy needs clarification. Furthermore, the timing of when, or if, it is safe to restart anti–TNF-α therapy in such patients is unclear.

Defective IL-12-IFN-γ Axis

The IFN-γ–IL-12 axis is another important player in controlling mycobacteria as well as other opportunistic pathogens.[59] High-titer neutralizing anti–IFN-γ autoantibodies cause a syndrome of disseminated NTM and other opportunistic infections which may be prevented by anti-CD20 (rituximab) treatment.[60-61] MSMD is a state of predisposition to weakly virulent mycobacteria as well as other pathogens such as salmonella, and is linked with mutations in the genes involved in the IL-12/IFN-γ axis. These include different components of the IFN-γ receptor (IFNGR) downstream signaling pathways.[62,63] Based on the type of inheritance pattern and the affected component, which are mainly due to IFNGR1 and IFNGR2 genes, partial or complete deficiencies may arise.[63]

Other Risk Factors for NTM Infection

Age increases the susceptibility to pulmonary NTM (p-NTM) disease with the mean age at presentation in the US being 68.2 years.[64] In addition, the prevalence of pulmonary NTM is greater in females than in males[65-67] and females with non-CF bronchiectasis had the highest risk.[68,69] Experiments in ovariectomised mice showed that estrogen enhances the clearance of MAC and the greater susceptibility of females may be because of low post-menopausal estrogen levels.[70] However, this has not been supported conclusively in humans.[5,71]

Severe vitamin D deficiency may also contribute to pulmonary NTM disease.[72] There is a link with vitamin D receptor (VDR) polymorphisms but, overall, the mechanism is not as clear as it is for *M. tuberculosis.*[73-76] A systematic review showed that the prevalence of NTM disease is increasing as the burden of TB declines.[47] This may reflect NTM being misdiagnosed as TB. In a previous study on 27 subjects with multi-drug resistant TB (MDR-TB) in Iran, our team reported NTM in 10%-30% of subjects with suspected MDR-TB.[10,77] The financial burden imposed both on the patient and the healthcare system necessitates considering NTM infections in every patient with suspected MDR-TB.

NTM Infection Manifestations

NTM Pulmonary Disease

Multiple isolates of NTM species from respiratory secretions might be indicative of true disease. Haematopoietic stem cell and solid organ transplant (SOT) recipients are in risk for pulmonary NTM with an incidence rate of 0.2–5%.[68,78,79] Pulmonary infection resulted from rapidly growing mycobacteria is the most common NTM infection among stem cell transplant recipients. NTM is also the second most common cause of catheter-related infections in this group of patients.[78] Graft versus host disease is a risk factor for NTM which mainly occurs within the first half-year post-transplantation. A high mortality rate occurs in organ transplant patients with NTM pulmonary disease. For instance, there is a 3-year mortality rate of 69% in patients with *M. xenopi* pulmonary disease in a French cohort.[80]

However, other factors such as NTM disease severity, the precise NTM species,[81,82] patient age and underlying comorbidities may explain the poor outcome and mortality in lung transplant recipients compared to hematologic malignancies (lung, 15 months; kidney, 24 months; heart, 30 months).[78] NTM treatment should be instituted according to published guidelines.[67,68] Drug interactions between antibiotics and immunosuppressive agents pose a potential risk and patients should be closely monitored for side effects.[68,83]

NTM Cutaneous Disease

After pulmonary disease, skin and soft tissues are the organs most commonly affected by NTM. Almost all NTM species can cause cutaneous infections, however, some species such as *M. marinum*, *M.*

abscessus, *M. fortuitum* and *M. chelonae* are most common.[84] Infectious post-operational complications are among the major adverse effects associated with cosmetic surgery.[85] Disruption of the skin barrier is necessary for NTM to cause infection and ablative resurfacing using lasers provides an ideal opportunity for saprophytic NTM to penetrate this barrier. Although uncommon, NTM infections constitute a considerable proportion of skin infections.[86]

The presence of anti-IFN-γ auto-antibodies causing adult immunodeficiencies can result in disseminated NTM infections. These might also manifest as reactive dermatological conditions such as the sweet`s syndrome, a type of neutrophil-mediated dermatosis.[87]

NTM-Induced Osteomyelitis

Defects in the IFN-γ-IL-12 axis, infection or other immunocompromising conditions enable disseminated NTM infections to occur in the skeletal system and joints. Although the prognosis is poor and the pathogenesis is not yet well-understood, long-term antibiotic therapy using combinations of drugs has improved the outcome of NTM-induced osteomyelitis.[88]

NTM Ocular Disease

Despite a few early reports of NTM-related ocular conditions such as choroid plexus inflammation and endophthalmitis, the emergence of laser-assisted in situ keratomileusis (LASIK) has resulted in a noticeable increase in the number of NTM-related keratitis cases.[89] NTM infections of the eye target a number of structures resulting in ocular, intraocular and periocular infections as well as keratitis and uveitis. Early diagnosis of NTM infections of the eye is a constant challenge for clinicians and despite being uncommon, delayed diagnosis can be highly detrimental to the patient. The most common species involved are *M. chelonae*, *M. abscessus*, and *M. fortuitum.*[90]

Future Directions and Perspectives

The mechanism(s) by which the human immune system responds to NTM is still unclear. Further investigations are required to determine the role of genetics in enabling NTM infections. Functional mutations due to single nucleotide polymorphisms in immune genes may be responsible for the increased susceptibility to NTM even in patients with underlying pulmonary diseases including COPD.

Concluding Remarks

NTMs are associated with a number of lung disorders particularly in patients with bronchiectasis, emphysema, TB, cystic fibrosis and with other chronic diseases such as RA. The compromised immune system is the pivotal risk factor giving rise to NTM infections. This can be the result of primary defects in the main pathways of the immune system as well as secondary causes of immunosuppression. Secondary causes include the use of immunosuppressive drugs, infections, and any other conditions that might contribute to a weakened immune response against mycobacterial infections, The infection is disseminated in HIV-infected patients or those with severely compromised immune systems. A major challenge for both clinicians and researchers is the lack of a definitive immune mechanism that drives the predisposition to NTM disease. The changing pattern of infections in many regions from TB to NTM highlights the importance of NTM infections as a clinical concern. More research into the epidemiology and immunology of NTM is required to enable improvements in clinical management. Moreover, identification of the infective species in individuals from different regions where NTM is prevalent may aid in the early diagnosis of NTM disease.

REFERENCES

1. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007; 175(4):367-416.
2. Adjemian J, Frankland TB, Daida YG, Honda JR, Olivier KN, Zelazny A, et al. Epidemiology of nontuberculous mycobacterial lung disease and tuberculosis, Hawaii, USA. Emerg Infect Dis 2017; 23(3):439-47.
3. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in US Medicare beneficiaries. Am J Respir Crit Care Med 2012; 185(8):881-6.
4. Mirsaeidi M, Farshidpour M, Allen MB, Ebrahimi G, Falkinham JO. Highlight on advances in nontuberculous mycobacterial disease in North America. Biomed Res Int 2014; 2014:919474.
5. 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(1):1.

6. Höflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Döcke W-D, et al. Naturally occurring anti–IFN-γ autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans. Blood 2004; 103(2):673-5.
7. Shima K, Sakagami T, Tanabe Y, Aoki N, Moro H, Koya T, Kagamu H, Hasegawa T, Suzuki E, Narita I. Novel assay to detect increased level of neutralizing anti-interferon gamma autoantibodies in non-tuberculous mycobacterial patients. J Infect Chemother. 2014 Jan;20(1):52-6. 8. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, et al. Anti-IFN-γ autoantibodies in disseminated nontuberculous mycobacterial infections. J Immunol 2005; 175(7):4769-76.
9. Koh WJ, Kwon OJ, Jeon K, Kim TS, Lee KS, Park YK, et al. Clinical significance of nontuberculous mycobacteria isolated from respiratory specimens in Korea. Chest 2006; 129(2):341-8.
10. Nasiri MJ, Dabiri H, Darban-Sarokhalil D, Shahraki AH. Prevalence of non-tuberculosis mycobacterial infections among tuberculosis suspects in Iran: systematic review and meta-analysis. PloS one 2015; 10(6):e0129073.
11. Shahraki AH, Heidarieh P, Bostanabad SZ, Khosravi AD, Hashemzadeh M, Khandan S, et al. "Multidrug-resistant tuberculosis" may be nontuberculous mycobacteria. Eur J Intern Med 2015; 26(4):279-84.
12. Velayati AA, Farnia P, Mozafari M, Malekshahian D, Seif S, Rahideh S, et al. Molecular epidemiology of nontuberculous mycobacteria isolates from clinical and environmental sources of a metropolitan city. PloS one 2014; 9(12):e114428.
13. Sexton P, Harrison A. Susceptibility to nontuberculous mycobacterial lung disease. Eur Respir J 2008; 31(6):1322-33.
14. Wu U-I, Holland SM. Host susceptibility to non-tuberculous mycobacterial infections. Lancet Infect Dis 2015; 15(8):968-80.
15. Holland SM, Dorman SE, Kwon A, Pitha-Rowe IF, Frucht DM, Gerstberger SM, et al. Abnormal regulation of interferon-γ, interleukin-12, and tumor necrosis factor-α in human interferon-γ receptor 1 deficiency. J Infect Dis 1998; 178(4):1095-104.
16. Jouanguy E, Dupuis S, Pallier A, Döffinger R, Fondanèche M-C, Fieschi C, et al. In a novel form of IFN-γ receptor 1 deficiency, cell surface receptors fail to bind IFN-γ. J Clin Invest 2000; 105(10):1429-36.
17. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, et al. A mutation in the interferon-γ–receptor gene and susceptibility to mycobacterial infection. N Engl J Med 1996; 335(26):1941-9.
18. Dorman SE, Holland SM. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. J Clin Invest 1998; 101(11):2364.
19. Chapgier A, Kong X-F, Boisson-Dupuis S, Jouanguy E, Averbuch D, Feinberg J, et al. A partial form of recessive STAT1 deficiency in humans. J Clin Invest 2009; 119(6):1502-14.
20. Dupuis S, Dargemont C, Fieschi C, Thomassin N, Rosenzweig S, Harris J, et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. Science. 2001; 293(5528):300-3.
21. Sampaio EP, Bax HI, Hsu AP, Kristosturyan E, Pechacek J, Chandrasekaran P, et al. A novel STAT1 mutation associated with disseminated mycobacterial disease. J Clin Immunol 2012;32(4):681-9.
22. Kreins AY, Ciancanelli MJ, Okada S, Kong X-F, Ramírez-Alejo N, Kilic SS, et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. J Exp Med 2015; 212(10):1641-62.
23. Hambleton S, Salem S, Bustamante J, Bigley V, Boisson-Dupuis S, Azevedo J, et al. IRF8 mutations and human dendritic-cell immunodeficiency. N Engl J Med 2011; 365(2):127-38.
24. Bogunovic D, Byun M, Durfee LA, Abhyankar A, Sanal O, Mansouri D, et al. Mycobacterial disease and impaired IFN-γ immunity in humans with inherited ISG15 deficiency. Science 2012; 337(6102):1684-8.
25. Filipe-Santos O, Bustamante J, Haverkamp MH, Vinolo E, Ku C-L, Puel A, et al. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. J Exp Med 2006; 203(7):1745-59.
26. Nedorost ST, Elewski B, Tomford JW, Camisa C. Rosacea-like lesions due to familial Mycobacterium avium-intracellulare infection. Int J Dermatol 1991; 30(7):491-7.
27. Deffert C, Cachat J, Krause KH. Phagocyte NADPH oxidase, chronic granulomatous disease and mycobacterial infections. Cell Microbiol 2014; 16(8):1168-78.
28. Dickinson RE, Milne P, Jardine L, Zandi S, Swierczek SI, McGovern N, et al. The evolution of cellular deficiency in GATA2 mutation. Blood 2014; 123(6):863-74.
29. Spinner MA, Sanchez LA, Hsu AP, Shaw PA, Zerbe CS, Calvo KR, et al. GATA2 deficiency: a protean disorder of

hematopoiesis, lymphatics, and immunity. Blood 2014;123(6):809-21.
30. Collin M, Dickinson R, Bigley V. Haematopoietic and immune defects associated with GATA2 mutation. Br J Haematol 2015; 169(2):173-87.
31. Hsu AP, Sampaio EP, Khan J, Calvo KR, Lemieux JE, Patel SY, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. Blood 2011; 118(10):2653-5.
32. Marciano BE, Huang C-Y, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. J Allergy Clin Immunol 2014; 133(4):1134-41.
33. Ahmad DS, Esmadi M, Steinmann WC. Idiopathic CD4 Lymphocytopenia: Spectrum of opportunistic infections, malignancies, and autoimmune diseases. Avicenna J Med 2013; 3(2):37.
34. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992; 165(6):1082-5.
35. Mirsaeidi M, Vu A, Leitman P, Sharifi A, Wisliceny S, Leitman A, et al. A Patient-Based Analysis of the Geographic Distribution of Mycobacterium avium complex, Mycobacterium abscessus, and Mycobacterium kansasii Infections in the United States. Chest 2017; 151(4):947-50.
36. Ristola MA, von Reyn CF, Arbeit RD, Soini H, Lumio J, Ranki A, et al. High rates of disseminated infection due to non-tuberculous mycobacteria among AIDS patients in Finland. J Infect 1999; 39(1):61-7.
37. Amran FS, Kim K, Lim A, Thomson R, Lee S, Waterer G, et al. Is Pulmonary non-Tuberculous Mycobacterial Disease Linked with a High Burden of Latent Cytomegalovirus? J Clin Immunol 2016; 36(2):113-6.
38. Chen C-Y, Sheng W-H, Lai C-C, Liao C-H, Huang Y-T, Tsay W, et al. Mycobacterial infections in adult patients with hematological malignancy. Eur J Clin Microbiol Infect Dis 2012; 31(6):1059-66.
39. Almyroudis N, Fabian J, Hahn T, Segal B, Wetzler M, McCarthy Jr P. Late infectious complications after cord blood stem cell transplantation. Eur J Clin Microbiol Infect Dis 2009; 28(11):1405-8.
40. Au W, Cheng V, Ho P, Yuen K, Hung I, Ma S, et al. Nontuberculous mycobacterial infections in Chinese hematopoietic stem cell transplantation recipients. Bone Marrow Transplant 2003; 32(7):709-14.
41. Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 2004; 38(10):1428-39.
42. Weinstock D, Feinstein M, Sepkowitz K, Jakubowski A. High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2003; 31(11):1015-21.
43. Khan K, Wang J, Marras TK. Nontuberculous mycobacterial sensitization in the United States: national trends over three decades. Am J Respir Crit Care Med 2007; 176(3):306-13.
44. Lai C-C, Tan C-K, Chou C-H, Hsu H-L, Liao C-H, Huang Y-T, et al. Increasing incidence of nontuberculous mycobacteria, Taiwan, 2000–2008. Emerg Infect Dis 2010; 16(2):294-6.
45. Marras TK, Chedore P, Ying AM, Jamieson F. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997–2003. Thorax 2007; 62(8):661-6.
46. Simons S, van Ingen J, Hsueh PR, Van Hung N, Dekhuijzen PN, Boeree MJ, van Soolingen D. Nontuberculous mycobacteria in respiratory tract infections, eastern Asia. Emerg Infect Dis 2011; 17(3):343-9.
47. Wallis R, Broder M, Wong J, Hanson M, Beenhouwer D. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004; 38(9):1261-5.
48. Furst D, Breedveld F, Kalden J, Smolen J, Burmester G, Sieper J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis 2007; 66(suppl 3):iii2-iii22.
49. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001; 27(2):269-81.
50. Allaire S, Wolfe F, Niu J, Zhang Y, Zhang B, LaValley M. Evaluation of the effect of anti–tumor necrosis factor agent use on rheumatoid arthritis work disability: the jury is still out. Arthritis Rheum 2008; 59(8):1082-9.
51. Mirsaeidi M, Hadid W, Ericsoussi B, Rodgers D, Sadikot RT. Non-tuberculous mycobacterial disease is common in patients with non-cystic fibrosis bronchiectasis. Int J Infect Dis 2013; 17(11):e1000-4.
52. Hyrich K, Symmons D, Watson K, Silman A, Consortium BCC. Baseline comorbidity levels in biologic and standard DMARD treated patients with rheumatoid arthritis: results from a national patient register. Ann Rheum Dis 2006; 65(7):895-8.
53. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis

associated with infliximab, a tumor necrosis factor α–neutralizing agent. N Engl J Med 2001; 345(15):1098-104.
54. Mohan AK, Timothy RC, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis 2004; 39(3):295-9.
55. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. Emerg Infect Dis 2009; 15(10):1556-61.
56. Van Ingen J, Boeree M, Janssen M, Ullmann E, De Lange W, De Haas P, et al. Pulmonary Mycobacterium szulgai infection and treatment in a patient receiving anti-tumor necrosis factor therapy. Nat Clin Pract Rheumatol 2007; 3(7):414-9.
57. Maimon N, Brunton J, Chan AK, Marras TK. Fatal pulmonary Mycobacterium xenopi in a patient with rheumatoid arthritis receiving etanercept. Thorax 2007; 62(8):739-40.
58. Mori S, Sugimoto M. Is continuation of anti-tumor necrosis factor-α therapy a safe option for patients who have developed pulmonary mycobacterial infection? Clin Rheumatol 2012; 31(2):203-10.
59. Dorman SE, Holland SM. Interferon-γ and interleukin-12 pathway defects and human disease. Cytokine Growth Factor Rev 2000; 11(4):321-33.
60. Browne SK, Zaman R, Sampaio EP, Jutivorakool K, Rosen LB, Ding L, et al. Anti-CD20 (rituximab) therapy for anti–IFN-γ autoantibody–associated nontuberculous mycobacterial infection. Blood 2012; 119(17):3933-9.
61. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-γ. J Clin Invest 2005; 115(9):2480-8.
62. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol 2014; 26(6):454-70.
63. Cottle L. Mendelian susceptibility to mycobacterial disease. Clin Genet 2011; 79(1):17-22.
64. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med 2015; 36(1):13-34.
65. Griffith DE, Girard WM, Wallace Jr RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria: an analysis of 154 patients. Am Rev Respir Dis 1993; 147(5):1271-8.
66. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 2008; 178(10):1066-74.
67. Prevots DR, Shaw PA, Strickland D, Jackson LA, Raebel MA, Blosky MA, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med 2010; 182(7):970-6.
68. Mirsaeidi M, Hadid W, Ericsoussi B, Rodgers D, Sadikot RT. Non-tuberculous mycobacterial disease is common in patients with non-cystic fibrosis bronchiectasis. Int J Infect Dis 2013; 17(11):e1000-e4.
69. Mirsaeidi M, Sadikot RT. Gender susceptibility to mycobacterial infections in patients with non-CF bronchiectasis. Int J Mycobacteriol 2015; 4(2):92-6.
70. Tsuyuguchi K, Suzuki K, Matsumoto H, Tanaka E, Amitani R, Kuze F. Effect of oestrogen on Mycobacterium avium complex pulmonary infection in mice. Clin Exp Immunol 2001; 123(3):428-34.
71. Danley J, Kwait R, Peterson DD, Sendecki J, Vaughn B, Nakisbendi K, et al. Normal estrogen, but low dehydroepiandrosterone levels, in women with pulmonary Mycobacterium avium complex. A preliminary study. Ann Am Thorac Soc 2014; 11(6):908-14.
72. Jeon K, Kim SY, Jeong BH, Chang B, Shin SJ, Koh WJ. Severe vitamin D deficiency is associated with non-tuberculous mycobacterial lung disease: A case-control study. Respirology 2013; 18(6):983-8.
73. Chun RF, Adams JS, Hewison M. Immunomodulation by vitamin D: implications for TB. Expert Rev Clin Pharmacol 2011; 4(5):583-91.
74. Mirsaeidi M. Personalized medicine approach in mycobacterial disease. Int J Mycobacteriol 2012; 1(2):59-64.
75. Banoei MM, Mirsaeidi MS, Houshmand M, Tabarsi P, Ebrahimi G, Zargari L, et al. Vitamin D receptor homozygote mutant tt and bb are associated with susceptibility to pulmonary tuberculosis in the Iranian population. Int J Infect Dis 2010; 14(1):e84-5.
76. Chen C, Liu Q, Zhu L, Yang H, Lu W. Vitamin D receptor gene polymorphisms on the risk of tuberculosis, a meta-analysis of 29 case-control studies. PLoS One 2013; 8(12):e83843.
77. Shahraki AH, Heidarieh P, Bostanabad SZ, Khosravi AD, Hashemzadeh M, Khandan S, et al. "Multidrug-resistant tuberculosis" may be nontuberculous mycobacteria. Eur J Intern Med 2015; 26(4):279-84.
78. Hojo M, Iikura M, Hirano S, Sugiyama H, Kobayashi N, Kudo K. Increased risk of nontuberculous mycobacterial

infection in asthmatic patients using long-term inhaled corticosteroid therapy. Respirology 2012; 17(1):185-90.
79. Chu H, Zhao L, Xiao H, Zhang Z, Zhang J, Gui T, et al. Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: a meta-analysis. Arch Med Sci 2014; 10:661-8.
80. Andrejak C, Lescure F-X, Pukenyte E, Douadi Y, Yazdanpanah Y, Laurans G, et al. Mycobacterium xenopi pulmonary infections: a multicentric retrospective study of 136 cases in north-east France. Thorax 2009; 64(4):291-6.
81. Andréjak C, Lescure F-X, Douadi Y, Laurans G, Smail A, Duhaut P, et al. Non-tuberculous mycobacteria pulmonary infection: management and follow-up of 31 infected patients. J Infect 2007; 55(1):34-40.
82. Society RCotBT. First randomised trial of treatments for pulmonary disease caused by M avium intracellulare, M malmoense, and M xenopi in HIV negative patients: rifampicin, ethambutol and isoniazid versus rifampicin and ethambutol. Thorax 2001; 56(3):167-72.
83. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax 2013; 68(3):256-62.
84. Lamb RC, Dawn G. Cutaneous non-tuberculous mycobacterial infections. Int J Dermatol 2014; 53(10):1197-204.
85. Hypolite T, Grant-Kels JM, Chirch LM. Nontuberculous mycobacterial infections: a potential complication of cosmetic procedures. Int J Womens Dermatol 2015; 1(1):51-4.
86. Berliner JG, Aldabagh B, Mully T, Yu SS, Schwartz BS, Berger TG. Non-tuberculous mycobacterial infections following cosmetic laser procedures: a case report and review of the literature. J Drugs Dermatol 2015; 14(1):80-3.
87. Chan J-W, Trendell-Smith NJ, Chan J-Y, Hung I-N, Tang B-F, Cheng V-C, et al. Reactive and infective dermatoses associated with adult-onset immunodeficiency due to anti-interferon-gamma autoantibody: Sweet's syndrome and beyond. Dermatology 2013; 226(2):157-66.
88. Bi S, Hu F-S, Yu H-Y, Xu K-J, Zheng B-W, Ji Z-K, et al. Nontuberculous mycobacterial osteomyelitis. Infect Dis (Lond) 2015; 47(10):673-85.
89. John T, Velotta E. Nontuberculous (atypical) mycobacterial keratitis after LASIK: current status and clinical implications. Cornea 2005; 24(3):245-55.
90. Kheir WJ, Sheheitli H, Abdul Fattah M, Hamam RN. Nontuberculous mycobacterial ocular infections: a systematic review of the literature. Biomed Res Int 2015; 2015:164989.