Pomeranian J Life Sci 2023;69(3):48-51 doi: 10.21164/pomjlifesci.933

Mycobacteria other than tuberculosis – prevalence, symptoms, diagnostics and treatment

Marcin Kołodziej[1, A ✉], Dominik Puls[2, B], Justyna Puls[3, C], Bartłomiej Pala[4, D], Łukasz Więcek[5, E], Piotr Promiński[6, F], Martyna Promińska[6, G]

[1] Grochowski Hospital, Department of General, Oncological and Reconstructive Surgery, Grenadierów 51/59, 04-073 Warszawa, Poland
[2] Pomeranian Medical University in Szczecin Hospital No. 1, Department of Anaesthesiology and Intensive Care, Unii Lubelskiej 1, 71-252 Szczecin, Poland
[3] Independent Public Specialist Health Care Center Zdroje, Department of Paediatrics, Pediatric Nephrology, Dialysis and Acute Poisoning Treatment, Mączna 4, 70-780 Szczecin, Poland
[4] Pomeranian Medical University in Szczecin Hospital No. 1, Department of Paediatrics Neurosurgery and Neurosurgery, Unii Lubelskiej 1, 71-252 Szczecin, Poland
[5] Nicolaus Copernicus University in Toruń, Ludwig Rydygier Collegium Medicum in Bydgoszcz, Jagiellońska 13/15, 85-067 Bydgoszcz, Poland
[6] Independent Public Provincial Complex Hospital, Hospital Emergency Department, Alfreda Sokołowskiego 11, 70-880 Szczecin, Poland

[A] ORCID: 0000-0002-1216-4905; [B] ORCID: 0009-0003-8823-6703; [C] ORCID: 0009-0005-6133-4690; [D] ORCID: 0000-0002-4156-6604; [E] ORCID: 0009-0001-4267-2986; [F] ORCID: 0009-0002-6623-6932; [G] ORCID: 0009-0007-7760-8187

✉ kazno996@gmail.com

ABSTRACT
As a class of bacteria, mycobacteria other than tuberculosis (MOTT), also known as nontuberculosis mycobacteria (NTM), affect both immunocompetents and immunodeficients. Non-specific clinical symptoms caused by these bacteria include respiratory diseases, which often results in delayed diagnosis. This article discusses the spread, diagnosis, symptoms, and treatment of MOTT in the world. In view of the fact that NTM are prevalent in the environment, their isolation from the upper respiratory system of the respiratory tract does not necessarily indicate an active infection. To make an accurate diagnosis, clinical, radiographic, and microbiological factors must be considered. Clinical symptoms of NTM infection can be difficult to diagnose, even for experienced clinicians, due to their similarity to Mycobacterium tuberculosis infection. Based on the determined antibiogram, targeted treatment can be selected based on identification and drug susceptibility of the microorganism. There are a variety of therapeutic options, depending on the pathogen's growth rate. However, it is always important to keep in mind the side effects of the drugs used and to choose the best treatment based on the individual patient's clinical condition.
Keywords: mycobacteria other than tuberculosis; tuberculosis pneumonia; nontuberculosis mycobacteria; tuberculosis treatment.

INTRODUCTION

Mycobacteria other than tuberculosis (MOTT), also known as nontuberculosis mycobacteria (NTM), are bacteria that are widespread worldwide and affect both immunocompetent and immunodeficient individuals. In recent years, an increase in the prevalence of this group of bacteria has been noticed, especially in developed countries, and thanks to new molecular methods, new species and subspecies of these mycobacteria have been discovered and classified, which currently number over 190. These bacteria are the cause of non-specific clinical symptoms, the most common of which include respiratory disease, which often results in delayed diagnosis. For this reason, in this article, we will focus on discussing the spread of MOTT in the world, diagnosis, symptoms of infection, and available treatments.

PREVALENCE

Mycobacteria other than tuberculosis bacilli are widespread in nature. They are found in soil, lakes, ponds, natural streams, and rivers. In addition to the natural environment, they are also commonly found in the human domestic environment. The sources of MOTT bacilli are plumbing systems in residential buildings, drinking water distribution systems, fountains, Jacuzzis, spas and showers. Mycobacteria have also been isolated from house dust and potting soil [1, 2, 3]. Assessment of the geographic prevalence of MOTT is difficult due to the lack of confirmed data from many countries where NTB infection is not subject to mandatory notification to public health authorities [4]. A global study of NTM species isolated from human samples showed that 47% of them belong to the *Mycobacterium avium* complex (MAC). It is widespread worldwide; however, the relative prevalence varies greatly depending on the geographical region – MAC accounted for 31% of South American isolates, 52% of North American and 71% of Australian isolates [5]. Regionally important species include *M. xenopi* and *M. malmoense.* The distribution of *M. xenopi* is primarily restricted to Europe and eastern Canada. *M. malmoense* has not been found in Queensland (Australia), Asia or South America [4, 5]. The MAC, along with *M. gordonae*, *M. xenopi*, *M. fortuitum* complex, *M. abscessus* and *M. kansasii*, account for about 80% of the identified species [5].

The most common MOTT species isolated in Europe are: *M. avium*, *M. gordonae*, *M. xenopi, Mycobacterium intracellulare* and *M. fortuitum*. Together, they account for ⅔ of the isolated samples [6]. The prevalence of nontuberculous mycobacterial pulmonary disease (NTM-PD) in Europe is estimated at 6.2/100,000 people. It is comparable between countries. On the other hand, considerable heterogeneity can be observed within countries, especially in France and Great Britain, where the highest prevalence was recorded in the vicinity of Paris and England, respectively [7]. In Poland, *M. kansasii, M. avium, M. xenopi, M. gordonae* and *M. intracellulare* are the most frequently isolated. According to data from the National Institute of Hygiene, 1114 cases of mycobacteriosis were detected in Poland in 2013–2017. In a study analyzing clinical samples from this period of time, which included 2799 isolates, it was shown that the number of detected MOTT bacilli in Poland increased 1.6 times, from 420 in 2013 to 674 in 2017 [1]. This trend is also noticeable in other countries. In the last 4 decades, the frequency of isolation and the incidence of infections caused by MOTT have significantly increased [3, 8]. In Canada, there was a significant increase in the infection rate from 29.3/100,000 inhabitants in 1998–2002 to 41.3/100,000 inhabitants in 2006–2010 [9]. In the US, the average incidence of NTM-PD 1997–2007 was 31 cases/100,000 people. During this period, the annual incidence increased significantly by 8.2%, from 20–47 cases/100,000 people [10]. In the UK, MOTT was isolated in 2012 in 6.1/100,000 inhabitants, while in 2007 it was 4/100,000 [11]. An increase in the frequency of isolation of MOTT bacilli over the years has also been noted in East Asian countries and Australia [12, 13, 14, 15, 16].

DIAGNOSTICS

Isolation of NTM is currently a significant problem for diagnosticians. Since NTM are widespread in the environment, their isolation from the upper respiratory system of the respiratory tract does not necessarily indicate an active infection. In order to make a diagnosis, it is necessary to pay attention to clinical, radiographic and microbiological signs. In the case of a patient with symptoms of a respiratory tract infection, also confirmed by imaging tests, specific microbiological criteria should be used to identify NTM [3, 17, 18, 19, 20].

As far as image criteria are concerned, NTM infections are divided into 2 forms. The first is the fibrocavitary form with cavitary lesions mostly in the upper lobes – similar to standard pulmonary tuberculosis, most often occurring in older men with nicotinism, which is associated with an aggressive course of a disease. The second form is nodular bronchiectatic disease, which manifests as multifocal bronchiectasis, a cluster of small nodules and branching linear structures, mostly in the right middle lobe and also the lingular segment of the left upper lobe [3, 17, 19].

The criteria of the American Thoracic Society and Infectious Disease Society of America are widely used criteria for the diagnosis of pneumonia caused by NTM. According to them, the clinical picture should include symptoms of respiratory tract infection, X-ray and computed tomography images. Microbiological criteria that should be met include 2 positive sputum cultures and 1 positive bronchial wash or lavage sample, but may also include other evidence such as lung biopsy samples with cultures of NTM [17, 18]. The above-mentioned criteria are effective in detecting MAC and *M. kansasii* strains; however, due to the lack of sufficient research, it cannot be concluded whether they are sufficient to recognize other NTM strains [17]. In nonpulmonary NTM infections, specimens from affected tissues or organs should be used; for example, lymph node involvement should be biopsied, blood culture should be taken for sepsis and skin involvement should also be taken by biopsy instead of samples as they are with a higher risk of contamination [19].

In the case of laboratory diagnostics, there is no pathognomonic test for NTM; the most commonly used acidfast bacillus preparations are not able to distinguish between *M. tuberculosis* and NTM. For this purpose, specialized tests should be used; for example, kits using acid amplification technology [3, 17, 18, 19]. The American Thoracic Society and the Infectious Disease Society of America require the isolation and growth of pathogens on 2 separate media from material collected from the patient in order to exclude possible contamination [20]. All tests, due to the high risk of contamination with other bacteria, carry the risk of ineffective culture; in some centers preparations are decontaminated using N-acetyl-1-cysteine-NaOH-oxalic acid (NALC-NaOH-OxA) or chlorhexidine [1]. These methods are approved by the Clinical Laboratory Standard Institute, but there is a suspicion that the first of them may affect the reliability of the result [19]. Mycobacteria are inoculated on solid and liquid media. In the case of solids, the diagnostician is able to assess the appearance of the colony, its growth rate and its shape on an ongoing basis. Liquid media are more sensitive and allow for faster identification of the pathogen, but they are also sensitive to contamination with other bacterial colonies [17, 18, 19]. The reference method used for the identification of NTM is currently gene sequencing; other molecular methods are also used, such as line probe hybridization, real-time polymerase chain reaction (PCR), PCR-restriction fragment length polymorphism analysis, DNA sequencing, or matrix-assisted laser desorption ionization-time of flight spectrometers. Nontuberculosis mycobacteria show faster growth than *M. tuberculosis* – they are additionally divided into rapid growers (growing in less than 7 days) and slow growers (growing in more than 7 days) [3].

SYMPTOMS

Clinical symptoms of NTM infection, due to their similarity to *M. tuberculosis* infection, may cause difficulties in diagnosis even for experienced clinicians [3, 20]. Depending on the affected organ, clinical symptoms have been classified into 4 groups: chronic lung disease, lymphadenitis, cutaneous disease and disseminated disease [17]; 90% of cases involve the respiratory system, especially in the elderly with lung diseases [3, 17,

18, 19]. Due to the fact that the symptoms of NTM infection are non-specific, in order to make a diagnosis of lung disease associated with MOTT, the results of laboratory and radiological tests and clinical symptoms should be confronted [17, 19]. It is worth noting that infection should be suspected when clinical symptoms persist despite the introduction of traditional antibacterial therapy, and depending on the species of mycobacterium, the groups of symptoms may vary [19, 20].

Pulmonary symptoms will most often be caused by MAC, *M. abscessus* and *M. kansasii* [17, 18]. The literature mentions chronic or recurrent cough, which may be accompanied by expectoration, as well as fever, night sweats or weight loss, especially in the cavitary type [3, 19, 21]. Chest pain is also common, and the patient may experience malaise and progressive fatigue [3, 19]. Lymphadenitis may not involve systemic symptoms. In countries with a low tuberculosis burden, this form is the most common clinical manifestation of MOTT infection in younger children. The literature indicates MAC and *M. scrofulaceum* as the most common causes of these ailments [3]. It begins with the enlargement of lymph nodes, which are often not tender, most often in the cervical and submandibular regions [3, 19]. In severely immunocompromised people, enlarged lymph nodes may also be seen in the armpits or other regions of the body. In the next stage, pus may form in the lymph nodes and, after disintegration, form sinuses [3]. The skin form will be characterized by skin nodules, as well as penetrating wounds, erythema or ulcers. There may also be abscesses. It is worth mentioning that soft tissue infections can also occur, including muscles, where symptoms such as atrophy, stiffness, joint pain or the presence of sinuses appear [19]. Abscesses may also appear here. Both in cases involving the skin and soft tissues, the most common pathogens are *M. kansasii* and *M. ulcerans*. In the case of disseminated disease, MAC plays a special role, especially in people infected with HIV and presenting with AIDS symptoms, in particular with the level of CD4+ lymphocytes <50/μL [3]. Symptoms of this disease include fever with accompanying diarrhea and epigastric pain, weight loss and malaise; hepatosplenomegaly is also common [3, 19]. Lymphadenopathy, anemia and night sweats may occur as well. The second significant pathogen in this group of symptoms is *M. kansasii* [3].

TREATMENT

When an infection caused by MOTT is suspected in a patient, it is important to assess the individual risk of initiating therapy, taking into account the benefits and side effects it brings [17, 19].

The very beginning of treatment is controversial. According to some sources, therapy can be started without clinical, microbiological and radiological confirmation of NTM infection [17]. Other authors emphasize the need to meet these criteria before starting treatment, which is often poorly tolerated by patients [19]. The duration of treatment should also be taken into account. It is long-term – it takes 3–18 months, and often even longer [18, 19, 22]. However, regardless of when it is started, treatment of NTM infections is often conducted empirically [18, 19]. It is more beneficial for patients to start any treatment than to wait for the development of a full-blown disease [19].

In empirical treatment, NTM strains are divided into slow-growing and fast-growing. In the case of slow-growing NTMs, oral macrolides, rifamycin, ethambutol and amikacin are applicable. On the other hand, for fast-growing mycobacteria, the antibiogram should be checked for: amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline (or minocycline), imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole, and tobramycin [17, 19].

Identification of the microorganism and the determination of its drug susceptibility is the basis for the inclusion of targeted treatment, selected in accordance with the obtained antibiogram [17, 19, 21, 22]. Nontuberculosis mycobacteria infections usually do not respond to standard anti-mycobacterial treatment [18, 21]. It is necessary to use higher doses than in standard anti-drug therapy and, consequently, to pay special attention to emerging side effects [19, 21]. These include: shortness of breath, hearing loss, abdominal pain, nausea, vomiting, headaches, skin lesions, gynecomastia, kidney damage, hepatotoxicity, leukopenia, anemia, hypoglycemia, electrolyte disturbances or QT prolongation. In order to increase patients' tolerance to the introduced treatment, antibiotics are administered initially in small and then in gradually increasing doses. Other drugs are also added to the therapy at intervals of several days [19].

The range of antibiotics used in NTM infections is very wide and includes: amikacin, azithromycin, bedaquiline fumarate, cefoxitin, ciprofloxacin, clofazimine, delaminid, doxycycline, ethambutol, ethionamide, isoniazid, clarithromycin, levofloxacin, linezolid, minocycline, moxifloxacin, rifabutin, rifampin, streptomycin, tedizolid and tigecycline [19]. Usually, at least 2 antibacterial drugs are combined, but their final number depends on the stage of the disease, the patient's age, as well as comorbidities and interactions between the drugs taken [17, 19]. Macrolides and intravenous aminoglycosides are often used [18, 19, 23]. The healing process consists of 2 phases: the first, containing a larger number of antibiotics, which are usually administered intravenously, and the second, which is characterized by a smaller number of antibiotics administered, which are given orally to the patient, if possible [19]. In children, the therapy is based on clarithromycin or azithromycin, rifampicin and ethambutol [22]. Operative treatment is also used in all age groups, especially in the form of cervical lymphadenitis [21, 22].

SUMMARY

Mycobacteria other than tuberculosis is a group of bacteria that is common in various environments, especially in aquatic environments, including rivers, ponds, lakes, as well as in soils. In addition, we find them in man-made water systems, including hot tubs, fountains, plumbing or in dust. Among the many species of these bacteria, *M. kansasii, M. avium, M. xenopi, M. gordonae* and *M. intracellulare* are currently the most important in Poland. Diagnosis of NTM infections and their isolation is

a great challenge for clinicians; therefore the results of radiological and microbiological tests and clinical symptoms should be compared. The most common clinical syndrome of infection is the pulmonary form (NTM-PD). Depending on whether a given pathogen is classified as slow-growing or fast-growing, we have various therapeutic options; however, one should always remember about the side effects of the drugs used and the selection of the appropriate therapy for the individual clinical condition of the patient.

REFERENCES

1. Falkinham JO 3rd. Environmental sources of nontuberculous mycobacteria. Clin Chest Med 2015;36(1):35-41.
2. Honda JR, Virdi R, Chan ED. Global environmental nontuberculous mycobacteria and their contemporaneous man-made and natural niches. Front Microbiol 2018;9:2029.
3. Sharma SK, Upadhyay V. Epidemiology, diagnosis & treatment of non-tuberculous mycobacterial diseases. Indian J Med Res 2020;152(3):185-226.
4. Baldwin SL, Larsen SE, Ordway D, Cassell G, Coler RN. The complexities and challenges of preventing and treating nontuberculous mycobacterial diseases. PLoS Negl Trop Dis 2019;13(2):e0007083.
5. Hoefsloot W, van Ingen J, Andrejak C, Ängeby K, Bauriaud R, Bemer P, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. Eur Respir J 2013;42(6):1604-13.
6. van der Werf MJ, Ködmön C, Katalinić-Janković V, Kummik T, Soini H, Richter E, et al. Inventory study of non-tuberculous mycobacteria in the European Union. BMC Infect Dis 2014;14:62.
7. Schildkraut JA, Gallagher J, Morimoto K, Lange C, Haworth C, Floto RA, et al. Epidemiology of nontuberculous mycobacterial pulmonary disease in Europe and Japan by Delphi estimation. Respir Med 2020;173:106164.
8. Kwiatkowska S, Augustynowicz-Kopeć E, Korzeniewska-Koseła M, Filipczak D, Gruszczyński P, Zabost A, et al. Nontuberculous mycobacteria strains isolated from patients between 2013 and 2017 in Poland. Our data with respect to the global trends. Adv Respir Med 2018;86(6):291-8.
9. Marras TK, Mendelson D, Marchand-Austin A, May K, Jamieson FB. Pulmonary nontuberculous mycobacterial disease, Ontario, Canada, 1998–2010. Emerg Infect Dis 2013;19(11):1889-91.
10. 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(8):881-6. doi: 10.1164/rccm.201111-2016OC.
11. Shah NM, Davidson JA, Anderson LF, Lalor MK, Kim J, Thomas HL, et al. Pulmonary Mycobacterium avium-intracellulare is the main driver of the rise in non-tuberculous mycobacteria incidence in England, Wales and Northern Ireland, 2007–2012. BMC Infect Dis 2016;16:195.
12. Simons S, van Ingen J, Hsueh PR, Van Hung N, Dekhuijzen PNR, Boeree MJ, et al. Nontuberculous mycobacteria in respiratory tract infections, eastern Asia. Emerg Infect Dis 2011;17(3):343-9.
13. Morimoto K, Iwai K, Uchimura K, Okumura M, Yoshiyama T, Yoshimori K, et al. A steady increase in nontuberculous mycobacteriosis mortality and estimated prevalence in Japan. Ann Am Thorac Soc 2014;11(1):1-8.
14. Jing H, Wang H, Wang Y, Deng Y, Li X, Liu Z, et al. Prevalence of nontuberculous mycobacteria infection, China, 2004–2009. Emerg Infect Dis 2012;18(3):527-8.
15. Chou MP, Clements AC, Thomson RM. A spatial epidemiological analysis of nontuberculous mycobacterial infections in Queensland, Australia. BMC Infect Dis 2014;14:279.
16. Koh WJ, Chang B, Jeong BH, Jeon K, Kim SY, Lee NY, et al. Increasing Recovery of nontuberculous mycobacte-ria from respiratory specimens over a 10-year period in a tertiary referral hospital in South Korea. Tuberc Respir Dis (Seoul) 2013;75(5):199-204.
17. Koh WJ. Nontuberculous mycobacteria – overview. Microbiol Spectr 2017;5(1). doi: 10.1128/microbiolspec.
18. Gopalaswamy R, Shanmugam S, Mondal R, Subbian S. Of tuberculosis and non-tuberculous mycobacterial infections – a comparative analysis of epidemiology, diagnosis and treatment. J Biomed Sci 2020;27(1):74.
19. Pennington KM, Vu A, Challener D, Rivera CG, Shweta FNU, Zeuli JD, et al. Approach to the diagnosis and treatment of non-tuberculous mycobacterial disease. J Clin Tuberc Other Mycobact Dis 2021;24:100244.
20. Raju RM, Raju SM, Zhao Y, Rubin EJ. Leveraging advances in tuberculosis diagnosis and treatment to address nontuberculous mycobacterial disease. Emerg Infect Dis 2016;22(3):365-9.
21. Katoch VM. Infections due to non-tuberculous mycobacteria (NTM). Indian J Med Res 2004;120(4):290-304.
22. Meoli A, Deolmi M, Iannarella R, Esposito S. Non-tuberculous mycobacterial diseases in children. Pathogens 2020;9(7):553.
23. Rapp RP, McCraney SA, Goodman NL, Shaddick DJ. New macrolide antibiotics: usefulness in infections caused by mycobacteria other than Mycobacterium tuberculosis. Ann Pharmacother 1994;28(11):1255-63. doi: 101177/106002809402801109.