

MYCOBACTERIOSIS: THE PAST AND PRESENT

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Non-tuberculous mycobacteria (NTM) are ubiquitous organisms, they are found everywhere in the vicinity. Humans are in everyday contact with these microorganisms. Although tuberculosis (TB) cases have been declining worldwide, there is a growing incidence of NTM infections. NTM may cause both asymptomatic infection and symptomatic disease in humans. The most common are pulmonary infections of varying severity. Accurate diagnosis is of crucial importance because the treatment medications may have serious adverse effects, among other things. The treatment of mycobacteriosis is not directly analogous to the treatment of tuberculosis. Empiric therapy is not recommended. *In vitro* susceptibility of many NTM does not correlate with clinical response to antimycobacterial drugs.

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number of validly recognized NTM species (1-8). When guidelines of The American Thoracic Society-ATS and Infectious Disease Society of America-IDSA about NTM were published in 1997, there were about 50 NTM species identified. Until the ATS/IDSA guidelines in 2007 more than 125 NTM species have been identified. Currently, there are 233 NTM species and 23 subspecies described. This dramatic increase is not only in the number of new species, but also in the number of clinically important species. There are at least 60 mycobacterial species that cause disease in humans (9-11).

History

First reports on mycobacteria isolation, other than Koch's human tubercle bacilli, date back to 1885, when Alvarez and Tavel isolated smegma bacillus. Probably the earliest case of the disease caused by NTM was reported by Pappenheim in 1898, who described a young woman having 'gangrene of the lung'. In 1908, Duvall reported first, fully documented case of disseminated infection (12). Runyon and Timpe were the first to classify and describe NTM in the 1950s. Runyon observed mycobacteria as a biologist. He divided them into four groups according to their rate of growth, morphology of the colonies, and pigment production in the presence of light into slow-growers (non-photochromogens, photochromogens, scotochromogens) and fast-growers (13). This classification is less useful today since pigment production may vary, serotyping reveals closely related distant species and differences among close categories (14). In 1989, Davidson divided NTM according to their

Introduction

Although tuberculosis (TB) cases have been declining worldwide, there is a growing incidence of non-tuberculous mycobacterial (NTM) infections. Recent studies have shown an increase of NTM lung infections at an annual rate of 8.2%. The reasons of the increase have not been fully understood yet, but they are probably multifactorial, including environmental factors, host, and microbes. It is generally accepted that increasing prevalence of mycobacteriosis is a consequence of demographic changes, such as aging of the population that weakens immunity and causes a series of predisposing diseases, and increased exposure to, for example, chlorine water while bathing. Increased detection rate is the result of increased awareness of this pathogen and improved detection techniques. The availability of gene sequencing techniques improved the taxonomy of mycobacteria, with significant increase in the

clinical relevance into conditional pathogens, opportunistic mycobacteria, and pure saprophytes. It is not always easy to define boundaries between them, so it is believed that saprophytes may become pathogenic in certain conditions (9).

Epidemiology

Humans are in everyday contact with these microorganisms. NTM are ubiquitous organisms, isolated from water samples (natural waters – lakes and streams; pipeline systems), soil, dust, raw milk and other animal products. They can also be found in throat swab, sputum culture, gastric content, and urine in healthy persons. From human samples they can be isolated as:

- 1) an accidental isolate with low number of bacilli isolated once;
- 2) prolonged saprophyte colonization, especially in lower respiratory tract in patients with chronic pulmonary disease, but it is not known when local invasion into a tissue or the disease progression may occur;
- 3) real pathogens (12, 15).

Until recently, it has been believed that NTM infection originate from the environment without evidence on human-to-human or animal-to-human transmission, being the reason of less public importance because of not reporting it to epidemiological services, so the prevalence is unknown. However, owing to sequencing of NTM isolates, recent literature data suggest that indirect cross infection with *M. abscessus* is possible in patients with cystic fibrosis (CF), leading to changes in infection control standards in this group of patients (15).

The rate of disease due to NTM in developed, industrialized countries is in the range of 1.0 to 1.8/100000. The prevalence of NTM pulmonary infections in the United States of America (USA) and Australia range from 3.2 to 9.8/100000, whereas a study registered annual prevalence estimates in Hawaii up to 44/100000. In Europe, the prevalence estimate is generally lower, up to 3.3/100000. The prevalence is significantly higher in certain regions and groups of patients, so the prevalence in persons over 65 years of age in the USA in an 11-year period has been over 100/100000. Such approximate prevalence is calculated according to NTM isolates reports, conducted studies and medical insurance records (6, 10, 16).

The distribution of species varies according to regions. *M. avium* complex (MAC - *M. avium*, *M. intracellulare*) is predominant in North America and East Asia, but not in Europe, where *M. kansasii*, *M. xenopi* and *M. malmoense* are predominant (17). Pathogenicity of NTM species may differ by different geographic regions, and it significantly varies among species, from *M. gordonae* that rarely causes the disease in humans, to *M. kansasii* that is usually considered pathogenic (18, 19).

Inhalation of environmental aerosol particles is a primary transmission route of the infection. Infections are also possible by drinking contaminated water, or by using contaminated medical and

surgical equipment, hospital-acquired infections. High tolerance to different noxious substances is one of the main reasons of their pathogenicity in humans. Owing to the presence of lipid-rich outer membrane they develop resistance to disinfectants, primarily chlorine and ozone. It is believed that water conditioning and treatment with chlorine negatively selected resistant species. Also, they have the ability of biofilm formation (10, 15).

The mortality rate of NTM disease in HIV uninfected persons in the USA has increased in the period 1999-2014, especially in white, older women. Considering the fact that there has been a simultaneous decline in TB-related deaths, these findings show a change in fatal mycobacterial infections in the USA (20). The mortality rate of NTM pulmonary disease is significant, according to Denmark's population data, five-year mortality rate was 40.1%. In this study, patients with *M. xenopi* had the worst prognosis (21). The largest population-based cohort based on epidemiologic characteristics of NTM infection aimed at evaluating incidence, prevalence and mortality of NTM infection in Korea showed a rapid increase in incidence and prevalence in the last two decades, higher in women and elderly people. The mortality rate in persons with NTM infection was almost as twice as high than in general population. This trend should be closely monitored in order to provide optimal healthcare policies and treatment strategies for NTM infections (22).

Clinical forms of the disease

NTM may cause both asymptomatic infection and symptomatic disease in humans (10). It is believed that NTM-human relationship is mostly a transient colonization that goes away on its own, since the immune system in the majority of a population kills bacilli (9). The most common and distinct clinical problems include pulmonary disease, lymphadenitis, and disseminated infection, but the infection and disease can occur in other tissues, such as soft tissues, bones, joints, and genitourinary tract. Skin and soft tissue infections are usually iatrogenic, while visceral and disseminated infections are associated with severe immunosuppression (23-25). There are isolated cases of the diseases, such as meningitis, keratitis, mastoiditis, endocarditis, hepatitis, caused by different NTM species (12).

The most common are pulmonary infections of varying severity, from extremely progressive, destructive, to hardly visible changes with minimal physical signs of the disease. There are no specific features to differentiate NTM pulmonary disease from pulmonary TB. Coughing and expectorating are common symptoms and can be accompanied by hemoptysis, high temperature, night sweats, general fatigue, and weight loss, but all of these are much less seen than in TB (14). The most common pulmonary pathogens are: slowly growing - MAC, *M. kansasii*, *M. malmoense*, rapidly growing - *M. abscessus*, *M. xenopi*, *M. chelonae*, *M. fortuitum* (3).

Predisposing diseases for NTM infections are mostly chronic pulmonary diseases, such as chronic

obstructive pulmonary disease (COPD), or bronchiectasis, especially in the elderly. In a prospective cohort in COPD patients with frequent exacerbations, 22% of subjects had positive NTM culture (26). The association of previous TB, pneumoconiosis, CF, pulmonary alveolar proteinosis and silicosis, with NTM infection has become clear in time (3, 9). Studies have shown that prevalence in NTM patients with CF is 4-20%, and increases over time and with older age. Namely, when NTM pulmonary infection was studied in patients with CF over 40 years of age, the rates were close to 50% (3, 27). The risk is also higher in patients with rheumatoid arthritis, diabetes, in alcohol consumers, extrapulmonary malignancies, and gastrectomy patients as well. Chest deformities, such as scoliosis, or pectus excavatum present favourable environment for the development of mycobacteriosis. A slightly higher tendency in the NTM infections increased incidence is in cases of connective tissue diseases, as well as in patients with mitral valve prolapse (6, 9, 15). Rather common association can be seen between mycobacteriosis and immune deficiency syndrome. The best known is association with Acquired Immune Deficiency Syndrome (AIDS), with up to 40% of HIV positive patients' deaths due to NTM infections. NTM infections occur more commonly in immunocompromised patients as well, especially in leukemia, as well as in patients on long-term corticosteroid treatment, or some other immunosuppressive therapy (9). It has been identified that the incidence of NTM infection is increasing in lung transplant recipients (28).

Pulmonary syndrome due to NTM with a presentation similar to hypersensitivity pneumonitis, has also been recognized. The syndrome was pre-

viously referred to as 'hot tub lung'. It may also be related to occupational industrial metalworking fluids exposure. Exposure to such aerosols may result in a hypersensitivity-like pneumonitis syndrome similar to 'hot tub lung' that occurs from exposure to hot water from hot tubs, but is almost only associated with *M. immunogenum*, a fast-growing mycobacterium. These patients are usually younger than patients with MAC or other mycobacteriosis, non-smokers, similar to patients with other forms of hypersensitivity pneumonitis. The disease course is subacute. Although there are still no reports on chronic form of NTM hypersensitivity-like pneumonitis, it may be possible.

Health Care-and Hygiene-associated Disease and Disease Prevention: avoid chlorine-based disinfectants, as it allows *M. abscessus* growth. Endoscopes cleaned in tap water and clinical samples contaminated with tap water or ice are unacceptable (10).

Diagnosis

Accurate diagnosis is of crucial importance because the treatment medications may have serious adverse effects, among other things (10). Good communication between clinicians and microbiologist is of key importance. A clinician should ensure that adequate specimens are taken and sent to the microbiologist regarding the type of specimen and clinical details (23).

According to ATS/IDSA guidelines published in 1997 and updated in 2007, establishing the diagnosis of mycobacteriosis depends on the fulfillment of clinical, microbiological and radiological signs of the disease (Figure 1).

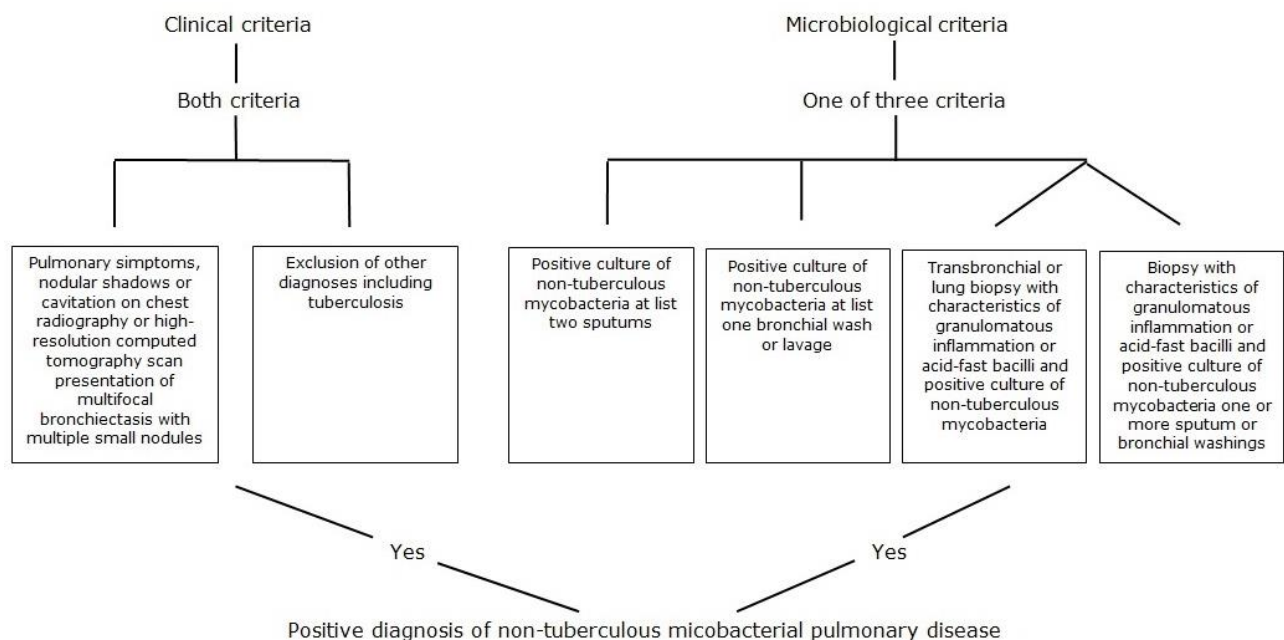


Figure 1. NTM pulmonary diseases diagnostic criteria

The onset of radiological signs has to be at the same time as NTM isolation, and the absence of some other etiologically recognized pathogenic microorganism or a disease is also important (3, 10).

Clinical suspicion is the first step in establishing the diagnosis. The minimum evaluation includes:

1) chest radiography or, in the absence of cavitation, chest high resolution computed tomography (HRCT);

2) three or more sputum specimens for acid-fast bacilli (AFB) analysis;

3) exclusion of other potential causes of the disease, such as TB or malignancies.

Both clinical criteria, along with one microbiological criterion must be met for NTM pulmonary disease. Such established criteria completely apply to only certain NTM isolated species and represent guidelines for pulmonary forms of the disease. These criteria are applicable best for MAC, *M. kansasii* and *M. abscessus*, and little is known about other species (10). In most cases a lung biopsy or bronchoscopy are not necessary for a diagnosis of pulmonary mycobacteriosis (3).

The diagnosis of NTM lymphadenitis is based on histopathological finding of necrotizing granulomas, with or without AFB within, and with negative tuberculin test in most cases. The definitive diagnosis is established by NTM finding in lymph nodes culture (10).

Disseminated NTM infection is seen among severely immunosuppressed patients, most often HIV-related. Patients at risk of the disease development are those with gastrointestinal and respiratory tract colonization. In more than 90% of cases infections are caused by MAC, with more than 90% due to *M. avium*. Other most frequent agents include *M. kansasii*, then *M. scrofulaceum*, *M. goodii*, *M. haemophilum*, and others. Diagnosis of disseminated disease is most commonly established noninvasively, with over 90% of patients with disseminated MAC disease having positive blood cultures (10).

Microbiologic data are of key importance in establishing the diagnosis of MAC hypersensitivity-like disease, but not isolated, nor without clinical, radiologic, or pathologic findings characteristic for MAC hypersensitivity-like disease. Cultures obtained from sputum, bronchial lavage, tissue biopsy, and hot-tub water show MAC isolate. Matching of MAC isolates from patient specimens and isolates from hot-tub water have been proven by analyzing DNA genes and enzyme electrophoresis (10).

In comparison to previous ones, ATS/IDSA guidelines from 2007 modified microbiologic criteria for diagnosing (one NTM culture from bronchial lavage in properly selected patients category, or two positive sputum cultures, are now sufficient for establishing the diagnosis), making clinical criteria more specific at the same time (3).

Diagnostic ATS/IDSA criteria for pulmonary mycobacteriosis in HIV positive and HIV negative cases from 1997:

- if three sputum/bronchial wash results were isolated in previous 12 months:

1) three positive cultures with negative direct microscopy results, or

2) two positive cultures and one positive direct microscopy finding;

- if only bronchial wash is available:

1) positive culture with 2+, 3+ or 4+ positive smears (direct microscopy), or

2) 2+ to 4+ growth on solid surface;

- if sputum/bronchial washes are not diagnosed, or another disease cannot be excluded:

1) transbronchial or lung biopsy obtained NTM isolate, or;

2) pathohistologic finding of granulomatous inflammation and/or AFB, and one or more sputums or bronchial washing positive for NTM, even with low number increase 1+.

Aforementioned criteria are applied in symptomatic patients with infiltrates, nodular or cavitary disease, or in patients with lung computed tomography (CT) scan showing multifocal bronchiectasis bronchiectasis and/or multiple small nodules (29).

Diagnostic criteria for pulmonary mycobacteriosis according to BTS guidelines from 1999 are similar. The diagnosis of pulmonary disease caused by *M. kansasii*, MAC, *M. malmoense* and *M. xenopi* established after positive multiple cultures develop in non-sterile specimens obtained during 7 days according to radiographically raised suspicion of mycobacteriosis in patients with or without symptoms, and one sample in primarily sterile sample with positive pathohistological finding. Isolated strain should be identified to the species level in order to distinguish pathogenicity between the species. Different skin tests are not reliable for accurate diagnosis, so they are not recommended. The diagnosis of NTM lymphadenitis is made by complete extirpation of the involved lymph node and culture of the material obtained. A decision on definite diagnosis and treatment is made by close cooperation between pulmonologist, pediatrician, and other specialists, including otorhinolaryngologist, surgeon and microbiologist. *M. fortuitum* or *M. chelonae* may cause skin or soft tissue infections after trauma or surgery, forming abscesses or fistulas. *M. marinum* infection known as 'swimming pool granuloma' or 'fish tank granuloma' is acquired in the swimming pool or fish tanks after a trauma. *M. ulcerans* may be a causative agent of chronic necrotic skin ulceration, known as Buruli ulceration, rarely occurring outside Africa. Infections of bones, joints, genitourinary tract are not common (23).

In the absence of strong evidence to support an alternative definition, as well as due to significant clinical and research advantages in using a uniform definition, BTS guidelines from 2017 recommend definition of NTM pulmonary disease issued by ATS/IDSA in 2007. In case of high clinical suspicion of NTM infection, but negative sputum culture, CT-guided bronchial washing is recommended in order to get targeted sample. If patients have been taking antibiotic therapy that can damage NTM growth (aminoglycosides, macrolides, tetracyclines, cotrimoxazole, linezolid), discontinuation of two weeks should be considered before collecting the samples. In high clinical suspicion, but negative specimen cultures, an option is discussion with reference laboratory microbiologist about the possibility of using alternative media, at different cultivation tempera-

ture, extended time of cultivation, or the use of molecular techniques (30).

Recent joint guidelines released by European Respiratory Society-ERS, European Society of Clinical Microbiology and Infectious Diseases-ESCMID and ATS/IDSA also recommend the utility of diagnostic criteria for NTM pulmonary disease, shown in Figure 1. But, it is pointed out that fulfillment of NTM pulmonary disease diagnostic criteria does not necessarily mean that antibiotic treatment should be started. A careful assessment of the pathogenicity of the organisms, symptoms, risk and benefits of the treatment, as well as the possibility of receiving the treatment and its goals, and the patient's wish about the therapy should be considered before initiating the treatment. In some cases 'watchful waiting' may be a rational procedure in treatment course (31).

In the end, the importance of NTM isolate in patients during pulmonary TB treatment is uncertain. The importance of two NTM isolates is also unknown (10).

Therapy

The treatment of mycobacteriosis is not directly analogous to the treatment of TB. Empiric therapy is not recommended (10). A fundamental rule is never to use only a single antibiotic, since it can result in negative selection of mutants from mycobacterial population. It is very important to note that majority of NTM are resistant to pyrazinamide (Z), so it should not be used in mycobacteriosis treatment. In general, isoniazid (H) and (Z) are not effective in slow-growing mycobacteria, and sensitivity is different to rifampicin (R), quinolones and macrolides. The spectrum of effective drugs against rapidly growing mycobacteria is broader and includes ciprofloxacin, clarithromycin, tobramycin, amikacin, cefoxitin, imipenem, and sul-famethoxazole. Some studies have pointed out the synergy between R and ethambutol (E) in NTM that showed resistance to individual aforementioned drugs (9).

In vitro susceptibility of many NTM does not correlate with clinical response to antimycobacterial drugs (32). A clinician may utilize *in vitro* suscepti-

bility, having in mind its limitations. According to the ATS/IDSA guidelines from 2007, clarithromycin susceptibility testing is recommended for new, previously untreated MAC isolates. It is a standard for testing of the newer macrolides because clarithromycin and azithromycin have cross-susceptibility and cross-resistance. The importance of first-line anti-tuberculous agents testing using methods for MAC is still unknown. Previously untreated *M. kansasii* isolates should be treated *in vitro* only to R, because those that show susceptibility to R will also show susceptibility to rifabutin. *M. kansasii* isolates resistant to R should be tested against a panel of secondary drugs, including rifabutin, E, H, clarithromycin, fluoroquinolones and sulfonamides. *M. marinum* isolates do not require susceptibility testing, except in case of treatment failure after several months. There are no current recommendations for a specific method of *in vitro* susceptibility testing of fast-growing NTM isolates and some not so common NTM isolates (10). Susceptibility testing to NTM drugs is useful, but only for antibiotics well documented in having correlation between *in vitro* activity and microbiological response to treatment, as recommended by the latest ATS/ERS/ESCMID/IDSA guidelines. They include macrolides, (clarithromycin and azithromycin) and amikacin for MAC and *M. abscessus*, and R for *M. kansasii*. In patients with *M. xenopi* pulmonary disease, the board members believe that there is not enough evidence to make a recommendation 'for' or 'against' susceptibility-based treatment (31).

Treatment recommendations by ATS/IDSA guidelines from 2007 for MAC pulmonary diseases are given in Table 1, and for treatment and prevention of disseminated MAC disease in HIV positive patients in Table 2. Treatment recommendations for not so common NTM are made on the basis of only a few reported cases. Having in mind this limitation, the duration of treatment for the most of pulmonary disease NTM pathogens is based on treatment recommendations for most commonly isolated NTM, such as MAC and *M. kansasii*, negative culture for at least 12 months while on therapy.

Table 1. Therapy for MAC pulmonary disease – recommendations depending on the disease status and/or its severity

	Initial Th for nodular/ bronchiectatic form	Evidence quality	Initial Th for cavitary disease	Evidence quality	Advance (severe) forms, or previously treated disease	Evidence quality
Macrolide	Clarithromycin 1000 mg T or Azithromycin 500/600 mg T	B, II	Clarithromycin 500/1000 mg daily or Azithromycin 250-300 mg daily	A, II	Clarithromycin 500*/1000 mg daily or Azithromycin 250-300 mg daily	B, II
Ethambutol	25 mg/kg T		15 mg/kg daily		15 mg/kg daily	
Rifampicin	600 mg T		450*-600 mg daily		450*-600 mg or Rifabutin 150-300mg daily	
IV Aminoglycoside	none		Streptomycin or Amikacin 25 mg/kg T, first 2-3 months		Streptomycin or Amikacin 25 mg/kg T, first 2-3 months	

Th - therapy; IV - intravenous; T - three times a week; * lower dose for weight under 50 kg

Table 2. Recommendations for the treatment and prevention of disseminated MAC disease in HIV positive patients

Recommended therapy (A, I)	Alternative therapy (B, I)
Clarithromycin 500 mg 2x a day	Azithromycin 500 mg daily
+	
Ethambutol 15 mg/kg daily	Ethambutol 15 mg/kg daily
+/-	
Rifabutin 300 mg daily	Rifabutin 300-450 mg* daily
Prevention ⁺	
Azithromycin 1200 mg orally weekly	Clarithromycin 500 mg 2x a day or Rifabutin 300 mg* daily

* possibility of Rifabutin dose modification due to interactions with other drugs

+ preventive therapy indicated in less than 50 CD4+ cells/nl, may be discontinued if > 100 cells/nl

In disseminated infection, the duration of treatment of most NTM pathogens is the same as in disseminated MAC infection, the treatment can be discontinued with the withdrawal of symptoms and reconstruction of cellular immunity. Recommendations for the treatment of hypersensitive pneumonitis associated with NTM include corticosteroids and short-term antibiotic therapy. There are no widely accepted criteria for selecting patients with mycobacteriosis for resection surgery. In general, more severe cases are treated medically, milder cases should be considered for surgical treatment, having in mind its risks and benefits. Expert opinion is of great importance. Resection of a solitary MAC

pulmonary nodule is believed to be curative. The best response to treatment options is the first time it is applied, so it is very important to have a complete recommended therapeutic regime the first time the treatment is introduced. In case the treatment response is not satisfactory, expert consultation is needed (10).

BTS guidelines from 1999 are shown in Tables 3 and 4. Treatment with R and E was recommended as sufficient for most patients with *M. kansasii* pulmonary disease for 9 months, but in immunocompromised patients it should continue until 15-24 months, or until sputum cultures have been negative for 12 months.

Table 3. Suggested treatment for HIV negative patients with NTM disease

	Treatment	Duration
Pulmonary disease:		
<i>M. kansasii</i>	Rifampicin 450 mg < 50 kg; 600 mg > 50 kg daily Ethambutol 15 mg/kg daily	9 months
<i>M. avium</i> complex	as listed +/- Isoniazid 300 mg daily	2 years
<i>M. malmoense</i>	as listed	
<i>M. xenopi</i>	as listed	
Lymphadenitis:		
<i>M. kansasii</i> <i>M. malmoense</i> <i>M. xenopi</i>	Excision. In relapse, excision + Rifampicin and Ethambutol (in aforementioned doses)	2 years
<i>M. avium</i> complex	Excision. In relapse, excision + Rifampicin and Ethambutol (in aforementioned doses) and Clarithromycin 500 mg daily	2 years
Intolerance to Rifampicin or Ethambutol	substitution with Clarithromycin and/or Ciprofloxacin	

Table 4. Suggested treatment for HIV positive patients with NTM disease

	Treatment	Duration
Pulmonary or disseminated disease:		
<i>M. avium</i> complex <i>M. kansasii</i> <i>M. malmoense</i> <i>M. xenopi</i>	Rifampicin 450 or 600 mg (or Rifabutin 300 mg) daily, Ethambutol 15 mg/kg daily, and Clarithromycin 500 mg daily	Lifelong
Prophylaxis MAC:		
Possibility	Azithromycin 1200 mg orally, weekly Clarithromycin 500 mg daily Azithromycin 1200 mg orally weekly + Rifabutin 300 mg daily	Undefined

Table 5. Suggested antibiotic treatment for MAC pulmonary disease in adults

	Treatment	Duration
MAC pulmonary disease, mild to Moderate stage:	Rifampicin 600 mg 3x per week Ethambutol 25 mg/kg 3x per week Azithromycin 500 mg 3x per week or Clarithromycin 1g (2x500 mg) 3x per week	12 months after culture conversion
Severe form:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily and consider intravenous Amikacin for up to 3 months or nebulised Amikacin	12 months after culture conversion
Clarithromycin-resistant MAC pulmonary disease	Rifampicin 600mg and Ethambutol 15mg/kg and Isoniazid 300mg (+pyridoxine 10mg) daily or Moxifloxacin 400mg daily and consider intravenous Amikacin for up to 3 months or nebulised Amikacin	12 months after culture conversion

Table 6. Suggested antibiotic treatment for *M. kansasii* pulmonary disease

	Treatment	Duration
Rifampicin-sensitive <i>M. kansasii</i> pulmonary disease:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Isoniazid 300 mg (with pyridoxine 10 mg) daily or Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily	12 months after culture conversion

Table 7. Suggested antibiotic treatment for *M. malmoensae* pulmonary disease

	Treatment	Duration
Mild to moderate <i>M. malmoensae</i> pulmonary disease:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily	12 months after culture conversion
Severe form:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily and consider intravenous Amikacin for up to 3 months or nebulised Amikacin	12 months after culture conversion

Table 8. Suggested antibiotic treatment for *M. xenopi* pulmonary disease

	Treatment	Duration
Mild to moderate form:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily and Moxifloxacin 400 mg daily or Isoniazid 300 mg (+ pyridoxine 10 mg) daily	12 months after culture conversion
Severe form:	Rifampicin 600 mg daily Ethambutol 15 mg/kg daily Azithromycin 250 mg daily or Clarithromycin 500 mg x2 daily and Moxifloxacin 400 mg daily or Isoniazid 300 mg(+pyridoxine 10 mg) daily and consider intravenous Amikacin up to 3 months or nebulised Amikacin	12 months after culture conversion

Table 9. Suggested antibiotic treatment for *M. abscessus* pulmonary disease

	Treatment	Duration
Clarithromycin sensitive isolates or inducible macrolide resistant isolates:	Initial phase: 1 month or more ⁺ IV Amikacin 15 mg/kg daily or 3x per week [§] IV Tigecycline 50 mg x2 daily and if well tolerated IV Imipenem 1 g x2 daily and if well tolerated Clarithromycin 500 mg daily or Azithromycin 250-500 mg daily Continuation phase: Nebulised Amikacin [§] and oral Clarithromycin 500 mg x2 daily or Azithromycin 250-500 mg daily and 1-3 antibiotics based on their susceptibility and tolerance: Clofazimine 50-100 mg daily ^{&} Linezolid 600 mg daily or x2 daily Minocycline 100 mg x2 daily Moxifloxacin 400 mg daily Cotrimoxazole 960 mg x2 daily	12 months after culture conversion
Constitutive macrolide-resistant isolates:	Initial phase: 1 month or more ⁺ IV Amikacin 15 mg/kg daily or 3x per week [§] and IV tigecycline 50 mg x2 daily and if tolerated well IV Imipenem 1 g x2 daily Continuation phase: Nebulised Amikacin [§] and 2-4 antibiotics based on susceptibility and tolerance: Clofazimine 50-100 mg daily ^{&} Linezolid 600 mg or x2 daily Minocycline 100 mgx2 daily Moxifloxacin 400 mg daily Cotrimoxazole 960 mg x2 daily	12 months after culture conversion

⁺ Due to poor response in patients with inducible or constitutive macrolide-resistant isolates and high efficacy of antibiotics administered intravenously, prolonging the duration of intravenously administered antibiotic to 3-6 months in patients with good antibiotic tolerance may be the most appropriate treatment strategy in this subgroup of patients

[§] Substitute IV/nebulised amikacin with an alternative antibiotic if *M. abscessus* resistant to amikacin

[&] Start clofazimine during the initial phase if tolerated, since serum concentrations cannot be achieved until 30 or more days of treatment
IV – intravenous

Patients with no response to R and E treatment have been treated with adjuvant prothionamide 1 gr/daily orally and streptomycin (S) 0.75-1 gr/daily. The aforementioned treatment was also recommended for extrapulmonary disease caused by *M. kansasii* (23).

BTS recommendations from 2017 for treatment of more common forms of NTM pulmonary diseases are given in Tables 5, 6, 7, 8 and 9. Interferon gamma is not recommended as adjuvant therapy in patients with NTM pulmonary disease without a clearly defined immunodeficiency resulting in its decrease. Follow-up of patients means that microbiological sputum samples should be tested every 4-12 weeks during the treatment and 12 months upon the treatment completion. In patients who do not expectorate sputum, a CT-directed bronchial wash can be performed after 6 and 12 months of treatment in order to assess microbiological response. As for radiological response, it is necessary to perform a CT scan at the end of the treatment (30, 32). In patients with MAC-susceptible pulmonary

disease, ATS/ERS/ESCMID/IDSA guidelines recommend a three-drug regimen (Table 10). Due to less interactions, azithromycin is preferred over clarithromycin. For patients with cavitory or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease, parenteral amikacin or S are recommended for the initial treatment regimen. A parenteral drug is usually administered for 2-3 months at least. In patients with nodular/bronchiectatic form of the disease, drug administration 3 times a week is recommended, and a daily macrolide-based regimen is recommended in patients with cavitory disease. Recommended treatment duration is at least 12 months after culture conversion. If culture conversion fails after 6 months of recommended therapy administration, amikacin inhalation form of the drug is recommended for further treatment. In patients with macrolide-resistant MAC, expert consultation is needed. Pulmonary disease caused by R sensitive *M. kansasii*, should be treated according to the suggested regimen: R, E and H or macrolide (Table 10).

Table 10. Recommended treatment for MAC, *M. kansasii*, *M. xenopi* pulmonary disease – depending on the disease status and/or its severity

Organism	Initial Th for nodular/bronchiectatic form	Initial Th for cavitary disease	Refractory form of the disease
MAC	Azithromycin 500 mg T (Clarithromycin)	Azithromycin 250/500 mg (Clarithromycin) daily Azithromycin 500 mg T (with aminoglycosides)	Azithromycin 250/500 mg (Clarithromycin) daily Azithromycin 500 mg T (with aminoglycosides)
	Rifampicin 450/600 mg T (Rifabutin)	Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Rifampicin 600 mg T (with aminoglycosides)	Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Rifampicin 600 mg T (with aminoglycosides)
	Ethambutol 25 mg/kg T	Ethambutol 15 mg/kg daily Ethambutol 25 mg/kg T (with aminoglycosides) Amikacin IV 15-25 mg/kg T (Streptomycin)	Ethambutol 15 mg/kg daily Ethambutol 25 mg/kg T (with aminoglycosides) Amikacin IV 15-25 mg T (Streptomycin) or ALIS® 590 mg daily
<i>M. kansasii</i>	Azithromycin 250-500 mg daily (Clarithromycin) Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Ethambutol 15 mg/kg daily	Azithromycin 500 mg T (Clarithromycin) Rifampicin 600 mg T (Rifabutin) Ethambutol 25 mg/kg T	Isoniazid 5 mg/kg max 300 mg daily Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Ethambutol 15 mg/kg daily
<i>M. xenopi</i>	Azithromycin 250/500 mg (Clarithromycin) daily and/or Moxifloxacin 400 mg daily Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Ethambutol 15 mg/kg daily	Azithromycin (Clarithromycin) 250/500 mg daily and/or Moxifloxacin 400 mg daily Azithromycin 500 mg T (with aminoglycosides) Rifampicin 10 mg/kg max 600 mg (Rifabutin) daily Rifampicin 600 mg T (with aminoglycosides) Ethambutol 15 mg/kg daily Ethambutol 25 mg/kg T (with aminoglycosides) Amikacin IV 15-25 mg/kg T	

IV - intravenous; T - three times a week; & amikacin liposome inhalation suspension

Amikacin and S are not recommended for routine use. In patients with nodular/bronchiectatic form of the disease macrolide-based treatment is suggested, R and E 3 times per week, but in patients with cavitary disease a daily regimen of this treatment is suggested. In patients with R resistant *M. kansasii* or intolerance to one of the first-line antibiotics, fluoroquinolone (e.g. moxifloxacin) is suggested as a part of second-line regimen. Unlike ATS/IDSA guidelines from 2007, suggested duration of treatment regimen is 12 months, not 12 months after sputum conversion. As usual time for sputum conversion based on R in these patients is 4 months, if there is no conversion in this period of time, expert consultation is recommended. In patients with *M. xenopi* pulmonary disease, a daily regimen of at least three drugs is suggested: R, E and macrolide and/or fluoroquinolone (e.g. moxifloxacin) (Table 10). In severe form of *M. xenopi* pulmonary disease, addition of parenteral amikacin to the treatment regimen is recommended, as well as expert consultation if needed, given the poor prognosis of treatment outcome. The treatment should be continued for 12 months after culture conversion. The optimal drugs, treatment regimen and treatment duration of M abscessus pulmonary disease are not known. If the disease is caused by strains without inducible (typically *M. massiliense*) or mutational macrolide

resistance, a multidrug treatment containing macrolide is suggested, including at least three active drugs (guided by *in vitro* susceptibility) in the initial phase of treatment (the phase including intravenous agents) (Table 11), and opposite, if the disease is caused by strains with inducible or mutational macrolide resistance, a regimen of at least 4 active drugs is recommended if possible. A macrolide-containing regimen is recommended due to its immunomodulatory features, although macrolide is not considered to be an active drug in the multidrug regimen. For the continuation phase of therapy (after discontinuation of parenteral component), at least 2 to 3 active drugs are administered. Some experts suggest a multidrug intermittent therapy regimen instead a transition to prolonged treatment phase, although almost all published studies reported treatment duration of > 12 months. In the absence of data that support shorter or longer treatment regimen of *M. abscessus* pulmonary disease, the panel members suggest expert consultation before the initiation of the therapy in order to help in designing the regimen and in determining whether a shorter or longer treatment regimen should be applied (31). In selected patients with NTM pulmonary disease, surgical resection adjuvant to medical therapy is possible after expert consultation.

Table 11. Suggested antibiotic treatment for *M. abscessus* pulmonary disease

Macrolide susceptibility	Initial phase	Continuation phase
Mutational and inducible macrolide sensitive isolates:	parenteral (choose 1-2) Amikacin 10-15 mg daily (Amikacin 15-25 mg T) Imipenem 500-1000 mg 2-3x daily (or Cefoxitin) Tigecycline 25-50 mg 1-2x daily oral (choose 2) Azithromycin 250-500 mg (Clarithromycin)# Clofazimine 100-200 mg daily Linezolid 600 mg 1-2x daily	oral/inhaled (choose 2-3) Azithromycin 250-500 mg (Clarithromycin)# daily Clofazimine 100-200 mg daily Linezolid 600 mg 1-2x daily Inhaled amikacin 590 mg daily
Mutational sensitive, inducible macrolide resistant isolates:	parenteral (choose 2-3) Amikacin Imipenem (or Cefoxitin) Tigecycline oral (choose 2-3) Azithromycin (Clarithromycin)* Clofazimine Linezolid	oral/inhaled (choose 2-3) Azithromycin (Clarithromycin)* Clofazimine Linezolid Inhaled amikacin
Mutational resistant, inducible sensitive or resistant isolates:	parenteral (choose 2-3) Amikacin Imipenem (or Cefoxitin) Tigecycline oral (choose 2-3) Azithromycin (Clarithromycin)* Clofazimine Linezolid	oral/inhaled (choose 2-3) Azithromycin (Clarithromycin)* Clofazimine Linezolid Inhaled amikacin

Dosage: daily (aminoglycosides may be administered 3 times a week).

Mutational resistance: none, when isolate phenotypic sensitivity is detected at 3-5 days of incubation in culture.

Present: when isolate phenotypic resistance is detected at 3-5 days of incubation or *rrl* mutation, known to be responsible for the resistance, identified on sequencing.

Inducible resistance: functional *erm* (41) gene: isolate phenotypic resistance identified after 14 days of incubation or functional gene sequence identified on sequencing.

Non-functional *erm* (41) gene: isolate identified to be resistant after 14 days of incubation or truncated sequence or C28 mutation (*abscessus* subgroup) on sequencing. Initial phase refers to the timing that the parenteral agents are given. Continuation phase refers to the next phase of the treatment, usually including oral antimicrobial agents sometimes combined with inhaled agents.

* azithromycin (clarithromycin) is active in this environment and should be used whenever possible.

azithromycin (clarithromycin) activity is questionable, but it can be added for its immunomodulatory effects, although it should not be taken into consideration as active against *M. abscessus* with functional *erm* (41) gene. In this situation, frequent sputum cultures should be taken to detect a potentially new organism like MAC.

Since the treatment duration is based on culture conversion, it is necessary to collect culture specimens every 1-2 months to confirm the recommended treatment duration. Apart from microbiological response, clinical and radiological responses to treatment should also be monitored.

Possible adverse effects of applied treatment regime are numerous: hepatitis, fever, rash, peripheral neuropathies, nausea, vomiting, diarrhea, anemia, thrombocytopenia, leukopenia, pancytopenia, renal failure, polymyalgia, polyarthralgia, vertigo, ataxia, tinnitus, headache, insomnia, anxiety and others, so it is necessary to individualize monitoring approach, based on concurrent drugs, age, comorbidities, and possible drug interactions. Determination of therapeutic blood levels of drugs may be beneficial in patients with sputum conversion or treatment effect failure not due to drugs resistance or non-adherence, and for reducing the risk of ototoxicity and nephrotoxicity in those receiving

aminoglycosides, or in patients with comorbidities, such as renal failure (10, 31).

Conclusion

Owing to demographic changes, modern lifestyle and living conditions, development of modern technologies, along with current trends in spreading the infection caused by *M. tuberculosis*, and increased understanding of this type of pathogen, mycobacteriosis importance in human pathology has been growing.

Accurately and timely diagnosis, as well as adequate therapy, are of great importance, having in mind numerous treatment-related adverse effects as well.

Future studies and randomized control trials are needed to further optimize the treatment.

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Pregledni rad**UDC: 616.98:579.873.2**
doi:10.5633/amm.2022.0312**MIKOBakterioze – NEKAD I SAD***Zoran Stamenković¹, Lidija Ristić^{1,2}, Ivana Stanković^{1,2}, Milan Radović^{1,2}, Slavica Golubović¹,
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Netuberkulozne mikobakterije (NTM) su ubikvitarnе i nalaze se svuda u okolini. Ljudi su svakodnevno izloženi kontaktu sa ovim mikroorganizmima. Dok broj slučajeva obolelih od tuberkuloze (TB) u celom svetu opada, učestalost infekcija izazvanih NTM je u porastu. NTM mogu uzrokovati kako asimptomatsku infekciju, tako i simptomatsku bolest kod ljudi. Najčešće su plućne infekcije različitog stepena težine. Tačna dijagnoza veoma je važna, između ostalog i zbog toga što lekovi koji se koriste u lečenju ove bolesti mogu imati značajne sporedne efekte. Terapija mikobakterioza, uopšteno, nije direktno analogna terapiji tuberkuloze. Empirijska terapija se ne preporučuje. *In vitro* osetljivost mnogih NTM nije u korelaciji sa kliničkim odgovorom na antimikobakterijske lekove.

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Ključne reči: mikobakterioze, epidemiologija, dijagnostika, terapija

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