

Non-tuberculous mycobacterial pulmonary infections

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BACKGROUND

Pulmonary infections with non-tuberculous mycobacteria are regularly encountered in clinical practice. Diagnosis and treatment are challenging, and international guidelines are largely based on experience and case studies. There is a brief and general account of the subject in the Norwegian Institute of Public Health's tuberculosis guidelines. Other than that, there are no national guidelines on the subject. This article summarises the most recent knowledge on the subject, with the emphasis on diagnosis and treatment.

METHOD

We searched in PubMed, Embase and Cochrane for all reviews and systematic reviews in the period 2007–2017 on non-tuberculous mycobacteria as the cause of pulmonary disease.

RESULTS

When diagnosing and treating pulmonary infections with non-tuberculous mycobacteria, clinical, radiological and microbiological findings must be taken into account before a decision can be made whether treatment is indicated. Identifying the species and any subspecies of a detected mycobacterium and the drug resistance pattern is very important. Treatment consists of a combination of several drugs over a long period, and these frequently have many adverse reactions and drug interactions.

INTERPRETATION

Treatment outcomes for pulmonary infections with non-tuberculous mycobacteria vary. It is important to decide whether the benefit of treatment is expected to outweigh the disadvantages it may entail. For many patients, optimising other treatment of the underlying pulmonary disease will be most important. Patients must be followed up regularly with sputum tests and monitoring of adverse reactions.

Mycobacteria are aerobic, non-spore-forming rod bacteria, are non-motile and acid-fast, i.e. they cannot be decolourised by acid-alcohol in special staining. Their growth rate is generally low, but varies. This forms the basis for their subdivision into fast- and slow-growing species, defined as growth in a solid medium before or after seven days, when spread from a liquid bacterial culture. Non-tuberculous mycobacteria (NTM) have varying pathogenicity and are normally found in the environment, e.g. in soil and water, but can cause infections in both humans and animals. The bacteria may also colonise medical equipment. The most common causes of NTM pulmonary infections in the USA and Europe are the *Mycobacterium avium* complex (MAC), followed by *M. kansasii*, the *M. abscessus* complex and *M. malmoense*, in slightly varying order, depending on the geographical area. In some places, *M. fortuitum* and *M. xenopi* are more common (1, 2). The *M. abscessus* complex and *M. fortuitum* are fast-growing species, the others are slow-growing.

With the introduction of new molecular methods, a growing number of non-tuberculous mycobacteria have been identified: to date, 186 species and 13 subspecies (3, 4). The classification into groups/complexes, species and subspecies is constantly changing, and may vary depending on method. This may be of clinical significance and influence the choice of antibiotics. This applies in particular to the fast-growing species *M. abscessus*, which is now classified as a complex and divided into three different subspecies: *abscessus*, *bolletii* and *massiliense*. Inducible macrolide resistance is found in the first two subspecies and is associated with poorer treatment outcomes (5).

The probability of mycobacterial infection varies with the pathogenicity of the species, the degree of exposure and the person's susceptibility. It was formerly believed that human-to-human infection did not occur, but recent case histories indicate that it can take place between patients with cystic fibrosis (6, 7). To the best of our knowledge, however, there is no consensus on whether this calls for special infection control measures.

Up to the 1950s, *M. tuberculosis* was the predominant mycobacterial pulmonary infection, and non-tuberculous mycobacteria were generally regarded as non-pathogenic. As the prevalence of tuberculosis fell, an increasing number of patients were diagnosed with NTM pulmonary infections. During the HIV epidemic of the 1980s, the prevalence of systemic NTM infections increased, and the need for better treatment received more attention.

NTM infections are not notifiable in most countries, including Norway, and detection of pulmonary infections is based on clinical, radiological and microbiological criteria. It is therefore difficult to obtain a good overview of prevalence. Nevertheless, studies from other countries indicate an increase in recent years that cannot be explained by the HIV epidemic or improved diagnostics (1, 8). Many reasons have been proposed for this, such as a larger proportion of elderly in the population, lower BCG vaccination coverage, more people

living longer with structural pulmonary diseases (bronchiectasis, chronic obstructive pulmonary disease) and diseases that impair the immune system (malignancy, diabetes mellitus etc.) (9), in addition to increased use of immunomodulatory therapy (10). In contrast to tuberculosis, it is difficult to say whether the prevalence of NTM infections is higher in people from countries other than Norway, as we do not have an overview of the prevalence in Norway.

Diagnosing and treating NTM pulmonary infections is a challenge. International guidelines build largely on experience and case studies (11–13). There is a brief general account of the subject in the Norwegian Institute of Public Health's tuberculosis guidelines. Other than that, there are no national guidelines on the subject. This article summarises the most recent knowledge on the subject, with the emphasis on diagnosis and treatment.

Method

In 2007, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) issued joint guidelines for the diagnosis, treatment and prevention of non-tuberculous mycobacterial diseases (11). These guidelines form the basis for many of the recommendations regarding diagnosis and treatment that are presented in this article. More recent findings and guidelines are also included. Guidelines for the treatment of patients with cystic fibrosis (CF) came in 2016 (12), and in 2017 the British Thoracic Society (BTS) issued its own recommendations (13), which are based on a review of relevant literature and the conclusions of a panel of experts.

We searched in PubMed, Embase and Cochrane for all reviews and systematic reviews on non-tuberculous mycobacteria as a cause of pulmonary disease published in the period 2007–2017 (see search strings in the appendix). The search cut-off date was 28 September 2017. There were a total of 215 hits. Articles in languages other than English or that were considered not to cover the topic (infections in animals, local epidemiological data and infections in children) and infections in HIV patients were excluded – 103 articles in all. A total of 112 articles were reviewed in their entirety. In addition, relevant original articles cited in the literature were reviewed – a total of 50 articles.

Diagnosis

The recommendations from the American Thoracic Society and the Infectious Diseases Society of America provide criteria for clinical, radiological and bacteriological findings for determining whether a suspected NTM pulmonary infection lends itself to treatment (11) (Box 1).

Box 1 Clinical, radiological and microbiological criteria for NTM pulmonary disease (11)

Clinical/radiological criteria

1. Pulmonary symptoms and nodular or cavitary opacities on chest radiographs or multifocal bronchiectasis with multiple small nodules on a CT thorax and
2. Appropriate exclusion of other diagnoses

Microbiological criteria

1. Positive culture result in at least two separate expectorated sputum samples. If the

results are non-diagnostic, consider repeat direct microscopy samples for acid-fast bacteria and culture

or

2. Positive culture result in one bronchial wash or bronchoalveolar lavage
or
3. Transbronchial or other lung biopsy with histological findings consistent with mycobacterial infection (granulomatous inflammation or acid-fast bacteria) and growth of non-tuberculous mycobacteria, or biopsy with findings consistent with mycobacterial infection and one or more sputum samples or bronchoalveolar washings that are culture-positive.

A doctor with experience in the field should be consulted in the event of growth of unusual microbes or microbes that usually represent contamination.

Patients suspected of having NTM pulmonary disease but who do not meet the criteria should be followed until the diagnosis has been confirmed or excluded.

The diagnosis NTM pulmonary disease does not, per se, mean that therapy must be instituted. This must be decided after carefully weighing up the potential risks and benefits to the individual patient.

CLINICAL EXAMINATION

Symptoms of NTM lung infection are non-specific as a rule. Coughing, increased mucous formation, weight loss, low-grade fever, haemoptysis and dyspnoea are common. In addition, patients often have an underlying disease that may produce similar symptoms. The clinical presentation may resemble that found with tuberculosis (14, 15).

Cystic fibrosis or bronchiectasis are overrepresented among patients with NTM pulmonary infections, and in a recently published meta-analysis, the condition was found in 9.3 % of patients with bronchiectasis (16). Overrepresentation of patients with mutation in the cystic fibrosis transmembrane regulator gene (CFTR gene) is also found, although these do not have clinical cystic fibrosis (heterozygous mutation) (17–20). The reason for this, and the part played by the CFTR gene, are still unknown.

An unusual disease manifestation is hypersensitivity pneumonitis. The cause is assumed to be an immunological reaction to inhaled non-tuberculous mycobacteria in aerosols from infected water, including swimming pools and hot tubs (21, 22); it is also called “hot tub lung”. Clinical and radiological findings are similar to other types of hypersensitivity pneumonitis.

RADIOLOGICAL EXAMINATION

When NTM pulmonary disease is suspected, the patient should undergo a CT thorax. The two most common radiological presentations are the fibrocavitary and nodular bronchiectasis forms (23, 24). The fibrocavitary form has cavitory lesions, most frequently in the upper lobes, with radiological findings that resemble tuberculosis (Fig. 1). This form often has a more aggressive course, and is seen most frequently in elderly men who smoke or have another pulmonary disease, such as chronic obstructive pulmonary disease, or have had tuberculosis. The nodular bronchiectasis form is characterised by multifocal bronchiectasis and small nodules, most frequently in non-smoking, elderly women. This form is also over-represented in patients with a low body mass index, scoliosis, pectus excavatum, mitral prolapse, and in tall persons (17, 19).



Figure 1 CT thorax of a patient with severe COPD with emphysema. Cavernous and fibrotic changes and infiltrates are seen. There was repeated growth of *M. intracellulare* in bronchial specimens.

MICROBIOLOGICAL EXAMINATION

Microbiological diagnosis of pulmonary disease due to non-tuberculous mycobacteria may be difficult because these bacteria occur naturally in the environment. Unlike tuberculosis, where findings of the bacteria confirm the disease, findings of non-tuberculous mycobacteria in a respiratory specimen do not necessarily imply clinically relevant infection. There is a strong risk of contamination of sputum or bronchoscopy samples (e.g. from the oral cavity), and a positive finding may also represent bronchial colonisation without this being the cause of the patient's complaint. Species identification is very important, as some species are more pathogenic than others (9, 25) (Fig. 2). The occurrence of a clinically relevant pulmonary infection with the various species in a population will also depend on the geographical distribution of the bacterium in the environment and the prevalence of risk factors in the population (1, 25). Growth in two or more sputum specimens taken at different times is a required microbiological criterion for NTM pulmonary infection. Alternatively, growth in only one specimen extracted via bronchoscopy (bronchoalveolar lavage, BAL), is accepted, or a culture positive lung biopsy (11). At the Departments of Pulmonary and Infectious Diseases at Oslo University Hospital we always want sputum samples to be taken some weeks apart to confirm persistent infection. There has been debate about these criteria, particularly that only one bronchoscopy specimen is sufficient, as contamination is a risk here too. In any case, the criteria must be used with discretion, with emphasis on which microbes are found, and whether other findings and clinical presentation are convincing.

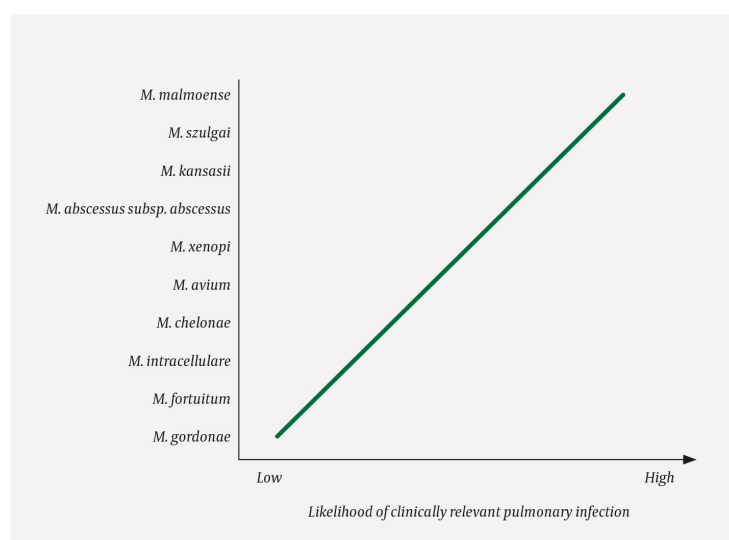


Figure 2 Findings of non-tuberculous mycobacteria in bronchial specimens and the likelihood of their representing clinically relevant infection (9, 25).

In addition to identifying the bacteria, it is important to perform relevant susceptibility testing in order to be able to choose the correct treatment regimen. For the fast-growing mycobacteria, it is recommended that resistance to a number of antibiotics be tested, while testing for fewer drugs is recommended for the slow-growing mycobacteria. Unfortunately, the connection between in vitro susceptibility determination and in vivo efficacy is uncertain for several of the drugs in question. In the case of infection with the *Mycobacterium avium* complex (MAC), for example, only macrolides and amikacin have similar in vitro and in vivo effect (26–28).

Macrolide sensitivity has proved to be an important prognostic indicator in the treatment of NTM infections (5, 29). In addition to acquired resistance due to mutations in the 23S rRNA gene (the *rml* gene), inducible macrolide resistance has been observed in some fast-growing, non-tuberculous mycobacteria in recent years. These may initially be susceptible to macrolides, but resistance can appear and is detected in vitro after exposure to macrolides for up to 14 days. This is associated with a functional *erm* gene in some species and subspecies (30). It is therefore important to take this into account when susceptibility testing is done and when choosing antibiotics regimens. The most important risk factor for the development of macrolide resistance is macrolide monotherapy (31). In light of this, and because macrolides play such a central part in the treatment of these infections, questions have been raised about long-term macrolide therapy for patients with pulmonary disease, for example patients with cystic fibrosis (32, 33).

Treatment

A few randomised, controlled studies have been conducted to evaluate the therapeutic efficacy of different regimens (34–38). However, these studies have several weaknesses, and do not provide unambiguous answers. Recommended treatment regimens are therefore based largely on experience and expert statements. We provide a brief account below, but for a more comprehensive review, we refer to the American and British guidelines (11, 13). Unless otherwise specified, the treatments recommended in the article are taken from these guidelines.

Treatment of NTM pulmonary infections is long-term, requires concurrent use of several antimicrobial drugs, and has varying effectiveness. Successful treatment is defined as negative sputum tests for 12 months during ongoing treatment. Treatment is generally recommended for at least 18 months. The exception is treatment of hypersensitivity pneumonitis, where treatment with antimicrobial agents has not been seen to have any definite effect. Recommended therapy for this is systemic glucocorticoids and avoidance of further exposure.

The treatment regimens are resource-intensive and often cause adverse reactions and drug interactions. At the same time, there is great variation in the natural course of these infections – from subclinical to rapidly progressing disease. It is therefore very important to make a thorough assessment of the patient with respect to whether initiating treatment would be appropriate. At the same time, it is important to optimise other treatment, such as mucous mobilisation and pulmonary physiotherapy, and to exclude other causes of disease. Monitoring of therapeutic effectiveness by means of sputum samples taken at 1–2 month intervals is recommended. If sputum is still culture-positive after six months of treatment, the treatment has probably failed. New samples should be taken for susceptibility testing before the antibiotic regimen is revised. Although the object of the treatment is usually cure, in some cases this will be unrealistic. The goal of the treatment may then be suppression of the infection.

RELEVANT ANTIBIOTICS

Macrolides have an important place in the treatment of non-tuberculous mycobacteria. No definite difference in efficacy has been found between clarithromycin and azithromycin, and the primary advantage of the latter is fewer drug interactions. The risk of drug interactions should also be borne in mind when rifampicin is used. The usual dosage of rifampicin is 600 mg for weights over 50 kg, 450 mg for lower weights. The aminoglycosides recommended in the international guidelines are streptomycin or amikacin, except for treatment of *M. chelonae*, where tobramycin has proved most efficacious. Determining the serum concentration of streptomycin is not easy, and in consequence amikacin is preferred of these two. If patients are to be treated with aminoglycosides, renal function must be assessed and serum concentration measured, and patients must be monitored for ototoxicity. If isoniazid is used, a daily supplement of 40 mg x 1 pyridoxine is recommended as prophylaxis for polyneuropathy, and when ethambutol is used, visual acuity and colour vision should be tested before commencement and in case of symptoms. ECG is recommended before commencement and after two weeks on therapy with drugs that may result in a prolonged QT interval, such as macrolides and fluoroquinolones (13).

Table 1 sets out our recommendations for treatment of the most common pulmonary diseases due to non-tuberculous mycobacteria, based on the American and British guidelines (11, 13).

Table 1

The authors' recommendations for treatment of the pulmonary diseases due to the most common non-tuberculous mycobacteria, based on American and British guidelines (11, 13)

| | Drug regimen | Duration |
|---|---|---|
| <i>Mycobacterium avium complex</i> | | |
| Nodular/bronchiectatic disease | Three times a week Clarithromycin 1 000 mg by mouth (alternatively azithromycin 500 mg by mouth) + ethambutol 25 mg/kg by mouth + rifampicin 450–600 mg by mouth or Daily Clarithromycin 500 mg x 2 by mouth (alternatively azithromycin 250–500 mg x 1 by mouth) + ethambutol 15 mg/kg by mouth + rifampicin 450–600 mg by mouth | 12 months after negative sputum culture |
| Cavitary lung disease | Daily Clarithromycin 500 mg x 2 by mouth (alternatively azithromycin 250–500 mg x 1 by mouth) + ethambutol 15 mg/kg x 1 by mouth + rifampicin 450–600 mg x 1 by mouth If indicated, also amikacin 15 mg/kg intravenously three times a week ≤ 3 months | 12 months after negative sputum culture |
| <i>M. kansasii</i> | Daily Rifampicin 450–600 mg x 1 by mouth + ethambutol 15 mg/kg x 1 by mouth + isoniazid 300 mg x 1 by mouth (alternatively azithromycin 250–500 mg x 1 by mouth or clarithromycin 500 mg x 2 by mouth or moxifloxacin 400 mg x 1 by mouth) | 12 months after negative sputum culture In cases of rifampicin resistance, a regimen with three drugs based on resistance pattern is recommended. |
| <i>M. malmoense</i> | Daily Rifampicin 450–600 mg x 1 by mouth + ethambutol 15 mg/kg x 1 by mouth + clarithromycin 500 mg x 2 by mouth (alternatively azithromycin 250–500 mg x 1 by mouth) or moxifloxacin 400 mg x 1 or isoniazid 300 mg x 1 by mouth) In cases of severe illness, amikacin 15 mg/kg intravenously three times a week can be considered | 12 months after negative sputum culture |
| <i>M. abscessus complex</i> | Intensive phase: Macrolide by mouth + 1–6 months with at least 2 parenteral drugs (e.g. amikacin, ceftazidime, imipenem and tigecycline) Maintenance phase: Macrolide by mouth + 1–2 other drugs by mouth (e.g. fluoroquinolones, linezolid, clofazimine) and/or amikacin for inhalation | 12 months after negative sputum culture Resistance patterns must be considered when choosing drugs (13). Treatment must be customised to the individual. Surgery must be considered. |

SLOW-GROWING NON-TUBERCULOUS MYCOBACTERIA

Macrolides are the cornerstone of treatment of most infections with slow-growing non-tuberculous mycobacteria (Table 1). There are only guidelines for susceptibility testing of some of these species. It is initially recommended that species in the *Mycobacterium avium* complex be tested only for resistance to macrolides and amikacin. If macrolides cannot be used, moxifloxacin and linezolid should also be tested. For *M. kansasii*, *M. malmoense* and *M. xenopi*, initial testing for resistance to rifampicin is recommended, and expanded testing if resistance to rifampicin is found.

THE MYCOBACTERIUM AVIUM COMPLEX (MAC)

The *M. avium* complex includes the species *M. avium*, *M. intracellulare* and *M. chimaera*. The recommended treatment regimen is macrolide, rifampicin and ethambutol for 12 months after the last negative culture, typically 18–24 months. For patients without cavitory lesions, an intermittent regimen with dosing three times a week has shown results equally as good as daily treatment (39, 40). Recent studies have also shown less severe adverse reactions with intermittent therapy (41, 42). The results of intermittent therapy are poorer for cavitory disease, and it is therefore not recommended. In cases of severe illness, it is recommended that an aminoglycoside be added for the first two to three months of the therapy. If there is a need for long-term aminoglycoside therapy, amikacin inhalation may be an option (43). In case of treatment failure, addition of moxifloxacin may increase the success rate (44, 45). Clofazimine may be used as an effective alternative to rifampicin, or for refractory MAC disease (46, 47).

The treatment results for MAC pulmonary disease are still relatively poor. Termination of treatment because of adverse reactions is common (10–30 %), and there is only 40–60 % total treatment success (29, 48). The outcomes are better (about 70–85 %) in patients without cavitory disease, but recurrence of the disease after successful treatment is common (30–50 %). This is usually due to reinfection with a new strain of the complex (42, 49). Resistance to macrolides substantially reduces therapeutic success and complicates treatment (31).

MYCOBACTERIUM KANSASII

This is generally the easiest species of all non-tuberculous mycobacteria to treat.

Studies have shown treatment success of up to 95 % (50). In contrast to other non-tuberculous mycobacteria, there is relatively good correlation between in vitro determination of resistance and clinical efficacy for rifampicin, macrolides and fluoroquinolones (51). The standard regimen has been daily treatment with rifampicin, ethambutol and isoniazid (11). However, there is uncertainty concerning the efficacy of isoniazid in the treatment, and a beneficial effect has been reported for macrolides and fluoroquinolones. Many therefore recommend replacing isoniazid with a macrolide or fluoroquinolone (52) (Table 1).

MYCOBACTERIUM MALMOENSE

There is no consensus regarding the optimal therapeutic regimen for this mycobacterium, and studies with different regimens have produced divergent outcomes (34, 53). A retrospective study from the Netherlands reported relatively high therapeutic success (70 %) (54). A regimen of isoniazid, rifampicin and ethambutol used to be recommended.

However, this has been changed in more recent guidelines, which replace isoniazid with a macrolide (13). In cases of serious illness, supplementary aminoglycoside therapy can be considered (13). A fluoroquinolone may also be added.

FAST-GROWING NON-TUBERCULOUS MYCOBACTERIA

Although the correspondence between clinical efficacy and susceptibility testing is uncertain, it is recommended that this should govern the choice of antibiotics. In the

current guidelines for fast-growing mycobacteria, testing is recommended for amikacin, cefoxitin, ciprofloxacin, moxifloxacin, clarithromycin, doxycycline, imipenem, linezolid, trimethoprim- sulfamethoxazole and tobramycin (11), even though not all drugs are relevant for all species. *M. chelonae* is the only species for which tobramycin is preferred to amikacin as aminoglycoside.

M. fortuitum is generally regarded as the easiest to treat, and is usually sensitive to a number of drugs (55), while infection with the *M. abscessus* complex, which is by far the most frequent cause of pulmonary infections, is particularly difficult to treat.

The effect of different treatment regimens on *M. abscessus* has been investigated in only two major studies. In 2009, a retrospective Korean study was published in which 65 patients who had received standardised treatment against *M. abscessus* were evaluated (56). They all received clarithromycin, ciprofloxacin and doxycycline by mouth. For four weeks initially, they also received intravenous therapy with amikacin and either cefoxitin or imipenem. Negative sputum culture tests for more than one year were achieved for 58 % of patients. Symptom improvement was experienced by 83 %, and radiological improvement by 74 % of patients. Twenty-two percent had undergone surgery. Only 63 % completed the therapy according to plan. It is noteworthy that macrolide resistance was strongly associated with a poor therapeutic outcome. Only 17 % in this group achieved a cure.

In 2011, a retrospective study was published by National Jewish Health in Colorado (57). Sixty-nine patients were followed for 34 months on average. In this study, the antibiotic regimen was customised on the basis of in vitro resistance determination and patient tolerance. The average treatment time was 52 months, six of them with intravenous treatment. Sputum samples from 48 % of the patients remained culture negative. It is noted here that substantially better results in terms of culture negativity for 12 months were achieved by those who had surgery – comprising 33 % of those in this study.

It is not possible on the basis of the literature to give an exact recommendation for which drugs should be selected to treat the *M. abscessus* complex. In addition to the resistance pattern, the side effect profile has to be taken into account. An intensive phase of 1–6 months with at least two parenteral drugs and a macrolide is recommended, followed by a maintenance phase with oral drugs for 12 months following negative sputum tests (Table 1). The most effective parenteral drugs include amikacin, cefoxitin, imipenem and tigecycline. After the intensive phase of treatment has been completed, treatment with macrolides is recommended and in addition one or two other oral antibiotics such as fluoroquinolones, linezolid or clofazimine. Amikacin inhalation is also an option. All patients infected with the *M. abscessus* complex should be considered for surgery if there is focal disease, as the success rate is higher for patients who have combined medical and surgical treatment (57–61).

Summary

The diagnosis and treatment of pulmonary infections with non-tuberculous mycobacteria are based on clinical and radiological findings and on microbiological test results. Identification of species and, if relevant, subspecies is very important, and susceptibility testing is often also important for choosing a medication regimen. Treatment consists of a combination of several drugs for a long period, sometimes has limited efficacy and can cause considerable adverse reactions and drug interactions. It is therefore important to decide whether the benefit of the treatment is expected to outweigh the disadvantages it can entail. If a decision is made to treat, patients should be followed up regularly with sputum cultures and monitoring of adverse reactions. We recommend that these patients be treated at hospitals with specialists in infectious diseases or pulmonary medicine (preferably working together), microbiology, radiology and thoracic surgery. We have established a multidisciplinary group of this kind at Oslo University Hospital, Ullevål, which discusses all patients who may be candidates for treatment.

MAIN POINTS

We found that diagnosing and treating pulmonary infections with non-tuberculous mycobacteria requires a thorough evaluation of clinical, radiological and microbiological findings.

The treatment is long-term and is conducted with a combination of antibiotics, and its efficacy varies.

There is a high incidence of adverse reactions and drug interactions

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Publisert: 26 november 2018. Tidsskr Nor Lægeforen. DOI: 10.4045/tidsskr.18.0077

Received 18.1.2018, first revision submitted 28.5.2018, accepted 27.8.2018.

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