

# Chapter 19: Non-Tuberculous Mycobacteria

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## Summary

- Many species of mycobacteria other than *M. tuberculosis* complex are recognised human pathogens. The spectrum of disease caused by non-tuberculous mycobacteria (NTM) is wide and overlaps with that caused by *M. tuberculosis*. NTM and the sites where they cause disease are shown in Table 19.1.
- Besides an overlap of disease spectrum with *M. tuberculosis*, infection with NTM may also give rise to positive acid-fast bacilli (AFB) smears and histopathology findings similar to those found in TB. However, the treatment and public health implications of NTM disease are very different from those of *M. tuberculosis*.

## Epidemiology

- Most NTM are isolated from water and soil, but some are isolated from other sources such as house dust.
- Environmental sources, especially natural waters, are the reservoir for most human infections of *M. avium* complex (MAC). The aerosolisation of water may be an important means of transmission. Animal-to-human transmission is not important in human disease.
- Rapidly growing mycobacteria such as *M. fortuitum*, *M. chelonae* and *M. abscessus* can be readily recovered from soil and natural water supplies. Investigations of some nosocomial outbreaks suggest that air, tap water and distilled water may be the sources for these mycobacteria.
- For sources of *M. kansasii*, *M. marinum* and *M. xenopi*, see full text.
- Human-to-human transmission is unlikely.
- The predominant NTM species responsible for human disease varies between countries.
- The reasons for the worldwide increase in incidence in both laboratory isolation and NTM disease remains uncertain.

## Clinical disease caused by NTM

### ***Pulmonary disease***

- Chronic pulmonary disease resembling TB is the most common clinical presentation of NTM infection. Patients are generally older adults – only rarely do children develop this type of NTM disease.
- Signs and symptoms of NTM pulmonary disease are variable and non-specific. They include productive cough, dyspnoea, haemoptysis, malaise and fatigue. Fever, weight loss and night sweats occur less commonly than with TB.
- Radiology findings in NTM lung disease: Type 1 and Type 2 patterns seen on CT scans are discussed in the full text.

### ***Lymphadenitis***

- Infection of the sub-mandibular, sub-maxillary or cervical lymph nodes in children aged between one and five years is the most common presentation of NTM lymphadenitis.
- In New Zealand and Australia approximately 80% of culture-positive cases of NTM lymphadenitis are due to *M. avium* complex.

- Only about 5% of culture-proven mycobacterial cervical lymphadenitis in children in Western countries is due to *M. tuberculosis*.
- More than 90% of culture-proven mycobacterial lymphadenitis at any site in adults is due to *M. tuberculosis*.

### ***Disseminated NTM disease in HIV/AIDS***

- *M. avium* is the most frequent bacterial opportunistic infection of AIDS.
- Average CD4 counts at the time of dissemination are < 50 cells/ $\mu$ l. Patients with < 100 CD4 cells/ $\mu$ l, not receiving prophylaxis, are at risk of developing disseminated disease at a rate of up to 20% per year.
- Fever, drenching night sweats and weight loss characterise disseminated disease. Widespread involvement of the reticuloendothelial system is common and results in hepatomegaly, splenomegaly and lymphadenopathy.

### **Diagnosis of NTM infection**

- Correct species identification of NTM is one of the most complex tasks performed in a mycobacteriology laboratory.

### ***Skin-test antigen testing***

- It is unlikely that skin-test reagents will become available in the near future to aid in the diagnosis of NTM disease.

### ***Positive cultures: contamination, colonisation or disease?***

- A single positive sputum culture, especially with small numbers of organisms, does not suffice to diagnose NTM disease.
- Minimum evaluation should include three or more sputum specimens for AFB and efforts to exclude other confounding disorders such as TB and lung malignancy.

### ***Diagnosis of pulmonary infection***

- The clinical, radiological and bacteriological diagnostic criteria proposed by the American Thoracic Society should be used. To secure a diagnosis of pulmonary disease, all three criteria must be met.
- At least three respiratory samples should be evaluated from each patient.
- Other reasonable causes for the disease should be excluded.
- If the clinical situation is non-acute, and the diagnosis has not been established, repeating three sputum specimens a few months later is suggested if the person still has symptoms or worsening symptoms. Expert consultation should be sought when diagnostic difficulties are encountered.

### ***Diagnosis of extra-pulmonary NTM disease***

- Biopsies from any site of suspected NTM infection should be sent for both histopathology and microbiology testing.

- Both laboratories must be alerted to the possibility of mycobacterial infection: media selection and temperature and duration of incubation depend on knowing that mycobacterial infection is suspected.
- TB should not be forgotten as a possible diagnosis.

#### **Laboratory tests for disseminated NTM infection in HIV/AIDS**

- Mycobacteraemia is readily detected in appropriate blood culture media. These should be done routinely with unwell HIV patients under investigation.
- A single blood culture has a sensitivity of around 90%, and therefore no more than two blood culture sets are required.

#### **Susceptibility testing for NTM**

- Testing should only be performed by reference laboratories on isolates strongly suspected of causing disease.
- Single isolates from a series of smear-negative sputum specimens are unlikely to be clinically significant and do not require routine susceptibility testing.
- For advice about susceptibility testing for individual NTM species, see full text.

#### **Treatment of NTM disease**

##### ***M. avium* complex**

- Drug therapy for *M. avium* complex disease involves multiple drugs, and because of this the risk of drug toxicity is relatively high. Drug side-effects and drug interactions make treatment difficult for both the patient and the clinician.
- A rifamycin, ethambutol and clarithromycin are the agents for disease in immuno-competent patients.
- The treatment of *M. avium* complex disease is best undertaken by clinicians experienced in treating mycobacterial diseases.

##### ***M. kansasii***

- The currently recommended treatment of *M. kansasii* pulmonary disease in adults is rifampicin with isoniazid and ethambutol. As isolates are normally susceptible to macrolides and these have been used as components of multi-drug treatment for this disease.

##### **NTM lymphadenitis**

- Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis. The success rate with this procedure approaches 95%.
- If medical treatment is being considered, specialist advice is required.

##### **Infections due to rapidly growing mycobacteria**

- Pulmonary disease due to *M. abscessus* is particularly serious, with a fatality rate of 20% in one series.

### ***NTM in HIV/AIDS patients***

- Because of the difficult management decisions involved, drug toxicity concerns, as well as drug interactions and compliance issues, therapy for and prophylaxis against disseminated *M. avium* infection should only be undertaken by those with experience in this area.

### ***Prognosis and referral***

- Patients with NTM infection can be regarded as being non-infectious; notification is not required.
- The response to therapy depends on the NTM species and the site of infection. An expectation of gradual rather than rapid improvement should be given to patients.
- Specialist referral is advisable for:
  - all patients with pulmonary NTM infection – establishing the diagnosis is not simple and therapeutic regimens may be complex and potentially toxic
  - children with probable NTM lymphangitis
  - patients, particularly the immunosuppressed, with cutaneous infection
  - HIV/AIDS patients with systemic symptoms – the differential diagnosis is long and therapeutic decisions difficult.

### ***Future developments***

- Infection due to NTM is not a notifiable disease. There are few data on the number, type, and epidemiology of NTM infections in New Zealand.
- Therefore it would be helpful if the three New Zealand level III laboratories published their combined results each year for their NTM isolates along with any available demographic data.
- These could be published in the ESR report so that, over time, a picture of the common and clinically important NTM in New Zealand would develop.

## Introduction

Many species of mycobacteria other than *M. tuberculosis* complex are recognised human pathogens. The spectrum of disease caused by non-tuberculous mycobacteria (NTM) is wide, and overlaps with that caused by *M. tuberculosis*. NTM and the sites they cause disease are shown in Table 19.1.<sup>1</sup>

Besides an overlap of disease spectrum with *M. tuberculosis*, infection with NTM may also give rise to positive AFB smears and histopathology findings similar to those of TB. However, the treatment and public health implications of NTM disease are very different from those of *M. tuberculosis*. This chapter gives an overview of the epidemiology, diagnosis and treatment of this diverse group of organisms.

In 1959 Runyon separated the NTM into four groups based on their pigmentation, colony morphology and growth rate. However many NTM do not fit into any of the four groups of the Runyon scheme. Clinical laboratories have moved away from the Runyon scheme and favour the identification of NTM to species level. An overview of the geography and laboratory characteristics of NTM is given in Table 19.1.<sup>1</sup>

## 19.1 Epidemiology

### 19.1.1 Sources of NTM infection

Most NTM are isolated from water and soil, but some are isolated from other sources such as house dust. It is now generally accepted that environmental sources, especially natural waters, are the reservoir for most human infections caused by *M. avium* complex (MAC). The aerosolisation of water may be an important means of transmission of infection, both in nature<sup>2</sup> and domestically. Although *M. avium* is an important cause of disease in poultry and pigs, serological tests have shown that different strains affect animals and humans, and animal-to-human transmission is not important in human disease.<sup>1</sup>

Water is also the likely source for *M. marinum*, which is commonly associated with fish tanks and swimming pools. In contrast, *M. kansasii* has yet to be recovered from soil or natural water supplies, but it has been isolated on numerous occasions from tap water.

The possibility of person-to-person transmission has been investigated. This was entertained for *M. malmoense*, but has been disproven by molecular epidemiology research.<sup>3</sup> Familial cases of NTM lung disease are uncommon. Two Japanese families affected by *M. avium intracellulare* lung disease (MAILD) were studied, and mycobacterial DNA restriction fragments revealed that none of the MAC strains isolated from the patients was epidemiologically related to any of the others.<sup>4</sup>

Rapidly growing mycobacteria such as *M. fortuitum*, *M. chelonae* and *M. abscessus* can be readily recovered from soil and natural water supplies. Investigations of some nosocomial outbreaks caused by these species have suggested that air, tap water and distilled water (used for dialysis or preparing surgical solutions) may serve as the sources for these organisms.

*M. xenopi* has been recovered almost exclusively from water, especially from hot water taps in hospitals, where it has been associated with cases of clinical disease.

Much remains to be understood about the pathogenesis of NTM infection and disease in humans. Epidemiological studies and skin-test surveys suggest that person-to-person transmission is not important in human disease. It is assumed that most persons become infected by environmental NTM. Of the likely sources of infection, airborne NTM may play an important role in respiratory NTM disease, whereas ingestion of NTM may be the source of infection for children with NTM cervical lymphadenitis and for patients with AIDS whose disseminated *M. avium* disease may begin with gastrointestinal infection. It is not known whether NTM disease develops soon after infection or, like TB, develops after a period of latent infection. Direct inoculation with NTM in water or other material is the likely source of infection for patients with soft-tissue infections.

**Table 19.1:** Non-tuberculous mycobacteria recovered from humans<sup>1</sup>

<b>Clinical disease</b>	<b>Common etiologic species</b>	<b>Features of the common species</b>		<b>Uncommon etiologic species</b>
		<b>Geography</b>	<b>Morphologic features*</b>	
Pulmonary disease	1. <i>M. avium</i> complex	Worldwide	Usually not pigmented; slow growth (> 7d)	1. <i>M. simiae</i> 2. <i>M. szulgai</i>
	2. <i>M. kansasii</i>	US, Europe	Pigmented; often large and beaded on acid-fast stain	3. <i>M. fortuitum</i> 4. <i>M. celatum</i>
	3. <i>M. abscessus</i>	Worldwide	Rapid growth (< 7d); not pigmented	5. <i>M. asiaticum</i> 6. <i>M. shimodii</i>
	4. <i>M. xenopi</i>	Europe, Canada	Slow growth; pigmented	7. <i>M. haemophilum</i>
	5. <i>M. malmoense</i>	UK, northern Europe	Slow growth; not pigmented	8. <i>M. smegmatis</i>
Lymphadenitis	1. <i>M. avium</i> complex	Worldwide	Usually not pigmented	1. <i>M. fortuitum</i>
	2. <i>M. scrofulaceum</i>	Worldwide	Pigmented	2. <i>M. chelonae</i>
	3. <i>M. malmonense</i>	UK, northern Europe (especially Scandinavia)	Slow growth	3. <i>M. abscessus</i> 4. <i>M. kansasii</i> 5. <i>M. haemophilum</i>
Cutaneous disease	1. <i>M. marinum</i>	Worldwide	Photochromogen; requires low temperatures (28–30°C) for isolation	1. <i>M. avium</i> complex 2. <i>M. kansasii</i> 3. <i>M. nonchromogenicum</i>
	2. <i>M. fortuitum</i>	Worldwide	Rapid growth; not pigmented	4. <i>M. smegmatis</i>
	3. <i>M. chelonae</i>	Worldwide		5. <i>M. haemophilum</i>
	4. <i>M. abscessus</i>	Worldwide	Grows slowly; pigmented	
	5. <i>M. ulcerans</i>	Australia, tropics, Africa, SE Asia		
Disseminated disease	1. <i>M. avium</i> complex	Worldwide	Isolates from patients with AIDS usually pigmented (80%)	1. <i>M. abscessus</i> 2. <i>M. xenopi</i> 3. <i>M. malmoense</i>
	2. <i>M. kansasii</i>	USA	Photochromogen	4. <i>M. genavense</i>
	3. <i>M. chelonae</i>	USA	Not pigmented	5. <i>M. simiae</i>
	4. <i>M. haemophilum</i>	USA, Australia	Not pigmented; requires hemin, often low temperatures, and CO <sub>2</sub> to grow	6. <i>M. conspicuum</i> 7. <i>M. marinum</i> 8. <i>M. fortuitum</i>

\* Photochromogen: isolate is buff-coloured in the dark but turns yellow after exposure to light.

### 19.1.2 Geography and NTM species causing disease

There is variation in the NTM species responsible for human disease in different countries.<sup>1</sup>

- *M. avium* is the most common NTM causing disease in the US, New Zealand, Australia and Hong Kong.<sup>5</sup> This is true both for immunocompetent and immunosuppressed individuals.
- *M. malmoense* is a major pathogen in northern Europe, including Scotland and Norway.
- *M. kansasii* is common in the central states of the US.
- *M. xenopi* is common in Canada and Europe, but less so in the US.

### 19.1.3 Increasing incidence of NTM laboratory isolation and disease

An increase in incidence in laboratory isolation of NTM and of disease caused by them has been recognised worldwide.<sup>1 5 6</sup> The reason for this remains uncertain. While increased awareness of disease caused by NTM will prompt increased testing for these organisms, other explanations are more likely, including:

- changes in living standards, such as the change to showering instead of bathing (this would increase exposure to aerosolised water)
- genetic transfer, leading to increased virulence of organisms (in contrast to *M. tuberculosis*, MAC is affected by plasmids)<sup>1</sup>
- climatic changes
- more sensitive laboratory isolation techniques<sup>7</sup>
- nosocomial acquisition (while there are many instances of different NTM infections being acquired in hospitals through contaminated tap water, distilled water, hot water systems, bronchoscopes, peritoneal dialysis fluid, injections and other sources, it is most unlikely that hospital sources account for more than a minority of all disease caused by NTM).

### 19.1.4 Ethnicity and NTM disease

The epidemiology of TB is well documented throughout most of the world (see Chapter 1 for the epidemiology of TB in New Zealand). The situation is the opposite for NTM, for which mandatory reporting and systematic data collection are not carried out. There is thus very little information about ethnicity and NTM disease.

The one exception is for NTM lymphadenitis. Caucasian ethnicity was a feature in children with NTM adenitis in both an Australian and two New Zealand studies of mycobacterial lymphadenitis.<sup>8-10</sup> This contrasts with TB, where non-Caucasian ethnicity is a risk factor for TB because many non-Caucasians come from, visit or have contact with people who have lived in countries with a high incidence of TB.

## 19.2 Clinical disease caused by NTM

### 19.2.1 Pulmonary disease

Chronic pulmonary disease resembling TB is the most common clinical presentation associated with NTM. In the US *M. avium* complex and *M. kansasii* are the most common NTM species affecting the lungs. Other pathogens occasionally causing pulmonary disease include *M. chelonae*, *M. fortuitum*, *M. abscessus*, *M. xenopi* and *M. malmoense*. The proportion of pulmonary disease caused by different NTM varies in different regions of the world. Patients are generally older adults, and only rarely do children develop this type of NTM disease.

#### **Signs and symptoms of NTM pulmonary disease**

These are variable and non-specific. They include productive cough, dyspnoea, haemoptysis, malaise and fatigue. Fever and weight loss can occur but are less common and less severe than with *M. tuberculosis*. While differences occur in the radiological findings in pulmonary disease caused by NTM and those of *M. tuberculosis*, no radiological finding is pathognomonic or diagnostic of NTM. Evaluation is often complicated by symptoms caused by other pre-existing lung disease, which include previous mycobacterial disease, chronic obstructive airway disease, bronchiectasis and malignancy.

#### **Radiology findings in NTM lung disease**

NTM lung disease is divided into two main radiological types (type 1 and type 2), seen on chest CT scan. These have been mainly described with *M. avium intracellulare* lung disease (MAILD). The same patterns are seen with many other NTM, but there is no review of the frequency with which all types of NTM fit into these patterns.

The type 1 pattern is seen on a standard CXR. Features include:

- cavities (usually with thinner walls than in TB)
- macro-nodules ( $\geq 0.5$  cm diameter)
- areas of consolidation.

Type 2 changes are only seen on chest CT (high-resolution films are preferable), and include:

- bronchiectasis
- micro-nodules (small) centri-lobular nodules ( $< 0.5$  cm)
- geographical light and dark areas on expiratory scans – the dark areas are abnormal and are indicative of delayed emptying of lung lobules caused by small airway disease (see below).

Sometimes a mixture of types 1 and 2 changes occurs. The significance of these patterns becomes evident with the management of NTM lung disease.

### 19.2.2 Lymphadenitis

Infection of the sub-mandibular, sub-maxillary or cervical lymph nodes in children aged between one and five years is the most common presentation of NTM lymphadenitis. The disease occurs insidiously, with minimal symptoms. The involved lymph nodes are practically always unilateral and generally not tender. Normally there is no history of exposure to TB, and the chest radiograph is normal.

Approximately 80% of culture-positive cases of lymphadenitis are due to *M. avium* complex, with most of the remainder being due to *M. scrofulaceum*. Only about 5% of culture-proven mycobacterial cervical lymphadenitis in children is due to *M. tuberculosis*. In contrast, more than 90% of culture-proven mycobacterial lymphadenitis at any site in adults is due to *M. tuberculosis*.

### 19.2.3 Skin, soft-tissue and injection-site infections

The NTM species that most commonly cause infections of the skin and subcutaneous tissue are *M. fortuitum*, *M. chelonae* and *M. marinum*. However, virtually all species of NTM have been described as a cause of cutaneous disease.

Localised drainage or abscess formation at the site of puncture wounds, or after open traumatic injuries or fractures, is most often due to the rapidly growing mycobacterial species *M. fortuitum* or *M. chelonae*. Wound infection following augmentation mammoplasty and cardiac surgery is well recognised. An outbreak of infection caused by *M. abscessus* occurred in two US states as a result of a physician administering contaminated, non-FDA-approved ‘adrenal cortex extract’ by IM injection.<sup>11</sup> Other NTM infections have resulted from IM injection.

*M. marinum* is the cause of ‘swimming pool granuloma’ or ‘fish tank granuloma’. The lesions usually appear as papules on an extremity, especially on the elbows, knees and dorsum of the feet and hands, progressing subsequently to shallow ulceration and scar formation. Clinical involvement of regional nodes is absent. The organisms may be introduced into the skin through abrasions in swimming pools and fish tanks, or by scratches or puncture wounds from fish, shrimp, fins, etc.

In Australia *M. ulcerans* is a well recognised cause of indolent necrotic lesions of the skin and underlying tissue.

### 19.2.4 Disseminated NTM disease in HIV/AIDS

*M. avium* is the most frequent bacterial opportunistic infection of AIDS. While many NTM species, including *M. kansasii*, *M. scrofulaceum* and *M. xenopi*, have caused disseminated NTM disease in HIV/AIDS, more than 95% of cases are due to *M. avium* complex isolates and most of these are *M. avium* rather than *M. intracellulare*.<sup>12</sup> In the era before treatment with combination anti-HIV agents, autopsy series suggested that 30–50% of patients with AIDS had disseminated *M. avium* complex disease at the time of their death.

CD4 cell counts predict the incidence of *M. avium* complex bacteraemia, with the average CD4 count at the time of dissemination being < 50 cells/ $\mu$ l.<sup>13</sup> Patients with < 100 CD4 cells/ $\mu$ l, not receiving prophylaxis, are at risk of developing disseminated disease at a rate of up to 20% per year.<sup>13</sup> Fever, drenching night sweats and weight loss characterise disseminated disease. Widespread involvement of the reticuloendothelial system is common and results in hepatomegaly, splenomegaly and lymphadenopathy.

### 19.3 Diagnosis of NTM infection

A large number of potentially pathogenic NTM can be encountered in the clinical laboratory. Correct species identification of these organisms is one of the most complex tasks performed in a mycobacteriology laboratory. The appearance of NTM on microscopy is indistinguishable from *M. tuberculosis*, except that *M. kansasii* is often longer and has a more beaded appearance.

#### 19.3.1 Skin-test antigen testing

‘Tuberculin-type’ antigens have been used in Australia but do not have widespread acceptance. Unfortunately, many antigens are shared by NTM and extensive cross-reactions are observed. It is unlikely that skin-test reagents will become available in the near future to aid in the diagnosis of NTM disease.

In the absence of specific diagnostic features in history and physical examination, CXR and differential skin testing, isolation of the NTM in a culture is usually required for diagnosis.

#### 19.3.2 Positive cultures: contamination, colonisation or disease?

As NTM organisms are commonly found in nature, contamination of culture material or transient infection does occur. Thus, a single positive sputum culture, especially with small numbers of organisms, does not suffice to diagnose NTM disease. It has been suggested that the respiratory tract may be infected with the organism without disease, particularly in patients with chronic respiratory disease. This condition was often referred to as ‘colonisation’, and was described most often with *M. avium* complex. More recent studies with high-resolution CT scans have shown that these patients often have a combination of multi-focal bronchiectasis and nodular parenchymal disease, with the latter or both now felt to be due to mycobacterial disease. Colonisation in the true sense (ie, no tissue invasion) is probably rare.<sup>1</sup>

Given these observations, the diagnosis of lung disease caused by NTM is usually not difficult if a combination of clinical, radiographical and bacteriological criteria (see below) are used. Minimum evaluation should include three or more sputum specimens for acid-fast bacilli (AFB) and efforts to exclude other confounding disorders such as TB and lung malignancy.

#### 19.3.3 PCR and DNA probe testing

Molecular methods do not have a significant role to play in the diagnosis of NTM disease. Species-specific probes for MAC are used by level III laboratories in New Zealand. Their use significantly reduces the time needed to report the presence of MAC as opposed to the previous method of biochemical testing.

In some instances, however (eg, histopathology suggestive of mycobacterial infection but with negative cultures or no cultures performed), molecular methods may be worth considering (eg, PCR amplification and sequencing to try to prove the presence of mycobacterial DNA and the probable causative organism – see following section).

#### **19.3.4 Organism identification by DNA sequencing**

The traditional method of speciating NTM takes into account their pigmentation, growth rates and biochemical reactions. The latter may vary between strains of the same species, and confident identification can at times be difficult. As a result many studies have evaluated molecular methods for speciating NTM isolates. One method involves amplification of a region of the *hsp65* gene, subjecting the amplicon to restriction enzymes and separating the different size sequences.<sup>14 15</sup> The *hsp65* gene codes for a 65-kDa heat-shock protein and this gene is present in all mycobacteria. The patterns produced allow for species identification.<sup>14 15</sup> The method can also identify the presence of non-culturable mycobacteria (eg, *M. leprae*).<sup>16</sup>

In addition the amplified heat-shock protein gene amplicon, or 16S ribosomal DNA sequences, can be sequenced and compared to known sequences stored in gene banks. The availability of gene bank data means that sequencing information is able to assist in establishing – and indeed confirm – the identity of an NTM isolate.<sup>17 19</sup> Sequence data does, however, need to be quality controlled and must be evaluated alongside other information about the isolate if reliable identification is to be made.<sup>20</sup> Sequencing methods are in use in Auckland, Waikato, Wellington and Christchurch Hospital laboratories. Isolates thought to require molecular identification must be discussed with the laboratory.

#### **19.3.5 Diagnosis of pulmonary infection**

Diagnosis of pulmonary NTM disease is not established by the mere isolation of a given isolate. The clinical, radiological and bacteriological diagnostic criteria proposed by the American Thoracic Society should be used to ensure, as far as possible, that a given isolate is responsible for disease.<sup>1</sup> To secure a diagnosis of pulmonary disease all three criteria must be met.

##### ***Criteria for diagnosing pulmonary NTM***

Clinical criteria are:

- a. compatible signs/symptoms (cough, fatigue most common; fever; weight loss haemoptysis, dyspnoea may be present, particularly in advanced disease) with documented deterioration in clinical status if an underlying condition is present, and
- b. reasonable exclusion of other disease (eg, TB, cancer) as alternative causes of the clinical condition, or adequate treatment of other condition which is causing increasing signs/symptoms.

Radiographical criteria are:

- c. any of the following CXR abnormalities; if baseline films are more than one year old, there should be evidence of progression:
  - infiltrates with or without nodules (persistent  $\geq$  two months, or progressive)
  - cavitation
  - nodules alone (multiple)
- d. any of these high-resolution CT abnormalities:
  - multiple small nodules
  - multi-focal bronchiectasis with or without small lung nodules.

Bacteriological criteria are:

- e. at least three sputum / induced sputum / bronchial wash samples within the previous 12 months:
  - three positive cultures with negative AFB smear results, or
  - two positive cultures and one positive AFB smear, or
- f. single bronchial wash and inability to obtain sputum samples:
  - positive culture with an AFB smear with  $\geq$  1–9 AFB/10 fields; or
  - positive culture with  $\geq$  100 colonies on solid media.
- g. If sputum / bronchial wash evaluations are non-diagnostic or another disease cannot be excluded, use:
  - transbronchial or lung biopsy yielding an NTM, or
  - biopsy showing mycobacterial histopathologic features (caseating granulomata with chronic inflammation and/or AFB) and one or more sputum specimens or bronchial washings are positive for an NTM even in low numbers, or
  - any growth from a usually sterile non-pulmonary site.

The above criteria fit best with *M. avium* complex, *M. abscessus* and *M. kansasii*. Too little is known of other NTM to be certain how applicable these criteria will be. At least three respiratory samples should be evaluated from each patient. Other reasonable causes for the disease should be excluded. If the clinical situation is non-acute, and the diagnosis has not been established, repeating three sputum specimens a few months later is suggested if the person still has symptoms or worsening symptoms. Expert consultation should be sought when diagnostic difficulties are encountered.

### **19.3.6 Diagnosis of extra-pulmonary NTM disease**

Biopsies from any site of suspected NTM infection should be sent for both histopathology and microbiology testing. Both laboratories should be alerted to the possibility of mycobacterial infection. This is essential information for the microbiology laboratory because media selection as well as temperature and duration of incubation depend on knowing that mycobacterial infection is suspected.

### 19.3.7 Diagnosis of NTM lymphadenitis

The presumptive diagnosis of NTM lymphadenitis is based on the histopathological appearance of the lymph node showing caseating granulomata with or without AFB, and a negative tuberculin skin test. Failure of the node to yield *M. tuberculosis* provides strong presumptive evidence for the diagnosis of NTM lymphadenitis. Recovery of an NTM, most commonly MAC, from lymph node tissue or aspirate is diagnostic.

### 19.3.8 Skin and soft-tissue infection

All skin and soft-tissue samples should be incubated at two temperatures: 35°C and 28–32°C. A number of common pathogens (eg, *M. haemophilum*, *M. ulcerans*, *M. marinum* and *M. chelonae*) may only grow at the lower temperature.

Inoculated media should be supplemented with hemin or ferric ammonium citrate to allow the growth of *M. haemophilum*. *M. genavense* may only grow from the blood in BACTEC13A medium or comparable broth culture. It requires incubation for at least eight weeks. Some have found better growth in the slightly acidic (pH 6) pyrazinamide test medium.

The presence of an AFB smear-positive sample with no growth on solid media should suggest the possibility of *M. haemophilum*, *M. conspicuum* or *M. genavense*.

### 19.3.9 Laboratory tests for disseminated NTM infection in HIV/AIDS

Mycobacteraemia is readily detected by blood cultures, and these should be routine tests with unwell HIV patients under investigation. A single blood culture has a sensitivity of around 90%, and therefore no more than two blood culture sets are required. Two negative sets practically exclude mycobacteraemia.

The blood culture request form needs to specify culture for mycobacteria because special blood culture bottles need to be inoculated. Routine blood culture bottles are designed to recover bacteria and yeasts, not mycobacteria. Culture of tissue from various sites may be indicated in individual patients, but is seldom required.

## 19.4 Susceptibility testing for NTM

While there is clear agreement on how to perform susceptibility testing and what anti-microbial agents to test for *M. tuberculosis*, the same cannot be said for NTM.<sup>1,21,22</sup> Testing should only be performed by reference laboratories on isolates strongly suspected of causing disease. The testing methods used should follow published standards.<sup>21,22</sup>

Single isolates from a series of smear-negative sputum specimens are unlikely to be clinically significant and do not require routine susceptibility testing. Ideally the laboratory should communicate with the person looking after the patient before deciding what antibiotic agents to test.

### 19.4.1 *M. avium* complex

Susceptibility testing against rifabutin and the anti-tuberculous drugs is not recommended.<sup>1</sup> Correlation between *in vitro* susceptibility test results for MAC isolates and clinical response has only been demonstrated in a clinical trial using a macrolide. Strains from patients who have not been treated with macrolides are highly unlikely to be resistant to them. Routine testing against clarithromycin should not be performed. Clarithromycin testing should be reserved for isolates from patients who have failed previous macrolide treatment or prophylaxis. An MIC of 32 µg/ml is recommended as the resistance breakpoint.<sup>1</sup>

### 19.4.2 *M. kansasii*

Routine testing should be restricted to rifampicin. Methods or breakpoints for other drugs have not been established.<sup>1</sup> Isolates resistant to rifampicin should be tested against other agents in an experienced reference laboratory.<sup>22</sup>

### 19.4.3 *M. marinum*

Routine testing is not recommended because the species is consistently susceptible to agents used for treatment and the risk of acquired mutational resistance to one or more of these agents is minimal.<sup>22</sup>

### 19.4.4 Rapidly growing mycobacteria

Testing should not be performed with the anti-tuberculosis agents.<sup>1</sup> The clinically significant species *M. fortuitum*, *M. chelonae* and *M. abscessus* should be tested against doxycycline, the fluorinated quinolones, a sulphonamide, cefoxitin and clarithromycin. Imipenem may be reported for *M. fortuitum*. Amikacin should be tested against *M. fortuitum* and *M. abscessus*. Tobramycin is the most effective aminoglycoside for infections caused by *M. chelonae* and should be the one tested with this species. Because of the variable drug susceptibility among these species, *susceptibility testing of all clinically significant isolates is essential for optimal patient management*.<sup>1</sup>

## 19.5 Treatment of NTM disease

### 19.5.1 *M. avium* complex

The early experience with medical treatment of MAC disease was disappointing, and the best outcomes were in those patients subjected to resectional surgery. No controlled clinical trials in this disease have been conducted, and treatment recommendations have been based largely on empirical data. Surgical resection can be contemplated only with localised MAILD. Hence, this will only be appropriate for people with type 1 disease. This pattern was described earlier (see section 19.2.1).

For most patients, especially those with non-cavitary disease, a period of observation of at least several months may be needed to assess the contribution of MAC disease to the overall clinical picture. During this time patients should receive therapy for underlying pulmonary disease, if present (eg, daily home-based chest physiotherapy for those with bronchiectasis, bronchodilators, broad-spectrum antibiotics and stopping smoking). If the disease remains undiagnosed, sputum AFB cultures may be needed on a regular basis (eg, every month for two months).

Drug therapy for *M. avium* complex disease involves multiple drugs, and because of this the risk of drug toxicity is relatively high. Drug side-effects and drug interactions make treatment difficult for both the patient and the clinician. Standard medical treatment involves the use of a rifamycin, a macrolide (clarithromycin or azithromycin) and ethambutol. The treatment of *M. avium* complex disease is best undertaken by clinicians experienced in treating pulmonary or mycobacterial diseases.

### 19.5.2 *M. kansasii*

Untreated strains of *M. kansasii* are susceptible to rifampicin, isoniazid, ethambutol, ethionamide, clarithromycin and streptomycin at concentrations readily achievable in the serum with usual therapeutic doses.<sup>1,23</sup> *M. kansasii* is also susceptible *in vitro* to sulphamethoxazole, amikacin and rifabutin, although there is limited information on the clinical usefulness of these drugs.<sup>1</sup>

There have been no randomised controlled trials of treatment for disease caused by *M. kansasii*, comparing one drug regimen with another or with no drug treatment at all. Early reports of treatment with anti-mycobacterial drugs in the pre-rifampicin period were disappointing. With rifampicin-containing therapy, the long-term relapse rate is very low. Surgery, therefore, is now considered to have no role in the management of routine cases of *M. kansasii* pulmonary disease. Although the currently recommended treatment of *M. kansasii* pulmonary disease in adults is rifampicin with isoniazid and ethambutol,<sup>1</sup> isolates are normally susceptible to clarithromycin,<sup>23</sup> and macrolides have been used as components of multi-drug treatment for this disease.<sup>24</sup> If macrolides are being considered as part of a treatment regimen, the patient should be asked if they have received a macrolide previously, because this has been associated with resistance and treatment failure.<sup>25</sup>

### 19.5.3 Lymphadenitis

Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis. The success rate with this procedure approaches 95%. For children with recurrent disease, a second surgical procedure is usually performed. A clarithromycin-containing multiple drug regimen such as that used for pulmonary disease should be considered for recurrent disease or for children in whom surgical risk is high (eg, risk of facial nerve damage). If medical treatment is being considered, specialist advice is required.

### 19.5.4 Infections due to rapidly growing mycobacteria

The majority of clinical disease (more than 90%) is due to *M. fortuitum*, *M. abscessus* or *M. chelonae*. *M. fortuitum* and *M. chelonae* are resistant to the first-line anti-TB agents, but they are susceptible (especially *M. fortuitum*) to a number of traditional anti-bacterial agents. Isolates of *M. fortuitum* are susceptible to amikacin (100%), ciprofloxacin (100%), sulphonamides (100%) and imipenem (100%); most are susceptible to clarithromycin (80%) and cefoxitin (80%); and 50% are susceptible to doxycycline. Isolates of *M. abscessus* are susceptible to clarithromycin (100%), imipenem/cilastatin (50%), amikacin (90%) and cefoxitin (70%). Isolates of *M. chelonae* are susceptible to amikacin (80%), tobramycin (100%), imipenem (60%), ciprofloxacin (20%), clarithromycin (100%) and doxycycline (25%).<sup>1</sup>

Treatment for serious disease requires a period of intravenous combination treatment determined by susceptibility results. Treatment may be possible with oral agents, depending on the response to intravenous treatment and susceptibility results. A period of four to six months' treatment is usually required.<sup>1</sup>

Surgery is often needed in extensive disease, abscess formation, or where drug treatment is difficult. Removal of foreign bodies such as breast implants, percutaneous catheters, etc. is probably essential for recovery.<sup>1</sup>

Pulmonary disease due to *M. abscessus* is a particularly serious condition. The disease course ranges from a slowly progressive disorder to fulminant rapidly progressive infection. Relapses are common and for some patients suppressive treatment to control the infection may be all that is possible. In one series the fatality rate of those with pulmonary *M. abscessus* infection was 20%.<sup>26</sup>

### 19.5.5 *M. marinum*

A number of treatment modalities have been used for cutaneous disease caused by *M. marinum*. These include simple observation for minor lesions, surgical excision, the use of anti-TB therapy, and the use of single antimicrobial agents. Acceptable treatment regimens include minocycline or doxycycline, trimethoprim-sulphamethoxazole, or rifampicin and ethambutol.

The rate of clinical response is variable, and a minimum of three weeks of therapy should be given before considering that a patient may not be responding. Recommendations for the duration of therapy vary. If infection is superficial and the response is prompt, treatment may only need to be continued for four to six weeks following resolution. Deeper infections and those slow to respond require prolonged therapy. Surgical debridement may also be important, especially for disease involving the closed spaces of the hand or for disease that responds poorly to drug therapy.<sup>1</sup>

#### **19.5.6 NTM in HIV/AIDS patients**

Many studies have documented that some individual drugs or multiple drug combinations reduce or eliminate mycobacteraemia.<sup>1</sup> Because of the difficult management decisions involved, drug toxicity concerns, as well as drug interactions and compliance issues, therapy for and prophylaxis against disseminated *M. avium* infection should only be undertaken by those with experience in this area.<sup>1</sup>

#### **19.5.7 NTM that rarely cause human disease**

Although almost any species can cause disease, especially in a severely immunocompromised patient, some species can be regarded as essentially non-pathogenic. These include *M. gordonae*, *M. scrofulaceum* (other than from a cervical node in a child), *M. terrae*, *M. nonchromogenicum* and *M. triviale*. Before any of these species are taken as being the cause of disease, the entire clinical history as well as any radiological and histopathology results must be considered.

#### **19.5.8 Prognosis and referral**

Patients with NTM infection can be regarded as being non-infectious and should be advised accordingly. The response to therapy depends on the NTM species and the site of infection, but may be slow, especially for pulmonary infections. The expectation of gradual rather than rapid improvement should be conveyed to patients.

Specialist referral is advisable for:

- all patients with pulmonary NTM infection – establishing the diagnosis is not simple, and therapeutic regimens may be complex and potentially toxic
- children with probable NTM lymphangitis
- patients, particularly the immunosuppressed, with cutaneous infection
- HIV/AIDS patients with systemic symptoms – the differential diagnosis is long and therapeutic decisions difficult.

## **19.6 Future developments**

Infection due to NTM is not a notifiable disease. There are few data on the number, type and epidemiology of NTM infections in New Zealand.

It would be helpful if the three New Zealand level III laboratories combined their results each year for their NTM isolates. It would be useful if these laboratories also recorded the number of isolates from each patient, the smear results and whether the isolates were treated.

Ideally, a yearly summary of NTM isolates could be published in the ESR report, so that over time a picture of the common and clinically important NTM in New Zealand could be developed.

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