



CENTRE FOR DISEASE CONTROL  
NORTHERN TERRITORY

**Guidelines for the  
Control of  
Nontuberculous Mycobacteria  
in the  
Northern Territory**

**October 2002**



Northern Territory Government  
Department of Health and Community Services

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## **Introduction**

The genus *Mycobacterium* includes the species responsible for causing tuberculosis (TB) (*M. tuberculosis*, *M. bovis*, *M. africanum*: also called *Mycobacterium tuberculosis* complex) and leprosy (*M. leprae*). There are several other species of mycobacterium that are collectively called nontuberculous mycobacteria (NTM). NTM have been recognised since late in the nineteenth century but only since the 1950s have they been well recognised as a cause of human disease. With advances in molecular biology and the ability to map the entire genome of a bacterium new NTM are now identified on a regular basis. More reliable identification techniques have helped elucidate the pathological potential of some infrequently isolated NTM. The pathological potential of several species however is still unclear. NTM disease is notifiable in the Northern Territory (NT) but not in other states of Australia.

## **Epidemiology**

### ***Incidence***

NTM disease presents most commonly as pulmonary disease. Other manifestations include: disseminated disease; skin, soft tissue and skeletal disease; and lymphadenitis. An extensive review of NTM occurring in the NT from 1989 to 1997, by O'Brien et al, was published in *Clinical Infectious Diseases* in 2000<sup>1</sup>. There is now data available to 30/06/02. There were 74 cases of NTM disease reported in the NT between January 1989 and June 2002. This gives an average incidence rate per year of 3.2 per 100 000 population.

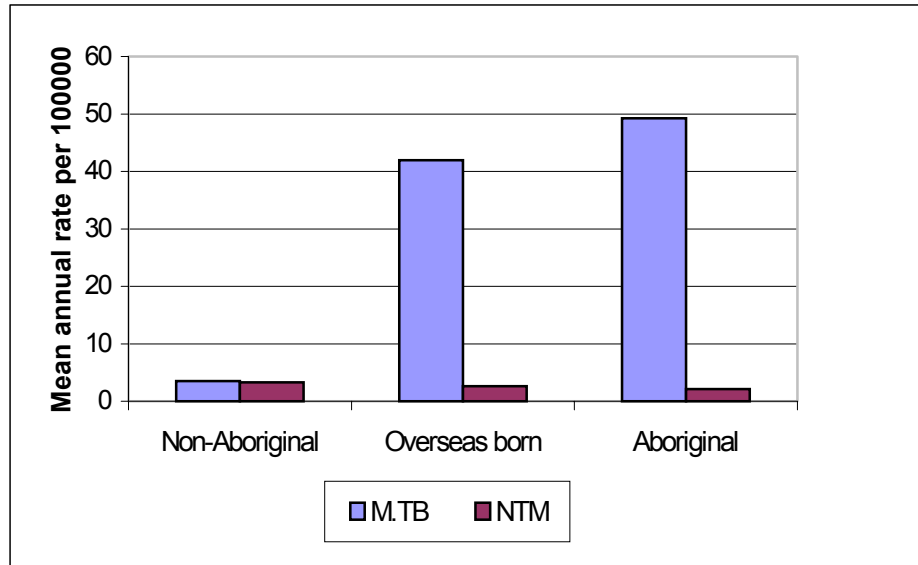
Rates of NTM disease are more than double for males compared with females. The majority (86%) of notifications are among people born in Australia. The mean duration of residence in Australia for people born overseas is 25 years. This suggests NTM infection is acquired locally and progresses to disease with limited latency, unlike TB. Also, unlike TB, the incidence of NTM disease is higher in non-Aboriginal people compared with Aboriginal people (Figure 1).

### ***Source of NTM***

NTM occur naturally in the environment and are therefore often referred to as environmental mycobacteria. Most NTM organisms have been isolated from water and soil. NTM disease occurs in animals but transmission from animals to humans is felt not to be important in human infection. Human to human transmission is rare. This means public health measures such as isolation and contact tracing are not necessary with NTM disease.

In the NT there is no significant difference in the likelihood of developing disease due to NTM in rural versus urban areas. Of the 74 cases notified in the NT in the last 13 years, 41 people came from the Darwin urban area as opposed to 33 people from other parts of the NT (RR = 1.1 (95% CI 0.7-1.7)).

**Figure 1. Ethnic background of persons in the NT with disease due to *M. tuberculosis* and NTM 01/01/89 to 31/12/2001.**



### ***Risk factors***

In O'Brien et al's review of NTM disease in the NT risk factors identified included: smoking; chronic lung disease; and immunosuppression due to HIV infection, alcoholism, and immunosuppressive therapy.<sup>1</sup>

### **Pathogenic species**

An extensive list of NTM recovered from humans is included in Table 1. Pathogenicity is unclear for some NTM (Table 2). This is usually because there are so few cases reported and some of the reports lack sufficient documentation of the organism's identification, or its disease association, to confirm the validity of the case. Though it is unclear, those listed in Table 2 are probably non-pathogenic. NTM fall into 2 categories, slow growing and rapidly growing. Mycobacteria that form colonies clearly visible to the naked eye within 7 days on subculture are termed rapid growers, while those requiring longer periods are called slow growers. Those identified in Tables 1 and 2 are categorised as either slow or rapidly growing in Table 3.

The clinical distribution of NTM disease in the NT is shown in Table 4. NTM isolated in association with disease in the NT are included in Table 5. Interestingly *M. kansasii*, which is commonly identified as a cause of NTM disease in the USA, Europe and other parts of Australia, has not been associated with disease in the NT in the last 13 years. Other common causative organisms such as *M. xenopi*, *M. malmoense*, *M. chelonae*, and *M. ulcerans* have not been associated with disease in the NT in this time period either.

**Table 1. Classification of NTM recovered from humans<sup>2,3,4</sup>**

Clinical disease	Common etiologic species	Disease ever notified in the NT	Unusual etiologic species
Pulmonary disease	<i>M. avium</i> complex (MAC)*	Yes	<i>M. asiaticum</i>
	<i>M. kansasii</i>	No	<i>M. branderi</i>
	<i>M. abscessus</i>	No	<i>M. celatum</i>
	<i>M. xenopi</i>	No	<i>M. fortuitum</i>
	<i>M. malmoense</i>	No	<i>M. haemophilum</i> <i>M. scrofulaceum</i> <i>M. shimoidei</i> <i>M. simiae</i> <i>M. smegmatis</i> <i>M. szulgai</i>
Lymphadenitis	MAC	Yes	<i>M. abscessus</i>
	<i>M. scrofulaceum</i>	No	<i>M. chelonae</i>
	<i>M. malmoense</i>	No	<i>M. fortuitum</i> <i>M. haemophilum</i> <i>M. interjectum</i> <i>M. kansasii</i> <i>M. szulgai</i>
Skin and soft tissue disease #	<i>M. marinum</i>	Yes	MAC
	<i>M. fortuitum</i>	Yes	<i>M. branderi</i>
	<i>M. chelonae</i>	No	<i>M. haemophilum</i>
	<i>M. abscessus</i>	Yes	<i>M. kansasii</i>
	<i>M. ulcerans</i>	No	<i>M. mucogenicum</i> <i>M. scrofulaceum</i> <i>M. simiae</i> <i>M. smegmatis</i> <i>M. szulgai</i> <i>M. terrae</i> complex <sup>ϕ</sup>
Disseminated disease	MAC	Yes	<i>M. abscessus</i>
	<i>M. kansasii</i>	No	<i>M. conspicuum</i>
	<i>M. chelonae</i>	No	<i>M. fortuitum</i>
	<i>M. haemophilum</i>	No	<i>M. genavense</i> <i>M. gordonae</i> <i>M. malmoense</i> <i>M. marinum</i> <i>M. scrofulaceum</i> <i>M. simiae</i> <i>M. szulgai</i> <i>M. xenopi</i>

\**M. avium* complex (MAC) consists of two distinct species *M. avium* and *M. intracellulare*.

#*M. marinum*, *M. fortuitum*, MAC, *M. scrofulaceum*, *M. haemophilum* and *M. szulgai* are also causative organisms for osteomyelitis.

<sup>ϕ</sup> *M. terrae* complex includes *M. terrae*, *M. nonchromogenicum*, and *M. triviale*.

**Table 2. NTM whose pathogenicity is unclear<sup>2,3</sup>**

<i>M. gastri</i>	<i>M. aichiense</i>
<i>M. flavescens</i>	<i>M. aurum</i>
<i>M. neoaurum</i>	<i>M. chubuense</i>
<i>M. thermoresistibile</i>	<i>M. gadium</i>
<i>M. mageritense</i>	<i>M. celatum</i>
<i>M. phlei</i>	<i>M. lentiflavum</i>
<i>M. vaccae</i>	<i>M. triplex</i>

**Table 3. NTM growth rate classification<sup>2,3</sup>**

<b>Slow growing NTM</b>	<b>Rapidly growing NTM</b>
MAC	<i>M. abscessus</i>
<i>M. asiaticum</i>	<i>M. aichiense</i>
<i>M. branderi</i>	<i>M. aurum</i>
<i>M. celatum</i>	<i>M. chelonae</i>
<i>M. conspicuum</i>	<i>M. chubuense</i>
<i>M. flavescens</i>	<i>M. fortuitum</i>
<i>M. gastri</i>	<i>M. gadium</i>
<i>M. genavense</i>	<i>M. mageritense</i>
<i>M. gordonae</i>	<i>M. mucogenicum</i>
<i>M. haemophilum</i>	<i>M. neoaurum</i>
<i>M. interjectum</i>	<i>M. phlei</i>
<i>M. kansasii</i>	<i>M. smegmatis</i>
<i>M. lentiflavum</i>	<i>M. thermoresistibile</i>
<i>M. malmoense</i>	<i>M. vaccae</i>
<i>M. marinum</i>	
<i>M. scrofulaceum</i>	
<i>M. shimoidei</i>	
<i>M. simiae</i>	
<i>M. szulgai</i>	
<i>M. terrae</i>	
<i>M. triplex</i>	
<i>M. ulcerans</i>	
<i>M. xenopi</i>	

**Table 4. Clinical distribution of NTM disease in the NT 01/01/89 to 30/06/02.**

<b>SITE</b>	<b>HIV associated case</b>	<b>Non-HIV associated case</b>	<b>HIV status not tested</b>	<b>Total</b>
Pulmonary	4	37	4	<b>45 (61%)</b>
Disseminated	9	1	-	<b>10 (13%)</b>
Skin/soft tissue	3	7	4	<b>14 (19%)</b>
Nodal	-	5	-	<b>5 (7%)</b>
<b>Total</b>	<b>16</b>	<b>50</b>	<b>8</b>	<b>74</b>
<b>Percentage</b>	<b>22%</b>	<b>68%</b>	<b>11%</b>	<b>100%</b>

**Table 5. NTM isolated from patients with NTM disease in the NT 01/01/89 to 30/06/02.**

<b>ORGANISM</b>	<b>Pulmonary</b>	<b>Disseminated</b>	<b>Skin/soft tissue</b>	<b>Nodal</b>	<b>Total</b>	<b>Percentage</b>
MAC	42	9	2	2	<b>55</b>	<b>74%</b>
<i>M. fortuitum</i>	-	1	6	-	<b>7</b>	<b>9%</b>
<i>M. haemophilum</i>	-	-	2	-	<b>2</b>	<b>3%</b>
<i>M. scrofulaceum</i>	2	-	-	-	<b>2</b>	<b>3%</b>
<i>M. terrae</i>	-	-	2	-	<b>2</b>	<b>3%</b>
<i>M. abscessus</i>	-	-	1	1	<b>2</b>	<b>3%</b>
<i>M. goodii</i>	-	-	-	2	<b>2</b>	<b>3%</b>
<i>M. marinum</i>	-	-	1	-	<b>1</b>	<b>1%</b>
<i>M. simiae</i>	1	-	-	-	<b>1</b>	<b>1%</b>
<b>TOTAL</b>	<b>45</b>	<b>10</b>	<b>14</b>	<b>5</b>	<b>74</b>	<b>100%</b>

**Table 6. Outbreaks of iatrogenic NTM infection reported in medical literature.**

<b>Mycobacterium</b>	<b>Disease</b>	<b>Cause</b>
<i>M. abscessus</i>	Surgical wound infections	Rinsing surgical equipment in contaminated tap water and then inadequate sterilisation of equipment <sup>5</sup>
<i>M. abscessus</i>	Injection site infection	Not identified but all cases from one physician's office <sup>6</sup>
<i>M. abscessus</i>	Injection site infection	Contaminated unlicensed injectable alternative medicine <sup>7</sup>
<i>M. chelonae</i>	Injection site infection	Contaminated external surface of penicillin vial lids <sup>8</sup>
<i>M. chelonae</i>	Post liposuction cutaneous abscesses	Rinsing surgical equipment in contaminated tap water and then inadequate sterilisation of equipment <sup>9</sup>
<i>M. chelonae</i>	Post podiatry procedure foot infection	Contaminated jet injector <sup>10</sup>
<i>M. chelonae</i>	Injection site infection	Contaminated normal saline solution <sup>11</sup>
<i>M. chelonae</i>	Post rhinoplasty nasal cellulitis	Rinsing surgical equipment in contaminated tap water and then inadequate sterilisation of equipment <sup>12</sup>
<i>M. chelonae</i>	Bacteraemia, soft tissue infection and disseminated disease post haemodialysis	Inadequate sterilisation of haemodialysis machines <sup>13</sup>
<i>M. fortuitum</i>	Post electromyography infection at site of electrode insertion	Needles sterilised then rinsed in tap water <sup>14</sup>

## **Outbreaks of NTM disease**

Outbreaks of NTM disease have been reported in the literature. Most reports are related to skin and soft tissue disease secondary to iatrogenic infection from medical intervention. A search of the Medline database back to 1990 identified many such outbreaks (see Table 6).

In 1992-1995 a large localised outbreak of 29 cases of *M. ulcerans* infection occurred in a 4km square area of Phillip Island, Victoria, Australia. Cases were mostly with the elderly and had distal limb lesions. A golf course irrigation system was suspected as the source of infection and with limitation of the use of this there was a reduction in the number of new cases.<sup>15</sup> In a northern Californian nail salon an outbreak of *M. fortuitum* furunculosis occurred as a result of contaminated foot baths. The inlet suction screens of these footbaths had large amounts of hair and skin debris behind them, as they were never cleaned.<sup>16</sup> In Colorado restriction fragment length polymorphism analysis was used to identify an indoor hot tub as the source MAC pulmonary disease in a family of 5, with varying degrees of respiratory illness.<sup>17</sup> No outbreaks of NTM disease have been reported in the NT.

Pseudo-outbreaks have been reported where NTM contamination has caused respiratory tract colonisation, rather than disease, and contamination of laboratory specimens. Ice machines and water fountains on hospital wards have been implicated as sources of NTM respiratory tract colonisation. Inadequate sterilisation of endoscopy, bronchoscopy, and colonoscopy equipment, and contamination of distilled water, and culture medium in the laboratory have been implicated in NTM contamination of diagnostic specimens.<sup>18-29</sup>

## **Clinical Manifestations**

### ***Pulmonary disease***

Patients with NTM lung disease are generally older adults. Except for patients with cystic fibrosis, children rarely develop this form of NTM disease. Although many NTM patients have a history of underlying chronic lung disease not all do. Signs and symptoms of NTM pulmonary disease are variable and non-specific. They include:

- Chronic cough
- Sputum production
- Fatigue

Less commonly:

- Malaise
- Dyspnoea
- Fever
- Haemoptysis
- Weight loss (usually with advanced NTM disease)

Evaluation is often complicated by the symptoms caused by co-existing lung diseases. These conditions include chronic obstructive airway disease often associated with smoking, bronchiectasis, previous mycobacterial disease, cystic fibrosis and pneumoconiosis (asbestosis and silicosis).

Though there is some uncertainty, it does seem that in an HIV negative person, NTM can colonise the respiratory tract in the absence of tissue invasion. To compensate for this uncertainty multiple isolations of the same NTM and evidence of progressive disease (chest x-ray and symptoms) are required for diagnosis. The interpretation of NTM in the sputum of an HIV positive person is difficult as these patients are frequently felt to be infected with NTM without evidence of pulmonary disease. Such infection may be transient but it may also reflect disseminated NTM disease or subclinical NTM pulmonary disease. In addition some NTM species that are generally considered non-pathogenic have been associated with pulmonary disease in the HIV infected host.<sup>2</sup> This is an area of ongoing evaluation. Since the advent of triple drug therapy, and in some cases on preventative regimens, NTM disease in those with AIDS has markedly decreased.

### ***Disseminated disease***

Dissemination of NTM occurs in adults and children. From a global perspective, and before HIV infection became prevalent, disseminated disease was rare and confined to immunocompromised individuals such as those with leukaemia, lymphoma, or on immunosuppressive therapy.<sup>2, 30-34</sup>

#### *Patients without AIDS*

In general, in patients without AIDS, disseminated disease caused by *Mycobacterium avium* complex (MAC) presents as fever of unknown origin whereas *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. haemophilum* generally present as multiple subcutaneous nodules or abscesses that drain spontaneously.<sup>2</sup>

#### *Patients with AIDS*

Disseminated disease due to NTM in patients with HIV infection usually occurs only in those with very advanced immunosuppression. The diagnosis is exceedingly rare in persons with >100 CD4 cells, but should be suspected in patients with <50 CD4 cells. Most patients have prolonged fevers, which may be as high as 39.5-40°C and also frequently have night sweats. Weight loss is common and some people complain of abdominal pain and diarrhoea. Physical findings may only be those of advanced HIV disease, although abdominal pain, retroperitoneal adenopathy and hepatosplenomegaly may be present.<sup>34</sup> Again disease has decreased with the advent of triple drug therapy and some preventative regimens.

### ***Skin, soft tissue, and skeletal disease.***

NTM skin, soft tissue, and skeletal disease may occur in any age group. In the NT *M. fortuitum* is the most common causative organism (see Table 5). NTM may cause localised abscess formation and drainage at the site of puncture wounds. Infection due to long term intravenous or peritoneal catheters, post injection abscess or surgical wound infection can also occur due to NTM. Chronic granulomatous infection caused by NTM may develop in tendon sheaths, bursae, joints and bones after direct inoculation of the organisms through accidental trauma, surgical incision or injections. Occasionally axial bones and extremities have been infected without apparent trauma and are due presumably to haematogenous spread.<sup>2</sup>

## **Lymphadenitis**

Infection of the submandibular, submaxillary, cervical, or periauricular lymph nodes in children between 1 and 5 years old is the most common presentation of NTM lymphadenitis. It is the most common disease manifestation of NTM in children in the absence of HIV infection and rarely affects adults. The 5 cases of NTM nodal disease in the NT in the last 13 years, have been aged 1, 2, 3, 9 and 14 years. Two of these 5 (40%) were Aboriginal children whereas for the same time period 21 of 25 (84%), aged less than 16 years, notified with TB were Aboriginal children. The involved lymph nodes are usually unilateral and non-tender. The nodes may enlarge rapidly and even rupture, with formation of sinus tracts that result in prolonged local drainage.<sup>2</sup>

## **Diagnosis**

### ***Diagnostic criteria for lung disease in HIV-seropositive and HIV-seronegative hosts.***

The following criteria (Figure 2) are from the Official Statement of the American Thoracic Society on the Diagnosis and Treatment of Diseases Caused by Nontuberculous Mycobacteria, 1997.<sup>2</sup> These criteria best fit for disease caused by MAC, *M. abscessus* and *M. kansasii*. Too little is known of other NTM to be certain how applicable these criteria will be.

**Figure 2. Diagnostic criteria for NTM lung disease.**

Applies to <i>symptomatic</i> patients with:
➤ infiltrative, nodular or cavitary disease <b>or</b>
➤ a high resolution CT that shows multifocal bronchiectasis and/or multiple small nodules
<b>A) If three sputum/bronchial washing results are available from the previous 12 months#:</b>
i) three positive cultures with negative AFB smear results <b>or</b>
ii) two positive cultures and one positive AFB smear
<b>B) If only one bronchial wash is available:</b>
i) positive cultures with a 2+, 3+, or 4+ AFB smear or 2+, 3+, or 4+ growth on solid media.
<b>C) If sputum/bronchial washing evaluations are nondiagnostic or another disease cannot be excluded:</b>
i) transbronchial or lung biopsy yielding a NTM <b>or</b>
ii) biopsy showing mycobacterial histopathologic features (granulomatous inflammation and/or AFB) and one or more sputums or bronchial washings are positive for an NTM even in low numbers

# Sputum samples must be collected at least seven days apart.

The traditional presentation of MAC lung disease has been as apical fibrocavitary lung disease, sometimes with huge cavities, in males in their late 40s and early 50s with a history of heavy cigarette smoking and, frequently, alcohol abuse. This form of disease is usually progressive within one to two years if left untreated. More recently it has become apparent that MAC lung disease also presents as bilateral nodular and interstitial/nodular disease or as isolated right middle lobe or lingular disease, predominantly in elderly non-smoking females.

Earlier it was thought that MAC colonised bronchiectatic lung. However, high resolution computerised tomography studies show some patients have MAC related parenchymal disease in addition to their bronchiectasis. The appropriate distinction is not between colonisation and invasive disease but between those patients with the disease of nodular bronchiectasis who require immediate therapy directed at MAC and those in whom such a decision can be delayed. If the decision is made to observe such a patient they need long term follow up as the MAC disease will likely progress at some stage and require treatment. Treating earlier rather than later is recommended.<sup>2</sup>

Differentiating NTM from *M. tuberculosis* complex is not possible radiographically or on acid fast bacilli (AFB) smear. Because of the public health risk of *M. tuberculosis* complex, disease suggestive of mycobacterial disease should be managed as TB until proven to be otherwise. The traditional method of identification is by culture and then biochemical testing. Some of these tests require inoculation of subcultures and subsequent delay in testing until adequate growth has occurred.

Genetic techniques are useful if a more urgent identification is required, for example to avoid the large public health undertaking associated with TB, or to definitively diagnose TB in someone who may need follow up. Detection and identification of *M. tuberculosis* complex directly from a clinical specimen can be done using the Polymerase Chain Reaction (PCR) test. Determining the presence of NTM or differentiation beyond *M. tuberculosis* complex using the PCR test is not possible, however, this can be done on special request using band techniques. The PCR test can be completed in one working day.

Once isolates arise on solid culture or from broth culture DNA probes can be used to identify the mycobacterium. Probes are available for *M. tuberculosis* complex, MAC, *M. kansasii*, *M. goodii* and others are being developed. Probes to further differentiate *M. tuberculosis* complex are not yet available. The DNA probe test, on the cultured specimen, takes about two hours.

Where NTM is deemed more likely than TB or a diagnosis of TB has very wide public health implications the laboratory used for diagnosis should be called directly to have a PCR test requested.

### ***Diagnosis of disseminated NTM disease***

#### *Patients without AIDS*

The isolation of organisms from sterile closed sites such as bone marrow, blood, liver or from a skin biopsy (in the setting of multiple lesions) is diagnostic.

### *Patients with AIDS*

The diagnosis of disseminated disease is most commonly confirmed by isolation of MAC in blood so it is important to request this investigation and liaise with the laboratory staff so they are aware of the organism being sought. Blood cultures will need to be collected in blood culture bottles containing mycobacterium culture medium. This media differs to the culture medium routinely used for non-mycobacterial bacteraemia. The bacteraemia is ongoing and a single blood culture in a symptomatic patient has a sensitivity of 90%. In a prospective study of HIV positive patients with < 50 CD4 cells approximately 67% of patients with MAC in sputum or stool had disseminated disease within one year however only one third of patients with disseminated disease had a prior positive stool.<sup>2</sup>

### ***Diagnosis of skin, soft tissue, and skeletal disease.***

Diagnosis is made by microscopy and culture of the specific NTM pathogen from drainage material or tissue biopsy if the site is sterile. If the site is not sterile microscopy and culture of an NTM in the absence of other more culpable pathogens may indicate NTM infection.<sup>2</sup> In a non-sterile site histological findings of granulomatous changes can support the diagnosis.

### ***Diagnosis of NTM Lymphadenitis***

When investigating lymphadenitis in the NT it is important to remember TB lymphadenitis is a much more common disease in an Aboriginal child. A definitive diagnosis of NTM lymphadenitis is made by recovery of the causative organism from lymph node cultures. Fine needle aspirate (FNA) or complete excision of the lymph node is recommended for diagnosis rather than biopsy or incision and drainage as these procedures may be followed by fistulae formation with chronic drainage. However, even with an FNA or excised node and compatible histopathology, only about 50% and 50-80% respectively will yield positive cultures.<sup>2</sup> See footnote\* History should involve questioning about exposure to patients with TB. A CXR should be taken looking for signs of *M. tuberculosis* disease or past infection. Dual skin testing with Tuberculin purified protein derivative (PPD) human and Avian Tuberculin PPD may contribute to a working diagnosis and empirical treatment if cultures are negative.

## **Treatment**

Because of the extensive list of NTM causing disease only treatment for the more common forms are discussed here. Treatment and outcomes for other types and for HIV positive patients will need to be discussed with a specialist. O'Brien et al reported treatment and outcomes of the 1989 to 1997 case series in the NT.<sup>1</sup>

\* Two FNA passes should be performed, one fixed on a slide for cytology and one for culture. FNA specimens for culture should be placed in a sterile container with a few drops of sterile saline on top. Lymph node biopsies should be placed in an empty sterile container. Unfortunately often FNA and lymph node biopsy specimens are not cultured because they are fixed onto a slide or placed in formalin immediately after collection. A reminder to the specimen collector, to place a specimen in saline, prior to the procedure may avoid this problem.

**MAC pulmonary disease in HIV negative adults**

Though there are no definitive trials to guide duration of treatment, generally treatment should continue until the patient is culture negative for 10 to 12 months. Sputum should be tested monthly. Clinical improvement is expected within 3 to 6 months. Sputum should clear within 12 months. Failure to improve or to clear sputum should warrant checks on compliance and sensitivity. Post treatment the patient should be followed and have sputum samples tested to check for relapse. One sputum sample should be collected at 4, 5, and 6 months post treatment and then 3 sputums a week apart at 18 months. If one of the sputum samples collected at 4, 5 or 6 months is negative then it should be followed by another 2 weekly sputum samples. The patient should be reviewed clinically at 6 and 18 months. Patients with disease localised to one lung and who can tolerate resectional surgery may be candidates for surgery if there has been poor response to drug therapy.<sup>2</sup>

**Figure 3. Treatment regimen for NTM pulmonary disease in HIV negative adults<sup>§</sup>**

<ul style="list-style-type: none"> <li>➤ Clarithromycin*: 500mg twice a day <b>or</b></li> <li>➤ Azithromycin*: 250mg/day <i>or</i> 500mg three times/week</li> </ul>
<p><b>AND</b></p> <ul style="list-style-type: none"> <li>➤ Rifabutin: 300mg/day <b>or</b></li> <li>➤ Rifampicin: 600mg/day</li> </ul>
<p><b>AND</b></p> <p>Ethambutol: 25mg/kg/day for 3 months <i>then</i> 15mg/kg/day</p>
<p>+/-</p> <ul style="list-style-type: none"> <li>➤ Intermittent Streptomycin for extensive disease for the first two to three months of treatment (see Table 5 for dosing schedule).</li> </ul>

<sup>§</sup> This regimen and its doses have not been validated in paediatric patients.

\*Patients with small body mass and/or >70 years clarithromycin at 250mg twice per day or azithromycin 250mg three times per week may be better tolerated.

**Table 7. Suggested doses of streptomycin relative to age and weight in patients with normal serum creatinine**

Weight and age	Initial therapy <sup>†</sup>	Maintenance therapy <sup>‡</sup>
≥50kg and ≤50 yrs	1g 5x/wk	1g 3x/wk
<50 kg and ≤50 yrs	500mg 5x/wk	750mg 2x/wk
>50 kg and 50-70 yrs	500mg 5x/wk	750mg 2x/wk
>70 yrs	750mg 2x/wk	750mg 2x/wk

<sup>†</sup> For the first 6 to 12 weeks of therapy as tolerated.

<sup>‡</sup> For subsequent therapy as tolerated.

**Table 8. Treatment plan for NTM pulmonary disease (disseminated disease - should follow the same plan except CXR and sputum may not be necessary if there is no pulmonary involvement).**

Pre-treatment	Treatment – monthly	Treatment – 3 monthly	Post treatment
HIV	Symptoms – NTM disease	First 3 months-stop	Sputum at 4, 5, 6 and
Glucose	and side effects	streptomycin	18 months. If any are
LFTs	Compliance		negative then do a
FBC	Weight	CXR 3-monthly	further 2 at weekly
U&Es	Vision*		intervals.
Vision*	Sputum <sup>§</sup>		
Weight	LFTs <sup>φ</sup>		
	FBC <sup>φ</sup>		

\*Visual acuity and colour discrimination.

<sup>§</sup> If the sputum is AFB smear negative then a week and 2 weeks later a further sputum sample should be collected.

<sup>φ</sup> Monthly for the first 3 months then reassess the need for monthly collection.

### ***Disseminated MAC disease***

Drug combinations will be as those for HIV negative patients with pulmonary disease. MAC prophylaxis should be strongly considered in high-risk patients and therapy should be offered to all patients with established disease.<sup>2</sup>

### ***Skin/soft tissue/bone disease***

The most common cause of skin and soft tissue disease in the NT has been *M. fortuitum*. In general with rapidly growing mycobacteria some minor infections will resolve spontaneously or after surgical debridement. For the more common types causing infection, *M. fortuitum*, *M. abscessus* and *M. chelonae*, no controlled trials of pharmacological treatment have been performed. However patients with cutaneous disease, due to rapidly growing NTM, treated on the basis of in vitro susceptibilities have shown good results.<sup>2</sup>

Because of variable drug susceptibility among rapidly growing NTM species susceptibility testing of all clinically significant isolates is essential for good management. A primary panel of drugs for testing could include amikacin, cefotaxim, ciprofloxacin, clarithromycin, doxycycline, imipenem and a sulphonamide.<sup>2</sup>

Several studies of post injection abscess in which no therapy was given revealed disease that persisted for eight to twelve months before spontaneously resolving. For serious disease a minimum of 4 months of treatment is recommended and for bone disease 6 months of treatment is recommended. Surgery is generally indicated with extensive disease, abscess formation or where drug therapy is difficult.<sup>2</sup>

**Figure 4. Treatment regimen for serious skin, soft tissue or bone disease caused by *M. fortuitum* and *M. abscessus***

- Amikacin 10-15mg/kg IV in two divided doses (average 400mg BD) in patients with normal renal function\*.
- Cefoxitin 12g/day IV is recommended for initial therapy (min 2 weeks) until clinical improvement is evident.

\*10mg/kg should be used in patients over the age of 50; once daily dosing is unproven clinically but appears reasonable.

### ***Lymphadenitis due to MAC***

Excisional surgery without chemotherapy is recommended for children with NTM cervical lymphadenitis. For children with recurrent disease a second surgical procedure is usually performed. When surgery is contraindicated the use of a clarithromycin multi drug regimen such as those used for pulmonary disease is recommended, however ethambutol should not be used in children who cannot reliably report loss of visual acuity.<sup>2</sup>

### **New treatments on the horizon**

Oxazolidinones are a new class of antibiotic active against gram positive bacteria. Linezolid, one of the first oxazolidinones to be registered for use, has been shown to be effective in vitro against rapidly growing mycobacteria.<sup>35</sup> Limited research has shown it to be successful in treating MAC disseminated skin disease.<sup>36</sup> Further research is necessary before its use can be widely recommended in NTM disease.

**Table 9. Drug side effects and interactions<sup>37</sup>**

SIDE EFFECTS		COMMON DRUG INTERACTIONS	
<b>CLARITHROMYCIN</b>			
<ul style="list-style-type: none"> <li>▪ GI upset</li> <li>▪ Hepatitis</li> <li>▪ Headache</li> <li>▪ Dizziness</li> <li>▪ Rash</li> <li>▪ Steven – Johnson Syndrome</li> <li>▪ Psychiatric and CNS effects</li> <li>▪ Pseudo – membranous colitis</li> <li>▪ Altered taste</li> </ul>	<p><b>Precautions</b></p> <ul style="list-style-type: none"> <li>▪ Duodenal ulcer</li> <li>▪ Renal impairment</li> <li>▪ Elderly</li> <li>▪ Pregnancy</li> <li>▪ Lactation</li> <li>▪ Children</li> <li>▪ Immunocompromised</li> </ul>	<p><b>Contraindicated with:</b></p> <ul style="list-style-type: none"> <li>▪ Astemizole</li> <li>▪ Terfenadine</li> <li>▪ Cisapride</li> <li>▪ Pimozide</li> </ul> <p>Increases the levels of:</p> <ul style="list-style-type: none"> <li>▪ Theophylline</li> <li>▪ Anticonvulsants</li> <li>▪ Warfarin</li> <li>▪ Ergot alkaloids</li> <li>▪ Benzodiazepines</li> <li>▪ Disopyramide</li> <li>▪ Digoxin</li> <li>▪ Tacrolimus</li> <li>▪ Cyclosporin</li> <li>▪ Rifabutin</li> </ul>	<ul style="list-style-type: none"> <li>▪ Cilostazol</li> <li>▪ Methyl – prednisolone</li> <li>▪ Quinidine</li> <li>▪ Sildenafil</li> <li>▪ Vinblastine</li> </ul> <p>Decreases levels of:</p> <ul style="list-style-type: none"> <li>▪ Zidovudine</li> </ul> <p>Clarithromycin levels increased by:</p> <ul style="list-style-type: none"> <li>▪ Fluconazole</li> <li>▪ Fluoxetine</li> <li>▪ Retinovit</li> </ul> <p>Rhabdomyolysis reported when taken with:</p> <ul style="list-style-type: none"> <li>▪ Simvastatin</li> <li>▪ Lovastatin</li> </ul>
<b>AZITHROMYCIN</b>			
<ul style="list-style-type: none"> <li>▪ GI upset</li> <li>▪ Superinfection</li> <li>▪ Pseudo-membranous colitis</li> <li>▪ Vaginitis</li> <li>▪ Angiooedema</li> <li>▪ Cholestatic jaundice</li> <li>▪ Hepatitis</li> <li>▪ Hearing impairment</li> </ul>	<p><b>Precautions</b></p> <ul style="list-style-type: none"> <li>▪ Renal impairment</li> <li>▪ Elderly</li> <li>▪ Pregnancy</li> <li>▪ Lactation</li> <li>▪ Severe hepatic impairment</li> </ul>	<p><b>Increases the levels of:</b></p> <ul style="list-style-type: none"> <li>▪ Ergot derivatives</li> <li>▪ Cyclosporin</li> <li>▪ Digoxin</li> <li>▪ Zidovudine</li> <li>▪ Terfenidine</li> <li>▪ Astemizole</li> <li>▪ Warfarin</li> </ul>	<p><b>Decreases levels of:</b></p> <ul style="list-style-type: none"> <li>▪ Zidovudine</li> </ul> <p>Levels decreased by:</p> <ul style="list-style-type: none"> <li>▪ Antacids</li> </ul>
<b>RIFAMPICIN</b>			
<ul style="list-style-type: none"> <li>▪ Pink/orange -urine</li> <li>▪ -sweat</li> <li>▪ -tears (stains contact lenses)</li> <li>▪ Nausea</li> <li>▪ Vomiting</li> <li>▪ Pseudo-membranous colitis</li> <li>▪ Hepatitis</li> <li>▪ Rash</li> <li>▪ Drug induced fever</li> <li>▪ CNS disturbance</li> </ul> <p>With prolonged unscheduled breaks:</p> <ul style="list-style-type: none"> <li>▪ Shock</li> <li>▪ Acute renal failure</li> <li>▪ Thrombocytopenia purpura</li> <li>▪ Haemolytic anaemia</li> <li>▪ Shortness of breath</li> <li>▪ Flu like syndrome (myalgia, arthralgia, fever, malaise, mild haemolysis)</li> </ul>	<p><b>Precautions:</b></p> <ul style="list-style-type: none"> <li>▪ Hepatic impairment</li> <li>▪ Malnourishment</li> <li>▪ Sodium metabisulphite allergy</li> <li>▪ Diabetes</li> <li>▪ Pregnancy</li> <li>▪ Lactation</li> <li>▪ Premature and newborn infants</li> <li>▪ Porphyria</li> </ul>	<p><b>Antacids may reduce absorption.</b></p> <p><b>Rifampicin causes decreased activity of:</b></p> <ul style="list-style-type: none"> <li>▪ Oral anticoagulants</li> <li>▪ Anticonvulsants</li> <li>▪ Antiarrhythmics</li> <li>▪ Antifungals</li> <li>▪ Barbiturates</li> <li>▪ Benzodiazepines</li> <li>▪ β blockers</li> <li>▪ Calcium channel blockers</li> <li>▪ Chloramphenicol</li> <li>▪ Clarithromycin</li> <li>▪ Corticosteroids</li> <li>▪ Cyclosporin</li> <li>▪ Cardiac glycosides (digoxin)</li> <li>▪ Clofibrate</li> <li>▪ Hormonal contraceptives</li> <li>▪ Dapsone</li> <li>▪ Enalapril</li> </ul>	<ul style="list-style-type: none"> <li>▪ Doxycycline</li> <li>▪ Fluoroquinolones</li> <li>▪ Oral hypoglycaemics</li> <li>▪ Levothyroxine</li> <li>▪ Narcotic analgesics</li> <li>▪ Methadone</li> <li>▪ Quinine</li> <li>▪ Tacrolimus</li> <li>▪ Theophylline</li> <li>▪ Tricyclic antidepressants</li> <li>▪ Zidovudine</li> </ul> <p><b>When taken with Rifampicin:</b></p> <ul style="list-style-type: none"> <li>▪ PAS decreases Rifampicin levels.</li> <li>▪ Atovaquone levels increase and Rifampicin levels decrease.</li> <li>▪ Halothane may cause hepatotoxicity</li> </ul>

SIDE EFFECTS		COMMON DRUG INTERACTIONS	
<b>RIFABUTIN</b>			
<ul style="list-style-type: none"> <li>▪ Pink/orange -urine</li> <li>▪ -sweat</li> <li>▪ -tears (stains contact lenses)</li> <li>▪ Nausea</li> <li>▪ Vomiting</li> <li>▪ Hepatitis</li> <li>▪ Rash</li> <li>▪ Drug induced fever</li> <li>▪ Myalgia</li> <li>▪ Arthralgia</li> <li>▪ Uveitis</li> <li>▪ Cytopenias</li> </ul>	<p><b>Precautions:</b></p> <ul style="list-style-type: none"> <li>▪ Hepatic impairment</li> <li>▪ Severe renal impairment</li> <li>▪ Pregnancy</li> <li>▪ Lactation</li> <li>▪ Children</li> </ul>	<p><b>Rifabutin causes ↓ activity of:</b></p> <ul style="list-style-type: none"> <li>▪ Oral anticoagulants</li> <li>▪ Anticonvulsants</li> <li>▪ Antiarrhythmics</li> <li>▪ Antifungals</li> <li>▪ Barbiturates</li> <li>▪ β blockers</li> <li>▪ Calcium channel blockers</li> <li>▪ Chloramphenicol</li> <li>▪ Clarithromycin</li> <li>▪ Corticosteroids</li> <li>▪ Cyclosporin</li> <li>▪ Cardiac glycosides (except digoxin)</li> <li>▪ Atovaquone</li> <li>▪ Bactrim</li> <li>▪ Cisapride</li> </ul>	<ul style="list-style-type: none"> <li>▪ Lignocaine</li> <li>▪ Terfenadine</li> <li>▪ Erythromycin</li> <li>▪ Lovastatin</li> <li>▪ Hormonal contraceptives</li> <li>▪ Dapsone</li> <li>▪ Benzodiazepines</li> <li>▪ Oral hypoglycaemics</li> <li>▪ Narcotic analgesics</li> <li>▪ Methadone</li> <li>▪ Quinidine</li> <li>▪ Tacrolimus</li> <li>▪ Antiretrovirals</li> </ul> <p>Many of the above drugs along with fluoroquinolones can increase rifabutin levels</p>
<b>ETHAMBUTOL</b>			
<ul style="list-style-type: none"> <li>▪ Optic neuropathy</li> <li>- Loss of visual acuity</li> <li>- Loss of red green discrimination</li> <li>▪ Nausea</li> <li>▪ Vomiting</li> <li>▪ Hepatitis</li> <li>▪ Rash</li> <li>▪ Arthralgia</li> <li>▪ Peripheral neuropathy</li> </ul>	<p><b>Precautions:</b></p> <ul style="list-style-type: none"> <li>▪ Renal impairment</li> <li>▪ Visual defects</li> </ul>	None noted	
<b>AMIKACIN AND STREPTOMYCIN</b>			
<ul style="list-style-type: none"> <li>▪ Auditory and vestibular impairment</li> <li>▪ Renal impairment</li> </ul>	<p><b>Precautions:</b></p> <ul style="list-style-type: none"> <li>▪ Renal impairment</li> </ul> <p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>▪ Pregnancy</li> <li>▪ Lactation</li> </ul>	The neurotoxic and nephrotoxic potential of this drug is increased by other Aminoglycosides, some diuretics, some anaesthetic and neuromuscular blocking drugs	
<b>CEFOXITIN</b>			
<ul style="list-style-type: none"> <li>▪ Superinfection</li> <li>▪ Pseudo-membranous colitis</li> <li>▪ Phlebitis</li> <li>▪ Local pain</li> <li>▪ Hypotension</li> <li>▪ Blood abnormalities</li> <li>▪ Hypotension</li> <li>▪ GI upset</li> <li>▪ Hepatitis</li> </ul>	<p><b>Precautions</b></p> <ul style="list-style-type: none"> <li>▪ Renal or hepatic impairment</li> <li>▪ Meningitis</li> <li>▪ Brain abscess</li> <li>▪ Pregnancy</li> <li>▪ Lactation</li> <li>▪ Neonates</li> <li>▪ Premature infants</li> </ul>	None noted	

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