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### Abbreviations used in these guidelines

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB</td>
<td>Acid fast bacilli</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>ATSI</td>
<td>Aboriginal and Torres Strait Islander</td>
</tr>
<tr>
<td>BGL</td>
<td>Blood glucose level</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre for Disease Control</td>
</tr>
<tr>
<td>CMP</td>
<td>Calcium magnesium phosphate</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiograph</td>
</tr>
<tr>
<td>FBE</td>
<td>Full blood examination</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine needle aspirate</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HRCT</td>
<td>High resolution computerised tomography</td>
</tr>
<tr>
<td>HTLV1</td>
<td>Human T-lymphotropic virus 1</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>MAC</td>
<td><em>Mycobacterium avium</em> complex</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NT</td>
<td>Northern Territory</td>
</tr>
<tr>
<td>NTM</td>
<td>Nontuberculous mycobacteria</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>RGM</td>
<td>Rapid growing mycobacteria</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>UEC</td>
<td>Urea electrolytes and creatinine</td>
</tr>
</tbody>
</table>
What’s new in these guidelines

In the 12 years since the first Northern Territory (NT) Centre for Disease Control (CDC) guidelines for control of nontuberculous mycobacteria (NTM) were written, there have been some significant developments.

Advances in molecular biology have made possible the identification of evermore NTM species in the environment. While the main pathological entities remain the same, there are now in excess of 150 NTM species known. Advances in treatment for the human immunodeficiency virus (HIV), namely highly active antiretroviral therapy (HAART), has led to a decrease in cases of disseminated NTM infection in HIV-infected patients.

While an uncommon disease presentation, several authoritative consensus statements have emerged since the first NT NTM guidelines. Compiling these for this second edition of the NT NTM guidelines has resulted in several modifications to the former treatment protocols:

* New diagnostic criteria for pulmonary NTM disease (p13)
* Expansion of therapeutic agents and adjuvant therapeutic options available (p15)
* A more comprehensive pre-treatment assessment (p16)
* Reduction in the initial dosage of ethambutol (p18)
* Streptomycin superseded by amikacin as the principal injectable therapeutic option (p18)
* Greater awareness of nosocomial transmission and prevention of NTM infection (p24)
* Initiation of enhanced surveillance for NTM disease in the NT from 2013 (p31).

Finally, this guideline is a ‘working document’ requiring regular updating. Feedback and suggestions are welcome and should be forwarded to:

Senior Nursing Advisor
Centre for Disease Control
TB Unit
Building 4, Royal Darwin Hospital, Tiwi, NT
Postal Address: PO Box 40596, Casuarina NT, 0811
Phone: 08 8922 8089
Facsimile: 08 8922 8310
Introduction

Nontuberculous mycobacteria (NTM) are mycobacterial species other than those belonging to the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum, M. microti*, and *M. canetti*) and *M. leprae*. They are free living organisms in the environment and to date 151 NTM species have been identified.² Diseases caused by NTM are notifiable in the NT. However, transient asymptomatic carriage or respiratory tract colonisation is not uncommon. These guidelines inform health practitioners regarding the diagnosis and management of NTM disease. Diagnosis and management of NTM is best done by, or in consultation with a specialist unit. In the Northern Territory (NT), the TB Unit at the Centre for Disease Control (CDC) manages and/or advises on the diagnosis and treatment of NTM disease. For advice please contact:

Centre for Disease Control
TB Unit
Building 4, Royal Darwin Hospital, Tiwi, NT
**Postal Address:** PO Box 40596, Casuarina NT, 0811
**Phone:** 08 8922 8804
**Facsimile:** 08 8922 8310

Methods

These guidelines were developed following the National Health and Medical Research Council process for guideline formation.³ Due to the uncommon nature of NTM disease, there are few randomised controlled trials or systematic reviews to guide policy formation. Instead we have relied on authoritative statements and peer-reviewed clinical resources. These include the American Thoracic Society (ATS)⁴, UpToDate® ⁵⁻⁻¹⁰ and Australia’s Therapeutic Guidelines.¹¹ Therefore, while not based on a high grade of evidence, the recommendations that follow are a synthesis of relevant peer-reviewed consensus statements.

These guidelines were peer-reviewed within CDC and were then externally peer-reviewed by Australian infectious diseases and respiratory physicians experienced in the management of NTM disease. We acknowledge the valuable contribution of Dr Justin Waring, Professor Daniel O’Brien, and Dr Anna Ralph who reviewed this document. These guidelines were also ‘road tested’ by health care providers and we thank Dr Frances Daily and Dr Vanessa Johnston for their insights and comments.
Background

NTM are free living environmental micro-organisms that have been isolated from tap water, soil, domestic and wild animals and food products. NTM can also colonise body surfaces and secretions presenting a challenge for clinicians to determine their pathological role. Our understanding of NTM disease has improved in-step with advances in microbiological techniques over the past 50 years. By far the most common disease presentation is NTM lung disease accounting for up to 90% of all NTM disease notifications.

NTM are classified as either slow growing (>7 days) or rapid growing (<7 days) based on laboratory culture. Overall, the most common NTM entity causing clinical disease in the NT and elsewhere is *M. avium* complex (MAC), accounting for approximately 80% of the NT NTM notifications.

Epidemiology

NTM are organisms that are ubiquitous in our environment. Therefore a positive culture result with a NTM organism can represent an environmental contaminant and is not necessarily enough to diagnose disease. Also, in contrast to *M. leprae* and *M. tuberculosis* complex, there is no evidence of animal to human or human to human transmission of NTM disease. Similar to reports elsewhere, the majority of NTM cases in the NT have been notified in the warmer and wetter ‘Top End’. Nosocomial outbreaks of NTM disease have been described in situations where sterile procedures are compromised. Furthermore, of relevance to the increasing trend in ‘medical tourism’ to developing countries, outbreaks have also been described associated with cosmetic procedures involving implants. NTM infections (especially *M. chelonae*) are also well-recognised complications of tattooing and mesotherapy (subcutaneous injection of various substances by practitioners of complementary medicine), including in Australia.

Incidence

The NT has a reported annual NTM disease incidence of between 2.3 and 3.9 cases per 100,000 population. Between 1989 and 1997, 43 cases of NTM disease were notified in patients without HIV infection in the NT. Of these 32 (74%) were pulmonary, 6 (14%) were soft tissue, 4 (9%) involved lymph nodes and there was 1 (2%) case of disseminated NTM disease. In the same period there were 15 cases of NTM disease in HIV-affected adults, predominantly disseminated disease. A forthcoming report on subsequent surveillance data (2003-2010) reports a NTM disease annual incidence of 2.3 cases per 100,000. Disseminated NTM disease in patients with HIV infection has declined markedly with the advent of HAART.

Pathogenesis of NTM disease

The pathogenesis of many NTM diseases is poorly understood. Pre-existing lung disease and increasing age can be associated with NTM lung disease but the commonest form of NTM lung disease now is bronchiectasis. There is good evidence that the bronchiectasis is caused by the NTM infection, rather than the bronchiectasis being pre-existing. Therefore predisposing factors do not have to be present, in fact usually are not. Inhalation or ingestion of NTM is the presumed mechanism of infection. NTM soft-tissue disease is thought to be caused by minor trauma or direct inoculation. The pathogenesis of NTM lymphadenopathy is poorly understood.

After entering the body, NTM are taken up by host macrophages wherein they multiply as intracellular pathogens. Host immunity is through T helper lymphocytes and natural killer...
cells which interact with infected macrophages to induce cellular destruction of the infected cell and mycobacteria. Cytokines crucial to the host immune response include interferon-gamma, interleukin 2, interleukin 12 and tumour necrosis factor alpha (TNFα). Genetic defects, acquired immune-suppression, or medications that interfere with these components of the host immune response (oral steroids use ≥15mg for ≥14 days, TNFα inhibitors, and immunosuppression following organ transplantation) are risk factors for developing NTM disease. A syndrome of adult-onset immune deficiency comprising production of antibodies to interferon-gamma, mimicking HIV, is a newly-recognised major risk factor for disseminated NTM infection, especially in Asian populations.

**Pathogenic species**

*M. avium* complex (*M. avium* and *M. intracellulare*) is by far the most common pathological entity. However, a number of other NTM species have also been described in NTM disease (Table 1, p7). Table 2 lists several NTM species that are almost always regarded as contaminants or as having a limited pathological role in immune-competent hosts (Table 2, p8). Among rapid growing mycobacteria (RGM) the three most important clinical entities causing disease are *M. abscessus*, *M. fortuitum* and *M. chelonae* (Table 3, p8).

### Table 1: NTM diseases, causal organisms and case notifications in the Northern Territory

<table>
<thead>
<tr>
<th>NTM frequently causing clinical disease</th>
<th>NTM cases</th>
<th>NTM infrequently causing clinical disease</th>
<th>NT cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NTM pulmonary disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>Yes</td>
<td><em>M. asiaticum</em></td>
<td>Yes</td>
</tr>
<tr>
<td><em>M. avium complex</em></td>
<td>Yes</td>
<td><em>M. celatum</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>Yes</td>
<td><em>M. chelonae</em></td>
<td>Yes</td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td>No</td>
<td><em>M. fortuitum</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td>No</td>
<td><em>M. haemophilum</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. scrofulaceum</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. shimoidei</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. simiae</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. smegmatis</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. szulagi</em></td>
<td>No</td>
</tr>
<tr>
<td><strong>NTM lymph node disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. avium complex</em></td>
<td>Yes</td>
<td><em>M. abscessus</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td>No</td>
<td><em>M. chelonae</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. scrofulaceum</em></td>
<td>No</td>
<td><em>M. fortuitum</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. genavense</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. haemophilum</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. kansasii</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. szulagi</em></td>
<td>No</td>
</tr>
<tr>
<td><strong>NTM skin and soft tissue disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>Yes</td>
<td><em>M. avium complex</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. chelonae</em></td>
<td>Yes</td>
<td><em>M. haemophilum</em></td>
<td>Yes</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>Yes</td>
<td><em>M. immunogenum</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>Yes</td>
<td><em>M. kansasii</em></td>
<td>No</td>
</tr>
<tr>
<td><em>M. ulcerans</em></td>
<td>Yes</td>
<td><em>M. malmoense</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. nonchromogenicum</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>M. terrae complex</em></td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Disseminated NTM disease

<table>
<thead>
<tr>
<th>NTM species</th>
<th>Isolated in the NT</th>
<th>Site of colonisation/contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. avium complex</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>M. chelonae</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. haemophilum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. kansasii</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. abscessus</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>M. celatum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. conspicuum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. haemophilum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>M. genavense</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. immunogenum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. malmoense</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. marinum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. mucogenicum</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>M. scrofulaceum</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. simiae</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. szulagi</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>M. xenopi</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Listed in alphabetical order, not by frequency of occurrence*

### Table 2: NTM species regarded as non-pathological in immune-competent patients

<table>
<thead>
<tr>
<th>NTM species</th>
<th>Isolated in the NT</th>
<th>Site of colonisation/contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. gordonae</td>
<td>Yes</td>
<td>Sputum</td>
</tr>
<tr>
<td>M. haemophilum</td>
<td>Yes</td>
<td>Venous catheters</td>
</tr>
<tr>
<td>M. mucogenicum</td>
<td>Yes</td>
<td>Sputum</td>
</tr>
<tr>
<td>M. nonchromogenicum</td>
<td>Yes</td>
<td>Sputum</td>
</tr>
<tr>
<td>M. terrae complex</td>
<td>Yes</td>
<td>Sputum</td>
</tr>
</tbody>
</table>

### Table 3: Clinically significant RGM and their common disease presentations

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease presentation in:</th>
<th>Immune-competent</th>
<th>Immune-suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. fortuitum</td>
<td>Skin (single lesion)</td>
<td></td>
<td>Catheter infection</td>
</tr>
<tr>
<td></td>
<td>Wound infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. chelonae</td>
<td>Wound infection</td>
<td></td>
<td>Disseminated skin infection</td>
</tr>
<tr>
<td></td>
<td>Corneal infection</td>
<td></td>
<td>Catheter infection</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>Lung infection</td>
<td></td>
<td>Disseminated skin infection</td>
</tr>
<tr>
<td></td>
<td>Wound infection</td>
<td></td>
<td>Catheter infection</td>
</tr>
<tr>
<td></td>
<td>Chronic Otitis media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. smegmatis</td>
<td>Wound infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis (open fracture)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. mucogenicum</td>
<td>Sputum contaminant</td>
<td></td>
<td>Catheter infection</td>
</tr>
</tbody>
</table>
Clinical presentations

NTM disease can be broadly classified into 4 clinical entities:\textsuperscript{5}

1. Progressive pulmonary disease
2. Skin and soft tissue disease
3. Lymph node disease
4. Disseminated disease.

Pulmonary disease

Pulmonary NTM disease is the most common NTM presentation (74\%) in the NT.\textsuperscript{12} There are 2 common and 2 uncommon clinical presentations of pulmonary NTM disease (Table 4).\textsuperscript{5} Treatment varies depending upon the clinical presentation and the causal organism (p 18).

Table 4: Clinical presentations of pulmonary NTM disease\textsuperscript{10}

<table>
<thead>
<tr>
<th>Common</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease in those without pre-existing lung disease (often anterior segment bronchiectasis)</td>
<td></td>
</tr>
<tr>
<td>Disease in those with pre-existing lung disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary pulmonary nodule</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
</tr>
</tbody>
</table>

Disease in those without pre-existing lung disease

Although the pathogenesis of NTM pulmonary disease in those without underlying disease is unclear, it is most common in non-smoking women over 50 years old with a morphotype of scoliosis, pectus excavatum, mitral valve prolapse and joint hypermobility.\textsuperscript{7} In addition to these well recognised associations, gastro-esophageal reflux and rheumatoid arthritis have also been reported.

Presenting symptoms are similar to those described below. However, radiographic findings differ and typically include multiple small nodules and fibrosis associated with cylindrical bronchiectasis in the mid-lung fields. These are best demonstrated by high resolution computerised tomography (HRCT) rather than plain chest X-ray. Acid fast bacilli (AFB) are only intermittently shed in pulmonary secretions making diagnosis more difficult.\textsuperscript{7} In these patients, disease is progressive and bronchoscopy or fine needle aspirate may be required to confirm the diagnosis (See p13).\textsuperscript{10}

Disease in those with pre-existing lung disease

Predisposing lung disease includes: chronic obstructive pulmonary disease, bronchiectasis (classically dependent lobe bronchiectasis), pneumoconiosis, cystic fibrosis and previous pulmonary TB. The clinical symptoms often mimic those of the underlying disease process and include cough, sputum production, fatigue, malaise, fever, weight loss, dyspnoea, haemoptysis and chest discomfort. Radiographic findings often mimic pulmonary TB with predominant upper lobe infiltrates and thin-walled cavity formation.\textsuperscript{5} Typically, acid fast bacilli (AFB) are shed readily in pulmonary secretions.
Solitary pulmonary nodule

NTM can present as a solitary pulmonary nodule and hence it is an important differential diagnosis for a primary lung cancer lesion. However, the pathogenesis and role of treatment is unclear and is dependent on evidence of disease progression (See p13).5

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis is also known as ‘hot tub lung’. The principal treatment is to avoid aerosolised water-borne NTM organisms, the offending stimulus.5

Skin and soft tissue disease

NTM disease affecting skin, soft tissue and/or bone is the second most common presentation (14%) in the NT and may occur in any age group.12 While a large number of NTM species are implicated (Table 1, p7), the most common organisms are M. marinum, M. ulcerans (Appendix 1, p29) and the RGM. This NTM presentation commonly arises as a result of direct inoculation via puncture wounds, trauma, colonisation of long-term venous or peritoneal catheters, or as a post injection abscess or surgical wound infection. Chronic granulomatous infections affecting bursae, joints, bones and tenosynovitis have also been described.4

Mycobacterium marinum

M. marinum is widely distributed in aquatic environments, particularly in stagnant waters. Infection is acquired through soft tissue injury (classically involving the hand) in the aquatic environment giving rise to a ‘swimming pool’ or ‘fish tank’ granuloma. Adequate chlorination of domestic swimming pools is the single most important preventive measure.4 Diagnosis is based on biopsy, histological examination and culture at 30°C.

Mycobacterium ulcerans

Named ‘Buruli ulcer’ after Buruli in Uganda where early case reports were described, it is also known in Australia as ‘Bairnsdale’ (from Bairnsdale, Victoria) and ‘Daintree’ ulcer (from far-north Queensland) following case reports in these jurisdictions. M. ulcerans is the third most common mycobacterial disease after tuberculosis and leprosy worldwide.29 While predominantly described in tropical latitudes, cases are described in temperate zones, including a recent cluster of cases from the Bellarine peninsula, Victoria.30,31 Cases have also occurred in the greater Darwin region. M. ulcerans is a slow-growing mycobacterium closely related to M. marinum that cultures at 29-33°C. While the transmission mechanism is uncertain, it probably involves skin trauma and biting insects have been postulated as one possible vector.32 Mammals can also be infected and may be an intermediate host in transmission to humans.33 In-vivo, M. ulcerans produces Mycolactone – a potent cytotoxin that suppresses the host immune response and induces necrosis and ulceration.34 The lesion usually begins as a painless nodule or plaque less than 5cm diameter, commonly affecting a limb. This breaks down within days to weeks to form a painless ulcer with undermined edges. Ulceration progresses slowly and can involve deeper tissues such as tendons, joints and bone.34 Rapidly progressive oedematous forms mimicking cellulitis can occur in approximately 5% of cases.31 Diagnosis of M. ulcerans is based on obtaining 2 dry cotton-tipped swab samples deep to the undermined edge of the ulcer, one sent for smear and mycobacterial culture and one for
Specimens for diagnosis of non-ulcerative forms (nodule, plaque, oedema) need to be obtained via tissue biopsy (see page 14).

**Rapidly Growing Mycobacteria**

RGM (*M. fortuitum, M. chelonae, M. abscessus*) can also cause skin and soft tissue disease. Typical lesions are skin nodules with purple discolouration, recurrent abscesses and chronic discharging sinuses. *M. fortuitum* lesions are more likely to present as a single lesion whereas *M. chelonae* and *M. abscessus* are more likely to cause multiple lesions. An important consideration with RGM is their potential role in nosocomial infection where sterilisation procedures are inadequate (Table 12, p24).

Skin and soft tissue NTM disease caused by RGM is classified into localised and severe disease. Severe disease is when the infection has progressed beyond localised involvement to include deep tissues; bone, pulmonary or disseminated infection. Treatment varies depending on the causal NTM, in-vitro antibiotic sensitivity and the severity of the infection (Table 10, p21).

**Lymph node disease**

Occurring predominantly in children under 5 years of age, the most common presentation is unilateral enlargement of tonsilar, pre-auricular and/or submandibular nodes. Enlarged nodes are firm, non-tender and slowly enlarge over weeks. *M. avium* complex is the most common organism isolated. If left untreated, suppuration and sinus formation is common. Surgical excision without chemotherapy is the treatment of choice (p17).

**Disseminated disease**

Disseminated NTM disease is now uncommon. It is associated with severe immune-suppression. Immuno-suppression can be: (i) acquired, such as in HIV infection (CD4 T-lymphocyte count <100/µL), (ii) iatrogenic, thorough the use of TNFα inhibitors, oral steroids use ≥15mg for ≥14 days or immune-suppression following solid organ transplantation or (iii) rare cases of genetic defects in interferon-gamma or interleukin 12 production or autoimmune disease with production of antibodies to interferon-gamma, mimicking HIV, in Asian populations.

**Patients without HIV infection**

For patients without HIV infection, disseminated MAC disease presents as fever of unknown origin. Disease caused by *M. kansasii, M. chelonae, M. abscessus*, and *M. haemophilum* presents as multiple subcutaneous nodules or abscesses that drain spontaneously.

**HIV-infected patients**

MAC is the most common cause of disseminated NTM disease in patients infected with HIV. The risk for MAC increases as the CD4 cell count declines below 50/µL. Disseminated infection is thought to follow recent acquisition rather than reactivation of latent infection and entry is via the respiratory or gastrointestinal tract. Symptoms are non-specific and include: fever, night sweats, abdominal pain, diarrhoea and weight loss. Diagnosis is confirmed by positive culture from blood, bone marrow or other tissue, for MAC. The incidence of disseminated NTM disease has declined with HAART and effective MAC prophylaxis with azithromycin. When HAART is instituted, localised MAC disease can present as
lymphadenitis associated with immune system reconstitution. Other NTM species can also cause disease in HIV-infected patients with a low CD4 count (Table 5).  

Table 5: Other (non-MAC) NTM disease presentations in HIV-infected patients  

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. kansasii</em></td>
<td>Pulmonary disease mimicking TB</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis/Discitis</td>
</tr>
<tr>
<td><em>M. haemophilum</em></td>
<td>Painful, erythematous, ulcerating skin nodules</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td></td>
<td>Arthritis, tenosynovitis, osteomyelitis</td>
</tr>
<tr>
<td><em>M. simiae</em></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td></td>
<td>Adenitis, tenosynovitis</td>
</tr>
<tr>
<td><strong>RGM:</strong></td>
<td><strong>Pulmonary disease</strong></td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>Pustular nodular cutaneous lesions</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td><em>M. chelonae</em></td>
<td>Multifocal osteomyelitis, adenitis</td>
</tr>
<tr>
<td><em>M. genavense</em></td>
<td>Massive adenopathy/organomegaly (spleen)</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td><em>M. szulagi</em></td>
<td>Pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>Disseminated infection</td>
</tr>
<tr>
<td></td>
<td>Cutaneous lesions</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis/septic arthritis</td>
</tr>
</tbody>
</table>

MAC disease, MAC prophylaxis and other disseminated NTM infections in patients with HIV is a specialised area, best managed by clinicians experienced in HIV medicine and infectious diseases.
Diagnosis of NTM disease

Pulmonary disease

Clinical, radiological and microbiological criteria are equally important and all must be met to confirm the diagnosis of NTM lung disease (Appendix 2 p31).\textsuperscript{4,10} This approach is required since isolation of an NTM organism from the non-sterile respiratory tract does not necessarily signify NTM disease, but may represent colonisation or contamination. Diagnosis often takes months to confirm and the decision to treat is not straightforward. The risks (Table 13) and benefits for individual patients need to be considered. Patients who are suspected of having pulmonary NTM disease but who do not fulfil the diagnostic criteria should be followed until the diagnosis is confirmed or excluded.

Table 6: Diagnostic criteria for NTM pulmonary disease\textsuperscript{4,10}

<table>
<thead>
<tr>
<th>1: Progressive clinical symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent and progressive and pulmonary symptoms with appropriate exclusion of other diagnoses</td>
</tr>
<tr>
<td>- Cough, sputum production, haemoptysis, weight loss, night sweats, dyspnoea, malaise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2: Progressive radiological changes*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest X-ray:</strong> Nodular or cavitary changes AND/OR</td>
</tr>
<tr>
<td><strong>HRCT chest:</strong> Multifocal bronchiectasis with multiple small nodules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3: Consistent microbiological findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Positive culture results for the same NTM from at least 2 expectorated (or induced) sputa at least 1 week apart within 12 months OR</td>
</tr>
<tr>
<td>b. Positive NTM culture results from at least 1 bronchial wash or lavage OR</td>
</tr>
<tr>
<td>c. Lung biopsy with compatible histology (AFB +/- granulomatous inflammation) and positive culture for NTM OR</td>
</tr>
<tr>
<td>d. Lung biopsy compatible (AFB +/- granulomatous inflammation but culture not done) + &gt;1 sputum or bronchial lavage that is positive on culture for NTM OR</td>
</tr>
<tr>
<td>e. A positive pleural fluid culture for NTM (normally sterile site)</td>
</tr>
</tbody>
</table>

Note: *Clinical, radiological and microbiological criteria are equally important and all must be present
**Skin and soft tissue disease**

Diagnosis is made on culture and in some cases polymerase chain reaction (PCR), of the offending NTM organism. Tissue biopsy for microscopy (AFB stain), histology and mycobacterial culture from a usually sterile site is the preferred diagnostic specimen. In a non-sterile site, histological changes of granulomatous inflammation can support the diagnosis.

Specifically for *M. ulcerans* (Buruli ulcer and Bairnsdale ulcer) the consensus guidelines of 2007\(^\text{30}\) highlight that for speed and accuracy of diagnosis of *M. ulcerans*, IS2404 PCR testing directly from ulcer swabs be done and this is still recommended.\(^\text{36,39}\) For non-ulcerative or pre-ulcerative lesions (oedematous, plaques or nodules) swabs are not appropriate specimens, as they produce false-negative results and fine-needle aspiration or punch, incisional or excisional biopsy is required to obtain tissue fluid or fresh tissue.\(^\text{39}\)

**Lymph node disease**

In the NT context, it is important to remember that TB lymphadenitis is more common in Aboriginal children than lymphadenopathy caused by NTM.\(^\text{1}\) Diagnosis is made on culture of a complete excisional biopsy or fine needle aspirate (FNA). Incision and drainage is not recommended due to the risk of sinus tract formation and poor cosmetic result. It is crucial to ensure that biopsy or FNA samples are placed in saline, not formalin, because formalin precludes culture confirmation of the diagnosis. Excisional biopsy is the preferred method of diagnosis, when safe to do so, because this usually provides definitive treatment with the best cosmetic result.\(^\text{35}\)

**Disseminated NTM disease**

Diagnosis of disseminated NTM disease is by culture from a usually sterile site: blood, urine, bone marrow, or tissue biopsy (in the setting of multiple lesions). (See p11) HIV infected patients with immune reconstitution syndrome following introduction of HAART may present with focal NTM lymph node disease.
Treatment of NTM disease

Treatment principles

Treatment of NTM disease is not always straightforward. Therefore, treatment decisions must be made following consultation with experienced practitioners in this field. In the NT the TB Unit can provide expert advice regarding the management of NTM disease.

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TB Unit
Building 4, Royal Darwin Hospital, Tiwi, NT
Postal Address: PO Box 40596, Casuarina NT, 0811
Phone: 08 8922 8804
Facsimile: 08 8922 8310

Some key principles in the treatment of NTM disease are:

1. Monotherapy can lead to the development of resistance, and should be avoided.
2. Monotherapy can be used for prophylaxis in defined situations (See Table 11, p23).
3. Different NTM behave very differently: e.g.
   a. *M. abscessus* pulmonary disease is generally incurable without radical surgery
   b. *M. kansasii* pulmonary disease closely resembles TB clinically, radiologically and in regards to treatment regimen.
4. Clarithromycin is not well tolerated by some people, in whom second-line alternatives are required
5. Surgery is generally indicated for skin/soft tissue disease due to rapidly-growing NTM if drug therapy is difficult, abscess formation is present, or there is extensive disease.
6. For several NTM (including *M. chelonae, M. malmoense, M. xenopi*) there is a lack of correlation of in-vitro susceptibility and clinical response.
7. Drug side effects and interactions with regular medications are common (more common in the elderly)
8. For pulmonary NTM disease, not all patients respond to treatment and disease relapse is not uncommon.

Treatment of NTM disease varies depending on the site of the disease (pulmonary or extra pulmonary) and the organism identified. A thorough workup of the patient needs to be completed prior to commencing treatment (Figure 1). A NTM treatment card is used for recording treatment (Appendix 3, p32)
Northern Territory NTM Treatment Guidelines 2014

Pre-treatment checklist

All 3 diagnostic criteria fulfilled?

- Clinical symptoms: Yes / No / NA
- Radiology: Yes / No / NA
- Microbiology: Yes / No / NA

Baseline weight _____

Bloods (circle result)

- FBE: Normal / Abnormal
- LFT: Normal / Abnormal
- UEC: Normal / Abnormal
- BGL/HbA1c: Normal / Abnormal
- Uric acid: Normal / Abnormal
- HIV: Positive / Negative
- HTLV1 (ATSI): Positive / Negative
- Hepatitis screen: Positive / Negative

Visual assessment (ethambutol treatment)

- Ishihara test: Pass / Fail / NA
- Acuity: R:6/ L:6/

ECG (macrolide/fluoroquinolone: QTc) Done / Not done / NA

Vestibular-acoustic assessment (amikacin treatment)

- Burrow test*: Pass / Fail / NA
- Audiometry: Normal / Abnormal

Contraception discussion (women) Done / Not done / NA

Review drug interactions Done / Not done / NA

Clarithromycin susceptibility (MAC) Done / Not done / NA

Clinical photography (skin lesion) Done / Not done / NA

*Note: See Appendix 4 p34.

Pulmonary disease

Treatment for pulmonary NTM disease is continued for 12 months following negative sputum culture. Most people who respond to treatment do so within the first 3 to 6 months.

Treatment failure is defined as those on appropriate treatment (Table 8, p18) with:

(i) no response to treatment (clinical or radiological or microbiological) at 6 months; OR
(ii) Sputum culture NTM positive for the same organism after 12 months.4

Clinical judgement must be used to determine the treatment duration for responding patients who are unable to produce sputum samples. There is no role for an induced sputum sample/bronchoscopy to determine culture conversion.
Skin and soft tissue disease

Treatment of skin and soft tissue NTM disease depends on the site, severity and the causative organism (See Table 9 and Table 10, p20-21).

Lymph node disease

Excisional biopsy without chemotherapy is the recommended treatment for children with NTM cervical lymphadenopathy. Diligence is required to ensure that biopsy specimens are always collected in saline, not formalin, to facilitate culture confirmed diagnosis and treatment. For children with recurrent disease, a second surgical procedure is recommended. If surgical resection of an affected node threatens the facial nerve (preauricular node), or cannot be safely performed, a clarithromycin-based multidrug regimen, such as that used for NTM pulmonary disease, may be considered in consultation with an experienced infectious diseases physician/paediatrician.

Clinical reviews while on treatment

The interval and content of reviews while on treatment will depend on the site of NTM infection, drug regimen and the age of the patient. Below is a suggested care plan for NTM pulmonary disease, the most common NTM disease presentation.

Table 7: Pulmonary NTM disease care plan

<table>
<thead>
<tr>
<th>Every visit - monthly</th>
<th>Every 3 months</th>
<th>Post treatment at 6 and 18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTM disease symptoms</td>
<td>Chest X-ray§</td>
<td>Chest X-Ray§</td>
</tr>
<tr>
<td>Drug side effects/interactions</td>
<td></td>
<td>NTM disease symptoms</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td>Sputum (if productive cough) for smear and culture§</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision: Acuity &amp; Ishihara*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum† (smear &amp; culture)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloods: FBE, LFT‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (if on amikacin/streptomycin):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UEC, audiometry, Burrow test‖</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: *If being treated with ethambutol  
†Continue even if culture negative for causal NTM  
‡Monthly for the first 3 months then reassess this requirement  
§Induced sputum is not indicated if unable to produce sputum  
‖See Appendix 4 p34  
¶For bronchiectasis consider replacing Chest X-ray follow up with repeat chest CT after 6 months treatment and/or post treatment.
## Table 8: Treatment of NTM pulmonary disease \(^4,11\)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Adjuvant therapeutic options</th>
</tr>
</thead>
</table>
| *M. avium* complex | Mild to moderate Nodular/Bronchiectatic disease | Three times weekly Treatment  
**Clarithromycin** 500 mg (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly, thrice weekly  
**OR**  
**Azithromycin** 500 mg (child: 10 mg/kg up to 500 mg) orally, thrice weekly  
**PLUS**  
**Ethambutol** (adult and child 6 years or more) 25 mg/kg orally, thrice weekly  
**PLUS**  
**Rifampicin** 600 mg (adult less than 50 kg: 450 mg) (child less than 50 kg: 10 mg/kg up to 450 mg; 50 kg or more: 10 mg/kg up to 600 mg) orally, thrice weekly | 12 months following sputum conversion  
(culture negative for causal NTM) | Additional therapeutic options for patients with severe disease or with poor response include addition of an aminoglycoside (amikacin or streptomycin 25 mg/kg IM 3 times weekly) and adjuvant interferon gamma.\(^{11}\)  
Surgical resection of localised disease or a solitary nodule may also be considered.\(^{11}\) |
| Severe Nodular/Bronchiectatic disease  
OR  
Fibrocavitatory disease | Daily Treatment  
**Clarithromycin** 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly  
**OR**  
**Azithromycin** 250 mg (child: 6 mg/kg up to 250 mg) orally, daily  
**PLUS**  
**Ethambutol** (adult and child 6 years or more) 15 mg/kg orally, daily  
**PLUS EITHER**  
**Rifampicin** 600 mg (adult less than 50 kg: 450 mg) (child less than 50 kg: 10 mg/kg up to 450 mg; 50 kg or more: 10 mg/kg up to 600 mg) orally, daily  
**OR**  
**Rifabutin** 300 mg (child: 5 mg/kg up to 300 mg) orally, daily | 12 months following sputum conversion | Surgical resection combined with multi drug therapy offers best chance of cure.\(^4\) |

\(M. abscessus\)  
Pulmonary disease  
Very difficult to treat. Currently, no drug regimens of proven or predictable efficacy for treatment of *M. abscessus* lung disease. Periodic multidrug treatment, including a macrolide and one or more parenteral drugs (amikacin, cefoxitin or imipenem) may help to control symptoms and disease progression\(^{11}\)  
12 months following sputum conversion  
Surgical resection combined with multi drug therapy offers best chance of cure\(^4\)
<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Adjuvant therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. kansasii</em></td>
<td>Pulmonary disease</td>
<td><strong>Isoniazid</strong> 300 mg (child: 10 mg/kg up to 300 mg) orally, daily PLUS <strong>Rifampicin</strong> 600 mg (adult less than 50 kg: 450 mg) (child less than 50 kg: 10 mg/kg up to 450 mg; 50 kg or more: 10 mg/kg up to 600 mg) orally, daily PLUS <strong>Ethambutol</strong> (adult and child 6 years or more) 15 mg/kg orally, daily PLUS <strong>Pyridoxine</strong> (adult: 25mg; Child: 5-11yrs 12.5mg; Child &lt;5yrs: 5mg), daily</td>
<td>12 months following sputum conversion</td>
<td><em>Isoniazid is less active against <em>M. kansasii</em> than it is against <em>M. tuberculosis.</em> Therefore a reasonable alternative for patients unable to tolerate isoniazid is: <strong>Clarithromycin</strong> 500 mg 12-hourly AND <strong>Rifampicin</strong> AND <strong>Ethambutol</strong>  **Rifampicin resistance is described in patients with <em>M. kansasii,</em> especially those with HIV infection.</em>&quot; The initial recommended regimen in rifampicin-resistant disease is clarithromycin, ethambutol, and high-dose isoniazid (900mg/day), with or without trimethoprim-sulfamethoxazole. The newer macrolides, the fluoroquinolones, ethionamide and streptomycin are other alternative agents in the setting of rifampicin resistance. Linezolid has good in vitro activity (MIC range ≤0.25-2 µg/mL) but with no clinical experience for this disease.&quot;</td>
</tr>
</tbody>
</table>

Note: *Treatment to be initiated by a specialist (e.g. Infectious Diseases) experienced in NTM treatment and co-managed by the TB/NTM unit.*
Table 9: Treatment of NTM skin and soft tissue disease caused by *M. marinum* and *M. ulcerans*\(^{11,39}\)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Adjuvant therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. marinum</em></td>
<td>Uncomplicated lesions</td>
<td><strong>Clarithromycin</strong> 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly OR <strong>Doxycycline</strong> 100 mg (child more than 8 years: 2.5 mg/kg up to 100 mg) orally, 12-hourly OR <strong>Trimethoprim+sulfamethoxazole</strong> 160+800 mg (child more than 2 months: 4+20 mg/kg up to 160+800 mg) orally, 12-hourly</td>
<td>The optimal duration of therapy is not known, but treatment is suggested for 1 to 2 months after the resolution of all lesions (typically 3 to 4 months in total).</td>
<td>Surgical resection of localised infection Antibiotic therapy may not be required if a single lesion is successfully excised(^{11})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Even in uncomplicated lesions, combination therapy may be preferable to monotherapy with addition of rifampicin or ethambutol as listed below</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>Complicated lesions, previous treatment failure or deep structure involvement (e.g.: bone)</td>
<td><strong>Clarithromycin</strong> 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly OR <strong>Azithromycin</strong> 250 mg (child: 6 mg/kg up to 250 mg) orally, daily PLUS <strong>Ethambutol</strong> (adult and child 6 years or more) 15 mg/kg orally, daily PLUS EITHER <strong>Rifampicin</strong> 600 mg (adult less than 50 kg: 450 mg) (child: 10 mg/kg up to 600 mg) orally, daily OR <strong>Rifabutin</strong> 300 mg (child: 5 mg/kg up to 300 mg) orally</td>
<td>Treat for 2 months following lesion resolution (Total 3-4 months)</td>
<td>Surgical debridement</td>
</tr>
</tbody>
</table>
### Table 10: Treatment of skin and soft tissue disease caused by rapidly growing mycobacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Adjuvant therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M. ulcerans</strong></td>
<td>* Skin Ulcer</td>
<td><strong>Multidisciplinary care:</strong> antibiotics are usually first line. Surgical indications: (i) a) debridement of necrotic wounds, and b) to repair large defects, reduce deformity or hasten closure of a wound (ii) antibiotics are refused/contraindicated (iii) very small lesion amenable to excision and direct closure. Relapse may occur if adjuvant antibiotics are not used <strong>Treatment:</strong> use rifampicin and one other companion drug (clarithromycin or a fluoroquinolone) <strong>Rifampicin</strong> 600 mg (adult less than 50 kg: 450 mg) (child: 10 mg/kg up to 600 mg) orally, daily PLUS <strong>Clarithromycin</strong> 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly (this is the WHO preferred companion drug) OR <strong>Ciprofloxacin</strong> 500-750 mg orally, 12-hourly (generally not recommended for pre-pubertal children) OR <strong>Moxifloxacin</strong> 400 mg orally, daily (generally not recommended for pre-pubertal children) <strong>Paradoxical reactions:</strong> 1 in 5 people treated with antibiotics develop worsening appearance of lesions due to immune reconstitution inflammatory reactions.</td>
<td>Treat for 8 weeks</td>
<td>Adjuvant heat therapy could be considered in extensive lesions where antibiotics are not tolerated or contraindicated, and curative surgery unlikely to produce an optimal outcome or is not possible. For severe disease could consider parenteral amikacin or streptomycin in conjunction with rifampicin recognising potential side effect profiles.</td>
</tr>
<tr>
<td><strong>Rapid growing mycobacteria species:</strong> M. fortuitum M. chelonae M. abscessus M. mucogenicum M. smegmatis</td>
<td>Limited skin/soft tissue infection</td>
<td><strong>Oral therapy with 2 drugs to which the NTM is susceptible</strong> <strong>Trimethoprim+sulfamethoxazole</strong> 160+800 mg (child more than 2 months: 4+20 mg/kg up to 160+800 mg) orally, 12-hourly OR <strong>Doxycycline</strong> 100 mg (child more than 8 years: 2.5 mg/kg up to 100 mg) orally, 12-hourly OR <strong>Ciprofloxacin</strong> 500-750 mg orally, 12-hourly (generally not recommended for pre-pubertal children) OR <strong>Clarithromycin</strong>* 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly</td>
<td>Treat for 4 months</td>
<td>Surgical resection of localised infection</td>
</tr>
<tr>
<td>Organism</td>
<td>Disease</td>
<td>Treatment</td>
<td>Treatment duration</td>
<td>Adjuvant therapeutic options</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| *M. fortuitum* and *M. chelonae* | Severe disease: Complicated lesions, previous treatment failure, deep structure involvement (e.g.: bone) or disseminated disease | **Initial parenteral treatment with 2 drugs to which the NTM is susceptible**  
A typical regimen includes an aminoglycoside plus 2 of the other 3 drugs although a combination of the other 3 drugs can be used particularly in patients who cannot tolerate aminoglycosides  
**Possible parenteral agents include:** Amikacin 10 to 15mg/kg/day for adults with normal renal function  
OR  
Tobramycin 5mg/kg/day  
AND/OR  
Cefoxitin 12g per day in divided doses  
AND/OR  
Meropenem 500mg 8-hourly OR imipenem 1 g 6-hourly  
AND/OR  
Levofoxacin 500-750mg daily  
**Oral agents to be used following parenteral therapy to which the NTM is susceptible**  
Trimethoprim+sulfamethoxazole 160+800 mg (child more than 2 months: 4+20 mg/kg up to 160+800 mg) orally, 12-hourly  
OR  
Doxycycline 100 mg (child more than 8 years: 2.5 mg/kg up to 100 mg) orally, 12-hourly  
OR  
Ciprofloxacin 500-750mg orally, 12-hourly (generally not recommended for pre-pubertal children) or Levofoxacin 500-750mg daily  
OR  
Clarithromycin* 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly or azithromycin 250-500mg daily | Initial parenteral Rx for 2-6 weeks until clinical improvement followed by oral treatment with 2 drugs to which the NTM is susceptible for 6-12 months | Surgical debridement – the mainstay of therapy, given poor response to antimicrobials even when in vitro testing reports susceptibility |
| *M. abscessus*            | Severe disease: Complicated lesions, previous treatment failure, deep structure involvement (e.g.: bone) or disseminated disease | **Surgical Debridement**  
**Initial parenteral/oral treatment with 3 drugs to which the NTM is susceptible**  
Amikacin 10 to 15mg/kg/day for adults with normal renal function  
AND/OR  
Cefoxitin 12g per day in divided doses  
AND/OR  
Meropenem 500mg 8-hourly OR imipenem 1 g 6-hourly  
AND  
Clarithromycin* 500 mg (adult less than 50 kg or more than 70 years: 250 mg) (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly | Initial parenteral Rx for 4-8 weeks followed by oral treatment with 2 drugs for 6-12 months | Further surgical debridement – the mainstay of therapy, given poor response to antimicrobials even when in vitro testing reports susceptibility |

Notes:  
*Clarithromycin should not be the first line choice because of inducible macrolide resistance.*  
*Treatment to be initiated by a specialist (e.g. Infectious Diseases) experienced in NTM treatment and co-managed by the TB/NTM unit.*
### Table 11: Treatment of disseminated NTM infection in HIV-infected patients

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Adjuvant therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M. avium complex</strong>&lt;br&gt; M. avium&lt;br&gt; M. intracellulare</td>
<td><em>Disseminated disease</em>&lt;br&gt;</td>
<td>Clarithromycin 500 mg orally, 12-hourly (preferred macrolide)&lt;br&gt; OR&lt;br&gt; Azithromycin 600 mg orally, daily&lt;br&gt; PLUS&lt;br&gt; Ethambutol 15 mg/kg orally, daily&lt;br&gt; Rifabutin 300 mg orally, daily</td>
<td>12 months&lt;br&gt; The appropriate duration of MAC therapy and the duration of immune reconstitution before stopping treatment have not been determined.&lt;br&gt; However, at least 12 months of therapy and six months of immune reconstitution may be reasonable parameters.</td>
<td>1) Additional medications (e.g., amikacin or streptomycin) should be considered in the patient with advanced immunosuppression (e.g., CD4 cell count ≤50 cells/mm³), high mycobacterial loads (&gt;2 log(20) colony forming units/mL of blood) or in the absence of effective ART. 2) HAART Wait until 2 weeks of NTM treatment completed prior to introduction in ART naive patients.</td>
</tr>
<tr>
<td><strong>M. avium complex</strong>&lt;br&gt; M. avium&lt;br&gt; M. intracellulare</td>
<td><em>Primary Prophylaxis</em></td>
<td>Commence when CD4 cell count less than 50/microlitre:&lt;br&gt; Azithromycin 1.2 g orally, weekly&lt;br&gt; OR&lt;br&gt; Clarithromycin 500 mg orally, 12-hourly</td>
<td>3 months after CD4 count increases to &gt;100/microlitre</td>
<td>ART Wait until 2 weeks of NTM prophylaxis completed prior to introduction in ART naive patients.</td>
</tr>
<tr>
<td><strong>Other NTM</strong>&lt;br&gt; M. kansasii&lt;br&gt; M. xenopi&lt;br&gt; M. haemophilum&lt;br&gt; RGM&lt;br&gt; M. genavense&lt;br&gt; M. szulagi&lt;br&gt; M. simiae&lt;br&gt; M. malmoense</td>
<td><em>Disseminated and focal disease</em></td>
<td>Liaise with infectious diseases specialist experienced in managing NTM disease in HIV-infected patients.</td>
<td>ART Wait until 2 weeks of NTM treatment completed prior to introduction in ART naive patients.</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Treatment to be initiated by a specialist (e.g. Infectious Diseases) experienced in NTM/HIV treatment, co-managed by the TB/NTM unit.
Public health response

The public health response to NTM infections is limited because of their absence of person to person transmission. An exception to this are clusters of nosocomial infections associated with RGM. Recommendations have been published regarding prevention of nosocomial NTM disease (Table 12).

Table 12: Prevention of nosocomial NTM disease

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients with intravenous or peritoneal catheters should avoid catheter contamination with tap water</td>
</tr>
<tr>
<td>2</td>
<td>Fibre-optic endoscopes should not be washed using tap water</td>
</tr>
<tr>
<td>3</td>
<td>Avoid multi-dose vials and benzalkonium skin preparation</td>
</tr>
<tr>
<td>4</td>
<td>Avoid the injection of unknown/unapproved alternative medicines</td>
</tr>
<tr>
<td>5</td>
<td>Surgery: avoid the use of tap water or ice prepared from tap water</td>
</tr>
<tr>
<td>6</td>
<td>Sputum collection: Don’t allow a mouth rinse with tap water prior to specimen collection</td>
</tr>
<tr>
<td>7</td>
<td>Recognise the potential for nosocomial outbreaks and intervene promptly to prevent transmission</td>
</tr>
</tbody>
</table>

Knowledge is limited regarding NTM disease epidemiology, and pathogenesis. A key recommendation arising from the ATS review was the need to collect prospective surveillance data on NTM diseases. To this end, NTM disease has been a notifiable condition in the NT since 1999. In addition, commencing in 2013, enhanced data on NTM disease will be collected routinely.

NTM notifications and data collection process

When NTM disease is suspected a CDC Notification form should be completed (Appendix 5, p35) The NT CDC commenced routine collection of enhanced data on confirmed cases of NTM disease in the NT in January 2013 (Appendix 6, p36). The enhanced data covers risk factors for NTM disease, disease presentations, treatment and patient outcomes. Data collection and entry will be coordinated by the TB medical officer employed in CDC Darwin.

Figure 2. NTM disease notification and data management process

Notes: NTM = Nontuberculous mycobacteria, CDC = Centre for Disease Control, TB = Mycobacterium tuberculosis, NTNDS = Northern Territory Notifiable Diseases System.
### Table 13. Drug side effects and interactions\(^{47,48}\)

<table>
<thead>
<tr>
<th>Drug side effects</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clarithromycin</strong>: Pregnancy (B3) Lactation (safe)</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong>: - known hypersensitivity or adverse reaction to macrolide antibiotic drugs - concurrent use of pimozide, ergotamine or dihydroergotamine</td>
<td><strong>Precautions</strong>: - renal failure, reduce dose if CrCl &lt;30 mL/minute, concurrent colchicine use</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Altered taste (3-9%)</td>
<td>Prolonged QT interval</td>
</tr>
<tr>
<td>Nausea or vomiting (3-6%)</td>
<td>Hepatitis, liver failure</td>
</tr>
<tr>
<td>Diarrhoea (3-6%)</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Abdominal pain (2%)</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Headache (2-9%)</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td><strong>Increases levels of</strong>:</td>
<td><strong>Theophylline</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Anticonvulsants</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Benzodiazepines</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dipyridamole</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Digoxin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tacrolimus</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cyclosporin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rifabutin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cilostazol</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Methylprednisolone</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Quinidine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Colchicine</strong></td>
</tr>
<tr>
<td><strong>Sildenafil</strong></td>
<td><strong>Decreases levels of</strong>:</td>
</tr>
<tr>
<td></td>
<td><strong>Zidovudine</strong></td>
</tr>
<tr>
<td><strong>Clarithromycin levels increased by</strong>:</td>
<td><strong>Fluconazole</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluoxetine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Ritonavir</strong></td>
</tr>
<tr>
<td><strong>Rhabdomyolysis</strong> reported when taken with statins</td>
<td></td>
</tr>
<tr>
<td><strong>Azithromycin</strong>: Pregnancy (B1) Lactation (safe)</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong>: - known hypersensitivity or adverse reaction to macrolide antibiotic drugs - concurrent use of pimozide, ergotamine or dihydroergotamine</td>
<td><strong>Precautions</strong>: - hepatic failure, consider dose reduction</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Nausea or vomiting (~13%)</td>
<td>Prolonged QT interval</td>
</tr>
<tr>
<td>Diarrhoea (4-12%)</td>
<td>Hepatitis, liver failure</td>
</tr>
<tr>
<td>Abdominal pain (2-14%)</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Headache (5%)</td>
<td>Eaton-Lambert syndrome</td>
</tr>
<tr>
<td>Abnormal LFTs (1-6%)</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Vision change (5%)</td>
<td>Corneal erosion</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td><strong>Azithromycin levels increased by</strong>:</td>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Digoxin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cyclosporin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Terfenidine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Astemizole</strong></td>
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<tr>
<td></td>
<td><strong>Phenytoin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Colchicine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Decreases levels of</strong>:</td>
</tr>
<tr>
<td></td>
<td><strong>Antacids</strong></td>
</tr>
<tr>
<td><strong>QT interval prolongation</strong>:</td>
<td><strong>Fluoroquinolones</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Antipsychotics</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Opiate analgesics</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluconazole</strong></td>
</tr>
<tr>
<td><strong>Rifampicin</strong>: Pregnancy (C) Lactation (safe)</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong>: - concurrent treatment with saquinavir and ritonavir - hepatic failure, jaundice</td>
<td><strong>Precautions</strong>: - hepatic impairment, porphyria</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Pink/orange urine</td>
<td>Blood dyscrasias</td>
</tr>
<tr>
<td>Sweat</td>
<td>Hepatitis, liver failure</td>
</tr>
<tr>
<td>Tears</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>Flu like syndrome</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Purpura</td>
</tr>
<tr>
<td>Headache, dizziness</td>
<td>Psychosis</td>
</tr>
<tr>
<td><strong>Reduces activity of</strong>:</td>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Anticonvulsants</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Antiarhythmics</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Antifungals</strong></td>
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<tr>
<td></td>
<td><strong>Barbiturates</strong></td>
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<tr>
<td></td>
<td><strong>Beta-blockers</strong></td>
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<td></td>
<td><strong>Ca channel blockers</strong></td>
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<tr>
<td></td>
<td><strong>Chloramphenicol</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Corticosteroids</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Sulphonyleureas</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Opiate analogues</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Macrolide antibiotics</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Ondansetron</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Quinine</strong></td>
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<tr>
<td></td>
<td><strong>Tacrolimus</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cyclosporin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Digoxin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Clotbrate</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Theophylline</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Oral contraceptives</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Tricyclic antidepressants</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Zidovudine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Dapsone</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Benzodiazepines</strong></td>
</tr>
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<td></td>
<td><strong>Doxycline</strong></td>
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<tr>
<td></td>
<td><strong>Fluoroquinolones</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Levoloxazine</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PAS decreases rifampicin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Atovaquone increases rifampicin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Halothane may cause hepatotoxicity</strong></td>
</tr>
<tr>
<td><strong>Ethambutol</strong>: Pregnancy (A) Lactation (safe)</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications</strong>: - optic neuritis, established retinopathy, established cataracts</td>
<td><strong>Precautions</strong>: - gout, renal impairment - reduce dose if CrCl ≤25 mL/minute or consider an alternative drug</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Serious</strong></td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>Blood dyscrasias</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Rash</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Optic neuritis (1-6%)</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Headache, confusion</td>
<td>Mania</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td><strong>Ethambutol levels decreased by</strong>:</td>
</tr>
<tr>
<td></td>
<td><strong>Aluminium containing antacids</strong></td>
</tr>
</tbody>
</table>

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Centre for Disease Control  
Department of Health is a Smoke Free Workplace


Non-healing ulcers

Including those caused by nontuberculous mycobacteria (NTM)

Many different medical conditions can cause non-healing ulcers. The conditions range from vascular disease and diabetes to foreign bodies, autoimmune diseases, cancer and infections. In the Northern Territory, some non-healing ulcers may result from diseases usually not experienced in the temperate southern zones. Awareness is required to consider and accurately diagnose the cause of the ulcers and provide appropriate treatment. Seeking early medical attention with an ulcer that is not healing is important, particularly for consideration of underlying causes and to take appropriate diagnostic samples or swabs. In addition, ulcers seen at an early stage, in general, can be treated much more easily than larger ulcers.

What diseases cause non-healing ulcers?

Diseases that commonly cause non-healing ulcers are vascular disease, diabetes, skin cancers and some infections. In the tropical climate of the Northern Territory, melioidosis and nontuberculous mycobacterial (NTM) skin infections can also cause non-healing ulcers, as well as leprosy.

Vascular Disease

The majority of chronic leg ulcers are from venous insufficiency, arterial insufficiency or a combination of both. Older people, particularly if they are, or have been smokers, may have disease of their arteries that reduces the flow of blood particularly to their lower legs and feet. These people often experience cold feet, and sometimes pain in their legs on walking. People with vascular disease with minor abrasions of their lower limbs can develop non-healing ulcers. Their impaired blood supply to the affected area reduces the body's ability to provide the healing response that normally follows an injury.

Diabetes

Non-healing ulcers commonly occur in people who have diabetes, particularly if their diabetes is poorly controlled and they smoke. Poorly controlled diabetes may result in vascular disease of the arteries that reduces the body’s ability to provide the healing response that normally follows an injury. The microvascular disease can result in the loss of sensation particularly to the lower limbs and feet, which results in people being less aware of any cuts or burns to their feet. Diabetes reduces the body’s overall ability to heal injuries and to prevent and combat infection. People with poorly controlled diabetes therefore are more prone to injuring their lower limbs, and developing non-healing ulcers.

Skin Cancers

Skin cancers can also present as a non-healing lesion or ulcer and early medical attention in this setting is particularly important. Skin cancers seen and treated at an early stage, normally result in a cure. A delay in seeking treatment may result in the need for more extensive surgery, and the possibility of invasive disease.

Melioidosis

In tropical areas, the bacterial infection melioidosis, in addition to causing potentially fatal pneumonia and sepsicaemia, can also result in non-healing skin abscesses and ulcers. These occur mainly by direct inoculation from the environment. Early medical attention and specific antibiotic treatment is important to the management of this condition.

Nontuberculous mycobacteria (NTM)

This group of organisms cause uncommon mycobacterial diseases seen both in temperate and tropical zones. In addition to pulmonary disease, NTM can cause lymphadenitis (swollen glands), wound infections and non-healing skin ulcers.

Exactly how the mycobacterial infections occur has not been well established, but the organisms are found throughout our environment (including in soil and water). NTM soft-tissue disease is thought to occur when organisms breach the skin barrier through a minor cut or abrasion or

through a procedure (e.g. surgery, injection etc.). There is no evidence of person-to-
person transmission of these infections. Outbreaks have occurred and have on
occasion been linked to contaminated surgical equipment and spas. Some cases cluster in
regional geographic areas.

**Clinical presentation of NTM skin ulcers**

NTM skin ulcers typically present with an
initial lesion similar to a mosquito bite. This
then develops into a non-healing skin lesion
or ulcer. In the Northern Territory these
lesions to date have mainly been in healthy
children residing in the Darwin – Palmerston
residential areas. In each case there has
been no apparent history of injury, and the
lesions have typically been on the upper limbs
or torso. Organisms responsible have included
*Mycobacterium fortuitum* and *M. ulcerans* (*
*M. ulcerans* lesions are also known as Buruli
or Bairnsdale ulcers).

**Management of NTM skin ulcers**

NTM skin ulcers are uncommon and do not
heal with the use of standard antibiotics. The
identification of an NTM ulcer is confirmed
through the presence of acid-fast bacilli on
microscopy and culture and/or PCR from a
wound swab or biopsy.

Treatment of NTM varies depending on the
species of NTM causing the infection, the site
and severity of the disease and consideration
of which antibiotics will work effectively
to combat the infection. Surgery is often
necessary. Treatment of NTM disease is not
straightforward therefore, the management of
NTM skin ulcers is usually undertaken through
the Centre for Disease Control, Darwin
normally in conjunction with a surgical and/or
infectious diseases specialist.

**Leprosy**

Leprosy is a chronic mycobacterial disease
of the skin and peripheral nerves. Leprosy
is now uncommon in the Northern Territory,
however occasional new cases still occur.

Most cases of leprosy are in people born
overseas. The involvement of the peripheral
nerves can lead to loss of sensation
particularly affecting the hands and lower
limbs. As in diabetes, the loss of sensation
results in people not being aware of any
cuts or burns that they may sustain. For this
reason people with leprosy are more prone
to developing hand and lower limb injuries,
which may develop into non-healing ulcers.
Leprosy always needs to be considered in the
presentation of a non-healing ulcer, especially
in the Indigenous population or those from
countries where leprosy is noted by the World
Health Organization to still occur at higher
levels. These areas include Angola, Brazil, the
Central African Republic, India, Madagascar,
Nepal and the United Republic of Tanzania
and in previously highly endemic countries,
such as the Democratic Republic of the Congo
and Mozambique. In our Region leprosy is
still present and cases have been identified in
recent years from e.g. the Philippines and East
Timor.

**Other infections**

Non-healing ulcers can also be
caused by other infections, including
necardia and actinomycosis infections,
chromoblastomycosis (deep skin infections
from various fungi), and from resistant
organisms such as methicillin resistant
Staphylococcus aureus. Non-healing ulcers
may also represent an underlying chronic
infection such as osteomyelitis or the presence
of a foreign body.

**For more Information contact the TB
Clinic in your region**

Alice Springs: 8951 7848
Darwin: 8922 8804
Katherine: 8973 3049
Nhulunbuy: 8997 0282
Tennant Creek: 8912 4259


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Non-healing ulcers
Appendix 2: NTM disease case definition

**Nontuberculous mycobacterial disease**

<table>
<thead>
<tr>
<th>Case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reporting</strong></td>
</tr>
<tr>
<td>Confirmed cases and probable cases should be notified.</td>
</tr>
<tr>
<td><strong>Confirmed case</strong></td>
</tr>
<tr>
<td>A confirmed case requires:</td>
</tr>
<tr>
<td>1. Laboratory definitive evidence</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2. Laboratory suggestive evidence AND clinical evidence.</td>
</tr>
<tr>
<td><strong>Probable case</strong></td>
</tr>
<tr>
<td>A probable case requires suggestive histological evidence AND clinical evidence.</td>
</tr>
<tr>
<td><strong>Laboratory definitive evidence</strong></td>
</tr>
<tr>
<td>Nontuberculous mycobacterium detected from an otherwise sterile site (e.g. CSF, blood culture, lymph node, lung biopsy) by culture or nucleic acid testing.</td>
</tr>
<tr>
<td><strong>Laboratory suggestive evidence</strong></td>
</tr>
<tr>
<td>1. Positive cultures from at least two sputum specimens OR</td>
</tr>
<tr>
<td>2. Positive culture results from at least one bronchial wash or lavage OR</td>
</tr>
<tr>
<td>3. Detection by culture or nucleic acid testing of nontuberculous mycobacterium from a non-healing skin lesion.</td>
</tr>
<tr>
<td><strong>Clinical evidence</strong></td>
</tr>
<tr>
<td>1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. OR</td>
</tr>
<tr>
<td>2. Non-healing skin lesion or soft tissue infection AND</td>
</tr>
<tr>
<td>3. Exclusion of other causes for the disease process (e.g. fungal, TB, melioidosis, malignancy etc.).</td>
</tr>
<tr>
<td><strong>Suggestive histological evidence</strong></td>
</tr>
<tr>
<td>Detection of acid-fast bacilli and granulomatous change on histopathology of a skin lesion (including nodule or subcutaneous abscess).</td>
</tr>
</tbody>
</table>

**Public Health Action**

**Summary:**
- No public health action required for sporadic cases.
- Be alert for clusters of cases.

**Source:**
- Guidelines for the control of nontuberculosis mycobacteria in the Northern Territory.

**Timeframe:**
- Not applicable.

**Precautions:**
- Make sure TB has been ruled out.
- Clusters of cases of skin lesions may

**Surveillance**
- Each case should be discussed with the Head of the TB Unit - ☎️ 28804.
- NTM notification form is available on Sharepoint and contains core and enhanced data.
- Enhanced data and forms kept and maintained by the TB medical officer.

**Data collection and entry**

<table>
<thead>
<tr>
<th>Data entry</th>
<th>All notifications entered in Darwin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism name</td>
<td>Must be completed.</td>
</tr>
<tr>
<td>Enhanced data</td>
<td>Managed by TB medical officer.</td>
</tr>
</tbody>
</table>

**Further information**
- NT CDC fact sheet: [Non-healing ulcers](#)
### Appendix 3: Nontuberculous Mycobacteria (NTM) treatment card

**Non Tuberculous (Atypical) Mycobacterium Treatment Card**  
NT Department of Health  

<table>
<thead>
<tr>
<th>Family Name:</th>
<th>HRN:</th>
<th>Given Name:</th>
<th>Sex: M / F</th>
<th>DOB:</th>
<th>Phone:</th>
</tr>
</thead>
</table>

**Organism Name:**  
**Site of specimen:**

**Dates of specimen/s:**  
**Pre Treatment:** (LFTs & FBC)  
**Date:** …/…/…

**CXR result:** …………..

**Date:** …/…/…

**LFT's:**  
- Bilirubin: Ap...  
- ALT: Ast...  
- AST: GGT...  
- Proteins: Alb...  
- Normal: Abnormal:

**Other (if applicable):**  
- HBV...  
- HCV...  
- HIV...  
- FBC...  
- WB...  
- WCC...  
- Pts...

**Drug:**  
- Dose: Daily  
- Date commenced:

**Drug:**  
- Dose: Daily  
- Expected date completion:

**Drug:**  
- Dose: Daily  
- Actual date stopped/finished:

**Drug:**  
- Dose: Daily  

(Attach further list if needed)

### MONTHLY CHECK LIST

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight</th>
<th>Dose Correct Y/N</th>
<th>Visual S&amp;S</th>
<th>Liver S&amp;S</th>
<th>Rash</th>
<th>Fever</th>
<th>CXR Y/N</th>
<th>Rx Given Y/N</th>
<th>LFTs taken Y/N</th>
<th>No. doses missed</th>
<th>Next appt</th>
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### TREATMENT COMPLETION

**Adherence:** …/…/… % in …..months

**TREATMENT CEASED:**
- If patient stopped early please complete
  - abnormal LFTs
  - rash
  - nausea
  - visual S&S
  - jaundice
- Client died
- Fever
- Default
- Developed TB
- Other...

**End of Rx CXR date and result:** …………………..

**Signature:** …………………..  
**Designation:** …………………..  

### COMMON SIDE EFFECTS:
- **Clarithromycin:** Nausea or vomiting (3-6%), Diarrhoea (3-6%), Abdominal pain (2%), Headache (2-9%), Fever, Rash
- **Ethambutol:** Hypersensitivity, Nausea or vomiting, Rash, Optic neuritis (1-6%), Headache, Confusion
- **Rifampicin:** Pink or orange urine, sweat & tears, Nausea or vomiting, abnormal LFTs, Fatigue, Headache, Dizziness
- **Azithromycin:** Nausea or vomiting (~13%), Diarrhoea (4-12%), Abdominal pain (2-14%), Fatigue (5%), Headache (5%), Abnormal LFTs (1-6%), Vision change (5%), Hearing impairment

April 2013

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Department of Health is a Smoke Free Workplace

**Non Tuberculous (Atypical) Mycobacterium Treatment Card**
**NT Department of Health**

**MONTHLY CHECK LIST**

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight</th>
<th>Dose Correct</th>
<th>Visual S&amp;S</th>
<th>Liver S&amp;S</th>
<th>Rash</th>
<th>Fever</th>
<th>CXR Y / N</th>
<th>Rx Given Y / N (mhs)</th>
<th>LFTs taken Y / N</th>
<th>No. doses missed</th>
<th>Next appt</th>
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</table>

**Comments**

---

**COMMON SIDE EFFECTS:**

**CLARITHROMYCIN:** Nausea or vomiting (3-6%), Diarrhoea (3-6%), Abdominal pain (2%), Headache (2-9%), Fever, Rash

**ETHAMBUTOL:** Hyperuricaemia, Nausea or vomiting, Rash, Optic neuritis (1-8%), Headache, Confusion

**RIFAMPICIN:** Pink/orange urine, sweat & tears, Nausea or vomiting, abnormal LFTs, Fatigue, Headache, dizziness

**AZITHROMYCIN:** Nausea or vomiting (~13%), Diarrhoea (4-12%), Abdominal pain (2-14%), Flatulence (5%), Headache (5%), Abnormal LFTs (1-8%), Vision change (5%), Hearing impairment
Appendix 4: Monitoring for patients receiving amikacin treatment

Amikacin
Amikacin is an aminoglycoside bactericidal antibiotic used to treat mycobacteria. It acts against rapidly dividing mycobacteria but has little to no action against bacilli which are not replicating. It has poor oral absorption and must be given parenterally.

Side effects: Ototoxicity
Approximately 2–4% of patients receiving aminoglycosides develop vestibular or cochlear ototoxicity. The most common presenting symptoms include nausea, vomiting, vertigo, unsteadiness of gait, hearing loss, tinnitus or a sensation of fullness in the ear. This side effect is irreversible in 50% of cases, particularly if not detected early and permanent deafness may occur.

Monitoring:
Aminoglycosides should always be commenced in an inpatient setting. For more information please see the Royal Darwin Hospital aminoglycoside policy (available via the Department of Health intranet: PROMPT). While in hospital the following baseline investigations should be performed and documented:

- Formal audiometry testing
- Baseline blood tests (UEC, LFT, FBE, CMP)
- Trough amikacin levels
- Visual acuity
- Vestibular function testing – ‘Burrow test’ (see below)

Once a patient is to be discharged to the ‘Hospital in the home’ unit, the following monitoring is advised and must be documented:

- Weekly clinical review and questioning about hearing or balance problems
- Weekly vestibular function testing (known at RDH as the Burrow test)
- Weekly UEC, LFT, FBE, CMP plasma trough amikacin. If stable after 1 month continue every 2 weeks
- Monthly audiometry testing

Burrow test
This is a simple test that assists in early diagnosis of vestibular toxicity.

For assistance in learning how to perform the test it may be useful to ask an Infectious Diseases or CDC Registrar to demonstrate. With the patient seated and with the head kept still at 6 metres from the Snellen chart determine their best visual acuity with both eyes open (no need to test eyes individually). Then do the same with examiner standing behind the patient and rotating the patient’s head side to side at a rate of approximately one cycle per second. A normal person will lose less than or equal to 2 rows on the Snellen chart. Anything greater than this indicates an abnormality of the vestibulocular reflex (i.e. in the case of amikacin - bilateral vestibular injury). Record both baseline and during rotation results to compare with prior and future tests.
Appendix 5: CDC Notification form*

Reporting of notifiable diseases by doctors

Centre for Disease Control


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Centre for Disease Control

Department of Health is a Smoke Free Workplace
Appendix 6: Nontuberculous Mycobacteria (NTM) Notification Form

**CORE DATA**

Surname: __________________________  HRN: _____________  DOB: / /  
Age: ______
First Name: ________________________  Other Names: ________________________  Sex: M / F  
Indigenous Status (circle)  
Aboriginal but not TSI  TSI but not A  A+TSI  Not A or TSI  Not Stated  
Address when diagnosed: ___________________________________________________  
Suburb/Community (resident location): ______________________________  Postcode: _______  
CDC Unit Notifying (circle): A/SP  DARWIN  East Arnhem  KATH  Barkly  
Notification received date (date when CDC Unit first informed): / /  
Notification date (date when Dr made the diagnosis): / /  
True onset date (date NTM symptoms began or signs noted): / /  
Case found by (circle): Clinical presentation  Contact tracing  Screening  Unknown  
Hospitalised: Yes / No / Unknown  Date admitted: / /  Date discharged: / /  
Died from NTM: Yes / No / Unknown  Date of death: / /  
Imported case: Yes / No / Unknown  
Place infected (if imported): ________________  

**LABORATORY DATA**

Micro specimen type*: Sputum, Induced Sputum, Bronchial lavage, Brian/CSF, Node, Node Aspirate, Urine, Blood, Gastric Aspirate, Pleura, Pleural Fluid, Pericardial Fluid, Peritoneal Fluid, Skin, Subcutaneous tissue, Surgical implant, venous catheter, Other: __________________________  

<table>
<thead>
<tr>
<th>Specimen type* &amp; date</th>
<th>Microscopy</th>
<th>Culture</th>
<th>PCR</th>
<th>Organism (e.g.: M. ulcerans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>/ /</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
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<tr>
<td>2</td>
<td>/ /</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
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<td>Neg / Pos / ND</td>
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<td>6</td>
<td>/ /</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
<td>Neg / Pos / ND</td>
</tr>
</tbody>
</table>

**ENHANCED DATA**

Transfer in: Yes / No / Unknown  From where: ________________________________  
Date of first health contact: / /  
Country of birth: ________________  Year of first arrival: ____________
### Case classification:
- New case  
- Relapse after partial Rx  
- Relapse after full Rx  
- Unknown

### HIV status (circle):
- Positive  
- Negative  
- Tested-unknown result  
- Not tested  
- Refused  
- Unknown

### BCG vaccination (circle):
- vaccinated  
- unvaccinated  
- unknown

### Disease site at presentation (circle all that apply):
- Pulmonary  
- Lymph node  
- Skin ulcer  
- Soft tissue  
- Surgical site/iatrogenic  
- Disseminated  
- Bone/Joint  
- Unknown/unstated  
- Other:

### Patient risk factors (circle all that apply):
- Excessive alcohol  
- Current smoker  
- Ex-smoker  
- COPD  
- Bronchiectasis  
- Cystic Fibrosis  
- Asthma  
- Other lung disease  
- Cancer (within 5Y)  
- Diabetes  
- Kava user  
- Leprosy  
- Malnourished  
- Old TB  
- Concurrent TB  
- Renal failure  
- Previous NTM disease  
- Current steroid Rx  
- Other immune suppression  
- Connective tissue disease  
- No risk factor identified  
- Unknown/unstated  
- Other:

### Patient exposures (circle all that apply):
- Penetrating injury  
- Insect bites  
- Fresh (unchlorinated) water injury  
- Marine (salt water) injury  
- Spa pools with jets  
- Wound contact with soil  
- Surgical procedure  
- Venous catheterisation  
- No exposures identified  
- Unknown/unstated  
- Other:

### Symptoms at presentation (circle all that apply):
- Cough  
- Sputum production  
- Haemoptysis  
- Fevers/night sweats  
- Dyspnoea  
- Weight loss  
- Lymphadenopathy  
- Soft tissue infection  
- Skin ulcer  
- Unknown/unstated  
- Other:

### Pulmonary radiological findings – pulmonary NTM cases only (circle all that apply):
- Unilateral disease only  
- Bilateral disease  
- Cavitation  
- Abscess  
- Nodules  
- Tree-in-bud changes  
- Bronchiectasis  
- Fibrosis  
- Other:

### Surgical Treatment? (circle):
- Yes / No / Unknown  
- Date of surgery (if yes): / /  

### Medical Treatment  
- Yes / No  
- Treatment start date / /  
- Treatment stop date / /  

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Drug reaction</th>
<th>Drug Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
</tr>
<tr>
<td>Azithromycin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
</tr>
<tr>
<td>Rifampicin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
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<tr>
<td>Ethambutol Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
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<tr>
<td>Ciprofloxacin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
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<tr>
<td>Amikacin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
</tr>
<tr>
<td>Cefoxitin Yes / No</td>
<td>Yes / No / unknown</td>
<td>Yes / No / NA (neg or no culture)</td>
</tr>
</tbody>
</table>
Moxifloxacin: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Rifabutin: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Isoniazid: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Doxycycline: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Bactrim: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Linezolid: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Imipenum: Yes / No Yes / No / unknown Yes / No / NA (neg or no culture)
Other: Yes / No / unknown Yes / No / NA (neg or no culture)
No treatment: Yes / No

First Name: ___________________ Surname: __________________________ HRN:_____________

Outcome - What was the outcome of the NTM Case? (tick only one box)

☐ Cured (bacteriologically confirmed — smear and culture negative)
☐ Completed Treatment (completed at least 80% of doses)
☐ Interrupted treatment (interrupted for 2 months or more but completed treatment)
☐ Died of NTM disease (please ensure this is the same as core data)
☐ Died of other cause (state cause): ________________________________
☐ Defaulter (failed to complete treatment)
☐ Failure (completed treatment but failed to be cured)
☐ Transfer out to an interstate unit Where:______ Date: __/__/__
☐ Transfer out to an overseas unit Where:______________ Date: __/__/__
☐ Outcome pending (still on treatment)

Notifier’s name: ___________________

Entered NTNDS: __/__/__ Name: __________________________ Signature: ____________