Skin and soft tissue infections due to non-tuberculous mycobacteria

The non-tuberculous mycobacteria (NTM) are composed of species other than Mycobacterium tuberculosis complex (M. tuberculosis, M. bovis including BCG, M. microti, M. africanum) and M. leprae. NTM are a diverse and growing group of more than 100 species that occupy a wide variety of environmental niches throughout the world, being particularly common in soil and water. For several species, survival in biofilms facilitates their presence in water distribution systems1, 2.

Whilst M. tuberculosis is always considered pathogenic to humans, NTM are usually incidental pathogens when inhalation or accidental or medical inoculation into skin or soft tissues results in infection. In addition to surviving well at a broad range of ambient temperatures, many NTM are resistant to the effects of common disinfectants3.

Skin and soft tissue infections caused by NTM can be associated with community acquired inoculation, e.g. garden fork injury, or may be hospital acquired. Usually such infections are confined to the site of entry but, in subjects with compromised immunity, disseminated infection may result.

While detailed characterisation of the NTM is best achieved in a mycobacterium reference laboratory (MRL), many of the clinically significant organisms are of the ‘rapid grower’ group and will grow readily in a routine microbiology laboratory, provided that sufficient time (5-7 days) and optimal temperatures are employed (see paper by Chris Gilpin in this edition of Microbiology Australia).

It is the rapidly growing mycobacteria (RGM) that are most commonly encountered as causes of skin and soft tissue infections4. Most organisms so encountered will be non-pigmented and belong to either the Mycobacterium fortuitum complex (includes M. fortuitum, M. fortuitum third biovariant, M. peregrinum, M. mucogenicum) or the Mycobacterium chelonae/abscessus group, representing two distinct but closely related species, M. chelonae and M. abscessus. Reduced temperature incubation (30˚C) will facilitate the isolation of the rapid growers but in particular, slower growing species such as M. marinum and M. haemophilum. A large general laboratory could expect almost two thirds of rapid growers to be detected at the pus bench rather than by specific mycobacterial cultures, as is our experience.

Organisms considered slow growing e.g. M. avium intracellulare may also be important causes of skin and soft tissue infection but are not likely to be encountered in a routine laboratory.

Community acquired infection

NTM produce a number of different community acquired disease syndromes including pulmonary disease, lymphadenitis, skin and soft tissue infections, and infections of tendons, joints and bones. Hospital acquired infection is considered below. Whilst pulmonary sites constitute 85% of the NTM isolated, skin and related site infection make up approximately 10-15%.

This article will focus on the non-pulmonary and non-lymphadenitis presentations, although the full spectrum of disease is included in Table 1 for completeness. Table 2 demonstrates non-pulmonary isolates identified by the Queensland MRL in 2003.

Clues to look for in RGM infection include the following clinical scenarios: injuries where there is soil or water contamination: major trauma, garden tools, barbed wire, penetrating nail injuries, insect or animal bites; bullet wounds, needle and injection sites; persistent skin lesions present for more than 2 months despite antibiotic therapy; and lesions in immunosuppressed patients. Clinically, infections are indolent with slow onset; there is often little local redness and swelling. Serosanguineous discharge is common, although frank pus may be present. Systemic symptoms are absent and dissemination is rare. M. ulcerans and M. haemophilum are classic skin and soft tissue pathogens but will be discussed separately in this issue.

M. marinum may be cultured on chocolate agar but prefers lower incubation temperatures (30˚C) and more prolonged culture (10-14 days). M. marinum infection is also known as ‘swimming pool’ or ‘fish tank’ granuloma. Most patients are clinically healthy and present 2-3 weeks after a local hand injury that becomes infected after exposures such as cleaning a fish tank, or sustaining scratches or puncture wounds from saltwater fish, shrimp, fins, or other environmental exposures contaminated with M. marinum.

In Focus

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References


In one Queensland series, the most frequent manifestation was skin and soft tissue infections in 52% of patients, followed by tenosynovitis and arthritis in 40 and 8% respectively.

Lesions are most often small violet papules on the hands and arms that may progress to shallow crusty ulcerations and scar formation. Lesions are usually singular. However, multiple ascending lesions can occasionally occur, so called ‘sporotrichoid’ spread. Diagnosis is often delayed. Rapid growers as well as the slowly growing species (M. avium complex, M. kansasii, and M. terrae complex, especially M. nonchromogenicum) and M. marinum have been implicated in chronic granulomatous infections involving tendon sheaths, bursae, bones and joints. These usually follow accidental trauma, surgical incisions, puncture wounds or injections. Most patients have no underlying immune suppression.

### Disseminated infection

Disseminated infection by RGM with involvement of skin and other organs is rare but well documented. In most, but not all cases, the patient is immuno-compromised, with corticosteroid use a common feature. Interestingly, HIV/AIDS is not a common predisposing condition. Patients may appear relatively well despite multiple cutaneous lesions and subcutaneous sinuses, or may be acutely unwell with associated bacteraemic illness. Most cases involve M. abscessus or M. chelonae.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Relatively common cause</th>
<th>Less frequent causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pulmonary disease</td>
<td>M. avium complex (M. intracellulare, M. avium), M. kansasii, M. abscessus</td>
<td>M. xenopi, M. malmoense, M. szulgai, M. smegmatis M. scrofulaceum, M. celatum, M. simiae</td>
</tr>
<tr>
<td>Cervical or other local lymphadenitis (esp. children)</td>
<td>M. avium complex</td>
<td>M. scrofulaceum, M. malmoense (northern Europe), M. abscessus, M. fortuitum</td>
</tr>
<tr>
<td>Skin and soft tissue disease</td>
<td>M. fortuitum, M. chelonae, M. abscessus, M. marinum</td>
<td>M. kansasii, M. haemophilum, M. smegmatis, M. ulcerans (Australia, other tropical countries)</td>
</tr>
<tr>
<td>Skeletal (bursae, bone, joint, tendon) infection</td>
<td>M. marinum, M. avium complex, M. kansasii, M. fortuitum group, M. abscessus, M. chelonae</td>
<td>M. haemophilum, M. scrofulaceum, M. haemophilum, M. terrae / nonchromogenicum complex</td>
</tr>
</tbody>
</table>

### Syndrome Relatively common cause Less frequent causes

**Chronic pulmonary disease**  
M. avium complex (M. intracellulare, M. avium), M. kansasii, M. abscessus  
M. xenopi, M. malmoense, M. szulgai, M. smegmatis M. scrofulaceum, M. celatum, M. simiae

**Cervical or other local lymphadenitis**  
M. avium complex  
M. scrofulaceum, M. malmoense (northern Europe), M. abscessus, M. fortuitum

**Skin and soft tissue disease**  
M. fortuitum, M. chelonae, M. abscessus, M. marinum  
M. kansasii, M. haemophilum, M. smegmatis, M. ulcerans (Australia, other tropical countries)

**Skeletal (bursae, bone, joint, tendon) infection**  
M. marinum, M. avium complex, M. kansasii, M. fortuitum group, M. abscessus, M. chelonae  
M. haemophilum, M. scrofulaceum, M. haemophilum, M. terrae / nonchromogenicum complex

**Disseminated infection**

**HIV - seropositive**  
M. avium, M. kansasii  
M. haemophilum, M. genavense, M. xenopi, M. marinum, M. simiae, M. intracellulare, M. scrofulaceum, M. fortuitum

**HIV - seronegative**  
M. abscessus, M. chelonae  
M. marinum, M. kansasii, M. haemophilum

**Catheter related infections**  
M. fortuitum, M. abscessus, M. chelonae  
M. mucogenicum M. haemophilum

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Table 1. Major clinical syndromes associated with NTM infections.  
Contact Cryosite for details  
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www.cryosite.com

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**In Focus**

HIV/AIDS is a significant risk factor for disseminated infection with *M. avium* complex, *M. haemophilum*, and *M. genovensae*. Skin and soft tissue manifestations are particularly features of the latter two. Other conditions of immune suppression may also predispose to such infections. Cases in apparently immunocompetent subjects have occurred. In all patients, it is likely that defects in macrophage activation occur and gamma interferon has been used where antibiotics alone proved unsuccessful.

**Treatment**

For skin and soft tissue infections, 10-20% of cases resolve spontaneously or following debridement. Until recently, the paucity of active agents meant surgery was often the only option available. Surgery remains important, but the advent of newer oral agents has greatly assisted the therapy of such infections.

NTM vary greatly in susceptibility to antimicrobial agents, although accurate speciation will enable appropriate empiric therapy in most cases. Some, such as *M. kansasii*, are susceptible to agents used principally for the treatment of tuberculosis; others, such as *M. fortuitum* and *M. chelonae*, respond to antibiotics used more commonly for pyogenic bacterial infections; and still others, especially *M. avium-intracellulare*, are broadly resistant.

Choice of appropriate therapy for non-tuberculous infections is further confounded because methodologies for susceptibility testing have yet to be standardised. However, chemotherapy

<table>
<thead>
<tr>
<th>Non-pulmonary n=121</th>
<th>Patient Cultures</th>
<th>Skin/ tissue</th>
<th>Blood/ fluids</th>
<th>Joint/ bone</th>
<th>Lymph nodes</th>
<th>Catheter</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. avium</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. avium ‘x’ var</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>M. intracellulare</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. scrofulaceum</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Slow grower Myco</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. abscessus</td>
<td>13</td>
<td>14</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>M. chelonae</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. fortuitum 3rd var</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>17</td>
<td>19</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>M. peregrinium</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. mucogenicum</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid grower Myco unspeciated</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. haemophilium</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. marinum</td>
<td>18</td>
<td>20</td>
<td>19</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. ulcerans</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. gordonae</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>121</td>
<td>80</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. NTM isolates from sites other than lung (Queensland mycobacterium reference laboratory, 2003).
for NTM infections based on susceptibility results is now feasible for many species. Table 3 summarises expected susceptibility patterns for the rapid growing mycobacteria. Agents most commonly used in therapy are indicated in bold. Routine laboratories can perform a nitrate test on rapid growers to distinguish the *fortuitum* group (positive) from the *chelonae/abscessus* group (negative) to help guide empiric therapy.

The limitations of the disc diffusion method for RGM susceptibility testing were recently discussed at the ASM Mycobacteriology Special Interest Group (SIG) in Brisbane, 2004. In general, species identification should be the major determinant guiding initial therapy. For *M. abscessus* testing intermediate or resistant to clarithromycin, an alternative method should be pursued.

Cefoxitin and amikacin are useful agents for *M. abscessus* and *M. fortuitum* infections but can only be given intravenously and for not more than 2-4 weeks in most cases. Clarithromycin, an oral macrolide, has proven to be an extremely useful agent in the treatment of many different NTM infections, although gastrointestinal side-effects can be problematic with higher doses.

Clarithromycin inhibits most NTM species (with the exception of 20% of *M. fortuitum* group and most *M. simiae*) at 4µg/ml or less. Whilst clarithromycin monotherapy may be appropriate for localised skin or soft tissue infection due to RGM, it should always be combined with other agents for the treatment of pulmonary or disseminated infection to prevent the emergence of macrolide resistance. Susceptibility testing has no clinically predictive value in infections due to *M. avium-intracellulare* except for clarithromycin.

For *M. marinum*, routine susceptibility testing is deemed unnecessary unless relapse occurs. Treatments have traditionally been a two-drug combination of rifampin plus ethambutol but monotherapy with doxycycline, minocycline, clarithromycin, or trimethoprim-sulfamethoxazole is also effective. Treatment duration is a minimum of 3 months.

### Hospital acquired infection

The RGM are the mycobacteria most likely to cause health care related infections. *M. fortuitum* accounts for

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**Case 2:** *M. abscessus* infection in an insulin dependent diabetic occurring at sites of insulin injections. Clinical photography courtesy Dr Paul Georghiou, Brisbane.

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<table>
<thead>
<tr>
<th>RGM</th>
<th>Usually susceptible</th>
<th>Variably susceptible</th>
<th>Usually resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. abscessus</em></td>
<td>Amikacin</td>
<td>Cefoxitin</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tobramycin</td>
</tr>
<tr>
<td><em>M. chelonae</em></td>
<td>Clarithromycin</td>
<td>Amikacin</td>
<td>Cefoxitin</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minocycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td><em>M. fortuitum</em> group</td>
<td>Amikacin</td>
<td>Minocycline /</td>
<td>Tobramycin sorbitol pos 3rd</td>
</tr>
<tr>
<td>(includes <em>M. peregrinum</em></td>
<td>Cefoxitin</td>
<td>Doxycycline</td>
<td>biovariant strains are resistant</td>
</tr>
<tr>
<td>and the un-named ‘3rd</td>
<td>Ciprofloxacin</td>
<td></td>
<td>to cefoxitin and clarithromycin</td>
</tr>
<tr>
<td>biovariant’)</td>
<td>Clarithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-trimoxazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Disc diffusion method may overestimate resistance for cefoxitin.*
many cases (60-80%) of mycobacterial post surgical wound infection and catheter related infections. Numerous outbreaks and sporadic cases have also been reported implicating both M. abscessus and M. chelonae in a variety of health care related infections, most notably following various plastic surgical procedures including augmentation mammoplasty (Case 1) and sternotomy infection following coronary artery bypass grafting. Contamination of injectable agents can result in abscesses at the grafting. Contamination of injectable infection following coronary artery bypass mammaplasty (Case 1) and sternotomy procedures including augmentation health care related infections, most America in 1993 affecting 350 people 8. Asbestos associated with peritonitis complicating bronchoscopes. Clinical disease due to used to disinfect endoscopes and glutaraldehyde, that is still commonly resistant to disinfectants, including bronchoscopes, automated endoscope washer/driers, and endoscopes, M. mucogenicum is commonly encountered, at least in Brisbane. Other rapid grower species have been reported elsewhere 4-10. North American investigators have found M. mucogenicum to be the most common mycobacterium isolated from tap water 2. The organism is relatively resistant to disinfectants, including glutaraldehyde, that is still commonly used to disinfect endoscopes and bronchoscopes. Clinical disease due to this organism is rare but it has been associated with peritonitis complicating peritoneal dialysis, soft tissue and wound infections and bacteraemia associated with intravascular catheter infection.

The finding of clusters of isolates of mycobacterium from medical equipment or patient specimens, but not actual patients, is considered a ‘pseudo-outbreak’. Contaminated equipment may contaminate samples collected for culture, e.g. via a bronchoscope but also pose a risk of patient inoculation, e.g. endoscopic biopsy forceps. Pseudo-outbreaks have been described with most rapid growers. Contaminated ice machines have been the focus of several reports.

Implantable devices may also be complicated by RGM infection. Recently at our institution, the removal of a pacemaker was required for infection by M. fortuitum.

Central venous vascular catheters, usually tunneled catheters such as Hickman catheters, may become infected and are the most common form of health care related RGM infection. M. fortuitum is the usual pathogen but M. chelonae, M. abscessus, M. haemophilum, M. immunogenum, M. peregrinum, M. smegmatis group, and M. mucogenicum have all been reported. While local infection may be the only manifestation, the patient is commonly immunosuppressed and the catheter itself facilitates haematogenous spread to distant sites.

Treatment of device or catheter infections requires removal of the ‘foreign body’ and a prolonged course of antibiotics (3-6 months) following the principles described above. Choice of antibiotic depends on the pathogen but clarithromycin remains a pivotal agent.

**References**