Clinical Medicine 24 (2024) 100016

Contents lists available at ScienceDirect

Clinical Medicine

journal homepage: https://www.sciencedirect.com/journal/clinical-medicine

Extrapulmonary nontuberculous mycobacterial infections: a guide for the general physician ☆

Akanksha Mimi Malhotra [a,*], Mauricio Arias [b], Matthijs Backx [c], Jessica Gadsby [d], Anna Goodman [e], Ysobel Gourlay [f], Heather Milburn [e], Olga Lucia Moncayo-Nieto [g], Deirdre Shimmin [h], Martin Dedicoat [i], Heinke Kunst [a]

[a] Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK
[b] King's College Hospital, London, UK
[c] University Hospital of Wales, Cardiff, UK
[d] University Hospitals of Leicester NHS Trust, Leicester, UK
[e] Guy's and St Thomas' NHS Foundation Trust, London, UK
[f] Greater Glasgow and Clyde Health Board, Glasgow, UK
[g] Scottish Mycobacteria reference laboratory, NHS Lothian, UK
[h] St James University Hospital, Leeds, UK
[i] University Hospitals Birmingham, Birmingham, UK

ARTICLE INFO

Keywords:
Non-tuberculous mycobacteria infection
Localised
Disseminated
Extrapulmonary

ABSTRACT

Non-tuberculous mycobacteria (NTM) infections predominantly present as pulmonary disease. Although relatively rare, 20–30 % originate from extrapulmonary sites resulting in a wide range of clinical syndromes. Immunocompromised individuals are particularly susceptible. Clinical manifestations include skin and soft-tissue infections, lymphadenitis, musculoskeletal infections and disseminated disease. Diagnosing extrapulmonary NTM is challenging, and management is complex, often involving multiple radiological and microbiological investigations, long courses of combination antibiotic regimens and may require adjuvant surgical interventions. We highlight both the importance of involving NTM experts at an early stage and the role of a multidisciplinary approach in the diagnosis and management of these infections.

Key points

- Cosmetic procedures or surgical procedures including prosthetic implants can cause extrapulmonary non-tuberculous mycobacteria (NTM) disease.
- For localised extrapulmonary NTM disease, treatment is not usually urgent. Ensure adequate samples are obtained for microbiology (acid fast bacilli smear, culture and molecular testing) and histology before starting treatment.
- Always ask for NTM expert advice before commencing treatment.
- Treatment for NTM extrapulmonary disease may require two or more antibiotics.
- In cases of disseminated disease further, investigation is required to look for immunosuppression including an HIV test.

1. Introduction

Non-tuberculous mycobacteria (NTM) are environmental opportunistic pathogens distributed widely in soil and water. The prevalence of NTM isolates is increasing in the UK and globally.[1,2,3] This may be attributable to an increased at-risk population (secondary to increased organ transplantation, and the use of immunosuppressive therapies, in particular biologics), alongside increased awareness and improved diagnostics. Despite this rising prevalence, NTM disease remains relatively rare and poorly understood.[4,5]

Broadly, NTM are classified into slow growing mycobacteria (SGM) and rapid growing mycobacteria (RGM). This is based on the time taken to form a colony on solid culture media. RGM usually grow within 7 days, whereas SGM often need up to 14 days. Their ability to cause disease is dependent on the site of inoculation and the ability of the

☆ 10.7861/clinmed.2023-0519.
* Corresponding author at: Blizard Institute, The Faculty of Medicine and Dentistry, Queen Mary University of London, The Blizard Building, 4 Newark Street, London E1 2AT, UK.
E-mail address: Akanksha.malhotra@nhs.net (A.M. Malhotra).
Social media: @Mimi_Malhotra (A.M. Malhotra)

https://doi.org/10.1016/j.clinme.2024.100016

host immune system to clear them. NTM infection primarily manifests as pulmonary disease, although can affect any organ.

Previous data indicate that 20–30% of NTM infections originate from extrapulmonary sites.[1,2,3,6,7] Extra-pulmonary disease is usually defined as a culture-confirmed NTM infection in the presence of clinical features suggestive of skin, soft tissue (wound or abscess) or lymphatic tissue disease, although it may also be found in the spine or joints. NTM may be isolated from body fluids such as urine, blood or cerebrospinal fluid. When culture is negative, molecular tests and/or histopathology are useful diagnostic tools in the presence of an appropriate clinical and epidemiological context.

Predominant NTM species vary according to country and geographical region. In recent years, outbreaks of extrapulmonary NTM (EP-NTM) have contributed to an increased awareness of EP-NTM related diseases and their associated high rates of morbidity and mortality. A notable example is a global outbreak from 2011–2016 of prosthetic valve endocarditis secondary to *Mycobacterium chimaera (M. chimaera)*, which was later traced to contamination of water heater-cooler units used during open-heart surgery.[8]

In this article, we aim to describe the clinical risk factors for EP-NTM, relevant diagnostic tests, pharmacological treatments and non-pharmacological interventions. National and international management guidelines specific to EP-NTM remain limited owing to few prospective clinical trials.[9] Therefore, expert clinical opinion and knowledge from relevant multidisciplinary NTM teams and advisory groups should be sought when there is a suspicion of EP-NTM disease.

1.1. Clinical presentation and risk factors

EP-NTM disease often affects a younger population but can occur at any age. There is a similar distribution between males and females.[10] Patients with EP-NTM disease are most likely to present to outpatient settings with recurrent or long-standing infections that have failed to improve after initial standard antimicrobial treatment. Due to reduced awareness and the wide variety of presenting symptoms, patients with EP-NTM may have had multiple encounters with varying health care professionals across primary care, community services and outpatient settings.

Clinical presentation of EP-NTM disease is dependent on the site(s) of infection. A spectrum of conditions exists ranging from localised disease secondary to inoculation, lymphadenitis, infections affecting skin, soft tissue or musculoskeletal (MSK) system and disseminated disease (Table 1).

Specific examples of EP-NTM disease secondary to inoculation include *M. marinum* infection following trauma to the skin in contaminated swimming pools or bodies of water containing tropical fish and *M. ulcerans* infection, which can cause chronic, indolent necrotic skin ulcers known as 'Buruli ulcers'. Whilst the latter has typically been rare outside of the African continent and in high-income settings, it has been reported with increasing incidence in Australia and attributed to changing climate.[11]

Cervical lymphadenitis is characteristically observed in immunocompetent children below the age of 5 years, and rarely affects adults unless immunosuppressed. This is usually a benign condition which is cured following surgical resection without the need for antibiotics. The most common NTMs causing lymphadenitis are *M. avium, M. haemophilum, M. intracellulare* and *M. malmoense*.

Skin and soft tissue EP-NTM infections often occur following traumatic injury, healthcare associated procedures or cosmetic procedures. Iatrogenic and/or nosocomial infections have been reported secondary to surgical site infections including post-laparoscopic surgery for peritoneal dialysis catheter insertion, abdominal wall abscesses from liposuction, and central intravenous line-associated blood stream infections. Prostheses including heart valves and musculoskeletal joints are also

Table 1
Extrapulmonary non-tuberculous mycobacterial (EP-NTM) disease – risk factors and clinical manifestations.

Risk factor	Causative organism	Clinical manifestations
Inoculation		
Fish tank +/- swimming pool granuloma	*M. marinum*	A slow growing, inflamed, erythematous nodule or plaque. Often painful and ulcerates over time. Associated with cellulitis
Buruli ulcer	*M. ulcerans*	Initially painless nodule that develops into large ulcers with a discoloured white/yellow base. Most commonly affects upper or lower limbs.
Lymphadenitis	*M. avium complex*[a]	Lymph node enlargement, most often cervical (usually affects children)
Skin and soft tissue infections		
Keratitis, choroiditis, endophthalmitis	*M. fortuitum*	Erythematous and nodular lesions to the skin, epiphora, purulent discharge and proptosis
Cosmetic surgery	*M. chelonae*	Wound dehiscence; erythema and induration; nodule and abscess formation
Post-traumatic wound infections	*M. abscessus*	
Musculoskeletal infections		
Tenosynovitis	*M. avium* complex*	Gradual and insidious onset of enlargement of the tendon and synovium with persistent slow progression. Rarely complicated by involvement of underlying muscles, bone structures and/or joint spaces
Osteomyelitis	*M. abscessus* *M. fortuitum* *M. chelonae*	Usually observed following trauma or joint replacement. Most commonly associated with disseminated NTM infection(s) and secondary to immunosuppression. Vertebral involvement – bone pain, neuropathic pain and neurological symptoms
Iatrogenic and post-procedural infections		
Joint replacement	*M. abscessus,* *M. fortuitum* *M. chelonae*	Gradual onset of joint infection with swelling, erythema and fevers
Prosthetic heart valve	*M. chimaera* *M. fortuitum* *M. chelonae* *M. abscessus*	Infective endocarditis – fever, weight loss, malaise, anaemia, pancytopenia, valve insufficiency on echocardiogram
Cardiac surgery	*M. chimaera*	Overlying sternal wound infection with wound dehiscence; erythema and induration; nodule and abscess formation
Peritoneal dialysis-associated infection	*M. fortuitum* *M. chelonae* *M. abscessus*	Peritonitis – abdominal pain, nausea, vomiting, pseudo bowel obstruction. Rarely complicated by loculated ascites and formation of abdominal adhesions
Disseminated disease		
HIV infection Post solid organ transplantation	*M. avium* complex[a]	Disseminated disease will usually present as persistent nonspecific symptoms including fever, night sweats, malaise and weight loss. Associated with respiratory (dry cough, dyspnoea) and/or abdominal (pain, diarrhoea, malabsorption) symptoms. Patients often have an associated pancytopenia and abnormal liver function tests indicating dissemination to bone marrow, liver and other organ systems

[a] *M. avium complex* refers to a group of multiple NTM species which includes *M. avium, M. intracellulare* and *M. chimaera*

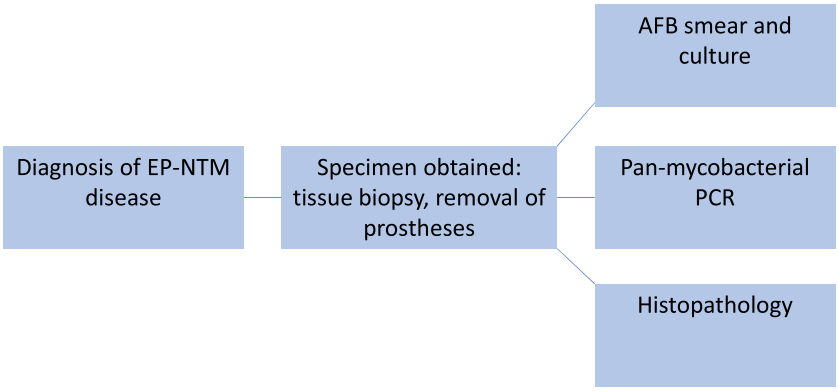

Fig. 1. Flow diagram of diagnostic strategy for extrapulmonary nontuberculous mycobacterial infections.

implicated. Outbreaks associated with acupuncture needle use and contaminated ultrasonography (US) gel have been reported in medical settings.[12,13] In addition, EP-NTM infections have been attributed to cosmetic procedures including tattooing, piercing, mesotherapy, hydrotherapy, pedicures, injection of dermal fillers, botulinum toxin and augmentation surgery.[14]

Focal MSK infections range from infections of tendon sheaths, bursa, joints and bones, to those with spinal involvement. Other rare but observed sites of EP-NTM include cerebral, ocular, oral, breast and bloodstream infections.[15]

Disseminated EP-NTM disease is defined as an infection in two non-contiguous sterile sites or a positive result for mycobacteria from blood or bone marrow culture.[3] This occurs primarily in immunocompromised individuals, for example those with advanced HIV infection or on long-term immunosuppression following solid organ transplantation (notably renal, cardiac, lung, liver transplants).[16] Other risk factors include haematological malignancies, biologic agents, chemotherapy, and chronic corticosteroid use.

1.2. Diagnosis of EP-NTM disease

Diagnosis of EP-NTM is complex as the organisms may be fastidious, slow growing and require specialised culture media. It is crucial to make an aetiological diagnosis before starting empirical treatment, since drug susceptibility tests (DSTs) greatly vary depending on the NTM species. A three-pronged approach including mycobacterial culture, molecular studies when available, and histopathology can facilitate rapid and accurate diagnosis (Fig. 1). Diagnosing lymphadenitis microbiologically requires either excisional biopsy or fine needle aspiration for microscopy, mycobacterial culture and/or PCR.

When NTM skin infections are suspected, skin biopsies for culture and histology are often sufficient to make a diagnosis. In some cases molecular testing may be required and offers a way to determine drug susceptibilities.[17] In disseminated disease, mycobacterial blood cultures, urine cultures, and stool cultures in combination with bone marrow aspirate may be helpful.

The most common SGM NTM species causing extra-pulmonary disease in the UK are *M. marinum* group and *M. malmoense*. The most common RGM species are *M. chelonae complex*, *M. abscessus complex, M. mucogenicum* and *M. fortuitum* group.[10]

Radiological findings may be variable and non-specific depending on the site of infection. For suspected skin and soft tissue NTM infections, imaging may not be routinely required unless a localised abscess or deep tissue infection involving adjacent bone is suspected. In these cases, modalities including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) may be used. NTM lymphadenitis may present as enlarged lymph nodes with central necrosis similar to TB lymphadenitis. MSK involvement that has progressed to osteomyelitis and/or involvement of the vertebra may be apparent on MRI of the spine or affected bones and joint. Positron Emission Tomography (PET)-CT may be helpful especially in suspected disseminated disease. Imaging may be indicated for monitoring response to treatment, particularly when abscesses are inaccessible, or drainage is not possible.

1.3. Management of extrapulmonary NTM disease

Optimal management of a patient with EP-NTM requires a well-coordinated multidisciplinary team approach. This may include a range of professionals such as those in infectious diseases, respiratory medicine, microbiology, plastic surgery or orthopaedic surgery as applicable, and dermatology. Histopathologists with interest in infectious diseases can provide valuable support.

1.4. Treatment of extrapulmonary NTM infections

Pharmacological management may be avoided in some instances with source control in the form of debridement surgery. Mycobacteria involved in EP-NTM disease may have resistance to multiple antibiotics and adverse effects induced by these antibiotics may make treatment challenging.

Due to the paucity of prospective, randomised controlled clinical trials, choice of medication is often guided by evidence from treatment of pulmonary NTM infections, clinical experience and expert opinion. Susceptibility testing has a role, but discussion with the Microbiology Reference Laboratory is crucial to ensure the right DST is performed to aid therapy. DSTs are not always predictive of treatment outcomes, nor always feasible due to slow or failed growth of NTM species and/or degradation of antibiotics in culture. Whole genome sequencing may be useful to identify gene mutations that predict resistance and susceptibility to some antibiotics. The treating clinician should use *in vitro* susceptibility tests with an appreciation of their limitations and with the awareness that, unlike with TB, some NTM disease may not be eradicated in a given patient with therapy based on *in vitro* susceptibility results.

Duration of therapy is often between 6–18 months, however there are no existing guidelines on duration of therapy for EP-NTM infections. Treatment is often guided by clinical experience, expert opinion and clinical progress (Tables 2 and 3). Antibiotic regimens may be altered during the course of treatment due to the frequent occurrence of adverse effects. Treatment for EP NTM infections should only be started by multidisciplinary teams with experience in managing patients with EP-NTM.

Surgical options can play a key part in management of EP-NTM and procedures vary from debridement, excision and drainage. In cases of bacteraemia, removal of devices, as well as anti-mycobacterial therapy, is indicated for a minimum of 2–3 months. Relapse of bacteraemia has been reported.[19]

Unlike with TB, patients with EP-NTM do not necessarily need to be isolated as person-to-person transmission of NTM is rare. Transmission,

Table 2
Recommended treatment regimens for mild and severe disease.

NTM Isolate	Organs affected	Recommended treatment regimen for severe disease	Recommended treatment regimen for mild disease
M. avium complex	Skin, soft tissue, tendons, joints, bone Disseminated infection	**Induction phase** Intravenous amikacin + rifampicin + ethambutol + azithromycin/clarithromycin **Continuation phase** Rifampicin + ethambutol + azithromycin/clarithromycin	Rifampicin + ethambutol + azithromycin/clarithromycin
M. abscessus	Osteomyelitis Peritoneal dialysis Catheter infections	**Induction phase** Intravenous amikacin + cefoxitin/imipenem + tigecycline +azithromycin/clarithromycin **Continuation phase** Azithromycin, clofazimine, linezolid and consider quinolones	Azithromycin, clofazimine, linezolid and consider quinolones
M. fortuitum	Cosmetic surgery	**Induction phase** Intravenous amikacin + quinolone + doxycycline, consider linezolid **Continuation phase** Fluoroquinolone + doxycycline	Fluoroquinolone + doxycycline
M. chelonae	Skin infections	**Induction phase** Azithromycin/clarithromycin + tobramycin ± imipenem **Continuation phase** Azithromycin/clarithromycin + clofazimine (or doxycycline, linezolid or fluoroquinolones)	Azithromycin/clarithromycin + clofazimine, doxycycline, linezolid, clofazimine, fluoroquinolones
M. marinum	Fishtank granuloma[a]	**Induction phase** (usually not required as localised disease) Azithromycin, clarithromycin + rifampicin + ethambutol **Continuation phase** Azithromycin/clarithromycin + rifampicin + ethambutol	Azithromycin/clarithromycin + rifampicin + ethambutol

Based on expert opinion and adapted from 1999 Joint Tuberculosis Committee British Thoracic Society and American Thoracic Society/International Diseases Society of America guidelines.[10,18] Treatment for EP NTM infections should only be started by multidisciplinary teams with experience in managing patients with EP-NTM.

[a] In cases that have not responded to macrolide monotherapy.

Table 3
Drugs used in the treatment of adult EP-NTM diseases and common adverse effects.

Drug	Dosage	Drug monitoring (Baseline screening and follow up)*	Common adverse effects
Amikacin	15 mg/kg once daily (max 1 g) intravenous Age >59 years: 10 mg/kg once daily (max 750 mg) intravenous Consider adjusted body weight in obese	• Bloods: renal function, calcium, magnesium, • Audiological and vestibular • Genetic testing (R.65 MT-RNR1 155A>G) • Pre- and post-dose serum amikacin concentration	**Nephrotoxicity**: accumulation if renal impairment **Ototoxicity and vestibular toxicity**: irreversible vestibulocochlear (eighth cranial) nerve damage leading to hearing loss, loss of balance or both
Azithromycin	250–500 mg once daily (oral)	• QTc interval ECG monitoring • Monitor for hearing loss, tinnitus and balance • Consider baseline audiometry if there is a history of hearing difficulties, and repeat if any hearing loss or tinnitus	**Dermatological**: rash, pruritus **Gastrointestinal**: nausea, vomiting, diarrhoea, dyspepsia, change in taste, abdominal pain, flatulence **General**: fatigue **Metabolism**: anorexia **Musculoskeletal and connective tissue**: arthralgia **Neurological**: dizziness, headache, paraesthesia **Ophthalmic**: visual impairment **Ototoxicity**: deafness **Other**: increased concentration of other drugs
Bedaquiline	400 mg daily for the first 2 weeks, followed by 200 mg three times per week (oral) (at least 48 h between doses)	• QTc interval ECG monitoring (contraindicated if QTc >500 ms) • Bloods: calcium and magnesium (repeat if QTc prolonged)	**Musculoskeletal and connective tissue disorders**: arthralgia, myalgia **Cardiovascular**: QTc prolongation **Gastrointestinal**: nausea, vomiting, diarrhoea **Neurological**: headache, dizziness **Respiratory**: haemoptysis
Clofazimine	200 mg once daily (oral) loading for 2 months. Continue with 100 mg OD	• QTc interval ECG monitoring • (contraindicated if QTc >500 ms) • Liver function testing	**Dermatological:** pigmentation from pink to brownish-black in 75–100 % of the patients within a few weeks of treatment; ichthyosis and dryness; rash and pruritus. Pigmentation resolves after cessation of treatment **Gastrointestinal:** abdominal and epigastric pain, diarrhoea, nausea, vomiting, gastrointestinal intolerance **Ocular:** diminished vision, conjunctival and corneal pigmentation due to clofazimine crystal deposits; dryness; burning; itching; irritation **Other:** discoloration of urine, faeces, sputum, sweat; elevated blood sugar; elevated erythrocyte sedimentation rate (ESR)

(*continued on next page*)

Table 3 (*continued*)

Drug	Dosage	Drug monitoring (Baseline screening and follow up)*	Common adverse effects
Doxycycline	100 mg twice daily (oral)	Routine monitoring	**Dermatological**: photosensitivity, rash **Gastrointestinal**: nausea, vomiting **Neurological**: headache, myasthenia gravis may be increased and SLE worsened **Immunological**: hypersensitivity, angioedema
Ethambutol	15 mg/kg once daily (Max dose 1.2 g) **Obesity:** where actual body weight (ABW) is >20 % above ideal body weight (IBW), use IBW	• Visual acuity via Snellen chart test • Colour discrimination via Ishihara plate • Symptom monitoring • Consider ophthalmology review	**Endocrine**: hyperuricaemia, **Gastrointestinal**: nausea and vomiting **Ocular:** optic neuritis
Imipenem	1000 mg two to three times daily (intravenous) Consider 500 mg two to three times daily (intravenous) for small, frail or elderly patients	Routine monitoring of liver function tests	**Dermatologic:** rash **Gastrointestinal:** diarrhoea, vomiting, nausea **Haematologic:** eosinophilia **Hepatic:** increases in serum transaminases, increases in serum alkaline phosphatase **Vascular:** thrombophlebitis
Moxifloxacin	400 mg once daily, depending on weight	• QTc interval ECG monitoring • (contraindicated if QTc > 500 ms) • Bloods: liver function tests	**Gastrointestinal:** diarrhoea, nausea, and vomiting **Skin:** photosensitivity, rash **Hepatic:** transient increases in LFTs **Other:** be aware of possible drug interactions **MHRA** important safety information: increased risk of tendon damage, aortic aneurysm, heart valve regurgitation, psychiatric reactions. Please see MHRA alert for further information
Linezolid	600 mg once daily (oral or intravenous)	• Bloods: full blood count, lactate (consider in those with symptoms of lactic acidosis) • Peripheral neuropathy • Visual acuity • Colour discrimination	**Gastrointestinal:** diarrhoea, nausea, vomiting **Neurological:** headache, dizziness, peripheral neuropathy **Haematological:** Bone marrow suppression **Hepatic:** transient increases in liver function tests **Dermatological:** urticaria, rash
Rifampicin	<50 kg: 450 mg once a day (oral or intravenous) > 50 kg: 600 mg once a day (oral or intravenous	• Bloods: liver function tests	**General:** flu-like syndrome **Gastrointestinal:** nausea, vomiting **Haematologic:** thrombocytopenia with or without purpura (usually associated with intermittent therapy). Reversible after discontinuing rifampicin **Hepatic:** transient increases in LFTs **Neurological:** headache, dizziness **Other**: reddish discolouration of urine, sweat, sputum, tears. Multiple drug interactions.
Tobramycin	4.5–7 mg/kg once a day (intravenous)	• Bloods: renal function, pre- and post-dose tobramycin concentration • Audiological and vestibular	**Gastrointestinal**: appetite decreased, diarrhoea, nausea, taste altered, oropharyngeal pain, vomiting **Neurological:** dizziness, headache **Dermatological:** skin reactions **Respiratory:** bronchospasm, chest discomfort, cough aphonia, dysphonia haemoptysis **Nephrotoxicity**: accumulation if renal impairment **Ototoxicity and vestibular toxicity:** irreversible vestibulocochlear nerve damage leading to hearing loss, and/or loss of balance **Other:** fever

The majority of drugs listed are currently used off-license in the treatment of NTM in the UK. The adult doses stated are based on normal hepatic and renal function. Treatment for EP NTM infections should only be started by multidisciplinary teams with experience in managing patients with EP-NTM.

* Routine toxicity monitoring tests (full blood count [FBC], urea and electrolytes [U&Es], liver function tests [LFTs]) should be performed at baseline and intermittently throughout antibiotic treatment. More specific monitoring, if required, is outlined above.

especially of pulmonary NTM, has however been reported.[20] Currently, NTMs are non-notifiable to public health services in the UK, they are notifiable in some other parts of the world.[19] This facilitates and enables public health services to detect outbreaks for example cutaneous infections arising from point-sources including cosmetic surgery and tattoo parlours. Whether NTM should be notifiable has led to much debate in the UK, not least due to the interesting dynamic with other notifiable mycobacterial diseases, predominantly TB, where person-to-person transmission predominates.

2. Conclusion

EP-NTM disease varies from localised to disseminated infection. Diagnosis is challenging and may require multiple biopsies and cultures to confirm a diagnosis, as well as the input of several specialties. Treatment is complex and often requires a prolonged and multi-drug regimen following expert opinion. Adverse effects are common, and patients require ongoing monitoring.

References

1. Jarchow-MacDonald A, Smith M, Seagar AL, et al. Changing incidence and characteristics of nontuberculous mycobacterial infections in Scotland and comparison with *Mycobacterium tuberculosis* complex incidence (2011 to 2019). *Open Forum Infect Dis*. 2022;10:ofac665.
2. Shih DC, Cassidy PM, Perkins KM, et al. Extrapulmonary nontuberculous mycobacterial disease surveillance – Oregon, 2014–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67:854–857.
3. Kobayashi T, Nishijima T, Teruya K, et al. High mortality of disseminated non-tuberculous mycobacterial infection in HIV-infected patients in the antiretroviral therapy era. *PLoS ONE*. 2016;11:e0151682.
4. Dahl VN, Mølhave M, Fløe A, et al. Global trends of pulmonary infections with nontuberculous mycobacteria: a systematic review. *Int J Infect Dis*. 2022;125:120–131.
5. Ahmed I, Tiberi S, Farooqi J, et al. Non-tuberculous mycobacterial infections – a neglected and emerging problem. *Int J Infect Dis*. 2020;92:S46–S50.

6. Hermansen TS, Ravn P, Svensson E, Lillebaek T. Nontuberculous mycobacteria in Denmark, incidence and clinical importance during the last quarter-century. *Sci Rep*. 2017;7:6696.
7. Simons S, Van Ingen J, Hsueh PR, et al. Nontuberculous mycobacteria in respiratory tract infections, eastern Asia. *Emerg Infect Dis*. 2011;17:343–349.
8. Wetzstein N, et al. Clinical characteristics and outcome of *Mycobacterium chimaera* infections after cardiac surgery: systematic review and meta-analysis of 180 heater–cooler unit associated cases. *Clin Microbiol Infect*. 2023;29:1008–1014.
9. Martiniano SL, Caceres SM, Poch K, et al. Prospective evaluation of nontuberculous mycobacteria disease in cystic fibrosis: The design of the PREDICT study. *J Cyst Fibros*. 2023;2023 S1569–1993(23)00876-7.
10. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.
11. Blasdell KR, McNamara B, O'Brien DP, et al. Environmental risk factors associated with the presence of Mycobacterium ulcerans in Victoria, Australia. *PLoS ONE*. 2022;17:e0274627.
12. Tang P, Walsh S, Murray C, et al. Outbreak of acupuncture-associated cutaneous Mycobacterium abscessus infections. *J Cutan Med Surg*. 2006;10:166–169.
13. Cheng A, Sheng WH, Huang YC, et al. Prolonged postprocedural outbreak of Mycobacterium massiliense infections associated with ultrasound transmission gel. *Clin Microbiol Infect*. 2016;22 382-e1.
14. Daniau C, Lecorche E, Mougari F, et al. Association of healthcare and aesthetic procedures with infections caused by nontuberculous mycobacteria, France, 2012–2020. *Emerg Infect Dis*. 2022;28:518.
15. Ricotta EE, Adjemian J, Blakney RA, et al. Extrapulmonary nontuberculous mycobacteria infections in hospitalized patients, United States, 2009–2014. *Emerg Infect Dis*. 2021;27:845.
16. Abad CL, Razonable RR. Non-tuberculous mycobacterial infections in solid organ transplant recipients: an update. *J Clin Tuberc Other Mycobact Dis*. 2016;4:1–8.
17. Cowman S, Burns K, Benson S, et al. The antimicrobial susceptibility of non-tuberculous mycobacteria. *J Infect*. 2016;72:324–331.
18. Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society*. Management of opportunist mycobacterial infections: Joint Tuberculosis Committee guidelines 1999. *Thorax*. 2000;55:210–218.
19. Dabaja-Younis H, Damouni-Shalabi R, Ganem-Zoubi N, et al. Nontuberculous mycobacteria blood stream infection in pediatric and adult patients: 15 years surveillance. *Pediatr Infect Dis J*. 2022;41:e216–e219.
20. Yan J, Kevat A, Martinez E, et al. Investigating transmission of Mycobacterium abscessus amongst children in an Australian cystic fibrosis centre. *J Cyst Fibros*. 2020;19:219–224.