Review Article

Cutaneous Atypical Mycobacterial Infections: A Brief Review

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Abstract

Nontuberculous mycobacterial (NTM) infections are increasingly recognized, particularly in tropical regions and are often found in immunocompetent individuals. These infections are emerging as significant health concerns, especially pulmonary NTM, which is reported more frequently and is known to be associated with hospital environments. While pulmonary NTM infections are on the rise, partly due to drug resistance and possible patient-to-patient transmission, there is no current evidence indicating an increase in cutaneous NTM infections. The clinical manifestations of NTM infections, except for well-known entities like Buruli ulcer and fish tank granuloma, are diverse and nonspecific, often mimicking other chronic infections. History of minor trauma at the site of infection can be misleading and may complicate the diagnosis of cutaneous NTM. Surgical-site and port-site NTM infections typically present with erythema, edema, and abscesses and are commonly caused by rapidly growing mycobacteria like *M. fortuitum* and *M. chelonae*. These infections may not respond to standard antibiotics, suggesting the need for NTM-specific treatment. Diagnostically, histopathology may not be conclusive, and standard staining techniques often lack sensitivity. Molecular methods offer better speciation and drug resistance profiling for pulmonary NTM but are expensive and not widely available for cutaneous forms. The high cost and limited availability of diagnostic tools necessitate an empirical treatment approach, which is also recommended by the INDEX-Tb guidelines for extrapulmonary tuberculosis. Empirical treatment regimens for NTM, such as combinations of clarithromycin, doxycycline, and cotrimoxazole or fluoroquinolones, have shown promise, but there is a lack of rigorous studies to establish standardized treatments. Monitoring for adverse effects and continued evaluation of the causative organism is essential during empirical treatment, allowing for adjustment if the initial regimen fails.

Keywords: *Atypical mycobacteria, empirical treatment, non-tuberculous mycobacterial infections, NTM infections, skin infections*

Introduction

Nontuberculous mycobacteria (NTM) include the bacteria in the whole *Mycobacterium* genus except *M. tuberculosis* complex and *M. leprae*. These ubiquitous saprophytic organisms are present in the air, soil, dust, natural and drinking water sources, wild animals, plants, milk, and other food products.[1] They are known to form biofilms and can be isolated from various settings, including hospitals. In clinical settings, some of the NTM caused diseases, are known as atypical mycobacterial infections.

Epidemiology

NTMs are increasingly being detected in both environmental samples and human pulmonary and extra-pulmonary specimens throughout the world.[2–4] This rise in detection may be attributed to their actual increase in prevalence and the improvement and wider availability of isolation techniques. They are prevalent in soil and natural water bodies, forming biofilms in these environments. Biofilms, a common feature in all types of NTMs, contribute to both pseudo-infections in the form of contamination or colonization and true infections.

With regards to the transmission, NTMs differ from *M. tuberculosis*. They spread through environmental exposure, through water reservoirs and soil, rather than aerosolization and patient-to-patient contact, with the exception possibly being the potential spread of *M. abscessus* during outbreaks in cystic fibrosis patients. Many developed countries report more pulmonary NTM infections than pulmonary tuberculosis. Due to different environmental factors and a lack of robust data reporting

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and worldwide comparison studies, it is not certain if cutaneous atypical mycobacterial infections are present more in developed countries than in developing countries, compared to *M. tuberculosis* infections.

In a review of 94 cutaneous NTM cases from Japan, Fujishima *et al*.[5] found that rapidly growing mycobacteria accounted for 58% of cases (n = 54), whereas slowly growing mycobacteria for 43% (n = 40). *M. marinum* (n = 20, 21%) was the most common cause, followed by *M. chelonae* (n = 18, 19%), *M. abscessus* (n = 15, 16%), and *M. ulcerans* (n = 11, 12%). The average age of the patients was 60 years, 53% were immunocompromised, and 24% showed evidence of disseminated infection involving multiple organs. The proportion of immunocompromised patients was higher than reports from other countries, likely because they selected only culture-positive patients, and immunocompromised patients are more likely to show culture positivity. Kumar *et al*.[6] reviewed reports of cutaneous NTM infections caused by rapid growers globally and the most common species identified in culture and drug susceptibility specimens was *M. abscessus* (184/475, 38.7%). This was followed by *M. fortuitum* (150/475, 31.5%), *M. chelonae* (72/475, 15%), and *M. chelonae–M. abscessus* complex (46/475, 9.6%).

Factors contributing to the increased prevalence of NTM infections

- ***Host factors:*** The rise in invasive and cosmetic procedures, which provide additional routes to bypass the skin barrier, such as injections, tattooing, skin piercings, acupuncture, pedicures, mesotherapy, plastic surgery, liposuction, laparoscopy (including indications like appendectomy, cholecystectomy, hernia repairs), cesarean section, hysterectomy, catheterization, endoscopy, and bronchoscopy.[2,7] This has also implied an increase in the proportion of rapid growers specifically, as they commonly cause infections after cosmetic or medically invasive procedures.[2,4,7] With advancements in healthcare, the population of people more susceptible to NTM infections, like geriatric people, immunocompromised individuals, and people with co-morbidities like diabetes have also increased.[2] A reduced herd immunity and cross-immunity due to a decrease in the tuberculosis burden has also been proposed as a host factor.[8] Female gender and occupations which increase exposure of acral areas to sources of infection like soil and wetlands, are also host factors predisposing to NTM infections, although they do not explain the recent increase in their incidence.
- ***Agent factors:*** Biofilm formation is a crucial factor contributing to NTM infections. It is postulated that some species might have some genetic mutations increasing virulence.[8]
- ***Environmental factors:*** The proliferation of human water reservoirs, increased exploration of wetlands by humans, closer proximity of humans to water reservoirs, reduced competition due to elimination of other pathogens in human water reservoirs through chlorination, and the presence of animal vectors and free-living amoeba reservoirs all contribute to the spread of NTMs.[9]

Microbiology

Conventionally, Runyon's classification was employed for the categorization of NTM based on their growth rate in culture and pigment production, considering light exposure. However, the landscape has transformed with the emergence of advanced technologies such as molecular sequencing, data banks, and other biochemical methods, facilitating enhanced species identification, differentiation, and classification.[10] New speciation criteria for NTM are based on the identification of a ≥1% difference in 16S rRNA gene sequence, compared to known species. Consequently, a plethora of novel NTM species have been discovered in recent years, particularly within the last decade.[11] NTM species are classified into rapid growers if they produce mature colonies on an appropriate solid media like Middlebrook 7H10 or 7H11 agar, or Lowenstein-Jensen agar (L-J), within 7 days under ideal conditions, and slow growers if later than 7 days.[12]

This classification is underpinned by a genetic framework, as phylogenetic analysis suggests that all slowly growing NTM species originated from rapid growers in a distinct branch. These species exhibit distinct housekeeping genes interlinked with each other, governing infectivity potential and pathogenicity in humans. As a result, most NTM species causing strict and opportunistic or potential infections are slow growers, while saprophytic or non-pathogenic strains tend to be rapid growers. The pathogenicity and disease-causing potential of many NTM species remain unknown, as they are often found to contaminate and colonize specimens and tissues without inducing disease. Various clinical, radiological, and microbiologic criteria are employed to establish the pathogenic nature of different NTM species, especially in the context of lung disease.[10,11] However, such criteria do not currently exist for cutaneous NTM disease. Single/one-time isolation irrespective of the bacterial load, along with the clinical context and histopathology, has been presumed to be indicative of a true NTM cutaneous infection.[13] In contrast, pulmonary NTM disease requires isolation from at least two sputum specimens or one bronchioalveolar lavage specimen, and radiological features. Histopathology/tissue specimen is usually required for skin disease, but not for pulmonary disease.[11]

Different NTM species exhibit significant variation in their growth rate, tolerance to different temperatures, and susceptibility to drugs. Correct species identification is

considered important because isolated NTM species differ in their response to treatment. Out of over 170 NTM species documented, about 25 species have been strongly linked to these diseases, while the rest are rarely identified in clinical samples.[1] To prevent unwarranted diagnoses and treatment of NTM disease, some researchers have highlighted the importance of usage of separate, more stringent criteria when species with low clinical relevance are isolated, and vice versa.[14] The classification, nomenclature, and speciation should also be consistent to allow comparisons.

Clinical Features

The infections caused by NTM can be grouped into six clinical syndromes, including skin and soft tissue infections, infections of deeper tissues of bones and joints, pulmonary infections, infections of lymph nodes, catheter-related infections, and disseminated infections.[4] Pulmonary infection is the commonest. Skin and soft tissue NTM infections are prevalent as the most common extra-pulmonary infections in many tertiary centers, as evidenced by microbiological data. Identifying patients who are at higher risk of developing NTM infections is also a significant challenge. It was believed that immunosuppressed patients and those with pre-existing lung disease were most predisposed to get pulmonary NTM infections, but many apparently healthy patients are also reported. In contrast, cutaneous NTM infections have mostly been seen in otherwise healthy patients. It is difficult to predict which patients will develop the disease, as almost everyone is likely to get exposed to NTM frequently.[1] While pulmonary NTM infections, and infections of the deeper structures like bone and joints, are typically caused by slow growers including the *M. avium* complex (MAC), in relatively older people, skin and soft tissue NTM infections are predominantly caused by rapid growers like *M. abscessus, M. fortuitum,* and *M. chelonae*, followed by the slow-growing MAC group, *M. marinum, M. ulcerans, and M hemophilum,* in relatively younger people.[15–18] In Asian countries including India, rapid growers like *M. abscessus* cause a significant proportion of pulmonary infections too.[15,16] Disseminated infections in the immunocompromised are more likely due to the MAC group,[16] while post-procedure infections are likely due to rapid growth.[4] Cutaneous lesions in patients with disseminated infections present as multiple abscesses, ulcers, and sinuses in widespread distribution over multiple areas of the body. The affected patients are usually immunocompromised and may have associated lung involvement. The clinical context, and not just the morphology of individual skin lesions, helps in guiding the clinician to investigate cutaneous NTMs.

The main sources of cutaneous NTM infections are trauma (apparent or otherwise), environmental exposure, and hospital-acquired infections, particularly after surgical procedures.[1] History of past trauma can be misleading, as many patients give a history of trivial trauma at the site of localized cutaneous disease. This history may range from a few days to years before the onset of lesions and cannot be relied upon in diagnosing a cutaneous NTM infection. Additionally, morphologies, like ulcerated or crusted plaques, nodules, abscesses, and sinuses, may represent non-specific morphologies of other chronic infections like deep fungal infections, particularly cutaneous sporotrichosis and actinomycosis, cutaneous tuberculosis, and even cutaneous leishmaniasis.

M. marinum and *M. ulcerans* infections result in well-defined clinicopathologic entities with specific context, geographical distribution, and morphology, also known as fish tank/swimming pool granuloma and Buruli ulcer, respectively. *M. marinum* disease is acquired from infected fish or water through damaged skin, and presents commonly as a nodule, and less commonly as an abscess, ulcer, or pustule on extremities. One-third of cases show a sporotrichoid pattern. Deeper tissues including tenosynovium can be involved in one-third of cases. *M. ulcerans* are commonly seen in tropical rainforests, with childhood being the most common age in which patients present with Buruli ulcers. It progresses through three stages, starting from pre-ulcerative lesions (like papules, nodules, or plaques), which extend to deep necrosis and lead to the formation of undermined ulcers, followed by scarring and spontaneous healing of ulcers. Scarring leads to contractures and disability.

Other NTM skin diseases have no pathognomonic characteristics with heterogeneous clinical manifestation and incubation period depending on the modality of mycobacterial acquisition, bacterial load, virulence, and host immune status. They can present with papules, plaques, nodules, abscesses, sinuses, folliculitis, cellulitis, and lesions in sporotrichoid distribution. Surgical-site and port-site NTM infections present as erythema, edema, inflammation, abscesses, nodules, sinuses, and pus discharge around sites of a surgical incision or port [Figure 1]. These infections are caused by rapidly growing NTM species, such as *M. fortuitum* and *M. chelonae*, which colonize soil, sewage, and tap water. Failure to respond to adequate courses of antibiotics (including beta-lactams and metronidazole for anaerobic coverage) used for more common bacteria causing early surgical and port-site infections, such as *Staphylococcus*, *Pseudomonas*, and *Enterobacteriaceae* family, is indicative of an NTM infection.[19,20] Common surgical site infections usually appear 3–7 days postprocedure, and by definition have to occur by 30 days postprocedure (although in cases of implants, this duration can be extended up to 1 year). In comparison, infections by rapid growers take 3–8 weeks to manifest. In a study, the median incubation period was 27 days, with a range of 23–64 days.[20]

Disseminated and multisite infections are most commonly caused by slow growers, while rapid growers usually cause

single-site lesions.[2] Out of the rapid growers, infections by *M. fortuitum* usually present with a single lesion.[7] Dermatologists are more likely to see infections by rapid growers, in both primary and post-surgical cases. Table 1 summarizes the clinical pointers for NTM infections.

Investigations

Investigations are required for diagnosis, extent of involvement, speciation, and drug susceptibility testing. For a definite diagnosis of NTM infections, pulmonary guidelines are required, and studies on cutaneous infections have used, the demonstration of NTM organisms as an essential criterion. Culture is considered the gold standard for demonstrating NTM infections, and it can help in speciation and drug sensitivity. In contrast to *M. tuberculosis*, where we have developed good molecular techniques using patient samples directly (pus, sputum, body fluids, and lesser yielding cutaneous tissue) for detection and drug resistance testing, molecular methods for NTM infections are usually deployed on cultures. It is recommended to use a combination of both solid (like Middlebrook 7H10 or 7H11 agar, or L-J agar) and liquid media {like Mycobacteria Growth Indicator Tube (MGIT) or broth-based automated methods), as solid media allow for the enumeration of NTM colonies, while liquid media can detect lower concentrations of NTM.

Table 1: Clinical pointers of cutaneous non-tuberculous mycobacterial (NTM) infections

In a patient with chronic lesions suggestive of infective pathology (soft/fluctuant nodules, abscesses, pus discharging sinuses, ulcers with or without granulation tissue, scars/sequelae of healing of some lesions, etc.), suspect cutaneous NTM infections when
Non Iatrogenic
• Acral sites
• Occupation that predisposes to contact with soil or water reservoir
• History of trauma at that site, or interventions done
• Lack of classic clinical features of other chronic infections (grains and induration of eumycetoma, scarring away from active margin/verrucous morphology in cutaneous tuberculosis)
• No or unsatisfactory response to therapeutic trial or treatment targeting other diseases (anti-tubercular or anti-fungal therapy)
• History of travel to endemic countries, along with classical presentation (for *M. marinum* and *M. ulcerans*)
Iatrogenic
• Commonly associated surgeries (laparoscopy/port surgeries/ cosmetic surgeries)
• Incubation period greater than 3 weeks
• Failure of response to first-line antibiotics like beta-lactams and metronidazole

However, culture is time-consuming and requires the use of multiple media types and incubation temperatures, which can be difficult outside of reference laboratory setups.[8] Moreover, the yield of samples for NTM cultures is significantly low due to other factors like the use of swabs which results in limited culture material and increased risk of contaminants during skin sampling, being prone to desiccation; failure of cold chain; and prevalent use of antibiotics before taking samples. To prevent contamination of NTM cultures from skin samples, specimens should be collected with proper asepsis, swab use should be avoided, and the sample should not be put in saline or other liquid or wrapped in gauze. In case of ulcerative lesions, the sample should be collected from the periphery of the ulcers. Two sets of cultures, at 37°C and 30°C (to allow for organisms like *M. haemophilum*, *M. marinum*, and *M. ulcerans*), should be incubated.[1] In centers seeing a significant volume of suspected cutaneous NTM cases, it is worthwhile to establish dedicated protocols for sampling and handling such cases.

Bedside tests, such as acid-fast staining to demonstrate mycobacterial organisms, Giemsa staining, and potassium hydroxide (KOH) mount of pus or tissue to rule out other chronic infections, lack sensitivity, and may need to be repeated several times to yield a diagnosis. Ziehl-Neelsen (ZN) microscopy is unable to differentiate between the *M. tuberculosis* complex and

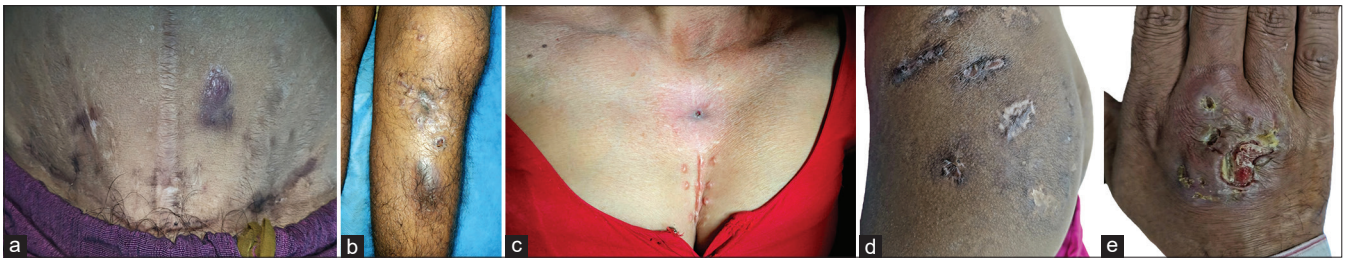

Figure 1: Suspected cases with cutaneous atypical mycobacterial infections. a) Multiple nodules and abscesses, with scars of healed abscesses, which started a few weeks after laparoscopic surgery. b) Nodules and abscesses forming sinuses after arthroscopic surgery through ports over the left knee, with no response to amoxicillin-clavulanic acid given for 2 weeks. c) A persisting pus-discharging sinus, appearing after the breakdown of a few pustules at the same site, after sternotomy for open heart surgery for valve repair. d) Linear scars following rupture of abscesses and healing of sinuses after initial abscess formation due to intramuscular injections for pain and multiple incision and drainage procedures for recurrent furuncles over the left buttock. e) Deep wide ulcers with pus discharge, swelling, and inflammation, which started months after intralesional steroid injections and excision for the hypertrophic scar over the hand, and did not respond to cefixime given for a week

NTM.[21] Biochemical tests (including *p*-nitro benzoic acid inhibition test, niacin accumulation test, arylsulfatase test, nitrate reduction, and catalase estimation) are low-cost easy-to-perform tests used earlier for differentiation from *M. tuberculosis*, identifying certain groups of NTM, but not definite speciation.[8] Most of them are performed over culture growths, rather than pus or tissue samples, hence their utility in the absence of a growth on culture remains limited. With the advent of more specific molecular techniques and a reduction in the cost of sequencing, biochemical tests are almost obsolete.

Histopathology usually shows a mixed cell inflammatory tissue reaction with or without epithelioid cells and granulomas, signifying a suppurative granulomatous tissue reaction. Although the mixed pattern is most common (80%), predominant suppuration with neutrophilic abscess formation and necrosis without any granulomas at one end (15%), and predominant granuloma formation with few or no neutrophils, with or without caseous necrosis in the form of typical tuberculoid granulomatous reaction at the other end (4%), have also been reported.[22] The former is more commonly seen in immunosuppressed individuals and yields a high acid-fast bacilli positivity on special staining, while the latter is seen in immunocompetent patients with a low detectable yield of bacilli. Other histopathological soft pointers considered to indicate an immunocompromised state include deeper infiltrate affecting subcutaneous tissue, and a rare presentation as diffuse infiltrate in the form of foamy histiocytes without any epithelioid cells or granulomas, resembling lepromatous leprosy. Features more commonly seen in immunocompetent patients include epidermal changes like acanthosis or pseudoepitheliomatous hyperplasia.[23] These features are soft clues and do not predict the immune status of the patients, as a mixed pattern is the most common type in both immunocompromised and immunocompetent patients, and chronic lesions of immunocompromised patients also frequently have granulomas.

Histopathology for NTM infections is not very specific. These features are also seen in other chronic cutaneous infections like multibacillary forms of cutaneous tuberculosis, deep fungal infections, leishmaniasis, etc., which are also clinical differentials of cutaneous NTM infections. The yield of special staining to differentiate between NTM and fungal organisms is not particularly high, ranging from 27% to 39.3% of cases overall, varying from 11% in immunocompetent cases to 90% in immunocompromised cases.[23–25]

Although the yield of special staining to demonstrate NTM organisms is low, biopsies and special stains should be done in all cases of suspected NTM infections. They can be supportive of the diagnosis and rule out other chronic infections. Table 2 summarizes some key studies on the histopathology of cutaneous NTM infections.[22,23,25–27]

Molecular methods performed on samples of cultures are very useful for speciation. The targets of designed probes are usually 16S rRNA, *rpoB* gene, and *hsp65* genes. Restriction fragment length polymorphism analysis techniques have also been used. Similar to *M. tuberculosis*, line probe assay and microarray-based kit systems that can rapidly check for multiple species in high-throughput settings, and can be deployed directly on patient samples, have also been designed. They are expensive, have limited commercial availability, and are not extensively validated, especially with other chronic infections as negative controls.[8] We must continue to develop and validate newer kits based on molecular methods in the hope of getting validated, economical, commercially available, rapid, diagnostic, and speciation tests that can be directly deployed on clinical samples, such as skin tissue samples.

High-performance liquid chromatography (HPLC)-based analysis of mycolic acid was used for NTM identification in the past. Although this method identifies slowly growing NTM species such as MAC and *M. kansasii*, it is less specific in identifying rapid growers accurately. It also has low discriminatory power to identify closely related slow-growing and rapid-growing mycobacterial species.[8] It is more economical than sequencing and has also been explored on direct patient samples.

Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry is a novel proteomics-based technique that can be used for identifying NTM species. However, the best method for protein extraction from mycobacteria and the level of discrimination offered by this method is yet to be determined. It has a high initial cost and cannot differentiate between subspecies of *M. abscessus* and within the MAC, *M. fortuitum*, and *M. mucogenicum* groups, and other closely linked NTM species.[8]

While speciation is useful to direct antibiotic therapy based on reported response rates for slow growers, this does not hold true for rapid growers. *M. ulcerans* and *M. marinum* do not need susceptibility testing, the MAC group needs to be checked only for clarithromycin, and *M. kansasii* only for rifampicin. Within rapid growers, the same species might show a wide variety of resistance patterns, and a wide variety of antibiotics need to be tested, usually through the microbroth dilution method.[11] Another factor complicating the choice of therapy is that appropriate breakpoint threshold definitions have not been established for some antibiotics/some species, and *in-vitro* susceptibility does not always correlate with *in-vivo* susceptibility.

Other investigations include radiological studies to know the extent of involvement. Deeper involvement can dictate management, in terms of longer duration of antibiotics, usage of parenteral antibiotics as first-line, and additional surgical methods. Table 3 summarizes an approach for investigations in a suspected case of cutaneous NTM infection.

Table 2: Summary of studies on histopathology of cutaneous atypical mycobacterial infections

	Abbas *et al.*[26]	Min *et al.*[22]	Song *et al.*[27]	Li *et al.*[25]	Bartralot *et al.*[23]	
N	17	10	7	13	28	
Year	2005–2008	2012	2009	2017	2000	
Place	Beirut, Lebanon	Seoul, Korea	Incheon, South Korea	Liverpool, New South Wales Australia	Barcelona, Spain	
Histopathological features (%)					IS=10	IC=18
Epidermal changes						
• Epidermal hyperplasia	74	80	43	15	30	83
• Pseudoepitheliomatous hyperplasia	21	10	29	62	20	39
• Intra-epidermal neutrophilic abscess	47	0	0	38	0	0
• Ulceration	5	10	0	15	10	5.5
• Exocytosis	-	80	-	-		56
Depth of infiltrate						
• Papillary dermis		60	0		10	5.5
• Superficial reticular dermis		80	29		20	28
• Deep reticular dermis		80	49		70	72
• Subcutaneous tissue		90	29		100	39
Infiltrate distribution						
• Perivascular superficial		20	0		20	56
• Diffuse superficial		60	29		20	33
• Perivascular deep		10	14		40	33
• Diffuse deep		70	57		100	61
Type of granulomas						
• Suppurative	47	80	43	85	50	28
• Tuberculoid	30	0	14	15	20	5.5
• Sarcoidal	11	20	0	0	20	56
• Palisading	11	10	14	0	0	17
• Interstitial	5	40	0	0	0	
• Vague and ill-defined	-	80	-	85	-	
• Granulation tissue-like changes	58	-	-	-		
• Dermal fibrosis	58	-	-			
• Dermal necrosis	16	40	43	38	60	50
Inflammatory cells						
• Multinucleated giant cells	47	10	57		80	72
• Lymphocytes	100	50	100		60	89
• Histiocytes	100	30	100		90	94
• Neutrophils	79	100	43		100	89
• Plasma cells	58	10	43		20	33
• Eosinophils	32	60	14		-	-
Small vessel proliferation		100	100			

IS - Immunosuppressed, IC - Immunocompetent

Prevention

Because of increasing NTM infections secondary to surgical procedures, many interventions are proposed to prevent this complication of these procedures, especially laparoscopic procedures.[20] They include-

1. Using a higher glutaraldehyde concentration (3.4% instead of 2.5%), using the ideal minimum exposure time of 8–12 h, and keeping a diligent record of usage of glutaraldehyde (maximum of 100 cycles or 28 days for 3.4%), avoiding washing the instruments with boiled tap water to rinse off the glutaraldehyde
2. Using ethylene oxide gas sterilization, gas plasma technology, and autoclaving instead of glutaraldehyde
3. Usage of disposable laparoscopic instruments if feasible.

Table 3: Investigations in patients of suspected cutaneous non-tuberculous mycobacterial (NTM) infections

Investigations to confirm the diagnosis

- Acid-fast staining- from pus/tissue sample
- Skin biopsy- also helps in ruling out other infections
- Culture- can be sent to same labs where *M tuberculosis* cultures done, try to include drug susceptibility
- Biochemical, proteomics, and molecular testing- depending upon availability and affordability

Other investigations

Imaging (ultrasound/CT/MRI) to look for deeper involvement

- Clues to deeper involvement
  - lesion morphology- deep ulcer/sinuses fixed to the underlying structures/disseminated lesions
  - restriction of movement of the limb/joint involved
  - immunosuppression

Investigations to look for immunosuppression- as per history and clinical context

Investigations to monitor adverse effects of treatment

- Weekly renal function tests if on parenteral aminoglycosides or carbapenems
- Baseline audiometry, and clinical monitoring if amikacin used
- Hemogram and monitoring for other side effects of long-term cotrimoxazole and linezolid if clinically indicated

Treatment

The 2007 joint statement by the American Thoracic Society and the Infectious Disease Society of America outlined management guidelines for NTM infections, encompassing skin and soft tissue infections (SSTIs) and bone infections. The 2007 guidelines advise a minimum of 4 months of combination therapy for SSTIs, typically recommending surgery for adequate source control.[13] These are generally species-specific, targeting different agents as per species. This poses many challenges because often treatment without identification of the causative organism is required in clinical settings, either due to low yield or unavailability of investigations. Species-specific antibiotics are summarized in Table 4.[28]

There are no guidelines for treatment duration after healing for other cutaneous NTM infections. Various researchers have recommended continuing treatment for 6–12 weeks after clinical remission or a total treatment duration of 4 months for superficial and 6 months for deeper rapid grower infections. For MAC a total of 6–12 months of treatment is recommended.[20] The duration of parenteral antibiotics is usually an initial 4–6 weeks, and if an initial response is obtained, further maintenance can be done using oral drugs alone. The lack of randomized controlled trials looking at the efficacy of antimicrobial agents means that empiric therapy may result in treatment failure, necessitating prolonged combinations of antibiotics, and thus increase the probability of side effects, and diminished compliance. The treating physician should ideally be well versed with the prevalence of various NTM species in the geographical area of his/her practice, but the uncertainty of the treating physician is understandable.

A combination of medical and surgical therapy (for source control and debulking, e.g., Wide-local excision of abscesses) can be tried whenever feasible. A study revealed that patients solely undergoing medical therapy had a median treatment duration of 8.5 months, while those receiving both medical and surgical treatments had a median duration of 4 months. Though not conclusive, this suggests the potential significance of adjunctive surgery in reducing the duration of antimicrobial therapy.[13]

Jagadeesan *et al*.[29] reported 3 cases of *Mycobacterium chelonae* infections treated using clarithromycin and doxycycline, clarithromycin with ofloxacin, and linezolid with doxycycline. Kumar *et al*.[6] reported 4 cases of NTM infections from Delhi, where *M. abscessus* isolates (n = 3) were susceptible to clarithromycin, amikacin, and linezolid, while susceptibility to levofloxacin was seen in 2/3 (66.6%) isolates. The *M. fortuitum* isolate (n = 1) was susceptible to amikacin, linezolid, clarithromycin, and clofazimine. Kannaiyan *et al*.[30] reported 19 cases of surgical site *M. fortuitum* and *M. chelonae* infections, where all isolates analyzed for antimicrobial susceptibility pattern were sensitive to clarithromycin, linezolid, and amikacin but showed variable susceptibility to ciprofloxacin (82% susceptible), tobramycin (30% susceptible) and rifampicin (58% susceptible). In a study by Ghosh *et al*.,[31] 15 cases (*M. abscessus = 13, M. fortuitum = 2*) of rapid-growing mycobacterial infections, showed the highest susceptibility to both clarithromycin and amikacin (93.3%).[31] Indian studies on treatment response or antibiotic sensitivity analysis have mostly been on rapid growers, and are summarized in Table 5.

As mentioned before, the yield of culture is suboptimal, and the facilities are not available everywhere. There are discrepancies between the results obtained through *in-vitro* susceptibility testing and the actual response of patients to treatment.[8] In such scenarios, an empirical treatment and therapeutic trial approach are justified, similar to the approach developed for cutaneous tuberculosis infections, recognizing that the organism cannot be identified in the majority of cases. The INDEX-Tb Indian national guidelines for the treatment of extra-pulmonary tuberculosis endorse this approach.[32] However, such an empirical regimen might be difficult to establish for NTM infections. The NTM group is considered to be heterogeneous with respect to antibiotic susceptibility patterns, and not much data is available regarding cutaneous NTM infections. The maximum duration for which a multi-drug antibiotic should be given to observe for a response is also not defined and consistent. Parenteral vs oral antibiotics is also a concern. Some very effective antibiotics like aminoglycosides

Table 4: Summary of species-specific treatment of cutaneous atypical mycobacterial infections

Organism	Drugs
Rapid growers	
M. abscessus	*M. abscessus* group is usually susceptible to parenteral antibiotics like aminoglycosides (streptomycin 15 mg/kg/day), carbapenems, and cephalosporins like cefoxitin. They also respond well to macrolides, but can express inducible macrolide resistance. The initial drug regimen for it should still include a macrolide like clarithromycin 500–1000 mg/day or azithromycin 250–500 mg/day. Surgery can be used in addition to medical therapy. Initial parenteral treatment for 4–8 weeks followed by oral treatment for 6–12 months may be required.
M. fortuitum and *M. chelonae*	Macrolide agents are the cornerstone of medical therapy for *M. chelonae* infections and generally, clarithromycin 500–1000 mg/day is the preferred agent. Aminoglycosides also show excellent activity against *M. chelonae*. Fluoroquinolones (ciprofloxacin 500 mg twice daily or levofloxacin 500 mg once daily) and tetracyclines (doxycycline 100 mg once daily or minocycline 100 mg twice daily) too are effective agents and there are reports of excellent sensitivity to linezolid. However, *M. chelonae*, but not *M. fortuitum*, is resistant to cefoxitin. They are resistant to conventional anti-tubercular drugs. Initial parenteral treatment for 4–8 weeks followed by oral treatment for 6–12 months may be required, however, shorter regimens have shown to work in multiple studies without recurrence.
Slow growers	
M. marinum	Similar group of antibiotics as for *M. chelonae*, along with rifampicin (450–600 mg/day), ethambutol (15 mg/kg/day), and cotrimoxazole (400/80 mg twice daily), are effective for *M. marinum*,. Monotherapy with clarithromycin, doxycycline, and contrimoxazole for at least 3 months can be used for limited infections, and rifampicin and ethambutol for at least 2 months after clinical healing for severe infections. Surgical treatment is a useful adjuvant.
M. ulcerans	Rifampicin (450–600 mg/day), combined with oral clarithromycin (500–1000 mg/day)/fluoroquinolone or parenteral streptomycin (15 mg/kg/day) for 8 weeks is the ideal first-line therapy.
M. avium complex (MAC)	Treatment with at least 3 drugs (usually rifampin, ethambutol, and clarithromycin,) for 6–12 months is required. For severe cases, amikacin is recommended for the first 6 weeks
Mycobacterium kansasii	Traditional anti-tubercular regimens have been reported to be effective in the same dosage and duration as used for tuberculosis
Mycobacterium haemophilum	Polychemotherapy containing clarithromycin (500–1000 mg/day), ciprofloxacin (500 mg twice daily), and rifabutin (150–300 mg/day) is suggested, with variable duration

are available only in a parenteral formulation. However, choosing them implies that the patients have to be admitted for injectables for a few weeks, which entails significant costs in terms of money and time. Alternatively, if feasible the patients can go to a dispensary/nursing home/local hospital near their place of residence once or twice a day for getting the parenteral drug, or they can get it supervised at their home by a healthcare professional if they can afford it. There is no evidence that a parenteral regimen with aminoglycosides works better or faster than an oral regimen comprising another highly effective drug such as clarithromycin, which is especially useful in the *fortuitum-chelonae complex*, although it is preferred as the first-line for deeper tissue infections.

For NTM infections, we have used an empirical oral regimen consisting of clarithromycin 500 mg once or twice daily, doxycycline 100 mg once or twice daily, and cotrimoxazole single or double strength 800/160 mg twice daily, which showed complete resolution in some patients within a few months [Figure 2]. Fluoroquinolones (ciprofloxacin 500 mg twice daily or levofloxacin 500 once daily) and linezolid (600 mg once or twice daily) are other oral alternatives to cotrimoxazole. We prefer twice daily dosing for clarithromycin and doxycycline, although once daily has also been recommended and can be used if there is intolerance with twice daily dosing. Similarly, we prefer cotrimoxazole double strength twice daily, however, regular strength can also be used. This is one of the most commonly used empirical regimens at some centers, with significant cure rates.[2,4] Cure requires prolonged antibiotic treatment, with mean time to remission being 40 weeks in a study,[4] and can show relapses, with 7 (9.5%) out of 74 relapsing within 6 months of remission in a study.[4] The cure rate is decent, reported close to 100% in various studies, excluding the patients who die of unrelated causes or who were lost to follow-up.[2,4,13]

We consider waiting for 2–3 months to observe a response to consider the regimen to fail or if an alternative diagnosis is to be considered. We treat 4–6 months beyond clinical remission, though shorter courses can also be tried. We use parenteral amikacin 15 mg/kg/day, or gentamicin 80 mg twice daily, or imipenem as second-line, or first-line if deeper infection (suspected or shown to involve deeper soft tissue, muscle or bone) or immunosuppression is suspected. General care and surgeries are done as required. The recommendation that patients should be off any antibiotics for at least 2 weeks before investigations complicates things. An approach would be to send baseline investigations and wait for results. If no growth is seen in 2–4 weeks (the usual time for slow growers to show a positive culture), the empirical regimen can be started. Alternatively, in disseminated infections or immunosuppression, empirical

Table 5: Summary of Indian studies on treatment of cutaneous atypical mycobacterial infections

Author	Year	Place	Conditions covered	*n*	Species	Treatment, with duration and response
Jagadeesan *et al*.[29]	2018	Kochi, Kerala	Isolate confirmed as *M. chelonae* using multiplex polymerase chain reaction	3	*M. chelonae*	Case 1: Doxycycline and linezolid. Lesions healed fully within 4 weeks. Treatment continued for a total of 10 weeks with no recurrence during the 6-months follow-up period. Case 2: Clarithromycin and doxycycline. The ulcer healed in 6 weeks. Treatment continued for 4 more weeks after the resolution of the lesion with no recurrence during the 3 months follow-up period. Case 3: Clarithromycin and ofloxacin. Lesions healed fully within 6 weeks. Treatment continued for 6 more weeks after the resolution of the lesion with no recurrence during the 3 months follow-up period.
Kannaiyan *et al*.[30]	2012–2013	Puducherry	Postoperative wound infections with signs of inflammation of the skin and abscesses or drainage at the wound site in addition to not responding to incision and drainage and antibiotics used for pyogenic infections, which were culture confirmed for rapid grower mycobacteria	19	*M. fortuitum* and *M chelonae*	Only sensitivity testing done, not treatment. Isolates were sensitive to clarithromycin, linezolid, and amikacin but showed variable susceptibility to ciprofloxacin (82% susceptible), tobramycin (30% susceptible) and rifampicin (58% susceptible).
Kumar *et al*.[6]	2021	Delhi	One case of breast abscess and three cases of postsurgical wound infections	4	*M. abscessus* and *M. fortuitum*	*M. abscessus* isolates (*n*=3) were susceptible to clarithromycin, amikacin, and linezolid, while susceptibility to levofloxacin was seen in 2/3 (66.6%) isolates. The *M. fortuitum* isolate (*n*=1) was susceptible to amikacin, linezolid, clarithromycin, and clofazimine.
Ghosh *et al*.[32]	2017	Kolkata	Port-site infections after laparoscopic surgery with the evidence of delayed wound healing, breakdown of wounds after initial healing, redness or discharge from any wound, nodules in or around the vicinity of the wounds, and nonresponsive to empiric antibiotic therapy.	15	*M. abscessus*=13, *M. fortuitum*=2	Only sensitivity testing done, not treatment. Isolates showed highest susceptibility to both clarithromycin and amikacin (93.3%). Only one isolate of *M. abscessus* was resistant to these two drugs. Susceptibility to imipenem, gentamicin, ofloxacin, and linezolid in *M. abscessus* cases was 77%, 61.5%, 41.5%, and 30.8%, respectively. All 13 isolates of *M. abscessus* were resistant to tetracycline, cefoxitin, and polymyxin B. Of the two isolates of *M. fortuitum*, one showed sensitivity to all antimicrobials tested, except vancomycin, while the other was resistant to cefoxitin, tetracycline, erythromycin, ciprofloxacin, and vancomycin.

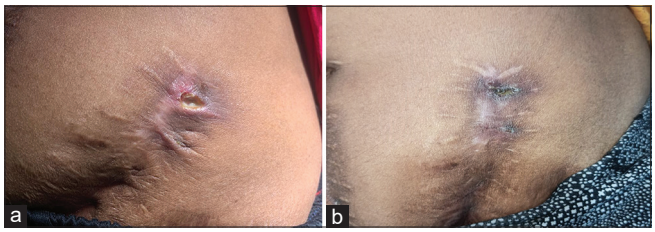

Figure 2: Empirical treatment for post-surgical cutaneous atypical mycobacterial infection by rapid growers. a) Development of multiple abscesses which ruptured to form sinuses over port sites, 5 weeks after laparoscopic surgery. b) Good response in terms of stoppage of pus discharge and healing of sinuses after 1 month of treatment with clarithromycin 500 mg, doxycycline 100 mg, and cotrimoxazole 800/160 mg, each twice daily. There was complete healing with scarring with 3 months of therapy

antibiotics can be started directly without waiting, after sending the first set of samples. If the empirical regimen does not show any response or shows just minimal response, the magnitude of which can be ascribed to natural fluctuation, it is reasonable to stop the treatment for 2 weeks, look for any increase in symptoms, and then send repeat samples and start second-line treatment. As close monitoring to observe changes is required, good baseline and follow-up photos, sensitization of the patient to quantify the symptoms accurately to gauge treatment, and ideally, follow-up with the same dermatologist/team should be done.

However, our protocol is just anecdotal, and rigorous studies are required to establish such regimens. The lack

of good diagnostic techniques for the infective agents and their drug susceptibility justifies the prolonged use of multiple empirical antibiotics despite manageable adverse effects, cost, and an inherent failure rate. There are other disadvantages of empirical therapy. These drugs are also used in drug-resistant cutaneous tuberculosis, which is increasingly being described in India. Empirical therapy should not be overused as a replacement for directed therapy. Efforts should be directed to have good laboratory facilities at tertiary centers, and referral and notification systems and policies at lower centers, for detecting and managing NTM infections. If the empirical regimen succeeds, then that individual patient may have a successful result, but like any other multidrug regimen, the actual efficacy of any individual drug cannot be vouched for. Treatment recommendations have been summarized in Table 6.

Conclusion

With increasing laparoscopic and other minimally invasive procedures, infections with rapid grower species are frequently seen. The clinical presentation of cutaneous NTM infections, except for *M. marinum*, *M. ulcerans*, and rapid growers, is diverse and non-specific. Although newer diagnostic techniques and the increasing availability of sequencing techniques yielding antibiotic sensitivity patterns help, the availability and sensitivity of these techniques remain limited. In resource-limited settings, an empirical multi-drug therapy approach is justifiable, while attempts to identify the organism and its drug sensitivity patterns continue. The enigma of NTM will continue till we evolve a specific regimen with more studies and evidence.

Table 6: Management of suspected cutaneous non-tuberculous mycobacterial (NTM) infections

General care

- Ulcer/wound dressing
- Pain control
- Disability management

Medical management

- Can be started after sending the first set of investigations, including the first culture and drug susceptibility
- Empirical regimen- clarithromycin, doxycycline, cotrimoxazole/ciprofloxacin
- Parenteral drugs like aminoglycosides (amikacin/ gentamycin) can be started as first-line if deeper infection/ immunosuppression
- Duration of treatment- not fixed, can treat till few months after clinical remission
- If no response in symptoms/signs within 3 months of therapeutic trial
  - To change to the second-line, as directed by the drug susceptibility report, or next in the hierarchy (e.g., if initially only oral regimen was used, doxycycline can be replaced with parenteral aminoglycosides, if aminoglycosides were used as first-line then can shift to carbapenems, cotrimoxazole and clarithromycin can be replaced with linezolid or fluoroquinolones)
  - Consider adding surgical methods
  - Also consider alternative diagnosis

Surgical management

- To be considered in addition to medical management rather than as a single modality
- Can be added as first-line itself rather than limited to cases with sub-optimal response to medical management
- To be individualized based on the risk-benefit ratio, and how debilitating it can be to the patient

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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