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REVIEW ARTICLE OPEN ACCESS

A Comprehensive Review and Update on Epidemiology, Symptomatology and Management of Nontuberculous Mycobacteria (NTM)

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Abstract

Nontuberculous mycobacteria (NTM) are free-living organisms ubiquitously present in the environment. In recent times, NTM gained much importance due to the increase in incidence globally. They are potential agents in causing both pulmonary and extrapulmonary infections in both immunocompromised and immunocompetent individuals. The problem arises when the possible NTM cases are misdiagnosed as drug-resistant tuberculosis (DR-TB). Hence, it is essential to correctly identify the NTMs causing disease due to two major reasons. One is to prevent clinicians from starting anti-tuberculous drugs and the other is that treatment regimen differs for certain NTM from tuberculosis. Apart from conventional methods like smear microscopy, culture, in the current era newer diagnostic modalities like matrix-assisted laser desorption of ionization-time of flight mass spectrometry (MALDI TOF MS), line probe assay, genomic sequencing, are used in referral laboratories which allows identification and speciation of the organism. A thorough literature search was done in PubMed, Google Scholar, Cochrane Library, Embase, Scopus on nontuberculous mycobacteria. The search keywords include nontuberculous mycobacteria, atypical mycobacteria, case reports, and original articles on NTM. In this review, we have summarised the current knowledge on epidemiology, pathogenesis, clinical features, and treatment of NTM.

Keywords: Nontuberculous mycobacteria, Epidemiology, Pathogenesis, Clinical features, Management, Drug resistance

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INTRODUCTION

Discovery and classification of atypical mycobacteria

In the hunt for Koch bacillus in the environmental sources, several mycobacteria were isolated from soil, water, cheese, animals, etc. In 1935 Pinner called these organisms atypical organisms. Costa Cruz in 1938 isolated *Mycobacterium fortuitum* from abscess followed by Linell and Norden in discovering *Mycobacterium marinum* in 1952. An important pathogenic NTM identified by Buhler and Pollak from a necropsy was later named *Mycobacterium kansasii* in 1955 by Hauduroy. Pigmented NTM that produces a yellow-orange colony in a dark and red colony on exposure to light was named *Mycobacterium scrofulaceum* by Prissick and Masson in 1957. In the same year, Battey bacillus was identified from a patient's sputum in Battey state tuberculosis hospital in Georgia. Later in 1977, a strain isolated from patients in Malmo, a place in Sweden was given the name *M. malmoense*. The next year from a Hodgkin's lymphoma patient *Mycobacterium haemophilum* was isolated. From an HIV patient in Genavense in 1991 *Mycobacterium genavense* was isolated.[1,2]

More than 200 species of NTM are prevalent globally but only a few species have pathogenic potential. There are rapidly growing mycobacteria (RGM) containing six groups which include *M. fortuitum* group, *M. chelonae abscessus* group, *M. mucogenicum* group, *M. smegmatis* group, early pigmenting RGM, non pigmented groups. *M. fortuitum* group includes *M. fortuitum*, *M. neworleansense, M. peregrinum, M. brisbanense, M.senegalense, M. setense, M.boenickei, M. houstonense, M. chelonae abscessus* group includes *M. chelonae, M. salmoniphilum, M. saopaulense M. franklinii, M. immunogenum, M. abscessus. M. mucogenicum* group contains three species namely *M. mucogenicum, M. aubagnense, and M. phocaicum*. *M. smegmatis* group includes *M. smegmatis* and *M. goodii.* Early pigmenting RGM includes *M. flavescens, M. vaccae, M. psychrotolerans, M. phlei, M. neoaurum, M. canariasense, M. cosmeticum. M. celeriflavum, M. hippocampi, M. anyangense, M. mageritense, M. wolinskyi* are the sixth group of non pigmented species. Slowly growing mycobacteria include *Mycobacterium avium complex, M. xenopi, M. kansasii, M. simiae complex, M. terrae–M. nonchromogenicum* complex, *M. szulgai, M. malmoense*, *M. scrofulaceum.*[3]

Epidemiology

In the 20th century, mycobacteriosis occurred in small numbers due to rare interactions between the NTM and host. But at present due to multifactorial factors, the incidence of NTM related infections are on the rising trends.[4]

Environmental factors

Two models which include the "susceptible dose" and "unusual dose" model for disease acquisition are described.[5] Susceptible model states that irrespective of the level of exposure to the pathogen individual will get the disease and the unusual dose model states that increased dose of the bacteria leads to the disease besides the immune status. The name 'Environmental bacteria' as such explains the wide distribution of the organism which includes plumbing system in households, water distribution system in hospitals, drinking water supply system, hot tubs and spas, potting soil, household aerosols, metal removal fluid system, refrigerated water and ice, catheters, heated nebulizers, vacuum cleaners.[5-7]

Mycolic acids, arabinogalactan, trehalose containing lipooligosaccharides, glycopeptidolipids, and phenolic glycolipids are responsible for hydrophobic surface and increased thickness of NTM both of which are responsible for adherence to the above surfaces and biofilm formation.[8] Characteristic features like the ability to resist high temperature and requirement of very low level of oxygen and nutrition contribute to its successful survival in the environment.[9]

Due to overlapping of habitats of protozoa like *Acanthamoeba castellanii* and certain NTM like *M. scrofulaceum, M. avium,* phagocytic protozoa plays a very important role in the epidemiology and ecology of these atypical mycobacteria.[10] 88% of amoeba-like *Acanthamoeba, Echinamoeba, Protacanthamoeba, Vermamoeba* from drinking water was found to contain *M. chelonae* and *M. llatzerense* both of which showed increased resistance to antibiotics.[11] *M. avium* identified from a patient with NTM lung disease was isolated from the patient's home showerhead biofilm.[12] *M. intracellulare* has been frequently recovered from potable and house hold water supply.[13]

M. chimaera found in heater-cooler units used during open-heart surgery caused an outbreak that has provided challenges to the medical field.[14] *M. fortuitum* isolated from pedicure associated whirlpool footbath[15] and *M. chelonae* from contaminated water used for diluting tattoo ink has been documented in causing skin infections.[16] Thorel et al. stated that 85% of soil, mosses, woods contained *M. chelonae, M. fortuitum*, and *M. kansasii* thus proving their distribution in mountain elevations.[16] Australian ringtails and brushtails possums are the potential reservoirs of *M. ulcerans*.[17] *M. avium* isolated from pigs showed some similar genetic characteristics to those that were isolated from humans as a result of which pigs were considered as an important source of infection.[18] *M. marinum* which is present in aquatic environments and mostly coinhabit aquatic organisms like shellfish, shrimp, eels, oysters, etc is associated with fish tank granulomas in humans.[19] *M. fortuitum* has been recovered from the tissue of feral buffaloes and raw milk.[20]

In health care settings NTM related infections occurring in hospitalized patients ranges from colonization to outbreaks. 60% to 100% NTM colonization is found in hemodialysis units and hospitals. Outbreaks related to NTM injection site abscesses due to the use of contaminated syringes and reusable injection devices are reported. Infections of central venous catheters and NTM cardiac pacemaker infections are also documented. Bronchoscope suction valves and channels commonly get colonized with NTM mycobacteria, which leads to transmission of NTM to uninfected patients.[21] Contaminated otolaryngostomy equipment and tympanostomy tube placement has led to *M. chelonae* otitis media and *M. fortuitum* mastoiditis.[22,23]

Host factors

Three main groups which include immunocompromised patients, the ageing population, and malnutrition are highly susceptible to NTM. It occurs at an increased level in susceptible populations called mendelian susceptibility to mycobacterial disease (MSMD).[24] Immunocompromised conditions like AIDS, anti-cytokine autoantibody, intake of TNF alpha inhibitors like infliximab, adalimumab, steroidal consumption increases the risk.[25] Incidence of NTM is also expected to increase in the elderly population. Elderly men with risk factors like alcohol consumption, smoking, chronic pulmonary obstructive disease, bronchiectasis, cystic fibrosis, and elderly women without the above-mentioned risk factors are highly susceptible.[26] People with malnutrition may have a defect in inspiratory drive and weakness of inspiratory muscles which leads to defect in clearance mechanism. Eating disorders like anorexia nervosa by causing alteration in the immune system increases the risk of infection.[27]

Agent factors

A. Global distribution of NTM

Geographical distribution of NTM helps to gain information about the factors that are responsible for causing NTM lung disease (NTM-LD) highly specific to a location. *Mycobacterium avium complex* (MAC) is the common organism isolated worldwide followed by rapidly growing mycobacteria like *Mycobacterium abscessus* and *Mycobacterium fortuitum*. 80% of lung diseases associated with Non-tuberculous mycobacteria are caused by *Mycobacterium avium* complex, *M. kansasii* in the United States, and *M. abscessus* from Southeastern parts of U.S.[28] In northern Europe MAC and in Southern Europe *M. xenopi* were isolated predominantly. *M. kansasii* is the most common NTM in London and United Kingdom. *M. lentiflavum* and *M. gordonae* are the predominant species isolated in Greece and Canada, respectively. *M. intracellulare* was isolated commonly in Australia with *M. abscessus* being commonly recovered from Southern Australia. MAC species predominantly *M. intracellulare* has been increasingly reported from China. In Taiwan MAC is common in the north and *M. abscessus* in the south. In Gulf countries, MAC and *M. abscessus* are the most common NTMs. MAC, *M. simiae,* and *M. marinum* were frequently observed in Omen. *M. fortuitum* and *M. flavescens* are more prevalent in Iran. *M. abscessus* is more common in Singapore. *M. abscessus*, *M. fortuitum*, and *M. intracellulare* are common in Indian subcontinent.[29]

B. Global prevalence of NTM

The prevalence and incidence of NTM have increased globally.[30] According to a study conducted in the United States in 2013, the prevalence was estimated to be 13.9 per 100,000 population.[31] Prevalence of NTM pulmonary disease in Germany is about 3.3 cases per 100,000 population during 2009–2014.[32] A multicenter

study from Japan has shown the incidence of NTM pulmonary disease to be 10.1 per 100,000 population during 2001–2009.[33] Age-adjusted incidence and prevalence was estimated to be 17.9 and 33.3 per 100,000 population in Korea in 2016.[34] Iranian study conducted in 2021 showed the prevalence to be less than 15%.[35]

C. Indian prevalence of NTM

The prevalence of NTM in India varied from 0.7% to 34%.[36] According to a study in Northern India prevalence was estimated to be about 29%.[37] In Chandigarh, the incidence of NTM was estimated to be around 7.4% and in Delhi, it was found to be 8.3%.[38] Prevalence in pulmonary specimens was around 17.4% in Kolkata.[39] In south India, the prevalence of NTM was around 3.9%, according to a study in Vellore.[40] In our study we found the prevalence to be 1.1% with 0.7% among pulmonary specimens and 0.4% among extra pulmonary specimens.[41]

D. Virulence factors

The most important virulence factor is the thick waxy cell envelope. They protect them from host defense and antibiotics. Lipids account for 60% of the cell envelope compared to the gram-negative bacteria which have only 20%.[42] Two types of glycopeptidolipids (GPL) namely non-specific GPL and serovar-specific GPL are the other important virulence factors of NTM. Biofilm formation and the characteristic sliding motility are mainly induced by these GPL.[43] Lipoarabinomannan (LAM) is the next most potent virulence factor for NTM. According to the caps that are covering the LAM they will be called MANLAM, PILAM, AraLAM.[44]

E. Pathogenesis of NTM

NTM are initially bound to macrophages through fibronectin receptors, complement components like C3b and C4b, and receptors for mannose and fucose residues of the mycobacterial cell wall on their surface. The atypical mycobacteria that were bound to the macrophages will be phagocytosed. These mechanisms by which NTM were able to enter macrophages demonstrate that the intracellular niche provides survival adaption for the bacilli provided that the phagocytes are not sensitized to kill the bacilli. Production of defensins, toxic oxygen products, and acidification will take place to kill the intracellular bacilli.[45] But the NTM was able to evade the above host defenses by the inhibition of phagosome-lysosome fusion, intracellular anaerobic environment, induction of Genes that enhance replication, down regulating Bcl-2 gene. As a result of which apoptosis of macrophages will be induced.[46]

Macrophages process atypical mycobacterial antigens and present them to T lymphocytes. This results in the expansion of T lymphocyte that recognizes those atypical antigens and forms the basis of both immunologic memory and acquired immunity which are highly specific to host defense against mycobacteria. Once CD4 lymphocytes have been recruited to the site of mycobacterial infection they will secrete interleukin 2 and interferon-gamma. Both of them will activate macrophages and will increase cytotoxic lymphocyte activity.

If the inhaled organism survives its initial host defenses within the alveolar macrophages, then macrophages and monocytes will be recruited to the site of infection. The CD4 cells then will interact with infected macrophages leading to either destruction of infected macrophages or intracellular destruction of the mycobacteria. Among the immune cells, T helper lymphocytes form the basis of acquired immunity and natural killer (NK) cells form the basis of innate immunity.

These events will be demonstrated histopathologically in the formation of granulomas where the infected foci will be surrounded by epithelioid cells and other inflammatory cells. But areas of fibrosis and necrosis will be encountered in the nearby areas due to the release of certain enzymes which will be cytolytic. Two forms of pulmonary disease namely the fibrocavitary and fibronodular forms occur due to the above-stated events.[47]

Role of cytokines

Cytokines predominantly having antimycobacterial immune response are the interleukin-12 (IL-12), tumor necrosis factor-alpha (TNFa), and interferon (IFN) gamma. IL-2 enhances the ability of NK cells to lyse NTM -infected monocytes. Once IL-12 has binded it will result in the transcription of IL-12 responsive genes mainly the IFN-gamma. After the release of IFN-gamma, the production of superoxides and nitric oxide will be enhanced through the activation of neutrophils, macrophages. IFN-gamma also decreases lysosomal pH, increases the surface

display of MHC molecules and Fc receptors. It has been proved that IFN-gamma increases the intracellular concentration of certain antibiotics. TNF-alpha produced by activated macrophages is an important immune modulator for mycobacterial infection. The release of TNF-alpha is stimulated by IFN-gamma and once produced it will be responsible for the IFN-gamma's antimycobacterial effects.[48]

Evasion of the host response

Mycobacteria evade the host immune responses by several defense mechanisms. The most important ones are biofilm formation and inhibition of inflammatory cytokine production. These mechanisms promote both colonization and invasion of the bronchial epithelium. Mycobacterial cell wall plays an important role in host evasion by scavenging toxic oxygen intermediates, downregulating the lymphocyte proliferation, inhibiting the production of cytokine, blocking the acidification of phagocytes. The glycopeptidolipids (GPL) produced by NTM form a layer that covers the mycobacterial TLR2 ligand phosphatidyl-myo-inositol mannosides, thereby preventing the glycolipid from being recognized by TLR2.[49]

Biofilm formation is an effective survival strategy for environmental NTM. NTM in biofilms is highly resistant to disinfectants thereby making the eradication of NTM a troublesome process. They are resistant not only to disinfectants but also to antimicrobial drugs. Resistance to antibiotics may be due to enhancement of virulence in biofilms.[50]

Clinical features

Clinically infections caused by non-tuberculous mycobacteria manifest as pulmonary infections, lymphadenitis, skin, and soft tissue infections and then disseminated form.

Pulmonary infection

The pulmonary form remains one of the most common forms of NTM infections.[51] They are predominantly community-acquired. Pulmonary symptoms caused will be highly non-specific. Pulmonary disease constitutes nearly 85% of total cases. Patients with conditions like cystic fibrosis, emphysema, and bronchiectasis are prone to acquire NTM infections. *Mycobacterium avium complex* (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus* are the frequently encountered species. Nodular bronchiectasis and upper lobe fibrocavitary disease are the two important forms of pulmonary NTM.[52] The characteristic feature is the formation of granulomatous lesions in the respiratory tract which in due course of time leads to cavitation. The radiological feature in pulmonary form may be bronchiectatic or thin-walled cavity or nodule formation. In Asia, MAC was reported in 68% of all cases and RGM such as *M. abscessus, M. chelonae,* and *M. fortuitum* accounted for 14% of all cases.[53] In our study we found pulmonary infections to be predominantly caused by *M. intracellulare* (26.6%) followed by *M. abscessus* (17.7%) and *M. kansasii* (12.7%).[41]

Lymphadenitis

It occurs most commonly in children less than 5 years of age. Submandibular nodes are the most common lymph node involved in 87 percent of cases. It is followed by preauricular nodes in 9 percent and submental nodes in 3 percent of cases. Rarely supraclavicular nodes are involved.[54] the main route of entry for causing cervical lymphadenitis is the oropharyngeal mucosa or following penetrating trauma. Adults are affected if underlying comorbidities are present. Involved nodes gradually increase in size and mostly they will be unilateral. Occasionally they will rapidly increase in size leading to sinus tract formation once they have ruptured. Systemic symptoms occur if the nodes are infected secondarily by other bacterial infections. Histopathology plays a very prominent role in the identification of NTM related lymphadenitis. MAC contributes to 80% of lymphadenitis cases. In India common, NTM involved in causing lymphadenitis are *M. scrofulaceum, M. avium complex, M. kansasi,* and *M. fortuitum*.[55] Decreased echogenicity were detected in ultrasound in earlier stage preceded by edema in surrounding soft tissue, matting of the nodes in the latter. CT scan shows a hypodense lesion in the center with ring enhancement and also the absence of fat strands in the nodes which helps to distinguish them from bacterial lymphadenitis.[56]

Skin and soft tissue infections

Individuals acquire the infection by either the abrasion of the skin or through the penetrating injury. Especially after trauma in water bodies like swimming pools, paddling pools, and injuries following procedures like surgical and dental

sections, there are high chances of acquiring NTM infections. Infection can also occur at the site of vascular catheters, tattooed areas, or at the piercing site.

The lesions caused by NTM will be polymorphic consisting of ulcers, papules, plaques, or nodules. Initially begins as induration which will be progressing slowly and this indurated area will ulcerate in a few weeks. Except for lesions caused by *Mycobacterium haemophilum* other NTM causing skin lesions will be painless without any systemic manifestations. A study by Bartralot et al. showed cutaneous manifestations caused by NTM can be classified as localized lesions or disseminated cutaneous lesions. The localized lesions can further be differentiated as either lymphocutaneous (sporotrichoid) or non-lymphocutaneous form.[57] But the manifestation of the lesions in disseminated form varies depending on the immune status of the patient. In normal individuals the disseminated lesions manifest in the form of folliculitis and the immunosuppressed patient's lesions may take the form of plaques, nodules, or ulcers. The most common agent causing these forms of the lesion is the rapidly growing NTM. Species like *M. kansasii, M. avium complex* are also responsible for the above described disseminated infections.[58]

The most common skin manifestation caused by NTM will be in the form of fish tank granuloma caused by *M. marinum* or Buruli ulcer caused by *M. ulcerans* or lesions caused by rapidly growing NTM causing non-specific lesions.

Lesions caused by *M. marinum* commonly affect the upper extremity (95%), among which 80% of cutaneous involvement in the upper limb occurs in hands. The type of lesion following *M. marinum* occurs in a sporotrichoid pattern without involving any nodes. For treatment, lesions are categorized into three main types which are as follows: Type 1, Type 2, and Type 3 lesions.

Type 1 are superficial lesions that rarely require antibiotics if no remission was observed; In Type 2 lesions, subcutaneous granulomas are formed for which treatment with an antibiotic is mandatory; finally, in Type 3 lesions there will be deeper structures like tendons, bones which are involved for which both surgical excision and antibiotic therapy will be given. A rare case of tenosynovitis caused by *M. marinum* infections have been reported.[59]

One of the neglected diseases that are caused by NTM which requires increased surveillance is the bankruptcy wound also known as Buruli ulcer caused by *M. ulcerans.* Other names for this ulcer are Searls ulcer, Mossman ulcer, or Kumasi ulcer. Although the highest number of cases is found in Africa, the disease has also been documented in America, Asia, and the Pacific regions. Presenting as a painless lesion in the form of a nodule which eventually undergoes necrosis and forms an ulcer. The manifestation of this pathogen is due to the production of a toxin called mycolactone which binds to WASP protein and SEC61 and causes cell death. According to World Health Organization, lesion caused by *M. ulcerans* is classified into three categories. Based on the size and type of lesions they are categorized as the first, second, and third categories. Lesions less than 5 cm are considered as first and the lesion between 5 to 15 cm comes under the second category and those that are more than 15 cm or involve sites like bones, eyes, and breast are called the third category. Again category three is classified into three groups as 3a, 3b, and 3c if there is additional involvement of bone in the form of osteomyelitis, at sites that are critical and numerous tiny lesions respectively.[60]

Disseminated form of NTM

Disseminated form of the NTM infections occurs in immune-compromised patients causing vague symptoms like high-grade fever, night sweats, weight loss, hepatosplenomegaly. The most common atypical organism causing disseminated forms are *M. avium complex, M. genavense*. Patients at high risk of acquiring disseminated NTM infections include AIDS patients if the CD4 count is less than 100/µL, patients receiving treatment for the inflammatory disease by consuming antibodies against interferon-gamma and hemodialysis patients. Genetic susceptibility was observed in those patients in which HIV is negative.[61] In our study we found the extrapulmonary infection to be predominantly caused by *M. intracellulare* (21.1%) followed by *M. scrofulaceum* (15.8%) and *M. fortuitum* (10.5%).[41]

Treatment

Mere isolation of NTM cannot be considered for starting treatment. NTM causes

pulmonary manifestation similar to tuberculosis but the characteristic feature is that certain NTM does not respond to the routinely used anti-tubercular drugs so there is a possibility that NTM cases may be misdiagnosed as drug resistant TB in resource-poor settings as already discussed.[62] Added burden in this regard is the cost spend for treatment. According to the study conducted by Strollo et al., it was found that 815 million dollars were spent in 2010 to treat 86,244 NTM cases.[63] Apart from problems like misdiagnosis as TB, increased cost spent in treatment there are other issues like a prolonged period of treatment, relapses which make the treatment of NTM diseases, a cumbersome process.[64]

The empirical therapy for suspected NTM lung disease is not recommended by the ATS guidelines. Antimycobacterial susceptibility should be performed according to the Clinical and Laboratory standard institute (CLSI) M24 document and should be reported with the minimum inhibitory concentration (MIC). Before starting the treatment certain patient-related factors need to be considered which include comorbidities, type of risk factors that the patient is harboring, and severity of the disease.

For MAC-associated disease, combination rifampin, ethambutol, and clarithromycin or azithromycin either daily or intermittently based on the severity of the disease is recommended. Injectable aminoglycosides are usually preferred for patients with severe diseases. But patients in whom injectables are contraindicated, the use of nebulized aminoglycosides can be suggested. Similar to MAC treatment, the regimen of choice for the treatment *M. malmoense* also includes the same regimen.[65]

NTM-PD due to *M. kansasii* is treated with rifampicin, ethambutol with macrolide, or isoniazid. In addition to the above-mentioned drugs either isoniazid or fluoroquinolone will be added in case of infections due to *M. xenopi*.[65]

M.abscessus causing disease will be treated in two phases which include initially the intensive phase followed by the continuation phase. The initial phase includes intravenously given amikacin, tigecycline, and imipenem and orally tolerated azithromycin or clarithromycin followed by a continuation phase with amikacin given in nebulized form along with azithromycin or clarithromycin. Based on antibiotic susceptibility, up to three can be added among clofazimine, linezolid, minocycline or doxycycline, moxifloxacin or ciprofloxacin, and co-trimoxazole.[65]

M. chelonae which mainly causes skin and soft tissue infections and bone infections will be treated for 4 months and 6 months respectively. Drugs like tobramycin (superior to amikacin), imipenem, ciprofloxacin, doxycycline, clarithromycin, and linezolid can be given in combinations. If the patient is not responding to drugs then surgery will be indicated in appropriate conditions.[65]

For *M. fortuitum* causing lung infections, 12 months of therapy containing two drugs that show invitro activity is given. The extrapulmonary infections caused by them will be treated like those caused by *M. chelonae.*

M. genavense, highly fastidious NTM shows susceptibility to streptomycin, amikacin, macrolides, fluoroquinolones, and rifamycins. *M. marinum* is found to be susceptible to ethambutol, clarithromycin, cotrimoxazole, rifabutin, and rifampin. They are found to be resistant to first-line anti-TB drugs like pyrazinamide and isoniazid. A combination of two agents namely clarithromycin and ethambutol are given for a total of nearly 3 to 4 months. *M. haemophilum* causing infections are treated with ciprofloxacin, rifampin, clarithromycin, and rifampin.[65]

Pulmonary infections and certain intraabdominal infections caused by *M. simiae* are treated with moxifloxacin which shows higher activity against this species in combination with cotrimoxazole and clarithromycin. *M. smegmatis* which mainly causes extrapulmonary disease are treated with two principle drugs namely cotrimoxazole and doxycycline both of which are given in oral formulations. But parenteral route can be used if the organism causes severe infection.[65] *M. szulgaiis* peculiar in being susceptible to some antitubercular drugs like pyrazinamide, rifampin, and isoniazid and was also found to be sensitive to quinolone and macrolide.[65]

M. ulcerans, the third most common mycobacterial infection causing skin lesions are usually treated by the debridement procedure. Since the lesions caused by *M. ulcerans* are usually painless, clinicians mostly prefer performing excision followed by primary closure of the excised

lesion. After surgical debridement rifampin is given as monotherapy or combination with clarithromycin is given.[65]

M. xenopi causing lung disease specifically in patients who are suffering from obstructive pulmonary disease show variable responses to the treatment. Some isolates were found to be susceptible to first-line anti-tubercular drugs and others were resistant to them. The ideal drug combination for the infections caused by *M. xenopi* is rifampicin, clarithromycin, and ethambutol. In some cases, moxifloxacin was added to the above regimen for the effective response.[65]

Mechanisms of resistance

The most common types of resistance mechanisms described in NTM are natural resistance, inducible resistance, and mutational resistance

Natural resistance

Natural resistance of the non-tuberculous mycobacteria to the hydrophilic drugs is provided by a lipid-rich cell wall which imparts hydrophobicity to the cell wall and the porin channels. The lipid-rich cell wall mainly acts as an impermeability barrier. Some genetic mechanisms are responsible for maintaining the hydrophobic cell wall. kasB gene protein kinase G, fbpA, asnB in *M. marinum,* the mtrAB system in *M. smegmatis* and Maa2520, and pks12 in *M. avium* are some of them. Glycopeptidolipids responsible for different phenotypes of the atypical bacteria like smooth and rough variants also play an important role in showing the difference in susceptibility to antibiotics.[66] Porin channels are required for the uptake of hydrophilic antibiotics, so deletion of genes coding for them like MspA leads to resistance to hydrophilic fluoroquionolones.[67]

Due to the production of beta-lactamases by the NTM, there is an inherent resistance to the use of beta-lactams. Resistance to drugs like fluoroquinolones, aminoglycosides have been documented due to the production of enzymes like acetyltransferases and phosphotransferases. In *M. fortuitum*, Streptomycin resistance occurred due to the phosphotransferase system.[68] Rifampicin inactivation ribosyl transferase proteins in *M. fortuitum* has been documented.[69]

Inducible resistance

Inducible resistance has been reported in *M. fortuitum* and other rapid growers except *M. chelonae* due to erythromycin resistance methylase gene which causes methylation of the binding site of the macrolide thereby conferring resistance.[70] RNA polymerase binding protein conferring inducible resistance to rifampicin has been studied. Inducible resistance to rifampicin has been well documented in *M. smegmatis.*

Mutations

In MAC and *M. abscessus* high level of resistance to macrolides occurs due to mutations in codon 2058 or 2059 of rrl gene.[62] Aminoglycoside resistance in *M. abscessus* and *M. chelonae* occurs due to mutation in codon 1408 rrs gene. Similar to *M. tuberculosis,* resistance to rifampicin occurs due to mutation in rpoB gene in *M. kansasii*.[71]

CONCLUSION

The incidence of NTM is on the rise across the globe with many clinical cases being misdiagnosed and mismanaged as MDR TB. It is essential to accurately identify the disease-causing pathogen because the treatment option for certain NTM varies from the Mycobacterium tuberculosis complex. In this review, we tried to illustrate the epidemiology, pathogenesis, symptomatology, and treatment of NTM. Accurate identification of these organisms to species level is required for prompt treatment and mitigation of adverse events.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

AUTHOR'S CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript

ETHICS STATEMENT

Not applicable.

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