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Management of Infection with Nontuberculosis Mycobacteria

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1. INTRODUCTION

The nontuberculosis mycobacteria are often naturally resistant to the conventional antibiotics and to antituberculosis drugs *(1–3)*. In addition, providing advice for the treatment of nontuberculosis is complicated by the variable and changing designations of these organisms, the heterogeneity of the clinical syndromes and patients, and the relative lack of controlled clinical trials *(1,2)*. This chapter discusses the management of these difficult infections.

1.1. Nomenclature

The clinical importance of *Mycobacterium tuberculosis* as a major cause of death has meant that microbiologists have rightly focused on this organism. The remaining *Mycobacterium* species, which appeared to lack the potential to cause infection in healthy individuals, were often dismissed as "anonymous" or "atypical" *(4)*. This approach was neither accurate nor clinically helpful. As environmental organisms, their low pathogenic potential and failure to produce diseases that resemble tuberculosis is expected. Thus, the term *nontuberculosis mycobacterium* (NTM) is preferred *(2)*.

Now that conventional and molecular taxonomic techniques have been applied to this group of organisms, clinicians will increasingly be able to identify the invading mycobacteria accurately and to detect previously unrecognized species. As the pathogenic potential of each species is more accurately defined, it will become easier to choose the most appropriate drugs and management strategies.

1.2. Epidemiology

Mycobacteria are organisms that mainly live in the inanimate environment or as colonizers of humans and animals *(5)*. In one sense, it is the pathogenic species *M. tuberculosis* and *Mycobacterium leprae* that are atypical in that they lack an environmental reservoir. Most other species of the *Mycobacterium* genus are found in the environment and can be isolated from soil, water, and carriage sites in animals and humans *(6)*.

The number of cases of NTM infection has been increasing throughout the world *(7)*. The reasons for this are varied, but are important and need to be considered to

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understand the interaction of the epidemiology of NTM and therapeutic strategies. There has been a genuine increase in the number of cases because of changes in medical practice that provide opportunities for colonization and infection, for example, colonization of intravenous long lines with rapidly growing mycobacteria *(8)*. The increase in the number of patients who are receiving immunosuppressive therapy also provides opportunities for NTM to cause disease. The human immunodeficiency virus (HIV) epidemic brought about an enormous increase in the number of *Mycobacterium avium-intracellulare* cases *(9,10)*.

The number of cases has also been increasing because the diagnostic methods employed for mycobacteria have improved significantly over the last 20 yr *(11)*. In addition, simpler identification techniques, including molecular methods, have simplified diagnosis sufficiently that it is no longer the province of a reference laboratory. This has led to increased recognition, which has helped define the patterns of disease caused by different species and in the description of many new species *(12–14)*.

1.3. Scope of the Chapter

This chapter discusses the diagnosis and management of the NTM that are difficult to treat by virtue of their natural resistance to antibiotics. The major clinical syndromes discussed include bacteremia with *M. avium-intracellulare*, cervical lymphadenopathy and pulmonary infection with NTM, and infection with rapidly growing mycobacteria.

2. DIAGNOSIS OF NONTUBERCULOSIS MYCOBACTERIA

The isolation of *M. tuberculosis* from a specimen is sufficient to indicate a diagnosis of tuberculosis. The only other possible explanation of this finding is cross-contamination of the specimen either in the clinical setting or in the laboratory. The diagnostic problem is more difficult for NTM. As many of these organisms can form part of the normal flora or represent environmental contaminants, a single isolate is often not sufficient to make a diagnosis *(1,2)*.

2.1. Pulmonary Disease

The radiological appearances of NTM pulmonary disease exhibit subtle differences from that of tuberculosis. Cavities, when present, are thin walled, and there is less surrounding infiltrate. Spread is more contiguous with more marked involvement of the pleura. Occasionally, NTM may cause a single pulmonary nodule. An important part of confirming a diagnosis of NTM infection is to exclude potential confounding diagnoses, such as tuberculosis and lung malignancy. As *Mycobacterium kansasii, Mycobacterium xenopi, Mycobacterium malmoense*, and the rapid growers can form part of the normal flora, multiple isolates of an NTM are required from sputum or bronchial washings obtained at different times to support a positive diagnosis *(10)*. More weight is to be placed on single specimens that are also smear positive *(1,2)*. Alternatively, a single isolate from a biopsy specimen is diagnostic provided it is supported by compatible histology *(2)*.

Sputum is usually an adequate specimen with which to obtain a positive diagnosis of infection with *M. kansasii, M. xenopi,* and *M. malmoense*. In contrast, in HIV-seronegative individuals infected with *M. avium-intracellulare*, sputum is insensitive, and a more aggressive approach using bronchial lavage should be adopted *(15)*.

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2.2. Lymphadenitis

The most important part of diagnosis of lymphadenitis is to exclude tuberculosis. The diagnosis depends on granulomata in a biopsy of lymph glands in the context of a negative tuberculin test. A single isolate from a biopsy specimen is sufficient to make the diagnosis, although yields may be less than 50% of cases *(16,17)*. This in part may be because of the methods employed and the presence of fastidious mycobacterial species such as *Mycobacterium haemophilum* and *Mycobacterium genavense*.

2.3. Cutaneous Infection

The presence of rapidly growing mycobacteria in skin specimens must be evaluated carefully. Multiple isolates are required in clinical circumstances that support the diagnosis, for example, the presence of a plastic catheter or prosthetic device. Alternatively, individual cases may form part of known outbreaks with contaminated injections or prostheses. For *Mycobacterium ulcerans* and *Mycobacterium marinum*, the situation is often simpler as these species are likely to be isolated from patients with characteristic cutaneous lesions, making diagnosis easy. The management of these specific cutaneous infections is not discussed further.

2.4. Disseminated Infection in HIV-Infected Individuals

Disseminated infection with *M. avium-intracellulare* is usually only found in patients with advanced HIV infection who have not received antiretroviral therapy or have failed to take it. The CD count is usually low (<50), and the patient has clinical signs of advanced disease *(18)*. Patients are usually febrile and wasted and with significant anemia. Alkaline phosphatase is often elevated as hepatic involvement by *M. avium-intracellulare* is common. Usually, a single isolate from the blood is sufficient to confirm the diagnosis of disseminated *M. avium-intracellulare* infection *(1,2)*.

2.5. Role of Susceptibility Testing

The role of susceptibility testing in treatment choice for NTMs is controversial. There are many older studies that indicate that in vitro susceptibility test results do not correlate well with clinical outcome *(19,20)*. A more recent study of *M. avium* complex, *M. malmoense*, and *M. xenopi* found only one significant correlation of resistance and treatment failure for *M. xenopi (21)*. Similarly, a study of *M. avium-intracellulare* infection in HIV-seronegative patients found no correlation between the in vitro susceptibility and outcome *(22)*. However, such relationships are difficult to demonstrate unequivocally because all therapeutic regimens are with multiple drugs, and most centers only have a few patients, with the effect that these studies lack statistical power. One study of 256 patients showed a significant association ($p < 0.001$) between partial or no in vitro resistance to 1 mg/L of isoniazid and the time required for conversion of sputum from culture positive to negative, whereas complete resistance to isoniazid had a statistically significant adverse effect *(23)*. Others have found susceptibility testing for rapid growers valuable for planning chemotherapy *(24)*. Also, patients who responded to treatment for pulmonary *M. avium-intracellulare* received significantly more drugs to which their isolate was susceptible *(25)*.

Much of the contradiction provided by these articles may be because mycobacterial susceptibility tests are designed for use with *M. tuberculosis*. NTM may be inhibited

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with antibiotic concentrations achievable in serum, but at concentrations higher than that required for tuberculosis. Thus, in vitro test results based on a breakpoint for tuberculosis will produce false resistance for an isolate of NTM *(21,22)*. The use of methods that provide minimum inhibitory concentration (MIC) data will enable regimens to be constructed specifically for NTM that take into account the achievable concentrations of antibiotics *(26,27)*.

3. MANAGEMENT OF *MYCOBACTERIUM KANSASII* INFECTION

3.1. Pulmonary Infections

Mycobacterium kansasii is an important pulmonary pathogen with a tendency to affect older male patients with pre-existent pulmonary disease. Mortality rates are high, but this is often because of the severe underlying conditions that coexist in these patients *(28)*. All authorities agree that it is the inclusion of rifampicin that is responsible for favorable outcomes of culture conversion in almost all patients within 4 mo. On the other hand, resistance to this agent or its absence in the regimen underlies many of the reported examples of treatment failure *(23,29,30)*. With regimens that contain rifampicin, relapse rates are typically low, with figures of between 2.5 and 9% *(23,28)*.

The current American Thoracic Society (ATS) recommendation for treatment of pulmonary disease caused by *M. kansasii* in adults is the regimen of isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg body weight for the first 2 mo, then 15 mg/kg body weight) given daily for 18 mo and with at least 12 mo of negative sputum cultures. In patients who are unable to tolerate one of these three drugs, clarithromycin would seem a reasonable alternative, but its effectiveness has not been established by clinical trials (*see* below). Pyrazinamide has no role to play in therapy for *M. kansasii* infections because all isolates are resistant *(2)*.

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A prospective clinical trial performed by the British Thoracic Society (BTS) in 173 patients with two sputum cultures positive for NTM showed that *M. kansasii* pulmonary infection responded well to 9 mo of treatment with rifampicin and ethambutol, but patients who contract this disease have a high mortality rate from other causes. Isoniazid did not appear to be a necessary part of the regimen *(28)*. Consequently, the BTS recommend that 9 mo of rifampicin and ethambutol is adequate treatment for most patients, but when there is evidence of compromising conditions, treatment can be extended to 15–24 mo *(1)*. The use of intermittent drug regimens or short-course therapy has not been studied sufficiently for advice to be given.

In patients who have an inadequate response or who are unable to tolerate the standard agents, prothionamide (1 g/d orally) and streptomycin (0.75–1 g/d im) could be added *(1)*, but both are associated with frequent adverse events. Both clarithromycin and fluoroquinolones are highly active against *M. kansasii* and are likely to be beneficial *(3,31)*, although there is no clinical trial data available. These agents have proved useful in the treatment of *M. avium-intracellulare* infection (*see* below) and may be useful as part of the regimen.

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Rifampicin resistance among *M. kansasii* appears to be increasing in part because of the HIV epidemic. Although rifampicin is the most important drug in the treatment of *M. kansasii* infection if patients are treated with a regimen that includes three drugs to which the infecting organism is susceptible a good outcome is likely. Many of these regimens include clarithromycin and ciprofloxacin *(26)*.

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3.2. Extrapulmonary Infection

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The treatment of extrapulmonary disease should probably be similar to the pulmonary regimens. For lymphadenopathy, excision is recommended as this is the optimal treatment for *M. avium-intracellulare* infection, the most common cause (*see* below) *(1,2)*.

4. MANAGEMENT OF *MYCOBACTERIUM MALMOENSE* DISEASE

4.1. Pulmonary Disease

Retrospective studies have shown that patients treated for 18–24 mo with regimens that included rifampicin and ethambutol did better than those treated with other regimens or who had shorter durations of treatment *(32)*. The addition of second- or third-line drugs increased the rate at which adverse events were reported without improving the outcome. Surgery has an important role to play for those who are suitable for operation, and chemotherapy should be continued afterward for at least 18 mo. A clinical trial of chemotherapy in *M. malmoense* infection showed that treatment of *M. malmoense* with rifampicin and ethambutol for 2 yr is preferable to a regimen that contains isoniazid, although there was a nonsignificant reduction in the relapse rate for the three-drug regimen. However, there was a higher death rate for the three-drug regimen *(1)*.

Macrolides and quinolones are active in vitro *(3,31)*, and there are some anecdotal reports of treatment response when these agents are used in the management of patients who are very susceptible to infection *(33)*. New clinical trials have been designed and are under way to evaluate the role of macrolides and quinolones in therapeutic regimens and to detect the value of immunizing with *Mycobacterium vaccae (1)*.

4.2. Mycobacterium malmoense Extrapulmonary Disease

Lymphadenitis is the most common form of *M. malmoense* extrapulmonary disease, and this syndrome should be treated with excision. Otherwise, extrapulmonary disease should be treated in the same way as pulmonary disease.

5. MANAGEMENT OF *MYCOBACTERIUM XENOPI* DISEASE

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5.1. Pulmonary Disease

Mycobacterium xenopi poses many diagnostic and therapeutic problems. In some patients, *M. xenopi* may act as a colonizer without causing disease *(34–36)*. Therefore, it will be present in multiple specimens, thus passing the test for "significance," although in many such cases it is not responsible for clinical symptoms. In addition, infection with *M. xenopi* is normally indolent, with disease developing over a number of years *(32)*. Thus, an isolate in an apparently asymptomatic patient cannot be lightly dismissed, especially in HIV-infected individuals. To overcome the diagnostic difficulty, it has been proposed that the criteria for diagnosis of *M. xenopi* infection be two sputum isolations in the absence of other likely causes of symptoms *(37)*.

Early studies have suggested that regimens should contain rifampicin and isoniazid together with ethambutol or streptomycin *(32,38)*. A clinical trial suggested that a regimen of rifampicin and ethambutol is optimum, although there is a trend to a higher cure rate when isoniazid is added, but the complication rate is increased *(39)*. In view of the

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higher complication rate with added isoniazid, guidelines suggest that this drug should be included only if treatment fails to render the sputum culture negative *(1)*.

Macrolides and quinolones may have an important role in the treatment of *M. xenopi* infections as they are active in vitro and in animal models *(3,31,40)*. There are anecdotal reports of the value of these agents *(33)*. Clinical trial data are not yet available to inform therapeutic choice, but these could rationally be added to treatment of patients who fail to respond.

The results of medical therapy can be poor, with a 5-yr mortality of up to 57% (although a minority of these deaths were directly attributed to mycobacterial infection) *(39)*. Pulmonary resection is often necessary as an adjunct to treatment *(41)*. Pulmonary resection should be considered in patients who are failing on therapy, but who otherwise have good pulmonary function and whose disease is localized. When these criteria are applied, sputum conversion is complete in all but the patients who have incomplete resection *(42)*.

6. MANAGEMENT OF *MYCOBACTERIUM AVIUM-INTRACELLULARE* DISEASE

Infection with *M. avium-intracellulare* was once rare and was found as sporadic disease and in severely immunocompromised patients *(2,10)*. This situation was transformed by the HIV epidemic, in which disseminated *M. avium-intracellulare* infection and bacteremia were common late complications, usually when the CD4 count fell below 50. Management of *M. avium-intracellulare* infection is so influenced by the severity of HIV infection, it is considered separately.

6.1. HIV-Seronegative Patients

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6.1.1. Mycobacterium avium-intracellulare Pulmonary Disease

Pulmonary disease caused by *M. avium* complex in HIV-seronegative patients usually occurs in those with concomitant chronic lung disease or deficient cellular immunity, and its prevalence is increasing *(10)*. The predisposing conditions include pneumoconiosis and silicosis because of chronic and long-term exposure to occupational dusts (e.g., from coal mining and farming) *(43)*. For example, in one study, 73% of patients had pre-existing pulmonary disease, 38% smoked, and 33% reported alcohol abuse.

The prognosis in *M. avium* complex pulmonary infections was strongly correlated with the underlying condition *(44)*. Older studies of treatment and the natural history of disease showed that patients who are symptomatic have progressive disease that is difficult to treat, whereas many of those who were asymptomatic at the time of isolation went on to develop invasive disease *(20)*.

Isolated pulmonary disease in otherwise healthy women has been described *(45)*. Surveys suggest that approximately half of these patients fail therapy *(15)*.

Treatment with three drugs, including rifampicin and isoniazid, coupled with either streptomycin or ethambutol were thought to give the best results *(20)*. A clinical trial of treatment of *M. avium-intracellulare* pulmonary infection in HIV-seronegative patients suggested that the optimum treatment regimen is with rifampicin and ethambutol, and that isoniazid reduced the failure and relapse rate *(39)*. Five-year follow-up of patients treated with this regimen showed that 15% of patients failed therapy, and 14% relapsed *(46)*.

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The activity of clarithromycin and quinolones suggests that they may have a role to play, and clinical trials are under way to evaluate this *(39)*. Open trials suggested that sputum conversion rates greater than 75% can be achieved with regimens that include a macrolide *(47–49)*. Thus, although no comparative clinical trials have yet been reported, macrolides should probably now always be included in regimens used to treat *M. avium-intracellulare* infections in immunocompetent patients. Intermittent therapy (three times a week) is also reported to have a similar conversion rate *(50)*.

A recent article may give some insight into the reasons for the high relapse rate. Study of the organisms obtained from patients treated with clarithromycin who had suffered late relapses after 4 consecutive months of negative culture showed that the majority of these isolates were different from the original infecting strain. This suggests that many late relapses are caused by reinfection from this common environmental organism among patients who are highly predisposed to infection *(49)*.

Some authorities suggest that rifabutin should be the rifamycin of choice for treatment of *M. avium-intracellulare* infection because of its greater in vitro activity. However, this drug has a different adverse event profile, and only comparative clinical trials can tell whether the additional activity is gained without increased adverse events.

6.1.2. Management of Lymphadenitis

Mycobacterium avium-intracellulare is the commonest cause of cervical lymphadenopathy in children in countries where tuberculosis has been controlled *(51)*. Surgical excision is essential for diagnosis as the yield from fine-needle aspiration is not complete, and there is a considerable risk of sinus formation *(2)*. Optimal treatment of this condition is surgical excision, which has a lower reoperation rate than incision and drainage, curettage, or aspiration *(17)*. Relapse and sinus formation are rare, occurring in less than 5% of cases *(16,52)*. Antimicrobial chemotherapy appears to be unnecessary *(2)*, although there are reports of successful management with clarithromycin monotherapy *(53)*.

6.1.3. Management of Disseminated Infection in HIV-Seropositive Patients

Disseminated *M. avium-intracellulare* infection is a late complication of HIV infection. Since the introduction of highly active antiretroviral therapy (HAART), it has become much less common in developed countries, occurring in patients who are untreated or who have been unable to tolerate therapy. The optimal regimen has not yet been established, partly because patients with this infection are at a very late stage of HIV disease for which the clinical course is complicated by other opportunistic infections and the consequence of HIV itself. In the era of HAART, the management of disseminated *M. avium-intracellulare* infection is underwritten by therapeutic efforts to reduce the HIV viral load, increase the CD4 count, and bring about reversal of the immune deficit.

Antibiotics have an important role in reducing bacteremia, and the antibiotics able to do that include macrolides such as clarithromycin and azithromycin, quinolones such as ciprofloxacin, and rifabutin, a rifamycin. The macrolides are highly active and are the cornerstones of all regimens. They are capable of reducing the count of bacteria in the blood when given alone *(54,55)*. Monotherapy results in the rapid emergence of resistance; thus, combination therapy should be chosen.

Clinical trials have supported the superiority of clarithromycin, ethambutol, and rifabutin over rifampicin, ethambutol, clofazimine, and ciprofloxacin *(56)*. A compara-

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tive trial suggested that lower doses of rifabutin (300 mg daily) together with ethambutol are more effective than a four-drug regimen of rifampicin, ethambutol, clofazimine, and ciprofloxacin, still retaining much of the activity of clarithromycin (1000 mg twice daily) and rifabutin (600 mg daily) doses *(56)*.

6.1.4. Prophylaxis of Mycobacterium avium-intracellulare

Prophylaxis is necessary to prevent infection in patients with late-stage HIV infection with low CD4 count. Macrolides have been shown to be more effective than rifabutin, which also is an effective agent, but is associated with a higher rate of intolerance *(57,58)*. Ultimately, the choice of prophylactic agent will depend on the choice of HAART because rifabutin interacts with protease inhibitors, and patients differ considerably in their ability to tolerate drugs *(59)*.

7. MANAGEMENT OF INFECTION WITH RAPID GROWERS

7.1. Pulmonary Disease

More than 80% of cases of pulmonary disease are caused by *M. abscessus*, which is the naturally most resistant member of the group of organisms *(60)*. Treatment of *M. abscessus* infections is often disappointing. Treatment can bring about clinical improvement, but cure is rare. When surgery is technically possible, it is recommended *(1)*. Susceptibility testing of rapidly growing mycobacteria is thought to give a good guide to treatment, and regimens should be constructed based on susceptibility test results *(24)*. Regimens should probably include rifampicin (450 mg if the patient weighs less than 50 kg, 600 mg if the patient weighs more than 50 kg), ethambutol (15 mg/kg body weight), and clarithromycin (500 mg twice daily). There are reports of the value of fluoroquinolones, sulfonamides, amikacin, cefoxitin, and penems in treatment *(1,24,61)*.

7.2. Extrapulmonary Disease

Many cases of infection by rapid growers occur in the context of an infected prosthetic device, for example, intravenous canullae or other implants. Successful therapy of these catheter-related infections involves removal of the catheter and antimicrobial therapy, usually for 2 to 4 mo. Although disease caused by *M. fortuitum* may resolve if the catheter is removed, reinsertion of another catheter in a similar location without drug therapy usually results in disease recurrence (as in the above case) *(8)*. Adjunctive therapy should be with ciprofloxacin, amikacin, and clarithromycin for up to 4 mo. When there is a tunneled line that also has a tissue infection, then treatment may need to be extended for 6 mo *(12)*.

Postinjection abscesses should be treated by surgical drainage and clarithromycin for between 3 and 6 mo. This advice comes as a result of the experience obtained from a series of outbreaks *(62,63)*.

Wound infections are one of the most common manifestations of infection with rapidly growing mycobacteria. Infections have often been associated with augmentation mammoplasty and other plastic surgery procedures *(12,64,65)*. Therapy depends of the removal of any infected foreign material, followed by 6 mo of chemotherapy *(66,67)*. Clarithromycin is the main choice, with other drugs added to prevent the emergence of resistance *(68)*.

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Disseminated cutaneous infection is mainly with *M. abscessus*, usually in patients who are compromised by renal failure or corticosteroid therapy *(69)*. This is one of the most common presentations of nonpulmonary infection with rapidly growing organisms *(12)*. Treatment includes drainage of any abscesses coupled with clarithromycin for 6 mo and with another agent to which the isolate is susceptible during the first 2 mo *(68)*.

8. SUMMARY

Infections with NTM continue to pose significant diagnostic and therapeutic problems for clinicians. Infection often occurs in the context of other serious disease, which may influence the outcome more than the infective process. Diagnosis can be difficult, but modern laboratory methods are improving rapidly. For several important infections, clinical trial information is helping to inform clinicians *(39)*. The results of trials currently under way to elucidate the activity of quinolones and macrolides may soon improve the evidence base on for defining more effective regimens.

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