Current treatment of atypical mycobacteriosis

Jaime Esteban & Alberto Ortiz-Pérez
Department of Clinical Microbiology, Fundación Jiménez Díaz, Av. Reyes Católicos 2, 28040-Madrid, Spain

Background: Atypical mycobacteria are a heterogeneous group of organisms that are of increasing importance because of the growing number of infections they cause. This rising rate of infection is due mainly to the increase in the number of susceptible (and especially immunosuppressed) patients.

Objective: To revise the currently used treatment schemes of the most commonly isolated atypical mycobacteria.

Methods: Literature review using reference books and PubMed with specific keywords for each mycobacteria.

Results/conclusion: The first important step in the management of atypical mycobacteria is to recognize the true infections caused by these organisms. The treatment required varies according to species. Well-characterized combinations exist for most common isolates, with the use of first-line antituberculous drugs (isoniazid, rifampin, ethambutol), clarithromycin, aminoglycosides and/or quinolones for slowly growing species (Mycobacterium avium complex, Mycobacterium kansasii, Mycobacterium xenopi, Mycobacterium ulcerans, Mycobacterium marinum, Mycobacterium lentiflavum, Mycobacterium malmoense) and macrolides, quinolones, amikacin and other antibiotics for rapidly growing mycobacteria (Mycobacterium abscessus, Mycobacterium chelonei, Mycobacterium fortuitum). Surgical therapy is also important for some species (Mycobacterium ulcerans, Mycobacterium scrofulaceum) and for localized infections. The treatment of uncommon species is not well defined and is determined by the results of in vitro tests of individual strains. Because of the increasing number of resistant strains, new antibiotics need to be used for the treatment of these strains.

Keywords: atypical, mycobacterium, nontuberculous, treatment
atypical mycobacteria (the classic name, which will be used in this review) remains high. The arrival of new genetic tools represents a new development in the knowledge of these organisms, with an extremely high number of species described in recent years. So, the initially low number of organisms has now become more than 120 different species, more than one-third of which are described as potential human pathogens [3].

With the recognition of the pathogenic nature of atypical mycobacteria, it became necessary to treat the infections caused by these organisms. Again, comparison with tuberculosis was unavoidable. Treatment of tuberculosis was clearly established, with specifically defined protocols both for therapy and for susceptibility testing. Initially, atypical mycobacteria were treated with therapeutic schemes similar to that of tuberculosis [2]. However, the differences in susceptibility of these organisms made a more specific approach necessary for some species, especially those causing a high number of cases (like M. avium for AIDS patients), both for susceptibility testing and for the development of therapeutic schemes.

This review analyzes these aspects of the most commonly pathogenic species of atypical mycobacteria (Box 1). A key review covering most of issues about this therapy appeared in 2007 [2]; here, we discuss the currently recommended guidelines, together with a review of more recent aspects in mycobacterial treatment. It is difficult to establish proper guidelines for those species that cause only a few cases because the anecdotal nature of the cases means that it is not possible to analyze them properly to reach a recommendation.

2. Recent pharmacodynamic and pharmacokinetic insights of the most important antimycobacterial drugs

The main characteristic of almost all therapeutic protocols of these infections is the use of a combination of several drugs over long periods of time. The most important antibiotics all have the property of a high intracellular accumulation of drug. The use of a combination of drugs also allows a higher synergistic effect and minimizes the appearance of antimicrobial resistances. However, combinations have the risk of a large number of side effects (Table 1).

Different pharmacokinetic parameters have been studied for most of the drugs, mainly during tuberculosis treatments. Plasma concentrations of antibiotics can be affected by age, sex, HIV infection, dosage and by bilirubin and albumin levels, so it is necessary to perform an individualized evaluation of the patient to prevent therapeutic failures due to low concentrations of antibiotics [4]. Antagonism between isoniazid and the combination of rifampin–pyrazinamide has recently been described in an experimental model of tuberculosis [5], with a high effect for increasing concentrations of isoniazid. However, the author of this study state that this effect does not happen when isoniazid is combined separately with rifampin and pyrazinamide.

Rifamycins (rifampin, rifabutin and rifapentin) have a special place in combination therapies because of their role as enzymatic inducers. This effect is especially apparent when they are combined with moxifloxacin, and a reduction of the area under the curve (AUC) and drug peak concentration can be detected for this antibiotic [6,7]. This effect has also been observed with clarithromycin in the treatment of Mycobacterium avium complex (MAC) disease, with a high production of the hydroxylate metabolite of clari-thromycin with lower activity than this drug, and so a decreasing activity against the mycobacteria [8-10]. Moreover, the continuous use of rifamycins can result in an autoinduction of their metabolism, lowering the plasma levels during the treatment. This phenomenon has led to increased rifampin dosage to obtain proper therapeutic levels [11].

2.1 Mycobacterium avium complex

The MAC includes a group of species that are the most commonly isolated atypical mycobacteria in clinical samples [12]. The species M. intracellulare and M. avium (including all subspecies) are the most common members of the complex, and new species have recently been added to the complex [13-15]. These organisms are environmental mycobacteria that can be isolated from different environmental sources, including animals. Human infections caused by these organisms can be differentiated according to the immune status of the patients. Among immunocompetent patients, MAC was described many decades ago as the cause of localized respiratory tract infections [1], being the most common atypical mycobacteria that causes these diseases [16]. These syndromes included a tuberculosis-like
### Table 1. Adverse effects of the most important antibiotics used in antimicrobial therapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major side effects</th>
<th>Used with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycines (rifampin, rifabutin)</td>
<td>Orange discoloration of urine and secretions, Liver toxicity (hepatitis, hyperbilirubinaemia, jaundice, high levels of ALT and AST in blood), Increased hepatic metabolism of drugs, Haematological (thrombocytopenia, anaemia), Gastrointestinal disturbance (nausea, vomiting), Arthralgia, myalgia (rifabutin only), Uveitis (rifabutin only)</td>
<td>MAC, M. kansasii, M. genavense, M. haemophilum, M. malmoense, M. marinum, M. szulgai, M. xenopi, M. lentiflavum</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy related to pyridoxine deficiency, Liver toxicity, hepatitis, Gastrointestinal disturbance (nausea, vomiting)</td>
<td>M. kansasii, M. malmoense, M. szulgai, M. xenopi</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis (loss of visual acuity, blurred vision, loss of red/green colour discrimination), Hypersensitivity (dermatitis, erythema, pruritus)</td>
<td>MAC, M. kansasii, M. malmoense, M. marinum, M. xenopi, M. lentiflavum</td>
</tr>
<tr>
<td>Macrolides (clarithromycin, azithromycin)</td>
<td>Gastrointestinal disturbance (nausea, vomiting, diarrhoea, abdominal pain), Headache, Hypersensitivity (rash, pruritus, swelling)</td>
<td>MAC, M. kansasii, M. abscessus, M. chelonae, M. fortuitum, M. genavense, M. haemophilum, M. malmoense, M. marinum, M. xenopi, M. celatum, M. lentiflavum</td>
</tr>
<tr>
<td>Quinolones (ciprofloxacin, moxifloxacin, gatifloxacin)</td>
<td>Gastrointestinal disturbance (nausea, vomiting, diarrhoea), CNS disturbance (agitation confusion, insomnia, headache)</td>
<td>MAC, M. kansasii, M. chelonae, M. fortuitum, M. genavense, M. haemophilum, M. malmoense, M. xenopi, M. celatum</td>
</tr>
<tr>
<td>Aminoglycosides (streptomycin, amikacin)</td>
<td>Vestibular dysfunction and auditory toxicity (vertigo, tinnitus, dizziness, hearing loss), Nephrotoxicity</td>
<td>MAC, M. kansasii, M. abscessus, M. chelonae, M. fortuitum, M. genavense, M. haemophilum, M. xenopi</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Gastrointestinal disturbance (nausea, vomiting, diarrhoea), Haematological (thrombocytopenia, anaemia, leukopenia), Hypersensitivity (rash, pruritus), Neuropathy</td>
<td>M. kansasii, M. abscessus, M. chelonae</td>
</tr>
</tbody>
</table>

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CNS: Central nervous system; MAC: Mycobacterium avium complex.
syndrome, with the appearance of cavitations, cough and haemoptysis. Another frequently described syndrome is the presence of infected nodular bronchiectasis, a disease known as ‘Lady Windermere syndrome’ [17]. Patients are usually tall, thin women with CFTR gene mutations and other anatomical problems (e.g., scoliosis, mitral valve prolapse) but no pre-existing pulmonary disease or history of smoking [18].

Among AIDS and other immunosuppressed patients, MAC causes disseminated infections and bacteremia, with the involvement of the liver, spleen and bone marrow, and with the appearance of unspecific symptoms such as fever, malaise, weight loss, anorexia, abdominal pain and night sweats [19,20]. Moreover, localized lung infections [21] or cutaneous disease [22] have also been described.

From an epidemiological point of view, the isolation of the different species seems to have regional differences, with *M. intracellulare* being the most commonly isolated species in some cases [18], whereas *M. avium* is predominant in other geographic settings [23].

The role of susceptibility testing of MAC is a matter for discussion. Clinical studies have shown no relationship between *in vitro* and *in vivo* results for antituberculous drugs [24]. *In vitro*, MAC isolates commonly appear resistant against first-line antituberculous drugs, whereas therapy with a combination of some of these agents showed clinical results [2,24-26]. The Clinical Laboratory Standards Institute (CLSI) recommends testing susceptibility only against macrolides, with clarithromycin as the specific antibiotic to be used [27], using broth dilution as the reference technique.

Treatment of infections caused by MAC must be carried out with a combination of different antibiotics. Such combinations must include at least two drugs, one being a macrolide (clarithromycin or azithromycin are preferred), associated with rifampin (or other rifamycins, e.g., rifabutin) and ethambutol [25]. The introduction of macrolides has been one of the most important steps in MAC treatment, being especially effective in the treatment of disseminated infections among AIDS patients. Together with rifabutin, clarithromycin and azithromycin were also used for prophylaxis in AIDS patients before the highly active antiretroviral therapy (HAART) era [28,29]. They showed a significant decrease of infection in patients with a leukocyte count < 50 cells/mm³ [30]. Clarithromycin and azithromycin also showed better results than rifabutin, and are active against other potential pathogens that can affect HIV-positive patients [31]. The development of macrolide resistance among oropharyngeal microbiota is an important problem that has appeared with macrolide monotherapy [32]. However, the introduction of HAART made macrolide prophylaxis obsolete, with progressive removal of therapy as the immune system recovers [30,33-35].

Thus, treatment for respiratory infections in immunocompetent hosts includes a combination therapy with macrolides, rifampin/rifabutin and ethambutol [2,36]. Alternative schemes that include aminoglycosides have also been effective in these patients [2]. However, a recent study showed no difference between rifampin plus ethambutol associated to clarithromycin or ciprofloxacin [37]. This study, however, did not include *in vitro* susceptibility testing of the strains against clarithromycin (for MAC cases), so the resistance or susceptibility of the strains is unknown. Despite this, this study is the largest randomized study of macrolides or quinolones for the evaluation of pulmonary atypical mycobacteriosis, so its results must be taken into account when the treatment of such infections is being considered. In this sense, it is important to emphasize that intermittent regimes showed worse results than continuous therapy among patients with cavitary disease, although it is probably useful for milder diseases, such as nodular bronchiectatic syndrome [38].

One important fact to be taken into account in antimicrobial therapy is the potential development of antibiotic resistance. Macrolide resistance has been described among MAC strains and is due to mutations in positions 2058 and 2059 of the 23S rRNA gene [39]. However, the appearance of such resistance is unusual when a combined treatment is used [39]. Another potential problem is the appearance of adverse effects that can sometimes result in the provisional suspension of therapy.

Other potentially useful drugs to be used in the treatment of MAC disease are the quinolones, especially moxifloxacin and gatifloxacin. These drugs have a methyl group in position 8, which confers antimicrobial properties against MAC strains, and so are useful as second-line drugs when macrolide resistance appears [40]. Of interest, quinolones are useless when combined with macrolides, because antagonism or indifference have been described for this combination; however, they are useful when combined with ethambutol or used in experimental models of monotherapy regimes [40,41]. The usefulness of quinolones together with rifampin plus ethambutol was assessed recently in humans, and found to have a similar efficacy to clarithromycin–rifampin–ethambutol [37].

Aminoglycosides are another therapeutic option when therapeutic failure appears with first-line schemes [39,42]. The lack of truly useful alternatives to classical combinations, and the appearance of macrolide resistances made it necessary to develop new drugs active against this group of mycobacteria [43]. A new ATP synthase inhibitor (R207910) has shown promising *in vitro* results against MAC and other atypical mycobacteria [44], but further development is necessary to know its true value in the therapy of MAC disease.

For those patients with localized infections, surgery has been used together with antimicrobial therapy to minimize the bacterial load and to cure life-threatening symptoms such as haemoptysis [1,25,39,42].

### 2.2 Mycobacterium kansasii

*Mycobacterium kansasii* is a slowly growing, photochromogenic mycobacterium. It is one of the most frequently isolated atypical mycobacteria in clinical samples [12]. Seven subtypes have been described, 1 and 2 being the most prevalent and both having been associated with infections in immunosuppressed patients or among those with chronic respiratory
diseases. The other subtypes were not so clearly related with infections and are isolated mainly from samples of elderly people; most are considered as nonsignificant [49].

*M. kansasii* is the cause of a respiratory tract infection that appears as a tuberculosis-like syndrome, with fever, weight loss, cavitations, haemoptysis and alveolar infiltrates [46]. Extrapulmonary diseases include disseminated infection in HIV patients [47] and osteoarticular infection [48] associated with risk factors like traumatisms, prosthesis, corticoid therapy or immunosuppression [48-50].

The treatment of *M. kansasii* infections includes the use of first-line antituberculous drugs. As with other atypical mycobacteria, no standardized procedure exists for *in vitro* susceptibility testing, and so the *M. tuberculosis* protocols are used [51]. Recommended therapy includes the combination of isoniazid, rifampin and ethambutol for 12 months after sputum conversion of cultures to negative [2]. For localized extrapulmonary infections, surgery has been used together with the same antibiotic regime as for respiratory infection [49].

Rifampin is the most important antibiotic in *M. kansasii* therapy. Although it usually shows a high *in vitro* activity [51,52], resistance has been described following the appearance of *rpoB* gene mutations [53]. When resistance to rifampin is detected, therapy must be continued with a combination of isoniazid, high-dosage ethambutol and sulfamethoxazole, combined with amikacin or streptomycin for 3 months, followed by intermittent therapy with streptomycin or amikacin for a further 3 months [2].

Clarithromycin is the main alternative for resistant strains. It is important to note that *in vitro* resistance against isoniazid is frequently detected, and that alternative schemes including clarithromycin have been suggested [54]. Moreover, the use of clarithromycin in HIV patients has been demonstrated to increase the average life of the patients [47]. *In vitro* and experimental studies have shown high activity of clarithromycin, both alone and combined with rifampin, quinolones or linezolid [51,55,56]. These studies also showed a low number of clarithromycin-resistant strains. Other antimicrobials that showing good *in vitro* activity against *M. kansasii* are moxifloxacin, azithromycin and linezolid, which are suggested to be a future alternative in the treatment of rifampin-resistant strains [51,56,57].

### 2.3 Mycobacterium xenopi and Mycobacterium celatum

*Mycobacterium xenopi* is a slow-growing mycobacterium that was first described in 1959. It is one of the most common isolated atypical mycobacteria in clinical laboratories [3], although its geographic distribution seems to be irregular [58-60]. A thermophilic bacterium, it has an optimal growth temperature of 45°C [2,61]. *M. xenopi* is isolated from respiratory samples taken from patients with chronic diseases; often, other organisms are also present [61,62]. Its frequent isolation, together with the fact that it is a potential cause of human disease, made it necessary to perform a detailed evaluation of the isolates, with frequent application of the ATS guidelines [2] or other similar criteria [58,59,63] to consider the isolated strain a true pathogen or a colonization.

*M. xenopi* has frequently been described as the cause of respiratory tract infections, even among immunosuppressed hosts. This disease resembles tuberculosis, with appearance of lung cavitations [2,58,62,63]. Other syndromes have been described, including disseminated infections and pleural and bone infections, some of them in AIDS patients [59,63]. Disease seems to be more frequent in immunosuppressed patients [58,60,63], although immunocompetent patients can also be affected [58,62]. Among all cases, the identification of *M. xenopi* isolates as pathogens is essential for the proper management of the patients [58,62].

Susceptibility testing of *M. xenopi* is difficult to interpret because of the lack of correlation between *in vitro* and *in vivo* results [2,24,26,59]. This mycobacterium shows susceptibility to second-line antituberculous drugs and most strains appear as susceptible to first-line drugs, such as rifampin, isoniazid or ethambutol [59,62]. Recent reports suggest susceptibility of the strains against quinolones or clarithromycin [62], including some experimental evidence for the use of clarithromycin [64].

Current recommendations for the treatment of *M. xenopi* infections include the combined use of clarithromycin, rifampin and ethambutol until cultures are persistently negative for at least 12 months [2]. Other combinations, including other antituberculous drugs like pyrazinamide, clofazimine, ansamycin, ciprofloxacin or streptomycin, have also been used [63]. A study by the Research Committee of the British Thoracic Society showed minimal differences between isoniazid + rifampin + ethambutol and rifampin + ethambutol, but such differences were not statistically significant; the authors stated that isoniazid has no place in the treatment of *M. xenopi* disease [24]. A more recent report showed similar results for both rifampin–ethambutol–clarithromycin and rifampin–ethambutol–ciprofloxacin regimens for lung disease caused by this organism [37]. Although the strains showed better *in vitro* susceptibility against second-line drugs, such as capreomycin, protonamide or kanamycin [62], the lack of correlation between *in vitro* and *in vivo* results made this difference difficult to assess.

Surgery also has a role in some cases, when it can be performed to reduce bacterial load or for surgical debridement in soft-tissue disease [2].

*Mycobacterium celatum* is an atypical mycobacterium [65] that is phenotypically similar to MAC. Its biochemical profile is similar to that of *M. xenopi* [66] and mycolic acid HPLC profile or DNA sequencing are necessary for a proper identification of the strains [66]. *M. celatum* has been described mainly as the cause of severe disease in AIDS patients [66-68], but there are also cases of lung disease in immunocompetent hosts [66]. Because of the low number of cases, specific recommendation for treatment cannot be based on clinical trials. The strains are usually susceptible to macrolides (clarithromycin and azithromycin) or ciprofloxacin, and resistant to rifampin or isoniazid [66]. Because of the difference in the susceptibility profile with *M. xenopi*, proper
2.4 Mycobacterium ulcerans

In 1897, in Uganda, Sir Albert Cook provided the first descriptions of a disease that was re-described in the 1940s in Australia. Named Bairnsdale ulcer or, more frequently, Buruli ulcer, the disease was later diagnosed as being caused by Mycobacterium ulcerans [69]. This atypical mycobacterium is extremely slow growing and its isolation requires more prolonged periods than for M. tuberculosis [1,69]. The disease is considered the third most common caused by mycobacteria, after tuberculosis and leprosy [70]. It is mainly cutaneous, characterized by the appearance of chronic ulcers, which lead to frequent disabilities [69]. Occasionally, it progresses through contiguous tissues, with the occasional appearance of bone involvement [71].

The disease affects only tropical and subtropical areas, and it is considered that M. ulcerans must be an environmental organism that infects tissues through direct contact [69]. Treatment of the disease has classically been surgical, but recently antibiotic therapy has been recommended to reduce the number of disabilities and improve the patient’s outcome.

Experimental data in mice suggest that a combination of rifampin plus one aminoglycoside is effective in the treatment of experimental infection due to M. ulcerans [72,73], although the appearance of resistance to rifampin during therapy can be a matter of concern [74]. Further studies in humans demonstrated the efficacy of a combined regime of rifampin and an aminoglycoside (streptomycin or amikacin) during 8 – 12 weeks treatment of the disease [75,76]. A recently published, provisional guideline from the World Health Organization (WHO) recommends the combination of rifampin and streptomycin for 8 weeks, together with surgical procedures if necessary [70].

Recent studies have showed the promising efficacy of other combinations, including quinolones (especially moxifloxacin), linezolid, clarithromycin or new experimental drugs such as the diarylquinoline R207910 or the nitroimidazopyran PA-824 [77,79]. In vitro data and the results from experimental models showed similar or superior efficacy of combinations that include these new drugs over the recommended regime, although no broad human studies have been performed yet. However, some clinical data support the use of rifampin plus ciprofloxacin [71]. This combination and others (e.g., rifampin plus moxifloxacin or clarithromycin) were recently recommended in Australia as an alternative to the WHO-recommended therapy [80].

3. Rapidly growing mycobacteria

Almost half the species of the genus Mycobacterium are considered to be rapidly growing mycobacteria. The main characteristic of this group is the ability of their members to grow macroscopic colonies in < 7 days. However, despite the high number of species included in this group, few have been described as human pathogens. Moreover, nonpigmented species are the most common pathogens in this group; cases due to pigmented species being extremely rare [81,82]. The most common strains causing human disease are Mycobacterium fortuitum, Mycobacterium chelonae and Mycobacterium abscessus [81-83]. M. abscessus isolates cause human infection in most of the cases. However, the frequency of isolation of the different species can have regional differences [3,83].

Nonpigmented, rapidly growing mycobacteria (NPRGM) are environmental organisms isolated from different environmental sources. These species have been described as the cause of a broad spectrum of diseases, ranging from mild syndromes (such as folliculitis or wound infections) to extremely severe ones (endocarditis, osteomyelitis, respiratory tract infections and disseminated infections). One of the most important pathogenic properties of these organisms is their ability to develop biofilm [84]. This complex structure has important implications, not only in the pathogenesis of the disease but also in the management of patients. As a result of biofilm development, many foreign-body-related infections require the removal of biomaterial to cure the patient [81,82].

Therapy of these infections is quite different to that of slowly growing mycobacteria. The common pathogenic species of this group are resistant to first-line antituberculous drugs but susceptible to other common antibiotics, such as macrolides, quinolones, beta-lactams, tetracyclines or cotrimoxazole. Common susceptibility patterns can be found for the clinically relevant species, with M. fortuitum usually being susceptible to quinolones and resistant to macrolides, and M. abscessus and M. chelonae usually being quinolone resistant and macrolide susceptible; all species are usually susceptible to amikacin. However, the susceptibility of the isolates is variable, so each treatment requires an in vitro susceptibility test of the individual strain to select a proper therapeutic scheme for the patient.

Susceptibility testing of these mycobacteria is greatly influenced by the growth rate of these organisms. Methods used to test the susceptibility of slowly growing mycobacteria (especially M. tuberculosis) are not recommended for NPRGM by the CLSM. The broth microdilution test is the reference technique [27], and has been used for susceptibility testing of new drugs [85-88] and also for studies involving a large number of strains [83,89]. However, individual susceptibility for clinical strains can be difficult to perform for many clinical mycobacteriology laboratories because of difficulties in microtitre plate preparation and in reading the results. Other methods of performing these evaluations have been assessed, for example, the disc diffusion assay [90] and the E-test assay [91]; however, the results were discouraging.

The treatment of these organisms must take several important issues into account. First, monotherapy of severe infections must be avoided, because of the possibility of acquisition
of resistance through target mutations [2,92] or the presence of inducible resistance mechanisms (e.g., methylases of efflux pumps), which have been described in most clinically significant species [93,94]. Of interest, erm methylases have been described among several species of these mycobacteria, although their presence does not always correlate with phenotypical resistance [93]. This phenomenon can be due to the fact that these are inducible enzymes, and macrolide resistance can appear only after induction by a macrolide [95]. We can only speculate about the importance of these enzymes in the management of the patients, especially for those strains that have these enzymes but appeared susceptible to macrolides, and more studies are needed to assess the actual importance of these resistance mechanisms.

Combination therapy using a macrolide (clarithromycin has the best activity for M. abscessus or M. chelonae [2,82,86]) or a quinolone (especially for M. fortuitum strains [2,82,86]) and a parenteral antibiotic (amikacin showed almost uniform activity against these organisms [82]), the activity of cefoxitin and imipenem being less predictable [2,82,86]) is recommended for severe infections. For mild infections with a small number of bacteria, monotherapy has been used with success for folliculitis or other skin and soft-tissue infections [22], although the development of resistance during clarithromycin treatment has been described in some cases [96].

The important second issue is the presence of foreign bodies or other clinical conditions that imply biofilm development (e.g., respiratory tract infections in cystic fibrosis patients). If foreign material is involved, such as prosthetic valves, pacemakers, orthopaedic prosthesis or catheters, these must be removed if the patient is to be cured. As biofilms are common among clinical isolates of NPRGM [84], this result is extremely important for patient management, because sessile bacteria are more resistant to antibiotics than planktonic ones.

The duration of therapy also depends on the nature of the infection. For severe diseases, such as bone infections, a minimum of 6 months therapy has been recommended [2,81]. Mild disease can be treated successfully for shorter periods [22,25].

Respiratory tract infections are difficult to treat and some authors consider that they cannot be cured in the present moment [81]. Treatment periods include at least 12 months after sputum culture conversion [2,81] using two or three antibiotics that are active in vitro against the individual strain. M. fortuitum disease has been considered to have a better outcome than M. abscessus or M. chelonae respiratory disease [81]. Surgery has also been used as part of the treatment of these infections.

New antibiotics that have shown in vitro activity against these mycobacteria include the new quinolones (moxifloxacin, levofloxacin) [85,86,97], telithromycin [85], tigecycline [86,98], linezolid [87,97] and other oxazolidinones [88]. Despite their good in vitro activity, no clinical experience exists for their use in the treatment of clinical infections, although there are anecdotal reports of patients cured with these antimicrobials [99,100].

One syndrome with a specific management is corneal disease caused by these organisms. This can be treated with topical antibiotics (quinolones, macrolides or amikacin are commonly used) [2], although some cases require corneal transplantation.

3.1 Mycobacterium marinum

Mycobacterium marinum is a photochromogenic mycobacterium with unique culture characteristics. Its optimal temperature for growth is 30°C, and it grows rapidly at this temperature. However, it grows slowly or not at all at 37°C [101]. This property explains the characteristic disease caused by this mycobacterium in humans.

M. marinum is the cause of the disease called ‘fish tank granuloma’ or ‘swimming pool granuloma’, a cutaneous disease related with fish tanks or, more rarely, with the use of swimming pools [22,101]. This disease can spread to contiguous structures, such as joints or bone, with variable rates according to the series [101]; it can even cause rare disseminated infections [102].

Susceptibility to this mycobacterium is difficult to evaluate, because studies involving a high number of strains are scanty [103]. These studies showed a good activity of rifampin, rifabutin, minocycline, doxycycline, clarithromycin, imipenem, sulfamethoxazole, amikacin and imipenem [103]; activity is lower for quinolones, other macrolides, quinupristin/dalfopristin, trimetoprim, isoniazid or ethambutol [103]. Moreover, these studies used agar dilution as technique. Because of the need to test individual strains in clinical laboratories, the E-test was evaluated to be used for this purpose with variable results [103,104]. However, routine testing is not recommended by the CLSI, although breakpoints have been described for rifampin, ethambutol, doxycycline/minocycline, clarithromycin, cotrimoxazole and amikacin [27].

It is difficult to recommend a therapeutic scheme based on clinical studies because most data came from case reports of groups of a low number of cases [22]. Current therapeutic practices include the use of different antibiotics, alone or in combination. Monotherapy has been used for cutaneous disease without complications; minocycline, doxycycline or clarithromycin are the antibiotics used for this purpose [101]. Combination therapy has also been used for this syndrome [22,101] but this tends to be used for deeper infections [101] or even disseminated disease [102]. Combination schemes include the use of the previously cited antibiotics plus cotrimoxazole, rifampin, quinolones and/or ethambutol [101,102].

Length of treatment is another topic for discussion. In general, mild cutaneous disease can be treated for a minimum of 6 weeks; longer periods are needed for more severe diseases, such as osteomyelitis or disseminated disease [101,102]. Antibiotic therapy has been associated in some cases with other therapies, including surgery, cryotherapy, X-ray therapy or...
Current treatment of atypical mycobacteriosis

electrodessication. Prognosis of the disease is usually good, and mild disease can cure spontaneously, although only after several months or even years [101].

3.2 Mycobacterium lentiflavum, Mycobacterium malmoense and other uncommon mycobacteria

Mycobacterium lentiflavum was described in 1996 as slowly growing, yellow-pigmented mycobacteria [105]. It has been described as a human pathogen in cases of disseminated infections in immunosuppressed patients [106,107], respiratory disease [108] and lymphadenitis, especially in children [109]. Because of the relatively scanty number of cases, there is no standardized therapy for this organism. However, therapeutic schemes have included macrolides (usually clarithromycin) associated with rifabutin and ethambutol [106]. In some cases, quinolones have been added to this combination [107], but with no better results than the first scheme. Lymphadenitis has been treated mainly with surgery [109], although in some cases it was followed by the previously cited antibiotic treatment.

Mycobacterium malmoense is a slowly growing mycobacterium that is frequently isolated from patients in northern European countries [110]. This species tends to cause respiratory diseases in immunocompetent hosts [110,111], although it is occasionally the cause of extrapulmonary disease [110,112]. No standardized technique has been described for susceptibility testing, although the proportion method using a liquid medium has been used for this purpose [113]. However, no relationship between the in vitro and in vivo results of treatment has been found [111], except for correlation of resistance against ethambutol [26]. Therapeutic schemes include rifampin plus ethambutol, with or without isoniazid, for 18 – 24 months [110]. Although 2007 ATS guidelines include isoniazid in the recommended treatment [2], studies by the Research Committee of the British Thoracic Society found no differences in outcome between both regimes [24,111]. Recent studies including quinolones or clarithromycin have also found no differences, although they demonstrated a greater number of side effects [37]. Because these results, a therapy with rifampin plus ethambutol for 18 – 24 months is currently recommended.

Mycobacterium haemophilum is an atypical mycobacterium with unique culture characteristics because of its need for supplementation with haemin or ferric ammonium citrate for growth [112]. It causes disseminated disease and extrapulmonary disease (especially cutaneous), especially in AIDS patients and other immunosuppressed hosts [61,112]. M. haemophilum seems to be resistant against first-line antituberculous drugs, although no standardized susceptibility tests exist. Management of this disease includes a recommended regimen with clofazimine, rifampin/rifabutin and clarithromycin [61,114]. Surgery for localized disease has also been used in some cases [114].

Mycobacterium scrofulaceum is a slowly growing mycobacterium once considered to be one of the leading causes of cervical lymphadenitis among children [1]. However, it seems that in recent times this mycobacterium has disappeared, being replaced by MAC as the cause of such syndrome [2]. Surgery was considered to be the cornerstone therapy for this syndrome [115], but treatment regimes for other syndromes caused by this organism are not defined [2].

Other unusual mycobacteria have also been described as the cause of human diseases, but their number is very low and no clear recommendations can be made [2,36,61,115]. In general, susceptibility testing of individual strains of these uncommon isolates is used to select a therapeutic scheme. The proportion method tends to be used for slow-growing organisms and broth microdilution for rapid growers. Usually, rifampin, ethambutol and clarithromycin are the recommended drugs for unusual slow-growing species, with macrolides (usually clarithromycin), quinolones and amikacin, together with cefoxitin, cotrimoxazole, tetracyclines or other drugs, the selected antibiotics for uncommon rapidly growing mycobacterial isolates. Surgery has also been used for localized disease as coadjuvant therapy in some cases.

4. Expert opinion

Atypical mycobacteria are a heterogeneous group of organisms that includes both true human pathogens, such as M. ulcerans, and environmental mycobacteria never described as cause of human disease. Among these organisms is a group of mycobacteria that are of environmental origin but, under some circumstances, can be described as the cause of human disease. The first (and probably crucial) step in the treatment of these diseases is to determine if the isolate is a true pathogen or a colonization/contamination. Specific guidelines have been developed to determine this issue [2], but in clinical practice this can be more difficult to assess than in published reports.

If the isolated organism is considered to be a pathogen, treatment is necessary to cure the patient. Different antibiotics or antibiotic combinations can be used (essentially first-line antituberculous drugs and, in some organisms, other ‘common’ antibiotics such as macrolides or quinolones); the regime must be selected after a proper identification of the isolate. Not all mycobacteria can be treated with the same scheme, so knowledge of the identity of the mycobacteria is another important point in the management of the patients.

The treatment schemes for some mycobacteria are relatively clear. The number of cases of infection with MAC, M. kansasii, M. xenopi, M. ulcerans, nonpigmented rapidly growing mycobacteria, M. marinum and some other species has provided researchers with the experience necessary to recommend a specific treatment. For slowly growing species, these schemes usually include a combination of isoniazid, rifampin and ethambutol and – in some cases – clarithromycin or an aminoglycoside. A special case is the treatment of the M. ulcerans disease (Buruli ulcer), which includes rifampin and an aminoglycoside (usually streptomycin); surgery is probably as essential as antibiotics.

The antibiotics used for rapidly growing organisms are different, because these species are intrinsically resistant to
first-line antituberculous drugs. The recommended combinations include a macrolide (clarithromycin has the best activity) and/or a quinolone plus amikacin for moderate to severe disease, although other antibiotics (cefoxitin, doxycycline, cotrimoxazole) can also be used. However, for these organisms, individualized therapy guided by *in vitro* results is crucial because of the different susceptibility patterns between species.

The number of described species has increased recently and, as it has done so, so too has the number of cases of infection due to newly described mycobacteria. Recent discoveries about the pathogenesis and resistance mechanisms of ‘classical’ mycobacteria have also shed new light on the management of the infections. These discoveries (e.g., biofilm development) are important for the development of new therapeutic schemes in the next years because their implications in drug resistance.

The number of drugs that can be used is still limited and new antibiotics must be tested against a high number of strains (usually by reference laboratories) to increase the possibilities for treatment. At the same time, there needs to be an increased number of multicentre studies, evaluating greater numbers of cases of infection.

The isolation of atypical mycobacteria by the clinical laboratories is usually considered to be an anecdotal finding, because most of these laboratories are aiming to diagnose and manage tuberculosis. The atypical mycobacteria that are isolated are often considered to be contaminants in clinical practice. True collaboration between microbiologists, clinicians and even surgeons (many therapeutic schemes include surgery) is necessary to obtain the best possible diagnosis, including the correct interpretation of an isolate, and treatment of the patients, so that the outcome for these patients is improved.

**Declaration of interest**

J Esteban has received a grant from Wyeth for the study of Tigecycline and rapidly growing mycobacteria.

**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


27. NCCLS. Susceptibility testing of mycobacteria, nocardiae and other aerobic actinomyces; approved standard. NCCLS document M24-A. 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA: NCCLS; 2003

28. Current recommended protocols for susceptibility testing of mycobacteria, including the most important atypical species.


68. Esteban & Ortiz-Pérez
Current treatment of atypical mycobacteriosis

83. First European study about epidemiology of infections caused by nonpigmented rapidly growing mycobacteria.
102. Streit M, Boehm LM, Hunziker T, et al. Disseminated Mycobacterium marinum infection with extensive cutaneous...
eruption and bacteremia in an immunocompromised patient.
Eur J Dermatol 2006;16(1):79-83


Affiliation
Jaime Esteban & Alberto Ortiz-Pérez
†Author for correspondence
Department of Clinical Microbiology, Fundación Jiménez Díaz, Av. Reyes Católicos 2, 28040-Madrid, Spain
Tel: +34 91550 4900; Fax: +34 91544 2636; E-mail: jestebanmoreno@gmail.com