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Review Article

Treatment for *Mycobacterium abscessus* complex—lung disease

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Nontuberculous mycobacterial infections and colonization are becoming more prevalent worldwide. *Mycobacterium abscessus* complex (MABC) is one of the predominant pathogens capable of a wide spectrum of infections, with 50% of infections involving the lungs. The decision to commence treatment is determined according to the severity of the disease, risk of progressive disease, presence of comorbidities, and goals of treatment. MABC is resistant to standard antituberculous agents and has variable drug susceptibility across different geographical locations, therefore, antibiotic susceptibility testing of all clinically significant isolates is crucial for selecting a treatment strategy. Pulmonary infections due to MABC is difficult to cure using the currently recommended regimens from the American Thoracic Society and British Thoracic Society. Macrolides are the cornerstone of treatment, but the efficacy of macrolide-based chemotherapy may be compromised by resistance. Despite the introduction of new drugs for treatment, treatment outcomes remain unsatisfactory. The combination of surgical resection of limited lung disease regions with a multidrug, macrolide-based therapy offers the optimal chance of achieving clinical cure of the disease. This review focuses on medical treatment of MABC—lung disease and the efficacy of new agents, such as clofazimine, amikacin inhalation therapy, tigecycline and linezolid, for treating MABC—lung disease.

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Introduction

Mycobacterium abscessus complex (MABC) is a group of rapidly growing nontuberculous mycobacteria (NTM) that are ubiquitous in soil and water.[1] MABC includes several subspecies, such as *M. abscessus* subspecies *abscessus* (hereafter *M. abscessus*), *M. abscessus* subspecies *bolletii* (hereafter M. *bolletii*), and *M. abscessus* subspecies *massiliense* (hereafter *Mycobacterium massiliense*).[2] MABC is associated with pulmonary and extrapulmonary infections, including soft tissue infections and ocular infections, and may present as disseminated infections and bacteremia in immunocompromised hosts.[3,4] Pulmonary infections account for approximately 50% of MABC infections.[5,6] Characteristics associated with MABC—lung diseases include Caucasian race, female sex, nonsmoking status, age over 50 years.[7–9] However, MABC-lung diseases can involve patients who do not have any predisposing conditions or previously recognized lung disease.[7] However, the rapid progression of NTM—lung diseases has been reported to be associated with several lung conditions and risk factors, such as chronic obstructive pulmonary disease, bronchiectasis, lung fibrosis, radiation lung injury, α-1 antitrypsin deficiency, cystic fibrosis, disordered ciliary motility, tracheobronchomegaly, prior pulmonary tuberculosis or nontuberculous mycobacterial infections or other granulomatous disease, achalasia, panhypopituitarism, Cushing syndrome, and IFN-γ or interleukin-12 defects.[3,10,11]

Drug susceptibility in MABC

MABC is resistant to standard antituberculous agents, such as isoniazid, rifampin, ethambutol and pyrazinamide, but susceptible to other antimycobacterial agents, including macrolides, aminoglycosides, cefoxitin, imipenem, and several novel agents. The drug susceptibility varies widely across geographical locations and over time. Most studies reporting the antibiotic susceptibility testing is based on the CLSI document M24-A2.[12] In Taiwan, the susceptibility of MABC was reported to be 93%—96% to amikacin, 53%—93% to clarithromycin (CLR), 52% to azithromycin (AZM), 90% to ofloxacin, 3%—36% to ciprofloxacin, 8%—23% to moxifloxacin, 4%—50% to minocycline, 0%—8% to doxycycline, 3%—40% to cefoxitin, 12%—29% to imipenem, 1%—8% to trimethoprim-sulfamethoxazole, 32% to linezolid, and 97%—100% to tigecycline (Table 1).[13–16] In one study done in Taiwan the MABC was identified into subspecies level, and showed that the drug resistance profiles of *M. massiliense* and *Mycobacterium bolletii* were similar to that of *M. abscessus*, except for susceptibility to clarithromycin. *M. massiliense* was intrinsically susceptible to clarithromycin.[16]

Macrolides (e.g., CLR and AZM) are the mainstay of treatment, because these are the only oral agents that often exhibit *in vitro* susceptibility against MABC. Antibiotic susceptibility testing of all clinically significant isolates is recommended because of the considerable variation in *in vitro* susceptibility to drugs other than macrolides.[7] According to the 2007 American Thoracic Society recommendations and 2017 British Thoracic Society guidelines, susceptibility testing for *M. abscessus* should include clarithromycin, cefoxitin and amikacin, and preferably also tigecycline, imipenem, minocycline, doxycycline, moxifloxacin, linezolid, co-trimoxazole and clofazimine if a validated method is available to guide treatment regimens.[7,10] The efficacy of macrolide-based chemotherapy may be compromised by resistance. Inducible resistance to CLR occurs in some MABC subspecies that encode a functional erythromycin ribosome methyltransferase gene, *erm*(41), by modifying the binding site for macrolides.[17] Polymorphism at nucleotide 28 of the *erm*(41) gene confers resistance, with wild-type T28 sequevars demonstrating inducible CLR resistance while C28 sequevars remain susceptible.[18] Acquired resistance to macrolides may be caused by point mutations in the *rrl* gene, which encodes the peptidyltransferase domain of 23S rRNA.[16] CLR may have higher resistance compared with AZM because of its ability to induce greater *erm*(41) expression in *M. abscessus* infection.[19] Other studies have reported that the minimum inhibitory concentrations of AZM were consistently higher against *M. abscessus* subspecies than those of CLR, with similar inducible resistance.[18,20] *M. massiliense* was discovered to have a deleted *erm*(41), conferring susceptibility to CLR in most clinical strains and an absence of inducible resistance to CLR, which is not the case for *M. abscessus* and *M. bolletii*.[21,22] Therefore, the treatment success rate is higher in patients with *M. massiliense* infection than those with *M. abscessus* infection.[23,24] Identification of MABC isolates to the subspecies level is crucial and may have a clinical impact on treatment strategies. Caution is required when using either AZM or CLR for the treatment of MABC infections.

Aminoglycosides are the cornerstone of antimicrobial chemotherapy against MABC infections. Aminoglycosides target the 16S rRNA gene in the rRNA operon and inhibit protein synthesis by interfering with the proof-reading process, resulting in premature termination caused by errors in synthesis. However, *Mycobacterium chelonae* and *M. abscessus* of the *M. abscessus* complex contains only a single copy of the rRNA operon, which makes phenotypic expression of single-point mutations in the ribosome much more likely compared with bacterial species that have multiple copies. A1408G, T1406A, C1409T, and G1491T (*Escherichia coli* numbering system) position mutations at 16srRNA have been reported to confer a high level of resistance to all 2-deoxystreptamines, including amikacin, kanamycin, and tobramycin.[25,26] However, no change was discovered in the minimum inhibitory concentrations for streptomycin.[25] MABC also contains enzymes that render aminoglycosides inactive through the modification of key positions by transferring acetyl or phosphate residues.[27–29]

In studies using data from Japan, South Korea, and China, the susceptibility of MABC was found to be 99%—100% to amikacin, and widely variable for other antibiotics (Table 1).[30–32] None of these studies identified isolates to the subspecies level. Because of the small number of isolates in some studies, the rates of susceptibility were relatively varied.

Limited data are available on drug susceptibility to MABC globally. The reported susceptibility of MABC from Europe and America countries and Thailand is 52%—92% to amikacin, 49%—85% to CLR, 85% to AZM, 0%—3% to ciprofloxacin, 0%—5% to minocycline, 2%—5% to doxycycline, 0%—27% to

Table 1 *In vitro* susceptibilities of *M. abscessus* complex to 15 antimicrobial agents in Taiwan.

	Susceptibility (%)				
	Taiwan			North-east Asia[30–32]	European and American countries[9,33,34,36,37]
	North[12,13]	Central[12,14,15]	South[12]		
Amikacin	95–96	90–95	98	99–100	52–92
Tobramycin	27–100	17	33	NA	NA
Ofloxacin	92	93	83	NA	NA
Ciprofloxacin	3–42	10–22	48	0–57	0–3
Moxifloxacin	8	23	NA	73	NA
Minocycline	61	4–41	45	15–44	0–5
Doxycycline	0–5	0–8	7	7–35	2–5
Cefoxitin	3–56	22–33	45	66–99	0–27
Imipenem	12–21	13–25	45	31–55	0–37
Erythromycin	51	27	17	NA	NA
Clarithromycin	54–79	58–93	43	62–91	57–85
Azithromycin	52	NA	NA	78	85
TMP-SMX[a]	1	8	NA	0–75	NA
Linezolid	32	NA	NA	77–96	29
Tigecycline	NA	97–100	NA	NA	100

[a] TMP-SMX, trimethoprim-sulfamethoxazole; NA, not available.

cefoxitin, 0%–37% to imipenem, 15%–29% to linezolid, and 100% to tigecycline (Table 1).[9,33–37] This variation in in drug susceptibility may due to the small number of isolates in these studies.

Treatment initiation

Currently, no randomized controlled trials have addressed the issue of when NTM treatment should be initiated. Considerations should be given to treatment when patients fulfill the diagnostic criteria of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for NTM–lung disease.[7,10] In a French study including 1582 patients with cystic fibrosis, isolation with MABC was most likely to fulfill the ATS bacteriological criteria for NTM–lung disease.[45] The predominant isolate of NTM–lung disease was MABC or *Mycobacterium avium* complex in several studies.[5,8,38–42,44,46–48] In 2007, the ATS/Infectious Disease Society of America (IDSA) recommended that an NTM–lung disease diagnosis should be made on the basis of clinical, radiographic, and microbiologic criteria, which were considered to be of equal importance.[7] Clinical symptoms are often variable and nonspecific, but most patients have either chronic or recurring cough. Associated symptoms include sputum production, hemoptysis, dyspnea, fever, fatigue, malaise, chest pain, and weight loss. Typical radiographic findings include nodular or cavitary opacities on chest radiographs and multifocal bronchiectasis with multiple small nodules on a high-resolution computed tomography scan. Microbiologic criteria include (1) a positive culture from at least two separate expectorated sputum samples, (2) a positive culture from at least one bronchial wash or lavage, and (3) a lung biopsy with histopathologic features of mycobacterial infection and a positive culture for NTM. Other disorders, such as tuberculosis, should of course be excluded. The 2017 British Thoracic Society guidelines suggest that when patients fulfill the ATS/IDSA criteria for NTM–lung disease, consideration should be given to initiating treatment, but the guidelines emphasize that this does not necessarily imply that treatment must commence at the time of diagnosis. The decision to initiate treatment is influenced by the severity of the disease, the risk of disease progression, comorbid diseases, and the treatment goals. Risk factors for progressive disease include severe symptoms, low body mass index, cavitary lung lesions, comorbidities, smear positivity, isolation of the same pathogen from two or more cultures, and certain specific mycobacterial species.[10]

Treatment recommendations

Treatment of MABC is challenging and requires long-term treatment with multiple antibiotics; however, effective treatment options are currently under development. In 2007, the ATS/IDSA recommended a macrolide-based multidrug therapy of parenteral amikacin plus cefoxitin or imipenem according to the results of drug susceptibility tests.[7] For patients with macrolide-resistant MABC isolates or intolerance to macrolides, a combination of parenteral drugs selected on the basis of *in vitro* susceptibility is recommended. A treatment guideline from the Northern Territory government cautioned that MABC-lung disease is very difficult to treat, and suggested that periodic multidrug treatment, including a macrolide and one or more parenteral drugs (amikacin, cefoxitin or imipenem) may help to control symptoms and disease progression.[49] However, the limited effectiveness of antibiotic options renders MABC–lung disease a chronic, incurable infection for most patients. Thus, the 2017 British Thoracic Society guidelines recommend a new regimen with an initial treatment phase of at least 4 weeks of intravenous

Table 2 Recommended antibiotic regimens for adults with MABC—lung disease.

	ATS/IDSA, 2007[7]		BTS, 2017[10]
Clarithromycin-sensitive isolates or inducible-macrolide-resistant isolates	For limited lung disease, combined surgical resection of the involved lung with multidrug therapy is the only curative treatment. Clarithromycin, and ≥1 of the following parenteral agents: amikacin, cefoxitin, or imipenem for 2—4 months with periodic administration may help control the disease	Initial phase (≥1 month)	amikacin, tigecycline, and if tolerated, imipenem, and if tolerated, clarithromycin or azithromycin
		Continuation phase	Nebulized amikacin, and clarithromycin or azithromycin, and 1—3 of the following antibiotics, as guided by drug susceptibility results and patient tolerance: clofazimine, linezolid, minocycline, moxifloxacin, cotrimoxazole
Constitutive macrolide-resistant isolates	Combination of parenteral drugs based on *in vitro* susceptibility	Initial phase (≥1 month)	amikacin and tigecycline, and if tolerated, imipenem
		Continuation phase	Nebulized amikacin, and 2—4 of the following antibiotics, as guided by drug susceptibility results and patient tolerance: clofazimine, linezolid, minocycline, moxifloxacin, cotrimoxazole
Goal	Recommended duration: minimum of 12 months after culture conversion		

ATS, American Thoracic Society; BTS, British Thoracic Society; IDSA, Infectious Disease Society of America; MABC, *Mycobacterium abscessus* complex.

amikacin, tigecycline, and imipenem administration with a macrolide.[10] A continuation phase is suggested with nebulized amikacin and a macrolide in combination with one to three additional oral antibiotics. The recommended oral antibiotics include clofazimine, linezolid, minocycline, moxifloxacin, and cotrimoxazole. When a specific agent is being selected, the antimicrobial susceptibility of the isolate and patient's tolerance to the antibiotic should be considered (Tables 2 and 3). Cure of the disease often requires surgical resection in those with limited lung disease, combined with multidrug, macrolide-based therapy. The recommended duration of antibiotic treatment for MABC—lung disease in the two guidelines is a minimum of 12 months after culture conversion. Guideline for diagnosis and management of NTM organized by the Northern Territory Government also suggested treating pulmonary NTM disease for 12 months following a negative sputum culture.[49] The treatment goal of culture conversion is often not achievable with the current drug regimens; thus, alternative therapy goals are more realistic in clinical practice, such as symptomatic improvement, regression of radiographic infiltrates, and reduced sputum culture positivity. A long-term suppressive antibiotic regimen may benefit individuals who fail to achieve culture conversion.

Outcomes with treatment

In a study conducted 20 years ago in South Korea, 65 patients with MABC—lung disease who were treated with the standard regimens in the ATS guidelines were enrolled.[7] Sputum conversion and maintenance of negative cultures for 1 year was achieved in 58% of patients. Most isolates from these patients were susceptible to cefoxitin and amikacin (96%—98%). Treatment success was independently associated with CLR susceptibility; the cure rate was significantly lower in CLR-resistant patients than in patients with isolates that had full or intermediate susceptibility to CLR (17% vs. 64%, $p = 0.007$).[50] The more favorable response may have been due to more than half of the patients having infection of *M. massiliense*, formerly identified as *M. abscessus*, which does not harbor a functional *erm* gene.[51] Another study conducted between 2004 and 2009 reported radiographic improvement in the majority of patients with *M. massiliense* infection compared with only one-third of patients with *M. abscessus* infection (88% vs. 33%, $p < 0.001$).[52] Several other studies have reported that patients with *M. massiliense* infection had superior clinical outcomes to those with *M. abscessus* infection.[23,24,53]

Another study conducted in South Korea between 2002 and 2012 evaluated treatment outcomes in 67 patients with *M.*

Table 3 Recommended antibiotic dosing for treatment of MABC—lung disease in adults.

	ATS/IDSA, 2007[7]	BTS, 2017[10]
Clarithromycin, PO	1000 mg QD	500 mg BID
Azithromycin, PO		250—500 mg QD
Amikacin, IV	10—15 mg/kg amikacin QD or 25 mg/kg amikacin TIW	15 mg/kg IV amikacin QD or TIW
Cefoxitin, IV	12 g daily in divided doses	
Imipenem, IV	500 mg BID to QID	1 gm BID, if tolerated
Tigecycline, IV		50 mg BID
Clofazimine, PO		50—100 mg QD
Linezolid, PO		600 mg QD or BID
Minocycline, PO		100 mg BID
Moxifloxacin, PO		400 mg QD
Cotrimoxazole, PO		960 mg BID

ATS, American Thoracic Society; BID, twice daily; BTS, British Thoracic Society; IDSA, Infectious Disease Society of America; IV, intravenous; MABC, *Mycobacterium abscessus* complex; PO, oral; QD, once daily; QID, four times daily; TIW, three times weekly.

abscessus—lung disease after subspecies differentiation. These patients received treatment according to the ATS guidelines with an initial 4-week course of amikacin and cefoxitin. During the first 12 months of treatment, the cumulative rate of culture conversion using antibiotics alone was low (34%) but increased to 42% when surgical resection was combined with antibiotics. Compared with patients with persistently positive cultures, patients with culture conversion were significantly more likely to have smooth colonies (45% vs. 8%, $p = 0.020$), susceptibility to CLR (35% vs. 4%, $p = 0.015$), and the C28 sequevar of the *erm*(41) gene.[54] Wild-type T28 sequevars have inducible resistance to CLR, whereas isolates with a T→ C polymorphism at nucleotide 28 of the *erm*(41) gene (C28 sequevars) remain susceptible and thus enable a superior clinical response.[22,55—57]

In a study conducted from 2006 to 2012 in southern Taiwan, the treatment outcomes of 26 patients with MABC—lung disease who were treated for more than 3 months were evaluated. Sputum conversion was observed in 69% (18/26), which is higher than the rates calculated in previous studies (58% in a Korean study[50] and 48% in a US study[9]). The rate of clinical failure did not differ between patients who received a macrolide-based regimen, macrolide-quinolone regimen, or intravenous drug regimen. The risk factors for persistent MABC—lung disease include previous mycobacterial lung disease ($p = 0.011$) and cavitary lung lesions ($p = 0.034$).[43]

A study performed in Denver between 2001 and 2008 enrolled 69 patients with MABC—lung disease. Individualized antibiotic treatment based on drug susceptibility and patient tolerance was administered, and 74% of patients received a macrolide and intravenous amikacin with or without another antibiotic. A mean number of 4.6 drugs were administered over the course of therapy with a median of duration of intravenous antibiotics of 6 months. Thirty-five percent (24/69) of the patients underwent a surgical procedure. Culture conversion and cultures remaining negative for at least 1 year were significantly more frequent in patients treated with a combined surgical and medical strategy than in those treated with antibiotics alone (57% vs. 28%, $p = 0.022$).[9]

A more recent study conducted between 2012 and 2017 in China retrospectively analyzed 244 patients with MABC—lung disease.[23] In this study, 75.8% of the patients had *M. abscessus* infection and 24.2% *M. massiliense* infection. A significantly higher success rate was achieved among the patients with *M. massiliense* infection compared with *M. abscessus* infection (81.4% vs. 33.5%). The administration of amikacin [adjusted odds ratio (AOR), 3.275], imipenem (AOR, 2.078), linezolid (AOR, 2.231), and tigecycline (AOR, 2.040) was correlated with increased treatment success.

Two recent meta-analyses reported treatment outcomes for MABC—lung disease. These two studies enrolled 1013 and 303 patients, respectively.[58,59] The sustained sputum conversion rates were 33%—35% for patients diagnosed with *M. abscessus*—lung disease and 45.6%—54% for all MABC—lung disease types. For patients with *M. abscessus* infection, treatment success was correlated with the use of AZM (AOR, 3.29; 95% confidence interval, 1.26—8.62), parenteral amikacin (AOR, 1.44; 95% confidence interval, 1.05—1.99), and imipenem (AOR, 7.96; 95% confidence interval, 1.52—41.6). However, the treatment outcome for MABC—lung disease remains unsatisfactory.

Treatment outcomes of novel drugs for MABC lung disease

Clofazimine

Because a clinical cure is difficult to achieve in cases of MABC—lung disease, more effective and better-tolerated therapies are required. Clofazimine was introduced as part of a multidrug therapy for the treatment of rapidly progressing mycobacterial infections. Clofazimine has promising *in vitro* activity against MABC, with a susceptibility rate of 97%—99%. The combination of clofazimine and amikacin has demonstrated significant synergistic activity, with susceptibility achieved in 82%—100% of MABC isolates.[60,61] A few studies have demonstrated that clofazimine-containing regimens can achieve microbiological response in 24%—50% of cases[62,63] and result in a sustained clinical cure after 12 months of posttreatment follow-up in 43% of patients with MABC—lung infection.[64] Gastrointestinal disturbance and reddish-brown skin discoloration have been reported to be the most common adverse effects of a clofazimine-containing regimen.[62,63]

Amikacin inhalation therapy (powder and liposomal forms)

The British Thoracic Society guidelines recommend consideration of nebulized amikacin therapy instead of intravenous amikacin in individuals with MABC—lung disease when intravenous administration is impractical or contraindicated or if prolonged treatment with an aminoglycoside is required.[10] Nebulized amikacin may also play a role in the treatment continuation phase of MABC—lung disease. A few studies have analyzed the efficacy of inhalational amikacin therapy for MABC—lung disease, and most of these studies enrolled patients with disease refractory to treatment. Amikacin inhalational salvage therapy may improve treatment response in patients with refractory MABC—lung disease, and the reported sputum conversion rates are 13%—100%.[65–67] The relatively few patients analyzed in these studies (2, 15, and 48 patients in each study, respectively[65–67]) resulted in wide variation in the results. Discontinuation of inhalational amikacin or dose reduction due to adverse effects such as ototoxicity, hemoptysis, nephrotoxicity, dysphonia, or candidiasis occurred in 35%—50% of patients. None of the patients with amikacin-resistant isolates achieved culture conversion.[67] Doses varied widely among the different study protocols, ranging from 500 mg thrice weekly to 15 mg/kg once daily. The optimal dosage and intervals for inhalational amikacin therapy require further investigation.

Recently, liposomal amikacin was introduced as another treatment option for inhalation therapy. Nebulization of a liposomal amikacin inhalation suspension improved amikacin uptake into cultured macrophages by a factor of 4 compared with use of free amikacin.[68] Compared with intravenous free amikacin, liposomal amikacin inhalation suspension yielded a 42-, 69-, and 274-fold greater mean area under the concentration—time curve in lung tissue, the airway, and macrophages, respectively.[65] A randomized controlled trial conducted between 2012 and 2015 investigated the efficacy of liposomal amikacin inhalation as part of treatment for refractory NTM—lung disease, including *M. avium* complex—lung disease and MABC—lung disease.[69] In this trial, more patients treated with liposomal amikacin inhalation therapy achieved negative sputum cultures compared with those given a placebo (32% vs. 9%, $p = 0.006$), and the time to negative sputum culture conversion was also superior when liposomal amikacin inhalation was employed ($p = 0.0129$). None of the patients with an amikacin-resistant isolate achieved culture conversion. Therapy was discontinued for 15.9% of patients in the liposomal amikacin inhalation group because of adverse effects, such as exacerbation of dyspnea, cough, pneumonia, oropharyngeal pain, or respiratory disorder.

Tigecycline

Tigecycline is a glycylcycline antibiotic that is structurally related to tetracycline. It reportedly has favorable *in vitro* activity against rapidly growing nontuberculous mycobacteria.[34,70] Tigecycline was demonstrated to be effective against *M. abscessus* in the hollow-fiber model of lung disease. In this model, a daily dose of 200 mg achieved 1-log kill target exposure in nearly 90% of patients, suggesting that this is the optimal dose for a bactericidal effect in these patients.[71] Tigecycline has a synergistic effect against 92.9%, 68.8%, and 100% of *M. abscessus*, *M. massiliense*, and *M. bolletii* when combined with clarithromycin in an *in vitro* setting but has antagonistic activity against rapidly growing NTM when combined with amikacin.[16] Limited data are available on the efficacy of tigecycline in the treatment of MABC—lung disease in a clinical setting. One study conducted between 2002 and 2006 involved the analysis of 52 patients with MABC infection who were treated with a tigecycline-containing regimen. Tigecycline was given as part of a multidrug regimen for more than 1 month, and improvement was noted in >60% of patients with MABC and *M. chelonae* infection. In more than 90% of cases, patients experienced adverse events, the most common of which were nausea and vomiting. Nausea, vomiting, and anorexia were the major side effects that caused reduction of tigecycline dose in approximately half of patients. Slow dose titration and the use of antiemetics, such as ondansetron, improved patient tolerability.[72] In a case report from Taiwan of a patient with MABC—lung infection, both cure and eradication were achieved after tigecycline had been administered for 2 weeks with the administration of clarithromycin for 8 months.[15]

Linezolid

Linezolid has been approved for the treatment of drug-resistant gram-positive bacterial infections and for multiple-drug—resistant tuberculosis. Because of the limited choice of drugs available for treatment of rapidly growing mycobacteria, the *in vitro* efficacy of linezolid against rapidly growing mycobacteria, including MABC, was evaluated in one study. Analysis of 249 clinical isolates of rapidly growing mycobacteria between 1998 and 2000 revealed that linezolid has excellent potential for treatment against these bacteria, but MABC was the least susceptible group to linezolid (only 23% susceptibility).[73] Another study analyzed 53 clinical isolates of NTM and discovered variable susceptibility of all strains.[74] Linezolid is associated with treatment-limiting adverse events, such as cytopenia and neuropathy, which may complicate long-term use. One study reported the tolerability of linezolid for treatment of 102 patients with NTM in North America. The median linezolid therapy duration was 21.4 weeks, and a daily dose of 600 mg effectively achieved clinical benefits with a low rate of toxicity. Adverse events attributable to linezolid occurred in 45% of patients, with peripheral neuropathy being the most common, even with concomitant vitamin B6 use. Linezolid is a viable option in the multidrug therapy of NTM disease.[75]

Conclusions

The incidence of NTM infection and colonization is increasing worldwide, and MABC is one of the predominant isolates. The decision to commence treatment is determined according to the severity of the NTM—lung disease, risk of progressive disease, presence of comorbidities, and goals of treatment. Because MABC is resistant to standard

antituberculous agents and susceptibility to antimycobacterial agents varies widely across geographical locations and over time, antibiotic susceptibility testing of all clinically significant isolates is crucial for selecting a treatment strategy. Despite the introduction of new drugs for the treatment of MABC—lung disease, its treatment outcomes remain unsatisfactory. The combination of surgical resection of limited lung disease regions with a multidrug, macrolide-based therapy offers the optimal chance of achieving clinical cure of the disease.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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