REVIEW ARTICLE

Pulmonary Mycobacterium abscessus complex in children with cystic fibrosis: A practical management guideline

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Abstract: The treatment of Mycobacterium abscessus complex (MABSC) pulmonary infections is an emerging challenge in patients with cystic fibrosis (CF). Multidrug therapy for prolonged durations is required and carries the significant burden of drug-related toxicity, cost and selective pressure for multiresistant bacteria. International guidelines acknowledge that clinical and in vitro data to support treatment regimens are limited, particularly in children. As part of a collaboration between the infectious diseases and respiratory units at our institution, we have developed a modified treatment guideline that aims to balance the aims of MABSC eradication and slowing disease progression with minimising drug toxicity and resistance. The outcomes of this treatment approach will be monitored and reported. In this manuscript, we discuss the available evidence for treatment choices and present our treatment guideline for paediatric patients with CF and MABSC infection.

Key words: cystic fibrosis; Mycobacterium abscessus; non-tuberculous mycobacteria; paediatric.

Addressing the challenges associated with diagnosing and treating non-tuberculous mycobacterial (NTM) pulmonary disease in patients with cystic fibrosis (CF) is an increasing priority. Isolation of Mycobacterium abscessus complex (MABSC) from the respiratory tract is particularly concerning given its potential pathogenicity and frequent multidrug resistance. MABSC comprises the few rapidly growing mycobacteria pathogenic to humans, although differences in clinical and microbiological features between its three subspecies (M. abscessus subsp. abscessus, M. abscessus subsp. bolletii and M. abscessus subsp. massiliense) are increasingly evident.

Over the last two decades, the prevalence of NTM infection among CF patients has increased. In Australia, NTM sputum culture positivity in CF patients increased from 1.5 to 2.8% between 2012 and 2015. In the USA, the overall NTM prevalence increased from 11.0% in 2010 to 13.4% in 2014, with a period prevalence of 8% for MABSC culture positivity. Among paediatric CF patients, the prevalence of MABSC infection varies between 3.4 and 5.8% in European centres. Children with MABSC infection tend to have more severe lung disease and are younger at the time of infection compared with other NTM pulmonary infections. The rising prevalence of NTM infection in CF patients is likely attributable to increased screening and improved methods of MABSC detection. Furthermore, improved life expectancy among CF patients and increased antibiotic use (both systemic and inhaled) are also contributing factors. Certain geographical regions have also been shown to have a higher prevalence of MABSC infections, such as North Queensland. A recent population genomic analysis suggests that the majority of MABSC infections are transmitted by indirect cross-infection via fomites and, potentially, also aerosols, although this has not been demonstrated in all studies. The clinical significance of NTM infection in CF patients is controversial as data show that there is no association with clinically significant disease in more than half of CF patients with transiently or persistently positive sputum cultures of NTM. Indeed, a significant number of patients with CF with documented NTM infection demonstrate culture conversion in the absence of specific treatment.
Current international guidelines recommend that treatment should be considered in children with CF who (i) have worsening symptoms or lung function despite general CF care and treatment of other infections and CF-related morbidities (diabetes and allergic bronchopulmonary aspergillosis), (ii) have had at least two MABSC-positive sputum cultures and (iii) have radiological features consistent with NTM pulmonary disease (inflammatory nodules, new tree-in-bud opacities and cavitition). The current recommended prolonged treatment strategies for MABSC lung infection in CF patients present a challenge in terms of tolerability, toxicity and cost. Furthermore, there are high rates of treatment failure. To date, the optimal duration of treatment is unknown, and the definition of clinical and microbiological response is variable. Therefore, current guidelines recommend that treatment is ‘guided, but not dictated’ by in vitro susceptibilities.

The expression of the inducible erythromycin ribosome methyltransferase 41(erm(41)) gene by MABSC is one of the primary mechanisms of intrinsic macrolide resistance. Along with subspeciation, laboratory assessment of the activity or functionality of the erm(41) gene is now the most important laboratory test to guide antibiotic therapy. In vitro macrolide resistance has been shown to predict treatment failure, and therefore, routine testing for inducible macrolide resistance is now recommended by CLSI using techniques such as extended incubation with a macrolide.

In vitro susceptibility varies between MABSC subspecies, and therefore, the identification of isolates to a subspecies level may predict treatment outcomes, and this should specifically be requested from the laboratory. M. abscessus subsp. abscessus, and possibly M. abscessus subsp. bolletii, carries a full-length functionalerm(41) gene and exhibits extensive intrinsic and acquired resistance mechanisms. M. a. massiliense carries a partialerm(41) gene and demonstrates less macrolide resistance. Subspeciation, and ideally the identification oferm gene activity, provides the first critical step in devising an antibiotic regimen.

Although not currently widely available, testing for other genetic mutations that confer antimicrobial resistance is another option. For subspecies M. a. abscessus, following exposure to macrolide monotherapy, acquired resistance to macrolides and cross-resistance to other macrolides, streptogramins and lincosamides can occur through mutations in the 23SrRNA gene. Furthermore, resistance of M. a. abscessus and M. a. massiliense to aminoglycosides and macrolides with in vitro exposure to these drugs has been reported through mutations of genes rrs and rrl, respectively.

Our treatment guideline recommends testing for macrolide sensitivity prior to commencing intravenous therapy as testing for in vitro susceptibilities to other antimicrobials is unreliable. If there is no clinical response to first-line therapy, then in vitro susceptibilities to other antimicrobials are reviewed, and the treatment regimen is tailored accordingly (Fig. 1).

Which Drugs to Use?

The choice of antimicrobial therapy for MABSC must consider available clinical efficacy data, in vitro activity, synergy or antagonism between drugs, drug toxicity, spectrum of activity and cost, as well as co-infecting organisms such as Pseudomonas aeruginosa (Table 1). Antimicrobial choice and dosing also requires consideration of a patient’s comorbidities and potential drug interactions (e.g., ivacaftor with clarithromycin). Prior antibiotic use should also be considered given the risk of ototoxicity with cumulative exposure to aminoglycosides.

Clinical efficacy data

Table 2 summarises the studies involving adult patients with non-CF MABSC pulmonary disease on which the current

Testing and Interpreting Laboratory Susceptibilities

Compared with other rapidly growing mycobacteria, MABSC is susceptible to few antibiotics in vitro, and the correlation between in vitro susceptibility and in vivo clinical response is poor.
international guidelines are based. Applying the results of these studies to the paediatric CF population is difficult as none of these studies provided data on *M. abscessus* subspecies or *erm* gene activity. Furthermore, all studies included patients who underwent pulmonary surgical resection, which is not a practical option in the paediatric CF population whose lung disease is rarely localised. Differences in pharmacokinetics (oral absorption, volume of distribution and clearance) in CF patients compared with non-CF patients must also be considered. There are no paediatric efficacy studies of CF MABSC pulmonary disease beyond case reports.

**In vitro activity**

The parenteral antibiotics active *in vitro* against MABSC include amikacin, cefoxitin, imipenem and tigecycline.23–25 Clarithromycin or azithromycin are also routinely used depending on macrolide sensitivity of the isolate. All of these drugs are bacteriostatic against MABSC,33,34 with the possible exception of tigecycline.35

**Amikacin**

Amikacin is considered the cornerstone of treatment for MABSC infection and is currently recommended as the standard of care.
Table 1  Antimicrobials commonly used for treatment of *Mycobacterium abscessus* complex

<table>
<thead>
<tr>
<th>Drug + dosing</th>
<th>Antimicrobial susceptibility</th>
<th>Cost AUD (50 kg child for 8 weeks)</th>
<th>Bioavailability in CF patients</th>
<th>Major ADR</th>
<th>ADR monitoring(^3,27)</th>
</tr>
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<tbody>
<tr>
<td>Amikacin (IV or intramuscular)(\dagger)</td>
<td>70–94%</td>
<td>$20 160</td>
<td>IV</td>
<td>Nephrotoxicity</td>
<td>1 Month 1–2: UEC weekly</td>
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<tr>
<td>1 month–12 years: 22.5 mg/kg once daily (maximum dose: 1.5 g) 10–18 years: 18 mg/kg once daily (maximum 1.5 g)</td>
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<tr>
<td>Macrolide choice</td>
<td>M. abscessus subsp. abscessus ≈20%</td>
<td>Azithromycin</td>
<td>Azithromycin: 35%(^28,29)(\dagger)</td>
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<tr>
<td>Azithromycin: 10 mg/kg once daily; maximum dose: 500 mg/dose</td>
<td>M. abscessus subsp. massiliense 97%(\dagger)</td>
<td>Clarithromycin</td>
<td>No significant difference compared with non-CF controls 35 vs. 40%</td>
<td>Hepatitis</td>
<td>1 ECG at baseline, week 2 and then every 3 months 2 Repeat if any new QT-prolonging medication added</td>
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<tr>
<td>Clarithromycin: 7.5 mg/kg/dose (maximum: 500 mg/dose) twice daily</td>
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<tr>
<td>Cefoxitin</td>
<td>50 mg/kg/dose three times daily (maximum daily dose: 12 g daily)</td>
<td>50%</td>
<td>$8400</td>
<td>IV</td>
<td>Cytopenias</td>
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<tr>
<td>Imipenem</td>
<td>25 mg/kg/dose four times daily (maximum daily dose: 12 g daily)</td>
<td>≈50%</td>
<td>$5600</td>
<td>IV</td>
<td>Cytopenias</td>
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<tr>
<td>Linezolid (oral or IV)</td>
<td>&lt;12 years old: 10 mg/kg/dose every 8 h, maximum dose: 600 mg ≥ 12 years old: 600 mg every 12 h</td>
<td>≈50%</td>
<td>$19 040–$20 160(\dagger)</td>
<td>85% Reduced compared with non-CF controls (85 vs. 100%)(^29)</td>
<td>As above</td>
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</table>

EC Andrew et al.
<table>
<thead>
<tr>
<th>Drug + dosing</th>
<th>Antimicrobial susceptibility</th>
<th>Cost AUD (50 kg child for 8 weeks)†</th>
<th>Bioavailability in CF patients</th>
<th>Major ADR</th>
<th>ADR monitoring³,²⁷</th>
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</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>≈15%</td>
<td>$728</td>
<td>Higher compared with non-CF controls (80 vs. 57%)</td>
<td>Prolonged QT interval</td>
<td>As above</td>
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<tr>
<td>10 mg/kg/dose every 24 h;</td>
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<td></td>
<td>Cytopenias</td>
<td>As above</td>
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<tr>
<td>maximum dose: 400 mg/dose</td>
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<td></td>
<td>Nephrotoxicity</td>
<td>As above</td>
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<td></td>
<td></td>
<td></td>
<td>Hepatitis</td>
<td>As above</td>
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<td></td>
<td></td>
<td></td>
<td>Tendonitis</td>
<td>As above</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia, agitation, anxiety†</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea, vomiting, diarrhoea</td>
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<tr>
<td>Tigecycline</td>
<td>70%</td>
<td>$17 100</td>
<td>IV</td>
<td>Anaemia</td>
<td>As for cytopenias above</td>
</tr>
<tr>
<td>≥ 8 years old: 1.2 mg/kg/dose every 12 h;</td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis</td>
<td>As above</td>
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<tr>
<td>maximum dose: 50 mg/dose</td>
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<td></td>
<td></td>
<td>Pancreatitis</td>
<td>Serum lipase†††</td>
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</tbody>
</table>

†Calculations based on formulary costs at our centre at the time of publication and upper limit dosage recommendations by Floto et al.³ ††Follow local protocol to individualise dosage by monitoring amikacin concentration after the first dose. Concentration monitoring is unnecessary if treating children with normal renal function for up to 48 h. §Pharmacogenomic testing for A1555G mitochondrial mutation may help prevent aminoglycoside-induced hearing loss. Further studies are needed.³⁰ ¶Clinical monitoring for symptoms of adverse effects. ††Lower cost for tablet and higher for suspension. †††No bioavailability data for clarithromycin in CF. §§Susceptibility break-point defined as minimum inhibitory concentration ≤2.25. ¶¶No bioavailability data for moxifloxacin in CF. ¶¶¶For patients with pancreatic sufficiency. ADR, adverse drug reaction; CF, cystic fibrosis; ECG, electrocardiogram; FBE, full blood examination; IV, intravenous; LFT, liver function tests; UEC, urea, electrolytes and creatinine.
higher proportion of susceptible isolates (up to 94%).\(^{16,23,25}\) In models comparing the choice of macrolide is not straightforward. Animal therapy has been associated with encouraging clinical responses.\(^{6}\) For MABSC isolates without a functional erm(41) gene, macrolides as the most active antibiotic against MABSC in vitro have been reported.\(^{16,23,25}\) Most agents against MABSC are among the most active parenteral agents against MABSC in vitro.\(^{23,25}\) A broad-spectrum beta-lactamase (BlαMab) produced by MABSC is the main underlying factor for resistance to all beta-lactam agents except for cefoxitin and imipenem, which are affected only slowly by this enzyme.\(^{33}\) Most in vitro studies have found a higher proportion of isolates susceptible to cefoxitin than imipenem.\(^{16,23,25}\) Although a recent study comparing cefoxitin and imipenem showed that imipenem was superior for both in vitro and intra-macrophage activity against MABSC.\(^{33}\) Neither drug was bactericidal when used alone but, when used in combination, were synergistic and achieved bactericidal activity.

### Macrolides
For MABSC isolates without a functional erm(41) gene, macrolide therapy has been associated with encouraging clinical responses. However, the choice of macrolide is not straightforward. Animal models comparing the in vitro and in vivo response in MABSC pulmonary infection showed that clarithromycin was significantly less effective than azithromycin in treating M. a. abscessus infection due to the stronger induction of erm(41) gene expression.\(^{41}\) For M. a. massiliense infections, however, clarithromycin and azithromycin had comparable efficacy. In contrast, a recent study reported higher MICs for azithromycin compared with clarithromycin and also found both drugs capable of inducing in vitro macrolide resistance.\(^{42}\)

### Beta-lactams
Cefoxitin and imipenem are among the most active parenteral agents against MABSC in vitro.\(^{23,25}\) A recent in vitro study comparing cefoxitin and imipenem showed that imipenem was superior for both in vitro and intra-macrophage activity against MABSC.\(^{33}\) Neither drug was bactericidal when used alone but, when used in combination, were synergistic and achieved bactericidal activity.

### Tigecycline
Tigecycline has potent in vitro activity against MABSC\(^{23,33,42}\) and was previously considered to exert a bacteriostatic effect. More recently, a hollow-fibre model against subspecies M. a. abscessus demonstrated a significant reduction in MABSC colony-forming units below the stasis line on exposure to tigecycline,\(^{33}\) suggesting bactericidal activity against MABSC.\(^{1,34}\) However, a study of 36 adults and children treated with tigecycline-containing...
regimens showed a clinical improvement in only 36%.\textsuperscript{44} Of note, in this study, 94% of patients experienced drug toxicity, predominantly nausea and vomiting, which may be prevented with preemptive anti-emetic therapy and gradual dose increases. The use of anti-emetic drugs combined with tigecycline requires particular caution due to the risk of prolonged QT interval on electrocardiogram. Tigecycline is also generally not recommended for prolonged treatment in children younger than 8 years of age due to the potential risk of tooth discoloration.

**Linezolid**

Linezolid is an attractive option given its oral route of administration with excellent bioavailability and twice-daily dosing. However, it has only moderate \textit{in vitro} bacteriostatic activity against MABSC, and there are no clinical studies to support linezolid use in CF patients with MABSC infection.\textsuperscript{3,20,45} Linezolid may have significant drug interactions (e.g. with anti-emetics such as metoclopramide) and is associated with significant adverse effects, such as myelosuppression, peripheral neuropathy and optic neuropathy, although these occur less frequently in children.\textsuperscript{46}

**Moxifloxacin**

The rationale for moxifloxacin therapy for MABSC is based on its effectiveness against other mycobacterial infections. However, a recent \textit{in vitro} study investigating its use against a single strain of MABSC found it to have poor efficacy and, when used alone, that it resulted in rapid emergence of resistance.\textsuperscript{47} In a static \textit{in vitro} study, moxifloxacin was shown to have an antagonistic effect when combined with macrolide therapy against MABSC, although some \textit{in vitro} synergy was demonstrated when this combination was used against subspecies \textit{M. a. massiliense}.\textsuperscript{48} However, these findings have not been confirmed in dynamic hollow tube or \textit{in vivo} studies.

**Rationale for Drug Choice**

The available data on \textit{in vitro} efficacy, spectrum of activity, drug pharmacokinetics, toxicity and cost were used to inform the choice of first-line therapy in our treatment guideline (Fig. 1). Of note, clofazimine is not registered for use in Australia and was therefore not considered for inclusion in the regimen. In addition to amikacin, the following drugs were chosen:

1 Macrolide: For those patients with macrolide-susceptible MABSC isolates who require prolonged therapy, azithromycin enhances compliance given its single daily dosing. Furthermore, azithromycin may have a reduced risk of induction of the \textit{erm(41)} gene and fewer drug interactions than clarithromycin.\textsuperscript{3}

2 Beta-lactam: Cefoxitin was selected to prevent long-term carbapenem exposure in children who are likely to have chronic colonisation with potential multidrug-resistant organisms. While recognising the limitation of \textit{in vitro} susceptibility, a greater proportion of MABSC isolates is susceptible to cefoxitin \textit{in vitro} compared with imipenem.

3 Linezolid: For macrolide-resistant MABSC isolates, linezolid was chosen due to its high oral bioavailability in CF patients and bacteriostatic activity \textit{in vitro}. However, linezolid must be used judiciously in CF patients with methicillin-resistant \textit{Staphylococcus aureus} co-infection,\textsuperscript{3} and clear protocols for the monitoring of adverse effects must be outlined.

4 Moxifloxacin: To reduce the burden of parenteral therapy during the continuation phase, moxifloxacin was chosen for its high bioavailability with oral administration and for its superior tissue penetration.

For patients who do not respond to first-line therapy in whom another attributable cause for deterioration of lung function cannot be identified, re-induction with a regimen containing tigecycline should be considered in children over 8 years of age.

**Duration of Treatment and Number of Drugs**

The primary aim of treatment of MABSC infection continues to be microbial eradication; however, only 50% of patients achieve this.\textsuperscript{24,31} There has been a recent discussion about alternative markers of treatment effectiveness, including assessment of lung function (improvement in forced expiratory volume (FEV1), slowed rate of decline in FEV1), radiological changes (improvement in changes on serial imaging), pulmonary exacerbation rate, time spent in hospital and patient-reported measures such as health-related quality of life.\textsuperscript{3} Irrespective of the treatment goal, these outcomes should be predefined and regularly assessed.

Current guidelines recommend treatment with 12 months of therapy beyond culture conversion.\textsuperscript{3} Furthermore, current recommendations advocate for a continuation regimen that includes up to five drugs; however, there is no evidence to support the use of more than three antibiotics.

While there are no longitudinal data available to identify when patients either achieve eradication or recurrence of MASBC infection, there is some evidence to suggest that initial parenteral treatment should be maintained for at least 1 month. An open-label study of 52 patients demonstrated no clinical improvement in patients treated with parenteral tigecycline for less than 1 month.\textsuperscript{44} Similarly, in a study of 65 patients receiving standardised MABSC treatment regimens, 72% of the cohort culture converted at a median duration of 1 month.\textsuperscript{24} There are no data to advocate for an optimal duration of intravenous therapy beyond 1 month. International guidelines recommend an intensive intravenous treatment duration of 3–12 weeks as determined by the severity of infection, response and tolerability of the regimen.\textsuperscript{3} We have adopted a pragmatic approach and recommend 6–8 weeks of intensive phase therapy.

If there has been documented clinical improvement after 6–8 weeks of intravenous therapy, the patient continues on oral combination therapy for a further 2 months (Fig. 1). If the clinical improvement is sustained at the end of continuation therapy, treatment is ceased regardless of the sputum culture response. Patients are then reviewed every 3 months with a sputum culture and FEV1, as well as having annual high-resolution computed tomography. If the patient was to have a subsequent clinical deterioration in the setting of a positive sputum culture or a recurrence of disease based on symptoms, spirometry or radiological findings, recommencement of intensive-phase parenteral treatment is considered. Alternatively, if, at the end of intensive
intravenous therapy, the patient has not had a clinical response, further assessment is made for potential comorbidities, and the in vitro susceptibility to antimicrobials other than macrolides are reviewed. At this stage, intravenous therapy is recommended, tailored to the additional antimicrobial susceptibilities. We intend to monitor and report the microbiological and clinical outcomes of our treatment approach. Relevant microbiological outcomes include rates of cure (sputum culture conversion without relapse), relapse, reinfection with a different strain and/or emergence of a resistant strain and failure to culture convert. Clinical outcomes include improvement or no response based on changes in reported symptoms, lung function testing and high-resolution computed tomography imaging.

Clinical studies to date have demonstrated significant drug toxicities causing the discontinuation of treatment in almost two-thirds of patients (Table 2). Furthermore, when dealing with the treatment of an already multi-resistant organism, there is a risk of invoking further resistance. In one case series of 69 patients on individualised regimens, patients were treated for a mean duration of 52 antibiotic-months (standard deviation 40.6 antibiotic-months) with a median parenteral treatment of 6 months; of those patients who did not become M. abscessus culture negative, a quarter of their isolates had developed resistance to at least one additional drug. To limit side effects and the risk of antimicrobial resistance, we recommend continuation therapy for a maximum duration of 2 months.

Conclusion

Treatment of MABSC pulmonary infection in patients with CF is challenging due to the lack of clinical and in vitro data to support treatment regimens. Given that these infections are associated with significant morbidity and mortality, it is important to attempt microbial eradication. However, the treatment approach must take into account the greater imperative in children to minimise drug toxicity, the effects of which may be lifelong. Furthermore, prolonged use of broad-spectrum antibiotics may lead to antimicrobial resistance, thereby restricting future therapeutic options for these patients.

We propose a treatment approach for paediatric CF patients aiming for eradication of MABSC infection and recommend it is undertaken in collaboration with clinicians with expertise in managing pulmonary MABSC (Fig. 1). Our proposed treatment guideline seeks to balance the aim of MABSC eradication with minimisation of drug toxicity by recommending 6–8 weeks of intensive therapy followed by a 2-month continuation period before reassessing treatment outcomes. We intend to monitor the outcomes of our treatment approach and report these findings.

Multiple Choice Questions

1 Which of the following parenteral antibiotics does not have in vitro activity against the Mycobacterium abscessus complex (MABSC)?
   a) Amikacin
   b) Cefoxitin
   c) Imipenem
   d) Vancomycin
   e) Tigecycline
   
   Answer: d. There are a limited number of parenteral antibiotics with activity against MABSC. Most Mycobacteria have intrinsic resistance to glycopeptides. Glycopeptide antibiotics are hydrophilic and large molecules and therefore may be too large to pass through mycobacterial porins.

2 Which of the following is not a potential side effect of prolonged amikacin therapy?
   a) Vestibular ototoxicity
   b) Cytopenias
   c) Irreversible auditory ototoxicity
   d) Neurotoxicity
   e) Renal impairment
   
   Answer: b. Side effects of amikacin are more commonly seen with prolonged use. Some of these effects may be permanent, for example, hearing loss due to ototoxicity. Cytopenias have not been described with amikacin therapy.

3 Why is subspeciation so important in determining the treatment regimen for MABSC pulmonary infection in cystic fibrosis?
   a) This helps predict treatment outcomes based on intrinsic macrolide resistance.
   b) This helps predict treatment outcomes based on intrinsic aminoglycoside resistance.
   c) This determines the duration of intensive-phase treatment.
   d) This determines the duration of continuation-phase treatment.
   e) This influences eligibility for lung transplantation.
   
   Answer: a. M. abscessus subsp. abscessus, and possibly M. abscessus subsp. bolletii, exhibit extensive intrinsic resistance to macrolides due to a full-length functional ermA(41) gene. Patients with these subspecies of M. abscessus should be treated with an intensive-phase treatment regimen that does not include a macrolide. Ideally, sequencing of ermA(41) and rrl genes would also be undertaken to fully inform the macrolide resistance phenotype of the isolate.

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Mycobacterium abscessus in cystic fibrosis


