Journal of Paediatrics and Child Health

doi:10.1111/jpc.14427

REVIEW ARTICLE

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

Eden C Andrew [1], Tom Connell,[1,2,3] Phil Robinson,[2,4,5] Nigel Curtis,[1,2,3] John Massie,[2,4,5] Colin Robertson,[2,4,5] Joanne Harrison,[2,4,5] Shivanthan Shanthikumar,[2,4,5] Penelope A Bryant,[1,2,3] Mike Starr,[1,2] Andrew Steer,[1,2,6] Sarath Ranganathan[2,4,5] and Amanda Gwee[1,2,3]

[1]Infectious Diseases Unit, Department of General Medicine, and [4]Department of Respiratory and Sleep Medicine, Royal Children's Hospital Melbourne, [2]Department of Paediatrics, University of Melbourne, [3]Clinical Infectious Diseases Group, [5]Respiratory Diseases, and [6]Group A Streptococcal Research Group, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

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.[1] 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.

Key Points

1 The treatment of *Mycobacterium abscessus* complex (MABSC) pulmonary infections is an emerging challenge in patients with cystic fibrosis and requires multidrug therapy for a prolonged duration.
2 There is a paucity of clinical and *in vitro* data to support recommendations for treatment regimens, particularly in children.
3 We propose a modified treatment guideline that aims to balance the goals of MABSC eradication and slowing disease progression with minimising drug-related toxicity, cost and selective pressure for multiresistant bacteria.

Correspondence: Dr Amanda Gwee, Infectious Diseases and Clinical Pharmacology Units, Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville, Vic. 3052, Australia. Fax: +61 39345 4751; email: amanda.gwee@rch.org.au

Conflict of interest: None declared.

Accepted for publication 10 February 2019.

Over the last two decades, the prevalence of NTM infection among CF patients has increased.[2–4] In Australia, NTM sputum culture positivity in CF patients increased from 1.5 to 2.8% between 2012 and 2015.[5] 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.[6] Among paediatric CF patients, the prevalence of MABSC infection varies between 3.4 and 5.8% in European centres.[7–9] 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.[10] 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.[2,3] Certain geographical regions have also been shown to have a higher prevalence of MABSC infections, such as North Queensland.[11] A recent population genomic analysis suggests that the majority of MABSC infections are transmitted by indirect cross-infection via fomites and, potentially, also aerosols,[12] although this has not been demonstrated in all studies.[13] 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.[14,15]

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 cavitation). 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.[3,16] Treatment includes intensive therapy followed by continuation therapy. Recommended intensive phase therapy includes a macrolide; parenteral amikacin; and one of tigecycline, imipenem or cefoxitin for 3–12 weeks. The continuation phase of therapy comprises an oral macrolide and inhaled amikacin together with two to three oral agents chosen from minocycline, clofazimine, moxifloxacin and linezolid for at least 12 months following culture conversion.[3] For monitoring, acceptable microbiological specimens include sputum, induced sputum, bronchial washings or bronchoalveolar lavage samples and not oropharyngeal swabs. These recommendations were predominantly based on consensus expert opinion and were extrapolated from adult data.[3,16] There are no randomised controlled trials assessing the treatment of MABSC pulmonary infection in CF, and current guidelines are largely derived from retrospective studies of MABSC pulmonary infection in non-CF patients.[3,17] However, a large multinational adaptive platform trial on the treatment of MABSC pulmonary disease in children and adults with either CF or bronchiectasis will commence soon (anzctr.org.au, ACTRN12618001831279p).

In the paediatric CF population, it is particularly important to minimise exposure to drugs with the potential to cause long-term toxicity or to broad-spectrum antibiotics that cause antibiotic-resistant colonising organisms. The Royal Children's Hospital Melbourne, Australia is a tertiary paediatric centre providing multidisciplinary sub-specialist care for over 250 children with CF. To develop a standardised approach to treatment with the aim of reducing antibiotic exposure and improving the monitoring of clinical outcomes, the infectious diseases and respiratory physicians at our institution devised a modified NTM treatment guideline (Fig. 1). The outcomes of this treatment approach will be closely monitored and reported. As the goal of eradicating MABSC is often unachievable, our approach aims to balance the slowing of disease progression with minimising drug toxicity associated with MABSC therapy. Notably, this guideline does not apply to the important subgroup of CF patients with end-stage lung disease requiring lung transplantation who should be treated aggressively with the aim of eradication or a significant reduction of bacterial load due to the risk of disseminated mycobacterial infection in the peri-transplant period. Whether CF patients with MABSC infection should be eligible for lung transplantation remains controversial.[18]

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.[3,19–21] Clinical and Laboratory Standards Institute (CLSI) guidelines provide minimum cut-off inhibitory concentrations (MICs) for MABSC; however, these have not been clinically validated in the CF population, and pharmacodynamic studies to guide treatment in this context are limited.[3,22] Therefore, current guidelines recommend that treatment is 'guided, but not dictated' by *in vitro* susceptibilities.[3,17,23]

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.[20] *In vitro* macrolide resistance has been shown to predict treatment failure,[24] and therefore, routine testing for inducible macrolide resistance is now recommended by CLSI using techniques such as extended incubation with a macrolide.[20,22,25]

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 functional *erm*(41) gene and exhibits extensive intrinsic and acquired resistance mechanisms.[23] *M. a. massiliense* carries a partial *erm*(41) gene and demonstrates less macrolide resistance.[20,23] Subspeciation, and ideally the identification of *erm* 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.[3,23] 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.[20,23] 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.[23]

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

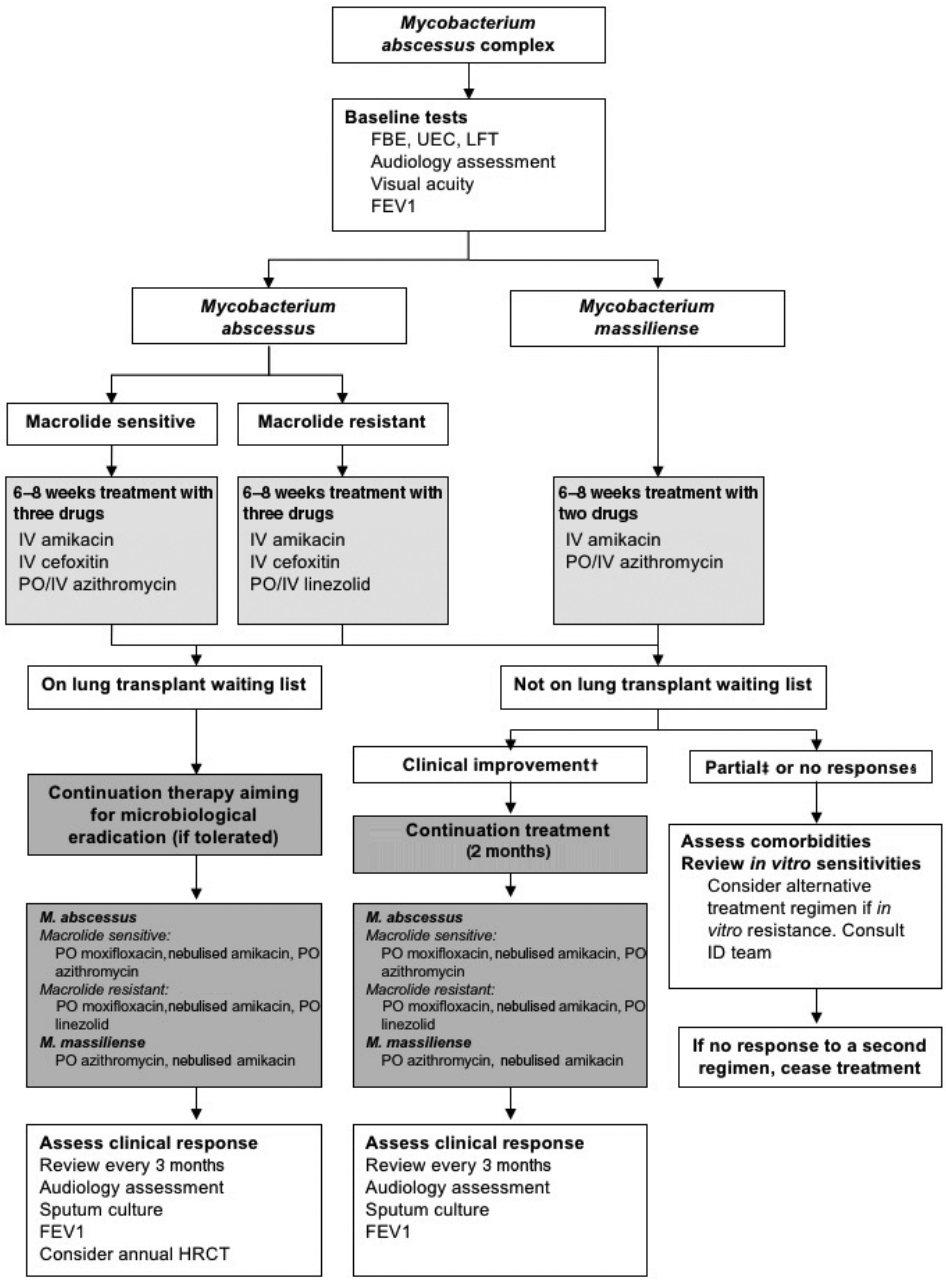

Fig. 1 Treatment of MABSC guideline. †Clinical improvement – As defined by improved respiratory symptoms (such as dyspnoea, cough, chest pain, sputum production), improved constitutional symptoms (such as weight gain, fevers) and/or improvement in lung function tests. ‡Cases with partial improvement are discussed at multidisciplinary team meetings to make decisions regarding ongoing treatment. §No response – As defined by the absence of 'clinical improvement' and/or worsening of symptoms or lung function. (▭), Intensive-phase therapy; (▭), continuation-phase therapy. FBE, full blood examination; FEV1, forced expiratory volume; HRCT, high-resolution computed tomography; ID, infectious diseases; IV, intravenous; LFT, liver function tests; PO, per oral; UEC, urea, electrolytes and creatinine.

international guidelines are based.[3] 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

Drug + dosing	Antimicrobial susceptibility[23,25,26]	Cost AUD (50 kg child for 8 weeks)†	Bioavailability in CF patients	Major ADR	ADR monitoring[3,27]
Amikacin (IV or intramuscular)‡ 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)	70–94%	$20 160	IV	Nephrotoxicity	1 Month 1–2: UEC weekly 2 Month 3 to end of treatment: UEC every 2 weeks
				Auditory-vestibular toxicity§¶	1 Baseline audiology and then monthly until end of treatment 2 Final review 2 months after end of treatment
				Neurotoxicity¶	
Macrolide choice	*M. abscessus* subsp. *abscessus* ≈20%	Azithromycin $47–$728††	Azithromycin: 35%[28]‡‡	Prolonged QT interval	1 ECG at baseline, week 2 and then every 3 months 2 Repeat if any new QT-prolonging medication added
Azithromycin: 10 mg/kg once daily; maximum dose: 500 mg/dose	*M. abscessus* subsp. *massiliense* 97%§§	Clarithromycin $42–$242††	No significant difference compared with non-CF controls 35 vs. 40%	Hepatitis	1 Months 1–2: LFT weekly 2 Month 3 to end of treatment: LFT every 2 weeks
Clarithromycin: 7.5 mg/kg/dose (maximum: 500 mg/dose) twice daily				Auditory-vestibular toxicity¶	As above
				Nausea, vomiting, diarrhoea¶	
Cefoxitin 50 mg/kg/dose three times daily (maximum daily dose: 12 g daily)	70%	$8400	IV	Cytopenias	1 Months 1–2: FBE weekly 2 Month 3 to end of treatment: FBE every 2 weeks
Imipenem 25 mg/kg/dose four times daily (maximum daily dose: 12 g daily)	≈50%	$5600	IV	Cytopenias	As above
				Hepatitis	As above
				Nausea, vomiting, diarrhoea¶	
				Seizures	
Linezolid (oral or IV) <12 years old: 10 mg/kg/dose every 8 h, maximum dose: 600 mg ≥ 12 years old: 600 mg every 12 h	≈50%	$19 040–$20 160††	85% Reduced compared with non-CF controls (85 vs. 100%)[29]	Cytopenias	As above
				Hepatitis	As above
				Delayed-type hypersensitivity¶	
				Nausea, vomiting, diarrhoea¶	
				Neuropathy (peripheral, optic)¶	1 Visual acuity and colour vision every 6 weeks 2 Ophthalmology referral as required

Table 1 (Continued)

Drug + dosing	Antimicrobial susceptibility[23,25,26]	Cost AUD (50 kg child for 8 weeks)†	Bioavailability in CF patients	Major ADR	ADR monitoring[3,27]
Moxifloxacin 10 mg/kg/dose every 24 h; maximum dose: 400 mg/dose	≈15%	$728	80%¶¶ Higher compared with non-CF controls (80 vs. 57%)	Prolonged QT interval	As above
				Cytopenias	As above
				Nephrotoxicity	As above
				Hepatitis	As above
				Tendonitis¶	
				Insomnia, agitation, anxiety¶	
Tigecycline ≥ 8 years old: 1.2 mg/kg/dose every 12 h; maximum dose: 50 mg/dose	70%	$17 100	IV	Nausea, vomiting, diarrhoea¶	
				Anaemia	As for cytopenias above
				Hepatitis	As above
				Pancreatitis	Serum lipase†††

†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.[22] ¶¶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.

Table 2 Summary of clinical evidence to support treatment of *Mycobacterium abscessus* complex (MABSC) pulmonary disease in non-cystic fibrosis adults

Study	Subjects	Antimicrobial therapy	Drug Toxicity	Outcomes
Jarand *et al*.[31]	69 adults	42 individualised combinations Mean 4.6 antibiotics Median duration 6 months IV therapy	65% discontinued at least 1 drug (usually amikacin or cefoxitin)	36 (52%) failure to culture converted or relapsed 26 (38%) culture negative at 1 year (half not on continuation therapy) 17 (16%) mortality (causes not reported)
Jeon *et al*.[24]	65 adults	4 weeks IV amikacin + cefoxitin plus oral clarithromycin + ciprofloxacin + doxycycline Oral component continued at least 12 months post-culture conversion	60% discontinued due to cefoxitin toxicity after median of 22 days Replaced with imipenem with full resolution of toxicity	9 (19%) relapse 18 (28%) failure to culture convert 38 (58%)† culture negative at 1 year 3% mortality attributed to MABSC disease progression
Griffith *et al*.[32]	119 adults	Treatment regimens not described Drugs included amikacin (58%), cefoxitin (43%), erythromycin (31%), sulphonamides or cotrimoxazole (28%), anti-tuberculous agents (37%)	Not reported	10 (8%) 'cured' 15% mortality attributed to MABSC progression

†High proportion of *M. abscessus* subsp. *massiliense* subspecies. IV, intravenous.

in international guidelines.[3] Amikacin has been frequently cited as the most active antibiotic against MABSC *in vitro* due to a higher proportion of susceptible isolates (up to 94%).[16,23,25] In addition, it exhibits more effective bacterial killing after 24 h relative to clarithromycin and cefoxitin.[36] However, the range of MICs of MABSC to amikacin varies widely, and a recent pharmacokinetic/pharmacodynamic model suggested that the current standard amikacin dose does not achieve the target C_{max}/MIC ratio for *M. abscessus* for more than 75% of patients.[37] Therefore, the bactericidal activity against MABSC of current dosing ranges for amikacin has been questioned.[34,37] Furthermore, the doses required to achieve the C_{max}/MIC target of 3.2 would incur a significant risk of ototoxicity,[36,37] although clinical studies are required to confirm this pharmacodynamic target.

Inhaled amikacin is recommended in international guidelines as part of the continuation therapy regimen. Studies of its efficacy are limited to retrospective audits.[38,39] Theoretically, the reduced systemic absorption associated with inhaled therapy may improve the tolerability of amikacin in these patients, although this route of administration would also lower the E_{max} and the resultant bactericidal effect.[37] Despite this, available clinical data have reported significant adverse effects, including ototoxicity, haemoptysis, nephrotoxicity, dysphonia and vertigo.[38,39] Inhaled liposomal amikacin is not currently approved for use but may be beneficial in the future by improving lung tissue levels of amikacin via macrophage uptake of liposomes.[40]

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 broad-spectrum beta-lactamase (Bla_{Mab}) 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.

Tigecycline

Tigecycline has potent *in vitro* activity against MABSC[25,35,43] 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,[35] suggesting bactericidal activity against MABSC.[3,34] However, a study of 36 adults and children treated with tigecycline-containing

regimens showed a clinical improvement in only 36%.[44] Of note, in this study, 94% of patients experienced drug toxicity, predominantly nausea and vomiting, which may be prevented with pre-emptive 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 discolouration.

Linezolid

Linezolid is an attractive option given its oral route of administration with excellent bioavailability and twice-daily dosing. However, it has only moderate *in vitro* bacteriostatic activity against MABSC, and there are no clinical studies to support linezolid use in CF patients with MABSC infection.[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.[46]

Moxifloxacin

The rationale for moxifloxacin therapy for MABSC is based on its effectiveness against other mycobacterial infections. However, a recent *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.[47] In a static *in vitro* study, moxifloxacin was shown to have an antagonistic effect when combined with macrolide therapy against MABSC, although some *in vitro* synergy was demonstrated when this combination was used against subspecies *M. a. massiliense*.[48] However, these findings have not been confirmed in dynamic hollow tube or *in vivo* studies.

Rationale for Drug Choice

The available data on *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 *erm*(41) gene and fewer drug interactions than clarithromycin.[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 *in vitro* susceptibility, a greater proportion of MABSC isolates is susceptible to cefoxitin *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 *in vitro*. However, linezolid must be used judiciously in CF patients with methicillin-resistant *Staphylococcus aureus* co-infection,[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.[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.[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.[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.[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.[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.[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 recommenced, 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.[31] 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 *erm*(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 *erm*(41) and *rrl* genes would also be undertaken to fully inform the macrolide resistance phenotype of the isolate.

References

1 Rowbotham NJ, Smith S, Leighton PA *et al*. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax* 2018; **73**: 388–90.
2 Bryant JM, Grogono DM, Greaves D *et al*. Whole-genome sequencing to identify transmission of *Mycobacterium abscessus* between patients with cystic fibrosis: A retrospective cohort study. *Lancet* 2013; **381**: 1551–60.
3 Floto RA, Olivier KN, Saiman L *et al*. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax* 2016; **71**: 88–90.
4 Qvist T, Pressler T, Hoiby N, Katzenstein TL. Shifting paradigms of nontuberculous mycobacteria in cystic fibrosis. *Respir. Res.* 2014; **15**: 41.
5 Ruseckaite R, Ranger T, Tacey M *et al*. *The Australian Cystic Fibrosis Data Registry Annual Report, 2016.* Melbourne: Monash University, Department of Epidemiology and Preventive Medicine; 2018. Report No. 19.
6 Adjemian J, Olivier KN, Prevots DR. Epidemiology of pulmonary nontuberculous mycobacterial sputum positivity in patients with cystic

fibrosis in the United States, 2010–2014. *Ann. Am. Thorac. Soc.* 2018; **15**: 817–26.
7 Pierre-Audigier C, Ferroni A, Sermet-Gaudelus I *et al*. Age-related prevalence and distribution of nontuberculous mycobacterial species among patients with cystic fibrosis. *J. Clin. Microbiol.* 2005; **43**: 3467–70.
8 Roux A-L, Catherinot E, Ripoll F *et al*. Multicenter study of prevalence of nontuberculous mycobacteria in patients with cystic fibrosis in France. *J. Clin. Microbiol.* 2009; **47**: 4124–8.
9 Sermet-Gaudelus I, Le Bourgeois M, Pierre-Audigier C *et al*. *Mycobacterium abscessus* and children with cystic fibrosis. *Emerg. Infect. Dis.* 2003; **9**: 1587–91.
10 Catherinot E, Roux AL, Vibet MA *et al*. Mycobacterium avium and *Mycobacterium abscessus* complex target distinct cystic fibrosis patient subpopulations. *J. Cyst. Fibros.* 2013; **12**: 74–80.
11 Chou MP, Clements ACA, Thomson RM. A spatial epidemiological analysis of nontuberculous mycobacterial infections in Queensland, Australia. *BMC Infect. Dis.* 2014; **14**: 279.
12 Bryant JM, Grogono DM, Rodriguez-Rincon D *et al*. Population-level genomics identifies the emergence and global spread of a human transmissible multidrug-resistant nontuberculous mycobacterium. *Science* 2016; **354**: 751–7.
13 Tortoli E, Kohl TA, Trovato A *et al*. *Mycobacterium abscessus* in patients with cystic fibrosis: Low impact of inter-human transmission in Italy. *Eur. Respir. J.* 2017; **50**: 1602525.
14 Levy I, Grisaru-Soen G, Lerner-Geva L *et al*. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, Israel. *Emerg. Infect. Dis.* 2008; **14**: 378–84.
15 Martiniano SL, Sontag MK, Daley CL, Nick JA, Sagel SD. Clinical significance of a first positive nontuberculous mycobacteria culture in cystic fibrosis. *Ann. Am. Thorac. Soc.* 2014; **11**: 36–44.
16 Griffith DE, Aksamit T, Brown-Elliott BA *et al*. An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am. J. Respir. Crit. Care Med.* 2007; **175**: 367–416.
17 Waters V, Ratjen F. Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis. *Cochrane Database Syst. Rev.* 2016; 12: CD010004.
18 Lobo LJ, Noone PG. Respiratory infections in patients with cystic fibrosis undergoing lung transplantation. *Lancet Respir. Med.* 2014; **2**: 73–82.
19 Petrini B. *Mycobacterium abscessus*: An emerging rapid-growing potential pathogen. *APMIS* 2006; **114**: 319–28.
20 Griffith DE. Mycobacterium abscessus subsp abscessus lung disease: 'Trouble ahead, trouble behind…'. *F1000Prime Rep.* 2014; **6**: 107.
21 Heginbothom ML. The relationship between the in vitro drug susceptibility of opportunist mycobacteria and their in vivo response to treatment. *Int. J. Tuberc. Lung Dis.* 2001; **5**: 539–45.
22 Clinical and Laboratory Standards Institute. *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes*, 2nd edn. Wayne, PA: The Institute; 2011. CLSI Document M24-A2.
23 Nessar R, Cambau E, Reyrat JM, Murray A, Gicquel B. *Mycobacterium abscessus*: A new antibiotic nightmare. *J. Antimicrob. Chemother.* 2012; **67**: 810–8.
24 Jeon K, Kwon OJ, Lee NY *et al*. Antibiotic treatment of *Mycobacterium abscessus* lung disease. *Am. J. Respir. Crit. Care Med.* 2009; **180**: 896–902.
25 Brown-Elliott BA, Nash KA, Wallace RJ Jr. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. *Clin. Microbiol. Rev.* 2012; **25**: 545–82.
26 Koh W-J, Jeon K, Lee NY *et al*. Clinical significance of differentiation of *Mycobacterium massiliense* from *Mycobacterium abscessus*. *Am. J. Respir. Crit. Care Med.* 2011; **183**: 405–10.
27 Potter JL, Capstick T, Ricketts WM, Whitehead N, Kon OM. A UK-based resource to support the monitoring and safe use of anti-TB drugs and second-line treatment of multidrug-resistant TB. *Thorax* 2015; **70**: 297–8.
28 Beringer P, Huynh KMT, Kriengkauykiat J *et al*. Absolute bioavailability and intracellular pharmacokinetics of azithromycin in patients with cystic fibrosis. *Antimicrob. Agents Chemother.* 2005; **49**: 5013–7.
29 Keel RA, Schaeftlein A, Kloft C *et al*. Pharmacokinetics of intravenous and oral linezolid in adults with cystic fibrosis. *Antimicrob. Agents Chemother.* 2011; **55**: 3393–8.
30 Veenstra DL, Harris J, Gibson RL, Rosenfeld M, Burke W, Watts C. Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: Potential impact on clinical, patient, and economic outcomes. *Genet. Med.* 2007; **9**: 695–704.
31 Jarand J, Levin A, Zhang L, Huitt G, Mitchell JD, Daley CL. Clinical and microbiologic outcomes in patients receiving treatment for *Mycobacterium abscessus* pulmonary disease. *Clin. Infect. Dis.* 2011; **52**: 565–71.
32 Griffith DE, Girard WM, Wallace RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria: An analysis of 154 patients. *Am. Rev. Respir. Dis.* 1993; **147**: 1271–8.
33 Lefebvre A-L, Dubée V, Cortes M, Dorchêne D, Arthur M, Mainardi JL. Bactericidal and intracellular activity of β-lactams against *Mycobacterium abscessus*. *J. Antimicrob. Chemother.* 2016; **71**: 1556–63.
34 Maurer FP, Bruderer VL, Ritter C, Castelberg C, Bloemberg GV, Böttger EC. Lack of antimicrobial bactericidal activity in *Mycobacterium abscessus*. *Antimicrob. Agents Chemother.* 2014; **58**: 3828–36.
35 Ferro BE, Srivastava S, Deshpande D *et al*. Tigecycline is highly efficacious against *Mycobacterium abscessus* pulmonary disease. *Antimicrob. Agents Chemother.* 2016; **60**: 2895–900.
36 Ferro BE, van Ingen J, Wattenberg M, van Soolingen D, Mouton JW. Time-kill kinetics of antibiotics active against rapidly growing mycobacteria. *J. Antimicrob. Chemother.* 2015; **70**: 811–7.
37 Ferro BE, Srivastava S, Deshpande D *et al*. Amikacin pharmacokinetics/pharmacodynamics in a novel hollow-fiber *Mycobacterium abscessus* disease model. *Antimicrob. Agents Chemother.* 2016; **60**: 1242–8.
38 Olivier KN, Shaw PA, Glaser TS *et al*. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. *Ann. Am. Thorac. Soc.* 2014; **11**: 30–5.
39 Yagi K, Ishii M, Namkoong H *et al*. The efficacy, safety, and feasibility of inhaled amikacin for the treatment of difficult-to-treat nontuberculous mycobacterial lung diseases. *BMC Infect. Dis.* 2017; **17**: 558.
40 Olivier KN, Griffith DE, Eagle G *et al*. Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. *Am. J. Respir. Crit. Care Med.* 2016; **195**: 814–23.
41 Choi G-E, Shin SJ, Won C-J *et al*. Macrolide treatment for *Mycobacterium abscessus* and *Mycobacterium massiliense* infection and inducible resistance. *Am. J. Respir. Crit. Care Med.* 2012; **186**: 917–25.
42 Maurer FP, Castelberg C, Quiblier C, Böttger EC, Somoskövi A. Erm (41)-dependent inducible resistance to azithromycin and clarithromycin in clinical isolates of *Mycobacterium abscessus*. *J. Antimicrob. Chemother.* 2014; **69**: 1559–63.
43 Wallace RJ, Brown-Elliott BA, Crist CJ, Mann L, Wilson RW. Comparison of the in vitro activity of the glycylcycline tigecycline (formerly GAR-936) with those of tetracycline, minocycline, and doxycycline against isolates of nontuberculous mycobacteria. *Antimicrob. Agents Chemother.* 2002; **46**: 3164–7.
44 Wallace RJ, Dukart G, Brown-Elliott BA, Griffith DE, Scerpella EG, Marshall B. Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of *Mycobacterium abscessus* and *Mycobacterium chelonae* infections. *J. Antimicrob. Chemother.* 2014; **69**: 1945–53.
45 Wallace RJ, Brown-Elliott BA, Ward SC, Crist CJ, Mann LB, Wilson RW. Activities of linezolid against rapidly growing mycobacteria. *Antimicrob. Agents Chemother.* 2001; **45**: 764–7.

46 Garazzino S, Tovo P-A. Clinical experience with linezolid in infants and children. *J. Antimicrob. Chemother.* 2011; **66** (Suppl. 4): iv23–41.
47 Ferro BE, Srivastava S, Deshpande D *et al*. Moxifloxacin's limited efficacy in the hollow-fiber model of *Mycobacterium abscessus* disease. *Antimicrob. Agents Chemother.* 2016; **60**: 3779–85.
48 Choi G-E, Min K-N, Won C-J, Jeon K, Shin SJ, Koh WJ. Activities of moxifloxacin in combination with macrolides against clinical isolates of *Mycobacterium abscessus* and *Mycobacterium massiliense*. *Antimicrob. Agents Chemother.* 2012; **56**: 3549–55.