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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Mycobacterium abscessus Complex Infections in Children: A Review

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Abstract
Purpose of Review Infections in children with *Mycobacterium abscessus* complex represent a particular challenge for clinicians. Increasing incidence of these infections worldwide has necessitated focused attention to improve both diagnostic as well as treatment modalities. Published medical literature was reviewed, with emphasis on material published in the past 5 years.
Recent Findings Increasing availability of new diagnostic tools, such as matrix-assisted laser desorption ionization-time of flight mass spectrometry and custom PCRs, has provided unique insights into the subspecies within the complex and improved diagnostic certainty. Microbiological review of all recent isolates at the University of Minnesota Medical Center was also conducted, with description of the antimicrobial sensitivity patterns encountered in our center, and compared with those published from other centers in the recent literature. A discussion of conventional antimicrobial treatment regimens, alongside detailed description of the relevant antimicrobials, is derived from recent publications.
Summary Antimicrobial therapy, combined with surgical intervention in some cases, remains the mainstay of pediatric care. Ongoing questions remain regarding the transmission mechanics, immunologic vulnerabilities exploited by these organisms in the host, and the optimal antimicrobial regimens necessary to enable a reliable cure. Updated treatment guidelines based on focused clinical studies in children and accounting especially for the immunocompromised children at greatest risk are very much needed.

Keywords *Mycobacterium abscessus* complex · Pediatric · Atypical mycobacterium · Nontuberculous mycobacterium · Cystic fibrosis

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Introduction

Since their first descriptions as agents of human disease, the nontuberculous (also called "atypical") mycobacteria have posted unique challenges to clinicians. Despite considerable advances in the past several decades towards achieving a more complete understanding of their microbiological ecology, role in human disease, and susceptibilities to novel antimicrobial agents, contemporary medical practice still faces considerable difficulty in dealing with infections caused by these organisms. In particular, the *Mycobacterium abscessus* group, now found to be a closely related genetic assemblage of at least three distinct subspecies, has emerged as particularly problematic for clinicians.

Pediatric diseases attributable to atypical mycobacterial infections remain thankfully uncommon; however, the past decade has demonstrated an increasing role for the *M. abscessus* group as a causative agent of illness in children, especially in those with particular immunologic vulnerabilities. It remains a serious and increasingly significant threat to children with

cystic fibrosis, transplants of all kinds, and in rare circumstances, healthy children with specific environmental risk factors.

This review will discuss the contemporary issues facing pediatricians relating to infections in children with *M. abscessus* complex, with particular emphasis on the antimicrobial susceptibilities and regimens currently available for treatment of this difficult infection.

Mycobacterium abscessus Complex

M. abscessus is a rapidly growing, nonpigmented, nontuberculous cosmopolitan saprophytic mycobacterium typically encountered in environmental water sources that was first described by Moore and Frerichs in 1953 and implicated as a cause of human disease shortly thereafter. It has historically been grouped alongside similar nontuberculous mycobacteria capable of intracellular survival in the human host, *Mycobacterium chelonae* and *Mycobacterium fortuitum*, commonly grouped as a triad of closely related species producing a spectrum of human diseases, chiefly pulmonary in manifestation. Among the three, *M. abscessus* is widely considered both the most virulent and the most resistant to antimicrobial therapy [1].

Analysis of the genomes of *M. abscessus* and several similar nontuberculous mycobacteria of recent description has led to the taxonomic reassignment of *Mycobacterium bolletii* and *Mycobacterium massiliense* into a species complex, hereafter referred to collectively as *M. abscessus* complex [2, 3]. Laboratory differentiation of the individual subspecies within the complex has become relevant recently, owing to differences in the typical antimicrobial susceptibility profile and clinical outcomes from treatment of each [4–7].

M. abscessus subsp. *abscessus* is the most commonly encountered of the three subspecies. It possesses an inducible macrolide resistance gene, *erm*, which conveys inducible resistance to azithromycin and clarithromycin, characterized by minimum inhibitory concentrations (MICs) that drift upwards during treatment [8–10]. Moreover, a single copy of an aminoglycoside resistance gene renders the organism more susceptible to mutational-induced amikacin or streptomycin resistance [10]. Two colony morphologies are seen in human isolates grown on agar: smooth and rough [11]. Conversion between these forms may portend more severe or fatal pulmonary infections owing to biofilm production, although it has no bearing on antimicrobial susceptibility. Cohabitation with other water-borne microorganisms (such as *Pseudomonas aeruginosa*) is theorized to contribute to the acquisition of virulence genes, resistance elements, and cross-species transfer of factors promoting persistence in the human host [12].

M. abscessus subsp. bolletii, the least commonly encountered, possesses similar resistance to macrolides, with clarithromycin resistance having been described. Interestingly, a plasmid-mediated kanamycin resistance phenotype was described in a large outbreak in Brazil. This is the first instance of plasmid-mediated resistance described in mycobacteria [13].

M. abscessus subsp. massiliense was described in France in 2004, but is widely distributed worldwide. Most notably, this subspecies often lacks a functional *erm* gene, possibly accounting for the more favorable clinical outcomes from treatment compared to the other two members of the species complex [14–16]. Some authors have shown sustained culture conversion in infection with this subspecies despite absence of parenteral therapy, although this has yet to be demonstrated in children. Outbreaks with this organism have been described in transplant centers serving cystic fibrosis patients. Of note, transmission was thought to be attributable to high organism loads in sputum rather than an environmental source.

Epidemiology

Both the incidence and severity of pediatric infection due to *M. abscessus* complex may be increasing over time [17, 18]. This may be due to a combination of enhanced detection methods, enabling greater species specificity among mycobacteria, in combination with an increased prevalence of predisposing conditions in children, such as HIV, malignancy, and cystic fibrosis. Longer lifespans in ill children may further result in more cumulative exposure, increased selective pressure from antimicrobials used during the lifespan, and increased clinical opportunity for detection. Declining worldwide use of the Bacille Calmette-Guérin vaccine has been posited as a partial explanation, via reduced cross-protection [19].

Pediatric presentations of *M. abscessus* complex infections can vary, although the most commonly encountered are skin and soft tissue infections following surgery or trauma, lymphadenitis, pulmonary infection (often in the context of cystic fibrosis or other underlying structural lung diseases), and disseminated infections in immunocompromised children with cancer, organ, and tissue transplants, or exposure to immune-modulating biologic agents [20–22]. Chronic postsurgical wounds in children have been attributed to *M. abscessus* complex [23]. Adenitis, especially isolated lymphadenitis, most commonly presents in the head or neck region, although cases have sporadically been described elsewhere [24]. The distribution of sites of infection may differ based on the putative source, such as in outbreaks, or among hospitalized cohorts [25••].

Lung disease is generally accompanied by indolent progression of reticulonodular opacification, patchy infiltration, interstitial and alveolar involvement, and upper lobe predominance with rare cavitation. Children with idiopathic bronchiectasis or occult reflux disease may not have these imaging

findings. Radiographic presentation is occasionally similar to those of children infected with tuberculosis. Cross-reaction with tuberculin skin testing is described in children with pulmonary involvement by *M. abscessus* complex, with rates of positives varying considerably across studies.

Chronic otitis media has been attributed to nontuberculous mycobacteria in children, especially in association with tympanostomy tubes. No CNS cases of infection have been thus far described in children [26]. Nosocomial infections in children are generally line-associated, although a source cannot always be identified, such as in an outbreak in a Kuwaiti PICU in 2011. An outbreak of rapidly growing mycobacteria (which included one patient with *M. abscessus* complex) in pediatric hematopoietic stem cell transplant patients was linked to high levels of mycobacteria in hospital drinking water and ice machines [25••]. Interestingly, this one patient with *M. abscessus* complex in the sputum had only colonization and no invasive lung disease.

Guideline statements by the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) in 2007 cast doubt on human-to-human transmission of *M. abscessus* complex, although recent work supports at least some scenarios where transmission is possible [27•,28–30]. Organism survival in respirable aerosols has been demonstrated [31]. Analysis of strains across the world reveals significant genomic similarities, suggesting global spread of a few clones among susceptible children or possibly a specific common avenue of exposure [32].

The environmental niche of the *M. abscessus* complex is water sources. Among others, these nontuberculous mycobacteria have been detected in tap water (despite chlorination), household showers, bathwater, and not infrequently in water piping if the temperature of the system does not exceed 45 °C [33, 34].

As a consequence, outbreaks of *M. abscessus* complex infections as well as with other atypical mycobacteria in the community and in healthcare facilities have been traced to contamination originating from water delivery devices producing aerosols, such as showerheads, drinking water or ice from ice machines, or from delivery of substances exposed to or admixed with contaminated water. Current ATS/IDSA guidelines suggest avoiding tap water, or similar fluids, in contact with surgical wounds, IVs, central lines, tunneled catheters, or endoscopic equipment due to risk of infection with these organisms [27•].

An outbreak of *Mycobacterium mucogenicum* (another rapidly growing mycobacterium closely related to *M. chelonae*) bacteremia in an adult and pediatric hematopoietic stem cell transplant unit was ultimately traced to colonized showerheads and connected shower hoses [34]. Typing by multilocus enzyme electrophoresis and randomly amplified polymorphic DNA revealed a genetic match between a blood *M. mucogenicum* isolate from one case patient and the shower water sample from the bone marrow transplant (BMT) unit room the patient had stayed in at the time of his positive blood culture. This outbreak led to several infection control measures that remediated the problem. These measure included replacing showerheads and hoses on the BMT inpatient units and protecting intravenous (IV) central catheters from water by disconnecting catheters when feasible while bathing and covering IV catheter connections with moisture-proof material during water exposures [34].

Persistent mycobacterial colonization and environmental amplification of their growth have been noted in hospital drinking water and ice machines (affecting both the water and ice when separately evaluated). This led to an outbreak of rapidly growing mycobacterial colonization and infection on a pediatric BMT unit, including one patient with *M. chelonae/abscessus* complex colonization of the sputum [25••]. The cause of this outbreak was determined to be high heterotrophic plate counts (bacterial colony forming units/ml water), including rapidly growing mycobacteria, in the water and ice from the drinking water and ice machines on the pediatric BMT unit. Ultimately, the high heterotrophic plate counts in drinking water and ice were reduced by several different interventions, including 0.005-μm filters for the water entering the drinking water and ice machines, silver-impregnated components in the machines and copper tubing for pipes leading to the drinking water and ice machines, and the addition of UV disinfection devices to the machines [25••, 35].

An outbreak of *M. abscessus* subsp. *massiliense* occurred in a lung transplant and cystic fibrosis center, in Seattle [36]. Despite obtaining multiple environmental cultures, no environmental source of *M. abscessus* was found in that outbreak. The authors hypothesized that high *M. abscessus* load in the sputum of the index case, who was 4+ sputum AFB positive, may have contaminated the clinic environment and allowed person-to-person spread. The authors emphasized the importance of rigorous, diligent, repeated surface cleaning and consideration of airborne isolation, when caring for patients with this infection. In this outbreak, the isolates from the index case and subsequent outbreak cases were genetically identical on pulse field gel electrophoresis [36].

These outbreaks underscore the importance of considering environmental factors as relevant contributors to a child's risk for infection with *M. abscessus* complex. It is not clear, however, to what degree (if any) stringent reduction in environmental exposures from water would have on carriage, colonization, or transmission among children who are not severely immunocompromised.

In the USA, the area of highest endemicity is the southeast, stretching from roughly Florida to Texas, although cases are described throughout the broader USA as well as the rest of the world, with endemicity in eastern Asia [37, 38]. To what degree globalization, multicultural societies, and increased travel (especially for medical tourism) are affecting the

epidemiology of *M. abscessus* complex infections in children is as yet incompletely understood [39].

Special Pediatric Populations at Risk

Several groups of children are at increased relative risk of acquiring colonization or overt infection with *M. abscessus* complex. Immunodeficiency of all types involving children represents a theoretical risk; however, specific risks have been described in children with novel interferon gamma defects, as well as several inborn errors of immunity [40]. Risk may similarly be conveyed via tracheostomy and ensuing ongoing tracheal epithelial damage, aspiration, and the consequences of airway management such as suctioning, irrigation, and exposure to contaminated water.

M. abscessus complex is the second most commonly identified nontuberculous mycobacteria isolated in all persons with cystic fibrosis worldwide (after *Mycobacterium avium* complex, "MAC"). Although *M. abscessus* complex is more commonly isolated in children, it is most often associated with extant clinical disease and is more likely to be found in a child meeting the ATS criteria for diagnosis [41–43]. Despite this, most children with cystic fibrosis do not progress to active disease attributable to these organisms despite having the organism detectable in culture [44]. In those children with cystic fibrosis with demonstrable lung infection, treatment does confer measurable benefits in quality of life [45].

Studies of colonization persistence suggest that single strains may be implicated in many cases [46]. It is possible that *M. abscessus* complex and MAC may be targeting separate populations under the broader cystic fibrosis umbrella; children with more severe illness may be susceptible to over-attribution if their decline is coincident with having *M. abscessus* grown in their sputa. Differentiation of the subspecies within the complex has potential prognostic implications in the cystic fibrosis population as well [47].

Regardless, children with cystic fibrosis represent a special population at considerable risk from infection with this difficult microorganism [48, 49••]. No consensus has emerged regarding transmissibility between colonized patients and those susceptible to infection [30, 50]. Yearly screening for nontuberculous mycobacteria is advised, as is screening prior to the institution of any immunomodulating macrolide therapy. Significant clinical decline, or nonresponse to usual antimicrobial therapy, may further stimulate screening for *M. abscessus* complex. Despite the risk of comparatively poorer outcomes in children with cystic fibrosis, no specific or separate guidelines govern treatment of *M. abscessus* complex in cystic fibrosis populations [49••, 51]. A Cochrane database review published in December 2016 concluded that it was reasonable to follow currently published guidelines for the diagnosis and treatment of *M. abscessus* in patients with cystic fibrosis [50]. The Cystic Fibrosis Foundation and the European Cystic Fibrosis Society 2015 guidelines recommend that nontuberculous mycobacterium treatment should be considered for individuals with cystic fibrosis who have ATS-/IDSA-defined nontuberculous mycobacterial pulmonary disease and that treatment of *M. abscessus* complex pulmonary disease should involve an intensive phase followed by a continuation phase [49••].

Debate continues as to whether colonization or active infection with *M. abscessus* complex represents a relative or absolute contraindication to lung transplantation in children [52–54]. A Danish study of five patients undergoing transplant found no excess attributable deaths, although outcomes may depend on which subspecies is present [52]. Post-transplantation bronchiolitis obliterans may be more commonly seen in patients colonized with *M. abscessus* complex; however, survival has been similar to noncolonized patients [54].

Diagnosis

Establishing a definitive diagnosis of *M. abscessus* complex infection in children depends foremost on consideration of nontuberculous mycobacteria in the differential diagnosis, excluding competing clinical entities, and obtaining sufficient specimens for a reliable and specific microbiological identification. Historically, each of these steps was fraught with difficulty. In the past 10 years, however, significant advances in diagnostic capabilities of microbiology laboratories of even marginal sophistication enable increased diagnostic confidence by way of leveraging new technologies based increasingly on molecular identification or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS).

Traditional identification of mycobacteria depended on the use of selective, differential growth media combined with phenotypic chemical testing. Identification in this way quintessentially depends on obtaining a viable organism that will grow under favorable laboratory conditions prior to being subject to multiple differential assays of varying reliability. Current ATS guidelines support a diagnosis in a favorable clinical context after obtaining two positive disparately sourced samples or single positive specimens from bronchial lavage or transbronchial biopsies in children. In the near term, it is unlikely that any laboratory technology will quickly displace viable organisms grown in culture as a standard means for diagnosing *M. abscessus* infections in children. Many pediatric referral centers and nearly all community facilities continue to rely on mycobacterial culture and phenotypic methods for speciation, frequently performed at national reference laboratories.

In lieu of these, methods of analysis that depend solely on organism growth without additional chemical workup, such as MALDI-TOF MS, permit highly accurate speciation of

Table 1 Current and emerging antimicrobial treatment options for children with *Mycobacterium abscessus* complex infections

Medication	Pediatric dose range	Administration	Major adverse effects in children	Comments	Reference(s)
Clarithromycin	7.5 mg/kg/dose, given twice daily, not to exceed 500-mg PO BID	PO	Vomiting, diarrhea, abdominal pain	Possible QT prolongation in combination with azole antifungals, antiarrhythmics, fluoroquinolones, clotrimazole, and anesthetic agents	
Azithromycin	5 mg/kg in a single dose, not to exceed 250 mg daily	IV, PO	GI disturbance, headache, QT prolongation	Putatively less *erm* induction compared to clarithromycin; may be antagonistic when combined with moxifloxacin; possibly i ncreased clearance compared with clarithromycin	[8, 16, 75]
Cefoxitin	80–160 mg/kg/day divided every 4–8 h, not to exceed 12 g/day	IV, IM	Diarrhea	Increased dosing intervals required with renal insufficiency	
Doxycycline	4.4 mg/kg/day, divided in two doses, for children over age 8 or ≤ 45 kg; 100-mg BID in older children	PO	Tooth discoloration, photosensitivity, esophagitis, transaminitis, acute kidney injury	Concentration in serum is decreased by coadministration with phenytoin	
Amikacin	15–30 mg/kg/day in a single dose; can be administered thrice weekly	IM	Vestibulo-cochlear toxicity, nephrotoxicity, fever, rash	Considered the most active parenteral agent; dosage adjustment in renal insufficiency; periodic audiometry, including baseline evaluation, should be conducted; monitoring of peak/trough levels is advised	[76, 77]
Ciprofloxacin	10–20 mg/kg/day PO, divided every 12 h, not to exceed 1.5 g daily; 20–30 mg/kg/day IV, divided every 12 h, not to exceed 800 mg daily	IV, PO	Nausea/vomiting, headache, tremor, QT prolongation	Avoid coadministration with multivitamins, antacids, or compounds containing divalent metal cations	
Moxifloxacin	10 mg/kg/day in a single dose, not to exceed 400 mg daily	IV, PO	Nausea/vomiting, headache, tremor, QT prolongation	Avoid coadministration with multivitamins, antacids, or compounds containing divalent metal cations; relative degree of QT prolongation is more pronounced with moxifloxacin compared to other fluoroquinolones	[78]
Trimethoprim/ sulfamethoxazole	15–20 mg/kg/day divided every 6–8 h	IV, PO	Myelosuppression, acute kidney injury, rash/ Stevens-Johnson syndrome, aseptic meningitis, pancreatitis, diarrhea	Possible QT prolongation with azole antifungals, macrolides, or anesthetics; requires periodic laboratory monitoring of CBC and electrolytes	
Minocycline	2 mg/kg Q12h	IV, PO	Tooth discoloration, photosensitive rash, diarrhea, esophagitis, transaminitis, acute kidney injury, vestibular toxicity	Oral forms should be given with plenty of liquid to avoid esophagitis and/or esophageal ulceration	
Streptomycin	20 mg/kg/day given twice weekly	IM	Vestibulo-cochlear toxicity, nephrotoxicity, fever, rash	Dosage adjustment in renal insufficiency; periodic audiometry, including baseline evaluation, should be conducted; monitoring of peak/trough levels is advised	
Linezolid	10 mg/kg/day in children 0–11 years; 600 mg Q12h for children ≥ 12 years	IV, PO	Anemia, CNS disturbance, peripheral neuropathy, nausea/vomiting, myelosuppression, optic neuropathy, pseudomembranous colitis	Smaller doses may have antimycobacterial effects while sparing severe side effects; requires weekly monitoring of CBC	

Table 1 (continued)

Medication	Pediatric dose range	Administration	Major adverse effects in children	Comments	Reference(s)
Imipenem	0.5–1.0-g Q6h	IV	Fever, rash, nausea/vomiting, diarrhea, seizure	Laboratory determination of MIC for imipenem can be unreliable [citation]; can be substituted for cefoxitin	[66, 79]
Clofazimine	1 mg/kg/day, not to exceed 100 mg/day	PO	Skin and conjunctival discoloration, itchy/dry skin, headache, dizziness, abdominal pain, vomiting, diarrhea, peripheral, neuropathy, transaminitis	Taken with food to increase absorption; requires periodic monitoring of liver enzymes	[80]
Tigecycline	1.8–6.4 mg/kg IV loading dose, followed by 2–6.4 mg/kg/day maintenance dose, divided every 12 h, in children 8–12 years; not to exceed 50 mg every 12 h in either loading or maintenance doses	IV	Headache, diarrhea, tooth discoloration, pancreatitis, photosensitivity, myelosuppression, anorexia	In adults, treatment with tigecycline has been associated with excess mortality in Gram-negative sepsis; due to reported variations in dosing in children, consultation with a pharmacist is recommended	[80–83]

Telithromycin (Ketek, a ketolide antimicrobial) has demonstrated in vitro activity against *M. abscessus*, but has not been clinically evaluated in children for treatment of nontuberculous mycobacteria

nontuberculous mycobacteria with significant advantages in cost, reproducibility, and turnaround time for pediatricians [55]. MALDI-TOF MS has further proved useful in cluster investigations. There remains ongoing debate as to the feasibility of using MALDI-TOF MS in differentiating the subspecies within the species complex [56, 57].

In circumstances in which laboratory growth of the mycobacteria cannot be achieved, identification yet remains possible through numerous molecular methods. While 16S ribosomal rRNA sequencing has proven its value elsewhere in microbiology, it remains of only marginal utility for identifying nontuberculous mycobacteria. Sequence analysis of PRA-hsp65, rpoB, and erm41 genes enables reliable identification of each subspecies in an assay that is considerably cheaper than whole-genome sequencing. A number of rapid PCR tests have been evaluated, although their availability remains restricted to research applications or to investigational use in large pediatric regional referral centers [58–60].

Molecular methods have found broader application in evaluation of the epidemiology of nontuberculous mycobacteria in children. Several studies have looked at multilocus sequencing typing (MLST) as well as variable-number tandem repeats (VNTR) [61]. A study in 2014 using VNTR combined with repetitive element sequence-based PCR in 17 pediatric patients suggested persistent infection with a single strain, with possible transfer of this strain between patients [4]. Whole-genome sequencing of these isolates of *M. abscessus* complex may establish patterns of transmission or single out particular clones worthy of clinical intervention.

Treatment

M. abscessus complex has historically been considered one of the most highly resistant of all microorganisms to antimicrobial chemotherapy, owing to its unfortunate combination of molecular resistance elements as well as the inherent difficulties that mycobacteria pose for in vivo action of chemotherapeutics by virtue of their physical composition. In general, the *M. abscessus* complex is inherently resistant by current CLSI guidelines to all current first-line antituberculous drugs, although recently, rifabutin has been demonstrated to have potential efficacy [62].

Above all, the decision of whether to treat or not must be predicated on the risks and benefits of treatment in each specific child. Cumulative, often severe, toxicities of the few antimicrobials available for treating *M. abscessus* complex infections necessitate great caution before embarking the child on what may be a prolonged course of therapy.

Current guidelines, as well as several Cochrane reviews, state that no established drug regimen in children has been demonstrated to be universally efficacious in achieving cure, although some antimicrobials have been more fastidiously

Table 2 General range of reported antimicrobial resistance patterns of *Mycobacterium abscessus* complex isolates worldwide, per literature review (rounded to the nearest whole percent)

Medication	*Mycobacterium abscessus* subsp. *abscessus* (% reported resistance)	*Mycobacterium abscessus* subsp. *massiliense* (% reported resistance)	*Mycobacterium abscessus* subsp. *bolletii* (% reported resistance)	Reference(s)
Clarithromycin	31–80 (inducible); 1–14 (constitutive)	7 (inducible); 0–10 (constitutive)	66.7 (inducible); 33 (constitutive)	[7, 16, 76, 84–86]
Azithromycin	23–38		5	[76, 84, 87]
Cefoxitin	3.6–32	8.7	4	[7, 16, 76, 84]
Doxycycline	100	90		[7]
Amikacin	1–14	2–10	100	[7, 16, 76, 80, 84, 87]
Tobramycin	36			[84]
Moxifloxacin	83–96	75–89	100	[7, 16, 76, 88]
Levofloxacin	77		100	[76, 84]
Ciprofloxacin	58–100	98	100	[7, 16, 76, 87, 88]
Linezolid	4–9	2–6	4	[7, 16, 76, 84, 85]
Imipenem	10–44	17–66.7	16	[7, 16, 66, 76, 88]
Clofazimine	N/A	N/A	N/A	[80]
Tigecycline	1			[80, 82, 87]
TMP/SMX	46			[84]

TMP/SMX trimethoprim/sulfamethoxazole

studied than others [51]. A summary of the agents in current clinical pediatric usage with the most accumulated clinical experience is presented in Table 1. Evidence of association for any particular disease manifestation and a specific treatment affecting a durable resolution is scant [63]. One exception is for localized adenitis; cervicofacial nontuberculous mycobacterial disease is often satisfactorily resolved following surgical resection as a first intervention prior to prolonged antimicrobial therapy [64].

Due to the difficulty in assuring the activity of any antimicrobial agent in acceptable concentrations in vivo, in vitro testing of all clinically relevant isolates should be performed, along with determination of inducible clarithromycin resistance and amikacin resistance where possible via broth microdilution [65, 66]. Periodic retesting may be necessary in prolonged treatment courses due to changing resistance under antimicrobial pressure. Some laboratories make use of synergy testing, such as for clofazimine and amikacin, to evaluate the effect on MICs of combination therapy [67]. These synergistic effects may be variable when accounting for the particular subspecies within the complex [68].

For pulmonary disease in children, localized infections may best achieve cure via combination of surgical resection alongside appropriately targeted antimicrobials. This appears to be similarly true in localized skin, bone, and lymphatic infections. More widespread infections including disseminated lung disease in children may benefit from surgical debulking of localized lung diseases, such as lobectomy or segmentectomy, in combination with prolonged intravenous and oral antimicrobial therapy [69].

Treatment courses range from 4 months for localized disease, 6 months for bone infections, and a minimum of 12 months for lung infections. Regardless of site of infection, most sources advocate an approach that includes parenteral therapy at initiation, generally 2 months. The 2016 cystic fibrosis (CF) consensus recommendations for management of nontuberculous mycobacteria in CF patients recommend two active IV antibiotic agents, usually IV amikacin plus imipenem or cefoxitin, with or without tigecycline, alongside oral azithromycin or clarithromycin for 2–3 months, for the initial intensive therapy, for *M. abscessus* [49••]. This is followed by continuation of the oral macrolide (in susceptible isolates) alongside one or two other active oral agents such as linezolid, clofazimine, moxifloxacin, or ciprofloxacin [49••]. This continuation phase with a combination of oral antibiotics usually lasts at least 12 months. As clinical eradication in lung disease may be impossible, a number of surrogate markers may serve as reasonable indicators for reduction in therapy, such as symptomatic or radiographic improvement [63]. Ongoing antimicrobial suppressive therapy has not been extensively evaluated in children; however, owing to the impracticality of cure in many cases, this may be occasionally reasonable.

Treatment plans are to be carefully crafted by pediatricians, factoring in the child's particular clinical presentation, suitability for the treatments being considered, relative risks of each treatment in kind (surgical or chemotherapeutic), and overall goal of care. Changes in therapy commonly occur; in one survey, amikacin was stopped or adjusted in 51% of cases [70]. Cure is not assured, regardless of which approach is

Table 3 Characterization of antimicrobial susceptibility of clinical isolates of *Mycobacterium abscessus* complex from the University of Minnesota, Fairview, from July 1, 2014, to June 30, 2017

	Year				Total
	2014	2015	2016	2017*	
Number of isolates (year total)	20	32	54	27	133
Pediatric isolates (age ≤ 18)	3	4	7	4	18 (13.5%)
Amikacin	*S* = 9 *I* = 4 *R* = 0	*S* = 6 *I* = 11 *R* = 1	*S* = 18 *I* = 6 *R* = 4	*S* = 17 *I* = 3 *R* = 0	*S* = 50 (63.3%) *I* = 24 (30.3%) *R* = 5 (6.3%)
Cefoxitin	*S* = 0 *I* = 13 *R* = 0	*S* = 1 *I* = 16 *R* = 1	*S* = 2 *I* = 21 *R* = 5	*S* = 2 *I* = 15 *R* = 3	*S* = 5 (6.3%) *I* = 65 (82.3%) *R* = 9 (11.4%)
Clarithromycin	*S* = 1 *I* = 0 *R* = 12	*S* = 2 *I* = 0 *R* = 16	*S* = 10 *I* = 0 *R* = 17	*S* = 8 *I* = 0 *R* = 12	*S* = 21 (26.9%) *I* = 0 (0%) *R* = 57 (73.1%)
Clofazimine	Single isolate tested; MIC ≤ 0.5	No isolates tested	Two isolates tested; MIC ≤ 0.5 for both	Two isolates tested; MIC ≤ 0.5 for both	N/A
Ciprofloxacin	*S* = 0 *I* = 0 *R* = 13	*S* = 1 *I* = 0 *R* = 17	*S* = 0 *I* = 1 *R* = 27	*S* = 0 *I* = 1 *R* = 19	*S* = 1 (1.3%) *I* = 0 (0%) *R* = 76 (98.7%)
Doxycycline	*S* = 0 *I* = 0 *R* = 13	*S* = 1 *I* = 0 *R* = 17	*S* = 1 *I* = 1 *R* = 26	*S* = 0 *I* = 1 *R* = 19	*S* = 2 (2.5%) *I* = 2 (2.5%) *R* = 75 (95%)
Imipenem	*S* = 0 *I* = 9 *R* = 4	*S* = 0 *I* = 12 *R* = 6	*S* = 2 *I* = 20 *R* = 5	*S* = 0 *I* = 17 *R* = 3	*S* = 2 (2.6%) *I* = 58 (74.4%) *R* = 18 (23.0%)
Linezolid	*S* = 0 *I* = 7 *R* = 6	*S* = 2 *I* = 8 *R* = 8	*S* = 8 *I* = 11 *R* = 8	*S* = 11 *I* = 7 *R* = 2	*S* = 21 (26.9%) *I* = 33 (42.3%) *R* = 24 (30.8%)
Moxifloxacin	*S* = 0 *I* = 0 *R* = 13	*S* = 0 *I* = 1 *R* = 17	*S* = 0 *I* = 1 *R* = 27	*S* = 0 *I* = 0 *R* = 20	*S* = 0 (0%) *I* = 2 (2.5%) *R* = 77 (97.5%)
Minocycline	*S* = 0 *I* = 0 *R* = 13	*S* = 1 *I* = 0 *R* = 17	*S* = 1 *I* = 3 *R* = 23	*S* = 0 *I* = 2 *R* = 18	*S* = 2 (2.6%) *I* = 5 (6.4%) *R* = 71 (91%)
TMP/SMX	*S* = 0 *I* = 0 *R* = 13	*S* = 0 *I* = 0 *R* = 18	*S* = 0 *I* = 0 *R* = 28	*S* = 0 *I* = 0 *R* = 20	*S* = 0 (0%) *I* = 0 (0%) *R* = 79 (100%)
Tigecycline	Single isolate tested; MIC ≤ 0.5	Single isolate tested; MIC ≤ 0.5	Four isolates tested; MICs ≤ 0.03, 0.12, 0.25, 1.0, respectively	Two isolates tested; MIC ≤ 0.03 and ≤ 0.5, respectively	N/A
Other			azithromycin MIC = 32 kanamycin MIC ≤ 8.0 tobramycin MIC 1.0 [amikacin + clofazimine] MIC 0.5/2.0		N /A

TMP/SMX trimetheprim/sulfamethoxazole, *S* sensitive, *I* intermediate, *R* resistant, per current CLSI guidelines

* Signifies that data extends only through August, 2017 and therefore does not represent an entire 12 month calendar year for data purposes as in preceding years of the table

pursued. Recent reviews suggest that chosen therapeutic regimens vary widely across practitioners and that adherence to ATS guidelines is generally poor. Robust evidence-based guidelines aimed at pediatricians may translate to improvements in the proportion of children cured over time.

With the use of aggressive antibiotic combination therapies for prolonged periods of time, it becomes important for the clinician to monitor antibiotic toxicity closely. Toxicity monitoring should include blood tests to monitor medication effects on blood counts, liver function tests, assessment of renal

function (including glomerular filtration rate), and electrocardiographic monitoring to identify QT prolongation. With IV amikacin, use of audiometric testing and amikacin serum drug levels should be monitored regularly, with immediate cessation of the drug in the presence of any evidence of ototoxicity. Sputum cultures should be monitored for eradication or suppression of acid-fast bacterial growth, and imaging studies, such as chest radiographs or intermittent chest CT scan, should be done to help gauge the response of the patient to treatment [48].

This variability of chosen drug regimens may be reflective of the relative heterogeneity in described antimicrobial susceptibilities among the members of the subspecies in the available medical literature, as well as attributable to differences in clinical outcomes when accounting for the infecting subspecies. Table 2 represents an aggregative summary of recently published antimicrobial susceptibility data for each *M. abscessus* subspecies. To date, no studies have focused exclusively on isolates obtained from children.

At our own center, a review of the past 3 years of *M. abscessus* complex clinical isolates sent for susceptibility testing revealed significant drug resistance with trends commensurate with those published elsewhere (Table 3). Fluoroquinolone resistance was near total, and clarithromycin resistance approached 75%. Of note, although only a small percentage of the total isolates were obtained from children, isolates obtained from children had a slight advantage over adult isolates in regards to likelihood of susceptibility to amikacin and linezolid (data not shown). In this time period, isolates of *M. abscessus* were from noninvasive sites in children, and the paucity of these children in a major pediatric referral center highlighted a possible regional difference in the epidemiology of invasive disease with this organism.

Areas of Future Research

Despite the worldwide threat posed to children by this species complex, current medical research has failed to provide actionable guidance to clinicians for some of the most pressing diagnostic or treatment questions.

The lack of an overarching disease registry hampers efforts to assemble large datasets that are sorely needed as a consequence of the difficulties posed by conducting clinical trials in pediatric populations, more so in the era of declining research resources or changing research priorities. Despite the importance placed on these organisms by clinicians for children with cystic fibrosis, comparatively little is known about the various clinicopathologic roles that the organism plays at large over the lifetime of many hosts. The lack of any animal model necessitates, therefore, that the near-term advances in understanding will likely derive from well-defined, large, robust cohorts of infected, colonized, and treated children monitored in various clinical contexts over time. Future studies may emphasize the importance of identifying which if any environmental, nosocomial, or human reservoirs are amenable to efforts to disrupt chains of transmission of the organism to vulnerable child hosts.

Few new antimicrobials suitable for pediatric use against nontuberculous mycobacteria are in the developmental pipeline; active research into novel agents or new uses of existing agents (such as avibactam) of a nontoxic and more easily administered nature, perhaps in combination with agents of known efficacy, would be of tremendous benefit in the face of evolving epidemiology for children at risk [71–73]. The lack of novel therapies is especially alarming in the context of contemporary evidence of mounting antimicrobial resistance by mycobacteria despite the advent of increasingly focused stewardship efforts worldwide [74].

Lastly, the latter-day explosion of affordable, high-fidelity molecular sequencing technologies enables increasingly more focused exploration into the molecular determinants of virulence, epidemiology of acquisition, colonization persistence, and antimicrobial resistance. Insights into the interplay between specific molecular determinants of disease and host immunology may yield fertile ground for developing targeted therapy. Such genome-level scrutiny of the *M. abscessus* species complex isolates made available through large databases or international collaborations may yield additional new species with definable clinical niches, as well as provide focus on specific populations of vulnerable children that may benefit from targeted molecular therapies to further improve disease outcomes.

Conclusion

Infections with *M. abscessus* will remain a significant challenge for pediatric practitioners in light of the numerous inherent difficulties imposed by diagnosing, treating, and studying these infections. Establishment of robust evidence-based consensus clinical guidelines for managing pediatric infections remains a high priority. A combination of emerging diagnostic technologies and an enhanced antimicrobial armamentarium will provide the critical tools necessary for clinicians to change the tide against this formidable and often incurable infectious disease.

Compliance with Ethical Standards

Conflict of Interest Drs. Sabin, Ferrieri, and Kline declare no conflicts of interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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- • Of importance
- •• Of major importance

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