Clinical characteristics and an evaluation of predictors for a favourable outcome of Mycobacterium abscessus otomastoiditis

Manders, Jordi; Leow, Theresa; van Aerde, Koen; Hol, Myrthe; Kunst, Dirk; Pegge, Sjoert; Jansen, Thijs; van Ingen, Jakko; Bekkers, Stijn

Published in:
International Journal of Infectious Diseases

DOI:
10.1016/j.ijid.2022.01.017

International Journal of Infectious Diseases 116 (2022) 397–402

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical characteristics and an evaluation of predictors for a favourable outcome of *Mycobacterium abscessus* otomastoiditis: a systematic review and meta-analysis of individual participant data ☆

Jordi Manders [1], Theresa Leow [1], Koen van Aerde [2,3], Myrthe Hol [1,4,5], Dirk Kunst [1,6], Sjoert Pegge [7], Thijs Jansen [1], Jakko van Ingen [3], Stijn Bekkers [1,*]

[1] Department of Otorhinolaryngology/Head and Neck Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[2] Department of Pediatric Infectious Disease and Immunology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, The Netherlands
[3] Radboudumc Centre for Infectious Diseases, Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, The Netherlands
[4] Department of Otorhinolaryngology/Head and Neck Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
[5] Research School of Behavioral and Cognitive Neurosciences, Graduate School of Medical Sciences, University of Groningen, Groningen, The Netherlands
[6] Department of Otorhinolaryngology/Head and Neck Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands
[7] Department of Medical Imaging, Radboud University Medical Centre, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 6 December 2021
Revised 5 January 2022
Accepted 7 January 2022

Keywords:
Humans
Mycobacterium abscessus
Non–tuberculous mycobacteria
Otomastoiditis
Otitis media

ABSTRACT

Background: Otomastoiditis caused by *Mycobacterium abscessus* is rare, but its incidence has increased over the past decades and its optimal treatment remains unknown. This study aims to summarise the clinical and therapeutic features and find characteristics of patients with *M. abscessus* otomastoiditis associated with favourable treatment outcomes.

Methods: We searched MEDLINE, Embase and Web of Science to identify studies including patients with *M. abscessus* otomastoiditis. A 1-stage individual patient data (IPD) meta-analysis was conducted. A 2-level mixed-effects linear regression model was provided for antimycobacterial treatment duration.

Results: Twenty-three studies reported a total of 85 patients. Children possess a unique clinical profile including a history of ear infections, tympanostomy tube placement and antibiotic treatment. Antimycobacterial treatment was administered for 26 (interquartile range [IQR]: 15-35) weeks. Macrolides were prescribed in 98.8% of the cases. Surgery was performed in 80.5% of the cases, of which, 47.1% required revision surgery. Otalgia was a significant predictor (β = 9.3; P = .049) of antimycobacterial treatment duration.

Conclusions: Mastoid surgery (regularly requiring revision) and a multidrug regimen for a minimum of 6 months, including a minimum of 3 active agents, are most often needed to attain cure. The presence of otalgia significantly extends the treatment duration of *M. abscessus* otomastoiditis.

Background

Mycobacterium abscessus is a rare, but virulent and multidrug-resistant non–tuberculous mycobacterium (NTM). Although it most commonly causes infections in the respiratory tract, extrapulmonary infections such as skin and soft tissue infections also occur (Johansen et al., 2020). Otomastoiditis, although rare, has been described well and an increase in its incidence has been observed over the past decades (Van Ingen et al., 2010). *M. abscessus* is unique even among the NTM because of its intrinsic resistance to most classes of antibiotics (Johansen et al., 2020). This renders treatment of *M. abscessus* otomastoiditis challenging.

Although previously published research suggest to combine surgery, even repeated, and systemic antibiotics for a minimum of 6 months (Van Ingen., 2010, Lundman et al., 2015, Yeh et al., 2015), more recent research suggest adding local treatment to this multimodal approach (Sedillot-Daniel et al., 2020, Van Wijk et al., 2020). These intensive multimodal treatment regimens commonly

☆ International Prospective Register of Systematic Reviews registration ID: CRD42020222459.

* CORRESPONDING AUTHOR. Stijn Bekkers, Department of Otolaryngology-Head and Neck surgery, Radboudumc, Philips van Leijdenlaan 15 (route 377), 6500 HB Nijmegen, The Netherlands.

E-mail addresses: Jordi.Manders@radboudumc.nl (J. Manders), stijn.bekkers@radboudumc.nl (S. Bekkers).

https://doi.org/10.1016/j.ijid.2022.01.017

result in several complaints and adverse effects, frequently resulting in cessation of therapy. There are currently no specific guidelines for the management of otomastoiditis caused by *M. abscessus* and therefore current treatment regimens are mostly extrapolated from pulmonary infections caused by *M. abscessus* (Daley et al., 2020; Richter and Cohen, 2019).

The primary aim of this systematic review is to combine all available literature to systematise and summarise the evidence for the treatment of otomastoiditis caused by *M. abscessus*. The secondary aim is to reveal clinical and therapeutic features associated with antimycobacterial treatment duration, which could aid the clinicians while choosing for a longer treatment regimen. Our hypothesis is that factors associated with extensive disease are correlated with a longer treatment duration.

Methods

The protocol of this systematic review can be accessed via International Prospective Register of Systematic Reviews with the registration ID CRD42020222459. This systematic review was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD statement (Supplementary Material) (Stewart et al., 2015).

Study eligibility criteria

We included patients who were clearly described to be positive for *M. abscessus* through mycobacterial culture or polymerase chain reaction (PCR) with or without a positive acid-fast stain test result. In addition, we included only the patients who were described to be having a chronic/recurrent infection of the middle ear and/or mastoid air cells. Study inclusion criteria included reporting of either information on clinical features, therapeutic features, or both. Other eligibility criteria of report characteristics were the use of English language and the availability of full text. Owing to the scarce literature, we included all types of studies and used no time frame. Checking for duplicates, screening, and assessing for eligibility was done independently in an unblinded manner by 2 authors using Endnote X8 and disagreements were resolved by discussion.

Data sources

We developed search strategies for MEDLINE via PubMed, Embase via Ovid, and Web of Science (Supplementary Material). The most recent search was conducted in November 2020. Full details are included in the Supplementary Data. ClinicalTrials.gov, Google Scholar, and the Cochrane Library were also consulted. Backward and forward references searching and the 'related articles' feature of PubMed were used to identify additional results. Data from additional patients treated at the Radboud University Medical Centre was retrieved from the institution directly.

Data items, collection process and risk of bias assessment

Most IPD were already present and additional information was requested by contacting the original authors. Data collection was performed using Castor EDC. A data collection form was prepared and discussed with other authors to increase the reliability before starting data collection. We used the duration of antimycobacterial treatment as the outcome measure for a favourable treatment outcome because it seemed the most objective and most likely available outcome from the NTM-NET criteria. Critical appraisal was performed using the tool designed by the Joanna Briggs Institute (Moola et al., 2020, Munn et al., 2020).

Methods of data synthesis

We conducted an IPD meta-analysis using a 1-stage approach. We described the clinical and therapeutic characteristics of included patients and performed a 2-level mixed-effects linear regression model with the Restricted Maximum Likelihood approach. Patients were nested in studies wherein all case reports were merged into 1 study on the basis of their study characteristics. We tested for heterogeneity using intraclass correlation. A prespecified selection was made, and on the basis of an initial exploration, the final selection of eight variables were included in multivariate linear regression analysis. Variables with more than 20% missing data, collinearity or unequal distribution of groups (>1:10) were excluded from the final selection. Fisher exact test and Student *t* test were used to test for significance between the variables. Statistical analyses were performed using Stata and SPSS.

Results

Study selection, characteristics and bias assessment

Figure 1 shows the PRISMA Flow Diagram. Additional searches did not retrieve any extra results. Every study was considered eligible to contribute after the risk of bias assessment (Table 1). Of note, 3 of the 82 included cases were identified as duplicates (Van Ingen et al., 2010, Chen et al., 2014, Hsiao et al., 2011, Lee et al., 2012, Van Aarem et al., 1998). An additional 6 cases were obtained directly from the Radboud University Medical Centre. The key study characteristics are summarised in Supplementary Table 1. Two patients had a relapse 6 months after curation (Ferguson and Saulsbury, 1996; Lundman et al., 2015). These relapses were treated as new patients while assessing treatment-associated data (n = 87).

Demographic data, predisposing factors and symptoms

Table 1 shows the patient characteristics of the included patients. Two groups were formed owing to the bimodal distribution of age (Supplementary Figure 1).

Local disease spread, histopathological examination and microbiology

Table 2 and Supplementary Table 2 show the radiological and microbiological features of included patients. Fisher exact tests showed a significant association between local disease spread and mastoid-osteomyelitis ($P < .000$) and between otalgia and local disease spread ($P = .001$) but not between otalgia and mastoid-osteomyelitis ($P = .378$). All included patients tested positive for *M. abscessus* by culture or PCR, of whom, only 25/49 (51.0%) showed positive acid-fast stain test.

Treatment

Table 2 and Supplementary Table 3 show antibiotic and surgical features of the included patients. The median duration of systemic antibiotics was 26.0 (IQR: 15-35) weeks. Of the 15 patients who received monotherapy, 2 patients received additional local antibiotics (17, 18). The first surgical procedure was most commonly performed before the start of NTM antibiotic treatment, because, in few patients, this was needed to establish the diagnosis of *M. abscessus* infection.

Outcome and adverse effects

Table 3 and Supplementary Table 4 show the outcome characteristics and adverse effects in included patients.

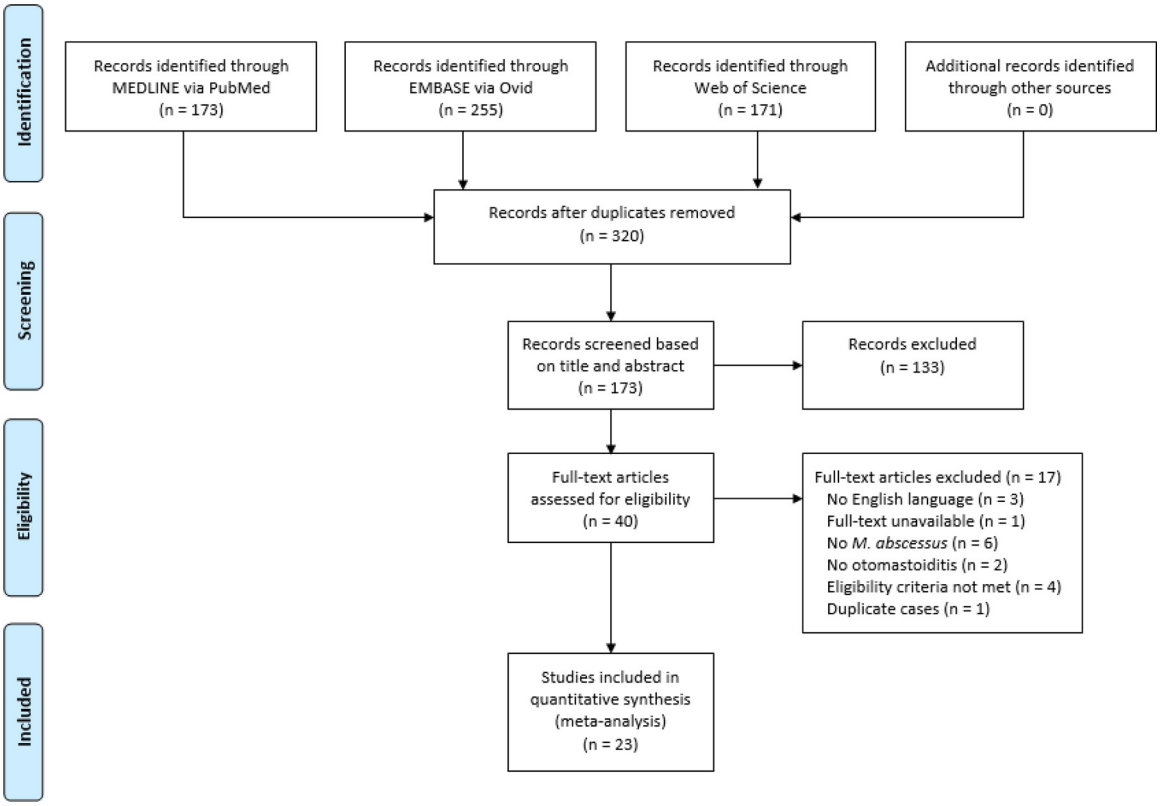

Figure 1. Flow diagram according to PRISMA (Moher et al., 2009).

Table 1
Clinical features of the included patients with otomastoiditis caused by *M. abscessus* (n = 85)

Clinical feature	Childrenn/N (%)	Adultsn/N (%)	*P* value
Median age, Years (IQR)	5 (4-8)	54.5 (49-58.8)	**.000**
Gender			**.003**
Male	39/53 (73.6%)	13/32 (40.6%)	
Female	14/53 (26.4%)	19/32 (59.4%)	
Predisposing factors			
History of tympanostomy tubes	49/53 (92.5%)	2/32 (6.3%)	**.000**
Perforation of eardrum	21/49 (42.9%)	23/28 (82.1%)	**.010**
Neither tubes nor perforation	1/53 (1.9%)	5/32 (15.6%)	**.026**
Previous ear infection			
Recurrent otitis media	28/51 (54.9%)	2/32 (6.3%)	**.000**
Serous otitis media	9/51 (17.6%)	0/32 (0%)	**.011**
Chronic otitis media	9/51 (17.6%)	10/32 (31.3%)	.184
No previous ear infection	3/51 (5.9%)	18/32 (56.3%)	**.000**
Previous antibiotic treatment	33/37 (89.2%)	4/22 (18.2%)	**.000**
Immunodeficiency	10/52 (18.9%)	0/32 (0%)	**.011**
Symptoms			
Otalgia	11/51 (21.6%)	12/32 (37.5%)	.136
Otorrhea	49/51 (96.1%)	30/32 (93.8%)	.637
Fever	9/51 (17.6%)	1/32 (3.1%)	.080
Face Palsy	1/51 (2.0%)	3/32 (9.4%)	.293
Headache	5/51 (9.8%)	5/32 (15.6%)	.498

IQR: Interquartile range.

Influence of clinical and therapeutic features on antimycobacterial treatment duration

The final selection of the 2-level multivariate linear regression model is shown in Table 4. Treatment with macrolides was excluded owing to unequal groups. Resistance to macrolides and amikacin were excluded on the basis of 62.4% of missing data. Local treatment was excluded because of the center bias arising from the 2 major studies contributing to this variable (Sedillot-Daniel et al., 2020, Van Wijk et al., 2020). Strong correlations were found for otalgia and mastoid-osteomyelitis versus local disease spread and sanation surgery versus sanation revision surgery. Therefore, we excluded local disease spread and sanation revision surgery. Values were imputed for mastoid-osteomyelitis (n = 3), otalgia (n = 2), and immunodeficiency (n = 1).

An intraclass correlation coefficient of 0.238 was observed for the heterogeneity between studies. Patients with otalgia were found to have a significantly longer antimycobacterial treatment duration than the patients without otalgia. Presence of otalgia

Table 2
Treatment features of the included patients with otomastoiditis caused by *M. abscessus* (n=87)

Treatment features	n/N (%)
Local disease spread	
Total	19/70 (27.1%)
Temporal bone	17/19 (89.5%)
Petrous part of the temporal bone*	10/17 (58.8%)
Dura mater	11/19 (57.9%)
Brain involvement	3/19 (15.8%)
Mastoid-osteomyelitis	23/72 (31.9%)
Combination of mastoid-osteomyelitis and local disease spread	
Mastoid-osteomyelitis (+), local disease spread (+)	12/65 (18.5%)
Mastoid-osteomyelitis (+), local disease spread (−)	8/65 (12.3%)
Mastoid-osteomyelitis (−), local disease spread (+)	1/65 (1.5%)
Mastoid-osteomyelitis (−), local disease spread (−)	44/65 (67.7%)
Antibiotic treatment	
Usage of systemic antibiotics	85/87 (97.7%)
Median duration of antibiotics, weeks (IQR) (n = 77)	26.0 (15-35)
Usage of intravenous treatment (amikacin, imipenem, cefoxitin)	45/85 (52.9%)
Monotherapy of antibiotics	15/85 (17.6%)
Local treatment during antimycobacterial treatment	22/87 (25.3%)
Surgery	
Initial surgery	70/87 (80.5%)
Revision surgery	33/70 (47.1%)

Asterisk (*): One study did not report the specific part involved but referred to it as 'temporal bone osteomyelitis' (3).
IQR: Interquartile range.

Table 3
Outcome characteristics of included cases (n = 87)

Outcome characteristics	n/N (%)
Outcome	
Cured	81/87 (93.1%)
Not yet completed at the time of publication	4/87 (4.6%)
Cured after relapse	2/87 (2.3%)
Type of curation according to the NTM-NET criteria	
Clinical curation	83/83 (100%)
Antimycobacterial treatment completed	81/81 (100%)
Microbiological curation	8/83 (9.6%)
Hearing loss	34/45 (75.6%)
Conductive hearing loss	14/33 (42.4%)
Sensorineural hearing loss*	1/33 (3.0%)
Unspecified	19/33 (57.6%)
Mean hearing loss, dB (95% CI) (n=26)	27.5 (22.4-31.6)
Mean follow-up time, months (95% CI) (n=26)	17.7 (7.4-28.1)

Asterisk (*): This case presented with conductive and sensorineural hearing loss and did not contribute to the presented mean hearing loss and follow-up time.
IQR: Interquartile range.

would increase treatment duration, with a mean duration of 9.3 (95% CI 0.1-18.5) weeks.

Discussion

This systematic review and IPD meta-analysis aimed to summarise patient and treatment characteristics of patients with otomastoiditis caused by *M. abscessus* to establish a clear overview and to reveal predictors related to antimycobacterial treatment duration.

Demographic data, predisposing factors, and symptoms

The population at risk according to our study are children aged 4-8 years and adults aged 49-59 years. Children possess a unique clinical profile including a history of recurrent otitis, ventilation tubes, and frequent use of (topical) antibiotics (Sedillot-Daniel et al., 2020). Tympanostomy tubes, a foreign body, promotes biofilm formation by *M. abscessus*, which could favour infection in the ear (Sedillot-Daniel et al., 2020). Recurrent otitis creates a permissive niche for the highly drug-resistant *M. abscessus* to grow and form biofilm by chronic local inflammation that causes a state of relative immunosuppression (Sedillot-Daniel et al., 2020). Repeated (local) antibiotics use also contribute to this state of relative immunosuppression.

Table 4
Two-level multivariate linear regression analysis of otomastoiditis caused by *M. abscessus* (n = 77) to identify clinical and therapeutic features for antimycobacterial treatment duration

	Univariate analysis Weeks (95% CI)	*P* value	Multivariate analysis Weeks (95% CI)	*P* value
Age				
Children	1 (ref.)		1 (ref.)	
Adults	6.8 (−4.3, 17.8)	.229	3.9 (−8.0, 15.7)	.523
Immunodeficiency	2.4 (−12.4, 17.1)	.754	1.3 (−13.7, 16.4)	.862
Otalgia	11.8 (3.5, 20.0)	**.005**	9.3 (0.1, 18.5)	**.049**
Mastoid-osteomyelitis	8.0 (−1.7, 17.8)	.103	6.9 (−3.2, 17.1)	.179
Amikacin IV	−1.8 (−9.7, 6.2)	.664	−3.7 (−13.7, 6.3)	.465
Beta-lactam IV	2.0 (−6.5, 10.4)	.648	3.0 (−7.3, 13.3)	.566
Monotherapy	−5.5 (15.5, 4.4)	.276	−2.4 (−13.6, 8.8)	.672
Sanation surgery	8.5 (−0.7, 16.3)	**.033**	1.2 (−8.0, 10.3)	.805

According to our study, otomastoiditis caused by *M. abscessus* in children manifest around the age of 5 years, which is a later presentation than that in the acute bacterial mastoiditis (2-3 years) (Loh et al., 2018). Adults often presented with no history of ear infections. Unfortunately, a clear clinical profile of adults with *M. abscessus* otomastoiditis remains unclear.

Based on the high frequencies of tympanostomy tubes and tympanic membrane perforation reported in our study, we assume that they are the bridge for *M. abscessus* between the outside world and the middle ear.

Local disease spread, histopathological examination and microbiology

This study confirms our hypothesis that otalgia is related to a longer antimycobacterial treatment duration with a mean increase of 9.3 weeks. Multivariate linear regression analysis, although non-significant, also suggested that a longer antimycobacterial treatment duration is needed to reach curation in patients with mastoid-osteomyelitis.

Almost all patients with local disease spread also presented with mastoid-osteomyelitis, whereas mastoid-osteomyelitis was also likely to present on its own. This suggests that mastoid-osteomyelitis precedes local disease spread. A significant association was found between otalgia and local disease spread, suggesting that pain arises from local disease spread rather than from the *M. abscessus* infection directly, which is also stated in previous literature (Yeh et al., 2015). However, because some patients with mastoid-osteomyelitis or local disease spread may still present without otalgia, every patient should receive radiological imaging to examine the extension of *M. abscessus* infection and assess the treatment response (Yeh et al., 2015, Sedillot-Daniel et al., 2020).

Isolates acquired from the patients with otomastoiditis caused by *M. abscessus* showed different rates of resistance compared with other *M. abscessus* infections (Griffith et al., 2007). Amikacin-resistance was more common in otomastoiditis-associated *M. abscessus* isolates, which is likely due to pretreatment with topical aminoglycosides (Van Wijk et al., 2020, Chen et al., 2014, Van Aarem et al., 1998, Franklin et al., 1994). Although we found high susceptibility to macrolides (75.8%) rates, frequent occurrence of inducible macrolide resistance has consequences for the treatment regime and, therefore, testing for the latter is essential (Daley et al., 2020). We advocate testing for tigecycline susceptibility because this potent drug could have an important role in *M. abscessus* treatment, although cut-offs to define resistance remain to be established (Van Wijk et al., 2020).

Systemic and local antibiotic treatment

According to the most recent literature, the multidrug regimen should contain at least 3 drugs with low MICs. If macrolides show inducible resistance, they would be given additionally and would not be considered in the total of 3 active drugs, resulting in a prescription of a total of at least 4 drugs to the patient (Daley et al., 2020). Our median duration of antimycobacterial treatment in otomastoiditis caused by *M. abscessus* matches the recommended antimycobacterial treatment duration for bone infection caused by *M. abscessus*, which is 6 months according to the 2007 American Thoracic Society (ATS)/Infectious Disease Society of America Statement (IDSA) (Griffith et al., 2007). Unfortunately, most drugs against *M. abscessus* come with several adverse effects. Thus, expert consultation is crucial because each regimen has both advantages and disadvantages, effectivity and adverse effects that require a careful and thoughtful approach for reaching the ultimate treatment regimen.

The role of topical antibiotic treatment remains uncertain. Topical administration of antibiotics with proven in vitro activity could be a valuable addition to the treatment regimen with limited risks and no systemic adverse effects, but their efficacy needs to be studied in clinical trials.

Our IPD meta-analysis reports 15 patients who received monotherapy, which is in contrast with the current guidelines. Strikingly only one-third of the monotherapy patients received sanation surgery. Local disease spread and mastoid-osteomyelitis were only present in 2 cases and required 32 weeks of therapy until curation was achieved (Pelkonen et al., 2011, Chen et al., 2014). Although it is unknown in what circumstances monotherapy is effective, absence of local disease spread and mastoid-osteomyelitis could possibly increase the chances of curation. However, monotherapy can induce acquired resistance to key antibiotics and is therefore not in accordance with the current guidelines.

Surgical treatment

Univariate linear regression analysis showed a significantly longer treatment duration when sanation surgery was performed. However, when corrected for otalgia and mastoid-osteomyelitis, this was no longer the case. This may suggest that more severe *M. abscessus* infections require sanation surgery and longer antimycobacterial treatment duration.

In contrast to the current guidelines, some articles mention conservative treatment without surgery to be favourable when there is only limited disease and the medical condition of the patient is good (Lundman et al., 2015, Sedillot-Daniel., 2020). Among included patients who did not receive surgery, curation was difficult (>1 year of treatment) only in 2 patients with presence of local disease spread on conservative treatment (Yeh et al., 2015, Vijayananthan et al., 2008). Thus, conservative treatment could yield desirable results in patients with only minimal disease extension/destruction, but it should always be discussed with a specialised team because it could complicate the curation.

According to the 2007 ATS/IDSA Statement, foreign body removal is essential to recovery from a disease caused by biofilm formation of *M. abscessus* (Griffith et al., 2007). Therefore, we suggest the use of laser to achieve this permanent communication while eliminating the risk of biofilm formation on tympanostomy tubes.

Outcome and hearing loss

In our IPD meta-analysis, 100% of the patients attained clinical cure according to the NTM-NET definitions (Van Ingen et al., 2018). These high cure rates may be an overestimation due to publication bias or because of the nature of the disease and young patients. Otomastoiditis caused by *M. abscessus* is most likely to cause conductive hearing loss, either owing to the infection or the treatment, with a mean hearing loss of 27.5 dB. However, these numbers are likely to be biased due to varying time of follow-up, missing information, and the fact that hearing loss commonly presents after mastoid surgery and often normalises after an adequate time of follow-up.

Strengths and limitations

This IPD meta-analysis is the first study to our knowledge that summarises the characteristics of patients with otomastoiditis caused by *M. abscessus* and is the first to report clinical and therapeutic factors that might influence treatment duration. Our biggest limitation is the quality of included studies, which consists of case reports and series owing to the rarity of the disease. Therefore, this study only makes assumptions and provides an overview of the reported patients with otomastoiditis caused by *M. abscessus* in the literature.

Conclusion

Mycobacterium abscessus otomastoiditis affects both children (aged 4-8 years) and adults (aged 49-59 years). Communication between the tympanic cavity and the outside world, in adults achieved by a tympanic membrane perforation and in children by tympanostomy tubes, seems to be a risk factor for *M. abscessus* infection. Other risk factors for children include previous (local) antibiotic administration and recurrent ear infections. Symptoms include chronic painless otorrhea that is refractory to the standard antibiotic treatment. The presence of otalgia may indicate local disease spread and predicts a significantly longer antimycobacterial treatment duration. Antimycobacterial treatment should follow a multidrug regimen for a minimum of 6 months, consisting of a total of 3 active drugs with a careful balance between effectivity and adverse effects. Surgery, occasionally requiring revision, is often needed because of the extensive characteristics of and biofilm formation by *M. abscessus*. Monotherapy and a conservative treatment should be proposed with caution but could possibly achieve cure in minimal disease. Foreign bodies need to be removed and a perforation in tympanic membrane is assured for effective delivery of the local treatment and drainage of the infectious discharge.

Transparency declaration

Funding statement

No specific funding was received from any bodies of the public, commercial or not-for-profit sectors to carry out the work described in this article.

Conflict of interest

The authors reported no conflict of interest.

Ethical approval statement

Ethical approval was not required for this study.

Acknowledgements

We gratefully acknowledge the help of Joanna in ‘t Hout in the statistical analysis and Alice Tillema for their assistance with the systematic literature strategy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.017.

References

Chen PY, Wu CC, Yang TL, Hsu CJ, Lin YT, Lin KN. Gradenigo syndrome caused by nontuberculous mycobacteria. Audiol Neurootol 2014;19(4):275–82.

Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 2020;56(1).

Ferguson PJ, Saulsbury FT. Successful treatment of chronic Mycobacterium abscessus otitis media with clarithromycin. Pediatr Infect Dis J 1996;15(4):384–5.

Franklin DJ, Starke JR, Brady MT, Brown BA, Wallace Jr RJ. Chronic otitis media after tympanostomy tube placement caused by Mycobacterium abscessus: A new clinical entity? American Journal of Otology 1994;15(3):313–19.

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(4):367–416.

Hsiao CH, Liu CM, Hsueh PR. Clinicopathological and microbiological characteristics of mycobacterial otitis media in a medical center, 2000 to 2009. J Infect 2011;62(3):243–6.

Johansen MD, Herrmann JL, Kremer L. Non-tuberculous mycobacteria and the rise of Mycobacterium abscessus. Nat Rev Microbiol 2020;18(7):392–407.

Lee MR, Tsai HY, Cheng A, et al. Otitis media and otomastoiditis caused by Mycobacterium massiliense (Mycobacterium abscessus subsp. bolletii). J Clin Microbiol 2012;50(11):3754–6.

Loh R, Phua M, Shaw CL. Management of paediatric acute mastoiditis: systematic review. J Laryngol Otol 2018;132(2):96–104.

Lundman L, Edvardsson H, Angeby K. Otomastoiditis caused by non-tuberculous mycobacteria: Report of 16 cases, 3 with infection intracranially. Journal of Laryngology and Otology 2015;129(7):644–55.

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. JBI; 2020.

Munn Z, Barker TH, Moola S, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evid Synth 2020;18(10):2127–33.

Pelkonen T, Aarnisalo A, Markkola A, Eskola J, Saxen H, Salo E. Prolonged otorrhea and mastoiditis caused by Mycobacterium abscessus. International Journal of Pediatric Otorhinolaryngology Extra 2011;6(4):388–91.

Richter WJ, Cohen KA. No Amikacin, No Problem: a Successful Treatment Approach for Pediatric Otomastoiditis Due to Amikacin-Resistant Mycobacterium abscessus. Antimicrob Agents Chemother 2019;64(1).

Sedillot-Daniel E, Voizard B, Vallieres E, Woods O, Quintal MC. Chronic suppurative otomastoiditis due to nontuberculous mycobacteria: A case series. International Journal of Pediatric Otorhinolaryngology 2020;138 (no pagination).

Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313(16):1657–65.

van Aarem A, Muytjens HL, Smits MM, Cremers C. Recurrent therapy resistant mastoiditis by Mycobacterium cheilonae abscessus, a nontuberculous Mycobacterium. International Journal of Pediatric Otorhinolaryngology 1998;43(1):61–72.

van Ingen J, Aksamit T, Andrejak C, et al. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. Eur Respir J 2018;51(3).

van Ingen J, Looijmans F, Mirck P, Dekhuijzen R, Boeree M, van Soolingen D. Otomastoiditis caused by Mycobacterium abscessus, The Netherlands. Emerg Infect Dis 2010;16(1):166–8.

van Wijk F, Waterval J, van Aerde K, et al. Successful Systemic and Topical Treatment of Mycobacterium abscessus Otomastoiditis. Antimicrobial Agents and Chemotherapy 2020;64(1).

Vijayananthan A, Arumugam A, Kumar G, Harichandra D. Mastoiditis secondary to mycobacterium abscessus imaged with gallium-67 scintigraphy. Biomed Imaging Interv J 2008;4(2):e23.

Yeh CF, Tu TY, Wang MC, et al. Emergence of Refractory Otomastoiditis Due to Nontuberculous Mycobacteria: Institutional Experience and Review of the Literature. Clinical Infectious Diseases 2015;62(6):739–45.