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PII: S1201-9712(22)00017-0
DOI: https://doi.org/10.1016/j.ijid.2022.01.017
Reference: IJID 5939

To appear in: International Journal of Infectious Diseases

Received date: 6 December 2021
Revised date: 5 January 2022
Accepted date: 7 January 2022

Please cite this article as: Jordi Manders, Theresa Leow, Koen van Aerde, Myrthe Hol, Dirk Kunst, Sjoert Pegge, Thijs Jansen, Jakko van Ingen, Stijn Bekkers, Clinical characteristics and an evaluation of predictors for a favorable outcome of Mycobacterium abscessus otomastoiditis: a systematic review and meta-analysis of individual participant data, International Journal of Infectious Diseases (2022), doi: https://doi.org/10.1016/j.ijid.2022.01.017

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Highlights

- M. abscessus otomastoiditis affects a specific bimodal child and adult population.
- Predisposers for children include tympanic tubes, recurrent otitis, and antibiotics.
- Absence of otalgia is a significant predictor for shorter treatment duration.
- Antimycobacterial treatment includes a multidrug regimen for 6 months minimal.
- Surgery, sometimes requiring revision, is often required for successful curation.
Clinical characteristics and an evaluation of predictors for a favorable outcome of Mycobacterium abscessus otomastoiditis: a systematic review and meta-analysis of individual participant data

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PROSPERO registration ID: CRD42020222459.

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ABSTRACT

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

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

Results.
Twenty-three studies reported a total of 85 patients. Children presented with an unique clinical profile of a history of ear infections, tympanostomy tube placement and antibiotic treatment.
Antimycobacterial treatment was administered for 26 (Inter Quartile Range (IQR): 15-35) weeks. Macrolides were prescribed in 98.8%. Surgery was performed in 80.5%, of which 47.1% required
revision surgery. Otalgia was a significant predictor ($\beta = 9.3; p = .049$) of antimycobacterial treatment duration.

**Conclusions.**

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

**KEYWORDS**

Humans, *Mycobacterium abscessus*; Non-tuberculous mycobacteria, Otomastoiditis, Otitis media

**BACKGROUND**

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

Where earlier published research states to combine surgery, even repeated, and systemic antibiotics for 6 months minimum (Van Ingen., 2010, Lundman et al., 2015, Yeh et al., 2015), more recent research suggests adding local treatment to this multi-modal approach (Sedillot-Daniel et al., 2020, Van Wijk et al., 2020). These intensive multimodal treatment regimens commonly result in several complaints and adverse events frequently resulting in cessation of
therapy. There is currently no specific guideline for the management of otomastoiditis caused by *M. abscessus* and therefore current treatment regimens are mostly extrapolated from pulmonary infections caused by *M. abscessus* (Richter et al., 2019, Daley et al., 2020).

The primary aim of this systematic review is to combine all available literature to systematize 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 clinician when to choose 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 PROSPERO with registration ID CRD42020222459. This systematic review was conducted in adherence with the PRISMA-IPD statement (see Supplementary Material) (Stewart et al., 2015).

**STUDY ELIGIBILITY CRITERIA**

We included patients of which was clearly described that they tested positive for *M. abscessus* with mycobacterial culture or polymerase chain reaction (PRC) with or without a positive Acid Fast Stain test. In addition we only included patients of which was described that they suffered from a chronic/recurrent infection of the middle ear and/or mastoid air cells. Study inclusion criteria included that studies reports either information on clinical features, therapeutical features or both. Other eligibility criteria of report characteristics were the use of English language and the availability of full text. Due to scarce literature, we included all types of studies and used no timeframe. Checking for duplicates, screening, and assessing for eligibility was done
independently in an unblinded manner by two 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 (see 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 the 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 was already present and additional information was requested by contacting the original authors. Data collection was done using Castor EDC. A data collection form was made and discussed with the other authors to increase reliability before the start of data collection. We used the duration of antimycobacterial treatment as the outcome measure for a favourable treatment outcome as it seemed the most objective and most likely available outcome from the NTM-NET criteria. Critical appraisal was done 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 one-stage approach. We described the clinical and therapeutic characteristics of the included patients and performed a two-level mixed-effects linear regression model with the Restricted Maximum Likelihood (REML) approach. Patients were
nested in studies wherein all case reports were merged into one study based on their study characteristics. We tested for heterogeneity using intraclass correlation. A prespecified selection was made and based on an initial exploration the final selection of eight variables were included in multivariate linear regression analysis. Variables with over 20% missing data, collinearity or unequal distribution of groups (> 1:10) were excluded from the final selection. The Fisher’s Exact Test and student’s t-test were used to test for significance between 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 retrieved no extra results. Every study was eligible to contribute after risk of bias assessment (table 1). Three 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 six 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 six months after curation (Lundman et al., 2015, Ferguson et al., 1996). 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 due 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 the included patients. Fisher’s 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 which only 25/49 (51.0%) showed positive Fast Acid Strain test.

TREATMENT

Table 2 and supplementary table 3 show the antibiotic and surgical features of the included patients. The median duration of systemic antibiotics was 26.0 (IQR: 15-35) weeks. Of the fifteen patients that received monotherapy, two patients received additional local antibiotics (17, 18). The first surgical procedure was most common to be done before the start of NTM antibiotic treatment, because in some patients this was needed to establish the diagnosis of *M. abscessus*.

OUTCOME AND ADVERSE EVENTS

Table 3 and supplementary table 4 show the outcome characteristics and adverse events of the included patients.

INFLUENCE OF CLINICAL AND THERAPEUTIC FEATURES ON ANTIMYCOBACTERIAL TREATMENT DURATION.

The final selection of the two-level multivariate linear regression model is shown in table 4. Treatment with macrolides was excluded due to the unequal groups. Resistance to macrolides and amikacin were excluded based on 62.4% missing data. Local treatment was excluded due to the
center bias arising from the two major studies contributing in 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 (ICC) of 0.238 was observed for the heterogeneity between studies. Patients with otalgia were found to have a significantly longer antimycobacterial treatment duration compared to patients without otalgia. Presence of otalgia 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 the 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 (4-8 y.o.) and adults (49-59 y.o.). Children present with an unique clinical profile of a history of recurrent otitis, ventilation tubes, and often (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 which causes a
state of relative immunosuppression (Sedillot-Daniel et al., 2020). Repeated (local) antibiotics also contribute to this state of relative immunosuppression.

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

*M. abscessus* enters through a communication between the outside world and the middle ear. Based on the high frequencies of tympanostomy tubes and tympanic membrane perforation reported in our study, we assume that they are the bridge 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, although non-significant, also suggests that a longer antimycobacterial treatment duration was needed to reach curation in patients with mastoid-osteomyelitis.

Almost all patients with local disease spread also presented with mastoid-osteomyelitis, while 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 assuming 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, as 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* 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 to 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 susceptible rates to macrolides (75.8%), inducible macrolide resistance frequently occurs has consequences for the treatment regime, so 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 three drugs with low MICs. If macrolides show inducible resistance they will be given additionally and will not count toward the total of three active drugs, prescribing a total of at least four drugs to the patient (Daley et al., 2020). Our median duration of antimycobacterial treatment in otomastoiditis caused by *M. abscessus* matches the recommended antimycobacterial duration of bone infection caused by *M. abscessus* is six months according to the 2007 ATS/IDSA Statement (Griffith et al., 2007). Unfortunately, most drugs against *M. abscessus* come with several adverse events. Thus, expert consultation is crucial because each regimen has advantages and disadvantages, effectiveness versus side effects, which requires 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 side effects, but their efficacy needs to be studied in clinical trials.

Our IPD meta-analysis reports fifteen patients which received monotherapy, which is in contrast with the current guidelines. Striking is that only one-third of the monotherapy patients received sanation surgery. Local disease spread and mastoid-osteomyelitis were only present in two cases which 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 chance for curation. However, monotherapy can induce acquired resistance to key antibiotics and is therefore not in accordance with current guidelines.

SURGICAL TREATMENT

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

In contrast to 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 the included patients who did not receive surgery, curation was only difficult (> one year of treatment) in the two patients with the presence
of local disease spread on conservative treatment (Yeh et al., 2015, Vijayananthan et al., 2008). Thus, conservative treatment could yield good results in patients with only minimal disease extension/destruction, but should always be discussed in a specialized team, because it could complicate curation.

According to the 2007 ATS/IDSA Statement foreign body removal is essential to recovery due to biofilm formation of *M. abscessus* (Griffith et al., 2007). Therefore we suggest to use 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 overestimated due to publication bias, or due to the nature of the disease and the young patients. Otomastoiditis caused by *M. abscessus* is most likely to cause conductive hearing loss either due to infection or 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 normalizes after an adequate time of follow-up.

STRENGTHS AND LIMITATIONS

This IPD meta-analysis is the first study to our knowledge that summarised 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 due to the rarity of the disease.
Therefore this study only makes assumptions and provides an overview of the reported patients in literature with otomastoiditis caused by *M. abscessus*.

**CONCLUSION**

*Mycobacterium abscessus* otomastoiditis affects children (4-8 y.o.) and adults (49-59 y.o.). A 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 which is refractory to standard antibiotic treatment. The presence of otalgia may indicate local disease spread and predicts a significant longer antimycobacterial treatment duration. Antimycobacterial treatment should follow a multidrug regimen for a minimum of six months consisting of a total of three active drugs with careful balance between effectivity and side-effects. Surgery, occasionally requiring revision, is most often needed because of the extensive character and biofilm formation of *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 local treatment and drainage of infectious discharge.
TRANSPARANCY DECLARATION

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

CONFLICT OF INTEREST
The authors: No reported conflicts of interest.

ETHICAL APPROVAL STATEMENT
Ethical approval was not required for this study.

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

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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**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                          | Children n/N (%) | Adults n/N (%) | P-value |
|------------------------------------------|------------------|----------------|---------|
| Median age, Years (IQR)                  | 5 (4-8)          | 54.5 (49-58.8) | 0.000   |
| Gender                                   |                  |                | 0.003   |
| 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%)    | 0.000   |
| Perforation of eardrum                   | 21/49 (42.9%)    | 23/28 (82.1%)  | 0.010   |
| Neither tubes nor perforation            | 1/53 (1.9%)      | 5/32 (15.6%)   | 0.026   |
| **Previous ear infection**               |                  |                |         |
| Recurrent Otitis Media                   | 28/51 (54.9%)    | 2/32 (6.3%)    | 0.000   |
| Serous Otitis Media                      | 9/51 (17.6%)     | 0/32 (0%)      | 0.011   |
| Chronic Otitis Media                     | 9/51 (17.6%)     | 10/32 (31.3%)  | 0.184   |
| No previous ear infection                | 3/51 (5.9%)      | 18/32 (56.3%)  | 0.000   |
| **Previous antibiotic treatment**        |                  |                | 0.000   |
| Immunodeficiency                         | 10/52 (18.9%)    | 0/32 (0%)      | 0.011   |
| **Symptoms**                             |                  |                |         |
| Otalgia                                  | 11/51 (21.6%)    | 12/32 (37.5%)  | 0.136   |
| Otorrhea                                 | 49/51 (96.1%)    | 30/32 (93.8%)  | 0.637   |
| Fever                                    | 9/51 (17.6%)     | 1/32 (3.1%)    | 0.080   |
| Face Palsy                               | 1/51 (2.0%)      | 3/32 (9.4%)    | 0.293   |
| Headache                                 | 5/51 (9.8%)      | 5/32 (15.6%)   | 0.498   |

Abbreviations: IQR: Inter Quartile Range.
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).

Abbreviations: IQR: Inter Quartile 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 NTM-criteria** |             |
| Clinical Curation                       | 83/83 (100%) |
| Antimycobacterial treatment completed   | 81/81 (100%) |
| Microbiological curation                | 8/83 (9.6%)  |
| **Hearing Loss**                        |             |
| 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. Abbreviations: IQR: Inter Quartile Range.
Table 4. Two-level multivariate linear regression analysis to identify clinical and therapeutical features for antimycobacterial treatment duration of otomastoiditis caused by *M. abscessus* (n=77).

| Feature                      | Univariate analysis | Multivariate analysis |
|------------------------------|---------------------|-----------------------|
|                              | Weeks (95%CI)       | p-value               | Weeks (95%CI) | p-value |
| **Age**                      |                     |                       |               |         |
| Children                     | 1 (ref.)            |                       | 1 (ref.)      |         |
| Adults                       | 6.8 (-4.3, 17.8)    | 0.229                 | 3.9 (-8.0, 15.7) | 0.523  |
| Immunodeficiency             | 2.4 (-12.4, 17.1)   | 0.754                 | 1.3 (-13.7, 16.4) | 0.862  |
| Otalgia                      | 11.8 (3.5, 20.0)    | 0.005                 | 9.3 (0.1, 18.5) | 0.049  |
| Mastoid-osteomyelitis        | 8.0 (-1.7, 17.8)    | 0.103                 | 6.9 (-3.2, 17.1) | 0.179  |
| Amikacin IV                  | -1.8 (-9.7, 6.2)    | 0.664                 | -3.7 (-13.7, 6.3) | 0.465  |
| Beta-lactam IV               | 2.0 (-6.5, 10.4)    | 0.648                 | 3.0 (-7.3, 13.3) | 0.566  |
| Monotherapy                  | -5.5 (15.5, 4.4)    | 0.276                 | -2.4 (-13.6, 8.8) | 0.672  |
| Sanation surgery             | 8.5 (-0.7, 16.3)    | 0.033                 | 1.2 (-8.0, 10.3) | 0.805  |