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The management of non-tuberculous cervicofacial lymphadenitis in children: A systematic review and meta-analysis

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Summary *Objectives:* Cervicofacial lymphadenitis is the most common manifestation of infection with non-tuberculous mycobacteria (NTM) in immunocompetent children. Although complete excision is considered standard management, the optimal treatment remains controversial. This study reviews the evidence for different management options for NTM lymphadenitis.

Methods: A systematic literature review and meta-analysis were performed including 1951 children from sixty publications. Generalised linear mixed model regressions were used to compare treatment modalities.

Results: The adjusted mean cure rate was 98% (95% CI 97.0—99.5%) for complete excision, 73.1% (95% CI 49.6—88.3%) for anti-mycobacterial antibiotics, and 70.4% (95% CI 49.6—88.3%) for 'no intervention'. Compared to 'no intervention', only complete excision was significantly associated with cure (OR 33.1; 95% CI 10.8—102.9; $p < 0.001$). Complete excision was associated with a 10% risk of facial nerve palsy (2% permanent). 'No intervention' was associated with delayed resolution.

Conclusions: Complete excision is associated with the highest cure rate in NTM cervicofacial lymphadenitis, but also had the highest risk of facial nerve palsy. In the absence of large, well-designed RCTs, the choice between surgical excision, anti-mycobacterial antibiotics

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and 'no intervention' should be based on the location and extent of the disease, and acceptability of prolonged time to resolution.

Background

Non-tuberculous mycobacteria (NTM) are ubiquitous bacterial organisms found in water, soil and other environmental sites. Although more than 100 different species have been identified, the majority of human NTM disease is caused by fewer than 10 species.[1] In immunocompetent individuals NTM most frequently cause pulmonary infection, lymphadenitis, or skin and soft tissue infections.[2]

In children, NTM lymphadenitis is the most common manifestation with the cervicofacial region predominantly being affected.[2] Reports on incidence of NTM lymphadenitis range from 0.8 to 3.5 per 100 000, with highest incidence rates in children below 4 years of age.[3–6] These patients typically present with a slowly progressing, unilateral, non-tender enlargement of one or several lymph nodes. After approximately four weeks of lymph node enlargement, a purple discoloration of the overlying skin and fistula or sinus formation with discharge of purulent material commonly occurs.[7] The majority of children with NTM lymphadenitis have no systemic symptoms and extension of disease beyond the local site is rare.[8]

Although timely complete excision of affected lymph nodes has been considered the standard treatment for decades,[8–11] more recently an increasing number of studies have reported successful treatment with anti-mycobacterial antibiotics[12–17] or observation alone without intervention.[7,18–20] Against this approach is the argument that a surgical procedure is needed for confirmation of diagnosis by culture or polymerase chain reaction (PCR), as specific immunodiagnostic tests for NTM infection are currently lacking.[21]

The low incidence of the disease and the difficulty of confirming the diagnosis without a surgical procedure make it currently difficult to address the question of best management with a sufficiently large randomised controlled study.[22] The aim of this study was to perform a systematic literature review and meta-analysis to advance knowledge on the optimal management including all types of surgical interventions, anti-mycobacterial treatment and no intervention of NTM cervicofacial lymphadenitis in immunocompetent children.

Methods

Search strategy

A systematic literature review was performed using Medline, EMBASE and Web of Science (1950—December 2013) using the search terms: (non-tuberculous OR atypical mycobacteria(l)) AND (lymphadenitis OR cervical) AND (treatment OR management). References were hand-searched for additional publications. Criteria for inclusion of publications were: (i) immunocompetent children, (ii) cervicofacial lymphadenitis and (iii) sufficiently detailed description of diagnostic criteria including at least number of individuals per treatment modality and outcome reported according to treatment modality. Only publications in English, French, German or Spanish were reviewed. The following variables were extracted from the included studies: year of study, country, number of patients, gender, mean or median age of patients, inclusion criteria (positive NTM culture and/or positive PCR and/or lymph node histology suggestive of NTM and/or positive skin test and/or clinical diagnosis), location of lymphadenitis, progression of disease (firm or fluctuant swelling, skin changes or fistula formation) culture result, type of intervention, complications (facial nerve damage, fistula formation, wound infection or scar formation), need for additional surgical intervention, all adverse events, number of cases receiving anti-mycobacterial antibiotics in addition to surgery (before or after), number of cured patients and time to resolution.

Statistical analysis

A database was created containing a dataset for each participant from the studies included in this review comprising a study identifier, the treatment used and treatment outcome. Generalised linear mixed model regressions for binary data were used to compare different treatment types.[23,24] The outcome variable was case cured (yes/no) and the predictor was the treatment type. The study identifier was included in the model as a random effect. For multiple comparisons the Dunnett—Hsu adjustment was used. PROC GLIMMIX with the quadrature methods was used for the analyses (SAS version 9.3, 2002—2010, SAS Institute Inc., Cary, NC, USA). For each included publication the level of evidence was determined using the Oxford Center for Evidence-based Medicine grading system.[25] Risk of bias was evaluated for RCTs using the risk of bias tool by the Cochrane Collaboration.[26]

Results

The results of the search and selection process are summarised in (Fig. 1). A total of 60 publications were included in the review, comprising three randomised controlled trials (RCTs), four prospective cohort studies, 38 retrospective cohort studies and 15 case reports. The risk of bias in the RCTs is summarised in Table 1.

Epidemiology, clinical manifestations and microbiology

The 60 publications reporting on the management NTM cervicofacial lymphadenitis included a total of 1951 children with a mean age of 3.4 years. The clinical characteristics of these children are summarised in (Table 2). The most prevalent site of disease was the submandibular/

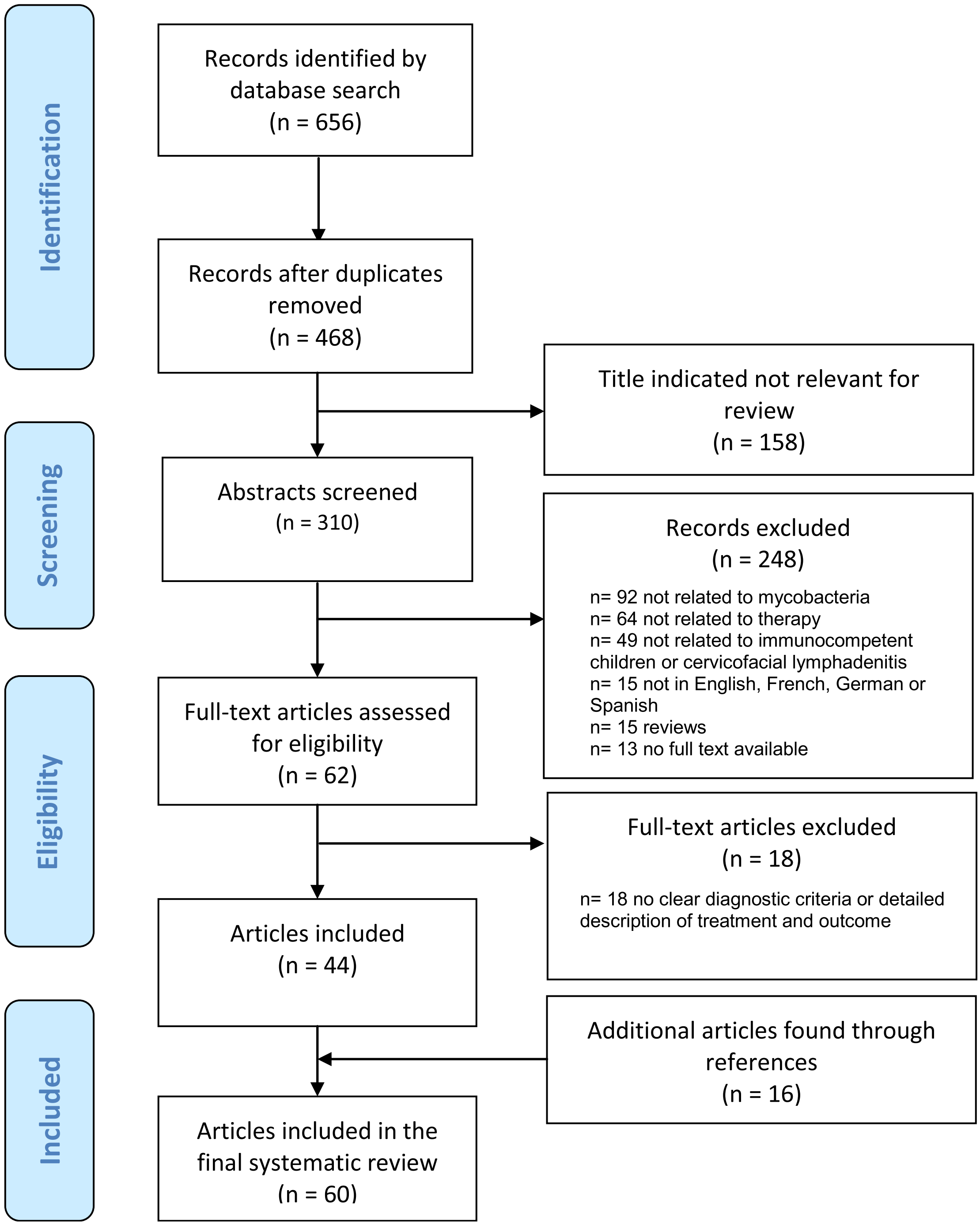

Figure 1 Flow diagram of selection of articles included in the review.

submental region followed by the cervical and the preauricular/parotid regions. Only 7% of cases showed multiple affected lymph node regions, and only 2% bilateral lymphadenitis. In 29% of the patients skin discoloration or fistula formation was reported. In 18% swelling of the lymph node was reported as firm or fluctuant without other changes. In 64% (n = 1247) the diagnosis of NTM disease was microbiologically confirmed by culture or PCR (Tables 2 and 3). In the remaining cases different combinations of clinical presentation, histopathology (acid-fast bacilli and/or granulomatous inflammation with or without caseous necrosis) and skin test results were used to support the diagnosis (Table 2).

A total of 578 (30%) children had previously failed treatment with antibiotics that have no activity against NTM for presumed pyogenic bacterial lymphadenitis before the diagnosis of NTM lymphadenitis was established. The interval between onset of clinical symptoms and diagnosis varied from 1 to 30 weeks.

In 1274 children the causative NTM species/complex was documented, with *Mycobacterium avium* being the most frequently identified species (34%) (Table 2).

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Table 1 Risk of bias summary: Review authors' judgements for each risk of bias measure for included randomised controlled trials.

	Selection bias Random sequence generation, allocation of concealment	Performance bias Blinding of participants and personnel	Detection bias Blinding of outcome assessment	Attrition bias Incomplete outcome data	Reporting bias Selective reporting
Lindeboom 2007[27]	+	−	−	+	+
Lindeboom 2011[18]	+	−	−	+	+
Lindeboom 2012[28]	+	−	−	+	+

Notably, many studies did not differentiate between *M. avium*, *Mycobacterium intracellulare* and *Mycobacterium scrofulaceum*, but reported the causative organism as 'Mycobacterium avium-intracellulare (MAC)-complex' or 'Mycobacterium avium-intracellulare-scrofulaceum (MAIS)-complex'. *M. avium*, MAC- and MAIS-complex combined accounted for more than two thirds of cases (68%). The next most frequent NTM species was *Mycobacterium haemophilum*, which accounted for 6% of cases. Of note, all cases of *M. haemophilum* cervicofacial lymphadenitis were identified in two countries only (the Netherlands and Israel).

Table 2 Demographic and clinical characteristics of the 1951 children with non-tuberculous mycobacterial lymphadenitis in the publications included in this review.

Characteristic	Number of patients (%)
Gender	
Female	1018 (52)
Male	726 (37)
Not specified	207 (11)
Location	
Submandibular or submental	926 (48)
Cervical	609 (31)
Preauricular/parotid	269 (14)
Cervicofacial not further specified	63 (3)
Other cervicofacial[a]	34 (2)
Other[b]	19 (1)
Not specified	144 (7)
More than one location	131 (7)
Bilateral	35 (2)
Local findings	
Detailed local findings not specified	1037 (53)
Additional skin changes or fistula formation	567 (29)
Painless, firm or fluctuant swelling without other changes	347 (18)
Diagnostic criteria	
Culture and/or PCR	1204 (62)
Clinical symptoms plus typical histology plus positive skin test	290 (15)
Clinical symptoms plus typical histology	210 (11)
Clinical symptoms or typical histology or positive skin test	158 (8)
Clinical symptoms plus positive skin test	69 (4)
Clinical symptoms	20 (1)

[a] 5 supraclavicular, 5 buccal, 3 retropharyngeal, 2 infraclavicular, 2 retroauricular and 2 occipital.
[b] 13 axillary, 14 inguinal, 6 limb and 1 mediastinal.

Treatment options for NTM lymphadenitis

By far the most commonly reported treatment was surgery. Fewer than 20% of patients were treated with either anti-mycobacterial antibiotics or observed without intervention (Table 4).

Table 3 Causative *Mycobacterium* species in the cases included in this review.

Mycobacterium species	Number of cases (%)
M. avium	432 (34)
MAI-complex[a]	370 (29)
MAIS-complex[b]	161 (13)
M. haemophilum	77 (6)
M. malmoense	42 (3)
M. kansasii	26 (2)
M. scrofulaceum	24 (2)
M. chelonae	9 (<1)
M. fortutium	9 (<1)
M. intracellulare	6
M. xenopi	3
M. simiae	3
M. celatum	2
M. interjectum	2
M. marinum	2
M. gordonae	1
M. lentiflavum	1
M. heidelbergense	1
M. bohemicum	1
Non-tuberculous mycobacterium, not further specified	102 (8)
Total	**1274 (100)**

[a] MAI-complex = *Mycobacterium-avium-intracellulare* complex.
[b] MAIS-complex = *Mycobacterium-avium-intracellulare-scrofulaceum* complex.

Table 4 Summary of treatment approaches and outcomes of children with non-tuberculous mycobacterial lymphadenitis.[a]

Treatment modality	Number of studies	Number of patients (% of total)	Pooled cure rate % (95% CI)[b]	Facial nerve palsy (%)[c]	Fistula formation (%)[c]	Wound infection (%)[c]	Scar formation (%)[c]	Additional surgical intervention (%)[c]
Complete excision	43	1077 (55)	88.5 (86.5—90.3)[1]	105 (10)	24 (2)	17 (2)	15 (2)	81 (8)
Incomplete excision	4	15 (<1)	100 (84.8—100)	1 (7)	4 (27)	0	1 (7)	0
Curettage	10	121 (6)	61.2 (52.3—69.5)[3]	0	20 (19)	0	0	22 (18)
Incision and drainage	24	246 (13)	34.2 (28.4—40.2)[2]	1 (0.4)	68 (28)	2 (1)	14 (6)	48 (20)
Fine-needle aspiration	6	32 (2)	37.5 (22.4—54.8)[4]	0	7 (29)	1 (4)	0	9 (28)
Other surgery or combination of surgeries	11	87 (5)	47.1 (36.9—57.6)	0	0	0	0	85 (98)
Anti-mycobacterial Antibiotics	19	171 (9)	67.8 (60.6—74.5) 5	0	7 (4)	0	9 (5)	53 (31)
No intervention	9	157 (8)	89.8 (84.4—93.8)	0	91 (60)	0	3 (2)	5 (3)

[a] Of note, this summary of cure rates does not account for potential methodological differences between studies.
[b] The outcome was not reported in a number of patients and were therefore not included in this calculation: [1] 41 patients, [2] 57 patients, [3] 16 patients, [4] 8 patients, [5] 2 patients.
[c] Of patients with the same treatment.

Surgical interventions: treatment outcomes and adverse effects

Complete excision of the affected lymph nodes was reported in 43 studies including 1077 children. This intervention was associated with a pooled cure rate of 88.5% (95% CI; 86.5—90.3%) (Table 4). The predominant complication was facial nerve palsy in 105 (10%) children, of which 82 were transient. One RCT comparing complete excision with anti-mycobacterial antibiotics in 100 children reported a 96% cure rate for those with complete excision.[27] A total of 7 patients (14%) had facial nerve weakness, which was permanent in one patient.[27] Another RCT comparing complete excision with curettage in 50 children with advanced disease (defined as fluctuation of the lymph node and discoloration of the skin) showed that patients with complete excision had a mean healing time of 3.6 weeks.[28] In this study 4 patients (16%) had self-limiting facial nerve weakness.[28]

Incision and drainage was the next most common surgical intervention, reported in 24 studies and associated with a pooled cure rate of 34.2% (95% CI; 28.4—40.2%). This intervention was associated with a high recurrence rate (89%),[29,30] fistula formation (28%) and poor cosmetic results.[31]

Curettage, reported in 10 publications, showed a pooled cure rate of 61.2% (95% CI; 52.3—69.5%). In the RCT comparing curettage with complete excision, the mean time to healing was 11.4 weeks and 9 patients (36%) had recurrent swelling 3—4 weeks after the intervention.[28]

Fine-needle aspiration was reported in 6 publications including 32 patients and showed a pooled cure rate of 37.5% (95% CI; 22.4—54.8).

Incomplete excision was reported in 15 patients, from only four publications, with a pooled cure rate of 100% (95% CI; 84.8—100%). In one of these reports persistence of skin sinuses for several months was reported in 4 of 5 cases, despite additional post-operative treatment with anti-mycobacterial antibiotics.[17]

Anti-mycobacterial antibiotics: treatment outcomes and adverse effects

There were 19 publications including 171 children with NTM cervicofacial lymphadenitis treated with anti-mycobacterial antibiotics with a pooled cure rate of 67.8% (95% CI; 60.6—74.5%). In the RCT comparing anti-mycobacterial antibiotics with complete excision, a 66% cure rate was reported in those receiving clarithromycin and rifabutin for at least 12 weeks.[27] A total of 4 patients (8%) had to stop antibiotics as a result of adverse effects and were classified as 'treatment failures'.[27] Another RCT in 50 children, comparing anti-mycobacterial antibiotics with no intervention in patients with advanced disease (defined as fluctuation of the lymph node and discoloration of the skin) showed that patients treated with clarithromycin and rifabutin for 12 weeks had a 100% cure rate with a mean healing time of 36 weeks.[18] In this study none of the patients had to stop antibiotics.[18]

In the remaining studies included, clarithromycin was the most commonly used anti-mycobacterial treatment. Typically clarithromycin was used in combination with rifampicin, rifabutin or ethambutol, and macrolide monotherapy was reported in 10%. Patients received different doses in the various studies (for example clarithromycin dose varying between 15 mg/kg and 30 mg/kg), and in some reports multiple different treatment regimens were used, often without doses being stated.[12,32] Treatment duration also varied widely between different reports (from 1 week to 52 weeks),[12,19] and in some instances even within the same report.[12,32,33] This heterogeneity precluded further analyses comparing different anti-mycobacterial treatment regimens.

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Adverse events were reported on in 116 (67.8%) of patients treated with anti-mycobacterial antibiotics but led to a change in management in only 5 (2.9%) of the patients.[12,15] Almost all adverse events were reported in patients treated with clarithromycin and rifabutin. The most common adverse events reported were reversible tooth discoloration in 29 (25%) patients, followed by fever in 27 (23.2%) and fatigue in 24 (20.7%) patients.[16–19,27] Other, less commonly reported adverse events included abdominal pain, abnormal stools, headache, elevated liver enzymes, neutropenia, allergic rash, vomiting and skin discoloration. None of the adverse events were reported as severe or life-threatening.

Combination of surgery and anti-mycobacterial antibiotics

Of the 1574 patients with surgery, 289 (18%) received anti-mycobacterial antibiotics before surgical intervention and 313 (20%) post-operatively. Macrolide monotherapy was used in 37%, combination therapy (most commonly with rifampicin or ethambutol) in 28% and in 36% the anti-mycobacterial antibiotics used were not specified. The majority of studies only listed the total number of patients additionally treated with anti-mycobacterial antibiotics and did not report further details, including outcome in this group, which precluded further analyses.

Observation without intervention

There were nine studies including 156 children with NTM lymphadenitis who were observed without intervention. Spontaneous resolution occurred in 89.9% (95% CI 84.4–93.9%). The RCT comparing no intervention with anti-mycobacterial antibiotics (see above) reported a 100% cure rate with a mean time to resolution of 40 weeks for those with no intervention.[18] In an observational study from Israel including 92 children without intervention, complete resolution occurred in 71% of the children within 6 months, and in all remaining cases within 9–12 months.[7]

Comparison of cure rates with different treatment modalities

To compare different treatment modalities generalised linear mixed model regressions were used, which included the study number as a random effect. The adjusted mean cure rate was 98% (95% CI 97.0–99.5%) for complete excision, 73.1% (95% CI 49.6–88.3%) for anti-mycobacterial antibiotics, and 70.4% (95% CI 49.6–88.3%) for 'no intervention' (Table 5). When all the treatment modalities were included in the model only complete excision had a significantly higher probability of cure than no intervention (odds ratio 33.3; 95% CI 10.79–102.92; $p < 0.0001$) (Table 5). When the model was reduced to three treatment modalities (complete excision, anti-mycobacterial antibiotics and no intervention) compared with 'no intervention' the odds ratios for cure were 15.4 (95% CI 5.6–42.6; $p < 0.0001$) for complete excision and 1.1 (95% CI 0.4–3.2; $p = 0.9748$) for anti-mycobacterial antibiotics.

Discussion

The current evidence for the optimal management of NTM cervicofacial lymphadenitis is limited, as there are only three RCTs, including a total of 200 patients.[18,27,28] All three RCTs were done in the same centre in the Netherlands, which may limit the generalisability of the results. Ours is the first systematic literature review and meta-analysis of the treatment of NTM cervicofacial lymphadenitis, and includes data from almost 2000 children.

Complete excision was the most frequently reported treatment option. This intervention was associated with the highest cure rates when compared to other treatment options. Other advantages of complete excision include the opportunity to obtain samples for histological analysis and microbiological confirmation, and faster cure compared with prolonged anti-mycobacterial antibiotics or spontaneous resolution. This strategy also reduces the risk of misdiagnosing an alternative aetiology such as tuberculosis, lymphoma and other malignancies. However, the results show that surgery is associated with a substantial risk of

Table 5 Odds ratios for cure and adjusted mean cure rates in function of different treatment modalities compared with 'no intervention' using a generalised linear mixed model for binomial data. The study number was included as a random effect. The p-value is corrected for multiple comparisons using the Dunnett–Hsu adjustment.

Intervention	Odds ratio for cure	95% CI for odds ratio	Adjusted mean cure rates %	95% CI for adjusted mean cure rates	p-value
Complete excision	33.32	10.79–102.92	98.7	97.0–99.5	<0.0001
Incomplete excision[a]	7.43	0.32–170.21	94.6	46.6–99.2	0.66
Curettage	3.04	0.79–11.71	87.9	70.3–96.7	0.41
Incision and drainage	0.26	0.08–0.86	38.3	19.0–62.1	0.13
Fine-needle aspiration	0.21	0.01–0.30	9.8	1.9–38.4	0.01
Other surgery or combination	0.49	0.13–1.87	54.1	27.5–78.5	0.81
Anti-mycobacterial antibiotics	1.14	0.35–3.72	73.2	49.6–88.3	0.99
No intervention (comparator)	–	1.0	70.4	40.4–89.3	–

[a] For incomplete excision, there were no cases with no cure reported in the included studies prohibiting calculation of the odds ratio; therefore one case was artificially set to 'not cured' to allow calculation.

facial nerve damage, which was reported to be permanent in a small proportion of cases. The risk for facial nerve damage in an individual patient depends on the proximity of the involved lymph node to the facial nerve (i.e. highest risk with involvement of preauricular lymph nodes) and the experience and skill of the surgical team. Complete excision is therefore most likely successful in the early stage of disease when the infection has not extended to the surrounding tissue. However, patients frequently present with more advanced stages of disease, which may preclude complete excision.

Importantly, we found that pooled cure rates for different treatment modalities overestimated the effectiveness of incomplete excision, fine-needle aspiration and no intervention. The use of a generalised linear mixed model resulted in more reliable estimates of adjusted mean cure rates. The difference between pooled cure rates and adjusted mean cure rates occurs as a result of confounding factors in individual studies being eliminated by a random effects model in the latter. Incomplete excision for example was somewhat surprisingly associated with high pooled cure rates. However, this finding is based on few cases, and despite the high odds ratio for cure, statistically this intervention was not significantly better than no intervention. All other surgical treatment modalities, including incision and drainage, curettage and fine-needle aspiration, were associated with considerably lower cure rates. In particular, fine-needle aspiration was associated with a statistically significantly lower cure rate compared with no intervention, suggesting that this intervention should be avoided. Moreover, all three interventions were associated with a significant risk of fistula formation.

In the studies that investigated anti-mycobacterial antibiotics without surgery, the cure rate was significantly lower than with complete surgical excision, and statistically not better than no intervention. However, the true effectiveness of this treatment modality may be underestimated as a result of the considerable heterogeneity regarding anti-mycobacterial antibiotic combinations and treatment durations between different studies (and in many instances within the same study). Only two studies were prospective and included more than 10 patients receiving the same anti-mycobacterial treatment (clarithromycin and rifabutin).

This drug combination was generally well tolerated with predominately minor adverse effects, including transient tooth discoloration. Although the safety of short-term use of clarithromycin is supported by numerous studies, safety data regarding long-term use are lacking.[34] Similarly, only very limited safety data exist with regard to the use of rifabutin in the paediatric setting, primarily because rifabutin is rarely used for infections other than NTM disease. Data from comparatively large adult trials and post-marketing surveillance suggest that fewer than 5% of patients treated with rifabutin experience adverse events, the majority of which are minor (mainly gastrointestinal symptoms); moderate to severe side effects, including uveitis (which affects fewer than 0.01% of patients) and neutropenia, are relatively rare.[35]

The choice of anti-mycobacterial treatment is mainly based on experience in treating NTM infection in immunocompromised, predominately adult patients and on *in vitro* data. Most NTM species are resistant *in vitro* to first-line drugs used for treatment of *Mycobacterium tuberculosis*, including isoniazid and pyrazinamide.[8,11,36] Unfortunately, with the exception of macrolides,[37] *in vitro* susceptibility test results do not correlate well with the *in vivo* response, especially in *M. avium* infection.[38] Notably, successful treatment with anti-mycobacterial antibiotics has been reported in several patients despite *in vitro* resistance to the drugs they were receiving.[18]

The benefit of pre- or post-operative administration of anti-mycobacterial antibiotics in conjunction with surgical excision remains uncertain. Among the cases included in this review, approximately one fifth of the patients received anti-mycobacterial antibiotics in addition to surgery. However, in the majority of studies, treatment outcome for those treated with surgery alone and those who additionally received anti-mycobacterial treatment was not reported separately, and therefore the influence of additional anti-mycobacterial antibiotics cannot be quantified.

The smallest proportion of reports included in this review described children with no intervention, a high proportion of which had a favourable outcome with spontaneous resolution of disease within 6–12 months. In comparison to treatment with anti-mycobacterial antibiotics there was no statistically significant difference with regards to cure rate. However, in the two largest studies of children observed without intervention, approximately one third of the cases had NTM lymphadenitis causes by *M. haemophilum*, which is thought to have lower pathogenicity than *M. avium*.[7,18] Notably, it has previously been highlighted that in many of those studies, fine-needle aspiration was done to confirm the diagnosis, and that this intervention may have aided the healing process.[22] However, data from this meta-analysis suggest that fine-needle aspiration by itself is associated with very low cure rates.

Finally, it has to be considered that the proportion of children with NTM lymphadenitis who never seek medical attention is unknown. In a Swedish study of asymptomatic children, 30% reacted to *M. avium* sensitin skin testing, suggesting that a substantial proportion of NTM infections are asymptomatic and consequently may never present to healthcare services.[39] This appears particularly likely if the lymph node enlargement is not severe enough to be disturbing or if the infection is resolving spontaneously. The potential for spontaneous resolution of NTM cervicofacial lymphadenitis may therefore be underestimated, and in clinical practice physicians and surgeons may primarily be dealing with children at the severe end of the spectrum of NTM lymphadenitis.

The main limitation of this meta-analysis lies in the significant heterogeneity of the studies included in the analyses, particularly in the studies investigating anti-mycobacterial antibiotics. In addition, the fact that in the majority of publications treatment assignment was not randomised results in an inherent risk of selection bias. Furthermore, several studies also included a proportion of children without culture- or PCR confirmation, and did not report outcomes separately according to culture/PCR results.

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In summary, the current evidence to guide the optimal treatment of NTM lymphadenitis is limited. Current evidence suggests that complete excision is the best treatment option for NTM cervicofacial lymphadenitis; however, this treatment modality also has the highest risk of adverse events, including facial palsy. Large, well-designed RCTs directly comparing the three main treatment modalities — complete excision, anti-mycobacterial antibiotics and no intervention — are lacking. Furthermore, better diagnostic tests for NTM are needed to enable studies without the need for a surgical intervention to obtain specimens. Until further evidence is available, treatment options should be carefully considered on an individual patient basis weighing potential risks against benefits. Factors that have to be taken into account include the certainty of the diagnosis, the location and extent of the disease, the experience and skill of the surgical team and the patient's/parent's attitude to the final physical appearance and time to resolution.

Conflict of interest

None declared.

The following references can be found in the supplementary data associated with this paper

40—78.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jinf.2015.02.010.

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