Long-term outcome of nonsurgical treatment of nontuberculous mycobacterial cervicofacial lymphadenitis in children

Jerome A. Lindeboom, MD, DDS, PhD

Objective. Chronic cervicofacial lymphadenitis in children is often caused by nontuberculous mycobacteria (NTM). Children with NTM infection who were not surgically treated were evaluated for long-term outcome with a follow-up of at least 10 years.
Results. Among the 117 nonsurgically treated children, the median age was 46 months (range, 9-155 months), 56 were male (47.9%), and 61 were female (52.1%). Of the overall group, 75 received antibiotic therapy consisting of clarithromycin and rifabutin (64.1%), and for 54, observation (a wait-and-see approach) was chosen (46.2%). In 100 patients, treatment was considered successful (85%), with a median resolution of 24 (range, 11-134) weeks in the antibiotic group compared to 44.5 (range, 18-130) weeks in the wait-and-see group ($P < .05$). After 6 months, 58 patients in the antibiotic group were successfully treated (77%), whereas 42 patients of the wait-and-see group demonstrated complete resolution after a median observation time of 44.5 weeks (100%).
In 10 patients who experienced complete resolution of the lymphadenitis, infection recurrence developed years later (10%).
Conclusion. Nonsurgical treatment of NTM infection can be considered an alternative in advanced and surgically challenging cases. However, healing will take months to years, and late recurrences are possible. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:195−201)

Nontuberculous mycobacterial (NTM) cervicofacial lymphadenitis is mainly seen in young otherwise healthy children between 1 and 5 years of age.[1-4] The plausible explanation is that children in this age group are more likely to ingest NTM organisms through the oral exploration of objects that have been exposed to colonized soil or water.[5] These microbes enter the body through lesions of the oral mucosa (e.g., eruption of teeth) and use dendritic cells as a carrier to the next lymph node station.[1] The disease most commonly presents as a persistent unilateral cervicofacial lymphadenopathy. As it progresses, the lymph node enlarges toward fluctuation with erythema and evolving into a violaceous discoloration.[2-4]

The infected lymph node will eventually rupture and drain to a cutaneous fistula, which can lead to a significant disfiguration of the skin.[6] In some cases, an open wound even may develop.[2-4] Surgical excision is considered the optimal treatment for NTM cervicofacial infections in children,[4,7-10] but management of advanced stage NTM lymphadenitis can be challenging. Adherence of infected tissue or lymph nodes to vital structures such as the branches of the facial nerve makes surgery difficult, and the location of the infection can lead to unwanted facial scars.[11-13] Nonsurgical alternatives include antibiotic treatment with clarithromycin and rifabutin or a wait-and-see approach with observation only.[4,14-17] Both antibiotic therapy and wait-and-see have the advantages of avoiding surgery and related complications such as wound infection and facial nerve damage.[18] Antibiotic therapy has been used with variable success for other forms of NTM infection, such as pulmonary *Mycobacterium avium* infection.[19,20] Optimal duration for antibiotic therapy remains undetermined, however, and 3 to 6 months of therapy usually is needed for resolution of the disease.[4,17] In an earlier study, we found that surgical excision of the infected lymph nodes was more effective than antibiotic treatment, with a cure rate of 96% with surgery vs 66% with antibiotics.[4] Studies of the wait-and-see approach for the treatment of NTM lymphadenitis have shown total resolution within 6 months in 71% of patients and within 9 to 12 months among the remainder.[15,16] In children with advanced stage NTM cervicofacial lymphadenitis, no significant differences have been reported in median healing time between wait-and-see and therapy with clarithromycin and rifabutin.[21]

Since 2000, the CHIMED trial[4] (surgery vs medical treatment) has focused on the diagnostics and optimal treatment of NTM cervicofacial lymphadenitis in children. In the present study, we evaluated the long-term outcomes of children with a diagnosis of NTM cervicofacial lymphadenitis confirmed by culture or

Statement of Clinical Relevance

Nontuberculous mycobacterial cervicofacial lymphadenitis in children is primarily treated with surgical excision of affected lymph nodes. Nonsurgical treatment is an option, but a long healing time to complete resolution is to be expected, with possible late recurrences.

Associate Professor, Department of Oral and Maxillofacial Surgery, Amsterdam University Medical Center and Amstelland Hospital, University of Amsterdam, Amsterdam, the Netherlands.
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polymerase chain reaction (PCR) who received a non-surgical treatment.

MATERIALS AND METHODS

Patients

The CHIMED study was a randomized, prospective, multicenter, multidisciplinary trial conducted from 2000 to 2006 on the optimal treatment of NTM cervicofacial lymphadenitis in children. Patients (aged 0-15 years) with a possible NTM lymphadenitis were referred by pediatricians, otolaryngologists, oral and maxillofacial surgeons, and general practitioners from various locations in The Netherlands. Inclusion criteria were enlarged cervicofacial lymphadenitis for >3 weeks and negative serologic test results for other infectious causes of chronic lymphadenitis (cytomegalovirus, Epstein-Barr virus, adenovirus, *Bartonella* species, and toxoplasmosis). Immunocompromised patients and patients using immunosuppressive drugs were excluded.

After the study period ended, our institute still served as a referral center, and for this study, children screened during 2007 to 2010 were added. The Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam (Amsterdam, The Netherlands) approved the study, and parents gave written consent before study enrollment. The Declaration of Helsinki guidelines were followed.

In children with a persistent cervicofacial lymphadenitis, fine-needle aspiration specimens were taken from affected lymph nodes to establish the diagnosis of NTM infection. Mycobacterial infection was diagnosed as described elsewhere.[4,22,23]

Patients' specimens were sent by courier to a central laboratory (Department of Medical Microbiology, Leiden University Medical Center, Leiden, The Netherlands) for microscopic evaluation, real-time PCR, and culture. Results of microscopic evaluation and real-time PCR were available within 48 h after arrival of the patient's specimen at the laboratory.

Samples were tested for contamination with rapidly growing bacteria by culturing on standard brain heart infusion agar. When contamination was found, the aspirates or biopsy specimens were decontaminated with an NaCl-NaOH decontamination protocol. Auramine staining was performed on directly obtained materials or on decontaminated materials for the detection of acid-fast rods. When auramine-positive rods were detected, Ziehl-Neelsen staining was performed to confirm the presence of acid-fast rods. Culturing was done at 35°C by using Bactec bottles with liquid mycobacteria growth indicator tubes (Becton Dickinson Microbiology Systems, Vianen, The Netherlands) medium and on solid Löwenstein-Jensen medium. Positive culture results for acid-fast bacteria were further investigated by using the INNO-LiPA assay (Innogenetics, Ghent, Belgium), a reverse hybridization assay in which the mycobacterial species is identified. When no growth was detected after 12 weeks of incubation, the culture results were listed as negative. Samples were also investigated for the presence of other bacterial pathogens by conventional bacterial culturing and by PCR for *Bartonella henselae*.

Mycobacterium haemophilum–specific culturing was performed at a temperature of 30°C on Löwenstein-Jensen medium, with added iron citrate, and in mycobacteria growth indicator tube medium with X-factor strip added. Mycobacterial species were identified using the INNO-LiPA assay (Innogenetics) and the INNO-LiPA V2 assay (Innogenetics). Susceptibility testing to clarithromycin and rifabutin was performed using a standard agar dilution method at the National Mycobacterial Reference Laboratory of the Rijksinstituut voor Volksgezondheid en Milieu (Bilthoven, The Netherlands). In addition, real-time PCR was performed for detection of the genus *Mycobacterium* and the species *M. tuberculosis, M. haemophilum*, and *M. avium*. NTM lymphadenitis was diagnosed if the species-specific PCR result or the mycobacterial culture result was positive for NTM.

Outcomes

The primary end point for successful treatment was cured lymphadenitis, defined as regression of lymph node enlargement by at least 75% compared to the size of the lymph node at the first clinical and ultrasound assessment, with resolved fistula and total skin closure and no local recurrence or de novo lesions after 6 months, as assessed by clinical and ultrasound evaluation.[4,21,24] Recurrence was defined as the reappearance of NTM lymphadenitis following the initial resolution of the disease. Follow-up was performed annually by telephone or email contact or a visit to the clinic. In case of a potential possible recurrence, the lymphadenitis/reinfection was assessed based on clinical observations and ultrasound examination.

Statistical analysis

Dedicated software was used for statistical analysis (IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY). All continuous variables are presented as means ± SD. Unpaired *t*-test was used for analysis of continuous variables, and chi-square test was used for the categorical variables. $P < .05$ was considered the threshold for statistical significance.

RESULTS

Patients

During the study period, 430 children with a suspected NTM infection were seen. Two children had an axillary NTM infection, and one child was diagnosed with an inguinal NTM lymphadenitis infection. A total of 427

patients with chronic cervicofacial lymphadenopathy thus were evaluated. Mycobacterial infection was diagnosed in 290 (3 cases involving *M. tuberculosis*, 1 case of *M. bovis*, and 286 involving NTM), *Bartonella henselae* infection[25] in 53, streptococcal infection in 14, staphylococcal infection in 11, and toxoplasmosis in 3. Eighteen children had persistent lymph node swelling from other causes (8 with a malignancy and 10 with a congenital cyst). In 38 children, no causative agent was identified, but for 22 in this group, the clinical presentation was consistent with NTM infection although no NTM species could be cultured or confirmed by PCR.

From the group of 286 confirmed NTM cervicofacial infections, 117 children were treated with antibiotics or a wait-and-see approach, and 169 children were surgically treated. Of the evaluated nonsurgical group, all children were healthy, without underlying disease. Their median age was 46 (range, 9-155) months, 56 were male (47.9%), and 61 were female (52.1%). Patients reported in this study are patients form 2 earlier randomized trials to which further patients were added.[4,21] Table I shows the baseline characteristics of the patients by group.

Submandibular lymphadenitis was seen in 88 patients (75%), and preauricular nodes were infected in 16 patients (13%). Most of the infections were caused by *M. avium* (94 patients; 80%) and *M. haemophilum* (18 patients; 15%). In the earlier study,[4] a patient with a nontypeable NTM species was randomized to the antibiotic group. Later this species was classified as *Mycobacterium mantenii*.[26]

Antibiotic therapy, consisting of clarithromycin and rifabutin, was administered in 75 children (64.1%), and a wait-and-see approach (conservative treatment) was used for 42 children (35.9%). All children in the antibiotic group completed a 12-week course except for 2 who had to cease the therapy because of severe side effects.[4] One of these children developed jaundice, and the other had an allergic reaction that manifested as a generalized rash. In 100 patients, treatment was considered successful (85%), with a median time to resolution of 24 weeks (range, 11-134 weeks; interquartile range = 23-31.5 weeks) in the antibiotic group compared to 44.5 weeks (range, 18-130 weeks; interquartile range = 33-58 weeks) in the wait-and-see group ($P < .05$).

Long-term outcomes

Of the patients in the antibiotic group, 58 were successfully treated (77%), because 17 patients were considered failures at the 6-month primary end point.[4] In the patients who were not successfully treated with antibiotics, surgical treatment was performed. In none of these patients was recurrence observed after 10 years of follow-up.

In 2 patients from the successfully treated antibiotic group, reactivation/recurrence of the infection was noted with redness of the area or a draining fistula during follow-up after the initial healing. In the conservatively treated wait-and-see group, reactivation/recurrences of the infection were observed in 8 patients who were considered cured after the wait-and-see period. Recurrence of the NTM infection occurred in the first year after the

Table I. Baseline clinical and microbiologic characteristics of nonsurgically treated NTM cervicofacial lymphadenitis

Characteristic		*Antibiotic group (n = 75)*	*Wait-and-see group (n = 42)*
Male, *n*		32	24
Female, *n*		43	18
Median age, months (range)		38 (9-148)	33 (11-155)
Location of NTM lymphadenitis			
Submandibular, *n* (%)	Right	26 (35)	20 (47)
	Left	27 (36)	15 (36)
Preauricular, *n* (%)	Right	3 (4)	2 (5)
	Left	9 (12)	2 (5)
Submental, *n* (%)		2 (3)	0 (0)
Multiple locations, *n* (%)		8 (10)	3 (7)
Mycobacterium species			
M. avium, n (%)		52 (70)	33 (79)
M. haemophilum, n (%)		18 (24)	8 (19)
M. mantenii, n (%)		1 (1)	0 (0)
M. kansasii, n (%)		1 (1)	0 (0)
M. scrofulaceum, n (%)		1 (1)	0 (0)
M. fortuitum, n (%)		1 (1)	0 (0)
M. chelonae, n (%)		1 (1)	0 (0)
M. xenopi, n (%)		0 (0)	1 (2)
Positive cultures, *n* (%)		51 (68)	30 (71)
Susceptibility to clarithromycin, %		88	90
Susceptibility to rifabutin, %		90	92

NTM, nontuberculous mycobacteria.

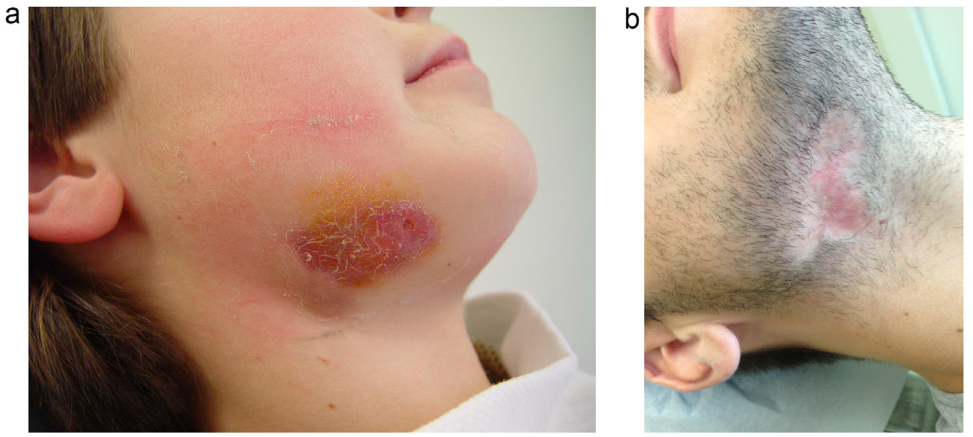

Fig. 1. **(A)** A patient treated with antibiotics at the start of therapy. **(B)** The same patient 10 years after treatment.

established healing in 3 of these patients, in the second year in 4 of them, in the third year in 2, and in the fourth year in 1 patient.

In 2 of these 10 children (1 child from the antibiotic group and 1 from the wait-and-see group), surgical excision was performed, whereas no intervention was used for the other 8. In another 6 months after the recurrence of the lymphadenitis, the disease process had resolved in all remaining cases, although 1 patient (from the original wait-and-see group) experienced another recurrence 2 years after resolution of the first recurrence of the lymphadenitis. This was finally treated surgically. Figure 1 shows a patient treated with antibiotics at the start of the therapy and 10 years later. Figure 2 shows a patient treated with the wait-and-see approach at the start of the therapy and 10 years later.

DISCUSSION

In the present study, we assessed the long-term outcomes for nonsurgically treated children with NTM cervicofacial lymphadenitis. Unfortunately, information on the long-term treatment outcome following NTM lymphadenitis is quite limited,[27] and this report offers much-needed information about recurrence and reinfection rates in this patient group after a follow-up of at least 10 years.

Surgical excision of the affected lymph nodes has been regarded as the treatment of choice for NTM cervicofacial lymphadenitis[4,7,28] and is associated with a high rate of resolution and a 2% recurrence rate.[4] In addition to wound infection, complications after surgery can include facial nerve dysfunction,[4,6,7,12,13,28] which can result from the proximity of the infected lymph nodes to the branches of the facial nerve. In advanced NTM lymphadenitis, lymph nodes are adhered to surrounding structures, which makes dissection difficult, with more risks for the branches of the facial nerve. The most serious complication in surgical excision is postoperative marginal mandibular weakness. In an earlier study, we found a temporary marginal mandibular nerve weakness in 12% of the cases, with a persistent grade 1 facial nerve weakness in 1 patient (2%).[4] Gonzales et al. found that 23% of their patients had postoperative marginal mandibular nerve weakness in cases involving surgical excision alone and 33% had weakness after high-risk lesions were treated with antibiotics and surgical excision.[6] Of their cohort, 4% of patients had a persistent mild marginal mandibular nerve weakness. Mahadevan et al. reported

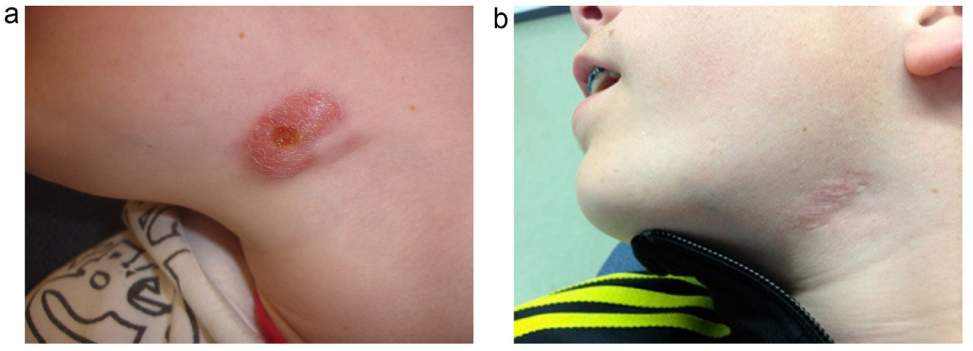

Fig. 2. **(A)** A patient treated with the wait-and-see approach at the start of therapy. **(B)** The same patient 10 years later.

a marginal mandibular nerve palsy in 7.2% of their patients, all related to surgery involving submandibular infected lymph nodes.[12]

Surgical curettage is considered an alternative if excision of the necrotic lymph nodes is difficult or implies major risk for facial nerve branches; however, it leads to prolonged healing times and persistent disease requiring further surgery.[9,24] Wound infection risk after surgery can be decreased with the prophylactic administration of amoxicillin/clavulanic acid because postoperative wound infections are usually caused by gram-positive *Staphylococcus* or *Streptococcus* species.[4]

Recurrent NTM lymphadenitis might be observed several years after initial resolution of the disease.[27] In 10 successfully treated patients in the present study (10%), a recurrence was seen at follow-up after the cervicofacial lymphadenitis was cured. Two patients had been treated with antibiotics (2%), and 8 patients were considered cured with a conservative wait-and-see approach (8%). Two of the 10 patients with recurrence were surgically treated and a wait-and-see approach was adopted successfully for the remainder. However, 1 in the latter group experienced a recurrence 2 years later that was ultimately treated surgically. Reuss et al. reported a recurrence rate of 7% (4 children out of 68) in their cohort, between 6 months and 5 years after completion of the initial course of the disease.[27]

In the head and neck region, submandibular lymph nodes are most frequently affected. The nodes tend to be solitary, and the overlying skin may be erythematous. In the present study, the submandibular nodes were affected in 75% of patients. This frequency is in accordance with results of a survey of the members of the American Society of Pediatric Otolaryngology and Infectious Disease Society of America Emerging Infectious Network, identifying 277 cases of NTM lymphadenitis, with most being cervical lymph nodes (84%).[5] Recently, Neven et al. found that 68% of affected lymph nodes were located in the submandibular area, near the angle of the jaw.[10] Gonzales et al. defined the extent of NTM cervicofacial lymphadenitis by the location of the infection in the head and neck, and lesions in close proximity to the branches of the facial nerve were considered complex or difficult to treat.[6] As such, most of the NTM cervicofacial lymph node infections can be considered complex because all of the submandibular and preauricular locations are close to the facial nerve branches. Even more important is the extent and stage of infection because advanced NTM cervicofacial lymphadenitis with abscess formation, skin discoloration, and adherence to surrounding structures is more challenging from a surgical point of view.

Mycobacterium avium was the most commonly isolated mycobacterial species in the present study, detected in 85 cases of NTM cervicofacial lymphadenitis (73%). This frequency is in accordance with other studies.[6,19]

Is there a place for antibiotics in the treatment of NTM cervicofacial lymphadenitis? The basis of antibiotic treatment for NTM infections is macrolides, which show the best correlation between in vitro susceptibility results and clinical in vivo response.[19] Usually, a combination of a macrolide (clarithromycin, azithromycin) and an antimycobacterial drug (rifabutin or rifampin) and ethambutol is used. Macrolides are active against many NTM species, but a regime of monotherapy with macrolides[14] risks drug resistance and consequent treatment failure.[29] Combination treatment consist of clarithromycin 7.5 mg/kg twice a day and rifabutin 5 mg/kg once a day. It is possible to include ethambutol as a third agent, but ocular toxicity is a major side effect and is more complicated to evaluate in small children.[4,20] In a randomized study comparing clarithromycin and rifabutin antibiotic therapy with surgical excision by our research group, 34% of the patients experienced failure of antibiotic therapy,[4] and in another randomized study comparing clarithromycin and rifabutin antibiotic treatment with a wait-and-see policy, no difference was found in time to resolution of NTM cervicofacial lymphadenitis.[21] The median time to resolution of the NTM cervicofacial lymphadenitis for the antibiotic group was 36 weeks compared to 40 weeks for the wait-and-see group.

In the present study, all children treated with nonsurgical therapy were analyzed (Table II). In the 17 patients for whom antibiotic treatment was not successful, surgical treatment was performed. The percentage of patients successfully treated with antibiotics was significantly lower than that in the group treated conservatively. This result is in contrast with our earlier finding comparing antibiotics with a wait-and-see approach for NTM lymphadenitis. This can be explained by the fact that in that earlier study,[4] the primary end point was defined as cure at 6 months after the start of antibiotic therapy, whereas in the 2011 study comparing antibiotic treatment versus a wait-and-see approach the primary end point was cured NTM lymphadenitis, defined as regression of lymph node enlargement by at least 75%, with cured fistula and total skin closure and no local recurrence or de novo lesions, as assessed by clinical and ultrasound evaluation without a specific time span.[21] The successfully treated patients from the 2007 study were also included in the current analysis, explaining the shorter healing time compared to the 2011 study, which defined no time restriction for successful cure. Keeping in mind that it might take longer for NTM lymphadenitis to resolve, this factor signifies that the percentage for successful antibiotic therapy alone could be higher were there more time to heal.

Table II. Outcomes for nonsurgically treated children with NTM cervicofacial lymphadenitis

Outcomes	*No. (%) of patients treated with antibiotics**	*No. (%) of patients treated with a wait-and-see approach*
Successful treatment (median resolution; range in weeks)	75 (64.1) (24, 11-134)	42 (35.9) (44.5, 18-130)
Failures	17 (22.7)	0 (0)
Long-term recurrences after initial successful treatment	2 (2)†	8 (8)

NTM, nontuberculous mycobacteria.
*Antibiotics: Clarithromycin and rifabutin.
†Long-term recurrence after antibiotic therapy only.

Some researchers have advocated a strategy of non-intervention, the so-called wait-and-see approach.[15,16] An argument against antibiotic use in NTM cervicofacial lymphadenitis is that resolution of the disease during the period of the antibiotic regimen may really represent the natural course of the disease. Zeharia et al. found resolution of the disease in 6 to 9 months in 71% of patients in their study using the wait-and-see approach.[16] In contrast, however, Naselli et al. never observed spontaneous reduction of NTM cervicofacial lymphadenitis.[28]

After a randomized trial established no significant difference in median healing times between a wait-and-see approach and antibiotic therapy in this population,[21] we concluded that no additional benefit from antibiotics was to be expected, and we stopped treating children with antibiotics. In addition, side effects of this treatment, such as fever, fatigue, and abdominal pain, were common. Given that and the difficulty of maintaining antibiotic administration for a prolonged period (up to 6 months) in young children, we decided to abandon antibiotic treatment for NTM cervicofacial lymphadenitis.

In the earlier study, in vitro susceptibility of the NTM species was 94% to clarithromycin and 96% to rifabutin.[4] In the present study, the in vitro susceptibility of the NTM species was also high, at 89% to clarithromycin and 91% to rifabutin. However, the in vitro susceptibility unfortunately does not reflect clinical effectiveness, calling the value of antibiotic therapy into question. This paradox is difficult to comprehend, but an explanation might be that most children are seen in the advanced stages with abscess formation and extensive skin involvement because of the delay in diagnosis.[4,6,8,21] Once central necrosis of the lymph nodes occurs, with progressing liquefaction and subsequent abscess formation, antibiotics will not reverse the process. The next step will be violaceous discoloration of the skin, which becomes notably thinner or parchment-like with a shiny appearance, and, in the end stage, a draining fistula to the skin. Antibiotics in these situations will not reverse the central necrosis in the affected lymph nodes. In surgically treated patients whom antibiotic therapy did not cure, multiple affected lymph nodes with central necrosis can still be encountered.

Can a wait-and-see strategy be justified? NTM cervicofacial lymphadenitis is a benign condition, and in immunocompetent children cases will ultimately resolve. Complete healing could, however, take months or years, often leaving extensive scarring. In cases with high risk for surgical complications, such as facial nerve palsy, this strategy is justifiable. Sometimes the clinical situation is unfavorable and immediate surgery should be delayed. A wait-and-see approach might be useful to diminish the disease to a less extensive area, and if it does not heal or it recurs, a surgical excision is easier to perform.

It might be difficult to convince parents and clinicians to opt for a wait-and-see approach. Amir stated that the main factors ensuring success are parental tolerance for a prolonged healing process, cosmetic outcome, complications, and costs.[30] Parents should be informed regarding the persistent drainage and long-lasting disease process in children treated with a wait-and-see approach.[11]

CONCLUSION

Excisional surgery should be considered the first-line treatment in the absence of risk for facial nerve injury. In earlier cases without abscess information, surgery is easier, and with the use of nerve stimulation, damage to the nerve can be avoided. In addition, the choice of incision in a skin crease leads to a better esthetic outcome. For extensive advanced submandibular lesions with obvious risks for facial nerve damage, initially adopting a more conservative approach is reasonable. A conservative wait-and-see nonsurgical approach as such is a good alternative for surgical excision in selected cases in the treatment of NTM cervicofacial lymphadenitis. However, recurrence is possible years after the initial resolution, although with a low incidence.

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Reprint requests:

Jerome A.H. Lindeboom, MD, DDS, PhD, Associate Professor
Department of Oral and Maxillofacial Surgery
Amsterdam University Medical Center and Amstelland Hospital
University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam
the Netherlands
J.a.lindeboom@amc.uva.nl