MAJOR ARTICLE

Surgical Excision versus Antibiotic Treatment for Nontuberculous Mycobacterial Cervicofacial Lymphadenitis in Children: A Multicenter, Randomized, Controlled Trial

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(See the editorial commentary by Nicol and Wilkinson on pages 1065–6)

Background. The optimal treatment of nontuberculosis mycobacterial cervical lymphadenitis in children has not been established. Until recently, surgical excision was the standard treatment, but the number of reports of successful antibiotic treatment is increasing, which questions whether surgery is the preferred treatment. In this randomized, multicenter trial, we compared surgical excision with antibiotic treatment.

Methods. One hundred children with microbiologically proven nontuberculous mycobacterial cervicofacial lymphadenitis were randomly assigned to undergo surgical excision of the involved lymph nodes or to receive antibiotic therapy with clarithromycin and rifabutin for at least 12 weeks. The primary end point was cure, defined as regression of the lymph node enlargement by at least 75%, with cure of the fistula and total skin closure without local recurrence or de novo lesions after 6 months, as assessed by clinical and ultrasound evaluation. Secondary end points included complications of surgery and adverse effects of antibiotic therapy.

Results. Intention-to-treat analysis revealed that surgical excision was more effective than antibiotic therapy (cure rates, 96% and 66%, respectively; 95% confidence interval for the difference, 16%–44%). Treatment failures were explained neither by noncompliance nor by baseline or acquired in vitro resistance to clarithromycin or rifabutin. Surgical complications were seen in 14 (28%) of 50 patients; staphylococcal wound infection occurred in 6 patients, and a permanent grade 2 facial marginal branch dysfunction occurred in 1 patient. The vast majority of patients who were allocated to antibiotic therapy reported adverse effects (39 [78%] of 50 patients), including 4 patients who had to discontinue treatment.

Conclusions. Surgical excision is more effective than antibiotic treatment for children with nontuberculous mycobacterial cervicofacial lymphadenitis.

Nontuberculous mycobacteria (NTM) are a common cause of chronic cervicofacial lymphadenitis in children, especially those aged 1–5 years [1]. The disease is usually unilateral, occurring in the submandibular or preauricular area. The lymph nodes suppurate and form a chronic sinus tract. Surgical excision of the infected lymph nodes is considered the treatment of choice, and cure rates in retrospective studies varied from 81% to 95% [2–7]. Risk of facial paralysis and excessive scarring, however, are drawbacks of surgical therapy.

The antimycobacterial agents clarithromycin and rifabutin have demonstrated considerable efficacy in the treatment of infection due to NTM in immunocompromised patients [8, 9]. Case reports suggest that these agents may also be effective for treating NTM cervicofacial lymphadenitis in children [10–15]. The advantage of antibiotic therapy over surgical treatment would be the avoidance of hospitalization and peri- and post-

Received 16 September 2006; accepted 5 December 2006; electronically published 2 March 2007.

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Clinical Infectious Diseases 2007; 44:1057–64

1058-4838/2007/4408-0007$15.00
DOI: 10.1086/512675

operative morbidity and the possible prevention of the development of scars.

No study has compared surgical excision with antibiotic therapy. We, therefore, performed a randomized, multicenter clinical trial to compare the effectiveness of surgical excision of the involved lymph nodes with that of antibiotic therapy with clarithromycin and rifabutin among children with NTM cervicofacial lymphadenitis. We hypothesized that antibiotic treatment was not inferior to surgical excision of the affected lymph nodes.

METHODS

The study was conducted during the period September 2001–December 2004. All parents gave their written consent before study enrollment, and institutional review boards at each study center approved the study design.

Patients. Children (age, 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). Excluded were immunocompromised patients and patients using immunosuppressive drugs.

Fine-needle aspirate specimens were taken from affected lymph nodes. 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 specimens at the laboratory. Standard mycobacterial culturing was performed at a temperature of 35°C in liquid mycobacteria growth indicator tube medium and on solid Löwenstein-Jensen medium. *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 and the Inno-Lipa V2 assays (InnoGenetics) [16, 17]. Susceptibility testing to clarithromycin and rifabutin was performed using a standardized agar-dilution method at the National Mycobacterial Reference Laboratory of the Rijksinstituut voor Volkgezononeid en Milieu (Bilthoven, The Netherlands). In addition, real-time PCR was performed for detection of the genus *Mycobacterium* and the species *Mycobacterium tuberculosis, M. haemophilum,* and *Mycobacterium avium* [18, 19]. Samples were also investigated by conventional bacterial cultures for the presence of other bacterial pathogens and by PCR for *Bartonella henselae* [18]. NTM lymphadenitis was diagnosed if the species-specific PCR result or the mycobacterial culture result was positive for NTM. Only children with a proven NTM infection were randomized.

Study procedures. Before randomization, a head and neck ultrasound was performed to assess the number, size, and aspect of the involved lymph nodes. The randomization and allocation of subjects to the surgical excision arm or the antibiotic therapy arm was done centrally at the coordinating center, using a balanced coin method to ensure an equal number of subjects in each therapy arm. Study personnel could not influence the treatment allocation.

Surgery was performed for patients under general anesthesia by an oral and maxillofacial surgeon (J.L.), using a modified neck dissection technique. Before surgery, 1 dose of flucloxacillin (50 mg/kg) was administered intravenously. In cases where skin was involved, excision of a skin island was combined with extirpation of all diseased lymph nodes. At the end of the surgical procedure, 2 mL of bupivacaine 0.25% was injected into the wound, and the wound was closed with resorbable sutures.

Patients allocated to the antibiotic therapy arm received oral suspensions of clarithromycin (15 mg/kg in 2 divided doses) and rifabutin (5 mg/kg once daily) for 12 weeks.

Follow-up. Patients were scheduled for follow-up visits at 2, 4, 6, 12, and 24 weeks after the initiation of therapy. Adverse effects of the medication, such as fever, fatigue, gastrointestinal complaints, and allergic reactions were scored. A follow-up ultrasound was performed by an independent radiologist 12 and 24 weeks after the initiation of therapy.

After surgery, patients were evaluated for wound healing and surgical complications, which were classified into 3 groups: facial nerve palsy or weakness, postoperative infection, and postoperative hematoma. Facial nerve complications were classified according to the House-Brackmann system [19, 20]. A physician not involved in the study assessed the healing of the surgical wound, fistula closure, and regression of lymphadenitis.

Among the patients who were randomized to receive antibiotic treatment, compliance with antibiotic therapy was assessed through parent questioning. Plasma rifabutin concentrations were determined at week 2, and if necessary, determination was repeated. The desired target concentration was 0.05–0.15 mg/L. The dose of rifabutin was adjusted for patients in whom plasma levels deviated from the target levels. Antibiotic therapy was continued if, at week 12, the ultrasound of the affected lymph nodes revealed regression of lymph node enlargement but in the continuing presence of a draining fistula. Among these patients, the ultrasound was repeated monthly until week 24. Surgical therapy was undertaken if the patient was considered to have experienced treatment failure after 6 months of antibiotic therapy.

Outcomes. The primary end point was cure, defined as

regression of the lymph node enlargement by at least 75%, with cure of the fistula and total skin closure without local recurrence or de novo lesions after 6 months, as assessed by clinical and ultrasound evaluation. Intolerance to the study drugs, no improvement at the 3-month evaluation, and evidence of a draining fistula with a hypoechoic lymph node at the 6-month ultrasound assessment were considered to indicate treatment failure. Secondary outcome measures were surgical complications and adverse effects caused by the medication.

Statistical analysis. Assuming that the true success rate of the therapies was equivalent at 90%, we estimated that at least 49 subjects were needed in each group to have a power of 80% to exclude the possibility that the success rate of antibiotic treatment was at least 15% less than that of surgery (noninferiority of antibiotic treatment; 1-sided P value of $<.05$). We did not anticipate loss to follow-up.

Differences between primary and secondary efficacy rates or event rates between the 2 treatments were determined using Fisher's exact test. All outcomes were analyzed on an intention-to-treat basis.

RESULTS

Patients and causative mycobacteria. Two hundred ten children with chronic cervicofacial lymphadenitis were assessed. After screening, 135 children received a diagnosis of NTM infection. One hundred patients were included in the study (figure 1). The reason for exclusion of the other 35 patients was refusal by either the referring physician or the parents to randomize treatment.

Fifty children underwent surgical excision of the involved lymph nodes, and 50 children were randomized to receive antibiotic therapy. Table 1 shows the baseline characteristics of the patients. The median age of the children was 45.5 months (range, 9–168 months). There were no marked differences between the treatment groups with respect to mean duration of lymph node swelling before presentation, location of lymph node swelling, and the size or stage of the lymph node swelling. Most of the children (82%) were seen during the stage of lymph node fluctuation with discoloration of the skin (figure 2, *top*), and 18% were seen during an early stage, before skin changes or lymph node fluctuation.

Diagnosis was made by both PCR and culture ($n = 54$), by PCR alone ($n = 32$), or by culture alone ($n = 14$). The most common *Mycobacterium* species were *M. avium* (in 71 patients) and *M. haemophilum* (in 22 patients) (table 1). The susceptibility of the NTM species could be determined among the 68 patients with positive culture results. Resistance to clarithromycin (defined as an MIC >32 μg/mL) was found in 8 patients, and resistance to rifabutin (defined as an MIC >5 μg/mL) was found in 8 patients. Resistance to both clarithromycin and rifabutin was found in only 3 patients (2 patients with *M. haemophilum* infection and 1 patient with *M. avium* infection). Two of these patients belonged to the surgical group and 1 to the antibiotic group.

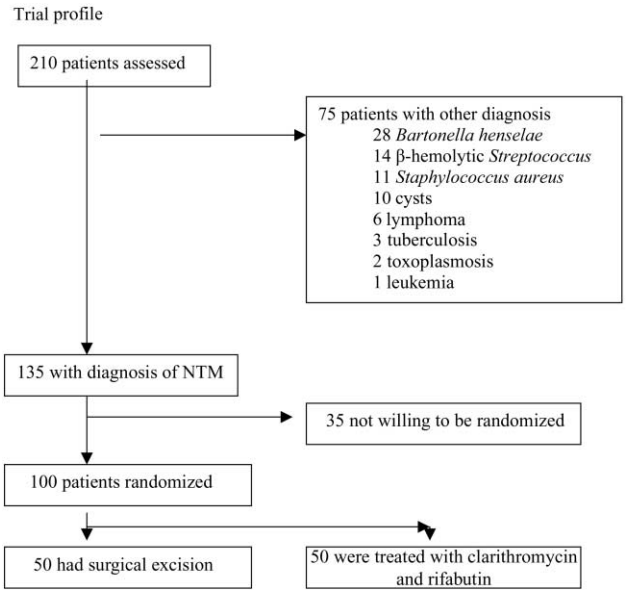

Figure 1. Trial profile. NTM, nontuberculous mycobacteria.

The mean time (±SD) between randomization and surgery was 9.6 ± 3.7 days (range, 1–16 days). In the antibiotic group, antibiotic therapy was started within 3 days after randomization. No patients were lost to follow-up.

Study outcomes according to treatment. Surgical excision was more effective than antibiotic therapy, with a 30% difference in cure rate (48 [96%] of 50 patients vs. 33 [66%] of 50 patients; 95% CI for the difference, 16%–44%). Lymph node stage or mycobacterial species did not affect the success rate. Four (22%) of 18 patients with early-stage lymph node infection experienced treatment failure, compared with 15 (18%) of 82 patients with fluctuating nodes with skin discoloration. Treatment failure was observed in 13 (18%) of 71 patients whose lymph nodes were infected with *M. avium,* compared with 5 (22%) of 22 patients with an *M. haemophilum* infection. The secondary outcomes are listed in table 2.

Outcome of surgery. The mean duration (±SD) of surgery was 88.8 ± 38.5 min (range, 24–180 min), with a mean duration (±SD) of hospitalization of 1.9 ± 0.6 days (range, 1–4 days). For 38 patients (76%), excision of the infected skin was necessary, and for the remaining 12 patients, the skin could be spared. The surgical wound healed completely without clinical or ultrasound evidence of recurrence of NTM infection at the 3- and 6-month evaluation in 48 patients (96%). Recurrence occurred in 1 patient (2%), and another patient (2%) developed a new lesion in the submental region. These lesions were successfully treated with a 3-month course of clarithromycin and rifabutin combination therapy.

Table 1. Baseline clinical and microbiological characteristics of children with nontuberculous mycobacterial (NTM) cervicofacial lymphadenitis.

Characteristic	Patients treated surgically	Patients treated with antibiotics
Sex, no. of patients		
Male	25	25
Female	25	25
Age, median months (range)	48.5 (15–168)	42.5 (9–148)
Duration of swelling before presentation, mean weeks ± SD	11.1 ± 4.8	11.4 ± 6.1
Location of NTM cervicofacial lymphadenitis		
Right submandibular	21 (42)	16 (32)
Left submandibular	21 (42)	19 (38)
Right preauricular	2 (4)	1 (2)
Left preauricular	0 (0)	6 (12)
Submental	1 (2)	2 (4)
Multiple locations	5 (10)	6 (12)
Stage of NTM cervicofacial lymphadenitis		
Early, with no skin discoloration	11 (22)	7 (14)
Skin discoloration	39 (78)	43 (86)
Size of infected nodes, mean cm ± SD	3.1 ± 0.8	3.2 ± 0.9
Mycobacterium species		
M. avium	38 (76)	33 (66)
M. haemophilum	8 (16)	14 (28)
M. malmoense	3 (6)	0 (0)
M. kansasii	1 (2)	0 (0)
M. fortuitum	0 (0)	1 (2)
M. chelonae	0 (0)	1 (2)
Nontypable NTM	0 (0)	1 (2)
Positive culture result only	6 (12)	8 (16)
Positive PCR result only	17 (34)	15 (30)
Positive culture and PCR results	27 (54)	27 (54)
Susceptible to clarithromycin, proportion of patients (%)	29/33 (88)	31/35 (89)
Susceptible to rifabutin, proportion of patients (%)	29/33 (88)	31/35 (89)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Complications of surgery were observed in 14 (28%) of 50 patients. Despite perioperative prophylaxis with flucloxacillin, *Staphylococcus aureus* wound infections were observed in 6 patients (12%) and occurred within 2 weeks after the operation. One patient required surgical drainage, whereas in the remaining patients, wound dehiscence led to drainage. Infection was treated with oral flucloxacillin for 1 week. Another patient developed a postoperative hematoma that resolved without additional therapy. Postoperative weakness of the marginal branch of the facial nerve was observed in 7 patients (14%) and was graded with a score of 2, according to the House-Brackmann scale. In 6 patients, nerve function returned to normal within 12 weeks, and in 1 patient, the weakness of the marginal branch was permanent.

Outcome of antibiotic therapy. Rifabutin plasma levels were in ($n = 41$) or above ($n = 9$) the desired range after 2 weeks and were in the therapeutic range in all children after dose adjustment. Two patients had to cease antibiotic therapy as a result of severe adverse effects: one patient developed jaundice, and the other had an allergic reaction that manifested as a generalized rash. Both patients were considered to have experienced treatment failure with regard to the primary end point.

At the 3-month clinical evaluation and ultrasound assessment, 22 patients (44%) experienced cure of the cervicofacial lymphadenitis, and 16 patients (32%) had partial regression of the lymph nodes. In 1 patient (2%), the clinical and ultrasound assessment did not show any change of the pretreatment status, and in 9 patients (18%), progression of the lymph node swelling was noticed. The 10 patients with no improvement of lymph node status were considered to have experienced treatment failure and, subsequently, were treated surgically. The bottom of figure 2 presents the clinical presentation of a patient considered to have experienced antibiotic treatment failure at the 3-month evaluation. In all 16 patients who showed only partial regression of lymph nodes at the ultrasound assessment, a

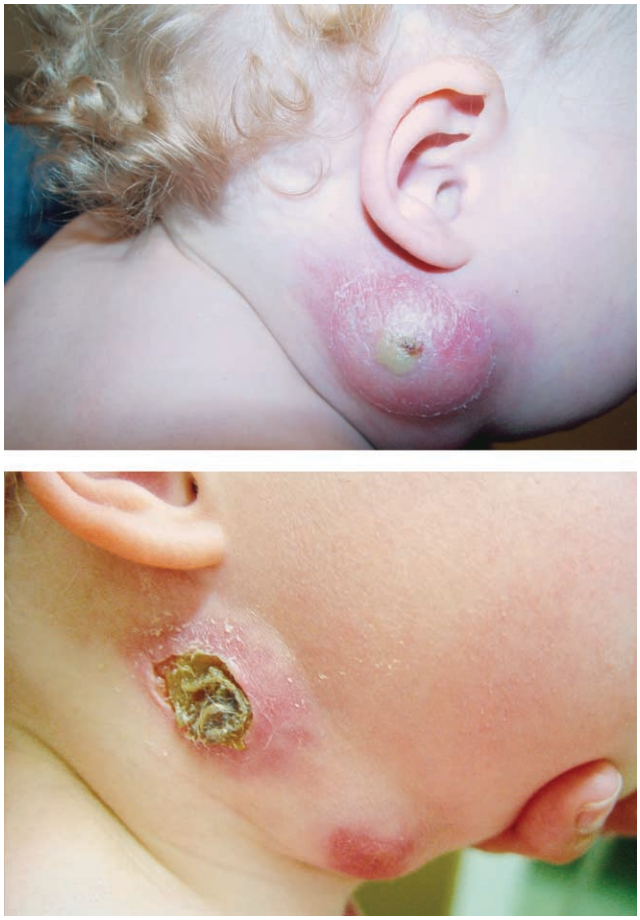

Figure 2. *Top,* Nontuberculous mycobacterial cervicofacial lymphadenitis in a 2-year-old girl. *Bottom,* Data for the same patient who was considered to have experienced antibiotic treatment failure at the 3-month evaluation.

draining fistula was found. Among these patients, antibiotic therapy was continued, and the ultrasound was repeated monthly. Three patients needed 4 months of antibiotic therapy, 6 patients needed 5 months, and the remaining 7 patients continued antibiotic therapy for 6 months. In this group, 2 additional patients had to stop antibiotic therapy because of an allergic reaction, and they were treated surgically. During the final ultrasonic assessment at 6 months, the 22 patients with complete regression at 3 months showed no evidence of recurrence or de novo lesions. Among the group that continued the antibiotic treatment, 11 were cured after 6 months, and 5 needed surgical excision of the affected lymph nodes, because they still had hypoechoic lymph nodes with a draining fistula.

Overall, 15 patients experienced treatment failure for reasons other than early drug intolerance. Of the 7 isolates (all *M. avium*) cultured from these 15 patients at baseline, none were considered resistant to clarithromycin or rifabutin. Cultures of specimens from the draining fistula were performed at 3 months in 16 patients. All culture results were negative, and the PCR results were positive, which confirmed the initial diagnosis and argued against acquired resistance to the study drugs. The culture results of the excised nodes at 6 months were also negative. The patient in whom the *Mycobacterium* species was resistant to both clarithromycin and rifabutin at baseline had a favorable response.

During the first 2 weeks of treatment, 37 patients (74%) in the antibiotic group reported adverse effects, compared with 10 patients (20%) in the surgical treatment group. This led to extra consultations of 28 patients (56%). For 16 patients, antibiotic therapy was stopped for 2 days, after which time, antibiotic therapy was continued successfully. Adverse effects of the medication were mainly reported during the first 6 weeks (table 2). Most drug-related adverse effects were considered to be mild in intensity and resolved spontaneously.

DISCUSSION

The main objective of this randomized trial was to investigate whether antibiotic therapy with clarithromycin and rifabutin would be an alternative to surgical excision of involved lymph nodes for the treatment of NTM lymphadenitis in immunocompetent children. Surgical excision showed a significantly higher success rate (96%) than antibiotic therapy (66%). Failures of antibiotic treatment were not likely to be explained by noncompliance or by baseline or acquired in vitro resistance to clarithromycin or rifabutin. In the group allocated to undergo surgery, 12% of the patients developed a postoperative wound infection. In 1 patient (2%), a persistent facial nerve dysfunction was seen, and in 12% of patients, a temporary facial nerve dysfunction occurred. Earlier retrospective studies have reported an incidence of nerve dysfunction varying from 0% to 9% [2, 5, 21–23]. Of the patients allocated to receive antibiotic therapy, one-third needed >12 weeks of antibiotic therapy to obtain regression of the lymph nodes, and the vast majority reported adverse effects, such as fever peaks and fatigue—especially during the first 6 weeks—including 4 patients in whom antibiotic therapy had to be discontinued because of adverse effects.

The clinical presentation of the NTM lymphadenitis in our study was in agreement with earlier publications on the clinical manifestations of NTM cervicofacial lymphadenitis [1, 4, 7, 14, 24]. Involvement of multiple lymph nodes, including submandibular, preauricular, or submental lymph nodes, was rare and seen in 11% of children who were equally divided between the 2 treatment arms. Infections of multiple infected lymph nodes were mainly caused by *M. haemophilum,* as was reported earlier by our study group [17, 25]. Single versus multiple lymph node infection did not significantly influence the outcome.

To our knowledge, our study is the first prospective, randomized study to determine the optimal treatment for NTM cervicofacial lymphadenitis. Strengths of the study are that mo-

Table 2. Secondary outcomes for children with nontuberculous mycobacterial cervicofacial lymphadenitis.

Outcome	No. (%) of patients who underwent surgery	No. (%) of patients treated with antibiotics	P^a
Surgical complications			
Facial nerve dysfunction			
Temporary	6 (12)	NA	…
Permanent	1 (2)	NA	…
Secondary wound infection	6 (12)	2 (4)	.27
Postoperative haematoma	1 (2)	NA	…
Adverse events			
Fever within 2 weeks	6 (12)	18 (36)	.01
Fever after 6 weeks[b]	0 (0)	12 (24)	<.001
Fatigue within 2 weeks	8 (16)	17 (34)	.06
Fatigue after 6 weeks	0 (0)	12 (24)	<.001
Abdominal pain within 2 weeks	2 (4)	14 (28)	.002
Abdominal pain after 6 weeks	0 (0)	4 (8)	.12
Extrinsic tooth discoloration within 2 weeks	NA	4 (8)	…
Extrinsic tooth discoloration after 6 weeks	NA	9 (18)	…
Headache within 2 weeks	1 (2)	7 (14)	.06
Headache after 6 weeks	0 (0)	4 (8)	.12
Vomiting within 2 weeks	2 (4)	5 (10)	.44
Vomiting after 6 weeks	0 (0)	1 (2)	1.0
Abnormal stools within 2 weeks	2 (4)	14 (28)	.02
Abnormal stools after 6 weeks	0 (0)	8 (16)	.08
Allergic rash within 2 weeks	NA	1 (2)	…
Allergic rash after 6 weeks	NA	2 (4)	…

NOTE. NA, not applicable.

[a] Calculated using Fisher's exact test.
[b] Temperature, >38.5°C.

lecular methods were applied for a rapid diagnosis, only patients with a culture- or PCR-proven NTM infection were treated, and no patients were lost to follow-up. Careful consideration was given to outcome assignment in this trial. Because surgery and antibiotic therapy are different treatment modalities, a double-blind trial is not possible. When possible, blinded and/or independent investigators assessed outcome measures, such as the ultrasound and surgical outcomes.

All surgical procedures were performed at 1 department, which might have influenced the surgical outcome or the complication rate. However, in general, surgical expertise in the head and neck region is the most important factor determining success rates or postsurgical complications. Another limitation of the study was the treatment of different types of NTM species according to the same treatment protocol. It is unknown whether all NTM types respond similarly to surgery or antibiotic therapy. In our study, the type of NTM species did not influence therapy outcome.

The choice of antibiotics was made on the basis of earlier successful case studies. Although some studies propose the use of clarithromycin with ethambutol, in our study, we used the combination of clarithromycin and rifabutin. Successful use of the clarithromycin and rifabutin combination has been reported [12]. Severe adverse effects of ethambutol are ocular complications [26, 27], which are hard to assess in young children. In addition, 57% of the NTM cultured in our study showed in vitro resistance to ethambutol, and 88% were susceptible to rifabutin. The correlation between treatment success and in vitro resistance to the antibiotics can be questioned in the case of NTM [28]. The possible influence of in vitro resistance on therapy success is difficult to assess from our data, because resistance to both study drugs was present in only 1 patient assigned to receive antibiotic treatment. This patient had a favorable response.

In conclusion, surgical excision in cases of NTM lymphadenitis clearly results in higher short-term cure rates. In addition, antibiotic treatment is compromised by a high rate of adverse effects. We doubt that the avoidance of a surgical intervention and hospitalization justifies the inferior results achieved by antibiotic treatment. In our opinion, antibiotic treatment should

only be considered in cases in which surgical excision has a high risk for facial nerve injury and in cases involving extranodal infection.

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Acknowledgments

We thank the children who took part in the study and their parents.

Financial support. The Netherlands Organization for Scientific Research (ZonMw; 945-02-019) and the Leiden Foundation of Microbiology.

Potential conflict of interest. All authors: no conflicts.

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