MAJOR ARTICLE

Conservative Wait-and-See Therapy Versus Antibiotic Treatment for Nontuberculous Mycobacterial Cervicofacial Lymphadenitis in Children

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Background. In this explorative study, 50 children with microbiologically confirmed nontuberculous mycobacterial cervicofacial lymphadenitis were randomized to either receive antibiotic therapy or follow a conservative wait-and-see approach. Our primary objective was to assess the time for all infected lymph nodes to heal in patients after the nonantibiotic, wait-and-see treatment, compared with patients after a 12-week course of clarithromycin and rifabutin.

Methods. Fifty children (19 boys and 31 girls) with a polymerase chain reaction (PCR)– or cultureconfirmed diagnosis of cervicofacial nontuberculous mycobacterial infection were included in our study. Twenty-five children were randomized to receive antibiotic therapy and 25 to be given a wait-and-see approach.

Results. The median age of the children was 35 months (range, 14–114 months). The median time to resolution of the disease for the antibiotic group was 36 weeks, compared with 40 weeks for the wait-and-see group. Adverse effects of antibiotic therapy included gastrointestinal complaints, fever, and reversible extrinsic tooth discoloration.

Conclusion. In children with an advanced stage of nontuberculous mycobacterial cervicofacial lymphadenitis, we observed no significant differences in median healing time between the wait-and-see group and the group receiving clarithromycin and rifabutin antibiotic therapy.

Surgical excision has been the recommended treatment for nontuberculous mycobacterial (NTM) cervicofacial lymphadenitis in children [1]. Esthetic results are excellent in early cases without skin discoloration or abscess formation [2]. However, surgery is less attractive in cases in which children exhibit skin redness and lymph node fluctuation, because of lymph node adherence to surrounding structures, such as facial nerve branches. Damage to branches of the facial nerve might lead to facial paralysis. Temporary facial nerve weakness has been reported in 20% of cases, and permanent facial weakness has been described in 2% of cases [1]. The dogma in literature is that excision of the infected tissue is the best therapy if it can be done safely [3]. Antibiotics or just a wait-and-see approach might be good alternatives for surgery, especially in more advanced cases.

Success percentages reported for antibiotic therapy vary from 66% to 100% [1, 4, 5]. An argument against antibiotic use in NTM cervicofacial lymphadenitis is that resolution of the disease while the patient is receiving a regimen of antibiotics may represent the natural course of the disease [5]. A strategy of nonintervention, the so-called wait-and-see policy, has been advocated by some researchers [6, 7]. Because NTM infection is a benign condition, in immunocompetent patients, all cases will ultimately resolve. It could,

Received 12 June 2010; accepted 22 September 2010.

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Clinical Infectious Diseases 2011;52(2):180–184

1058-4838/2011/522-0001$37.00
DOI: 10.1093/cid/ciq070

however, take months or even years before complete healing is achieved; however, the benefits of avoiding both surgical sequelae and an adverse reaction to antibiotics make the conservative (wait-and-see) option justifiable. However, in the absence of randomized controlled trials, nonsurgical treatment decisions are based on anecdotal reports and case series of treated patients.

The aim of this study was to assess the time to resolution of the NTM lymphadenitis in both treatment groups: antibiotic treatment or the wait-and-see approach.

METHODS

We conducted our study during the period January 2005–December 2007. All parents gave their written consent before study enrollment, and the institutional review boards of the Academic Medical Center, Amsterdam, The Netherlands, approved our study design.

Patients

Children (age, 0–15 years) with microbiologically proven NTM lymphadenitis were included in the study. Only patients with infected lymph nodes that were already in an advanced stage, characterized by fluctuation of the lymph node and discoloration of the skin, were included in the study. All children with enlarged NTM lymphadenitis without skin discoloration were treated with surgical excision. Immunocompromised patients and patients using immunosuppressive drugs were excluded. For included patients, the clinical suspicion of NTM lymphadenitis was supported by a positive result of polymerase chain reaction (PCR) or mycobacterial culture of fine needle aspirate specimens. Our diagnostic procedure has been described elsewhere [8].

Study Design

This randomized, non-inferiority study assessed the efficacy of clarithromycin and rifabutin antibiotic therapy, compare with a conservative nonantibiotic treatment in immunocompetent children with NTM cervicofacial lymphadenitis.

Treatment

Patients who met the study entry criteria were randomized to receive either oral suspensions of clarithromycin (15 mg/kg in 2 divided doses) and rifabutin (5 mg/kg once daily) for 12 weeks or no antibiotic therapy. No placebos were used.

Study Procedures

Before randomization, a head and neck ultrasound was performed to assess the number, size, and aspect of involved lymph nodes. The randomization and allocation of subjects to the conservative (wait-and-see) arm or the antibiotic therapy arm was performed with a randomization software program, using a balanced coin method to ensure an equal number of subjects in each therapy arm. Study personnel could not influence the treatment allocation.

Follow-up

Patients were scheduled for follow-up visits biweekly after the start of therapy. Adverse effects of the medication, such as fever, fatigue, gastrointestinal complaints, and allergic reactions, were scored. A follow-up ultrasound [9] was performed by an independent radiologist 12 and 24 weeks after initiation of therapy and for the final resolution assessment of infected lymph node(s). Among 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, were repeated. The desired target concentration was .05–.15 mg/L. The dose of rifabutin was adjusted for patients in whom plasma levels deviated from the target levels. Antibiotic therapy was to be continued if, at week 12, ultrasound of the affected lymph nodes did not reveal regression of lymph node swelling. Ultrasound was repeated monthly until final resolution of the affected lymph node(s) was achieved.

Outcomes

The primary endpoint 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. Secondary outcome measures were adverse effects caused by the medication. An independent investigator assessed the outcome on the basis of clinical observations and ultrasound examination.

Statistical Analysis

Differences between the 2 groups, compared in median time to resolution, were tested with the Mann-Whitney *U* test. Quantitative variables were expressed by their mean ± standard deviation (SD) when they followed a normal distribution or by their median and interquartile range (IQR) in cases with skewed distributions. All analyses were performed using SPSS software, version 16.0, for Windows (SPSS). Post-hoc sample size calculations indicated that, with a sample size of 25 in each group, we had 80% power to detect a probability of .70 that the number of weeks to total resolution in the antibiotic therapy group was less than that in the wait-and-see group with use of a Mann-Whitney rank-sum test with a 1-sided significance level of $P = .05$.

RESULTS

After screening, 79 children received a diagnosis of NTM cervicofacial lymphadenitis, and 29 patients were excluded from the study. The reason for exclusion was refusal by the parents to randomize treatment or refusal to receive nonsurgical treatment.

Table 1. Baseline Clinical and Microbiological Characteristics of Children with Nontuberculous Mycobacterial (NTM) Cervicofacial Lymphadenitis

Characteristic	Antibiotic group	Wait-and-see group
Sex, no of patients		
Male	7	12
Female	18	13
Median age in months (range)	36 (17–114)	29 (14–86)
Duration of NTM cervicofacial lymphadenitis (weeks)	8.3 ±4.6	9.7 ±2.8
Location of NTM cervicofacial lymphadenitis		
Right submandibular	10 (40%)	8 (32%)
Left submandibular	8 (32%)	10 (40%)
Right preauricular	2 (8%)	2 (8%)
Left preauricular	3 (12%)	2 (8%)
Multiple locations	2 (4%)	3 (6%)
Size of infected node (cm, mean ± SD)	2.68 ± .9	2.8 ± .8
Mycobacterium species		
M. avium	19 (76%)	16 (64%)
M. hemophilum	4 (16%)	8 (32%)
M. xenopi	0 (0%)	1 (4%)
M. kansasii	1 (4%)	0 (0%)
M. scrofulaceum	1 (4%)	0 (0%)
Positive cultures	16 (64%)	19 (76%)
Susceptibility to clarithromycin, proportion of patients (%)	92	96
Susceptibility to rifabutin, proportion of patients (%)	96	96

The excluded children were surgically treated. Fifty children (19 boys and 31 girls) with a PCR- or culture-confirmed diagnosis of cervicofacial NTM infection were included in the study. Twenty-five children were randomized to receive antibiotic therapy, and 25 observed a conservative wait-and-see policy. The median age of the children was 35 months (range, 14–114 months). Table 1 shows the baseline characteristics of the patients. All children had red, fluctuating lymphadenitis. There were no marked differences between treatment groups with respect to mean duration of lymph node swelling before presentation, location of lymph node swelling, and size of lymph node swelling. Most (72%) of the involved nodes were located in the submandibular region, and 20% were located in the preauricular region. Multiple locations (both preauricular and submandibular) were observed in the remaining cases. *Mycobacterium avium* (70%) and *Mycobacterium hemophilum* (24%) were the predominant NTM species. Culture results were positive for 70% of the patients, and the remaining patients received a diagnosis based on only PCR results.

All children in the antibiotic group completed the 12-week course of clarithromycin and rifabutin treatment. At the clinical and ultrasound assessments, ultrasound revealed regression of lymph node swelling so that continuation of medication was not required. All patients were available for all follow-up visits, and no patients were lost to follow-up.

The median time to resolution of the lymphadenitis for the antibiotic group was 36 weeks (range, 20–64 weeks; IQR, 28–52 weeks), compared with 40 weeks (range, 20-68 weeks; IQR, 31-47 weeks) for the wait-and-see group ($P = 0.38$, Mann-Whitney U test). NTM species showed in vitro susceptibility to clarithromycin in 91% of patients and susceptibility to rifabutin in 94%. In the 3 patients who had resistant strains, 2 had *M. avium* strains that were resistant to both clarithromycin and rifabutin. The infection was resolved in both patients at 30 and 47 weeks, respectively. The third patient had a *M. avium* infection that was not susceptible to clarithromycin. In this patient, total resolution was achieved by 47 weeks. Adverse reactions to the antibiotic therapy are listed in Table 2.

DISCUSSION

The present randomized study revealed no difference in the time to resolution of NTM cervicofacial lymphadenitis when comparing clarithromycin and rifabutin antibiotic treatment with a wait-and-see policy. Total resolution of the infected lymph nodes was the primary endpoint and was similar for patients treated with each treatment modality (median time, 36 weeks vs 40 weeks). Only children with lymph nodes characterized by violaceous changes of the skin and abscess formation were included in the study. Most reports of children with NTM

Table 2. Adverse Events Associated with Antibiotic Therapy

Outcome/adverse events	No. (%) patients with antibiotic treatment
Fever within 2 weeks	15 (60)
Fever after 6 weeks	1 (4)
Fatigue within 2 weeks	12 (48)
Fatigue after 6 weeks	3 (12)
Abdominal pain within 2 weeks	7 (28)
Abdominal pain after 6 weeks	1 (4)
Extrinsic tooth discoloration within 6 weeks	4 (16)
Extrinsic tooth discoloration after 6 weeks	16 (64)
Headache within 2 weeks	3 (12)
Headache after 6 weeks	0 (0)
Vomiting within 2 weeks	0 (0)
Vomiting after 6 weeks	0 (0)
Abnormal stools within 2 weeks	2 (8)
Abnormal stools after 6 weeks	0 (0)

cervicofacial lymphadenitis are also in these later stages. Surgery is recommended for the management of cervicofacial NTM lymphadenitis, but alternative treatments include antibiotics or conservative therapy. Surgical excision of involved lymph nodes leads to a quick resolution of the NTM infection; however, the decision for surgery versus nonsurgical therapy can be critical because infected lymph nodes can be close to the facial nerve. In addition, surgery can be complicated in cases with abscess formation and severe skin involvement, and unfortunately, most children are seen in later stages of the disease [1]. This study corroborates an earlier observational report on conservative treatment in which total resolution of the NTM lymphadenitis was achieved in 71% of the patients within 6 months [7]. Resolution was observed within a year in the remainder of the patients. In another report [10], 6 patients with NTM infection used a wait-and-see approach because the families refused initial treatment. Three of them healed spontaneously within 8 months, whereas the others were surgically treated after 10 months. Studies on antibiotic therapy with clarithromycin and rifabutin for NTM lymphadenitis reported resolution in 50%–100% of patients in 2–6 months [4,5,10–12]. However, many children were treated with antibiotics after failed, incomplete surgical excision. It is therefore safe to assume that surgery had already eliminated a large part of the necrotic lymph node(s). In a randomized trial comparing surgical excision with clarithromycin and rifabutin antibiotic therapy, a 66% cure rate was reported for the antibiotic therapy [1]. In that study, 66% of the patients were cured with antibiotics after 6 months. Ninety-four percent of the NTM species showed in vitro susceptibility to clarithromycin and 96% showed susceptibility to rifabutin. Two patients (1 in each treatment group) had NTM strains that were resistant to both clarithromycin and rifabutin. However, both patients were cured in 30 and 47 weeks, respectively. Therefore, the surplus value of antibiotic therapy for NTM lymphadenitis in immunocompetent children is questionable. It is accepted that in vitro susceptibility testing does not reflect the clinical response [6]. Some authors [4] consider performing routine in vitro susceptibility testing on NTM isolates to be inappropriate and unnecessary in most clinical situations, because the in vitro results lack correlation with therapeutic efficacy.

One can argue that fine needle aspiration biopsy also represents some form of treatment, and therefore, the patient population in the present study cannot be considered conservatively treated. However, fine needle aspiration plays a crucial role in determining the correct diagnosis, and it is currently impossible to reliably diagnose NTM lymphadenitis without some form of intervention to obtain material for microbiological investigation [3].

Most NTM infections in the present study were caused by *M. avium* (70%), whereas *M. hemophilum* was the cause in 24% of patients. Of note, a recent study [7] reported that *M. hemophilum* was responsible for infection in 35% of patients. Increasing numbers of *M. hemophilum* are probably reported as a result of newer PCR techniques and a better understanding of the unique growth conditions required for this microorganism [7].

Adverse effects reported in the present study were comparable to those reported in our previous report [1]. Extrinsic tooth discoloration was a long-term sequela in 64% of patients treated with antibiotics and required treatment by a dental hygienist. Adverse effects of the clarithromycin and rifabutin therapy were also described previously by Losurdo et al. [11]. Four of 7 patients treated with antibiotics experienced toxicity, presumably as a result of rifabutin therapy. Three children experienced neutropenia, and 1 patient developed skin pigmentation. These adverse effects disappeared after reduction of the rifabutin dose to 5 mg/kg/day. In the present study, we monitored the rifabutin blood level and kept it in a range from .05 to .15 mg/L.

A limitation of our study was that we used no placebo for the wait-and-see therapy group. After randomization, 1 group of patients received the antibiotics, and the control group did not receive any form of medication. When considering giving a placebo, we debated that the child's needs should prevail over our trial design, enrollment, and execution, especially because it is sometimes difficult to administer medication to young children for a prolonged time. The results of this explorative study should also be interpreted with caution because of the small sample size. It might, therefore, not be possible to demonstrate noninferiority of the conservative treatment. Although no recurrences have been reported in the present study with a follow-up of at least 2 years, a longer period of follow-up may be prudent to assess whether recurrences of NTM infection occur in the nonsurgically treated patients with NTM infection [13].

In conclusion, the results of the present study suggest that antibiotic therapy with clarithromycin and rifabutin may not be beneficial in immunocompetent patients with advanced NTM cervicofacial lymphadenitis. The cure rate in the antibiotic group did not differ significantly from that in the group who used the conservative wait-and-see approach. Moreover, disadvantages of the antibiotic therapy were the substantial cost of the 3-month antibiotic regimen and adverse effects.

Acknowledgments

Potential conflicts of interest. All authors: no conflict.

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