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Nontuberculous Mycobacterial Infection in Children: A 2-Year Prospective Surveillance Study in The Netherlands

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(See the editorial commentary by Valadas on pages 457–8)

We performed a prospective, 2-year nationwide study to assess incidence and disease characteristics of suspected infections with nontuberculous mycobacteria (NTM) in children, via the Netherlands Pediatric Surveillance Unit. Data for 61 children were reported (median age, 31 months; interquartile range, 22–50 months; female sex, 37 subjects); 2 subjects had an underlying disease. Most children (53 [87%] of 61) had cervical lymph node enlargement, with abscess in 25 (47%) and fistula in 11 (21%). The estimated annual incidence of NTM infection was 77 cases per 100,000 children. In 16 children, the diagnosis was based solely on the results of skin tests with mycobacterial antigens. Cultures were performed in 36 cases and yielded mycobacteria in 27 (75%); *Mycobacterium avium* was isolated from 18 cultures. Children with a culture positive for mycobacteria did not differ in presentation, complications, or treatment from those whose cultures showed no growth. Thirty children underwent surgery, and chemotherapy was the single treatment in 24 (39%) of the cases. The treatment of localized NTM infection in immunocompetent children by antimycobacterial drugs should be evaluated further.

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and constitute a continuous challenge to the human immune system [1]. This becomes apparent in patients with impaired cell-mediated immunity (e.g., due to immunosuppressive medication, AIDS, or a genetic deficiency in the pathway to macrophage activation) [2]. However, most infections with NTM occur in seemingly healthy children.

The clinical presentation of an NTM infection typically consists of a chronic unilateral cervical lymphadenopathy, without systemic illness, often followed by spontaneous drainage and fistula [3, 4]. Spontaneous regression can occur [3–6]. Declining rates of tuberculosis in most industrial countries have left NTM as the most common cause of mycobacterial cervical lymphadenitis in young children; it is estimated that it is responsible for 95% of such cases [7–9]. Some reports indicate an increasing incidence of infection with NTM [8, 10–12]. Several studies have focused on the characteristics of NTM infection in children, but most of these studies were retrospective and limited to hospitals and their direct surroundings [3, 9–11, 13–19]. Only a minority of studies was prospective [5, 20, 21] and based on a larger geographic area [7, 8, 12, 22, 23]. The present study is the first prospective, nationwide study of NTM infection in children in The Netherlands and evaluates the incidence, clinical characteristics, diagnostic methods, and treatment associated with NTM infection in this population.

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METHODS

Netherlands Pediatric Surveillance Unit. From April 2001 to April 2003, a prospective, nationwide surveillance study of infection with NTM in children was initiated via The Netherlands Pediatric Surveillance Unit (NSCK). Patients aged from 0 through 18 years who were diagnosed with assumed infection caused by NTM were eligible for enrollment. The NSCK is an investigational center for epidemiology of rare childhood diseases [24]. Reference pediatricians in academic and general hospitals throughout The Netherlands (~400 pediatricians) were requested to report the initials and birthdates of eligible patients monthly, by means of a standardized notification card. Pediatricians were requested to also return the card if they had not encountered a child with a suspected case of NTM infection; on a monthly basis, the NSCK sends reminders to those who fail to report. In 2002, the overall response rate of reference pediatricians was 92.1% [25].

Questionnaire. Pediatricians who reported a case of assumed infection with NTM were sent a standardized questionnaire, including questions regarding initials, postal code, age, sex, country of origin, bacille Calmette-Guérin (BCG) vaccination, symptoms and complications, date and results of diagnostic methods, underlying conditions, and treatment. The registry is anonymous, and patients could not be addressed later (e.g., to assess outcome of treatment).

For many children, tuberculin skin tests were performed using PPD of *Mycobacterium tuberculosis* (PPD-Tb), *Mycobacterium avium* (PPD-A), *Mycobacterium scrofulaceum* (PPD-S), and/or *Mycobacterium kansasii* (PPD-K). The reagents were purchased at the National Institute of Public Health and the Environment (Bilthoven, The Netherlands). The NTM-tuberculins were unavailable after January 2003. A positive skin test result was defined as an induration of ⩾10 mm at 48–72 h, in compliance with current 2000 guidelines of the American Thoracic Society.

The incidence of NTM was calculated with use of population age-distribution data from the Dutch Central Office of Statistics (Voorburg). Children were classified as native Dutch (both biological parents of Dutch origin), first generation immigrants (patient born outside of The Netherlands and at least 1 parent born outside of The Netherlands), or second-generation immigrants (patient born in The Netherlands and at least 1 parent born outside of The Netherlands).

RESULTS

Pediatricians reported data for 75 children with assumed NTM infection. Seven children, 2 of whom had BCG-itis after recent BCG vaccination, were excluded because the infectious agent appeared to be other than NTM (e.g, streptococci, *Bartonella* species, or BCG). In 5 cases, assumed NTM infection was reported twice in the same children, whereas 2 patients (3%) were lost to follow-up. In all, data from 61 patients were evaluable. In the 2-year surveillance, no seasonal variation was detected.

Demographic characteristics. The majority of the 61 patients were from 0 through 4 years old (range, 6 months–12.6 years) (table 1). The median age at first symptoms was 2 years and 7 months (interquartile range [IQR], 1 year and 10 months to 4 years and 2 months). There was a slight predominance of female sex. Forty-seven children (77%) were native Dutch. The proportion of children who were first- and second-generation immigrants was higher than expected. When the observed incidences were corrected for the number of (immigrant) children in the country as a whole, the proportions were 47 of 3,078,905, 4 of 136,350, and 10 of 464,480 for Dutch children, first-generation immigrants, and second-generation immigrants, respectively (ratio, 1:1.9:1.4) (table 1).

Clinical characteristics. The majority (92%) of children

Table 1. Demographic characteristics of 61 patients with suspected nontuberculous mycobacterial infection.

Characteristic	No. (%) of patients
Age at first symptoms, years	
0–4	49 (80)
0 to <1	3
1 to <2	18
2 to <3	17
3 to <4	8
4 to <5	3
5–9	9 (15)
10–14	3 (5)
Sex	
Male	24 (39)
Female	37 (61)
Country of origin for parents[a]	
The Netherlands	47 (77)
Elsewhere in Europe	4 (7)
First-generation immigrants	1
Second-generation immigrants	3
Morocco[b]	1 (2)
First-generation immigrants	0
Second-generation immigrants	1
Turkey, for both parents	2 (3)
First-generation immigrants	0
Second-generation immigrants	2
Asia, for ⩾1 parent	4 (7)
First-generation immigrants	1
Second-generation immigrants	3
Africa, for both parents	3 (5)
First-generation immigrants	2
Second-generation immigrants	1
BCG vaccination	1 (2)

NOTE. BCG, bacille Calmette-Guérin.

[a] Parents of immigrant children from Morocco, Turkey, and Africa both originated from the same country.

[b] In 2001–2002, a total of 600,799 immigrant children lived in The Netherlands.

presented with enlarged lymph nodes, mostly in the cervical region (in 87% of patients) (table 2). Patients with inguinal lymph node enlargement had cervical lymph node swelling as well. In 4 of the 16 cases with fever, fever was the only symptom besides lymphadenopathy. One child presented with fever, coughing, weight loss, and malaise, but without lymph-adenopathy; *M. avium* was cultured from this patient's sputum samples. Two of 5 children with coughing had pulmonary abnormalities; an enlarged mediastinal lymph node was found in 1 of them, and *M. avium* was cultured from a lymph node sample.

Infection progressed to cold abscess in 25 of 56 children with lymphadenopathy. In 3 patients without lymphadenopathy, the abscesses were localized in a foot (in a PPD-A–positive patient), gluteal region (in a patient who had *Mycobacterium chelonae* cultured), and in osteomyelitis of the right femur and left tibia (in a patient who had *Mycobacterium malmoense* cultured). The occurrence of an abscess (in 46% of cases) and fistula (in 20% of cases) was significantly correlated ($P = .004$).

The median duration of symptoms before the assumptive diagnosis of NTM infection was made was 2 months (IQR, 1–3 months). In all but 25 patients, several diagnostic tests were used (figure 1). In a patient with cervical lymph node enlargement and abscess, the pediatrician based the diagnosis of NTM infection on clinical features and a skin test response to PPD-S that was 7 mm in diameter. In 2 patients, NTM infection was diagnosed solely on the basis of skin tests that reacted positively for NTM, although other diagnostic methods had been used that gave negative results.

Skin test reactivity and diagnosis. In 32 children, dual skin tests with PPD-Tb and ⩾1 of PPD-A, PPD-S, or PPD-K were performed (table 3). Within this group, 8 children (25%) had a skin test positive for PPD-A, PPD-S, or PPD-K and tested negative with PPD-Tb. A positive PPD-Tb skin test result was always associated with a skin test positive for NTM, if performed, because of the cross-reactivity to tuberculins of various mycobacteria. Four patients (13%) tested negative on the skin test against PPD-Tb and NTM. Results of various NTM skin tests and of PPD-Tb tests were not significantly related (PPD-A, $r = -0.24$ and $P = .37$; PPD-S, $r = 0.26$ and $P = .41$; PPD-K, $r = 0.16$ and $P = .80$). In all but 7 cases, skin reactivity against the NTM exceeded that against PPD-Tb (figure 2).

Skin testing and culture of pathogens were the most often performed tests. Histological (or cytological) examination of material obtained by fine needle aspiration and biopsy, which was performed for one-third of all patients, showed granulomatous (often necrotizing) inflammation in most cases (table 4). There was no significant correlation between fistula and prior aspiration or biopsy: 17 children underwent aspiration, 4 of whom developed a fistula; 16 children underwent biopsy, 5 of whom developed a fistula; and none of the 4 patients who underwent both aspiration and diagnostic biopsy developed a fistula.

Table 2. Clinical characteristics of 61 patients with suspected nontuberculous mycobacterial infection.

Clinical characteristic	No. (%) of patients
Lymphadenopathy[a]	56 (92)
Cervical	53 (87)
Mediastinal	1 (2)
Abdominal	0
Inguinal	3 (5)
Axillar	3 (5)
Symptom	
Malaise	22 (36)
Fever	16 (26)
Weight loss	4 (7)
Anorexia	5 (8)
Coughing	5 (8)
Complication	
Abscess	28 (46)
Fistula	12 (20)
Osteomyelitis	1 (2)
Pulmonary abnormalities	2 (3)
Hepatosplenomegaly	0

[a] Total number exceeds 56 because enlarged lymph nodes could be present at several locations.

Mycobacterial culture. Twenty-seven patients had a positive culture result, with *M. avium* in 67% of the cases (table 4). One child was coinfected with *M. tuberculosis.* The median age of children with a positive mycobacterial culture result (2 years and 1 month) was significantly lower than the median age of children for whom the result of the mycobacterial culture was negative (5 years and 8 months) ($P = .002$). Otherwise, children with a positive culture result did not differ in symptoms and signs (e.g., fever, malaise, anorexia, and weight loss; $P > .20$ for all), complications (abscess or fistula; $P > .30$ for both), or treatment from those without a positive culture result (or for whom cultures were not done).

Treatment. A "wait-and-see" strategy was followed in 7 of the 61 cases, with subsequent nonsurgical drainage in 1 of these cases (table 5). Thirty-seven patients received anti-mycobacterial chemotherapy as the sole treatment ($n = 24$) or in addition to surgical excision of lymph nodes ($n = 13$). During the last part of the registry, an active nationwide surveillance (CHIMED) was initiated in The Netherlands, enrolling children with assumed NTM infection noted by pediatricians; by ear, nose, and throat physicians; and by oral-maxillofacial surgeons. In CHIMED, treatment is randomized between surgical and medical treatment. In 2 years, the total number of children with assumed NTM lymphadenitis asked to enroll (i.e., through

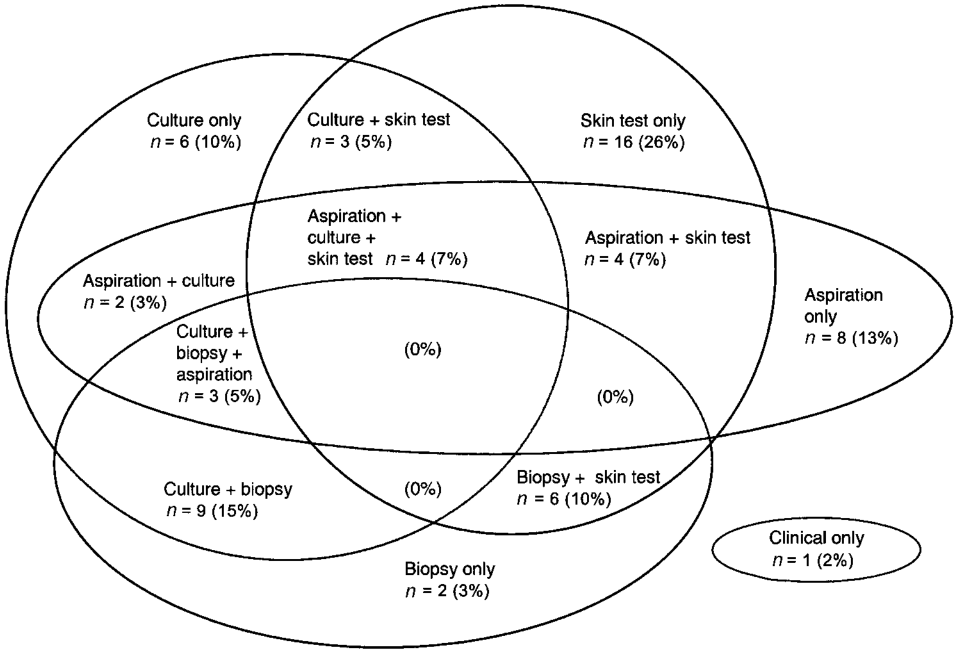

Figure 1. Means of diagnosing an infection with nontuberculous mycobacteria in 61 children. The areas in the figure do not correlate to percentages.

their parents) in CHIMED amounted to 95. The inclusion criteria were exactly those in our surveillance study. Of 95 subjects with assumed NTM infection, 69 (73%) had a positive culture and/or positive (experimental) PCR results confirming NTM infection (J.A.L.; data not shown). The preliminary data from CHIMED and our finding that children with positive culture results did not differ in disease characteristics from those without positive culture results made us conclude that it is likely that most children in our study indeed had NTM infection.

Underlying immune disorder. Two patients with NTM infection were immunocompromised: one received immunosuppressive medication because of reactive arthritis, and the other was infected with HIV. Yet another patient had an episode of *Salmonella* infection, which is suggestive of underlying immunodeficiency [2], but the anonymous registry precluded further investigation. Atopy was reported for 6 patients (10%) and for the family members of 15% of the patients.

Estimated incidence. On the basis of the surveillance and population size per age group, the annual incidence of children infected with NTM in The Netherlands was estimated to be 0.77 cases per 100,000 children aged 0–18 years (2.3 cases per 100,000 children aged 0–4 years, 0.5 cases per 100,000 children aged 5–9 years, 0.25 cases per 100,000 children aged 10–14 years, and 0 children aged 15–19 years). Given the CHIMED data outlined above, the annual incidence is likely to be somewhat higher (i.e., ~1.5-fold higher: 1.15 cases per 100,000 children) if ear, nose and throat physicians and oral-maxillofacial surgeons, in addition to pediatricians, would have included patients with assumed NTM infection.

Of all patients, 31 children (51%) lived in 3 of the 12 Dutch provinces (Brabant, 14 children; Gelderland, 11 children; Zuid-Holland, 6 children), which corresponds to the proportion of all children in The Netherlands in these provinces, which was 49% in 2001–2002. The incidence in the study of children who lived in the province of Brabant exceeded the expected rate by 5 children.

DISCUSSION

The main finding of the present prospective, nationwide surveillance study of children with assumed NTM infection is that cervical lymphadenitis is the most common presentation, with abscess formation in almost one-half of the subjects and fistulas developing in one-fifth. Systemic signs, such as fever and weight loss, were reported in approximately one-quarter of cases. Only 2 of 61 subjects had an underlying condition or risk factor (HIV infection and receipt of immunosuppressive medication). The annual incidence rate was estimated to be 0.77 NTM infections per 100,000 children; the age-specific infection rate was highest in the youngest age group, at 2.3 cases per 100,000 children. These findings extend previous data on the epidemiology of cervical lymphadenitis due to NTM [5, 9, 12, 13, 17, 23].

The estimated incidence must be seen as a low estimate of the true incidence—first, because compliance with the registry was 92%, and second, because the registry included pediatricians only. An ongoing prospective study indicates that enrollment by other specialists, such as ear, nose, and throat spe-

Table 3. Results of skin tests for 46 patients with suspected nontuberculous mycobacterial infection.

PPD	No. (%) of patients who underwent testing	No. (%) of patients with positive results	Indurations in positive test results, mm		
			Mean ± SD	Median	Maximum
Mycobacterium tuberculosis	38 (83)[a]	22 (58)[b]	15 ± 5.3	12	30
Mycobacterium avium	35 (76)	28 (80)	17 ± 6.8	15	45
Mycobacterium scrofulaceum	27 (59)	15 (56)	17 ± 6.9	15	35
Mycobacterium kansasii	32 (70)	7 (22)	14 ± 4.4	12	20

[a] In 32 of these 38 patients, atypical skin tests were performed as well.
[b] In 20 of these 22 patients, the results of atypical skin tests were positive. In 2 cases, atypical skin tests were not performed.

cialists, would raise the incidence estimate by ~1.5-fold (J.A.L.; data not shown). In other studies, the annual incidence rates in states or countries varied from 0.30 to 0.87 cases per 100,000 children [8, 9]. In our study, the number of first- and second-generation immigrant children was only slightly higher than expected on the basis of the population distribution with regard to origin. This argues in favor of the hypothesis that an infection with NTM follows recent environmental exposure.

There is no reference standard for diagnosis of NTM infection. In our surveillance, diagnosis could be based on a single positive diagnostic test result, on a combination of findings, or even on clinical presentation only. In decreasing order of frequency, diagnostic tests consisted of skin testing with PPD-A, PPD-S, and PPD-K, in addition to PPD-Tb that often shows cross-reactivity, and culture and cytological/histological examination of aspirate or biopsy specimens. The yield for each of these tests in children with assumed NTM was high (i.e., with a positive result in >75% of cases). Although the optimal diagnostic strategy cannot be deduced from our data, NTM-skin testing appeared a useful clinical tool: it was the most frequent single positive finding on which the diagnosis of NTM infection was based in one-quarter of all patients. Skin testing is cheap and easy to perform. However, interpretation of skin test results is not always straightforward as a result of cross-reactivity between mycobacterial antigens, as was illustrated by the 58% of positive PPD-Tb skin test results in our study. This is in agreement with the 25%–75% of positive PPD-Tb skin test results in previous studies of patients infected with NTM [5, 11, 26].

When performed, pathological examination of an aspirate or biopsy specimen was almost always indicative of mycobacterial infection. In this respect, we could not confirm the often assumed relation between fistula and prior invasive diagnostic procedures [5, 13, 19]. A yield of mycobacteria in 75% of cultures, with characterization of 67% of isolates, was higher than in previous reports [8, 19, 21, 22]. In patients with positive skin test results, mycobacteria were isolated in just over one-half of cases, in agreement with the findings of a previous study [9]. *M. avium* was the most common causative species [3, 7, 19, 23], but various other species were identified. In the future, PCR for NTM of aspirate specimens may become the diagnostic assay of choice. Significantly, children with a positive culture result did not differ in disease characteristics from those without a positive culture result or those for whom culture was not performed.

M. avium is highly prevalent in rural areas rich in stock farms [7, 23]. Molecular evidence suggests that *M. avium* strains causing disease in humans do not have an avian origin but carry characteristics identical to those of porcine strains [27]. A relatively large number of patients lived in the province of Brabant (i.e., a total of 14 patients, rather than the number expected [9 cases] on the basis of the distribution of children in The Netherlands). Of interest, most Dutch pig farms and many

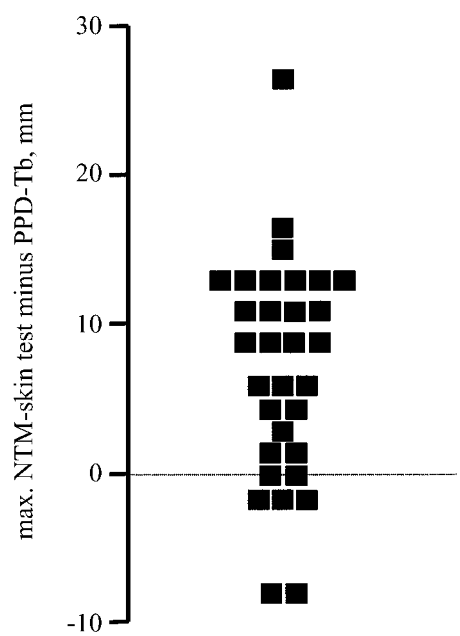

Figure 2. Difference between the maximum value of the induration response to nontuberculous mycobacteria (NTM) skin tests (mm) and to PPD of *Mycobacterium tuberculosis* (PPD-Tb) skin tests (mm) for 32 patients on whom both tests were performed.

Table 4. Diagnostic methods used to confirm infection with nontuberculous mycobacteria (NTM) and results for 61 patients.

Diagnostic test	No. (%) of patients	No. (%) of positive test results
Skin test		
All	46 (75)	35 (76)
PPD	38	22 (58)
NTM	40	33 (83)
Needle aspiration, finding		
All	21 (34)	18 (86)
Granulomatous inflammation	…	5 (24)
Necrotizing inflammation	…	5 (24)
Giant cells	…	0
Acid-fast stain positive	…	5 (24)
PCR positive	…	9 (43)
Biopsy, result		
All	20 (33)	20 (100)
Granulomatous inflammation	…	15 (75)
Necrotizing inflammation	…	9 (45)
Giant cells	…	2 (10)
Acid-fast stain positive	…	6 (30)
PCR positive	…	6 (30)
Culture		
All	36 (59)	27 (75)
Puncture/biopsy specimen	…	31 (86)
BAL/sputum	…	3 (8)
Fistula	…	1 (3)
Cerumen	…	1 (3)
No growth of mycobacteria	9 (25)	…
No growth	…	8 (22)
Bacteria, nonmycobacterial	…	1 (3)
Growth of mycobacteria	27 (75)	…
Unspecified	…	3 (8)
Mycobacterium avium	…	18 (50)
Mycobacterium scrofulaceum	…	1 (3)
Mycobacterium malmoense	…	2 (6)
Mycobacterium chelonae	…	2 (6)
Mycobacterium paratuberculosis	…	1 (3)

NOTE. BAL, bronchoalveolar lavage.

chicken farms are located in Brabant. The portal of entry of NTM is not known, but the predominance of cervical lymphadenitis suggests the oral route. Why the infection occurs in the very young remains speculative; it may be related to eruption of primary teeth, use of the mouth as explorative instrument, and intensive exposure to environmental mycobacteria in playing grounds [5, 16]. In NTM infection, an underlying immune disorder is often sought but rarely found. Nevertheless, an immune deficiency should always be considered, because this would have therapeutic consequences.

Tuberculosis is in the differential diagnosis of any subacute lymphadenitis. The incidence rate among native Dutch children of peripheral lymph node tuberculosis in 2001 amounted to 2 children aged 0–4 years, no children aged 5–9 years, and 1 child in the age group of 10–14 years. The number of cases among immigrant children (e.g., those with parents from Morocco, Asia, or Turkey) was 2, 1, and 7 in these age groups, respectively. Thus, NTM infections were more frequent than tuberculosis in children aged 0–9 years with lymphadenitis. In the age group 10–14 years, the index of suspicion of NTM infection should be higher in a native Dutch child than in an immigrant child originating from a country where tuberculosis is still endemic. All 3 children infected with NTM aged 10–14 years in our study were native Dutch, compared with 7 cases with typical tuberculous lymphadenitis among immigrant children in this age group. It is import for clinicians to be aware of the possibility of coinfection with NTM and *M. tuberculosis*, as was found in 1 African child.

A lack of consensus about optimal treatment of NTM infection in otherwise healthy children is reflected in our series. Spontaneous regression may occur in a significant proportion of cases; in our study, a conservative approach was followed in a minority (11%) of the patients. Other cases were treated with chemotherapy, surgery, or a combination of both. Treatment strategies were not standardized. Surgical treatment is generally advocated as the treatment of choice, but this may be biased by studying only the most severe cases. In 131 patients with lymphadenopathy due to NTM, lymph nodes were excised in 84% of the patients, with excellent outcome. Eleven patients were subjected to a "wait and see" strategy, resulting in persistent lymphadenopathy in 8 patients and local drainage in 2 patients [22]. However, surgery is not without complications. Especially in the submandibular region, surgery holds the risk of damage to the ramus marginalis of the facial nerve and nonaesthetic scarring [28]. In our study, 60% of children in-

Table 5. Treatment of 61 patients with suspected nontuberculous mycobacterial infection.

Proposed treatment	No. (%) of patients
"Wait and see"[a]	7 (12)
Medication only[b]	24 (39)
Complete surgical excision	17 (28)
Medication and surgery	13 (21)
Medication	
Total	37
Macrolide only	5
Macrolide and rifampin	15
Macrolide and ethambutol	9
Macrolide, rifampin, and ciprofloxacin	1
Other[c]	7

[a] The lymph node of 1 of these 7 patients was drained.
[b] The lymph nodes of 2 of these 24 patients were drained.
[c] Other medication consisted mainly of additional isoniazid.

fected with NTM received antimycobacterial drugs, most often including a macrolide. Chemotherapy was the sole treatment received by 39% of the patients. This is not in accordance with the generally held belief that antibiotics are not indicated because susceptibility patterns of most NTM are unfavorable and results obtained with surgery are good [5, 9–11, 13, 15–17, 19, 22, 29]. However, most studies of NTM infection in children were conducted before rifabutin and macrolides such as azithromycin and clarithromycin—agents with demonstrated in vitro as well as clinical activity against NTM—became available. It is likely that chemotherapy that contains one of these macrolides is beneficial [20, 28, 30]. If this is indeed the case, the effect of treatment with antibiotics could be awaited before surgery [3, 20]. The lack of consensus regarding the optimal treatment of NTM infection in otherwise healthy children and, especially, the value of antimycobacterial drugs is now being addressed in a prospective randomized trial.

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