

# Non-Tuberculous Mycobacterial Lymphadenitis in Children: Diagnosis and Management

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**ABSTRACT:** Lymphadenitis is the most common manifestation of non-tuberculous mycobacteria infection in children. Its frequency has increased over the past few decades. Diagnosis is based on clinical presentation, purified protein derivative skin test, and bacterial isolation. Management options are surgery, antibiotics, or "observation only"; however, the optimal therapy for this condition is still controversial.

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**N**on-tuberculous mycobacteria are a diverse group of mycobacterial species that cause a wide range of clinical infections in children and adults. They are environmental free-living organisms in water (including tap water), soil, animals and dairy products. The spectrum of clinical manifestations caused by these organisms in immunocompetent individuals comprises three major categories: lymphadeni-

tis, pulmonary infections, and skin/soft tissue infections. Lymphadenitis due to NTM strikes mainly young children, whereas pulmonary and skin/soft tissue infections are common only in adults, usually after the third decade [1,2]. This review will focus on the epidemiology, diagnosis and treatment of NTM lymphadenitis.

NTM lymphadenitis typically presents as a swelling of non-tender cervical/facial lymph nodes, followed by a purplish discoloration of the overlying skin and no systemic symptoms [2] [Figure 1]. The most commonly involved nodes are the submandibular, cervical or preauricular (usually one or two nodes on the same side) [3-5]. The disease usually affects children between the ages of 1 and 5 years; the median age is approximately 3 years, and it rarely presents after age 12 [3-7]. This age distribution may reflect an acquired natural immunity to NTM or maturation of the innate immune system.

The estimated annual incidence of NTM lymphadenitis in children is 1.21 cases per 100,000 and > 3 cases per 100,000 in children aged 0–4 years [7,8]. Since the 1990s, the annual number of affected children started to increase and continued climbing into the following decade [6,8-10]. The reason for this increase is unclear, although some researchers link these phenomena to the discontinuation of the BCG (*Bacillus Calmette-Guérin*) vaccination in developed countries [2,11,12]. The BCG vaccine provides protection against various NTM species; this has also been demonstrated in animal models [13].

The NTM species involved in pediatric lymphadenitis has changed over the last 50 years. *Mycobacterium scrofulaceum* was the most common cause in the 1970s [3], replaced by *M. avium-intracellulare* complex, which is now found in approximately 80% of cases [2]. However, in two recent studies, *M. haemophilum* was recognized as an important pathogen in children with NTM adenitis, and was isolated in 24–51% of cases with positive cultures [14,15]. The reason for the emergence of *M. haemophilum* as an important pathogen in immunocompetent children is probably related to improved laboratory processing procedures [16]. Many other species of

**Figure 1.** A child with non-tuberculous cervical lymphadenitis



NTM = non-tuberculous mycobacteria  
BCG = Bacillus Calmette-Guérin

**Table 1.** Isolated non-tuberculous mycobacteria species taken from children with lymphadenitis during the last 10 years

Species	% of positive isolates	References
<i>Mycobacterium avium</i> complex	55–80	[4,5,14]
<i>M. haemophilum</i>	24–51	[14,15]
<i>M. scrofulaceum</i>	< 10	[5]
<i>M. simiae</i>	< 10	[5]
<i>M. gordonae</i>	< 10	[5]
<i>M. chelonae</i>	< 10	[5,14]
<i>M. fortuitum</i>	< 10	[14]
<i>M. kansasii</i>	< 10	[14]
<i>M. malmoense</i>	< 10	[14]
<i>M. triplex</i>	<10	[17]

NTM are isolated in small numbers [Table 1], and new strains continue to be identified as technology improves [17].

## DIAGNOSIS

The differential diagnosis of chronic cervical lymphadenopathy presents a diagnostic challenge to pediatricians. Diagnosing NTM adenitis is determined by clinical presentation, tuberculin skin test (purified protein derivative), mycobacterial culture and, to a lesser extent, histology and imaging.

Children with NTM lymphadenitis usually present with painless unilateral cervical or facial (preauricular or cheek) swelling. The overlying skin is normal or has a purplish discoloration, whereas an undiagnosed longstanding disease may ulcerate with spontaneous drainage. In most children the disease presents after a therapeutic trial of anti-staphylococcal and anti-streptococcal antibiotics.

The PPD skin test is a practical and valuable tool for the early diagnosis of NTM adenitis, although controversy exists regarding interpretation of the results. Recommendations based on literature of the 1980s consider PPD  $\geq 15$  mm indurations to be more indicative of *Mycobacterium tuberculosis*, with a reaction of 5–9 mm more likely to indicate an NTM infection [18]. More recent studies have shown that a PPD of  $\geq 15$  mm and  $\geq 10$  mm are more common in children with NTM adenitis, 13–59% and 55–76%, respectively [10,19,20]. Skin tests with NTM-purified proteins are no longer produced commercially; consequently, the standard MTB-PPD remains the only available skin test. The reported variable reaction to the skin test may reflect

### ***M. haemophilum* was recognized as an important pathogen in children with NTM adenitis, and is isolated in 24%–51% of cases with positive cultures**

regional differences in the species cell wall structure and, accordingly, immunogenicity, or genetic variations that interfere with the skin response [21]. The main issue regarding PPD interpretation is the probability of MTB infection. Although NTM are the main cause of mycobacterial adenitis, when relying only on the skin test for diagnosis and management certain conditions need to be present, such as a low prevalence of tuberculosis, no exposure to adults with TB, and normal chest radiograph. The new assays, based on measurement of the release of interferon-gamma in whole blood or mononuclear cells after *in vitro* stimulation with specific MTB antigens, may enable us to differentiate between NTM and MTB infection [22].

Isolation and identification of the NTM causing the lymphadenitis is the definitive diagnosis, although it needs an invasive procedure such as fine needle aspiration, incision or excisional biopsy. However, the final results may take up to 6 weeks. The yield of FNA cultures has improved recently and positive FNA cultures of 64–80% have been reported in some clinical laboratories [5,14], a much higher rate than in previous reports [23,24]. Changing the sequence of handling these specimens, use of Gen-probes and real-time polymerase chain reaction, and better-defined growth requirements for fastidious Mycobacteria such as *M. haemophilum* [16] are the main reasons for the improved isolation rate. Routine use of PCR for rapid results is usually not available in many medical centers.

Tissue histology is used to rule out malignancy in children with lymphadenopathy. Although necrotizing granulomatous lymphadenitis or purulent material was found in most cases, attempts were made to differentiate between lymphadenitis caused by NTM or by MTB. The results have not been encouraging [25].

Imaging is frequently used to evaluate children with neck swelling. Chest X-ray is performed to rule out pulmonary tuberculosis. Sonographic findings in children with NTM lymphadenitis led to a decrease of echogenicity in early stages of the infection and intranodal liquefaction in advanced stages;

however, it is not entirely specific [26]. The appearance of NTM lymphadenitis in computed tomography and magnetic resonance imaging were

reported to be typical, characterized by an asymmetric cervical lymphadenopathy with minimal inflammatory stranding of the subcutaneous fat, and lack of surrounding inflammation [27]. However, extensive inflammatory reaction in the fat tissue was also reported in patients with NTM adenitis, and similar findings may be seen in other diseases such as lymphoma or metastatic lymphadenopathy [28,29]. In our experience, imag-

PPD = purified protein derivative  
MTB = *Mycobacterium tuberculosis*

FNA = fine needle aspiration  
PCR = polymerase chain reaction

ing of the cervical swelling plays a small role in diagnosing or managing NTM adenitis.

**TREATMENT**

The management of cervical lymphadenitis caused by NTM is controversial due to the lack of randomized controlled studies. There are three main options: surgical, medical management, and observational.

● **SURGERY**

For the past 20 years, complete excision of the infected lymph node has been considered the optimal therapy by most researchers [2,3,8,9,30]. This recommendation was not based on controlled trials but was the preferred choice for several reasons: a) surgical intervention is necessary to obtain tissue for diagnosis; b) the rate of complete cure with good cosmetic outcome is high, if surgery is performed early; and c) surgery avoids the toxicity and cost of long-term anti-mycobacterial treatment.

Incision and drainage are performed when the lesions are too large to be excised, concerns about facial nerve damage are raised, or when NTM adenitis is considered unlikely. For similar reasons, incision and partial curettage are performed. Few retrospective case series have demonstrated the superiority of complete excision over incision and drainage [30-34]. A cure rate of about 90% was reported with excision compared to < 20% post-incision and drainage [35].

The main side effects of complete excision are unacceptable scarring with or without keloid formation, wound breakdown, secondary staphylococcal infection, and facial nerve paresis. Most facial nerve damage is transient and only in about 2% was permanent palsy reported [32,36]. The procedure is performed under general anesthesia. For extensively involved nodes, surgery often takes a few hours. Most children stay 1-4 days in the hospital. Reoperation is needed in only 6-20% of the cases [4,10,24,36]. On the other hand, in most children who underwent incision and drainage only, another surgical procedure was necessary, usually excision [10,24,31].

● **MEDICAL TREATMENT**

Pharmacological therapy with clarithromycin, alone or combined with other anti-mycobacterial agents, such as rifampicin, rifabutin or ethanbutol, have been reported [review in 24]. Anecdotal case reports and small series have reported variable therapeutic effects of chemotherapy alone or in combination with surgery and chemotherapy [4,37,38]. However, there are no controlled clinical trials showing the efficacy of chemotherapy versus placebo. Recently, the only randomized controlled study

comparing surgical excision and medical treatment was published [36]. Surgical excision was found to be more effective than antibiotic therapy with clarithromycin and rifabutin, the cure rate being 96% compared to 66%, respectively. Nevertheless, surgical complications were reported in 28% of the children as compared to adverse effects to the antibiotic in 78%.

● **OBSERVATION-ONLY**

Only a few cases of observation-only in children with NTM lymphadenitis have been reported [39,40]. A recently published study described the natural history of cervical NTM lymphadenitis in 92 immunocompetent children [5]. In all cases, the NTM organism was isolated using FNA as the main diagnostic

**There are three main options for managing cervical NTM adenitis: surgical, medical and observation**

procedure. In most cases, the skin over affected lymph nodes underwent violaceous changes with discharge of purulent material for 3-8 weeks. Total resolution was achieved within 6 months in 71% of the patients, and within 9-12 months in the remainder. No complications were observed, and at 2 years follow-up a skin-colored flat scar in the region of the drainage was noted.

The healing time in these "observation-only" patients after 6 months was similar to the antibiotic therapy group from the Netherlands' CHIMED trial, 71% and 66%, respectively [36], taking into account that the endpoint results at 3 months were from the time of antibiotic initiation, about 3 months after the swelling of the lymph nodes had begun [36].

The definition of "successful treatment" in a self-limited condition like NTM lymphadenitis is not straightforward. While it is clear that lymphadenitis in normal hosts will eventually heal as shown above [5], the main factors ensuring success are parental

**The optimal therapy for this condition is still controversial**

tolerance to a prolonged healing process, cosmetic outcome, complications, and cost. Table 2 presents the reasons for and against surgical excision and spontaneous healing. The optimal way to manage this disease is still unclear.

**Table 2.** Comparison between two therapeutic modalities of NTM lymphadenitis in children: complete surgical excision versus observation only

	<b>Surgical excision</b>	<b>Observation</b>
Healing time	Short (wks)	Long (mos)
Suitable for all cases	No (only early diagnosed cases)	Yes
Complications [36]	Yes (28%)	No
Long-term sequelae [32,36]	Yes (VII nerve palsy)	No
Scar quality	Variable	Variable
Hospitalization	Yes	No
General anesthesia	Yes	No
Cost	High	Low

In conclusion, NTM adenitis is a common cause of neck swelling in children. The diagnosis is based on clinical presentation, PPD skin test and FNA culture. In countries with a low rate of MTB, most cases of mycobacterial lymphadenitis are caused by NTM. The optimal therapy for this condition is still controversial. However it seems that antibiotics are not effective in treating immunocompetent children. A randomized, controlled trial examining surgical excision versus spontaneous healing is warranted.

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