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British Association for Paediatric Otorhinolaryngology

Non-tuberculous mycobacterial cervical lymphadenitis (NTMCL):

Guideline for investigation and management

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Foreword

All Paediatric Otolaryngologists will immediately recognise the child with non-tuberculous mycobacterial lymphadenitis. While not a common disease it will feature in everyone's practice at some point. It is one of the few conditions with the potential to cause a fight, or at least spirited discussion, in a room full of, normally mild-mannered and tolerant, paediatric ENT surgeons. When I was a trainee and a young consultant, the management of this condition was by radical surgery. Since that time, however, there has been a realisation of the natural history of the condition and a move to less aggressive treatment, whether it may conservative, medical or surgical. What has always been lacking is a set of guidelines to aid and support the clinician is decision making and in discussion of the options for treatment with parents, carers and families.

In common with many uncommon Paediatric ENT conditions, the evidence on which to base decisions in this condition is limited. What these guidelines give us are an admirably pragmatic and practical approach to its diagnosis and treatment. The optimum management for this condition is likely to vary from child to child and family to family and arriving at the best decision depends on an honest discussion with them around the treatment options and natural history of the condition. This document should help clinicians in managing children and framing that discussion.

I would like to thank everyone involved in the production of this guideline, particularly Kate Blackmore who has been incredible in getting it to this stage. Guidelines such as this are one of the many ways that BAPO can support clinicians in Paediatric ENT and we are very fortunate to have such a dedicated group of people who are willing to apply themselves, unpaid, to producing them.

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President BAPO 2023-2024

Non-tuberculous mycobacterial cervical lymphadenitis (NTMCL): Guideline for Investigation and Management

Aim

The aim of this guideline is to provide clinicians seeing children with suspected or proven NTMCL recommendations on how to investigate and manage this condition.

Working group

This guideline has been developed following review of the literature along with the expert opinions of the working group representing the British Association of Paediatric Otorhinolaryngology (BAPO).

Background

Non-tuberculous mycobacterial cervical lymphadenitis (NTMCL) is a rare disease in the general population but a common cause of chronic cervical lymphadenopathy in the immunocompetent child. It predominantly occurs in children between 2-5 years and is rare over 12 years of age.

NTM are ubiquitous in the environment and found in soil, water, foodstuffs and a variety of animals Whilst over 190 species have been identified, the majority of disease in humans is caused by less than 20 of them. *Mycobacterium avium*, *intracellulare* and *haemophilium* are reported as being the most common bacteria identified however there is geographical variation. [1,2,3,4] For infections in the head and neck, the portals of entry are through the oral and pharyngeal mucosa, skin, conjunctiva and salivary glands.

Worldwide incidence is quoted as between 0.8-3.1 cases per 100,000 with geographical variability and a particularly high incidence in Canada. [5,6,7] The incidence is increasing and is felt, in part, to be due to the cessation of universal BCG vaccination in many countries. There has been a demonstrable rise in England, Wales and Northern Ireland from 0.9/100,000 to2.9/100000 between 1995-2006. [7]

Presentation is usually fairly classical with chronic unilateral and painless cervical lymphadenopathy in a systemically well child that does not respond to antibiotics and with no history of tuberculosis exposure. Occurring predominantly in the submandibular or parotid region and less commonly occurring in the jugulodigastric, submental or post triangle nodes, the mass initially presents as a firm, discrete swelling which enlarges. As the disease progresses, the overlying skin becomes violaceous, the swelling becomes fluctuant and the skin becomes parchment thin. Finally, the liquified and necrotic collection often breaks through the skin and if managed conservatively, will burn itself out over time and leave a resultant scar. Presentation to the otorhinolaryngologist is usually quite late with nearly half of cases not presenting for 8-12 weeks and in some cases, up to a year. [8,9]

Due to the low incidence of this disease there is a paucity of high-quality, large-scale studies on how we should be investigating and managing this condition. As a result, management remains controversial across all the specialties involved in care of these children and to date there is no

consensus on best care. The IPOG's recent document further confirmed the difficulty in creating a guideline; they too were unable to gain consensus.[10]

Diagnosis of NTMCL

For a **definitive** diagnosis of NTMCL, a positive mycobacterial culture or PCR is required but a diagnosis of **probable** NTMCL can be made from a classical clinical presentation with or without the use of additional investigations such as blood tests and radiology.

Children presenting with classical symptoms and signs where NTMCL is the most likely diagnosis may not require further investigation and the child can be managed accordingly.

When children present early to ENT without having progressed to developing skin changes and liquefaction of the affected node, further investigations are likely to be required. This is also indicated where there are unusual features or clinical concern of an alternative or malignant process.

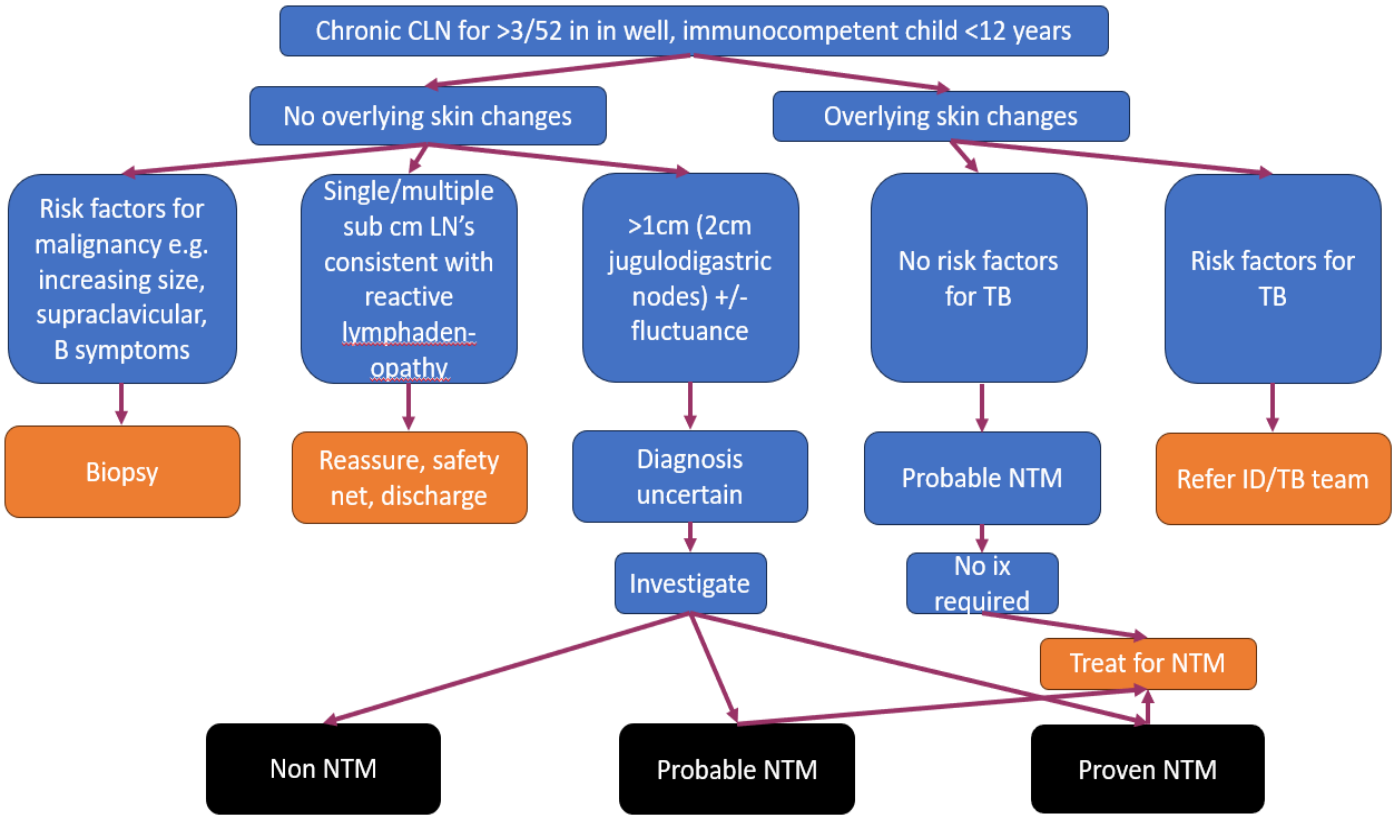

Figure 1 – Summary diagnostic flow chart

Test	Indication	Result in probable/definite NTMCL
Serology		
FBC, CRP	Possible suppurative lymphadenitis	Normal or mildly raised inflammatory markers
EBV, CMV, toxoplasmosis	Diagnostic uncertainty	Negative or evidence of previous infection
Radiology		
Neck ultrasound	Diagnostic uncertainty	Hypoechoic nodes +/- liquefaction, intranodal necrosis
CT/MRI	Rarely required. Diagnostic uncertainly, surgical planning	Low density, ring-enhancing masses with absence/minimal stranding of subcutaneous fat
CXR	High suspicion of TB	Normal
Microbiology		
Pus sample from swab/FNA • **Culture & sensitivity** • **PCR**	Diagnostic uncertainty or for definitive diagnosis	 48% sensitivity in identifying mycobacterium species 76% sensitivity in identifying mycobacterium species
IGRA • **QuantiFERON gold** • **T spot**	Risk factors for TB	Negative
TST		30-60% positive in NTMCL. A positive TST in BCG unvaccinated child with a negative IGRA is suggestive of NTMCL in the typical age group for NTMCL (infants may have a false negative IGRA with TB)
Histology/Cytology		
Biopsy from curettage or excision	Suspicion of alternative diagnosis e.g. malignancy	Histological changes may be indistinguishable from TB

Table one. Investigations when diagnostic uncertainty

Investigations

Serological

Bloods tests are required if an alternative diagnosis is being considered, but for NTM diagnosis blood tests are not routinely required.

If undertaken, FBC and CRP will be normal or only mildly abnormal in cases of NTMCL unless there is a secondary bacterial infection. CMV, EBV and toxoplasma serology can be considered to aid differential diagnosis. Bartonella serology is no longer available in the UK.

If tuberculosis is a differential diagnosis, a referral should be made to local TB services; a TST and QuantiFERON Gold/T Spot test would be advised, as well as an ESR, U&E and LFT as baseline prior to treatment.

Radiological

Ultrasound scan (USS) can be a useful first line investigation in the early stages of the disease where diagnosis is not obvious. However, if the diagnosis is clear due to clinical signs such as skin changes, then USS is not necessary. As a quick, easily accessible, cost efficient and generally well tolerated investigation, the ultrasound findings may help confirm diagnosis or indeed raise concerns of an alternative warranting further investigations. The classical ultrasound findings in NTMCL are of hypoechoic nodes with evidence of liquefaction, intranodal necrosis and nodal matting with adjacent soft tissue oedema.[11] Later in the disease process there may be evidence of intranodal calcifications.

CT and/or MRI are rarely required in the work up of a patient with NTMCL but may be used in diagnostic uncertainty, where there is a high degree of suspicion of an alternative diagnosis and, for some clinicians, in surgical planning.

CT findings are of asymmetrical cervical nodes and contiguous low density necrotic, ring enhancing masses involving the subcutaneous fat and skin. Unlike acute suppurative abscesses, inflammatory stranding of the subcutaneous fat is usually minimal or absent.[12] MRI has similar findings, and whilst this modality does not expose a child to radiation, given the usual age group affected by NTMCL, this is almost certainly going to require general anaesthesia; this needs to be taken into consideration.

Chest X-ray is not routinely required but may be helpful where there is a high degree of suspicion of pulmonary TB or lymphoma/malignancy.

Microbiology

For a definitive diagnosis, confirmation of the mycobacterium is required and this can be achieved by microbiological culture or PCR. Material for these investigations can be gained by FNA, pus swab from a discharging wound or a tissue sample from curettage, nodal excision or biopsy.

NTM are particularly fastidious and slow growing; cultures, even if positive, usually take several weeks. Whilst there is some variation between studies, PCR does tend to be superior to culture in diagnosis with sensitivities of 76.6% and 41.8% respectively in one study and a specificity of 100% for both methods.[13] PCR will also give a faster result. In cases where tuberculosis is suspected, a culture is required to obtain antimicrobial sensitivities as well. It is important to highlight a suspicion of tuberculosis as the microbiology laboratory requires this to ensure safe processing of samples.

Whilst some authors quote an increased risk of skin involvement from FNA this is disputed in other studies and felt to be simply due to the natural course of the disease. (Neven et al[14] reported a 64% 'fistula rate' however no increase in fistula in Olivas-Mazon et al study[15]).

Studies also report the use of tuberculin skin tests (TST) in diagnosis. However, a positive result could indicate either tuberculosis (TB) or NTM with studies reporting a 30-60% positivity of TST in children with NTM.[1,2,3] A positive test with a more modest induration diameter may suggest NTM infection rather than TB.[16] Interferon Gamma Release Assays (IGRA) such as QuantiFERON Gold or T Spot test are specifically designed to detect *M. tuberculosis* and can be an adjunct in NTMCL diagnosis with the principle that a positive TST and a negative IGRA in a BCG unvaccinated child are suggestive of NTMCL. Given the lack of sensitivity of these tests they should be used with caution and in selected cases. It is also important that they are collected and sent to the laboratory during working hours to ensure they are processed correctly.

It is the working group's opinion that invasive tests for a microbiological diagnosis are not required where the diagnosis is clinically clear.

Management

The 3 main management options comprise surgical excision, prolonged treatment with anti-mycobacterial antibiotics and observation. Optimal treatment remains controversial with no consensus on the best management of this disease.[10] This is in part due to the lack of high-quality evidence but also due to the heterogeneity of patients at presentation, the location, extent of disease and level of risk of complications in each individual case.

To date there are only 3 RCTs on treatment, all with methodological flaws.[17,18,19] A large systematic review of nearly 2000 patients provides the largest and most robust evidence in management of NTMCL (Zimmerman).

Before management options are discussed with the family it is imperative that there is a detailed consultation outlining the disease course.

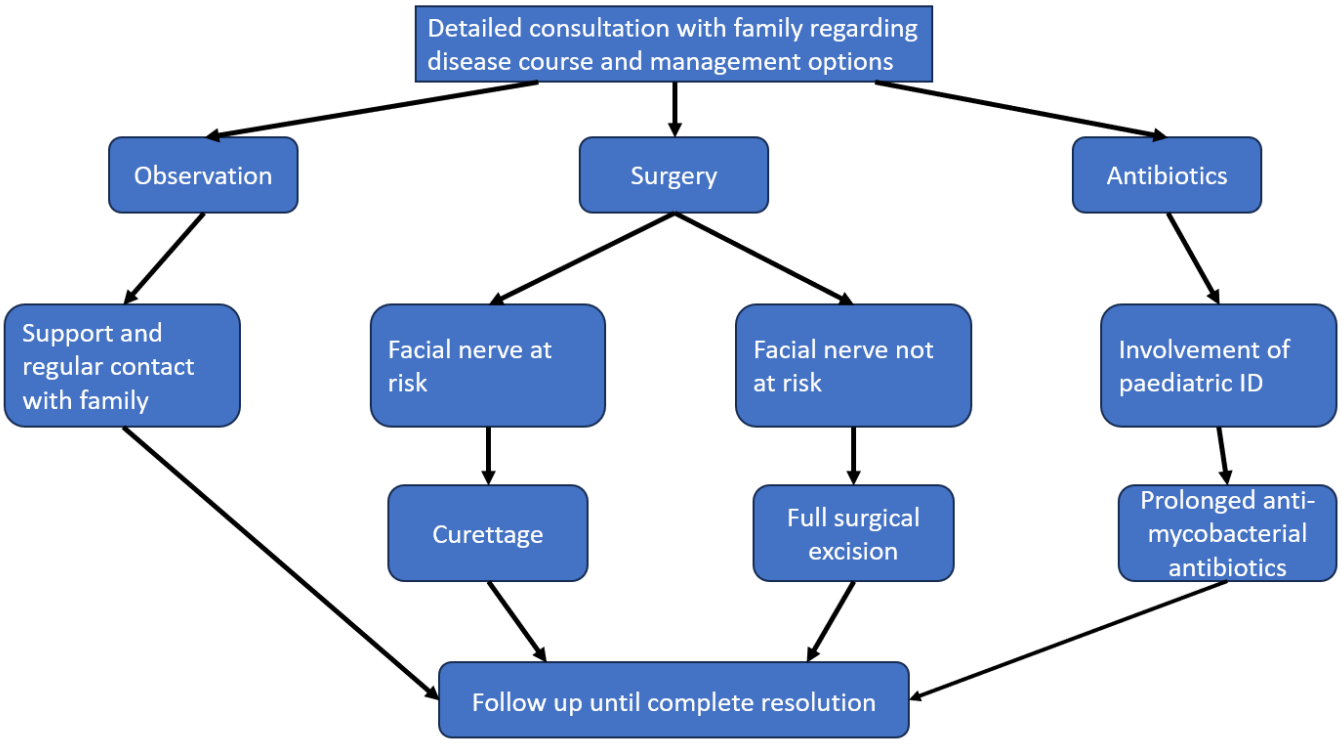

Figure 2 – Management of NTMCL flowchart

Observation

In cases where there is a high risk of facial nerve palsy from surgical intervention, it is the working group's preference to undertake watchful waiting and allow the disease to burn out without any risk of facial weakness.

This treatment option is anecdotally becoming more common practice, particularly in the UK as demonstrated from a recent survey of tertiary paediatric units (submitted for publication). The benefits of avoidance of surgery and facial nerve injury must be weighed against potential prolonged duration of healing and unpredictable scar result. Parents/carers should be advised that healing will likely take at least a year and, in certain cases, up to two years.

Several small-scale studies have undertaken observation alone, some in parallel with alternative treatment modalities. Zeharia et al followed 92 children with observation alone and reported complete resolution within 6 months in 71%, and within 9-12 months in the remainder. No children underwent a scar revision but there was only a 2 year follow up. [21]

Lyly's recent 10-year retrospective study compared surgery (curettage or complete excision) with observation. Observation was undertaken when it was deemed there was a risk to the facial nerve or parent preference and was undertaken in 63% of the cohort (33 patients). All had resolved within 12 months and in 42% any fistulous drainage was less than 2 weeks in duration. One patient underwent a scar revision at a later date. In the surgical arm, whilst there was no reported facial weakness, 2 patients required further surgery, and 3 had complications (infection and haematoma). In the 13 patients that underwent curettage, 10 had persistent drainage for more than 2 months post operatively (one more than 6 months). [22]

Whilst there have been studies on the aesthetic outcome of non-surgical management (in some studies compared with surgical outcomes) these have tended to focus on an objective assessment of the scar by surgeons as opposed to the patient or parent. The surgical scar is consistently reported as aesthetically superior when defined parameters for scar characteristics and quality were assessed (using the Observer Scar Assessment Scale (OSAS)).[23,24,25] However, when parents or patient opinion has been sought there has been no difference in their opinion of the scar and studies undertaking observation have a very low rate of scar revision reported.[23] This suggests that parents/patients are satisfied with the end scar result however it could represent parental preference to avoid surgery (and the initial reason for observation). Haimi-Cohen et al reported that 44% of parents were disturbed by the presence of the scar following observation only but 94% expressed contentment with the management pathway and would choose this again should the infection recur. [25]

Surgery

The risk to the facial nerve has to be carefully considered and discussed with the family. The usual location of NTMCL in the submandibular and parotid region puts the facial nerve at risk during most surgical procedure.

Zimmerman's meta-analysis concluded that complete surgical excision is associated with the highest resolution rate (88.5%) but is also associated with a 10% risk of temporary facial nerve palsy and a 2% risk of permanent facial palsy. This risk should be seen as significant in a disease that will burn itself out with observation alone. The risk of fistula formation, scar and wound infection was 2% for each, and requirement for further surgical intervention 8%. Partial interventions such as curettage, incision and drainage and incomplete surgical excision were associated with significant risk of fistula formation and did not achieve a statistically significant higher cure rate than observation alone.[20] However, it is difficult to extrapolate the data and draw conclusions when the studies have differing methodologies and a heterogenous population.

Our recommendation for surgical intervention that aims for complete excision with curative intent would be to limit surgery to patients presenting with early disease before significant skin involvement / break down / fistulation AND where the facial nerve is not at risk (due to the complications described particularly a permanent facial palsy). There is no role for incision and drainage in NTMCL with curative intent (but it may be needed for diagnosis), and curettage needs to be undertaken with caution given the lack of evidence of its superiority over observation.

Antibiotics

It is the view of the working group that anti-mycobacterial antibiotics do not have a role in the management of NTMCL, but we acknowledge that they are still used in management of this disease.

Typically, dual, or triple therapy (usually clarithromycin in combination with ethambutol and either rifampicin or rifabutin) treatment is prolonged (3-12 months) and due to the potential side effects, compliance is generally poor. Monotherapy is not advised due to the high risk of resistance with NTM.

Lindeboom's RCT compared complete surgical excision with 3 months of antibiotic treatment and concluded a 96% cure rate in the surgical arm compared with 66% in the antibiotic arm. Seventy-four % had side effects in the antibiotic group (tooth discolouration, headache, fatigue) and 8% did not complete the treatment. However, in the surgical group, 12% did require further surgery and 2% had a permanent facial palsy. [17]

A further, albeit small and underpowered, RCT by Lindeboom compared 3 months of anti-mycobacterial antibiotic treatment with watchful waiting in patients with "advanced disease" (characterised as fluctuance and skin discoloration) and showed no statistically significant difference in resolution rate between the two treatment arms. [18]

There is no high-level evidence to prove that anti-mycobacterial antibiotics offer any advantage over observation alone and indeed improvement whilst on antibiotics may merely be because of natural disease resolution.

If treatment with antibiotics is undertaken this needs to be under the supervision of the appropriate team e.g. infectious diseases, there needs to be microbiological sampling as a pre-treatment investigation, and on-treatment monitoring will need to be undertaken.

Consultation

When a child presents with a clinical picture of NTMCL it is paramount that there is a detailed consultation with the family to discuss the disease and its course. During this initial consultation the clinician should discuss any possible investigations (if required), treatment options and how the disease is likely to progress until resolution. The use of photographic images to accompany the discussion can be very helpful for parents (see Information for Parents/ Guardians pages). It is important to be clear about potential timeframe until resolution and to ensure that there is support during this period for the family if they have concerns along with regular contact. This may be via e-mail/telephone with photographic updates or face to face. Patients should be followed up until full clinical resolution of the infection.

Conclusion

NTMCL is a common presentation to paediatric otolaryngology but its management remains controversial with little high-quality research on which to base management decisions.

Diagnosis can be made on the classical clinical findings in most cases. Serological, radiological and/or microbiological investigations are only required when there is diagnostic uncertainty.

Management decisions will ultimately depend on many factors such as proximity of disease to the facial nerve, stage of disease, clinician expertise and preference plus parent choice. These many factors make a protocol unrealistic; this guideline aims to describe the management options with the working group's preferences highlighted.

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Appendix 1

british association for paediatric otorhinolaryngology

Information for parents/guardians

Non-tuberculous Mycobacterial Cervical Lymphadenitis (NTMCL)

What causes NTMCL?

Non-tuberculous mycobacterium (NTM) infections are caused by bacteria that are found in the environment, most commonly in water, soil, plants and animals. Although they are part of the same family of bacteria as *Mycobacterium tuberculosis* that causes tuberculosis (TB) they behave differently and don't usually make people feel unwell.

NTM infections are not contagious and can't be passed from person to person.

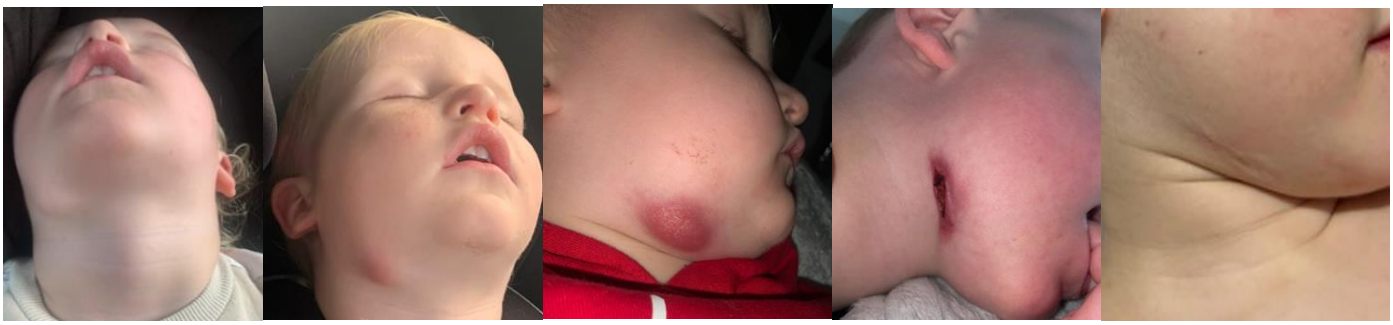
What is NTMCL?

In NTMCL the bacteria get into the body usually through the mouth and infect the lymph nodes ('glands') in the neck. This generally occurs in otherwise well children under the age of 12 (commonly 1-5 years).

What are the symptoms?

The presentation of NTMCL and the course of the infection tends to follow a predictable pattern.

- Swollen, painless glands in one side of the neck, usually in front of the ear or under the chin, that slowly enlarge and are not helped with antibiotics. The child is usually well in themselves without any fever.
- Skin overlying the swollen gland(s) starts to turn dark red after several weeks.
- Swelling goes from firm to very soft due to breakdown of the lymph nodes and the skin over the swelling becomes thin.
- Skin may or may not break down and the swelling starts to drain (fistulate).
- Swelling dries up and starts to heal.
- Scar remains from infection site



What tests are needed to confirm it is NTMCL?

In most cases the diagnosis of NTMCL is made by seeing the child in the clinic, asking questions and examining them with no additional tests required.

If there is some uncertainty about the cause of the swelling then your ENT doctor may advise blood tests, imaging of the area (usually an ultrasound) and sometimes for a sample to be taken from the swollen gland(s) to try and culture (grow) the bacteria or test for other causes.

What is the treatment?

There is no single agreed treatment for NTMCL. This is due to several reasons. It is not a common infection, so it is hard to do research studies comparing different treatment types on large groups of patients to draw a conclusion. Also, whilst the infection usually follows a predictable course, not all cases are exactly the same and different factors need to be taken into consideration in each case (e.g. where in the neck the infection is, if the skin has broken down, what are the risks from each treatment type).

The main treatment options are:

- Observation
- Surgery
- Antibiotics

Your ENT surgeon will speak to you about the benefits and risks of each and what they think is the best option for your child.

Why did my child get it?

It is not known why some children get NTMCL and others don't. It most commonly occurs in children without any other medical problems but can also be associated with other conditions. Your doctor will check for this when they see your child.

Is it dangerous?

In most cases, your child will remain well in themselves and able to carry on with most of their usual activities (swimming should be avoided if the skin has broken down or following surgery) and go to nursery or school or as normal.

How long will it last for?

This is very hard to predict. It can depend on the severity of the infection and the treatment your child has. It can take up to two years to fully settle down.

What if I am worried about my child after my appointment?

Your ENT doctor will follow up your child until the infection has fully settled. They will provide contact details if you have any concerns. It can sometimes be useful to bring or e-mail photographs of your child's neck swelling to your ENT team if you are worried.