EXPERT REVIEWS

Development of an algorithm for the management of cervical lymphadenopathy in children: consensus of the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Society of Pediatric Infectious Diseases and the Italian Society of Pediatric Otorhinolaryngology

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Cervical lymphadenopathy is a common disorder in children due to a wide spectrum of disorders. On the basis of a complete history and physical examination, paediatricians have to select, among the vast majority of children with a benign self-limiting condition, those at risk for other, more complex, diseases requiring laboratory tests, imaging and, finally, tissue sampling. At the same time, they should avoid expensive and invasive examinations when unnecessary. The Italian Society of Preventive and Social Pediatrics, jointly with the Italian Society of Pediatric Infectious Diseases, the Italian Society of Pediatric Otorhinolaryngology, and other Scientific Societies, issued a National Consensus document, based on the most recent literature findings, including an algorithm for the management of cervical lymphadenopathy in children. Methods: The Consensus Conference method was used, following the Italian National Plan Guidelines. Relevant publications in English were identified through a systematic review of MEDLINE and the Cochrane Database of Systematic Reviews from their inception through March 21, 2014. Results: Basing on literature results, an algorithm was developed, including several possible

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clinical scenarios. Situations requiring a watchful waiting strategy, those requiring an empiric antibiotic therapy, and those necessitating a prompt diagnostic workup, considering the risk for a severe underling disease, have been identified. Conclusion: The present algorithm is a practice tool for the management of pediatric cervical lymphadenopathy in the hospital and the ambulatory settings. A multidisciplinary approach is paramount. Further studies are required for its validation in the clinical field.

Keywords: cervical lymphadenopathy • children • algorithm • evidence based medicine

Introduction

Cervical lymphadenopathy is a common disorder in children due to a wide spectrum of diseases, including infectious, immunologic, neoplastic, and idiopathic disorders.[1–3] Among severe conditions (i.e. cancer or tuberculosis), cancer occurs at a rate lower than 1%. However, it should be bared in mind that more than 25% of malignant pediatric cancers involve the head and neck regions.[4–7] On the basis of a complete history and physical examination, pediatricians have to select, among the vast majority of children with a benign self-limiting condition, those at risk for other, more complex, diseases requiring laboratory tests, imaging investigations, and, finally, tissue sampling. At the same time, they should avoid expensive and invasive examinations when unnecessary.[4]

To date, there is no consensus in the international pediatric literature on a diagnostic/therapeutic algorithm for cervical lymphadenitis in children. Few practical algorithms have been published, reporting substantial discrepancies both in the diagnostic and in therapeutic management.[5,8–14] The most discussed issues include (a) the use of empirical antibiotic therapy; (b) when to perform blood tests and which ones; and (c) when to execute ultrasound scan, chest X-ray, and biopsy. In particular, the role on fine needle aspiration biopsy (FNAB) in children is highly discussed.

The Italian Society of Preventive and Social Pediatrics, jointly with the Italian Society of Pediatric Infectious Diseases, Italian Society of Pediatric Otorhinolaryngology, other Scientific Societies (listed in the title page), issued a National Consensus document, based on the most recent literature findings, including an algorithm for the management of cervical lymphadenopathy in children, defined as age <18 years, intended to be a practical tool for the pediatrician in the hospital and the ambulatory settings. The algorithm also underlines the importance of an integrated multidisciplinary approach.

Methods

The Consensus Conference method was used, following the National Institutes of Health and the National Plan Guidelines as previously reported.[15,16] Relevant publications in English were identified through a systematic review of MEDLINE and the Cochrane Database of Systematic Reviews from their inception through March 21, 2014. Search strategy: "(children[Title/Abstract] AND lymphadenitis[Title/Abstract]) AND English[lang] AND cervical[Title/Abstract] AND lymphadenopathy[Title/Abstract] AND (children[Title/Abstract] OR pediatric[Title] OR Pediatric [Title/Abstract]) AND English[lang]". Trained personnel performed the critical appraisal of the acquired literature using the Scottish Intercollegiate Guidelines Network methodological checklists.[17] Subsequently, the bibliographical material and a preliminary draft of the document were provided to the panel members. In the various meetings, literature evidence was reported and discussed and the Delphi method was used to reach a consensus when the evidence did not provide consistent and unambiguous recommendations.[17] The final text was revised on the basis of these discussions and submitted by e-mail to participants at the Consensus Conference for final approval. The full version is available at the website: http://www.sitip.org/files/fileusers/7113_linee_guida_linfoadenopatie_2014_21%20marzo.pdf.

The multidisciplinary panel of clinicians and experts in evidence-based medicine were identified with the help of the participating scientific societies. Specifically, the panel included experts in the fields of general pediatrics, otorhinolaryngology, microbiology, pharmacology,

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infectious diseases, immunology, nursing practice, and research methodology, and a member of the parents' association "We for You". No panel member declared any conflict of interest considering the guideline topics. The panel met on three occasions, and many of the consultations involved in the document development took place interactively by e-mail or telephone contact.

Definitions

Lymphadenopathy was defined as an alteration of lymph node in size, number, and consistency.[4] In children, a lymph node was considered abnormal if it has a diameter greater than 1 cm in the cervical or axillary site, 2 mm in the supraclavicular site, and 5 mm in the preauricular site.[2,3]

Lymphadenopathy may be categorized as acute (present for 1–2 weeks), subacute (present for 2–6 weeks), or chronic (persisting for more than 6 weeks), on the basis of duration, and as localized, including both monolateral or bilateral forms) or generalized (involving two or more non-contiguous sites on the basis of localization.[4,18]

Results from the systematic review

Patient's history and clinical examination

Several factors can initially suggest the etiologic diagnosis: age, time since onset, systemic symptoms (e.g. fever, night sweats, or weight loss), recent respiratory tract infection, earache, toothache, insect bite, trauma, rash, contact with animals, travel, tuberculous contact, ingestion of possibly contaminated food, immunization, and medications [2,3] (Tables 1,–3). The physical examination is paramount and should address localization and laterality, evolution (acute, subacute, chronic course), size, overlying skin changes, characteristics on palpation (soft, warm, firm, floating), relationship with surrounding tissues (mobility, immobility), soreness and achiness, and other associated systemic signs (i.e. hepato-splenomegaly, thoracic findings, rash).[2,3]

Benign viral-associated lymphadenopathy may be suspected in the event of an associated upper respiratory infection, pharyngitis, tonsillitis, or otitis media.[2,6] Involvement is usually bilateral and lymph node is generally small, soft, nontender, mobile, and without overlying skin changes. Citak *et al*. in a retrospective observational study, including 273 children aged <16 years, observed that 73.75% of children had bilateral cervical lymphadenopathy, associated with infectious mononucleosis in the majority of cases.[19]

Table 1. Drugs which can cause cervical lymphadenopathy.

antiretroviral drugs (abacavir, nevirapine)
Allopurinol
Aromatic anticonvulsants
Atenolol
Captopril
Carbamazepine
Quinidine
Phenytoin
Hydralazine
Penicillin
Primidone
Sulfonamides
Sulindac

Modified from [20,21].

On the other hand, bacterial cervical lymphadenopathy is typically unilateral, most commonly involving submandibular (50–60%) or upper cervical (25–30%) regions. Inflammatory signs, i.e. pain, tenderness, fluctuancy and skin changes, are frequent.[20,21]

Infections by *Bartonella henselae* or nontuberculous mycobacteria are frequently associated with subacute or chronic forms.[3] A child with cat-scratch disease typically presents with erythema, papules, or pustules occurring at the scratch line. Regional lymphadenopathy (most commonly axillary, submandibular, preauricular, or intraparotideal) becomes evident 2–3 weeks after the scratch or bite and may last up to 6 months. General malaise and fever may be present. Only in 50% of cases a previous cat scratch or bite is present, and dog can be affected by *Bartonella* spp. infection, as well. Thus, this disease may be suspected even in the absence of a cat scratch/bite. The nontuberculous mycobacteria lymphadenopathy is usually unilateral and persists for more than 3 weeks. The child, generally aged less than 5 years, appears in a good general condition and afebrile. Submandibular upper cervical regions, including intraparotideal lymph nodes, are most commonly involved. Erythema or a violaceous skin discoloration may be associated,

Table 2. Common causes of cervical lymphadenopathy, according to temporal evolution.

Acute lymphadenopathy	Subacute/chronic lymphadenopathy
Bacterial infections	Bacterial infections
Staphylococcus spp.	*Mycobacterium tuberculosis*
Streptococcus spp.	nontuberculous mycobacteria
Anaerobic bacteria	*Bartonella henselae*
Borrelia burgdorferi	*Brucella* spp.
Viruses	*Leishmania* spp.
CMV	*Francisella tularensis*
EBV	*Listeria monocytogenes*
Adenovirus	Viruses
Herpes simplex virus 1–2	HIV
Herpes simplex virus 6–7	CMV
Mumps virus	EBV
Influenza, parainfluenza virus, rhinovirus	Other
Rubella	Lymphoma and leukemia
Measles	Metastasis
Varicella	Sarcoidosis
Other	Juvenile idiopathic arthritis
Toxoplasma gondii	Lupus erythematosus systemic
Kawasaki disease	
PFAFA	

CMV, cytomegalovirus; EBV, Epstein–Barr virus; PFAFA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; HIV, human immunodeficiency virus.

Table 3. Common infectious causes of cervical lymphadenopathy, according to the child's age.

Age	Aetiology
1–4 weeks	*Staphylococcus aureus*
	β-hemolytic group B *Streptococcus pyogenes*
1–12 months	*Staphylococcus aureus*
	β-hemolytic group B *Streptococcus pyogenes*
	Toxoplasma gondii
	CMV
	EBV
1–5 years	Upper respiratory tract infections
	Beta-hemolytic group B *Streptococcus pyogenes*
	Staphylococcus aureus
	Nontuberculous mycobacteria
	Toxoplasma gondii
	CMV
	EBV
6–14 years	Upper respiratory tract infections
	Bartonella henselae
	Mycobacterium tuberculosis
	Anaerobic bacteria
	CMV
	EBV
	Toxoplasma gondii

CMV, cytomegalovirus; EBV, Epstein–Barr virus.
Modified from [6].

and central colliquative necrosis with possible subsequent fistulization is a common evolution.[6]

Malignancy may be suspected if lymph nodes are rapidly enlarging, nontender, and fixed. Cervical lymph node greater than 2 cm should be considered potentially malignant and this risk is substantially higher when diameter exceeds 3 cm.[6,22–24] Regardless of size, age >8 years, generalized lymphadenopathy, supraclavicular or lower cervical nodes involvement are associated with increased risk of malignancy.[6,22–24] In a retrospective study of 175 children, the involvement of the high, middle, and lower jugular nodes and the posterior triangle of the neck was significantly associated with an increased risk of malignancy compared with involvement of submental and submandibular regions (P = 0.001, 95% CI = 5.46 to 25.57).[25] This finding is also confirmed in an observational study including 120 Indian children.[26] Associated systemic symptoms, including weight loss, night sweats, unexplained fever, or fatigue, should also be addressed and suggest malignancy or a chronic inflammatory condition.[2]

According to the Referral for suspected Cancer Guidelines issued by the National Institute for Health and Clinical Excellence (NICE), urgent referral is advised if one or more of the following characteristics are present, particularly if there is no evidence of local infection: (a) lymph nodes are non-tender, firm, or hard; (b) lymph nodes are greater than 2 cm in size or are progressively enlarging; (c) other features of general illness, i.e. fever or weight loss; (d) the axillary nodes (in the absence of local infection or dermatitis) or the supraclavicular nodes are involved.[27] Also, the presence of hepatosplenomegaly or persistence for 6 weeks or more requires immediate referral.[27]

In several primary immunodeficiency diseases (PIDs), including severe combined immunodeficiency and X-linked agammaglobulinemia, lymph nodes and tonsils are small or absent. On the other hand, in other PIDs, lymphadenopathy is frequently present. According to the recent German guidelines,[28] lymphoproliferative disorders (including chronic benign lymphadenopathy) should be considered for the suspicion of PID, besides susceptibility to infections (recurrent infections with common pathogens, or infections with unusual/opportunistic pathogens) and chronic inflammation or autoimmune disorders.[28] These concepts are summarized in the German guidelines by the mnemonic acronyms ELVIS and GARFIELD, as reported in Table 4.[28] In the Omenn syndrome, the Chediak–Higashi disease in its "accelerated phase", or in the common variable immune

Table 4. The classic warning signs of primary immune deficiency, summarized for patients with increased susceptibility to infection in the acronym ELVIS, and other signs of immune system impairment, summarized by the acronym GARFIELD, on behalf of the German Association of the Scientific Medical Societies [AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., www.awmf.org].

ELVIS	GARFIELD
• Pathogen (Erreger): Infections due to opportunistic pathogens such as *Pneumocystis jirovecii* • Localization (Lokalisation): atypical localization of the infection, e.g., brain abscess due to *Aspergillus* cerebral toxoplasmosis, or pneumococcal arthritis, are suggestive of PID • Course (Verlauf): an unusual course in terms of chronicity/recurrence and an unsatisfactory response to antibiotic therapy represent signs [although difficult to differentiate) of PID • Intensity (Intensität): the same applies to infections that follow an unusually severe course • Number of infections (Summe der Infektionen): this parameter is distinctly age-dependent: ≥8 minor infections/year, ≥2 cases of pneumonia or severe sinusitis/year are considered abnormal in young children while the rule of thumb	• Granulomas: in particular in the lungs, lymph nodes, skin, as well as in other organs • Autoimmunity: in particular autoimmune cytopenia, as well as organ autoimmunity • Recurrent fever: periodic fever, hemophagocytosis • Eczema: often early-onset, atypical, refractory to therapy • Lymphoproliferative disorders: chronic benign lymphadenopathy, splenomegaly

Modified from [28].

deficiency (CVID), lymphadenopathy is commonly described. Indeed in these diseases, lymphoid tissue is often substituted by extensive histiocytic infiltrates. In chronic granulomatous disease, recurrent suppurative lymphadenopathy is frequent. This should be differentiated from cutaneous granulomas which are not related to infection but rather due to ineffective neutrophil function and dysregulated inflammatory response. In a recent case series, lymphadenopathy was the second most frequent clinical condition (59.4%), after recurrent pneumonia (76.8%). Other described features included granulomata (49.3%), skin infections (42%), chronic diarrhea (41.9%), otitis (29%), sepsis (23.2%), abscesses (21.7%), recurrent urinary tract infection (20.3%), and osteomyelitis (15.9%).[29]

Lymphadenopathy is common also in the autoimmune lymphoproliferative syndrome (ALPS). ALPS is a disorder of abnormal lymphocyte survival caused by dysregulation of the FAS apoptotic pathway. Patients with ALPS develop chronic non-malignant lymphoproliferation (lymphadenopathy, splenomegalia, hepatomegalia), autoimmune disease (i.e. autoimmune cytopenia), and secondary malignancies (i.e. NHL). Lymphadenopathy is usually multifocal, lasts more than 6 months, and lymph node sizes fluctuate with time. Cervical and inguinal lymph nodes are the most commonly involved.[30]

ALPS patients have highly heterogeneous phenotypes with clinical findings that overlap with several lymphoproliferative disorders (i.e.: Castleman disease, Rosai-Dorfman disease, X-linked lymphoproliferative disease, Kikuchi–Fujimoto disease, Caspase 8 deficiency syndrome, and Ras-associated leukoproliferative disorder). Tissue biopsy (bone marrow and/or lymph node] at initial presentation is therefore needed to obtain a specific diagnosis.

It should be remembered that in patients with CVID, ALPS, as well as other PIDs, lymphadenopathy may underline a malignant lymphoproliferative disease. Approximately 10% of patients with CVID and 10–20% of those with ALPS have a lymphoproliferative disorder, which manifests most frequently as splenomegaly, lymphadenopathy, and interstitial lung disease. Non-Hodgkin's lymphoma (NHL) is the commonest lymphoproliferative disorder in these patients. In general, PIDs are one of the strongest known risk factors for the development of NHL.[30]

Extra-pulmonary, cervical fungal lymphadenitis, including Aspergillosis, Candidiasis, Criptococcosis, Histoplasmosis, Coccidiomicosis, is a rare clinical disorder, mainly occurring in children with primary or acquired immunodeficiency. Aspergillosis is a saprophytic and ubiquitous infection due to the inhalation of airbone spores of *Aspergillus* spp. (mainly *Aspergillus fumigatus* and *Aspergillus flavus*), and, rarely, to the ingestion of contaminated food. Invasive aspergillosis may develop in granulocytopenic patients (i.e. leukemic children) and cystic fibrosis patients, and mainly affects the lungs. Head and neck involvement is possible, including cervical lymphadenitis, aspergillosis of the paranasal sinuses, and intraoral aspergillosis.[31] Histoplasmosis is an opportunistic infection caused by the inhalation of chicken droppings or bat guano containing spores (microconidia) of the dimorphic fungus *Histoplasma capsulatum*. Although histoplasmosis is commonly subclinical or gives rise to a flu-like syndrome, it may abrupt develop into a disseminated disease in about 10% of cases, especially in immunosuppressed patients (particularly those with T-cell impairment) and infants. Peripheral lymphadenitis mainly affects the cervical chains of children with histoplasmosis. Parotid involvement has also been described. A diagnosis may be reached by means of fungal culture, antigen detection, fungal staining of peripheral blood, and antibody testing.[31]

Cryptococcus is encapsulated yeast, which is present in environment, especially in soil contaminated with bird excreta. Approximately 85% of patients with cryptococcosis have impaired cell-mediated immunity, including patients undergoing solid organ transplant, those with hematology malignancy or HIV infection. It has been rarely reported in otherwise healthy children. Disseminates crypotococcosis can involve the lungs, central nervous system, skin, lymph nodes, and liver. Lymph node involvement as a presenting feature in cryptococcosis is not a common manifestation, but it has been reported in adults and children. Final diagnosis can be confirmed by cervical

lymph node biopsy for histopathologic investigations and fungal culture.[31]

Finally, in children who had received a solid organ transplantation or an allogeneic hematopoietic stem cell transplantation, the post-traplant lymphoproliferative disorder (PTLD) should be considered since lymphadenopathy is described in about 40% of these children.[32] PTLD is a complication associated with Epstein–Barr virus (EBV) infection of B cells, either as a consequence of reactivation of the virus post-transplantation or from primary EBV infection. Most cases of PTLD occur within the first post-transplant year. Whether PTLD presents as localized or disseminated disease, the tumors are often aggressive, rapidly progressive, and potentially life threatening. Clinical presentation is variable and includes fever (57%), lymphadenopathy (38%), gastrointestinal symptoms (including obstruction (27%), infectious mononucleosis–like syndrome that can be fulminant (19%), pulmonary symptoms (15%), CNS symptoms (13%), and weight loss (9%).[32] The EBV viral load in the peripheral blood, measured by quantitative PCR, is the most commonly used laboratory test to monitor patients who are at risk for developing PTLD after transplantation. A single elevated EBV PCR value is less informative than a trend of rising (or falling) values over time but a negative EBV PCR does not allow ruling out a PTLD. The diagnosis relies histologic confirmation on biopsy. The World Health Organization classification system recognizes four major histopathologic subtypes: (1) early hyperplastic lesions, (2) polymorphic lesions (which may be polyclonal or monoclonal), (3) monomorphic lesions, and (4) classic Hodgkin-type lymphomas.[32]

Considering the child's history and clinical presentation, four clinical scenarios have been identified by the expert panel, as reported in Figure 1. On this basis, an algorithm was developed.

Clinical scenarios

The first clinical scenario refers to children with unilateral or bilateral lymphadenopathy associated to pharyngitis, fever, and/or mononucleosis-like syndrome. Most commonly, this situation underlines a benign viral infection of the upper respiratory tract.[18] Streptococcal pharyngitis should also be considered according to the guidelines recommendations.[33] A watchful waiting for 3–5 days is recommended. In case of persistence and/or worsening of lymphadenopathy, a minimal workup is suggested (including count blood cell; C reactive protein [CRP]; liver enzymes; Epstein–Barr Virus Viral Capsid [VCA]-IgM). VCA-IgM becomes positive already during the first week of infection in more than 75% of cases. This percentage rises to 93–95% during the second week.[34] Other agents responsible for mononucleosis-like syndrome (i.e. cytomegalovirus [CMV]; Herpes simplex virus; Human Herpes virus-6; adenovirus; *Toxoplasma. gondii*), systemic bacterial infections, Kawasaki syndrome, or lymphoproliferative disorders should be considered if EBV serology is negative for acute infection and/or alterations of other blood tests are present and/or fever persist.[21] In children with one or more symptoms of Kawasaki syndrome, the execution of echocardiography is mandatory.[34] A careful clinical monitoring for 8–12 weeks is recommended in any case, even in the event of clinical improvement and/or normal blood tests.

A second clinical scenario includes children with mono/bilateral lymphadenopathy with diameter <2 cm without inflammatory signs. Even in this event, most commonly this scenario underlines a benign viral infection of the upper respiratory tract, and no empiric antibiotic treatment is recommended. A careful clinical monitoring over time is indicated, since any lymphadenopathy which does not regress in 4–6-week or incompletely resolves in 8–12 weeks should be investigated, and, eventually, surgical intervention may be required to achieve a final diagnosis (Figure 1).[24,27]

The third clinical scenario includes children with mono/bilateral lymphadenopathy with signs of inflammation, regardless of size. Soreness and tenderness suggest a rapid increase in volume of the lymph node, with tension of the capsule, which typically occur in infectious suppurative inflammatory processes.[35,36] Flogosis is defined by the presence of inflammatory signs including *rubor, calor, dolo*r, and the presence of fluctuations and suggests a bacterial infectious disease.[37] The most common pathogens involved in acute bacterial lymphadenopathy are *Staphylococcus aureus* and *Streptococcus pyogenes*. Acute bacterial lymphadenitis is most commonly caused by *S. aureus* in the neonate and in children up to age 4 years. Group B streptococcal infection should be considered in the newborns. In children aged 1– 4 years, Group A β-haemolytic streptococcal infection becomes more prevalent, though *S. aureus* is still the most common isolated pathogen in this age group.[9] Anaerobic infections should be considered in older children and adolescents, especially in the setting of dental infection or periodontal disease.[38]

In these cases, an empirical antibiotic treatment with amoxicillin or amoxicillin/clavulanic acid 80 mg/kg/day in three divided doses for 14 days is suggested (Figure 1). In severe forms (with compromised medical conditions and/or persistent fever, increased inflammatory markers), the recommended empirical antibiotic therapy is ampicillin + sulbactam or amoxicillin + clavulanic acid, intravenously (80 mg/kg/day, calculated on ampicillin or amoxicillin, in three divided doses).[10] In the absence of response to empiric antibiotic therapy within the first 48–72 h or in the presence of a high risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA), clindamycin, rifampicin, trimethoprim/sulfamethoxazole are recommended. Vancomycin or linezolid should be used in infections sustained by clindamycin-resistant MRSA. In Italy, more than 30% of hospital infections due to *S. aureus* are MRSA-associated diseases.[39] Few data are available regarding the epidemiology of community-acquired MRSA.[40,41] Revaluation of the child at 7 days after the end of therapy is also recommended. It should be reminded that, even if rarely, cancer may be associated with soreness and tenderness due to rapid volume in case of hemorrhage and necrosis of lymph node. Thus, in the absence of any improvement following the antibiotic treatment, further investigations are recommended, as reported in Figure 1.

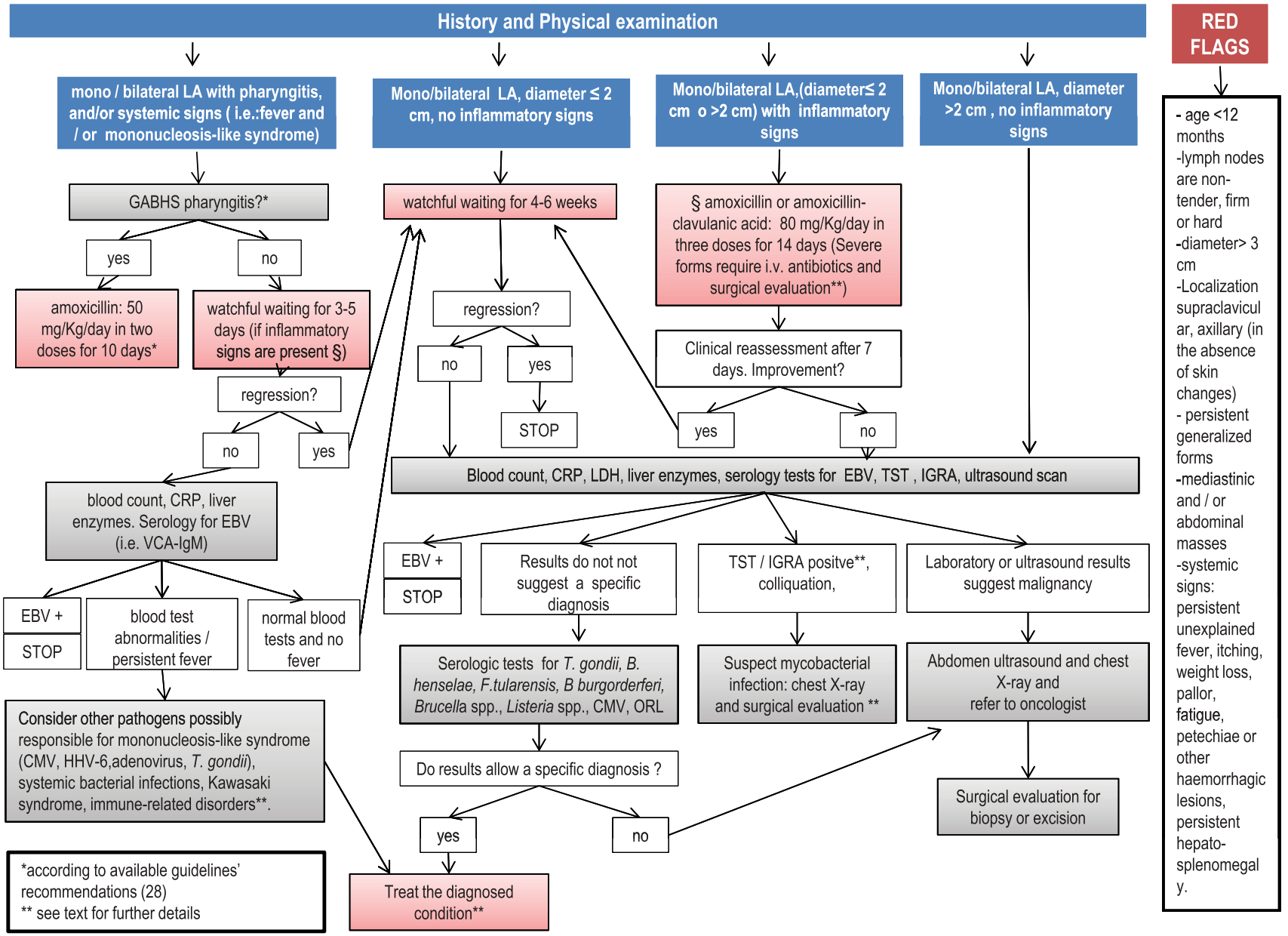

Figure 1. Algorithm for the management of cervical lymphadenopathy in children. LA: lymphadenopathy, CRP: C reactive protein, LDH: lactate dehydrogenase, EBV: Epstein–Barr virus, TST: tuberculin skin test, IGRA: interferon-gamma release assay.

A surgical approach may be considered, especially in the absence of response to antibiotics.[6,9,42]

When a PID is suspected on the bases of guidelines recommendations (Table 4),[28] initial laboratory testing should include screening for human immunodeficiency virus infection, complete blood count with differential, and measurement of serum immunoglobulin and complement levels. Second-level tests (i.e. lymphocyte subset analyses, the dihydrorhodamine test or the nitroblue tetrazolium NBT test) should be performed according to the immunologist's advice and following the available guidelines.

A fourth clinical scenario includes mono/bilateral lymphadenopathy with diameter >2 cm with no associated inflammatory signs. In these cases, investigations should be timely executed and empirical antibiotic therapy is not recommended. Particular attention should be given to the "red flags" reported in the algorithm, which may underline a malignancy, according the NICE guideline recommendation.[27] Investigations include a complete blood count, CRP, lactic dehydrogenase, liver enzymes, serological test for EBV, tuberculin skin test (TST), and Quantiferon Gold in Tube or T-SPOT.TB, plus an ultrasound scan.

In acute and subacute conditions, with or without inflammatory signs, a mycobacterial infection should also be investigated (Figure 1). QFT-IT or T-SPOT.TB are immunologic tests, otherwise called interferon-gamma release assay (IGRA), which investigated a cell-mediated immune response by measuring *in vitro* interferon-gamma production in response to stimulation by *Mycobacterium tuberculosis* antigens, derived from *M. tuberculosis* which are absent in BCG and most non-tuberculous mycobacteria. According to literature data, IGRAs seem to display higher specificity than TST for the diagnosis of active tuberculosis, since they are generally negative in patients with a positive TST due to a previous BCG vaccination or infection by non-tuberculous mycobacteria. On the other hand, a positive TST (usually with diameter 5–10 mm, but this is not an absolute cut-off) and a negative IGRA in a country with low prevalence for TB suggest a non-tuberculous mycobacterial infection. However, this interpretation of TST/IGRA discordance is not absolute. As an example, a false negative IGRA may be present in severe tuberculosis cases (i.e. miliary TB or pleuritis) or in young children. In general, both the TST and IGRA results should be interpreted with caution in children, taking into account BCG status, child's age, nutritional assessment, and immunologic status. Moreover, several infections sustained by non-tuberculous mycobacteria are associated with a concordant IGRA and TST positivity (i.e. infection by *Mycobacterium marinum, Mycobacterium szulgai, Mycobacterium kansasii*), since these mycobateria share with *M. tuberculosis* the same ESAT-6 (6 kDa early secretory antigenic) and CFP-10 (10 kDa culture filtrate antigen) encoding regions. To obtain a differential diagnosis between tuberculosis and infection by non-tuberculous mycobacteria, physicians should consider not only TST and IGRA results but also clinical/anamnestic/radiological findings, as well as results of microbiological investigations and response to eventual antitubercular therapy. Active TB disease should be considered in the presence of a recent TB contact, recent immigration or travel in a TB endemic area, suggestive findings at chest X-ray, fever/cough/weight/loss/swelling.[43] In every case, microbiological investigations should be performed according to the available TB guidelines.[44]

Nontuberculous mycobacterial lymphadenopathy is a benign condition with a spontaneous resolution, although this is often characterized by a prolonged course that adversely affects the children's and family's quality of life. Observation alone can be a strategy, although not optimal. When feasible, complete lymph node surgical excision is the most effective therapeutic option according to results of a randomized controlled trial including overall 100 children.[44] Cure rates were 96% for surgical excision and 66% for antibiotic therapy (95% confidence interval for the difference: 16–44%).[45] On the other hand, in a retrospective study including about 50 children, non-excisional surgery was associated with a higher risk of persistent/recurrent disease: of those who underwent complete excisional biopsy initially, 95% were cured compared with 63% patients cured with non-excisional surgery.[46] If the risk of facial nerve damage is substantial, the surgical approach may not be feasible.[46] Antibiotic therapy with clarithromycin (15 mg/kg in two divided doses) in combination with rifampicin (10–20 mg/kg in 1 daily dose) or rifabutin (5 mg/kg in one dose) or associated with ethambutol (20 mg/kg in 1 daily dose) is an alternative option in these cases.[47,48]

According to the American College of Radiology guidelines, ultrasonography scan is recommended as a first level investigation for the assessment of patients with solitary or multiple swelling of the neck.[49,50] This investigation, even if is operator-dependent, is not invasive, it does not require ionizing radiation, and sedation and has a low cost. It also allows to identify clearly the nature of lesion. In one single center observational study, among 126 children referred for lymphadenopathy, 22.2% indeed were demonstrated to suffer from another disease, mimicking lymphadenopathy, as.[51] Moreover, several ultrasound characteristics may orient the diagnosis: (a) malignancy may be suspected in case of a rounded shaped lymph node, (b) absence of hilum, (c) structural inhomogeneity, (d) extracapsular involvement and (e) chaotic lymph nodal vascularization.[50,52] However, it should be underlined that no single ultrasound feature is specific for a benign or a malignant disease. Literature data regarding the performance of ultrasound scan in differentiating benign from malignant lymphadenopathy, based on the ratio short/long axes (S/L) > 0.5, in children are contrasting. The reported predictive value for malignancy ranges from 20% to 95.8%.[25,48,51] Tashiro *et al.* [51] and Papakonstantinou *et al.* [49] reported that lymphadenopathy associated with infectious mononucleosis, bacterial lymphadenitis, lymphoma, tuberculous and non-tuberculous mycobacterial lymphadenopathy, cat scratch disease, and Kawasaki disease most often are round with S/L > 0.5. Therefore, in children, differently from adults, the lymph node shape would not allow to distinguish between benign and malignant diseases.

Considering the hilum, Papakonstantinou *et al*. [49] showed that the presence of a large hilum suggests a reactive hyperplasia (94%) such as in infectious mononucleosis, while a tight hilum is more commonly observed in or bacterial lymphadenitis or cancer, such as lymphoma.[52,53] Lymph nodes with non-tuberculous mycobacterial infection can show intranodal cystic necrosis, but the same feature is common in the event of a cancer especially in cases of Hodgkin's and NHL, after treatment.[52]

When second level investigations are recommended (Figure 1), these should include serological tests for *Toxoplasma gondii, Bartonella henselae, Francisella tularensis, Borrelia burgdorferi, Brucella* spp., *Listeria monocytogenes*, and CMV. Blood cultures should be limited to cases of systemic involvement with fever and/or suspected sepsis. Among serologic tests, determination of IgM specific for a particular micro-organism is generally useful for the diagnosis of an acute infection. *T. gondii*-specific IgM antibodies are in most cases detectable already after 15 days of infection.[35] However, in some circumstances, the sensitivity of specific IgM test is low or the test is not available. In these cases, the documentation of increase in specific IgG titer over time may be of help to confirm the diagnosis of acute/recent infection. The diagnosis of tularemia may be confirmed by a positive hemagglutination test and specific antibody titer >1:160 or a 4-fold increase after 2 weeks.[54] The sensitivity of the tests for Bartonellosis is very low when the ELISA test is used; indirect immunofluorescence assay is more sensitive, but not largely widespread.[55]

A chest X-ray, abdominal ultrasound, and referral to oncologist are recommended if previous investigations are not diagnostic and lymphadenopathy persists over time.

In a case of deep neck abscesses, which may require a surgical approach, or if malignancy is suspected, computerized tomography (CT) or magnetic resonance imaging (MRI) should be performed, according to ACR guidelines.[56] With respect to ultrasound scan, CT/MRI have the advantage of a higher precision in anatomical location, in the description of the shape, internal lymph nodal architecture, possible impregnation of lymph nodes, and a better characterization of the surrounding tissues. The use of FDG-PET should be limited to the assessment of the extent of any underlying disease, in the cases indicated (e.g. Hodgkin's lymphoma). The high dose of radiation is the major contraindication for this imaging in children.[56]

Literature data regarding the sensitivity and specificity of FNAB in children are conflicting. While in adults the specificity and sensitivity for the diagnosis of malignancy by FNAB are reported to be high [respectively 85–95% and 98–100%], the results are less encouraging in children, ranging from 63% to 85%.[57] The performance of FNAB in children is operator-dependent; the whole lymph node architecture is not evident; and high rate of false-negative results does not allow a definitive diagnosis in many cases. Therefore, the use of FNAB in in children has been not recommended, in general, by the panel, especially in case of suspected malignancy. Excisional biopsy is recommended when the first- and second-level investigations did not allow to reach a final diagnosis, and, in particular, in the presence of at least one of the following criteria: tender lymph nodes larger than 2 cm that is not reduced in size over a period of 4–6 weeks or does not normalize over a period of 8–12 weeks; localization at risk for malignancy (e.g., supraclavicular region); hard, fixed, and/or not painful lymph node; persistent systemic symptoms (fever with no known cause, night sweats, weight loss >10%).[27] Excisional biopsy should be performed on the largest lymph node, and capsule should be removed intact. When biopsy/excision is performed, appropriate histopathological analysis testing should be performed. If possible specimens should be immediately submitted fresh to the laboratory immediately after collection (within 30 minutes from excision).[58] Samples need to be processed such that investigations can be carried out if required, including microscopy on appropriately fixed and stained samples; immunological investigations by immunohistochemistry and/or flow-cytometry; cytogenetic analysis by Giemsa-banding (G-banding); FISH on cell suspensions, films, imprints or paraffin sections; molecular genetic analysis by PCR, real-time PCR, or gene sequencing.[58]

Conclusions

Comprehensive reviews of cervical lymphadenopathy in children have been previously published.[2–5] However, there is still no consensus for a definitive approach to the management of this condition. The purpose of our algorithm is to assist pediatricians in the diagnosis and timely treatment of cervical lymphadenopathy, suggesting situations in which a watchful waiting may be considered a safe approach, those in which empiric antibiotic therapy should be administered and those requiring a timely diagnostic workup, considering the high risk for a severe underling disease. The four scenarios described in our algorithm are the most frequent ones, according to literature reports. However, a child may have characteristics intermediate between two situations or evolving from one situation into the other, and an individualized diagnostic workup may be necessary. However, the algorithm is a useful evidence-based tool for the management of children with cervical lymphadenopathy, allowing a focused strategy according to the child's history and clinical situation, and a rational use of investigations. Further studies are needed for its validation in the clinical practice.

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Key issues

- The vast majority of children with cervical lymphadenopathy has with a benign self-limiting condition and cancer occurs at a rate lower than 1%, but >25% of malignant pediatric cancers involve the head and neck regions.
- The present practical algorithm may be followed in order to select children at risk for complex diseases requiring urgent referral to the oncologist (indicated by the red flags), those requiring laboratory tests, imaging investigations or tissue sampling, and those requiring an empirical antibiotic therapy or a watchful waiting.
- A careful follow-up is recommended in every child, since any lymphadenopathy which does not regress in 4–6 weeks or incompletely resolves in 8–12 weeks should be investigated.
- Ultrasonography scan is recommended as a first-level investigation. However, no single ultrasound feature is specific for a benign or a malignant disease.
- Fine needle aspiration biopsy (FNAB) in children is poorly useful, in general, in Western countries, especially in case of suspected malignancy, due to high proportion of false-negative results.
- Excisional biopsy is recommended in the suspicion of cancer or when the first- and second-level investigations did not allow to reach a final diagnosis.
- In nontuberculous mycobacterial lymphadenopathy, when feasible, complete lymph node surgical excision is the most effective therapeutic option.

References

Reference annotations

** Of interest*

*** Of considerable interest*

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