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# Lymphadenopathy in children: A streamlined approach for the surgeon — A report from the APSA Cancer Committee

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ABSTRACT

*Background/purpose:* Lymphadenopathy is a common complaint in children. Pediatric surgeons are often called upon to evaluate, treat, and/or biopsy enlarged lymph nodes. With many nonsurgical causes in the differential diagnosis, the surgeon plays the important role of providing reassurance and timely diagnosis while minimizing the pain and morbidity associated with surgical interventions in children. The purpose of this summary paper is to provide a management guide for surgeons working up children with lymphadenopathy.
*Materials/methods:* The English language literature was searched for "lymphadenopathy in children". All manuscript types were considered for review, regardless of medical specialty, with emphasis placed on published guidelines, algorithms, and reviews. After thorough review of these manuscripts and cross-referencing of their bibliographies, the attached algorithm was developed, with emphasis on the role and timing of surgical intervention.
*Results:* The APSA Cancer Committee developed the attached algorithm to fill a gap in the surgical literature. It outlines lymphadenopathy workup and treatment with emphasis on the role and timing of surgical intervention.
*Conclusion:* This review defines and summarizes the common etiologies and presentations of lymphadenopathy in children, and offers a straightforward algorithm for evaluation of and treatment with an emphasis on malignancy risk and surgical management.
*Type of study:* Summary paper.
*Level of evidence:* Level V.



**Contents**



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Lymphadenopathy is common in children and is often a diagnostic challenge for clinicians [1]. Lymph nodes may become enlarged through the proliferation of normal cells such as in a reactive or infectious process, infiltration with abnormal cells as in malignant processes, suppuration owing to necrosis of the nodal tissue, or deposition of foreign material within the node as in lipid storage disorders [2] Lymphadenopathy is classified as diffuse or isolated depending upon the number of nodal basins affected. Surgical biopsy often provides definitive diagnosis but may be unnecessary in some cases. While an exhaustive discussion of all causes of lymphadenopathy is outside the scope and goal of this review, we outline the most commonly encountered etiologies for lymphadenopathy in children, and make recommendations regarding evaluation, and diagnostic testing, and surgical intervention.

## 1. Methods

A comprehensive review of the current English language literature was searched for "lymphadenopathy in children". All manuscript types were considered for review, regardless of medical specialty, with more emphasis placed on published guidelines, algorithms, and reviews. After thorough review of these manuscripts by three of the authors (CG, JA, DR) and cross-referencing of their bibliographies, the attached algorithm was developed, with emphasis on the role and timing of surgical intervention (Fig. 1). The epidemiology, etiology, evaluation, and medical and surgical management of lymphadenopathy in children are summarized in this review.

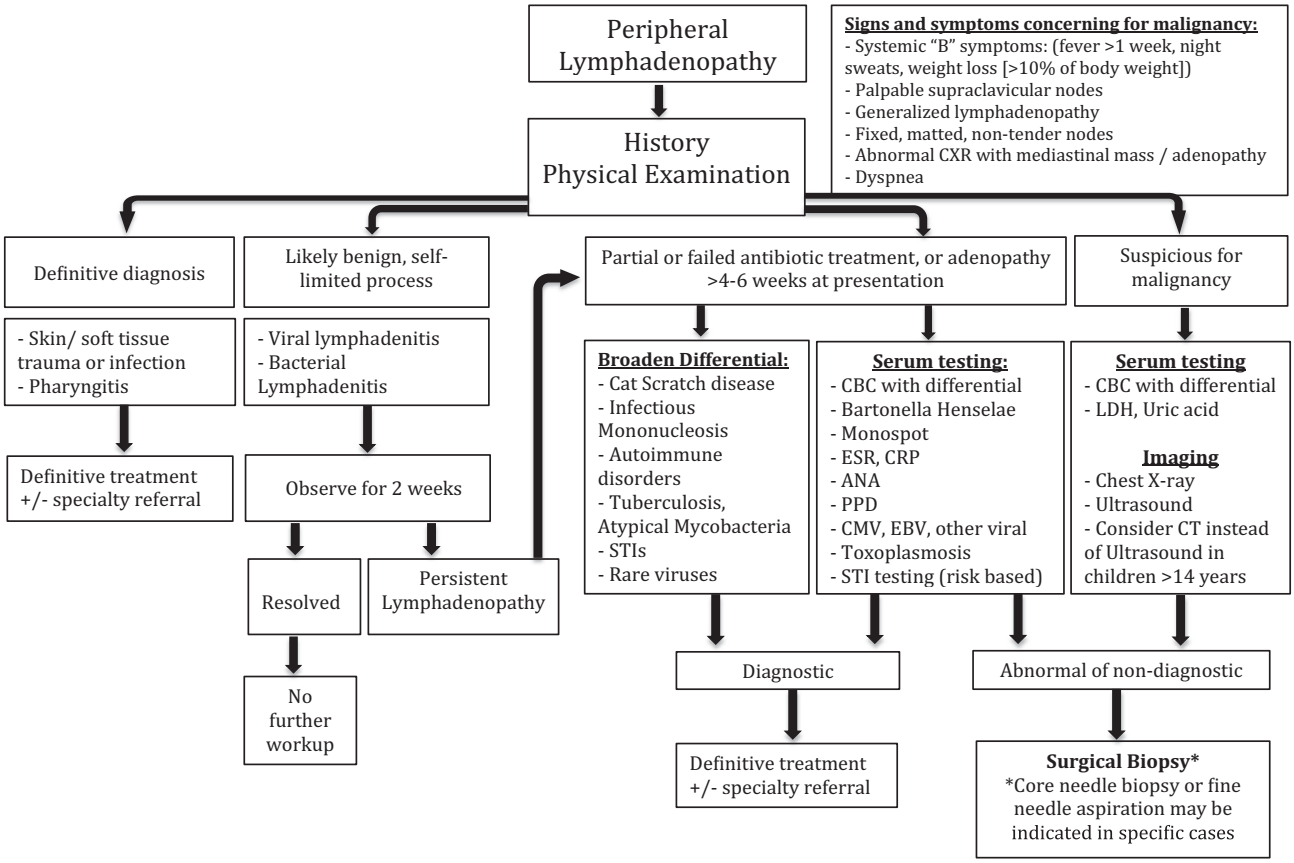


**Fig. 1.** Lymphadenopathy workup algorithm developed by the APSA Cancer Committee. **Flowchart:** Suggested algorithm for the workup and management of lymphadenopathy in children.

## 2. History

In the workup of peripheral lymphadenopathy (LAN), a complete medical history, history of present illness, and review of systems are critical. Focused questions such as the presence and duration of associated symptoms, and known exposure or travel will help to narrow the differential or confirm a diagnosis. The frequency of palpable lymphadenopathy ranges from 41% in children ages 2–5, to as high as 90% in those between 4 and 8 years of age [3,4]. Because up to 90% of healthy children will have palpable LAN at one time or another, it is important to minimize the risk of invasive procedures by following a diagnostic algorithm. The duration of adenopathy as well as prior treatment attempts may help to narrow the differential diagnosis and guide subsequent therapy. LAN is defined as acute when present for less than 2 weeks, subacute for 2–6 weeks, and chronic when persisting longer than 6 weeks [5]. In addition to duration, timing of onset, location, solitary or diffuse nature, and persistence of adenopathy are important details to ascertain [6,7,8].

A detailed review of systems identifying associated symptoms can aid in determining a differential diagnosis. Rashes, arthralgias, myalgias, and myositis suggest an autoimmune disorder. Infectious etiologies are more likely to be accompanied by fevers, overlying skin changes, upper respiratory symptoms, or a history of ill contacts. Response to previously prescribed antibiotics also suggests a bacterial source. Viral lymphadenitis is often accompanied by a viral prodrome. Older children and teens should be queried regarding sexual activity and other high-risk behaviors. “B symptoms” of fevers, night sweats, and unexplained weight loss should increase the suspicion for lymphoma [9]. Malignant causes are also suggested by any combination of recent fevers, unintentional weight loss of >10% body weight in under 6 months, lack of appetite, weakness, or unprovoked pain [10].

Confirming immunization status as well as family history may uncover unusual infectious, hereditary or autoimmune conditions. For example, posttransplant lymphoproliferative disorder (PTLD) should be considered in previously immunosuppressed transplant patients. In addition to family and social history, exposures to domestic or wild animals, and any other travel or environmental related history should be elicited. Local trends of infectious diseases and regional fungal and infectious causes should be kept in mind.

### 2.1. Physical exam

LAN is a common finding in children, frequently identified on routine physical examination. Location of palpable lymph nodes in children varies by age, with occipital and posterior auricular nodes present more commonly in infants than in older children, while cervical and inguinal nodes are more readily appreciated in children aged 2–6 years [11]. The incidence of palpable lymphadenopathy among healthy children has been reported to range between 41% and 67%, and varies by age, in one report as high as 90% in the 4–8 year age range [1,3,4,12]. In a study which included 218 children with cervical lymphadenopathy, 70 patients (41.3%) had a specific etiology identified, including infectious (27%), malignant (2.7%), or other causes (11.4%), while the remaining 59% had no identifiable cause [13]. A detailed physical exam should be performed, with the goal of delineating the characteristics and distribution of the involved nodes, as well as any associated physical findings. General appearance, weight changes and poor overall growth curves may point to a chronic disease or systemic illness [8]. Exposing the skin drained by the affected lymph node basin will allow a thorough inspection for signs of trauma, scratches, skin lesions, or rashes. Abdominal examination should be performed to evaluate for splenomegaly and/or hepatomegaly. The approach to examination of each region of LAN is outlined below, and clinical features associated with LAN concerning for malignancy are summarized in Table 1.

Normal lymph nodes are defined as <1 cm in longest diameter in most regions of the body [1,9,10,14]. Inguinal nodes may be slightly larger, up to 1.5 cm, while suboccipital, posterior auricular, preauricular, and epitrochlear nodes are typically less than 0.5 cm. Supraclavicular lymph nodes are not palpable unless abnormally enlarged. Palpation of the involved nodes will determine the size, number, mobility, and consistency. Tenderness, fluctuance, and hindrance to mobility should raise concern for suppurative lymphadenitis. Acute onset of associated tenderness, erythema, warmth, swelling, and skin changes usually indicates an acute infection [8]. Firm, matted, fixed nodes are a harbinger of more serious diagnoses such as malignancy or granulomatous disease, while small, soft, mobile lymph nodes in the neck, axilla, and groin may be observed if there are no other concerning clinical symptoms [15]. While the constellation of node characteristics can be predictive for diagnosis, Soldes and colleagues found that higher numbers of peripheral nodes are correlated with increased risk of malignancy [14]. Common causes for node enlargement in each area are outlined in Table 2.

Location of lymphadenopathy can also help the surgeon narrow the differential diagnosis. Noncervical LAN should prompt evaluation for rashes, trauma, superficial skin infections, and new or changing skin lesions that could provide an etiology. Enlarged supraclavicular nodes are associated with malignancy in about 25% of those less than the age of 40 [16], and should increase the index of suspicion for malignancy when palpated in a child. Right supraclavicular nodes drain the lungs, mediastinum and esophagus directly; while left supraclavicular nodes drain the left thorax, left supraclavicular lymphadenopathy should raise suspicion for intraabdominal or retroperitoneal pathology draining via the thoracic duct [16]. In one single institution study of 392 children with head and neck LAN, while supraclavicular location represented only 6.8% of the cohort, 81.4% of such children were diagnosed with malignancy [10]. Axillary LAN is commonly seen with cat scratch disease or local trauma, but malignancies such as lymphoma, leukemia, skin cancers, and soft tissue sarcoma remain in the differential [9]. Inguinal nodes may be normal up to 1.5 cm diameter in older children and teens. In addition to eliciting a history of sexual activity and sexually transmitted disease risk factors, the genitals should be examined for signs or rashes, exudates, and sexual abuse. Finally, generalized LAN, which involves more than two noncontiguous lymph node groups, suggests a diffuse process such as autoimmune disease, infection, or cancer such as lymphoma [16].

**Table 1**
Clinical features associated with peripheral lymphadenopathy concerning for malignancy [14,55,59,60,72].

| |
|---|
| Systemic symptoms (fever >1 week, fatigue, night sweats, weight loss [>10% of body weight]) |
| Supraclavicular (lower cervical) nodes |
| Generalized lymphadenopathy |
| Fixed nontender nodes in the absence of other symptoms; matted nodes |
| Nontender lymph nodes >1 cm with onset in the neonatal period |
| Nontender lymph nodes ≥2 cm in diameter that increase in size from baseline or do not respond to two weeks of antibiotic therapy |
| Abnormal chest radiograph (particularly mediastinal mass or hilar adenopathy) |
| Abnormal complete blood count (eg, lymphoblasts, cytopenias in more than one cell line) |
| Absence of symptoms in the ear, nose, and throat regions |
| Persistently elevated or rising erythrocyte sedimentation rate or C-reactive protein |

## 3. Differential diagnosis for lymphadenopathy

### 3.1. Malignancy

With a focus on peripheral adenopathy of unknown etiology, the evaluation of nodal disease for malignancies where nodal resection occurs as part of the primary tumor resection, such as Wilm's or neuroblastoma is beyond the scope of this paper. However, in the pediatric

**Table 2**
Differential diagnosis of lymphadenopathy based on region. Table compiled based on [8,9,10,16].

| Lymph node basin | Pathologic size | Locations drained by lymph node basin | Benign differential | Malignant differential |
|---|---|---|---|---|
| Suboccipital, preauricular, postauricular | >5 mm | Skin<br>Scalp | Skin, scalp infections | |
| | | Scalp | Skin infections | Lymphoma |
| Posterior cervical | | Skin | Mycobacterial infection: rubella, toxoplasmosis, mononucleosis | Skin malignancies |
| | | Scalp, neck, upper chest | | Squamous cell carcinoma |
| Submandibular, submental | | Oral cavity | Skin infections | Leukemia |
| Anterior cervical | | Larynx | Infectious mononucleosis | Lymphoma |
| | >1 cm | Tongue | URI | Squamous cell carcinoma |
| *Jugulodigastric node may be normal up to 1.5 cm | | Oropharynx | Mycobacterial infection | |
| | | Anterior neck | Dental disease | |
| Supraclavicular | Any size is suspicious for malignancy | GI, GU, pulmonary | Mycobacterial | Abdominal malignancy |
| | | Thyroid | Fungal | Thoracic malignancy |
| | | Larynx | Thyroid/larynx benign disease | |
| Infraclavicular | | Mediastinum<br>Chest | | NHL |
| Axillary | >1 cm | Breast | Skin infections | Lymphoma |
| | | Upper extremity | Trauma | Leukemia |
| | | Chest wall | Cat-scratch disease | Soft tissue sarcoma |
| | | | Sarcoidosis | Skin cancers |
| Epitrochlear | > 5 mm | Ulnar forearm hand | Infection | Lymphoma |
| | | | Cat scratch disease | Melanoma, other skin malignancies, soft tissue sarcoma |
| Inguinal | >2 cm | Lower abdomen | STIs | Lymphomas |
| | | External genitalia | Benign reactive adenopathy | Skin cancers, soft tissue sarcoma |
| | | Anal canal | Skin infections | |
| | | Lower 1/3 vagina | | |
| | | Lower extremities | | |
| Generalized | > 2 noncontiguous lymph node groups | | Infection | Leukemia |
| | | | Autoimmune disease | Lymphoma |
| | | | Viral illnesses (infectious mononucleosis) | Disseminated malignancy |
| | | | Drug side effect | |

population, a few common oncologic diagnoses warrant special mention.

Nodal disease occurs in some types of sarcomas especially at some primary tumor locations. Regional nodal disease is identified in up to 23% of patients with extremity rhabdomyosarcoma and is associated with worse outcomes [17]. Although it is less common, nodal involvement can also be seen in clear cell sarcoma, epithelioid sarcoma, angiosarcoma, and occasionally synovial sarcoma [18]. Some advocate the use of imaging alone to identify tumor spread to regional nodes in sarcoma patients. However, it is clear that up to 50% of patients with nodal disease will be missed and therefore undertreated resulting in worse outcomes, using imaging alone [19,20]. Therefore, regional nodal evaluation is required in rhabdomyosarcoma patients older than 10 years with paratesticular tumors and extremity tumors and is recommended for fusion positive alveolar tumors and truncal tumors. To help identify patients with nodal disease and to minimize the morbidity associated with excisional biopsy, alternative techniques have been sought. The potential to use PET/CT to identify regional nodal disease has been evaluated. Forty three percent of malignant sentinel nodes had negative cross-sectional and functional imaging findings (CT specificity, 71%; MRI specificity, 64%; PET specificity, 52%). PET–CT had a high false positivity rate with a positive predictive value of 29%; however, the negative predictive value was 79% (11/14). These results suggested that PET-CT is not specific enough for nodal metastases such that biopsy can be avoided [21].

The use of sentinel node biopsy in adult and pediatric melanoma is well established. Compared with adults, children were more likely to have nodal metastases [22]. On average, approximately 25%–37% of patients with melanoma will have positive sentinel lymph nodes and a positive SLN conveys a decreased survival (90%) compared to node negative (100%). Both outcomes are better than similar adult patients [23–26]. Completion lymph node dissection is no longer recommended [27].

Malignancy should be considered in the differential of any grossly enlarged or persistent lymphadenopathy (4–6 weeks) and is a frequent indication for surgical biopsy referrals. Owing to its invasive nature and potential need for sedation, surgical biopsy should be performed only after an initial medical evaluation has ruled out common etiologies that do not require tissue diagnosis. Lymph nodes suspicious for malignancy are large, firm, fixed, nontender, and may be localized to one nodal bed or diffuse (see Table 1). Palpable nodes in the supraclavicular region are abnormal and concerning for malignancy, and should therefore prompt additional imaging and consideration of biopsy [14]. Hodgkin lymphoma and non-Hodgkin lymphoma are the two most common malignant conditions presenting with lymphadenopathy, although malignant etiologies discussed above such as metastatic rhabdomyosarcoma, melanoma, salivary gland tumors, posttransplant lymphoproliferative disorder, and neuroblastoma should be considered. The surgeon should also keep thyroid carcinoma in the differential diagnosis of cervical lymphadenopathy, particularly in teenagers.

### 3.2. Infectious

#### 3.2.1. Viral infections

Numerous viral etiologies can cause lymphadenopathy in children. Common upper respiratory tract viral pathogens such as adenovirus, rhinovirus, enterovirus, influenza, and parainfluenza typically result in

cervical or submandibular lymphadenopathy. These viral etiologies should be entertained in the context of associated symptoms of fever, cough, pharyngitis, and rhinorrhea, length of symptoms, and potential exposure to vector sources [1,2,13]. Members of the herpesvirus family including Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are also common causes of lymphadenopathy among children and adolescents, affecting nearly 95% of the population at some time, most without acute or recognizable illness [28–30]. Surgical biopsy of affected lymph nodes is generally not indicated if serologic testing confirms its presence.

Infection with human immunodeficiency virus (HIV) results in nontender lymphadenopathy involving the cervical, axillary, and occipital lymph nodes in association with other symptoms such as fevers, oral thrush, diarrhea, parotitis, failure to thrive, recurrent bacterial or opportunistic infections, and hepatosplenomegaly [31,32]. The diagnosis of HIV can be made with polymerase chain reaction detection of the HIV viral genome in host blood of suspected individuals.

#### 3.2.2. Bacterial infections

Common bacterial infections that may present with localized lymphadenopathy include *Streptococcus*, *Staphylococcus aureus* (particularly methicillin resistant *Staphylococcus aureus*, MRSA), *Bartonella henselae*, *Mycobacterium* species including *Mycobacterium avium* complex (MAC), and *Mycobacterium tuberculosis*. In general, bacterial sources result in isolated adenopathy or lymphadenitis, compared to generalized involvement more commonly associated with viral processes.

Bacterial lymphadenitis most commonly affects cervical nodes, but occipital, submandibular, and inguinal nodes may also be frequently involved. *Staphylococcus* is the responsible pathogen in approximately 80% of cases, followed by *Streptococcus* in 15% [33]. Clinical history and evaluation are important to determine a likely etiology, as bacterial sources for isolated submandibular, cervical, or inguinal nodes are more commonly seen in young children, while axillary and inguinal nodes are more commonly involved in adolescents [5]. Acute bacterial lymphadenitis caused by these infections is usually successfully treated with specific antibiotic coverage, but some involved nodes may undergo liquefactive necrosis and/or abscess requiring surgical incision and drainage for source control. Failure to resolve despite 2–4 weeks of appropriate therapy should prompt further testing for alternate etiologies, with consideration of surgical biopsy to aid in the diagnostics [5].

Other less common bacterial pathogens resulting in lymphadenopathy include *Bartonella henselae*, the causative agent in cat scratch disease, affecting regional nodal sites including axillary (>50%), cervical (28%), and inguinal regions (<25%) depending on the site of inoculation [5], and *Mycobacterium tuberculosis* (scrofula) or nontuberculous strains of *Mycobacterium* resulting in chronic cervical lymphadenitis. These infections are more common in children between ages 1 and 5 years, and may reflect contact with sources of these bacteria including soil and contaminated water [34]. Initial presentation for both tuberculosis and nontuberculosis infection is similar, including rapid nodal enlargement over 2 to 3 weeks with overlying skin color changes. Surgical excision of all involved nodes, overlying involved skin, and sinus tracts is the optimal treatment for immunocompetent patients [5,34]. If surgical excision would result in unacceptable morbidity, then systemic multidrug antibacterial regimen according to treatment recommendations for complex pulmonary MAC disease should be initiated, consisting of clarithromycin, rifampin, and streptomycin [34].

#### 3.2.3. Fungal infections

The systemic fungal infections most frequently encountered during the evaluation of lymphadenopathy include histoplasmosis and coccidioidomycosis. These infections are localized to particular regions of North America, and therefore a careful patient history including travel is important for timely diagnosis and treatment [35]. Solitary pulmonary nodules and mediastinal or hilar lymphadenopathy are manifestations of recent or prior histoplasmosis infection, so must be differentiated from malignant etiologies. Location of involved nodes in the middle mediastinum and the presence of elevated anti-*Histoplasma* antibody titers favor an infectious source; therefore, biopsy usually can be avoided [36,37]. Coccidioidomycosis, or valley fever, is acquired in a similar manner to histoplasmosis, but is geographically endemic to the southwestern regions of the United States. Mediastinal and hilar adenopathy as well as pulmonary nodules may be detected on imaging, and diagnosis is made serologically or via culture [38].

### 3.3. Autoimmune disorders

Lymphadenopathy may be a manifestation of a number of autoimmune disorders. Systemic lupus erythematosus (SLE) is a chronic multisystem autoinflammatory disease primarily affecting females. Although lymphadenopathy is present in as many as 25%–50% of patients, its presence is not a criterion for diagnosis [39,40]. Lymphadenopathy may be the first presenting sign in patients with SLE and is more likely to be associated with constitutional symptoms such as fever, weight loss, fatigue, and rash, which are suggestive of active disease [39,41,42]. Clinical manifestations and laboratory investigations typically lead to a diagnosis of SLE without the requirement for a lymph node biopsy in most scenarios.

Although sarcoidosis is uncommon in children, the diagnosis should be considered in the evaluation of lymphadenopathy when other more common diagnoses have been ruled out. The presentation of sarcoidosis is characterized by involvement of multiple organ systems including mediastinal lymphadenopathy (95%), pulmonary symptoms (>90%), peripheral lymphadenopathy (30%), uveitis (20%–50%), and rash (25%) [43]. Histopathological evaluation of lymph nodes reveals noncaseating granulomas. Kikuchi–Fujimoto disease, chronic granulomatous disease, and autoimmune hemolytic anemia are additional immune-mediated disease processes that may lead to generalized or site-specific lymphadenopathy and should be entertained in the setting of specific symptoms or when other etiologies have been excluded.

### 3.4. Medication-related lymphadenopathy

Several medications can result in generalized lymphadenopathy as a side effect; therefore, a careful history including recent medications should be obtained [9,44]. Precipitating medications include phenytoin, phenobarbital, carbamazepine, sulfonamides, allopurinol, aspirin, isoniazid, penicillin, iodine, tetracycline, phenylbutazone, barbiturates, cephalosporins, atenolol, hydralazine, quinidine, pyrimethamine, and primidone. Other symptoms may be encountered with drug-associated lymphadenopathy, including fever, rash, jaundice, cytopenias, and hepatosplenomegaly.

## 4. Adjunct testing

If following a thorough history and physical examination a benign or self-limited process is diagnosed or deemed most likely, no further testing is required. In the case of concerning history or examination findings, laboratory testing and imaging may be required for clarification.

### 4.1. Laboratory evaluation

In patients with failure of resolution after 4–6 weeks or those with concerning associated findings, initial labs should include complete blood count (CBC) with differential, inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and lactate dehydrogenase (LDH) [8]. Leukocytosis is seen in bacterial lymphadenitis and infections and is often accompanied by tenderness, fever, and skin changes. Pancytopenia or presence of blast cells suggests leukemia. Infectious mononucleosis often causes atypical lymphocytosis. Throat cultures and viral serology should be obtained as indicated by associated symptoms. Rapid Strep antigen test detects streptococcal infections. In

patients with suggestive risk factors or overlying skin changes suggestive of mycobacterial infection, or recent BCG vaccination, a tuberculin skin test (PPD) should be placed [10]. Serologic testing for *Bartonella henselae*, CMV, toxoplasmosis, EBV, and others is widely available and should be included in the evaluation for LAN as clinically appropriate.

### 4.2. Imaging

When physical exam identifies abnormal nodes, ultrasound (US) is an excellent adjunct to define the number, character, and size of LAN. Ease of use, wide availability, lack of ionizing radiation, and the lack of a need for sedation make ultrasound an ideal imaging modality for peripheral LAN. Ultrasound imaging is helpful in all stages, from diagnosis, through treatment, and for follow up if necessary [45]. The American College of Radiology guidelines for imaging suggest ultrasound as the initial imaging study of choice in children <14 with cervical LAN given its lack of ionizing radiation. CT and MRI can be used to further characterize abnormalities seen on ultrasound and better assess deep neck adenopathy [46].

Ultrasonographically normal lymph nodes have an ovoid shape, homogenous echotexture, smooth borders, and a clearly distinguishable fatty hilum. Fixed, rounded nodes with irregular borders, hypervascularity, or loss of the central hilum are abnormal. Other findings that can be evaluated on US include echogenicity of the hilum, vascularity, and abnormal L/S ratio, a measure of the long/short axis. An L/S ratio around 1 is also considered abnormal, representing a node that is more rounded than oval shaped [10]. Strassen et al. reviewed a cohort of 262 patients, and found the following clinical and ultrasound characteristics to be highly predictive of malignancy: hilar vascularization, sonographic nonhomogeneity, large size, firm texture, lack of mobility, and supraclavicular location. However, in this cohort, only 4% were children, and generalization of these findings to children is unclear [47]. Further, they note that patients with lymphoma tended to have multiple small and hypervascular nodes compared to metastatic nodes associated with other malignancies which tend to be large and solitary with mixed vascularity [3,47]. Color Doppler evaluation helps to determine whether abnormal vascularity is present, pointing towards inflammatory or infectious etiologies [8]. Lymphomas show strong hilar vascularity, while metastatic disease tends to show peripheral or mixed vascularity [47]. Contrast enhanced ultrasound (CEUS) and elastography are newer technologies that may improve differentiation between malignant and benign disease; they are not yet widely used owing to cost and the need for specially trained personnel [47].

When US is nondiagnostic, and in anatomic areas requiring more detailed imaging, CT and MRI may be beneficial. Plain chest radiographs are useful in the evaluation of chronic localized and generalized LAN in trunk and neck LAN. It facilitates diagnosing some infectious and malignant etiologies of LAN and may be the first diagnostic clue of a systemic or disseminated illness. Chest x-rays are critically important in cases of suspected lymphoma, where mediastinal masses may preclude general anesthesia.

Taking into account the literature summarized to this point, and the paucity of guidance in the surgical literature, the APSA Cancer Committee developed this algorithm for the workup of lymphadenopathy in children. Specifically targeted to surgeons, it provides stepwise guidance from referral through biopsy where appropriate (Fig. 1).

## 5. Initial management

Acute, unilateral anterior cervical lymphadenitis should be treated with antibiotics covering the most common pathogens, *Staphylococcus aureus* and group A *Streptococcus* [48]. A typical treatment regimen for bacterial lymphadenitis includes oral clindamycin, amoxicillin/clavulanate, or macrolides. Failure of resolution may demand intravenous antibiotics. Antibiotic choice is also influenced by level of suspicion, local trends, and concern for MRSA [4]. When LAN is treated or observed in the outpatient setting, close follow up is mandatory. Failure of regression after 4–6 weeks should prompt diagnostic biopsy [45]. It is important that corticosteroids be avoided until a definitive diagnosis is made. Corticosteroids may mask or partially treat leukemia and lymphoma, causing a delay in or lack of diagnosis [3].

### 5.1. Lymph node biopsy

#### 5.1.1. Timing

Peripheral lymphadenopathy in children is usually benign, and a large percentage will resolve without intervention. It is therefore not always necessary to define the etiology at the time of initial presentation. The urgency of evaluation is determined by the patient's condition and the concerns for malignancy. Clinical features associated with peripheral lymphadenopathy that are concerning for malignancy or granulomatous disease in children are listed in Table 2 [14,45,49,50]. Early surgical evaluation of adenopathy is indicated for children with these malignant associated risk features, and in cases where lymphadenopathy persists without a diagnosis after 2 weeks of observation, or when the patient presents to the surgeon with greater than 4–6 weeks of ongoing adenopathy with or without empiric antibiotic therapy.

#### 5.1.2. Methods of biopsy

When biopsy is indicated, it is important to determine which node is most likely to provide a definitive diagnosis. As a general guideline the most abnormal (i.e. largest, firmest, most tender) node is selected, especially if adenopathy is generalized. If no single node predominates, the suggested order of preference for nodal location to biopsy is supraclavicular, cervical, axillary, and inguinal, since nonspecific results are more common with axillary and inguinal nodes [51]. In addition, complications such as infection, lymphocele, and injury to the neurovascular structures are also higher in those locations. These recommendations are general guidelines and do not apply to directed biopsy in the setting of a known malignancy or diagnosis or when using sentinel node or PET/CT techniques.

There are 3 methods that are utilized for the surgical evaluation of lymphadenopathy in children. These include excisional or incisional biopsy, core needle biopsy and fine-needle aspiration. Each of these techniques has instances when they are appropriate. In addition, institutional resources and practice patterns may impact how each institution manages the biopsy.

#### 5.1.3. Excisional biopsy

The current gold standard for lymph node biopsy in children is surgical biopsy, usually excisional but sometimes incisional, which can usually be accomplished under either local or general anesthesia. This technique is primary because most nodes are superficial and relatively accessible and there is a high likelihood that an adequate amount of tissue will be obtained to ensure diagnosis. Excisional biopsies provide enough tissue; approximately 1 $cm^3$ is required to allow morphological assessment, immunohistochemical stains, and chromosomal analysis testing for specific translocations, genes or point mutations. There are no specific data to support this recommended volume but it is the volume of tissue usually requested by Children's Oncology Group protocols and is sufficient to assure adequate sampling while minimizing the risk of needing to repeat surgical biopsy. Disaggregated cells can be analyzed by flow cytometry, and microbiological analysis of the tissue. Histologic examination of intact nodal tissue allows identification of abnormal cells and node architecture, which is important for the diagnosis of lymphoma. False-negative results occur if uninvolved nodes are biopsied. Careful review of radiologic and physical exam findings will help minimize this occurrence [52]. Drawbacks to excisional biopsy include its invasive nature, the potential need for general anesthesia, and the higher risk of infection, neurovascular injuries, and bleeding compared to other techniques. Incisional biopsy is acceptable in nodes that are greater than 2–3 cm to minimize potential complications that would be more likely

to occur with complete excision of large nodes in certain areas. However, this size is a recommendation and has not been empirically determined. Since the main purpose for biopsy is to rule out a malignancy, the risk of complications must be balanced against accurately identifying malignancy. Techniques such as dissecting on the surface of the node, adequate traction (such as using a braided suture to assist in retracting the node) and exposure, as well as preoperative imaging to identify the optimal approach and identify nearby structures are all potentially helpful to decrease the risk of complications. Quoted complication rates range from 0% to 6% with the majority of these being related to inadequate tissue for diagnosis leading to a second procedure [52–55].

#### 5.1.4. Needle (FNA/core) biopsy

Because of the risks associated with excisional biopsy and to improve cosmesis, the use of fine-needle aspiration (FNA) or core needle biopsy (CNB) may be utilized as a first step. These techniques may obtain sufficient tissue to allow diagnosis or identify a smaller population of patients that require surgical biopsy. FNA biopsy allows cytological evaluation for cell morphology and immunophenotyping, as well as microbiology studies; however, obtaining proper sampling and specimen interpretation is very user and infrastructure dependent. Core needle biopsy has the advantage of obtaining more tissue and allowing for assessment of architecture, which may allow increased diagnostic accuracy. Both FNA and CNB can be performed using local anesthesia and sedation and when guided by US has the benefit of obtaining tissue from nodes that would be difficult to access by open surgical techniques (mediastinal, abdominal, deep head and neck).

#### 5.1.5. FNA biopsy

In general, FNA cytology is a safe, quick, accurate, and minimally invasive technique to evaluate and triage patients with lymphadenopathy [56]. However, the incidence of an inadequate specimen using FNA is approximately 20% [57,58]. Fine needle aspiration is widely used in adults but not as prevalently in pediatric patients owing to a lack of experience in interpreting pediatric FNA samples as well as concerns regarding the accuracy of cytology in evaluating lymph nodes owing to the small amount of tissue taken.

FNA may be a useful triage tool for differentiating benign reactive lymphadenopathy from malignancy especially for the evaluation of pediatric cervical lymphadenopathy. In systematic reviews evaluating FNA in pediatric and adult patients with head and neck masses associated with lymphadenopathy, FNA had a specificity of 92%–100% and a sensitivity of 67%–100% for diagnosing cancer [59,60]. One study of pediatric cervical adenopathy FNA diagnosed benign diseases in 15 patients and malignant diseases in three patients. FNA had a diagnostic sensitivity of 100%, positive-predictive value of 93.3%, and accuracy of 94.5% in identifying the etiology of pediatric cervical lymphadenopathy [61]. In another study of 71 pediatric patients FNA identified benign lesions and malignant neoplasms with only 2 nondiagnostic specimens [62]. FNA was sufficient for diagnosis in 76% of cases. There were no missed malignancies.

The diagnosis of lymphoma should not be attempted on FNA since it is necessary to get histopathological confirmation and subtyping; in addition, it can be difficult to interpret a cell without the surrounding tissue [63]. Therefore, at this time the initiation of treatment based solely on FNA is only indicated in emergencies [53,64].

#### 5.1.6. Core needle biopsy

Core needle biopsy has been proposed as an alternative or adjunct to excisional biopsy for the evaluation of lymphadenopathy. A study in adult and pediatric patients with cervical lymphoma revealed that CNB was sufficient in 69% of patients compared to open biopsy that was sufficient in 98% [65]. Similar results were observed using CNB to evaluate lymph nodes localized in mediastinal, abdominal, retroperitoneal, or thoracic regions [66]. Core needle biopsies did not provide a definitive diagnosis in 8.3% of cases, compared to 2.8% for excisional biopsy ($p = 0.0003$). Their conclusion was that CNB appeared inferior to surgical excisional at providing a definite diagnosis and at classifying lymphoma. However, US guidance facilitates lesion localization and improves the adequacy and accuracy of biopsy with CNB. Sensitivity for the detection of malignancy was significantly better for US guided CNB (98.8%) than standard surgical biopsy (88.7%; $P < 0.001$). The estimated cost per biopsy performed with excisional biopsy was 24-fold higher than US guided CNB, and patients who received excisional biopsy had significantly more pain, numbness or paresthesia, larger scars, seroma, and wound infection [67] Similar results in patients with supraclavicular adenopathy have been published [68]. Core needle biopsy is also useful in the diagnosis of granulomatous diseases such as sarcoidosis and tuberculosis [69]. US guided CNB was successful in obtaining an adequate specimen for diagnosis in 96% of patients with sensitivity and specificity at 91% and 99% respectively.

Overall, the literature suggests that CNB is superior to FNA in providing a definitive diagnosis in peripheral adenopathy. In a study by Ryu et al. comparing FNA to CNB in the evaluation of cervical adenopathy in adult patients, there were no complications for either FNA or CNB. Inconclusive results occurred in 6.5% and 1.6% ($p = 0.012$) of patients for FNA vs. CNB respectively [70]. Similar results comparing FNA and CNB were observed in evaluation of axillary lymph nodes and in patients with breast cancer [71].

#### 5.1.7. Specimen handling

The biopsy should be performed at a medical institution specializing in pediatric care with the appropriate infrastructure and pathology available. This will ensure that the proper diagnostic studies such as immunohistochemical stains, flow cytometry, genetic markers, and cultures will be performed. The pathologist in collaboration with the surgeon should determine what proportion of the samples should remain unfixed to preserve the capability to permit marker studies (e.g., immunophenotyping, cytogenetics, and molecular studies), versus fixed for long-term storage. A multidisciplinary discussion before the procedure with the pathologist, oncologist, and the infectious disease team if involved will ensure that the appropriate studies are requested and the specimen is appropriately collected and processed. However, if this discussion has not occurred then ensure that the specimen is sent to pathology as a fresh specimen.

## 6. Summary

Lymphadenopathy is common in children and the pediatric surgeon is often called upon to consider surgical biopsy. Thorough history taking and a medical workup should be complete prior to any procedure. Surgical biopsy should be reserved for therapeutic intervention, to confirm a diagnosis or extent of disease, or to obtain a diagnosis when there is no other method that provides a clear etiology.

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