

LYMPHADENOPATHY

APRN/PA Pediatric Updates in Clinical Practice

Katelyn K Adler DMSc PA-C



Objectives



Lymphadenopathy

- Incidence
 - *~90% of children aged 4-8 years will have palpable lymphadenopathy at some time*
 - *~2/3 of cases have no identifiable etiology, but most commonly due to reactive hyperplasia from viral illness*
 - In those with an identifiable cause:
 - *Epstein-Barr virus 8.86%*
 - *Malignancy 4.69%*
 - Most commonly Non-Hodgkin's lymphoma
 - *Granulomatous disease 4.06%*
 - Most commonly tuberculosis
- Management can be difficult due to weighing the high likelihood of benign disease versus the low, but significant, incidence of malignancy
 - *Diagnostics can be invasive*
 - *Practice patterns vary among specialists*



Medical History

- Duration, timing of onset, location, solitary or diffuse, persistence
- ROS
 - *Autoimmune disorder- rashes, arthralgias, myalgias, myositis*
 - *Infectious- fevers, overlying skin changes, URI symptoms, history of sick contacts*
 - Bacterial- response to previous antibiotics
 - Viral- accompanied by viral prodrome
 - *Lymphoma- fevers, night sweats, unexplained weight loss*
- Immunization status
- Animal exposure
- Travel history
- Sexual activity
- Family history



Physical Examination

- Inspection of skin- trauma, scratches, skin lesions, rashes
- Abdominal exam- splenomegaly, hepatomegaly
- Normal lymph node defined as < 1 cm in longest diameter
 - *Inguinal nodes may be up to 1.5 cm*
 - *Suboccipital, posterior auricular, preauricular, and epitrochlear nodes typically < 0.5 cm*
 - *Supraclavicular nodes are not palpable unless enlarged*
- Abnormal lymph node
 - *Malignancy- firm, matted, fixed nodes, multiple*
 - *Lymphadenitis- tenderness, erythema, warmth, swelling, skin changes*

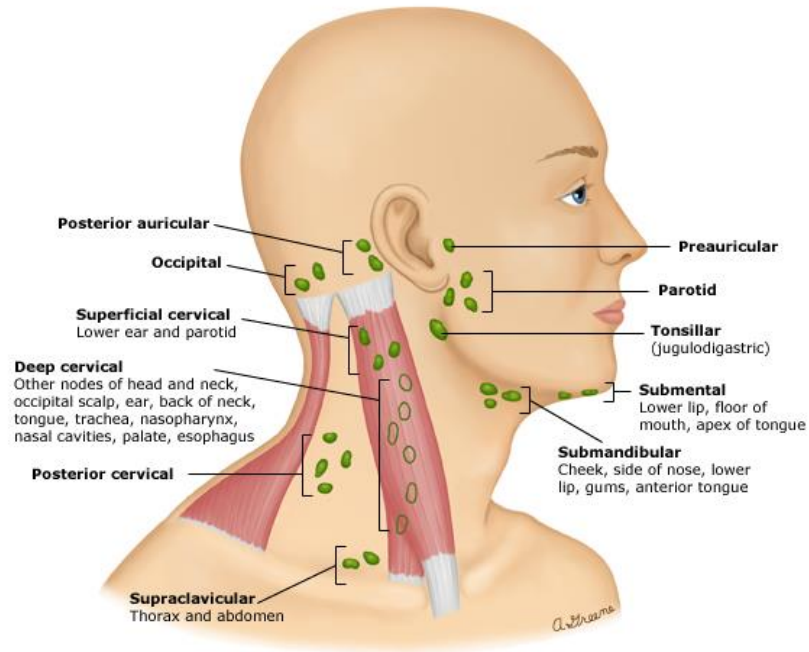


Physical Examination

- Lymphadenopathy location
 - *Supraclavicular lymphadenopathy associated with malignancy in 25% of patients less than 40 years*
 - Right nodes drain lungs, mediastinum, and esophagus
 - Left nodes drain left thorax and intraabdominal/retroperitoneal areas via thoracic duct
 - *Axillary lymphadenopathy commonly associated with cat scratch disease*
 - *Inguinal lymphadenopathy can be associated with sexually transmitted disease*
 - *Generalized lymphadenopathy involves > 2 noncontiguous lymph node groups*
 - Suggests diffuse process like autoimmune disease, infection, or cancer (lymphoma)



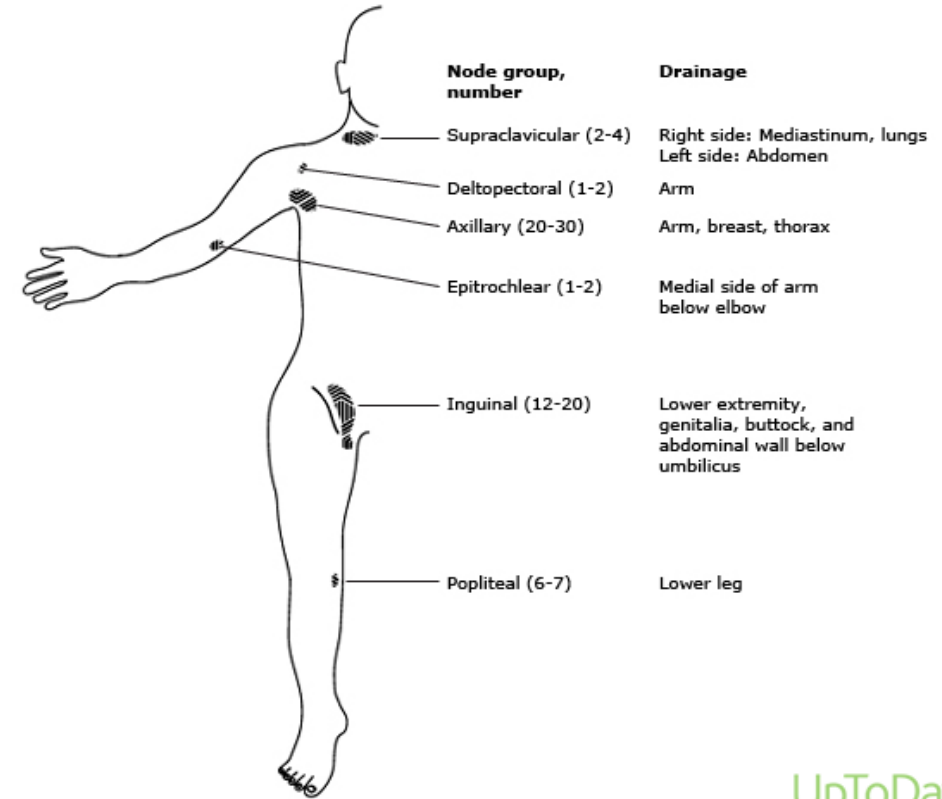
Lymph nodes of the head and neck



This drawing schematically depicts the major lymph nodes in the head and neck area that are likely to be enlarged on physical examination in patients with various local or systemic diseases. The major nodal groups are shown here in bold, with the areas draining into these nodal groups noted when appropriate. While enlargement of both the left and right supraclavicular lymph nodes may reflect disease in the thorax, left supraclavicular nodal enlargement, because of its drainage pattern, may also reflect the presence of abdominal involvement (ie, Virchow node).

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Lymph node regions in the body



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Causes of localized lymphadenopathy in children^[1-4]

Lymph node group	Area of drainage	Causes
Occipital	Posterior scalp, neck	Common: Scalp infections (including tinea capitis, lice); insect bites; seborrhea; roseola (human herpesvirus 6 [HHV6]) Less common: Rubella; acute lymphoblastic leukemia
Posterior auricular	Temporal and parietal scalp	Rubella; roseola (HHV6, HHV7)
Anterior auricular (preauricular)	Anterior and temporal scalp, anterior ear canal and pinna, lateral conjunctiva and eyelids	Common: Eye or conjunctival infections (eg, adenovirus, oculoglandular syndrome) Less common: Cat scratch disease; tularemia; listeriosis
Submental	Central lower lip, floor of mouth	Tongue, gum, buccal mucosal, and dental infections (eg, gingivostomatitis); group B streptococcal infection (in infants <2 months of age)
Submaxillary (submandibular)	Cheek, nose, lips, anterior tongue, submandibular gland, buccal mucosa	Tongue, gum, buccal mucosal, and dental infections; dental caries; chronically cracked lips
Cervical	Cranium, neck, oropharynx	Anterior: Common: Viral upper respiratory infections; infections of pharynx, oral cavity, or head and neck; primary bacterial adenitis; tuberculosis; Epstein-Barr virus; cytomegalovirus; cat scratch disease; nontuberculous mycobacterium Less common: Tularemia; toxoplasmosis; diphtheria; noninfectious causes (eg, Kawasaki disease, Hodgkin lymphoma, lymphosarcoma, neuroblastoma, rhabdomyosarcoma, sarcoidosis) Posterior: Toxoplasmosis; Epstein-Barr virus; rubella

Supraclavicular	Right: Inferior neck and mediastinum Left: Inferior neck, mediastinum, and upper abdomen	Malignancy (lymphoma or metastatic disease)
Axillary	Greater part of arm, shoulder, superficial anterior and lateral thoracic and upper abdominal wall	Common: Cat scratch disease; pyogenic infections of upper arms; reactive response to disruption in skin integrity Less common: Brucellosis; <i>Yersinia pestis</i> ; rat-bite fever; toxoplasmosis; filariasis; rheumatologic disease of the hand or wrist
Epitrochlear	Hand, forearm, elbow	Common: Viral diseases; sarcoidosis; infection of hands Less common: Cat scratch disease; tularemia; secondary syphilis; rheumatologic disease of the hand or wrist
Inguinal	Lower abdomen, genitalia (penis, scrotum, vulva), perineum, leg, and buttocks	Common: Genital herpes, primary; syphilis; gonococcal infection; lymphoma Less common: <i>Y. pestis</i> ; chancroid; lymphogranuloma venereum; filariasis; cat scratch disease; mpox (monkeypox)
Popliteal	Posterior leg and knee	Local infection

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1. Segal GB, Hall CB. Lymphadenopathy. In: *Primary Pediatric Care*, 4th ed, Hoekelman RA (Ed), Mosby, St. Louis 2001. p.1192.
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3. Malley R. Lymphadenopathy. In: *Textbook of Pediatric Emergency Medicine*, 5th ed, Fleisher GR, Ludwig S, Henretig FM (Eds), Lippincott Williams and Wilkins, Philadelphia 2006. p.421.
4. Hamilton W, Pascoe J, John J, et al. Diagnosing groin lumps. *BMJ* 2021; 372:n578.



“Red Flag” Signs & Symptoms

Systemic “B” symptoms

- *Fever > 1 week, night sweats, weight loss (>10% of body weight)*

Palpable supraclavicular nodes
(up to 75% associated with malignancy)

Generalized lymphadenopathy

Fixed, matted, non-tender nodes

Abnormal CXR with mediastinal mass or adenopathy

Dyspnea



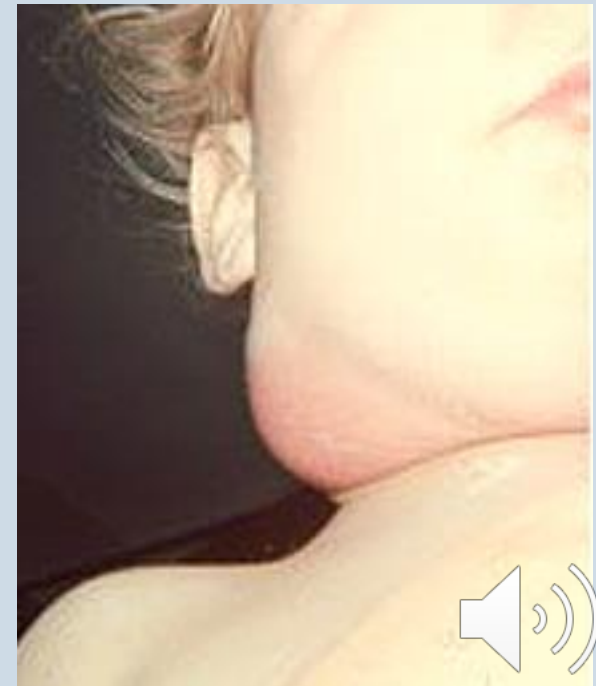
Differential Diagnosis- Infectious

- Viral- typically more generalized lymphadenopathy
 - *Adenovirus, rhinovirus, enterovirus, influenza, parainfluenza*
 - Fever, cough, pharyngitis, rhinorrhea
 - Cervical or submandibular lymphadenopathy
 - *Epstein-Barr virus (EBV)*
 - Tonsillopharyngitis, splenomegaly, fever, malaise, fatigue, periorbital edema
 - *Cytomegalovirus (CMV)*
 - Fever, malaise, fatigue, hepatosplenomegaly
 - *HIV*
 - Fevers, oral thrush, diarrhea, parotitis, failure to thrive, recurrent bacterial/opportunistic infection
 - Nontender lymphadenopathy of cervical, axillary, and occipital lymph nodes



Differential Diagnosis- Infectious

- Bacterial- typically more localized lymphadenopathy
 - *Acute Bacterial lymphadenitis*
 - Most commonly Staphylococcus (80%) followed by Streptococcus (15%)
 - Young children- isolated submandibular, cervical, inguinal nodes
 - Adolescents- isolated axillary or inguinal nodes
 - Treated with antibiotic therapy
 - *Clindamycin, augmentin, or macrolides*
 - May undergo liquefactive necrosis and abscess formation requiring incision and drainage



Differential Diagnosis- Infectious

■ Bacterial

– *Bartonella henselae* (cat scratch disease)

- Most commonly affects axillary (>50%), cervical (28%), inguinal (<25%) nodes

– *Mycobacterium tuberculosis*

- Chronic cervical lymphadenitis
- Most commonly affects children aged 1-5 years
- Contact with contaminated soil or water
- Rapid nodal enlargement with overlying skin color changes
- Treatment includes surgical excision of all involved nodes and antibacterial regimen of clarithromycin, rifampin, and streptomycin



Differential Diagnosis- Infectious

- Fungal
 - *Histoplasmosis*
 - Pneumonia, solitary pulmonary nodules and mediastinal/hilar lymphadenopathy
 - Travel/residence in endemic area (Ohio, Mississippi, Missouri River valleys)
 - *Coccidioidomycosis*
 - Pneumonia, pulmonary nodules and mediastinal/hilar lymphadenopathy
 - Travel/residence in endemic area (Southwestern US)
- Diagnosis may be made serologically to avoid biopsy



Differential Diagnosis- Infectious

- Parasitic
 - *Toxoplasmosis*
 - Myalgia, fever, fatigue, splenomegaly, maculopapular rash
 - Exposure to cats
 - *Malaria*
 - Fever, travel/residence in endemic area
- Spirochetal
 - *Syphilis*
 - Rash, fever, malaise, anorexia, weight loss, hepatomegaly
 - *Lyme Disease*
 - Erythema migrans, fever, headache, myalgia, malaise, arthralgia

Erythema migrans



Erythema migrans with central crust



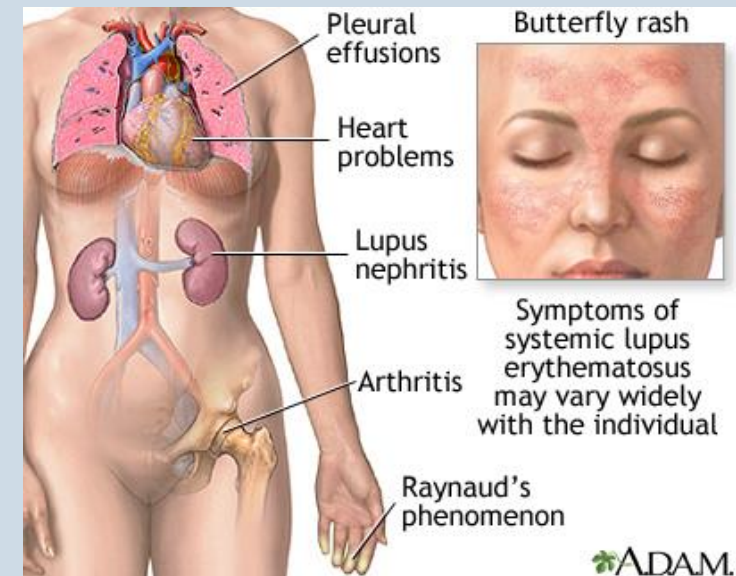
Differential Diagnosis- Malignancy

- Primary
 - *Hodgkin lymphoma*
 - Cervical lymphadenopathy, unilateral, respiratory distress
 - *Non-Hodgkin lymphoma*
 - Rapidly enlarging diffuse adenopathy, bilateral, abdominal pain, vomiting, respiratory distress
- Metastatic
 - *Acute lymphocytic or myelogenous leukemia*
 - *Neuroblastoma*
 - *Rhabdomyosarcoma*



Differential Diagnosis- Autoimmune Disorders

- Systemic lupus erythematosus (SLE)
 - *Lymphadenopathy present in 25-50% of cases*
 - *May be presenting symptom*
 - *Associated with fever, weight loss, fatigue, rash*
- Sarcoidosis
 - *Uncommon in children*
 - *Mediastinal lymphadenopathy, pulmonary symptoms, peripheral lymphadenopathy, uveitis, rash*



Differential Diagnosis- Medication Related

- Generalized lymphadenopathy
- Phenytoin, phenobarbital, carbamazepine, sulfonamides, allopurinol, aspirin, isoniazid, penicillin, iodine, tetracycline, phenylbutazone, barbiturates, cephalosporins, atenolol, hydralazine, quinidine, pyrimethamine, primidone



Initial Management

- Acute, unilateral cervical lymphadenitis
 - *Treat with oral antibiotics (clindamycin, augmentin, macrolides)*
 - *May require admission for IV antibiotics and I&D*
 - *Close follow up to ensure regression*
 - Failure to regress after 4-6 weeks should prompt biopsy
 - *Avoid corticosteroids until definite diagnosis is made*
 - May mask/partially treat leukemia and lymphoma



Adjunct Testing

- Indicated in patients with failure of resolution after 4-6 weeks or with concerning findings
- Labs
 - *CBC, ESR, CRP, LDH*
 - Leukocytosis- bacterial lymphadenitis
 - Pancytopenia or presence of blast cells- leukemia
 - Lymphocytosis- infectious mononucleosis
 - *Throat culture, rapid strep, RFA*
 - *Serologic testing for Bartonella henselae, CMV, toxoplasmosis, EBV*



Adjunct Testing

■ Imaging

– *Ultrasound (US)*

- Recommended as the initial imaging study of choice in children <14

- *Preferred due to lack of radiation, ability to complete without sedation, and widespread availability*

- Normal lymph node- ovoid shape, homogenous echotexture, smooth borders, clearly distinguishable fatty hilum

- Abnormal lymph node- fixed, rounded, irregular borders, hypervascularity, abnormal L/S ratio (measure of the long/short axis), no hilum

- Contrast enhanced ultrasound (CEUS) and elastography may improve differentiation but not widely available

– *CT/MRI*

- Used when US nondiagnostic or in areas requiring more detailed imaging (deep neck adenopathy)

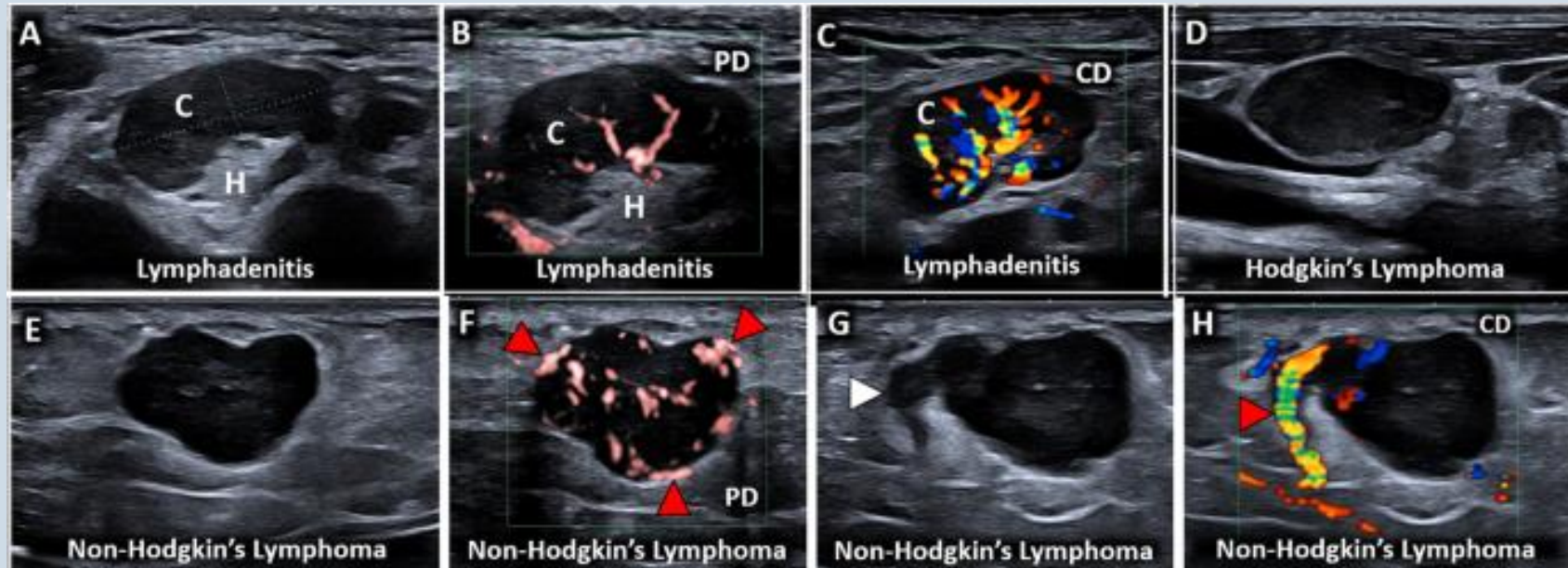
– *CXR*

- May identify systemic illness

- Evaluate for mediastinal mass in suspected lymphoma



Imaging

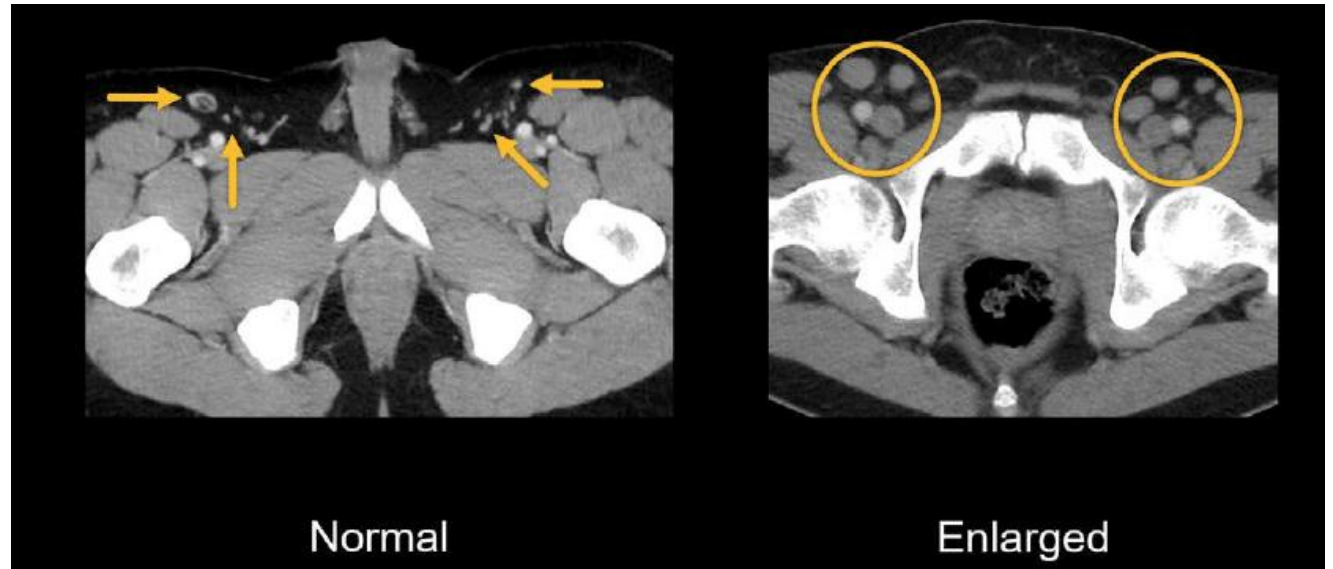


A glance-in-depth at the multiparametric sonographic assessment of lymph nodes. Benign lymphadenopathy (A) usually preserves the hyperechoic hilum (*H*), the hypoechoic cortex (*C*) and a unipolar vascularization with feeding vessels branching from the hilum to the cortex (B, C) Instead, a disappearance of the hilum (D), a rounded/globular shape (E) and a multipolar vascularization (F) with feeding vessels (*red arrowheads*) originating from the peripheral portion, can be considered the most common sonographic findings of malignant lymphadenopathy. Of note, considering the extreme variability of sonographic patterns of lymph nodes, several “atypical” findings can be identified in daily practice—e.g., serpiginous protrusions (*white arrowhead*) related to ectatic vessels (*red arrowhead*) (G, H) a normal lymph node (*white dotted line*) coupled with a “snowfall” lymph node (*green arrowheads*) due to particle depositions





CXR- mediastinal mass

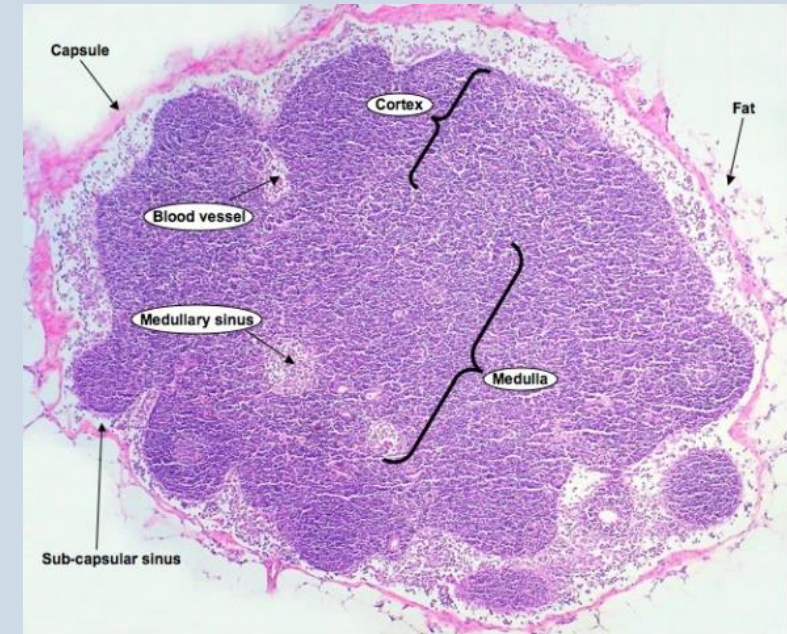


CT- inguinal lymphadenopathy



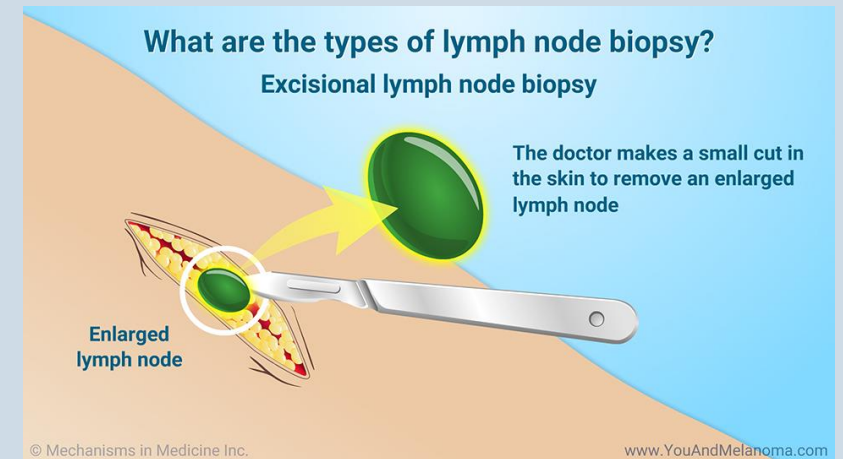
Lymph Node Biopsy

- Early surgical evaluation indicated when red flag symptoms/signs present or with persistent (>4-6 weeks) adenopathy with or without empiric antibiotics
- Methods of biopsy
 - *Most abnormal node biopsied (largest, firmest, most tender)*
 - *Preference for location- supraclavicular → cervical → axillary → inguinal*
 - Axillary and inguinal biopsy have higher risk of complications (infection, lymphocele, injury to neurovascular structures)
 - *Excisional vs core needle biopsy vs fine-needle aspiration*



Excisional Biopsy

- Gold standard in children
- Yields sufficient tissue
 - 1 cm^3 is required for morphological assessment, immunohistochemical stains, and chromosomal analysis
- May result in false-negative results if uninvolved node is biopsied
- Disadvantages- invasive, need for general anesthesia, higher risk of infection, neurovascular injury, and bleeding
 - *Complication rate ranges from 0-6%. Majority due to inadequate tissue requiring second procedure*



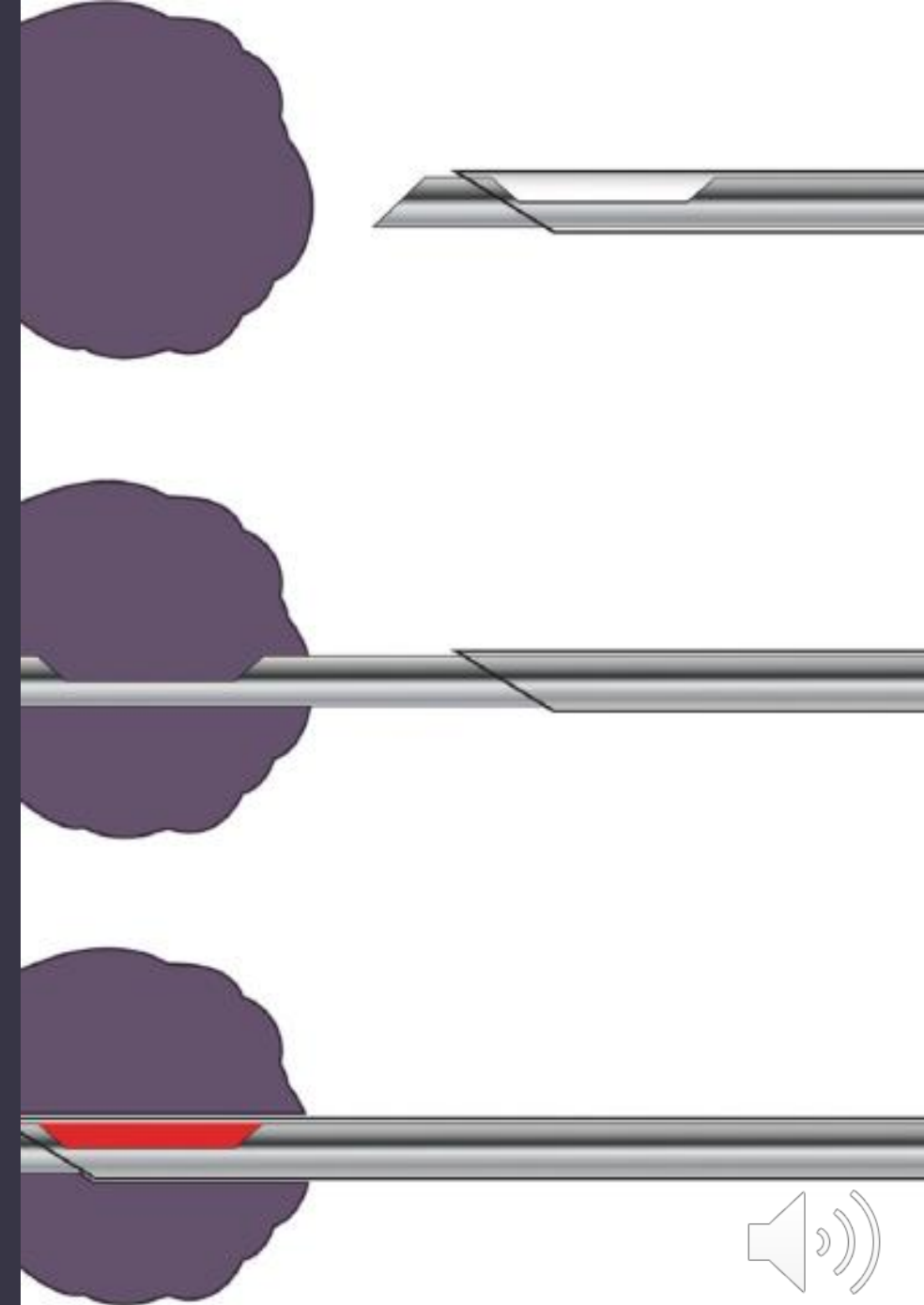
Needle Biopsy

- Core and fine-needle-aspiration
 - *Can be performed with local anesthesia and sedation*
 - *Able to obtain tissue from nodes that are difficult to access (mediastinal, abdominal, deep head and neck)*
 - *May obtain sufficient tissue for diagnosis or identify those who require excisional biopsy*
- FNA provides specimen for cytological evaluation for cell morphology, immunophenotyping, and microbiology studies
 - *Obtaining sample and interpretation user dependent*
- Core biopsy obtains more tissue which can be assessed for architecture, increasing diagnostic accuracy



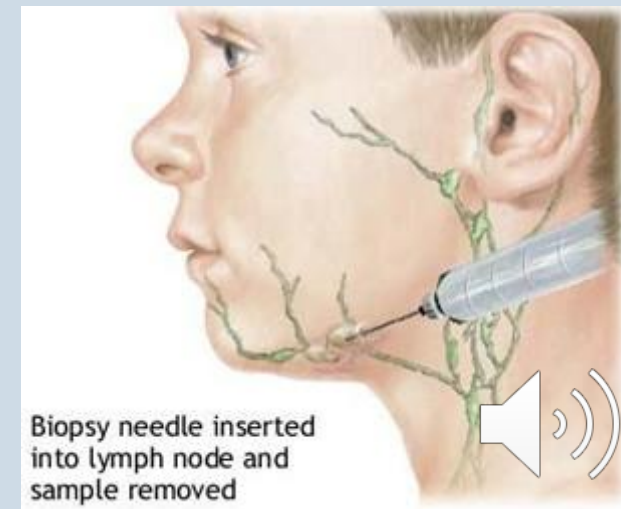
Core Needle Biopsy (CNB)

- Inferior to excisional biopsy at providing definite diagnosis
 - *Sufficient in 69% of patients with lymphoma compared to 98% with excisional biopsy*
- US guidance improves adequacy and accuracy
 - *Sensitivity for detection of malignancy reported at 98.8% compared to 88.7% with standard surgical biopsy*
 - *Lower cost, less pain, smaller scar, lower rate of seroma formation*
- Superior to FNA in providing definite diagnosis
 - *Inconclusive results in 1.6% of patients versus 6.5% with FNA*



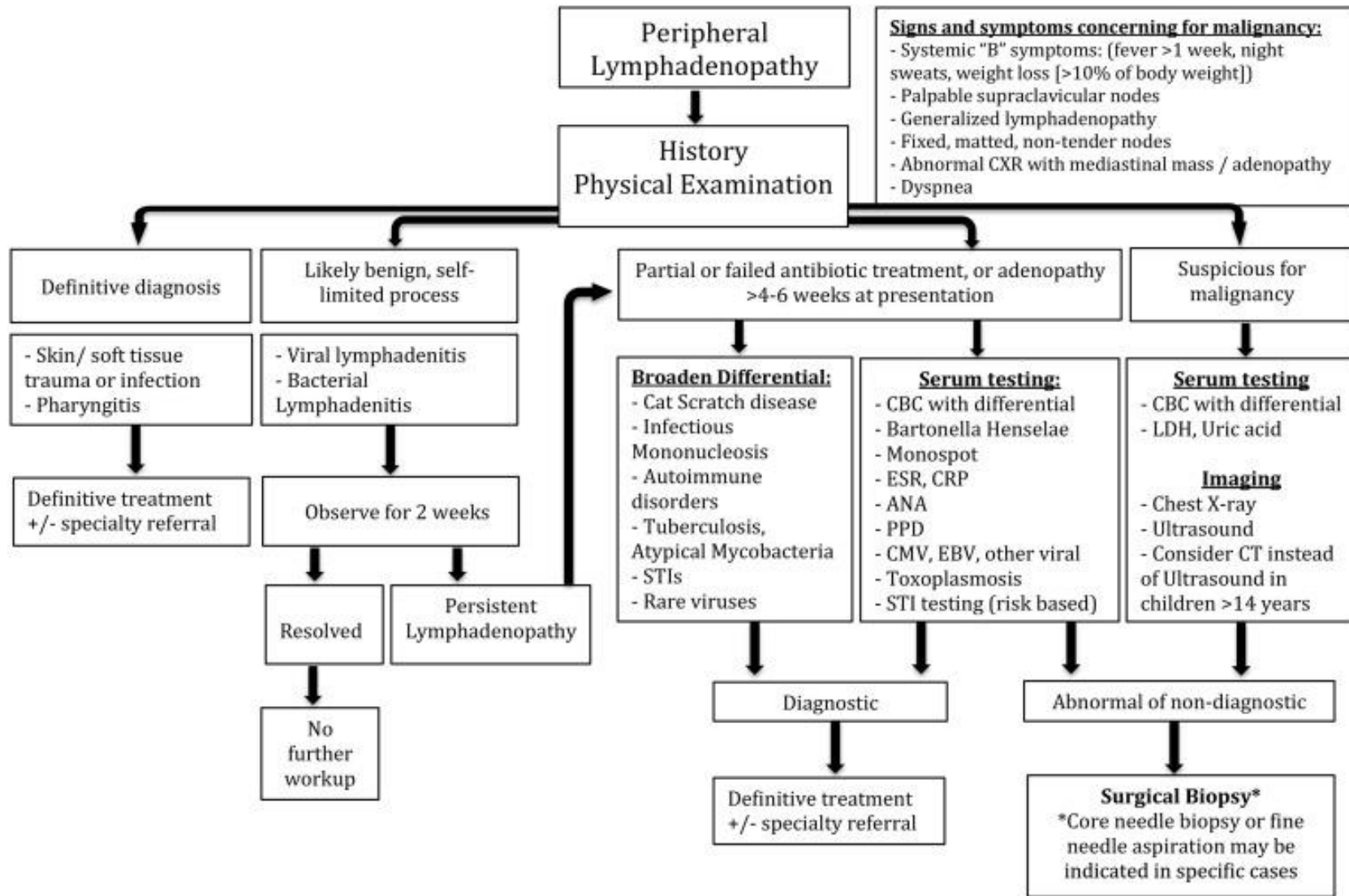
Fine Needle Aspiration

- More widely used in adults
- Incidence of inadequate sample approximately 20%
- Diagnosis of lymphoma should not be attempted with FNA
 - *Requires histopathological confirmation and subtyping*
 - *Initiation of treatment based solely on FNA only in emergent situations*



PROPOSED ALGORITHMS





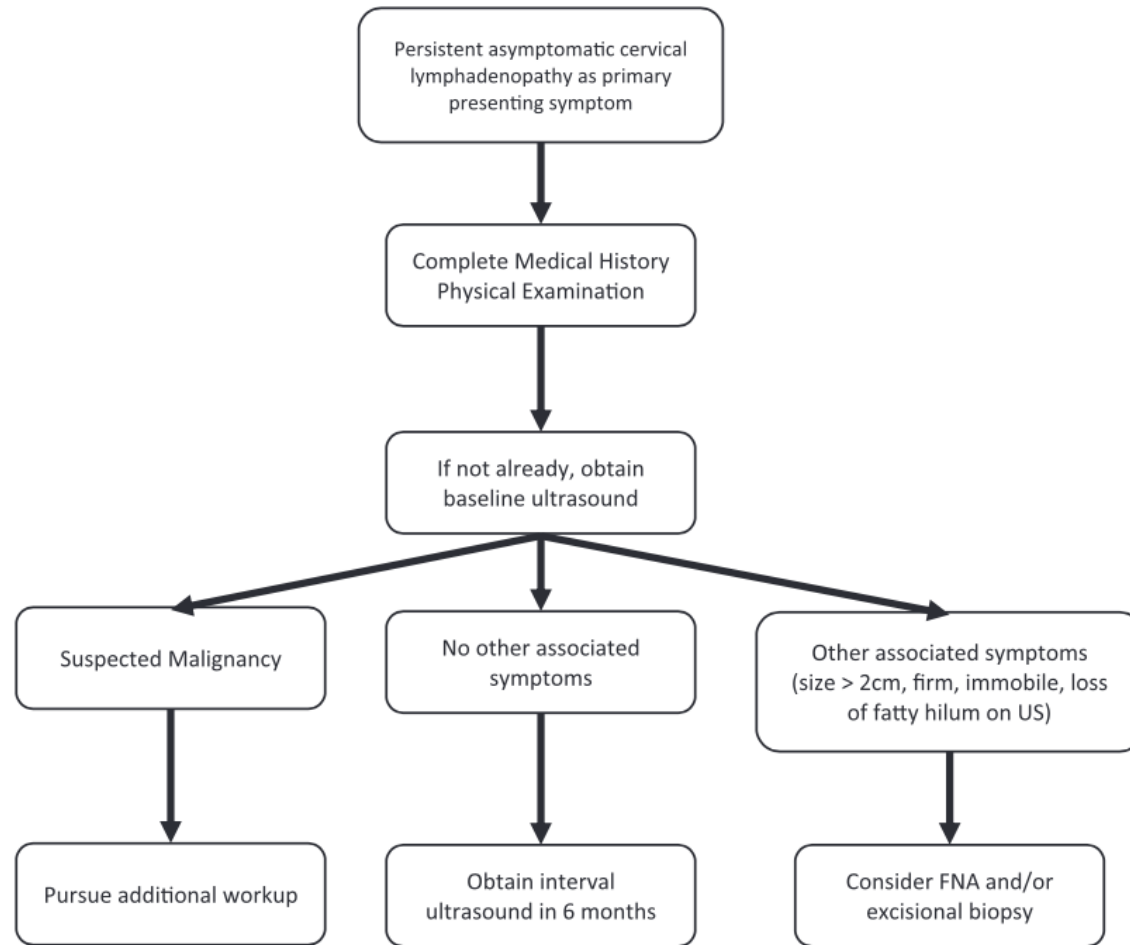


Figure 4. Proposed management algorithm for PACL. Flowchart describing our institution's approach to PACL, specifically when to pursue observation versus more invasive intervention. It does not describe an approach to infectious cervical lymphadenopathy or suspected malignancy. FNA, fine needle aspiration; PACL, persistent asymptomatic cervical lymphadenopathy; US, ultrasound.



Objectives Review

- Normal lymph node defined as < 1 cm in longest diameter
 - *Inguinal nodes may be up to 1.5 cm*
 - *Suboccipital, posterior auricular, preauricular, and epitrochlear nodes typically < 0.5 cm*
 - *Supraclavicular nodes are not palpable unless enlarged*
- ~90% of children aged 4-8 years will have palpable lymphadenopathy at some time

Define
lymphadenopathy and
its implications in the
pediatric population



Objectives Review

Systemic “B” symptoms

- *Fever > 1 week, night sweats, weight loss (>10% of body weight)*

Palpable supraclavicular nodes
(up to 75% associated with malignancy)

Generalized lymphadenopathy

Fixed, matted, non-tender nodes

Abnormal CXR with mediastinal mass or adenopathy

Dyspnea

Identify “red flag” signs and symptoms that warrant further diagnostics or treatment



Objectives Review

- Ultrasound is the initial imaging study of choice
 - *CT and MRI utilized when ultrasound is nondiagnostic or when more detailed imaging is required*
- Excisional biopsy is considered gold standard in children
 - *Needle biopsy useful when nodes difficult to access*

Compare imaging and biopsy modalities to further assess lymphadenopathy



References

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