Hello Clinical Problem Solvers! My name is Kaitlyn Thomas and I'm a 3rd year medical student at Lake Erie College of Osteopathic Medicine. I'm excited to share with you all a diagnostic schema of Diffuse Lymphadenopathy.

What is diffuse lymphadenopathy? It's the enlargement of more than 2 non-contiguous lymph node groups. We can split the possible etiologies of diffuse lymphadenopathy into 5 different "buckets". You can remember these buckets through the pneumonic "INADM", which I try to remember by saying "I need a doctor maybe".

The first bucket is infection. Let's start with the viruses. In, HIV the nodes may be soft and non-tender and general develop during the second week of acute symptoms, occasionally most prominent along the sternocleidomastoid. Ebstein Barr Virus causes mononucleosis which is generally associated with posterior cervical lymphadenopathy, but can also be associated with axillary and inguinal lymphadenopathy. CMV may have a pattern of mononucleosis-like illness but will be heterophile negative, distinguishing it from EBV. HTLV1 is associated w/ adult T cell lymphoma and usually presents w/ anemia, lymphadenopathy and hypercalcemia. Herpes simplex virus may cause lymphadenopathy in the setting of a mono-like illness and painful oral lesions, similar to adenovirus. Varicella Zoster Virus replicates in the lymph nodes and can be associated with lymphadenopathy in an immunocompromised host. HHV6 lymphadenopathy can be associated w/ reactivation in an immunocompromised host, but can also occur in immunocompetent individuals. Rubella is associated w/ lymphadenopathy, especially postauricular, suboccipital and anterior cervical lymph nodes. While cough, conjunctivitis and Koplik spots are a way of remembering measles, it's important to remember that other symptoms such as generalized lymphadenopathy can also be present.

On to bacteria! Mycobacteria is a possible culprit. Miliary tuberculosis should be considered with generalized lymphadenopathy, while primary tuberculosis often focuses around the lymph nodes in the neck. Our old pal syphilis can also cause diffuse lymphadenopathy, particularly in secondary infection or regional lymphadenopathy in primary syphilis. Lymphogranuloma venereum has 3 stages, and lymphadenopathy is generally found in the 2nd stage. While we may generally think of lymphogranuloma venereum as being based around pelvic and abdominal lymphadenopathy, some cases lead to diffuse lymphadenopathy instead. Some Rickettsia infections are associated in particular with diffuse lymphadenopathy, especially scrub typhus, also called Tsusugamushi (pronunc: sut-su-ga-mushi) disease. Brucella, while most commonly noted for its undulating fever, also may cause generalized lymphadenopathy with hepatomegaly or splenomegaly.

Fungal infections such as histoplasmosis, blastomycosis and coccidiomycosis can lead to diffuse lymphadenopathy when they have developed into systemic infection.

Various helminthic infections may cause diffuse lymphadenopathy, especially when a patient is HIV seropositive. Toxoplasma gondii, an oblígate intracelular parasite generally has "flu-like" symptoms over a long time course with diffuse lymphadenopathy.

Phew… that was a lot of infections that can lead to diffuse lymphadenopathy.

Our next bucket is neoplasms. Think of these in 2 categories: malignant and benign.

Risk factors for malignancy include age older than 40, lymphadenopathy lasting 4-6 weeks or longer, diffuse and non-tender lymphadenopathy and supraclavicular nodes. Leukemia and lymphoma may be suspected when present with fever, night sweats and weight loss. Metastatic cancer can lead to generalized lymphadenopathy, although earlier in the course it may be more common to see it in adjacent nodes to the primary tumor. Sarcomas may also be diagnosed via generalized lymphadenopathy.

Benign neoplasms are next! Castelman disease is associated w/ cytokines that are dysregulated leading to both systemic inflammatory symptoms and lymphadenopathy. Kikuchi's disease is a rare self-limiting disorder that generally affects cervical lymph nodes with some diffuse lymphadenopathy. Autoimmune lymphoproliferative syndrome is a disorder typically in adolescents caused by mutations of the FAS signaling pathway which leads to autoreactive T cells. This leads to cytopenias, splenomegaly, lymphadenopathy, autoimmune disorders, and increased risk of lymphoma. The lymph nodes will demonstrate follicular hyperplasia and paracortical expansion of lymphocytes, immunoblots and plasma cells.. Rosai-Dorfman Disease is characterized by sinus histiocytosis w/ massive lymphadenopathy. Extranodal manifestations are most common in the skin, upper respiratory tract and bone. Prognosis centers around the number of nodal groups and extranodal systems involved.

Our next bucket is autoimmune. Lupus is often associated w/ localized or generalized lymphadenopathy with coagulative necrosis or reactive follicular hyperplasia of the node. Sarcoidosis patients often may have extrapulmonary manifestations, of which skin lesions and lymphadenopathy are the most common. Sjogren's syndrome can have a variety of extraglandular manifestations, one of which being lymphadenopathy. Progression to regional or generalized lymphadenopathy should lend suspicion for lymphoproliferative complications of the disease as well. Still's disease includes the presence of arthritis and intermittent fever for at least 2 weeks plus one of several criteria, one of which is generalized lymphadenopathy. Hemophagocytic lymphohistiocytosis is diagnosed through a set of criteria, and diffuse lymphadenopathy can be one of them. Felty's syndrome is a sub-type or complication of rheumatoid arthritis that that is associated w/ splenomegaly, neutropenia and generalized lymphadenopathy. In children, who present acutely w/ diffuse lymphadenopathy, Kawasaki Disease should be considered.

Two more buckets to go! Remember, so far we've talked about infection, neoplasm and autoimmune conditions.

Now, we're going to discuss Drugs/Toxins. Silicosis is an occupational lung disease associated w/ respirable crystalline silica. While mediastinal lymphadenopathy is most common, diffuse lymphadenopathy may also be seen. Beryilliosis can also cause generalized granulomatous lymphadenopathy. A variety of medications including Hydralazine, Allopurinol and some

antiepileptics are associated with generalized lymphadenopathy. DRESS or Dish is also associated, which if you remember from our illness script video is caused by the 4 As: antibiotics, antipsychotics, antiepileptics and allopurinol. Serum sickness is a hypersensitivity reaction that involves fever, rash, polyarthritis and less commonly lymphadenopathy. It typically resolves after discontinuation of the offending agent or substance.

The last bucket is “molecules” or diseases that cause deposition of a molecule leading to the lymphadenopathy. First is amyloidosis. There are 3 common forms of amyloidosis. They are amyloid light chain, amyloid associated protein and beta amyloid. This disease is generally multisystem w/ various presentations. A rare presentation is lymphadenopathy w/o infiltration of other organs. The kidney is the most commonly affected and can present with nephrotic syndrome. Treatment is dictated by the type of amyloid and may involve chemotherapy, transplant or apheresis. Last is IgG related disease or IgG-4 related disease. This disease is a systemic, subacute fibroinflammatory disease leading to a high infiltrate of plasma cells positive for IgG4. Most common affected organs include the salivary and lacrimal glands, pancreas, biliary tract and the kidneys. Patients with asymptomatic lymphadenopathy can usually be watched without treatment.

Remember, diffuse lymphadenopathy is the enlargement of more than 2 non-contiguous lymph node groups. You can remember these through the 5 buckets, infection, neoplasm, autoimmune, drugs/toxins and molecules!

Thank you so much for joining us for this diagnostic schema of Diffuse lymphadenopathy!