APPENDIX 2. Lymphocytosis

Lymphocytes > 5

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Repeat CBC with differential and peripheral blood smear to confirm lymphocytosis and assess other cell lines to help clarify diagnosis

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History	• Duration of lymphocytosis:
	  ○ Transient (resolves between a few hours to 2 days)—suggests stress
	  ○ Hours to days—typically acute event (e.g., infection, acute leukemia)
	  ○ Weeks to years—typically other causes (e.g., chronic inflammatory status, hematologic malignancy)
	• Symptom review: constitutional symptoms (e.g., fever, night sweats, unintended weight loss)
	• Family history of cancer, particularly lymphoid malignancies
	• Past medical history: conditions associated with lymphocytosis
	• Medication review
	• Social history: smoking, travel, stress

Physical exam	• Vitals (fever) • Skin lesions or patches, maculopapular rash, easy bruising • Facial swelling (may signal DRESS*); jaw, facial bone, or periorbital masses (may indicate lymphoma) • Pleural effusion (may indicate T-cell prolymphocytic leukemia); crackles/shortness of breath (may indicate pneumonia) • Hepatosplenomegaly, lymphadenopathy

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Do history and physical findings suggest an underlying cause?

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Primary Lymphocytosis

- Signs/symptoms of hematologic malignancy (e.g., lymphocytes > 20, Hgb < 100, night sweats, weight loss, bulky or painful lymph nodes, splenomegaly, hepatomegaly)
- Progressive anemia or thrombocytopenia

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Referral or electronic/phone consult with hematology (if appropriate)
While referral pending, consider arranging for biopsy or nodal resection depending on the anatomic location

Secondary Lymphocytosis

Findings	Examples
Current infection	Viral—most common (e.g., Epstein-Barr, hepatitis, HIV) Bacterial (e.g., Bordetella pertussis) Parasitic (e.g., toxoplasmosis)
Signs/symptoms of autoimmune disease	Autoimmune thyroiditis
Signs/symptoms of inflammatory disease	Inflammatory bowel disease
Signs/symptoms of endocrine disease	Addison disease, hyperthyroidism
Causative medication	B-cell receptor signaling inhibitors (e.g., ibrutinib)
Hypersensitivity reaction	Serum sickness, DRESS*
Recent acute stress	Cardiac events, surgery, traumatic injury
Others	Vaccination, smoking, splenomegaly, asplenia

Further tests guided by likelihood of underlying cause (e.g., cultures of blood, urine, joint, or body fluid to confirm infection)

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Further investigations and treatment guided by underlying cause
Consider flow cytometry if available
Refer or electronic/phone consult as indicated

Sources: 1) Hamad H, Mangla A. Lymphocytosis. *StatPearls*. Treasure Island (FL) 2023; **2)** DynaMed. *Lymphocytosis in adults - approach to the patient*. 2022; **3)** *Complete blood count in primary care.* https://bpac.org.nz/Supplement/2008/May/complete-blood-count.aspx.

*DRESS (drug reaction with eosinophilia and systemic symptoms): a severe drug reaction with extensive skin rash, visceral organ involvement, lymphadenopathy and lymphocytosis, eosinophilia, and thrombocytopenia

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