The Foundation for Medical Practice Education
Practice-Based Learning for Family Physicians

Abnormal CBC In Adults: A Clinical Approach

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INTRODUCTION

The CBC is one of the most common laboratory tests ordered in primary care and is often the first indication of underlying disease. Several factors can complicate the interpretation and follow-up of an abnormal CBC, including borderline results, unclear cutoffs for clinical relevance, and false results (e.g., related to the process of testing).

OBJECTIVES

This module will enable clinicians to:

- Understand the parameters of a CBC and their meaning
- Interpret CBC abnormalities and associated differential diagnoses, and appropriately order and interpret follow-up tests
- Communicate abnormal CBC results to patients and initiate, if indicated, surveillance for hematologic malignancy

Box 1. Scope

- This module does not cover anemia in detail. For more information, refer to the PBLP module Anemia in Adults (August 2017) available at members.fmpe.org.
- This module includes management algorithms for erythrocytosis, lymphocytosis, and platelet abnormalities. Management algorithms for neutropenia and neutrophilia are available at members.fmpe.org.
- A Levels of Evidence box has not been included in this module as there are no evidence-based guidelines for the management of CBC abnormalities, only for their underlying causes which is outside the scope of this module.

Box 2. Reference Ranges

Reference ranges will vary by laboratory and province/territory. For this module, we will use the reference ranges outlined in Table 1.

Note: Reference ranges on a CBC are simply the ranges in which 95% of a sample population's results will fall. They do not necessarily align with clinically meaningful high and low values. There are variations in results based on age, sex, gender, ethnicity, and other factors. Use clinical judgment when applying information in this module to local lab ranges and patients.

Box 3. Units Used in this Module

RBCs	Total: x 10^{12} L Hemoglobin (Hgb): g/L Hematocrit (Hct): L/L Reticulocyte count: x 10^9/L	MCV: fL MCH: pg MCHC: g/L RDW: %
WBCs	Total, neutrophils, eosinophils, basophils, lymphocytes, monocytes: x 10^9/L	
Platelets	Total: x 10^9/L	

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distribution width; WBC = white blood cell

CASES

Case 1: Lloyd, age 53

Lloyd has been your patient for 10 years. He is generally healthy aside from a history of hypothyroidism and benign paroxysmal positional vertigo (BPPV). He has not had any surgeries and has no known drug allergies. He consumes 1 to 2 glasses of wine per week and has a 25 pack-year history of smoking. His mother had Guillain-Barré syndrome and hypertension; his father died of lung cancer. Lloyd's only medication is levothyroxine 125 mcg daily, and his TSH was in target range on recent blood work.

You noted a mild hemoglobin elevation when investigating him for fatigue years ago at the time of his hypothyroidism diagnosis. You have also been monitoring his Hgb (165–169) and Hct (0.48–0.50), which have been stable for years. Since he is a long-standing smoker and the rest of his CBC had been normal, you had attributed the elevation to his cigarette smoking. However, on his most recent blood work, you note the Hgb is 180 and Hct 0.53, a significant jump from previous values. He is asked to come in to review these results.

How would you interpret and communicate the CBC results?

What further information on history and physical exam would be helpful in Lloyd's case?

Part Two

Lloyd has been feeling well and denies any symptoms of fever, night sweats, weight loss, anorexia, headache, fatigue, or pruritus after hot showers/baths. There is no history of bleeding, bruising, or thromboembolism. He has not had any visual changes, shortness of breath, chest pain, abdominal pain, paresthesias, or facial flushing. He has not had a worsening cough. He snores occasionally, but his partner has not complained of any loud snoring or witnessed any apneic spells at night. Lloyd recalls that he met a friend for breakfast after he went to the lab and that he was fasting at the time the blood sample was taken. He does not endorse the use of testosterone or other androgens. There is no family history of hematologic malignancies, stroke, deep vein thrombosis, or pulmonary embolism.

Lloyd has tried to quit smoking several times in the past without long-term success. He is thinking about trying to quit again and is willing to follow up for smoking cessation counselling.

On exam, his BP is 136/84 and BMI 31. There is no facial plethora, palmar erythema, or peripheral adenopathy. His neck circumference is 37 cm. His respiratory, cardiovascular, and abdominal exams are all normal. You calculate his STOP-BANG score, which is 2 (low risk). You review previous labs and note his renal function was normal when checked 2 years ago at the ER visit that led to his BPPV diagnosis.

What would be your approach in managing Lloyd going forward?

Part Three

Lloyd ended up repeating his blood work 3 months later, ensuring good hydration at the time. His results were slightly improved but remained abnormal—Hgb 175 and Hct 0.51. His spirometry did not show any signs of COPD or asthma.

When he came in, you had a lengthy discussion about the common causes of erythrocytosis and the options for further investigation. Lloyd opted to work on smoking cessation and weight loss as a first step. He was reluctant to be referred to a hematologist for further testing (EPO is not covered in your jurisdiction if ordered in an outpatient setting).

You have been seeing him regularly for smoking cessation counselling. With a reduction-to-quit strategy, behavioural modifications, and varenicline, he was able to quit smoking 4 months ago. He also increased his exercise and adapted his diet. His BMI is now 29. He repeated his blood work a few weeks ago and his Hgb (181) and Hct (0.53) were elevated. The rest of the CBC was within normal range. A repeat CBC in 2 weeks confirmed the elevation.

What would you do now?

Case 2: Irina, age 48

Irina has been a patient of yours for 5 years. She has a history of mild lymphocytosis—lymphocytes have ranged from normal to 4.1. You had checked a CBC years ago as part of her workup for menorrhagia that was ultimately found to be related to her fibroids. The lymphocytosis was an incidental finding. Since she has been asymptomatic and levels only mildly elevated, you have simply been monitoring her over time.

She has a long-standing history of axonal sensory neuropathy, migraines (controlled with Botox injections), and psoriasis (controlled with UVB phototherapy and calcipotriol/betamethasone dipropionate ointment). She had a total abdominal hysterectomy and bilateral salpingo-oophorectomy 3 years ago for endometriosis and fibroids. Irina also takes estradiol gel 1.25 gram/actuation 2 pumps daily, vitamin B_{12} 1,000 mcg twice weekly, vitamin D 1,000 IU daily, and an omega 3 supplement daily. She has no known drug allergies. She does not smoke and consumes 2 glasses of wine per month. She is up to date on her routine immunizations and has been fully vaccinated for hepatitis A and B.

Irina was in the office 2 weeks ago to get a form signed. At that time, you ordered a CBC, B_{12}, and ALT due to her fluctuating lymphocyte levels and chronic medical conditions. She is in today to review her test results with you. She recently accessed her lab results online through a patient-facing e-portal and is concerned about her lymphocytes being high.

Her blood work results are:

- Hgb 145 (115–160)
- Hct 0.437 (0.38–0.48)
- RBC 4.94 (3.50–5.00)
- MCV 89 (80–100)
- MCH 29.4 (25–34)
- MCHC 332 (315–355)
- RDW 12.1 (11.5–15.5)
- WBC **10.8** (3.5–10.5)
- Neutrophils 4.8 (2.0–7.5)
- Lymphocytes **5.1** (0.8–3.3)
- Monocytes 0.6 (0.1–1.0)
- Eosinophils 0.2 (0–0.5)
- Basophils 0.1 (0–0.1)
- Platelets 234 (130–380)
- B_{12} 342 pmol/L (170–600)
- ALT 28 IU/L (17–63)

How would you address Irina's concerns about her lymphocyte level? What further information and assessment would be helpful?

Part Two

Irina has been feeling well and has no new symptoms to report. On exam, her thyroid is normal and there is no lymphadenopathy, hepatomegaly, or splenomegaly. You review with Irina the various elements of the CBC and some potential causes for her intermittent lymphocytosis. You order a peripheral smear and ask her to repeat the CBC in 12 weeks and follow up with you in the interim if she develops any new symptoms, including fever, chills, night sweats, bulky/painful lymph nodes, or unexplained weight loss. The repeat CBC shows that her lymphocytes are now 5.3.

What would be your next steps in managing Irina's lymphocytosis?

Case 3: Giselle, age 32, G1P0

Giselle is in to see you today for her 28-week prenatal visit. Her ultrasounds and prenatal screening have been normal. Her blood work was normal aside from a moderately reduced platelet level of 120 (150–380). On her last CBC done 2 years ago, her platelets were normal at 223.

Giselle has been feeling well and has not had any cramping, jaundice, bruising, or bleeding of any kind. She is not on any medications aside from her prenatal vitamin.

Her examination is normal and you do not note any jaundice, bruising, petechiae, lymphadenopathy, or splenomegaly. Her BP is 114/73. The urine dipstick is negative for protein.

What would be your next steps in managing Giselle's blood work finding?

How would your management differ if Giselle were not pregnant?

How would your management differ if Giselle's initial blood work during her pregnancy had shown an elevated platelet count of 475 instead?

INFORMATION SECTION

Complete Blood Count (CBC)

1. The CBC is one of the most used clinical laboratory tests, providing information on the 3 main types of blood cells: red blood cells (RBCs), white blood cells (WBCs), and platelets.[3]
   - Unless there are pertinent risk factors, a CBC should not be ordered for asymptomatic, nonpregnant adults. In this population, the pretest probability of disease is low, leading to a high rate of false positives with no reduction in mortality.[4] Up to 11% of results are abnormal but < 1% of those results necessitate a change in management.[5] According to Choosing Wisely Canada, annual screening blood tests are not recommended unless directly indicated by the patient's risk profile.[6]

2. There is no standard reference range used by laboratories for the parameters of the CBC. The World Health Organization's newer guidelines reduced the upper limits of normal for hemoglobin (Hgb) and hematocrit (Hct) to ensure cases of polycythemia vera were not missed.[7,8] These lower reference ranges may lead to more investigations and referrals to rule out polycythemia vera which, in turn, would be associated with greater resource utilization and potentially greater patient anxiety. Given the variability in reference ranges, it may be helpful to have patients use the same laboratory for repeat testing to allow for better comparison between readings and more accurate trending of results [Expert Opinion].

Table 1. CBC: Normal Values[3,9,10]

Cells	Parameter	Normal Values	What is Measured	Purpose
RBCs	Total count	Female: 3.50–5.00 Male: 4.00–5.50	Total quantity of RBCs	To help identify anemia (low) or erythrocytosis (high)
	Hgb	Female: 115–160 Male: 125–165	Quantity of hemoglobin in blood	
	Hct	Female: 0.38–0.48 Male: 0.38–0.49	Ratio of volume of RBCs to total volume of blood	
	Reticulocyte count (if requested)	23–90	Number of newly produced RBCs	To determine if RBCs are being created in the bone marrow at an appropriate rate
	RBC indices: useful for building a picture around patterns suggested by Hgb and/or Hct results[4]			
	MCV	80–100	Average size of RBCs	To classify type of anemia: • Microcytic (low) • Normocytic (normal) • Macrocytic (high)
	MCH	Female: 25–34 Male: 27–34	Quantity of hemoglobin per RBC	Interpret in the context of other CBC parameters
	MCHC	315–355	Concentration of hemoglobin per volume of RBCs	Indicates hyper- or hypochromia
	RDW (Info point 3)	11.5–15	Variation in size of RBCs (larger percentage = greater variation in RBC size)	To assess for thalassemia (generally normal) or deficiencies in iron, vitamin B_{12}, and folate (generally elevated)
WBCs	Total count	3.5–10.5	Total WBCs	To determine if the count is above or below the normal range, potentially indicating underlying conditions (e.g., hematologic malignancies, infection, inflammatory conditions) or causative factors (e.g., smoking, medications)
	Neutrophils	2.0–7.5	Quantity of each WBC type	
	Eosinophils	0–0.5		
	Basophils	0–0.1		
	Lymphocytes	Female: 0.8–3.3 Male: 0.8–3.5		
	Monocytes	0.1–1.0		
Platelets	Total count	150–380	Total quantity of platelets	

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RDW = red cell distribution width

3. The RDW reflects heterogeneity in red cell size and can be elevated when there are larger cells together with smaller cells. It is calculated by dividing the standard deviation of the RBC volume by MCV and expressed as a percentage. It is most useful in identifying a mixed iron and B_{12} deficiency.[11]

Abnormal CBC Results

4. Abnormal CBC results should be interpreted in the context of:[4,12,13]
   - Relevant findings on history and physical. Refer to the module sections/appendices that follow for specific findings on each abnormality.
   - Other related results. For example, total WBC count can be misleading when low neutrophils occur with high lymphocytes and produce a total WBC count that falls within the normal range. In most cases, the absolute count of each WBC type is more useful than the total WBC.
   - Patient's baseline/previous results.
   - Age, sex, gender, and ethnicity.

Box 4. Talking Tip: Clinical Relevance of Abnormalities

When multiple tests are done (there are about 16 on a CBC), there is a greater chance that an abnormal result is found that might not be important to your health [Reviewer Comment].

5. A CBC should be repeated in various circumstances:[4]
   - To verify abnormalities when first identified.
   - To assess borderline results as diseases will often demonstrate progressive abnormalities.
   - If the specimen is hemolyzed.
   - If there are any unexpected findings or findings that do not make sense. In this situation, it is reasonable to also order a peripheral blood smear or to speak to the laboratory pathologist. The peripheral smear yields important information. For example, in viral infections, lymphocytes look "activated" (bigger, more cytoplasm, granules); in chronic lymphocytic leukemia, they look small, mature, and the nucleus has a characteristic pattern [Expert Opinion].

6. It is important to communicate abnormal results in a direct and timely manner, particularly if the results are significant and/or a patient may have difficulty interpreting their meaning. This approach remains essential as many patients can access their test results via online portals. Patient portals do not tell the patient why a particular test was ordered in the first place, making communication of a test's relevance especially important for fostering patient engagement in testing and follow-up.[14]

7. In the past 20 to 25 years, notable improvements in survival have been observed for hematologic malignancies (particularly leukemia and non-Hodgkin lymphoma). This trend is largely attributed to improved treatment.[15]
   - Surveillance is important in patients with known familial cancer syndromes that predispose to hematologic malignancies. Most hematologic malignancies do *not* have an inherited component. In patients with a family history of long-standing cytopenias, known hereditary cancer syndromes in a 3-generation pedigree, or a personal or family history of multiple cancers, it is reasonable to draw a baseline CBC and consider electronic or in-person consultations with hematology and/or clinical genetics for appropriate screening approaches for the individual and other family members.[16]

RBC Abnormalities

Erythrocytosis

8. Erythrocytosis refers to an increased number of erythrocytes relative to plasma volume and can be due to reduced plasma volume (relative/apparent erythrocytosis), which is most commonly due to dehydration or increased RBC mass (absolute/true erythrocytosis).[17]

9. Absolute erythrocytosis can be divided into primary and secondary erythrocytosis:[1,5,18,19]
   - Primary: increased RBC production in bone marrow due to a myeloproliferative disorder such as polycythemia vera.
   - Secondary (more common than primary): increased RBCs due to a factor external to bone marrow, usually driven by erythropoietin (EPO). Causes include reactions to chronic hypoxia (e.g., smoking, COPD, obstructive sleep apnea, cyanotic heart disease), testosterone use, neoplasms (e.g., renal cell carcinoma), high altitude, and other less common conditions.

10. In Canada, up to 4% of men and 0.4% of women have erythrocytosis based on a Hgb > 165 and > 160, respectively, in the ambulatory setting. These percentages include both primary erythrocytosis and secondary erythrocytosis.[1]

11. Patients with polycythemia vera have an increased risk of thrombosis and can develop other complications from the disease. Secondary erythrocytosis does not necessarily carry that same risk [Expert Opinion].[2,20]

12. Investigations should be conducted if Hct is persistently elevated despite ruling out dehydration as a cause (for men, Hgb > 165 or Hct > 0.49; for women, Hgb > 160 or Hct > 0.48). Absolute erythrocytosis is likely if Hct is > 0.60 in males or > 0.56 in females.[21]

13. Follow-up testing for erythrocytosis generally includes a serum EPO. If the serum EPO is low or normal, Janus Kinase 2 (JAK2) mutation testing is reasonable.[1]
    a) EPO will be suppressed or normal in primary erythrocytosis but will be elevated in secondary erythrocytosis (refer to Appendix 1).
    b) The JAK2 mutation is present in 95% of patients with polycythemia vera.[1]
    c) There is variation by province in terms of coverage if ordered in the community versus a hospital clinic. In many regions, these tests cannot be ordered in outpatient settings. Given these limitations and the rarity and cost of JAK2 testing, a recommended approach is to order EPO first and, based on the results, order a JAK2 test if necessary. Test ordering may need to happen through a hematologist for it to be covered.

Refer to Appendix 1 for a detailed algorithmic approach to patients with erythrocytosis.

Anemia

14. Low Hgb and/or Hct counts indicate anemia. RBC indices (MCV, MCH, MCHC, RDW) and peripheral blood smear will help to identify the type of anemia. For further details, refer to the PBLP module Anemia in Adults (August 2017) available at members.fmpe.org.

WBC Abnormalities

Box 5. Talking Tip: WBCs

Levels of white blood cells can go up and down often. If this happens but you're feeling well, there is less cause for worry. Your doctor may repeat the CBC in 6 to 12 weeks just to be sure [Reviewer Comment].

Neutrophilia

15. Neutrophilia (high neutrophils) is the most common cause of leukocytosis (high WBC count). It is categorized into the following:[22,23]
    - Primary neutrophilia: direct result of a primary neoplastic process within the bone marrow or an inherited condition
    - Secondary neutrophilia: due to increased bone marrow production, such as a response to infection (the most common cause), inflammation, drug reaction, or other stimulus

16. Before investigating neutrophilia, it is first important to confirm the validity of the lab value, although spurious neutrophilia is very rare [Expert Opinion].

17. Identifying a population at risk for neutrophilia is difficult because many diverse factors contribute to its development.[22]

Refer to Supplementary Appendix 1 (available at Members Online) for a detailed algorithmic approach to patients with neutrophilia.

Neutropenia

18. Neutropenia (low neutrophils) is commonly defined as mild (1.0–1.5), moderate (0.5–0.9), or severe (< 0.5).[1,24] Acquired neutropenia is most often caused by medications or acute viral infection.[24]

19. A European study of a primary care population (n>370,000) found that neutropenia was present in 1.9% of adults. The lower the count, the more likely a diagnosis of viral infection (most common: hepatitis, HIV) or hematologic malignancy (most common: acute myelogenous leukemia, myelodysplastic syndromes) during the subsequent 4 years. It is important to note that the risk of hematologic malignancy decreased significantly in isolated neutropenia, emphasizing the fact that malignancies are not typically characterized by isolated neutropenia but by abnormalities in multiple cell lines.[25]

20. Duffy-null associated neutrophil count (DANC)—a benign variant that is often incorrectly considered to be neutropenia—affects 25 to 50% of people of African or Afro-Caribbean ancestry, as well as people of Black Ethiopian Jewish ancestry (15.4%), Yemenite Jewish ancestry (11.8%), and Arabic ancestry (10.7%). It is caused by the non-expression of an antigen on RBCs that is protective against Plasmodium vivax (most frequent cause of malaria). DANC should be suspected in these populations with a persistent count between 1.0 and 1.5 and the absence of secondary causes (refer to Supplementary Appendix 2).[26,27]
    - Further investigations are not needed in these populations if neutrophil counts are 1.0 to 1.5, but investigations would be indicated for recurrent infections, unusual site infections, severe infections, fever, or other signs of secondary causes.[27]

Refer to Supplementary Appendix 2 (available at Members Online) for a detailed algorithmic approach to patients with neutropenia.

Lymphocytosis

21. Lymphocytosis (high lymphocytes) is a common hematologic abnormality in adults[28] and, after neutrophilia, the second most common cause of leukocytosis. The prevalence of lymphocytosis depends on the underlying cause.[29] Refer to Appendix 2 for a list of possible causes.
    - A large Danish cohort study from the general population (n=104,607) found that higher tobacco consumption was causally associated with increased WBCs (including lymphocytes). The "observational smoking relationship" was long term for WBCs. All associations were dose dependent but also dependent on smoking cessation time in former smokers. The highest increases in WBCs were for < 1-year smoking cessation, while the lowest increases were for > 10-year smoking cessation.[30]

22. Evaluation of a patient with lymphocytosis should determine whether lymphocytosis is caused by an underlying malignancy and identify conditions that may require immediate medical management.[29]
    - In some provinces, flow cytometry can be ordered in the primary care setting to help diagnose and classify leukemias and lymphomas.

Refer to Appendix 2 for a detailed algorithmic approach to patients with lymphocytosis.

Lymphopenia

23. Lymphopenia (low lymphocytes) is a common, often incidental laboratory finding. A European general population study found a prevalence of 1% among adults with a median age of 68.[31] In many patients, it is often associated with acute illness and thus can be transient/reversible.[32]

24. Incidental, mild lymphopenia without an associated underlying condition does not typically require further follow-up. For moderate to severe lymphopenia (< 1.0), consider further evaluation for conditions/medications such as those listed in Table 2.[32]

Table 2. Lymphopenia: Causes

Cause	Examples
Infection	Commonly viral (e.g., HIV, hepatitis) although can occur with bacterial, parasitic, and fungal infections
Medications	Cytotoxic drugs, corticosteroids
Autoimmune disease	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome
Malignancies (rare)	Lymphoproliferative disorders, solid organ malignancies
Others	Recent surgery, trauma, radiation therapy, extensive burns

25. Incidental lymphopenia has been associated with increased risk of all-cause and/or cause-specific mortality.[32] A prospective cohort study (n=108,135, median age 68) found that, compared to participants with normal lymphocyte counts, those with lymphopenia (< 1.1) had a 1.6-fold increase in all-cause mortality and 1.5- to 2.8-fold increase in risk of mortality due to non-hematologic cancer, hematologic cancer, CVD, respiratory disease, infections, and other causes. The highest absolute risks were seen in those > age 80 who smoked with lymphocyte counts < 0.5. The authors suggested that this population "might benefit from additional surveillance, although there is no evidence that this will decrease mortality." Though the study did not provide specific monitoring guidance, lymphopenia was described as a general passive marker for frailty that "confers a high risk of death from any cause."[31]

Eosinophilia

26. Eosinophilia (high eosinophils) may be identified incidentally in asymptomatic patients or in those with symptoms of an underlying cause or organ damage secondary to eosinophil migration.[33] It has a prevalence of 4% in primary care,[34] although it may be higher in certain patient populations (e.g., those returning from travel in a tropical area).[33] Refer to Table 3 for causes and examples.

Table 3. Eosinophilia: Causes[33,35,36]

Type	Causes and Examples
Primary (rare)	Hematologic malignancies
Secondary (more common)	Allergic reaction—most common cause (80%) in developed world • Mild eosinophilia: allergic rhinitis, asthma, atopic dermatitis • More severe eosinophilia: chronic sinusitis, medications (anticonvulsants, antimicrobials, antiretrovirals, sulphonamides, NSAIDs, methotrexate, ranitidine, allopurinol), allergic bronchopulmonary aspergillosis, eosinophilic pneumonia
	Infection • Viral: HIV • Fungal: histoplasmosis, coccidioidomycosis, cryptococcosis • Parasitic: nematodes, filariases, flukes
	Gastrointestinal disorders • Eosinophilic esophagitis, gastritis or colitis, inflammatory bowel disease, celiac disease
	Connective tissue diseases, vasculitides • Systemic lupus erythematosus, rheumatoid arthritis, eosinophilic granulomatous polyangiitis
	Solid organ malignancy

27. An identified reversible cause should be treated (e.g., if allergy, avoidance of the trigger). In patients who are otherwise well with mild to moderate eosinophilia (0.5–1.5), further testing may be unnecessary and they could be followed with a CBC done periodically. Patients should be referred if:[36]
    - Systemic symptoms
    - Persistent eosinophilia (≥ 1.5) with or without suspected end-organ damage
    - Suspected end-organ damage or hematologic malignancy

Eosinopenia

28. Eosinopenia (low eosinophils) is not a cause for concern and does not require follow-up because the normal count in eosinophils is low in most people.[4]

Monocytosis

29. Monocytosis (high monocytes) is a common finding on CBC, with one study finding a prevalence of 4.6% in primary care. It has a broad differential but is most often associated with infection and inflammatory disease (Table 4) and often co-occurs with other CBC abnormalities.[4,37]

Table 4. Monocytosis: Causes[37,39]

Type	Causes and Examples
Primary	Acute: acute monocytic or myelomonocytic leukemia Chronic (examples): chronic myelomonocytic leukemia, chronic myeloid leukemia, B and T cell malignancies, solid tumours
Secondary	Transient: • Acute infection (e.g., mononucleosis, leptospirosis, listeriosis, COVID-19) • Bone marrow recovery • Stressful events (e.g., splenectomy, myocardial infarction, intense exercise) • Medication induced (e.g., corticosteroids, ziprasidone, cytokine therapy) Persistent: • Chronic infection (e.g., syphilis, brucellosis, tuberculosis) • Autoimmune/inflammatory disease (e.g., sarcoidosis, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus) • Cigarette smoking

30. A 2022 European study (n=663,184 primary care patients with no known hematologic malignancy) examined the predictive value of monocytosis for hematologic malignancy in primary care. The study observed an association between monocyte counts > 1.0 and a higher 3-year risk of all types of myeloid and lymphoproliferative neoplasm. The risk for chronic myelomonocytic leukemia was particularly high: odds ratio 105 (95% CI 38–289), with persistent monocytosis (at least 2 abnormal readings in 3 months) further increasing that risk. It is important to note, however, that this diagnosis was very rare, occurring in only 0.1% of participants. The authors concluded: "Relevant referral from primary care remains difficult, but based on our observations, suspecting hematologic malignancy is rational when monocytosis is sustained or—as always—the clinical presentation is consistent with hematologic malignancy."[38]

31. A mild elevation in monocytes is common and typically does not require follow-up. Persistent monocytosis (> 1.0), particularly accompanied by suspicious symptoms, should prompt a referral to hematology.[38]

Monocytopenia

32. Isolated monocytopenia (low monocytes) is an uncommon finding that is not clinically significant. If accompanied by other abnormalities on CBC, particularly neutropenia (Info points 18–20) and lymphocytosis (Info points 21, 22), it may indicate a lymphoproliferative disorder and referral would be indicated.[4]

Basophilia/Basopenia

33. Basophilia (high basophils) is an extremely rare finding. If present, it may indicate chronic basophilic leukemia or other obscure etiologies. Consider repeating the CBC and, if still present, refer to hematology.[4,13] Basopenia (low basophils) is not clinically significant as the normal basophil count is so low (Table 1).[4]

Platelet Abnormalities

Thrombocytosis

Note: Thrombocytosis is often referred to as thrombocythemia.

34. Thrombocytosis (high platelets) has a prevalence of 1.5 to 2.2% in primary care patients ≥ age 40.[40] It is essential to differentiate between primary and secondary thrombocytosis—only primary thrombocytosis has a well-established association with thrombotic complications that requires management.[40] Secondary thrombocytosis is most often caused by infection, inflammation, or iron deficiency.[41] Thrombocytosis due to iron deficiency anemia is quite common (estimated at 1 in 3 patients with iron deficiency anemia) though the underlying mechanism is not clear.[42]

35. A study of the clinical relevance of thrombocytosis in primary care compared the 1-year incidence of cancer between 40,000 patients ≥ age 40 with a platelet count of > 400 (thrombocytosis) and 10,000 matched patients with a normal platelet count. The study found:[43]
    - 11.6% of male participants with thrombocytosis developed cancer (95% CI 11.0–12.3) versus 4.1% without thrombocytosis (95% CI 3.4–4.9).
      Note: 11.6% is the positive predictive value (PPV) or likelihood that a male with thrombocytosis will develop cancer in the next year.
    - 6.2% of female participants with thrombocytosis developed cancer (95% CI 5.9–6.5) versus 2.2% without thrombocytosis (95% CI 1.8–2.6).
    - The risk of cancer increased by about 50% when a second raised platelet count was found within 6 months.
    - Lung and colorectal cancer were more commonly diagnosed.

    Note: To put these figures into context, the PPV of a breast lump in a female age 50 to 59 in primary care is 8.5%. The PPV of hypercalcemia to predict 1-year cancer incidence is 11.5% in males and 4.1% in females.[43] It is also important to note that thrombocytosis is associated with cancer risk factors (e.g., smoking, chronic inflammatory disease, obesity) and is a general finding associated with inflammation. Thus, the correlation between high platelets and cancer may be confounded by other factors [Expert Opinion].

36. Primary (i.e., essential) thrombocytosis is associated with pregnancy-related complications that include miscarriage in the first trimester (most common complication—risk increased 3-fold[44]), pre-eclampsia, placental abruption, preterm delivery, and low birth weight.[45,46]
    a) Low-dose aspirin is recommended in the absence of clear contraindications in all pregnant patients with essential thrombocytosis.[40,47] This may be started in primary care, although essential thrombocytosis (like any active hematologic cancer in a pregnant patient) merits urgent electronic/phone consultation and/or referral to a hematologist. The dose of aspirin in these patients is not well established, but 81 mg PO daily can be considered. ASA should be started as early as possible (ideally before 12–16 weeks' gestation) while advice is being sought on further interventions.
    b) Other interventions (e.g., interferon) both during pregnancy and postpartum depend on the patient's risk stratification [Expert Opinion]. These interventions would be managed by a hematologist along with an obstetrician/gynecologist.[40,47]

Refer to Appendix 3 for a detailed algorithmic approach to patients with thrombocytosis.

Thrombocytopenia

37. Thrombocytopenia (low platelets) is often an incidental finding on a CBC without an immediately apparent cause. The incidence depends on the clinical setting (much higher in acute care settings—e.g., up to 50% during an ICU stay) and underlying cause (e.g., 77–85% in cirrhosis, 7–10% in pregnancy).[48,49]
    a) Thrombocytopenia may be associated with increased bleeding, although clinically significant bleeding is not typical until the platelet count is < 30. It may indicate the presence of an underlying disorder that is "a greater risk than the low platelet count itself."[49]
    b) It is important to identify patients with pseudothrombocytopenia, which is a low platelet count that can occur when specimens are anticoagulated with ethylenediaminetetraacetic acid (EDTA), a standard anticoagulant used to improve the assessment of samples by automated hematological analyzers. EDTA, however, can cause platelets to activate and clump. If the lab indicates there is platelet clumping or platelet satellitism, the next steps in management include repeating the test in a tube containing a non-EDTA anticoagulant (typically heparin or sodium citrate) and requesting a peripheral blood smear from the lab.[48,50] It is also important to note that pseudothrombocytopenia is relatively rare [Expert Opinion].

Refer to Appendix 4 for a detailed algorithmic approach to patients with thrombocytopenia.

Thrombocytopenia in Pregnancy

38. Thrombocytopenia occurs in up to 10% of pregnancies and the etiology can range from benign to life-threatening.[51] Initial workup includes a repeat CBC and peripheral blood smear to rule out pseudothrombocytopenia as per the assessment of nonpregnant patients (Appendix 4).[52] A history, physical exam (Appendix 4), and additional testing can help to narrow the differential (Table 5).

Table 5. Thrombocytopenia: Most Common Pregnancy-Specific Causes and Features[48,51,52]

Cause*	Clinical Features	Evaluation
Gestational thrombocytopenia (75%)	• Mild thrombocytopenia • Can occur at any time but typically seen in mid-second to third trimester	• Unnecessary • Usually resolves after pregnancy, fetus unaffected
Pre-eclampsia/ HELLP syndrome	• Mild to moderate thrombocytopenia • Hypertension onset: after 20 weeks' gestation • Severe symptoms: altered mental status, visual disturbances, dyspnea, persistent headache, abdominal pain	• CBC • Evaluate for proteinuria • Hepatic/renal function • Uric acid • Hemolysis screen (haptoglobin, lactate dehydrogenase, bilirubin)
Eclampsia	• Similar to pre-eclampsia but with presence of tonic-clonal seizures	• As above
Acute fatty liver of pregnancy	• Third trimester • Symptoms: abdominal pain, malaise, nausea/ vomiting, altered mental status	• CBC • Hepatic/renal function • Coagulation studies (INR, PTT, fibrinogen) • Ammonia • Hypoglycemia (key feature) • Ultrasound or MRI

*In order of most to least common
HELLP = hemolysis, elevated liver enzymes, low platelets

39. In general, patients with mild gestational thrombocytopenia are not at increased risk for maternal or fetal bleeding complications and, therefore, additional testing/specialized care is not necessary except for follow-up platelet monitoring. There is no evidence to guide the frequency of this follow-up, although expert opinion advises a platelet count at each routine prenatal visit.[52] If further evaluation reveals other underlying causes of thrombocytopenia (Table 5), referral is indicated.

KEY POINTS

- Routine CBC testing is not recommended in asymptomatic, nonpregnant adults given the low pretest probability and high rate of false positives.
- EPO can help to differentiate secondary from primary erythrocytosis.
- Persistent thrombocytosis in the absence of secondary causes is concerning for malignancy.
- For thrombocytopenia, where the lab indicates platelet clumping or platelet satellitism, repeat the CBC to rule out pseudothrombocytopenia.
- Iron deficiency is a common cause of thrombocytosis.
- As with other topics within medicine, the differential diagnosis for an abnormal CBC can be broad. It would be important to consider multi-factorial scenarios (especially if an intervention is not working) or to consider risk factors of the individual.

CASE COMMENTARIES

Case 1: Lloyd, age 53

How would you interpret and communicate the CBC results?

Lloyd's elevated Hgb and Hct indicate erythrocytosis (Info points 8–13; Appendix 1).

While these results need to be investigated, Lloyd could be advised that not all conditions that cause this abnormality are harmful and many common causes are treatable (Appendix 1). Causes of erythrocytosis are associated with various risks, including thrombosis. Polycythemia vera carries a further increased risk of thrombosis and other conditions (Info point 11).

What further information on history and physical exam would be helpful in Lloyd's case?

It would be prudent to proceed with a history and physical exam at this juncture so as not to delay further investigations if any red flags arise. Relatively common causes of erythrocytosis include dehydration, cigarette smoking, COPD, sleep apnea, and testosterone use (Info points 8, 9; Appendix 1).

History (Appendix 1):
- Hydration status—was this a fasting bloodwork? If so, he may have avoided fluids and been dehydrated
- History of bleeding, bruising, or thromboembolism
- Review of systems—symptoms of hyperviscosity (e.g., visual changes, shortness of breath, fatigue, paresthesia, unilateral calf swelling, chest pain), snoring, witnessed apnea, facial flushing, or constitutional symptoms
- Smoking history and cessation attempts
- Any previous spirometry indicating COPD
- Testosterone use
- Family history of hematologic malignancies, stroke, deep vein thrombosis, or pulmonary embolism

Physical (Appendix 1):
- Height, weight, BMI, BP
- Assessment for facial plethora, palmar erythema, and peripheral adenopathy
- Neck circumference
- Respiratory, cardiovascular, and abdominal exams

Part Two

What would be your approach in managing Lloyd going forward?

It would be appropriate to repeat the CBC in 2 to 4 weeks to confirm the lab finding and advise him to hydrate well prior to having his blood drawn (Appendix 1). If the hemoglobin remains elevated and dehydration has been ruled out, an EPO could help to differentiate primary from secondary erythrocytosis (Info point 9; Appendix 1). In some jurisdictions, EPO can be ordered from an outpatient setting, while in others it can only be arranged through a specialist.

Encourage smoking cessation, continue to review his willingness to quit at subsequent visits, and, when appropriate, arrange for a follow-up smoking cessation counselling session. COPD testing (spirometry) and lung cancer screening (depending on provincial guidelines) would be warranted.

Since obesity can be a cause for erythrocytosis, weight reduction strategies could be attempted (Appendix 1). Although Lloyd is considered low risk for sleep apnea, a sleep study could be considered at some point in the future.

Part Three

What would you do now?

As the cause of the erythrocytosis remains unclear, an EPO should be arranged to differentiate primary from secondary erythrocytosis (Info point 9; Appendix 1). If the EPO is low or normal, consider testing for the JAK2 mutation (Info point 13). Investigation practices, coverage, and prerequisite laboratory work for molecular testing may vary across setting and jurisdiction, and EPO and JAK2 testing are often not available in community settings [Expert Opinion].
Note: If the patient in this case were female, the cut-off Hgb and Hct would be lower—160 and 0.48, respectively (Appendix 1).

If not already done, it would be prudent to arrange an electronic or phone consultation with a specialist (e.g., internist, hematologist) to decide if further workup is needed for conditions like polycythemia vera (Info point 9; Appendix 1). Finally, testing to definitively rule out sleep apnea (Appendix 1) would be appropriate.

Case 2: Irina, age 48

How would you address Irina's concerns about her lymphocyte level? What further information and assessment would be helpful?

You could explain that lymphocytes are a type of WBC in her immune system that help her body to fight disease and infection, and that there are several possible causes of high lymphocytes (Appendix 2). She could be reassured that her degree of lymphocytosis is not alarming and that her other blood cell levels are normal, but that a focused history, physical exam, and investigations (including a repeat CBC and peripheral blood smear) would be required. Consider adding a TSH test to rule out autoimmune thyroiditis (Info point 22; Appendix 2). In some jurisdictions, flow cytometry in a primary care setting can be ordered to help with both diagnosis and prognosis.

You could order a peripheral smear, which could help differentiate between viral or more serious causes. You could also consider an electronic or phone consultation with an internist or hematologist, depending on local availability, to discuss her case further (Appendix 2).

Part Two

What would be your next steps in managing Irina's lymphocytosis?

For persistent/progressive lymphocytosis, you could consider ordering flow cytometry. If Irina's CBC showed abnormalities in multiple cell lines or if concerning findings were noted on the smear, immediate referral to hematology would be indicated. A hematology referral could also be made if her lymphocyte count is > 5 and/or progressively increasing, and she had one of the following: constitutional symptoms, bulky or painful lymph nodes, splenomegaly, hepatomegaly, progressive anemia, or thrombocytopenia (Appendix 2).

Case 3: Giselle, age 32, G1P0

What would be your next steps in managing Giselle's blood work finding?

A repeat CBC and peripheral blood smear should be ordered. If there is a lab comment of platelet clumping or platelet satellitism, a repeat CBC would be indicated to rule out pseudothrombocytopenia, even though this phenomenon is rare (Info point 37b; Appendix 4).

Gestational thrombocytopenia is the most common cause of mild thrombocytopenia. If platelets are > 75 and the patient feels well, monitoring alone is reasonable (Info point 39; Table 5). However, when thrombocytopenia is more pronounced or if low platelets were observed earlier in pregnancy, further workup and/or referral to hematology would be warranted.

Giselle should be monitored at subsequent prenatal visits for any signs of bruising, petechiae, jaundice, bleeding, lymphadenopathy, and splenomegaly (Appendix 4). The CBC should be repeated at every routine prenatal visit (Info point 39) to monitor for worsening thrombocytopenia and to rule out other causes (Table 5).

As Giselle has moderately reduced platelets and appears to be asymptomatic, testing could include (Appendix 4):
- Coagulation panel (e.g., fibrinogen, d-dimer)
- Hemolysis screen (direct antiglobulin test, haptoglobin, lactate dehydrogenase)
- Renal and hepatic function tests
- Viral serology testing (e.g., Hepatitis B and C, HIV) if warranted/not already done
- *H. pylori* serology
- Vitamin B_{12} and folate levels
- TSH

Additional monitoring would include (Table 5):
- BP and urine for protein as pre-eclampsia would be on the differential in the second and, especially, third trimester
- ALT, bilirubin, and creatinine in the third trimester as HELLP syndrome is on the differential along with pre-eclampsia

An electronic/phone consultation or referral would be indicated as warranted (Appendix 4).

How would your management differ if Giselle were not pregnant?

A peripheral blood smear and repeat platelet count would still be indicated (Info point 37b; Appendix 4).

Repeat platelet testing would be indicated in 1 to 2 weeks. Consider additional testing to assess for secondary causes of low platelets. Referral or electronic consultation would be warranted if her platelets continued to decline and/or a cause for the thrombocytopenia was not identified (Appendix 4).

How would your management differ if Giselle's initial blood work during her pregnancy had shown an elevated platelet count of 475 instead?

A platelet level of 475 is not always dangerous. A ferritin should be ordered to rule out iron deficiency, the most common cause of elevated platelets in otherwise healthy people. When platelet levels are > 1,000, there is a higher risk of blood clots and urgent referral would be required. It would be important to counsel Giselle regarding monitoring of her high platelets, and to ensure that her platelet elevation is not due to a primary hematologic disorder. Some complications that can arise from very high platelets are eclampsia, placental abruption, intrauterine growth restriction, and stillbirth (Info point 36). Ongoing monitoring of her CBC would be indicated and, at minimum, an electronic or phone consultation with an obstetrician/gynecologist. If her platelets continue to rise, referral would be indicated (Appendix 3).

We always welcome your input. If you would like to provide feedback on this module, the following link will take you to an electronic survey: **http://members.fmpe.org/modulefeedback**.

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APPENDIX 1. Erythrocytosis[1,2,20,21,53]

Hemoglobin: > 160 for females, > 165 for males
Hematocrit: > 0.48 in females > 0.49 in males

→ Urgent referral if:
Hemoglobin > 200
Recent thrombosis or symptoms of hyperviscosity

↓

Confirm result in 2–4 weeks
If patient is dehydrated, repeat when patient is euvolemic

→ Resolved → Relative erythrocytosis
No further workup or treatment needed

↓

If persistent erythrocytosis, conduct history and physical exam
Order serum erythropoietin (EPO)
Consider ordering JAK2 if EPO is low or normal

History	• Symptom review:
	  ○ Symptoms of hyperviscosity—**fatigue, headache, dizziness, transient blurry vision, paresthesias, burning sensation in hands/feet**
	  ○ **Pruritus after hot shower**
	  ○ Epistaxis, gastrointestinal bleeding, easy bruising
	  ○ **Non-specific abdominal pain (suggests peptic ulcer)**
	  ○ **Left hypochondrial pain and early satiety (suggests splenomegaly)**
	  ○ Constitutional symptoms (e.g., fever, night sweats, unintended weight loss)
	• Past medical history: **history of thrombosis**, congenital heart disease
	• Medication review: particularly testosterone or anabolic steroids
	• Family history: polycythemia
	• Social history: cigarette smoking, alcohol intake, extended stay at high altitude

Physical exam	• BP, BMI • Cardiac, respiratory, abdominal exams, including assessment for **hepatomegaly** and **splenomegaly**

↓

Primary erythrocytosis
Suspect polycythemia vera if:
- Low or normal EPO and JAK2 positive
- **Bolded** symptoms above (suggestive)

↓

Referral
or electronic/phone consult with hematology (if appropriate)

Secondary erythrocytosis
Suspect if:
High EPO
History and physical exam suggest underlying cause

Type	Causes
Hypoxia-driven	*Cigarette smoking, COPD, obstructive sleep apnea,* obesity, intracardiac shunting, high altitude
Local renal hypoxia	Renal artery stenosis, hydronephrosis, polycystic kidney disease, end-stage renal disease
Medication-related	Androgen therapy (testosterone, anabolic steroids), EPO
Pathologic erythropoietin production	Renal cell, hepatocellular, or parathyroid carcinoma Cerebellar hemangioblastoma, uterine leiomyomata, meningioma, pheochromocytoma
Others	Renal transplantation, idiopathic

Note: Causes in italics are the most common in primary care

↓

Further investigations and treatment guided by underlying cause
Refer as indicated

JAK2 = Janus Kinase 2
EPO = erythropoietin

Refer to the Reference List for cited sources

APPENDIX 2. Lymphocytosis

Lymphocytes > 5

↓

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

↓

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

↓

Do history and physical findings suggest an underlying cause?

↓

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

↓

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)

↓

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

APPENDIX 3. Thrombocytosis

Platelets > 450

Urgent referral if:
- Platelets > 1,000
- Unexplained thrombosis

In 2–4 weeks, repeat CBC and peripheral blood smear to rule out spurious result (caused by counting of nonplatelet structures in peripheral blood by automated counters)

History	• Symptom review:
	  ○ Symptoms consistent with primary cause: vasomotor, headache, syncope, chest pain, erythromelalgia, acrocyanosis, visual changes
	  ○ Symptoms of infection/inflammation
	  ○ Constitutional symptoms (e.g., fever, night sweats, unintended weight loss)
	• Past medical history: thrombocytosis, thrombosis, bleeding episodes
	• Medication review
	• Surgical history: prior splenectomy, trauma
	• Family history: thrombocytosis, thrombosis, bleeding episodes

Physical exam	• Cutaneous or mucosal bleeding/bruising • Splenomegaly, hepatosplenomegaly, lymphadenopathy • Signs of arterial or venous thrombosis
Tests	Guided by likelihood of underlying cause (refer to following sections)

Do history and physical findings suggest an underlying cause?

Primary Thrombocytosis
- Signs/symptoms of hematologic malignancy (e.g., splenomegaly, elevated Hgb, elevated WBCs)
- History of familial thrombocytosis

Referral or electronic/phone consult with hematology or obstetrics/gynecology (if appropriate)

If patient is pregnant, low-dose aspirin may be started in consultation with hematologist or obstetrician/gynecologist. Other interventions (e.g., low molecular weight heparin) are managed in tertiary care.

Secondary Thrombocytosis

Findings	Examples
Most Common	
Signs/symptoms of anemia	Iron deficiency, hemolytic anemia
Current infection	Acute bacterial and viral infections, chronic infections
Malignancy	Metastatic cancer, lymphoma
Signs/symptoms of connective tissue disease	Rheumatoid arthritis, inflammatory bowel disease, sarcoidosis
Intense exercise	
Less Common	
Causative medication	Corticosteroids, adrenaline, thrombopoietin, thrombopoietin receptor agonists, vincristine, tretinoin, methimazole, recombinant erythropoietin
Others	Post-splenectomy, hyposplenic states, postoperative

Note: Further testing guided by likelihood of underlying cause

If secondary cause identified:

Investigate and treat as indicated
Electronic/phone consult as needed

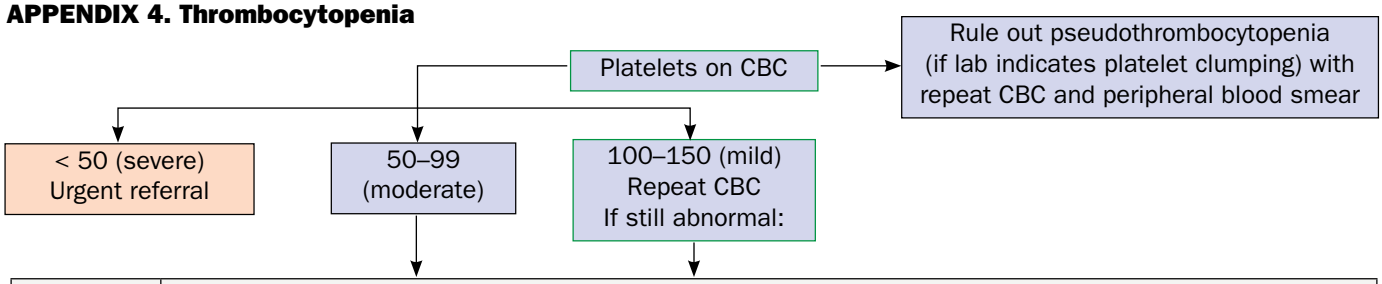
If no secondary cause identified:

Refer if platelets > 600

Follow platelets as clinically indicated if < 600
If platelets rise > 600, restart algorithm

Sources: 1) DynaMed. *Thrombocytosis - approach to the patient*. 2023; **2)** Rokkam VR, Killeen RB, Kotagiri R. Secondary thrombocytosis. *StatPearls*. Treasure Island (FL). 2023; **3)** Ashorobi D, Gohari P. Essential thrombocytosis. *StatPearls*. Treasure Island (FL). 2023.

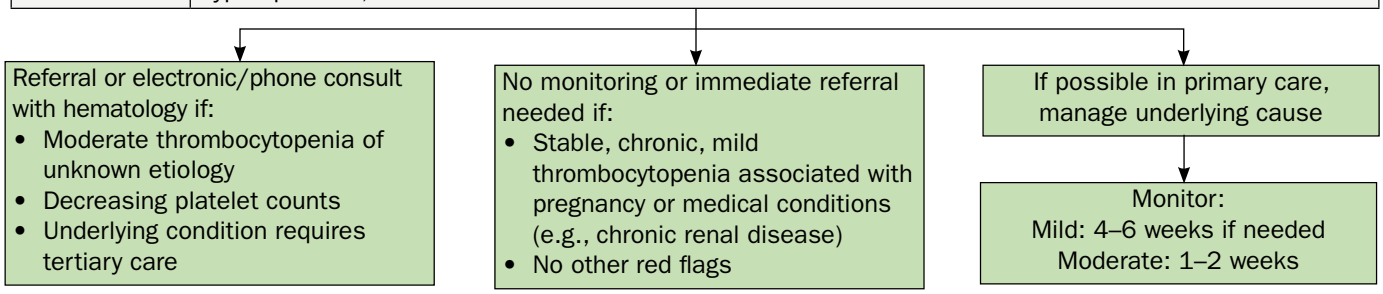
APPENDIX 4. Thrombocytopenia



History	• Onset of reduced platelets: acute versus chronic
	• Known or possible pregnancy
	• Symptom review:
	  ○ Bleeding: spontaneous and with hemostatic challenges (e.g., surgeries, childbirth)
	  ○ Constitutional symptoms (e.g., fever, night sweats, unintended weight loss)
	  ○ Abdominal pain: may indicate hepatitis disease, HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels), hemolytic uremic syndrome, hypersplenism
	  ○ Neurologic: may indicate CNS bleeding or underlying thrombotic microangiopathy
	• Past medical history:
	  ○ History of alcohol use disorder
	  ○ History of liver disease, autoimmune disorders, or malignancy
	  ○ Recent transfusions, vaccine
	• Medication review
	• Family history of thrombocytopenia
	• Social history: recent travel

Physical exam	• Skin and palate for bruising and petechiae • Lymphadenopathy, hepatosplenomegaly • Venous thromboembolism, vascular necrosis
Tests	Evaluate peripheral blood smear for presence of fragmented RBCs suggesting microangiopathic hemolytic anemia. If absent, further blood work guided by severity of thrombocytopenia and likelihood of underlying cause. Consider fibrinogen, d-dimer, hemolysis screen (direct antiglobulin test, haptoglobin, lactate dehydrogenase), renal/hepatic function, HIV, Hepatitis B/C, *H. pylori*, stool analysis, vitamin B_{12} levels, other tests as indicated by suspected cause (refer to following section)

Findings	Examples
Causative medication	Abciximab, captopril, cilastatin/imipenem, clopidogrel, dactinomycin/actinomycin, digoxin, dipyridamole, drospirenone/ethinyl estradiol, eptifibatide, famotidine, fluconazole, furosemide, gentamicin, hydrochlorothiazide, meropenem, phenytoin, piperacillin, quinine, spironolactone, TNF-alpha/interferon-gamma, trimethoprim/sulfamethoxazole, vancomycin, hepatitis B and flu vaccines
Current thrombosis	Disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenia purpura, heparin-induced thrombocytopenia, antiphospholipid antibody syndrome
Concurrent illness	Hepatitis B/C, HIV, Epstein-Barr virus, cytomegalovirus, *H. pylori*, parvovirus B19, Rocky Mountain spotted fever, ehrlichiosis, aplastic anemia, leukemia, myelodysplastic disorders
Pancytopenia	B_{12}, folate, or copper deficiency; paroxysmal nocturnal hemoglobinuria; autoimmune disease; hypersplenism; cirrhosis



Sources: 1) Gauer RL, Whitaker DJ. Thrombocytopenia: evaluation and management. *Am Fam Physician*. 2022;106:288-98. PMID 36126009; **2)** Temple RW, Burns B. Thrombocytopenia and neutropenia: a structured approach to evaluation. *J Fam Pract*. 2018;67:E1-E8. PMID 29989621; **3)** DynaMed. *Thrombocytopenia in adults - approach to the patient*. 2023.