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ONLINE EXCLUSIVE

Thrombocytopenia and neutropenia: A structured approach to evaluation

These algorithms and tables will help you quickly assess the severity of the 2 blood abnormalities and delineate between life-threatening and benign causes.

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PRACTICE RECOMMENDATIONS

› *Employ a systematic approach to the diagnosis and treatment of thrombocytopenia and neutropenia.* (C)

› *Do not transfuse platelets in patients with platelet counts >10,000/mcL who are stable and are not undergoing an invasive procedure.* (C)

› *Monitor patients on heparin therapy for >4 days for heparin-induced thrombocytopenia.* (C)

› *Monitor (for life) patients with a history of gastric bypass for the development of nutritional neutropenias.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Thrombocytopenia and neutropenia are commonly encountered laboratory abnormalities. The presence of either requires that you promptly evaluate for life-threatening causes and identify the appropriate etiology. This article identifies key questions to ask. It also includes algorithms and tables that will facilitate your evaluation of patients with isolated thrombocytopenia or isolated neutropenia and speed the way toward appropriate treatment.

Thrombocytopenia: A look at the numbers

Thrombocytopenia is defined as a platelet count <150,000/mcL.[1] The blood abnormality is either suspected based on the patient's signs or symptoms, such as ecchymoses, petechiae, purpura, epistaxis, gingival bleeding, or melena, or it is incidentally discovered during review of a complete blood count (CBC).

The development of clinical symptoms is closely related to the severity of the thrombocytopenia, with platelet counts <30,000/mcL more likely to result in clinical symptoms with minor trauma and counts <5,000/mcL potentially resulting in spontaneous bleeding. While most patients will have asymptomatic, incidentally-found thrombocytopenia, and likely a benign etiology, those with the signs/symptoms just described, evidence of infection, or thrombosis are more likely to have a serious etiology and require an expedited work-up. Although pregnancy may be associated with thrombocytopenia, this review confines itself to the causes of thrombocytopenia in nonpregnant adults.

Rule out pseudothrombocytopenia

When isolated thrombocytopenia is discovered incidentally in an asymptomatic person, the first step is to perform a repeat

CBC with a peripheral smear to confirm the presence of thrombocytopenia, rule out laboratory error, and assess for platelet clumping. If thrombocytopenia is confirmed and platelet clumping is present, it may be due to the calcium chelator in the ethylenediaminetetraacetic anticoagulant contained within the laboratory transport tube; this cause of pseudothrombocytopenia occurs in up to 0.29% of the population.[1] Obtaining a platelet count from a citrated or heparinized tube avoids this phenomenon.

Is the patient's thrombocytopenia drug induced?

Once true thrombocytopenia is confirmed, the next step is to review the patient's prescribed medications, as well as any illicit drugs used, for potential causes of drug-induced thrombocytopenia. DITP can be either immune-mediated or nonimmune-mediated.

Immune-mediated DITP typically occurs within 1 to 2 weeks of medication exposure and begins to improve within 1 to 2 days of stopping the offending drug.[2] (See **TABLE 1**[3] for a list of medications that can induce thrombocytopenia.) It should be noted that most patients who take the medications listed in **TABLE 1** do not experience thrombocytopenia; nonetheless, it is a potential risk associated with their use.

Heparin-induced thrombocytopenia (HIT) is a unique form of immune-mediated DITP in that it is caused by antibody complexes, resulting in platelet activation, clumping, and thrombotic events.[4] HIT occurs in <1% of patients in intensive care units, but can occur in any patient on long-term heparin therapy. It manifests as a >50% drop in platelet count within 5 to 14 days of the introduction of heparin; however, in those previously exposed to heparin, it can occur within 24 hours.[4,5]

Non-immune-mediated DITP, resulting from myelosuppression, chemotherapeutic agents, or valproic acid, is less common.[1,2]

Acute and chronic alcohol use. Although alcohol is not a drug per se, it can also result in thrombocytopenia. The mechanism is the direct suppression of bone marrow, although alcohol also causes B12 and folate deficiency, further contributing to the development of the blood abnormality.[1]

Immune-mediated drug-induced thrombocytopenia typically occurs within 1 to 2 weeks of medication exposure and begins to improve within 1 to 2 days of stopping the offending drug.

TABLE 1

Medications that can induce thrombocytopenia[3]

- Abciximab
- Captopril
- Cilastatin/imipenem
- Clopidogrel
- Dactinomycin/actinomycin
- Digoxin
- Dipyridamole
- Drospirenone/ethinylestradiol
- Eptifibatide
- Famotidine
- Fluconazole
- Furosemide
- Gentamicin
- Hydrochlorothiazide/triamterene
- Meropenem
- Phenytoin
- Piperacillin
- Quinine
- Spironolactone
- Tirofiban
- TNF-alpha/INF-gamma
- Trimethoprim/sulfamethoxazole
- Vancomycin
- Vaccines: Hepatitis B and influenza

Is there thrombosis?

In addition to exploring a connection between thrombocytopenia and the drugs a patient is taking, it's also important to look for evidence of thrombosis. The causes of thrombocytopenia that paradoxically result in thrombosis are: disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid antibody syndrome, and the previously mentioned HIT. **TABLE 2**[4,6-9] outlines the clinical settings, laboratory findings, and treatments of thrombocytopenia associated with thrombosis.

Is an infectious cause to blame?

If the patient is ill, consider infectious causes of thrombocytopenia. Thrombocytopenia associated with infection may result from an immune-mediated response to an illness itself, to treatment of an illness, to splenic sequestration, or to bone marrow suppression. **TABLE 3**[1,9-11] lists common infections that may cause thrombocytopenia.

Of note, infection with *Helicobacter pylori* can cause asymptomatic thrombocytopenia via an immune-mediated mechanism.[12] Eradication of *H pylori* results in a variable

TABLE 2
Thrombocytopenia associated with thrombosis[4,6-9]

Diagnosis	Clinical setting	Laboratory findings	Treatment
Disseminated intravascular coagulation	Sepsis Malignancy Trauma	↓ fibrinogen ↑ d-dimer Prolonged PT, aPTT	Treat underlying cause Cryoprecipitate Fresh frozen plasma
Hemolytic uremic syndrome	Kidney injury Shiga-toxin-producing *Escherichia coli* infection	↑ Creatinine Anemia Schistocytes	Supportive Dialysis
Thrombotic thrombocytopenic purpura	Neurologic deficit	↑ LDH Anemia Schistocytes ↓ ADAMTS13 gene	Plasmapheresis
Heparin-induced thrombocytopenia	Current or past heparin exposure	+ serotonin release assay Antibodies to heparin-platelet factor 4 complex	Anticoagulation (non-heparin)
Antiphospholipid antibody syndrome	Vascular thrombosis Pregnancy complications	Anticardiolipin antibody Lupus anticoagulant Anti-beta2 glycoprotein	Anticoagulation

aPTT, activated partial thromboplastin time; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH, lactate dehydrogenase; PT, prothrombin time.

elevation in platelets, on average 30,000/mcL in 50% of patients with the infection.[13]

Is there pancytopenia?

A review of the peripheral smear, with attention to abnormalities in other cell lines, may assist in arriving at a diagnosis. If the peripheral smear reveals pancytopenia, then, in addition to many of the etiologies described earlier, one should also consider vitamin B12 or folate deficiency, copper deficiency, drug- and viral-induced aplastic anemia, paroxysmal nocturnal hemoglobinuria, leukemias, myelodysplastic disorders, and systemic lupus erythematosis.[14] Pancytopenia is also seen with hypersplenism, which is often associated with cirrhosis.[15] If the etiology isn't readily apparent, a bone marrow biopsy may be required.

Is immune thrombocytopenia to blame?

Immune thrombocytopenia (ITP) is an autoimmune disorder resulting in the destruction of normal platelets and may be primary or secondary to processes described previously

TABLE 3
Common infectious causes of thrombocytopenia[1,9-11]

Viral	Cytomegalovirus, Epstein-Barr virus, hepatitis B and C, human immunodeficiency virus, parvovirus B19
Bacterial	Ehrlichiosis, *Helicobacter pylori*, Rocky Mountain spotted fever

(HIT, *H pylori* infection, etc). Consider ITP if, after a thorough work-up, a cause of isolated thrombocytopenia is not identified.[16] Treatment for ITP is outlined in **TABLE 4**.[16] **FIGURE 1** is an algorithm for the complete evaluation of thrombocytopenia in adults.

Treatment: Platelet transfusions

In general, patients who are not actively bleeding are considered stable and do not require platelet transfusions to minimize their risk of bleeding or prevent bleeding during a planned procedure unless their platelet

TABLE 4

Treatment of primary immune thrombocytopenia[16]

Signs/symptoms	Treatment
Asymptomatic patient, threshold for treatment: platelet count <30,000/mcL	Prednisone 1 mg/kg/d until platelets >50,000/mcL, then taper over 4 weeks (response typically in 1 week)
Symptomatic patient, bleeding, or platelet count <5000/mcL	Single dose of IVIg 1 g/kg initially (response typically in 24-48 hours) or a single dose of anti-D 75 mcg/kg if the patient is Rh positive, has a spleen, and has a negative Coombs test
Refractory to prednisone and/or IVIg	Splenectomy vs thrombopoietin receptor agonists

Anti-D, anti-D immunoglobulin; IVIg, intravenous immunoglobulin.

TABLE 5

Consider platelet transfusions in these situations[17]

Platelet count/mcL	Patient's status
10,000	Stable, not bleeding
20,000	Undergoing central venous line placement
50,000	Undergoing elective lumbar puncture or major elective nonneuraxial surgery

Heparin-induced thrombocytopenia occurs in <1% of patients in intensive care units and typically is manifested by a ≥50% drop in platelet count within 5 to 14 days of introducing heparin.

count falls below the levels specified in **TABLE 5**.[17] For patients who are actively bleeding, a more aggressive approach may be required. Locally-derived transfusion protocols typically guide transfusions for the actively hemorrhaging patient. The American Association of Blood Banks has put forth evidence-based guidelines for platelet transfusions when a patient is given a diagnosis of thrombocytopenia (see **TABLE 5**).[17] Single-donor platelets have a shelf life of 3 to 5 days, and one unit will raise platelets 30,000 to 50,000/mcL.

Neutropenia: Prevalence varies by ethnicity

An absolute neutrophil count (ANC) of <1500 cells/mcL traditionally defines neutropenia, with an ANC of 1000 to 1500 cells/mcL constituting mild neutropenia; 500 to 999 cells/mcL, moderate; and <500 cells/mcL, severe.[18] Similar to the evaluation of thrombocytopenia, it is important to repeat the CBC prior to initiating a work-up in order to confirm that the neutropenia is not a laboratory error. Additionally, patients with signs or symptoms of infection should be worked up expeditiously.

The prevalence of neutropenia varies by ethnicity. According to the National Health and Nutrition Examination Survey 1999 to 2004, the prevalence was 4.5%, 0.79%, and 0.38% in black, white, and Mexican-American participants, respectively.[19] **FIGURE 2** outlines the outpatient work-up of adult patients with neutropenia not related to chemotherapy.

Is the patient severely ill?

The prognosis of the patient is related both to the etiology of the neutropenia, as well as to the nadir of the neutrophil count. Patients who have an ANC <500 cells/mcL or who have inadequate bone marrow reserves are at highest risk for an overwhelming infection.20,21 The absence of oral ulcers and gingivitis and/or the presence of purulent material at the site of an infection are signs of adequate bone marrow reserves.

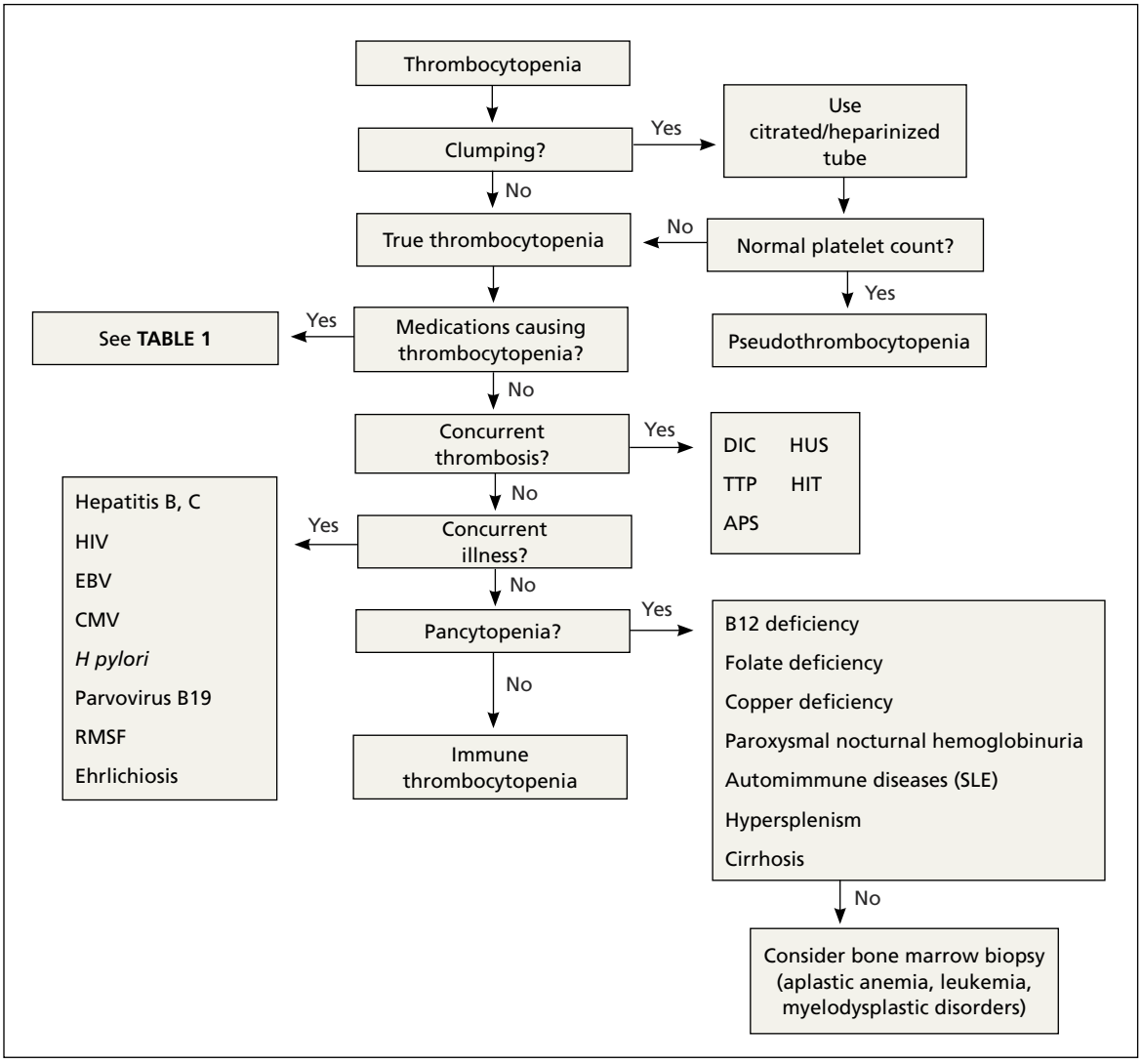
Additionally, neutropenia may be the source—or the result—of a serious life-threatening illness. This distinction may not be readily apparent at the time of the patient's presentation. If signs or symptoms of a severe illness are apparent (fever, hypotension, tachycardia, ANC <500 cells/mcL), admit the patient to the hospital for evaluation and initiation of antibiotics.

Is the neutropenia chronic?

A review of previous CBCs will identify

FIGURE 1

Algorithm for the work-up of thrombocytopenia in adults



APS, antiphospholipid syndrome; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; HIT, heparin-induced thrombocytopenia; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; RMSF, Rocky Mountain spotted fever; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

whether this condition is new or chronic. A persistent, mild neutropenia (ANC 1000-1500 cells/mcL) in a healthy individual is consistent with benign familial or ethnic neutropenia (see **TABLE 6**).[20] If prior CBCs are unavailable, then a diagnosis of chronic neutropenia may be established by verifying the persistence of mild neutropenia over time.

Cyclic neutropenia is a periodic neutropenia (occurring every 2-5 weeks) associated with mild illnesses that are related to the nadir of the neutrophil count. The diagnosis is established by obtaining serial CBCs twice weekly for 4 to 6 weeks, which reflect cycling of the neutrophil count.[20,22]

Are any medications contributing to the neutropenia?

Medications that suppress bone marrow or that interfere with other immune-mediated processes are the most common cause of acquired neutropenia.[23] Drug-induced

TABLE 6

Congenital causes of neutropenia[20]

Constitutional/ethnic neutropenia	-Mild, chronic (ANC >1000/mcL) -No history of recurrent infections -Mediterranean or African ancestry
Benign familial neutropenia	-Similar to constitutional, but not ethnically linked
Cyclic neutropenia	-Self-limited infections associated with nadir of neutropenia -Recurrence q2-5 weeks -Autosomal dominant

ANC, absolute neutrophil count.

TABLE 7

Medications that can be associated with agranulocytosis[25]

Drug class	Drug name
Analgesics	Diclofenac, diflunisal, ibuprofen
Antiarrhythmics	Disopyramide, procainamide, quinidine
Antibiotics	Ampicillin, cefotaxime, cefuroxime, imipenem-cilastatin, nafcillin, oxacillin, penicillin G, quinine, ticarcillin
Anticonvulsants	Carbamazepine, phenytoin, valproate
Antirheumatics	Infliximab
Antithyroid drugs	Propylthiouracil
Cardiovascular drugs	Clopidogrel, methyldopa, ramipril, spironolactone
Gastrointestinal drugs	Cimetidine, metoclopramide
Psychotropics	Chlorpromazine, clozapine, fluoxetine

TABLE 8

Infectious causes of neutropenia[23,27-29]

Bacterial	Brucellosis, paratyphoid, pertussis, tuberculosis, tularemia, typhoid Rickettsial: Ehrlichiosis, Rocky Mountain spotted fever
Parasitic	*Plasmodium vivax*, *P falciparum*
Viral	Cytomegalovirus, Epstein-Barr, human immunodeficiency, hepatitis, influenza, parvovirus B19

A persistent, mild neutropenia in a healthy individual is consistent with benign familial or ethnic neutropenia.

agranulocytosis is defined as an ANC <500 cells/mcL due to exposure to a drug that results in immunologic or cytotoxic destruction of neutrophils.[24]

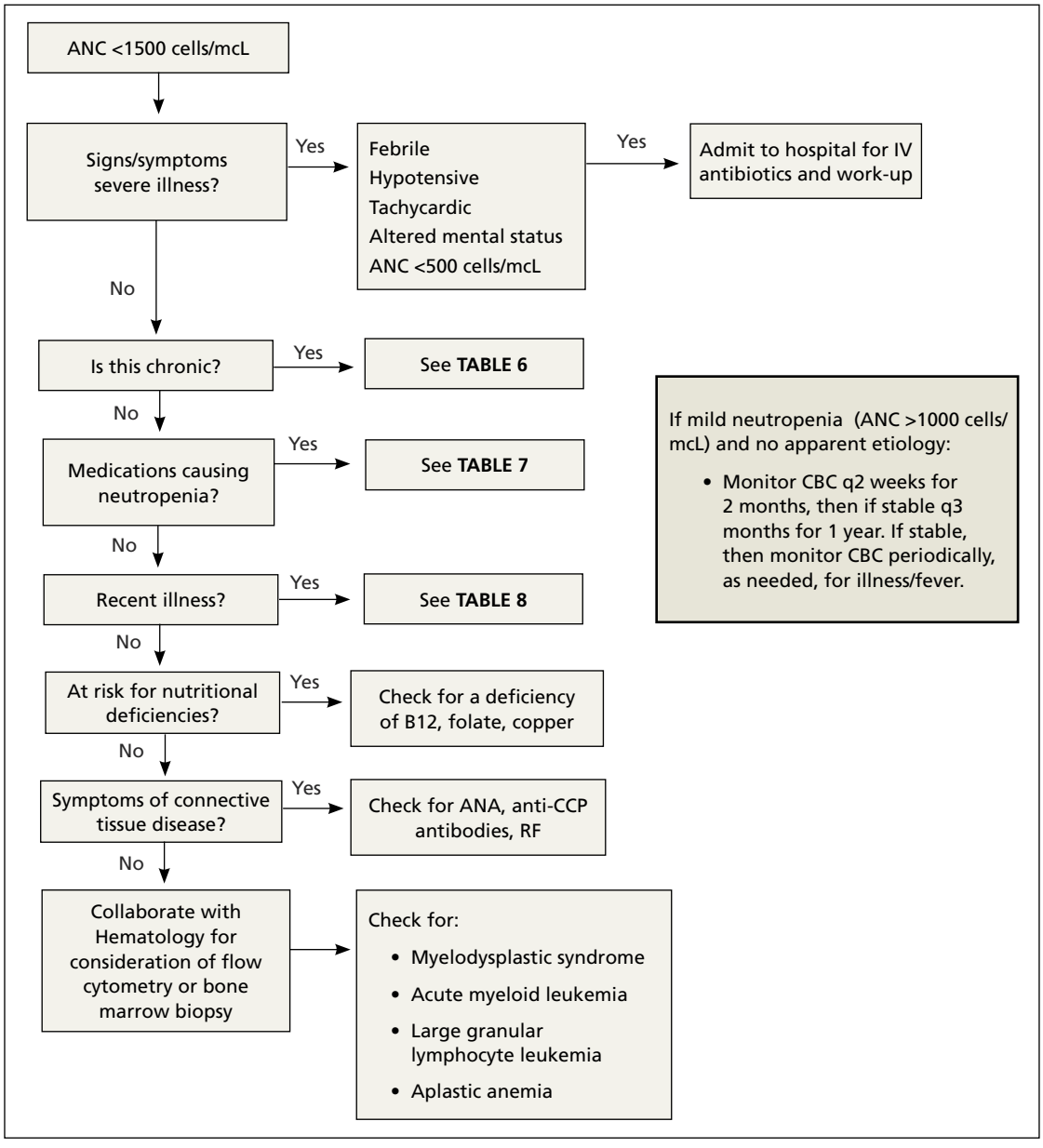
A systematic review of case reports of drug-induced agranulocytosis (a decrease in peripheral neutrophil count to <500 cells/mcL) revealed that although at least 125 drugs were probably related to agranulocytosis, only 11 drugs were responsible for 50% of cases (carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine), and fatality rates were higher (10% vs 3%) among those patients with a nadir <100 cells/mcL.[25] **TABLE 7**[25] lists medications that can be associated with agranulocytosis. Depending on prior exposure to a drug, neutropenia/agranulocytosis can occur within hours to months of exposure to the causal drug and can take a few days to 3 weeks to resolve after cessation.[25,26]

Has the patient had any recent illnesses?

The usual response to an infection is an

FIGURE 2

Algorithm for the outpatient work-up of neutropenia in adult patients who aren't receiving chemotherapy



ANA, antinuclear antibodies; ANC, absolute neutrophil count; anti-CCP, anti-cyclic citrullinated peptide; CBC, complete blood count; IV, intravenous; RF, rheumatoid factor.

increase in neutrophil count. However, certain bacterial, rickettsial, parasitic, and viral infections can result in neutropenia (see **TABLE 8**[23,27-29]). Viral infections may cause transient neutropenia because of either bone marrow suppression or increased peripheral destruction, while neutropenia related to an overwhelming bacterial infection results from the depletion of bone marrow reserves.[23,27]

Do you suspect a nutritional deficiency?

Patients with a nutritional deficiency of B12, folate, or copper are likely to exhibit a deficiency in more than just neutrophils.[23,27] In

developed countries, people with neutropenia may have a history of malnutrition due to a disease (eg, anorexia nervosa) or surgery (eg, gastric bypass) that causes severe calorie restriction.[20]

Does your patient have symptoms of a connective tissue disease?

Neutropenia, in association with arthralgias, joint swelling, splenomegaly, or rash may be a manifestation of an underlying collagen vascular disorder, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).[20] If the clinical scenario supports one of these diagnoses, undertake or refer the patient for a rheumatologic evaluation. This may include studies of anti-cyclic citrullinated peptide antibodies, rheumatoid factor to evaluate for RA, and/or antinuclear antibodies to evaluate for SLE.[30,31] While most neutropenias associated with autoimmune disease are mild, neutropenia associated with Felty syndrome (RA, splenomegaly, and neutropenia) may be severe (ANC <100 cells/mcL).[20,23]

Is the etiology unclear?

Patients with moderate to severe neutropenia without an apparent etiology, in the setting of aplastic anemia, or in the presence of splenomegaly and/or lymphadenopathy, should undergo a hematologic evaluation and/or bone marrow biopsy, given that hematologic malignancy is a potential cause.[20,27]

The treatment of neutropenia hinges on correctly identifying the etiology of the diminished neutrophil count. If the cause is a medication, infection, underlying rheumatologic condition, or nutritional deficiency, then either treating the entity or withdrawing the offending medication should result in resolution of the neutropenia. If the cause is determined to be familial or ethnic, then patient reassurance is all that is required. JFP

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