Diagnosing Thrombocytopenia in the Clinic

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Background

One of the most common incidental findings in the clinic is thrombocytopenia. With the multitude of blood tests run today many patients present to their physicians with either isolated thrombocytopenia or thrombocytopenia with anemia or leukopenia/leukocytosis. Some patients may be symptomatic and need hospitalization, while others will be asymptomatic and will require follow-up. The aim of this chapter is to help clinical practitioners work up thrombocytopenia in their clinic patients while learning when these patients should be admitted and/or referred to a hematologist.

The normal platelet count in adults ranges from 150,000 to 450,000/μL (some facilities have different normal ranges). Thrombocytopenia is defined as a platelet count less than 150,000/μL. Cases are considered mild if the platelet count is between 70,000 and 150,000/μL and severe if the platelet count is less than 20,000/μL (Buckley et al. 2000). Spontaneous bleeding is increased when the platelet count is acutely less than 10,000/μL and is considered a hematology emergency (Cines and Blanchette 2002; Veneri et al. 2009).

There are three major etiologies that can lead to thrombocytopenia in patients: (1) decreased platelet production; (2) increased platelet consumption; or (3) sequestration of platelets.

Decreased platelet production indicates either bone marrow suppression or primary bone marrow failure. Either process can be due to medications, radiation, alcohol use, neoplastic disorders infiltrating the bone marrow, vitamin deficiencies, infections, and congenital thrombocytopenias.

Increased platelet consumption indicates that platelets are being consumed faster than their 7–10-day average life-span. Alloimmune destruction from transfusions; autoimmune syndromes; disseminated intravascular coagulation; drug-induced thrombocytopenia; heparin-induced thrombocytopenia (HIT); infections; mechanical destruction; preeclampsia; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; or thrombotic thrombocytopenic purpura (TTP) and immune thrombocytopenic purpura (ITP) can lead to increased platelet consumption and can also cause bone marrow suppression leading to decreased platelet production.

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Sequestration of platelets is usually caused by hypersplenism and/or liver disease. There are other causes of thrombocytopenia which cannot be placed into these categories which include gestational thrombocytopenia, dilutional thrombocytopenia, and pseudothrombocytopenia.

Thrombocytopenia can also be evaluated as an isolated cytopenia versus being found in conjunction with leukopenia/leukocytosis or anemia. A systematic approach is needed in the work-up of thrombocytopenia. In an outpatient setting it is important to begin the workup by assessing if a patient is stable for outpatient workup or if they need to be in a hospital setting. Patients who have thrombocytopenia with mild to no symptoms can generally be worked up as an outpatient. These include patients with thrombocytopenia with platelet counts >10,000/μL, minor bleeding such as epistaxis that can be easily controlled, or other non-life-threatening bleeding. In situations where a patient requires more immediate attention, with life-threatening bleeding, or if they are at risk for spontaneous bleeding (platelet count <10,000/μL) immediate hospitalization is recommended to monitor and stabilize the patient (Fig. 7.1).

The approach to a patient with thrombocytopenia is based on the combination of assessment of the likelihood of the underlying etiology and the importance/severity of the underlying condition. It is mostly based on pseudo-physiologic reasoning. Empirical evidence supporting the outline strategies is lacking.

Clinical Vignette 1

A 40-year-old female presents to her primary care doctor after life insurance blood work showed an isolated thrombocytopenia with a platelet count of 90,000/μL. Large clumps of platelets were reported on her peripheral smear. The patient denied any recent illnesses, medication use, other medical problems, or bleeding or bruising. The patient is wondering if there is anything to be concerned about.

Diagnosis

Initially it is important to differentiate between isolated thrombocytopenia and thrombocytopenia with anemia or leukopenia/leukocytosis. In patients with thrombocytopenia with other blood line changes, hematology consultation may be required sooner than in those with isolated thrombocytopenia.

History

In order to treat our patient in the clinical vignette, the most important step in obtaining a diagnosis is to perform a complete history and physical exam of the patient. History should include questions about bleeding, bruising, petechiae, melena, rashes, fevers, or recent infections. Medication history should be reviewed in detail, and specific questions about over-the-counter medications, supplements including quinine, and herbal products should be discussed since many of these can cause thrombocytopenia (Table 7.1). Old laboratory values (was she always thrombocytopenic?), history of immunizations, recent travel, transfusion history, travel history, family history of bleeding or blood disorders, and any recent hospitalizations should be reviewed. Recent hospitalizations may indicate heparin exposure and the possibility of HIT. Acute and chronic alcohol use history, potential HIV exposure, and possible pregnancy should also be part of the history (Veneri et al. 2009; Achterbergh et al. 2012; Gauer and Braun 2012).

Physical Exam

Physical exam should focus on evaluating for changes consistent with thrombocytopenia or life-threatening bleeding. This includes a complete neurological exam to exclude deficits that may point towards intracranial bleeding; a fundoscopic exam to evaluate for retinal hemorrhage which is suggestive of intracranial bleeding; oropharyngeal exam to look for gingival bleeding or wet purpura; an abdominal exam to evaluate for hepatosplenomegaly, bruising, or masses that could represent an underlying malignancy or hematoma; and lymph node exam to rule out

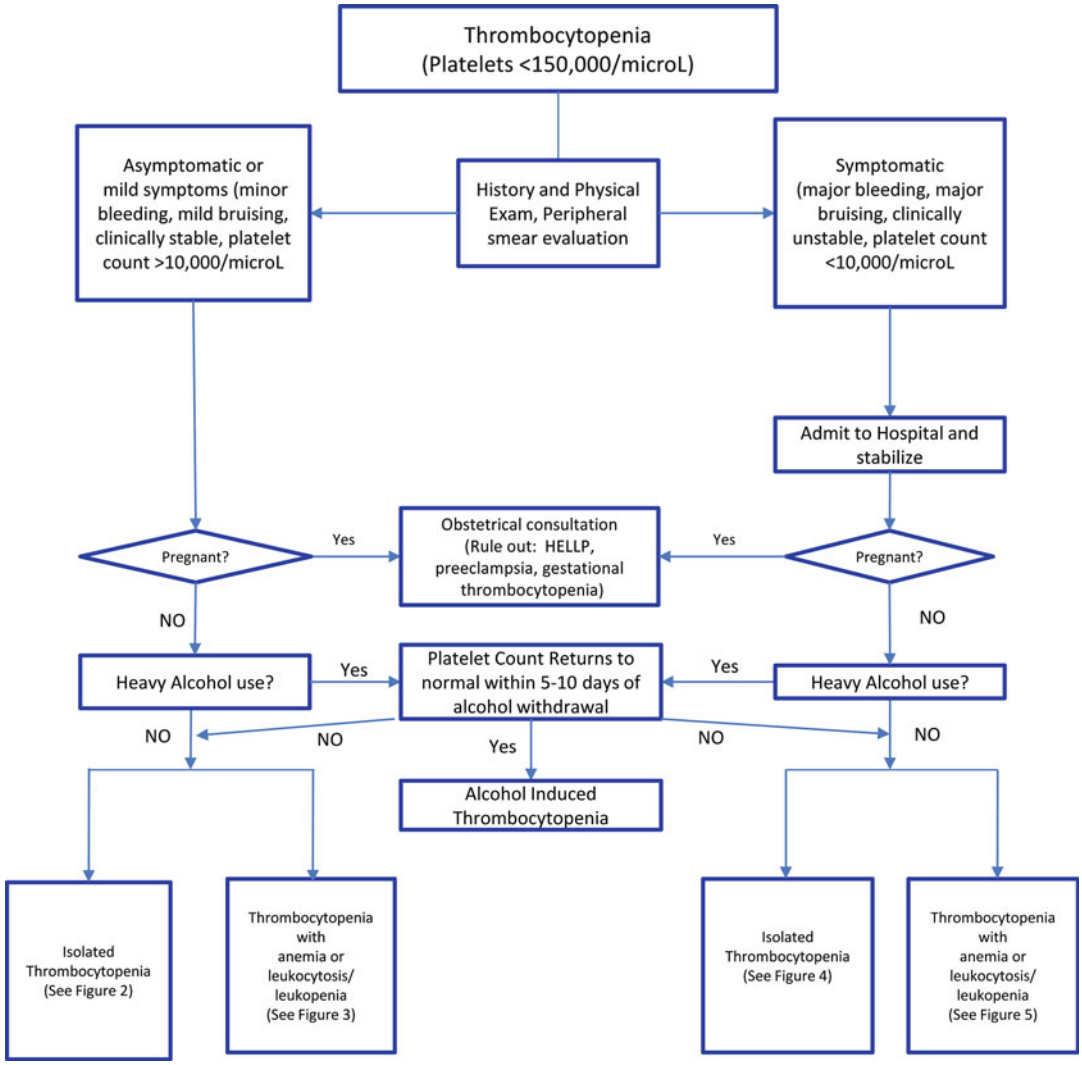

Fig. 7.1 Initial thrombocytopenia work-up

lymphadenopathy. Particular attention should be made towards a skin exam to look for petechiae, purpura, and bruising as well as assessment of epistaxis and mucosal, gastrointestinal, and genitourinary bleeding.

Laboratory Testing/Other Tests

A complete blood count (CBC), liver function testing, renal function testing, lactate dehydrogenase (LDH), and reticulocyte count are generally recommended in most patients presenting with thrombocytopenia. In patients presenting with thrombocytopenia alone, testing should be repeated in order to rule out pseudothrombocytopenia. A non-ethylenediaminetetraacetic acid (EDTA) anticoagulant such as citrate should be used for the repeat count to help differentiate pathologic from pseudothrombocytopenia which causes in vitro clumping caused by the EDTA. Other testing can be obtained based on the history and physical findings including bone marrow biopsy, HIV testing, hepatitis tests, and laboratory tests for autoimmune disorders. In patients with bleeding or who are hospitalized, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and fibrin split products can be checked in order to assess for a coagulation disorder. Peripheral blood smears should also be reviewed

Table 7.1 Non-chemotherapeutic agents commonly associated with thrombocytopenia. This table lists the most common drugs reported in the literature that have been shown to cause thrombocytopenia. For a more up-to-date database of drugs that cause thrombocytopenia check the reference database at http://www.ouhsc.edu/platelets

Abciximab	Hydrochlorothiazide
Alcohol	Interferon alpha
Acetaminophen	Methyldopa
Amiodarone	Naproxen
Ampicillin	Phenytoin
Carbamazepine	Piperacillin
Cimetidine	Procainamide
Chlorpropamide	Quindine
Cephalosporins	Quinine
Danazol	Ranitidine
Diclofenac	Rifampin
Eptifibatide	Sulfasalazine
Ethambutol	Trimethoprim/sulfamethoxazole
Gold salts	Simvastatin
Haloperidol	Valproic acid
Heparin (unfractionated and low molecular weight)	Vancomycin

in order to assess for platelet clumping (pseudothrombocytopenia), abnormalities in other blood lines including to assess for schistocytes which may indicate a hemolytic process, or abnormal blood cells such as leukemia cells.

Radiological testing can be obtained as indicated by history and physical exam. CT scanning of the abdomen can give the clinician information about the size of the spleen, and liver–spleen scanning (nuclear medicine) gives information about splenic activity (portal hypertension causes a colloid shift in this scan).

Figures 7.2–7.5 show algorithms for diagnosis of both asymptomatic and symptomatic thrombocytopenia.

Specific testing for disorders that present with thrombocytopenia is listed with each specific disorder.

Conditions and Treatment

Outpatient Conditions with Isolated Thrombocytopenia

Laboratory Error

There are multiple errors which may lead to a low platelet count. If the specimen is underanticoagulated or improperly drawn it can lead to small clots which result in thrombocytopenia. Secondly, blood samples may get mislabeled and could be reflecting thrombocytopenia on the wrong patient. There are also multiple technical errors that can occur in the laboratory which may result in thrombocytopenia.

CBC should be retested immediately in those cases of symptomatic thrombocytopenia and between 2 and 4 weeks in asymptomatic cases depending on the platelet count (Stasi et al. 2006).

Pseudothrombocytopenia

Pseudothrombocytopenia occurs when platelet clumping takes place in an EDTA-anticoagulated blood sample. This occurs in about 1 in 1,000 normal adults. Pseudothrombocytopenia can be ruled out with review of a peripheral blood smear showing platelet clumping. It has no clinical significance, and no further investigation is needed. A repeat platelet count can be done using an anticoagulant other than EDTA such as heparin or sodium citrate so that clumping does not occur (Onder et al. 1980; Bizzaro 1995; Froom and Barak 2011; Gauer and Braun 2012). Patients should be informed about their pseudothrombocytopenia and to tell other clinicians or hospitals that they should have blood counts done in non-EDTA anticoagulants.

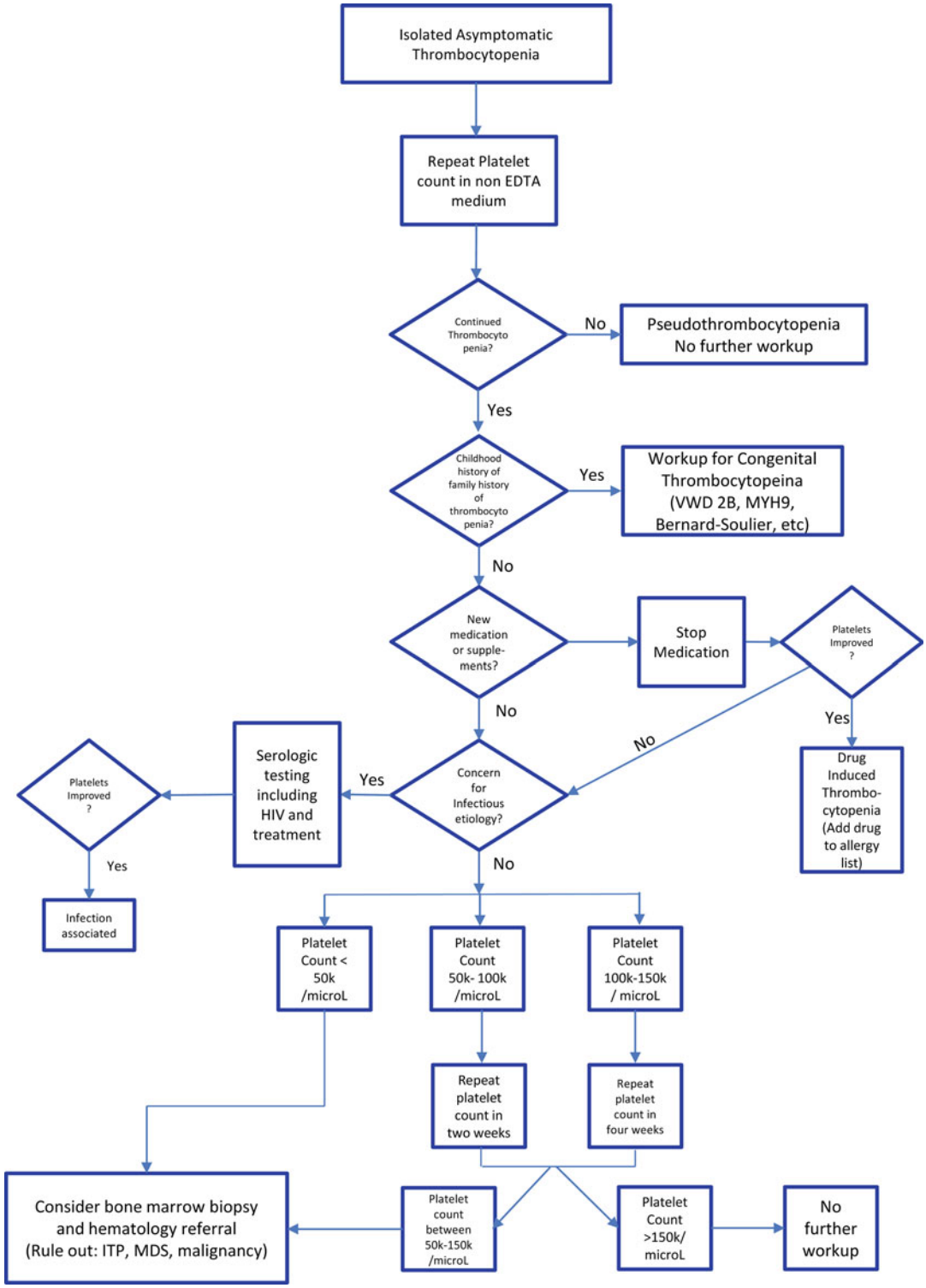

Fig. 7.2 Isolated asymptomatic thrombocytopenia work-up

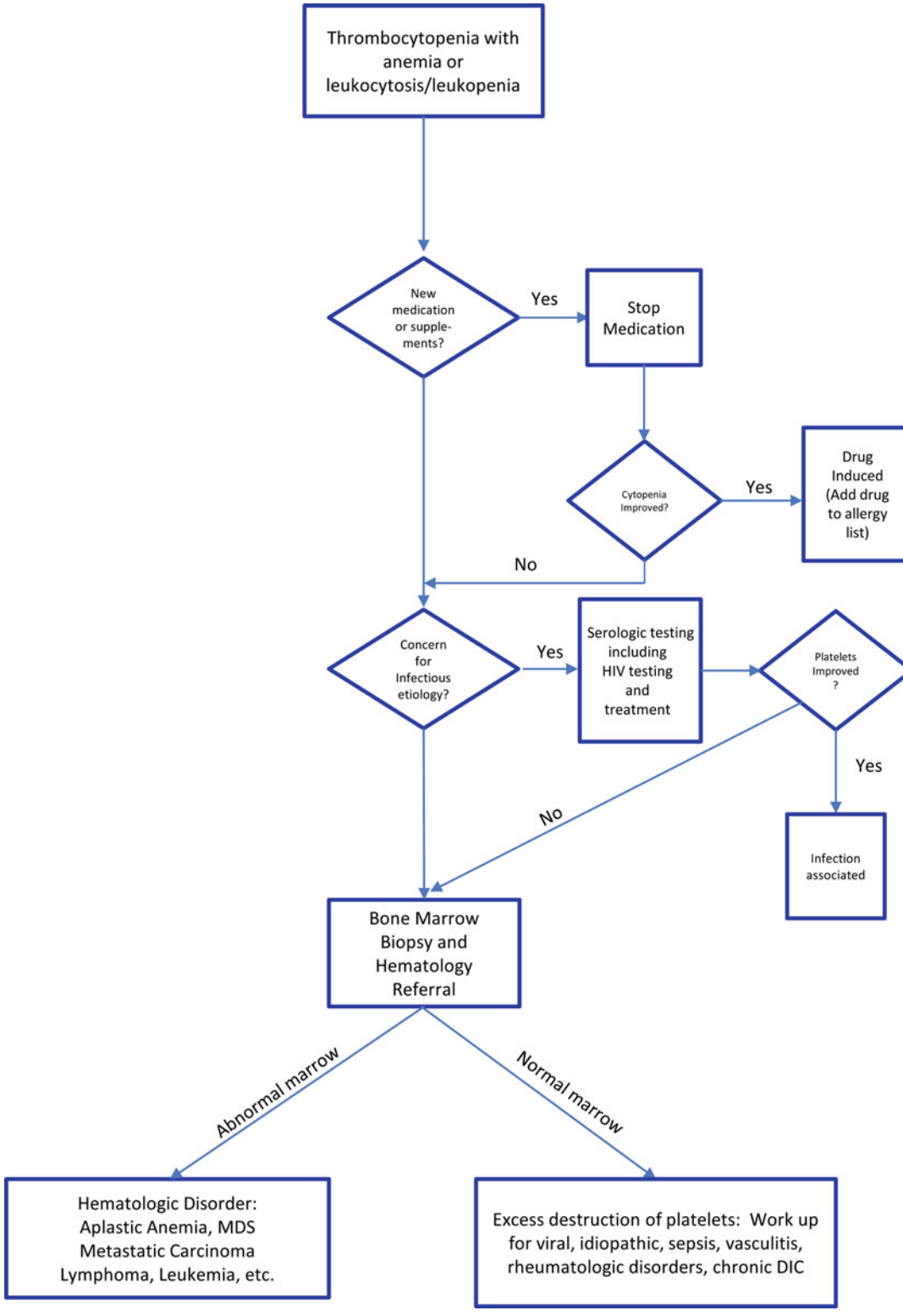

Fig. 7.3 Work-up for asymptomatic thrombocytopenia with anemia or leukocytosis/leukopenia

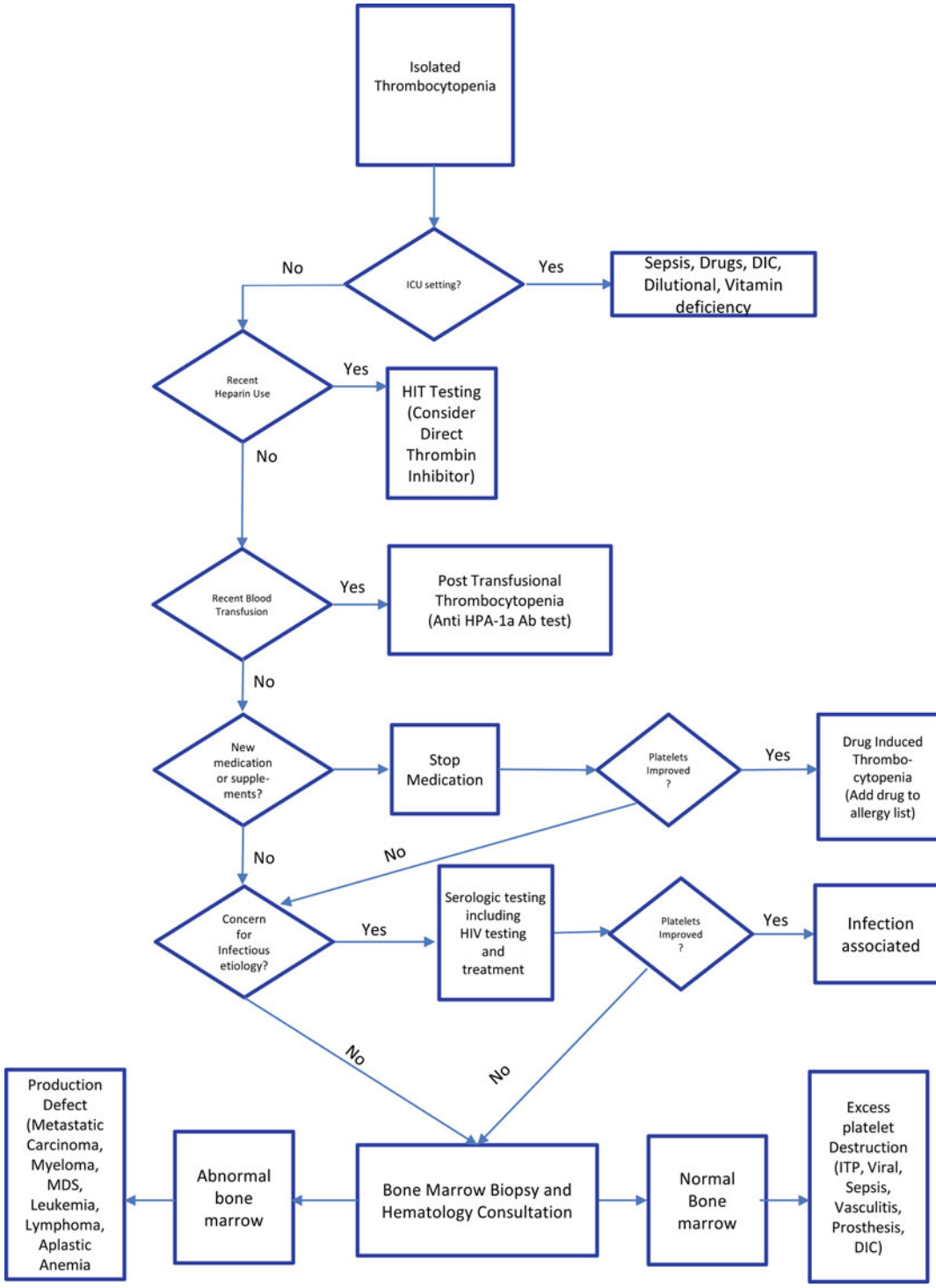

Fig. 7.4 Work-up for isolated symptomatic thrombocytopenia

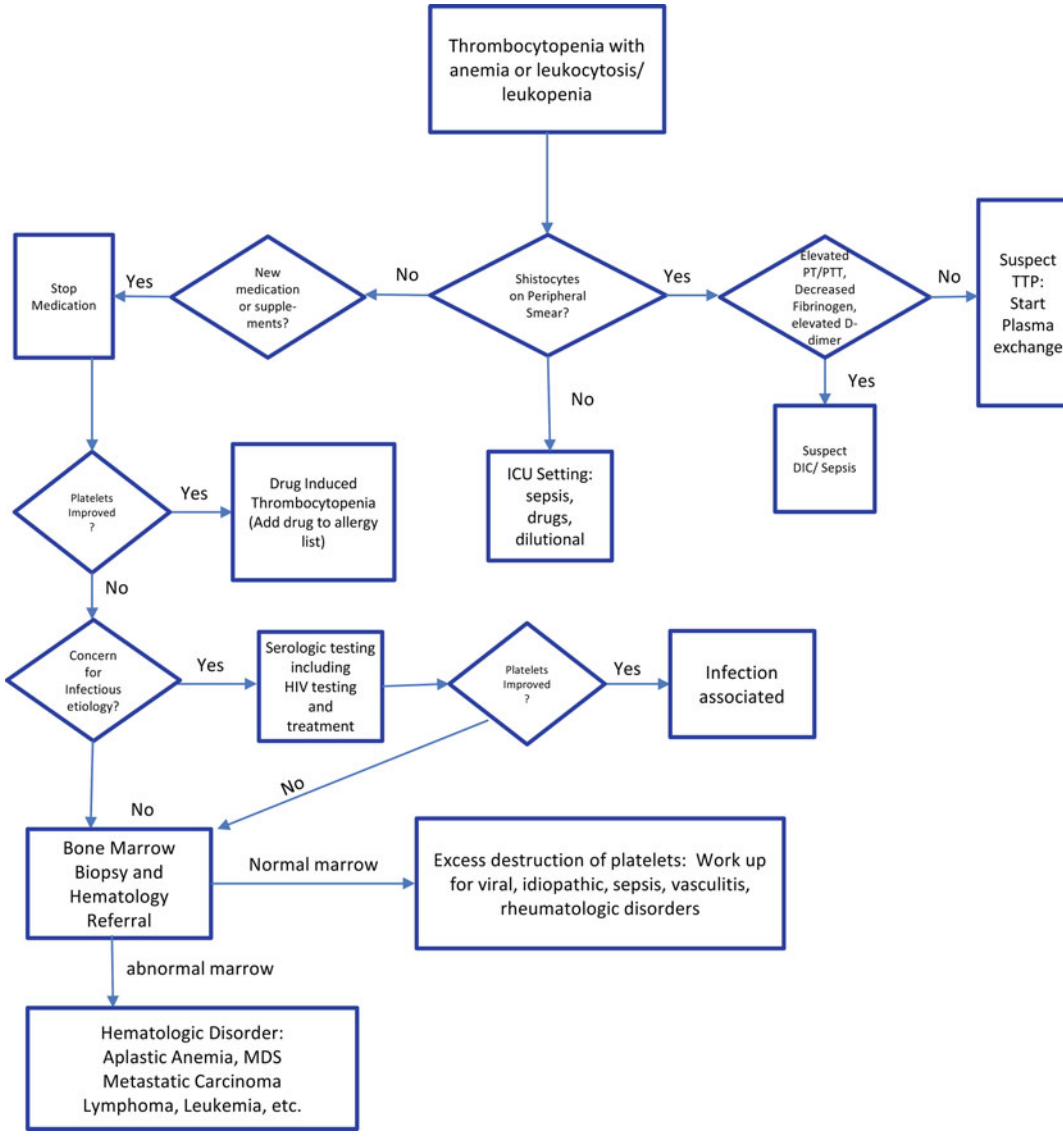

Fig. 7.5 Work-up for symptomatic thrombocytopenia with anemia or leukocytosis/leukopenia

Our 40-year-old had her platelets rechecked in a non-EDTA anticoagulant, and her platelet count was reported as 180,000/μL. The patient was alerted that future blood draws should be done in non-EDTA anticoagulants and that there was no other work-up or treatment required.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia is usually seen in a hospital setting after hemorrhage or excessive fluid infusion. Platelet counts generally return to normal within 24–48 h after fluid shifts take place (Wong and Rose 2012). Even after as few as two units of blood transfusions, the platelet count can fall by half.

Gestational Thrombocytopenia

Five percent of women develop mild asymptomatic thrombocytopenia known as gestational thrombocytopenia. The etiology of this disorder is unknown, and it is clinically unimportant unless the platelet count is below 80,000/μL when there can be a concern for epidural anesthesia (van Veen et al. 2010). Thrombocytopenia should resolve following delivery and does not cause thrombocytopenia in the infant (McCrae et al. 1992; McCrae 2003, 2010).

Congenital Thrombocytopenia

Congenital disorders are usually associated with the presence of giant platelets. Congenital thrombocytopenia is often seen in a patient with a prolonged history of low platelets or if another family member also has a history of isolated thrombocytopenia. von Willebrand disease 2B (VWD 2B) and platelet-type VWD deserve mention since patients can often be asymptomatic and present in adulthood. Platelet-type VWD is a rare autosomal dominant disorder and is characterized by a defect in the glycoprotein 1 (GP1) receptor on the platelet membrane which increases its affinity to bind to the von Willebrand factor (vWF). Large platelet aggregates and high-molecular-weight vWF multimers are removed from the circulation resulting in thrombocytopenia. VWD 2B is a gain-of-function defect. GP1 receptor binding on the platelet membrane is abnormally enhanced leading to its spontaneous binding to platelets and rapid clearance of bound platelets and of the large vWF multimers. Thrombocytopenia can occur and is typically mild but can present clinically with excessive mucous membrane, menstrual, and/or postpartum hemorrhage (Sadler 2005; Nurden et al. 2009; Othman 2011). The diagnosis of 2B VWD is typically confirmed my performing ristocetin-induced platelet aggregation using low concentration of ristocetin or by molecular testing.

Peripheral blood smear may show pseudothrombocytopenia (clumping of platelets), and platelet size can be normal to large. In both platelet-type and VWD 2B, vWF antigen and the ristocetin cofactor (vWF activity) will be low. Factor VIII activity will be low, and the multimer pattern will be abnormal. In platelet-type VWD there is a mutation in GP1b. Desmopressin should be avoided as treatment as thrombocytopenia may worsen because of increased VWF multimers and increased platelet agglutination and clearance.

Other congenital disorders include MYH9-releated diseases (such as May–Hegglin disorder) and Bernard–Soulier syndrome (Wong and Rose 2012). MYH9-related thrombocytopenias are genetic conditions caused by mutations of the MHY9 gene. Platelets are large, and there is a low platelet count. There may be an associated hearing loss, cataracts, or renal insufficiency. The MHY9 disorders include May–Hegglin anomaly and Epstein, Fechtner, and Sebastian syndromes.

Posttransfusional Thrombocytopenia

Posttransfusional purpura should be suspected in patients who have an acute drop in platelets anytime up to 2 weeks after a blood transfusion. A typical presentation is an older, multiparous woman who presents with bleeding and severe thrombocytopenia after receiving blood products. Thrombocytopenia is due to recipient antibody to a platelet-specific antigen (usually HPA-1a) in patients who lack HPA-1a antigens. Diagnosis is made by the typical timing of a platelet drop after transfusion (usually hours to 2 weeks) and a positive anti-HPA-1a antibody.

Treatment is supportive, and high-dose immunoglobulins can be used in cases with severe thrombocytopenia or bleeding. Response is usually seen within 2–3 days in greater than 90 % of patients (Murphy and Bussel 2007; Zimring et al. 2011; Wong and Rose 2012).

Outpatient Conditions That Can Present with Multi-penias

Infectious Etiologies

Multiple viral and rickettsial infections can lead to thrombocytopenia usually with anemia or leukocytosis or leukopenia. Hepatitis C virus, cytomegalovirus, Epstein–Barr virus, and varicella zoster virus are all commonly associated with thrombocytopenia. Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, and other tick-borne illnesses also can present with thrombocytopenia. Up to 10 % of initial presentation of

HIV cases are with thrombocytopenia (Franchini and Veneri 2006; Afdhal et al. 2008; Gauer and Braun 2012; Wong and Rose 2012). We recommend testing for HIV and hepatitis in all patients at high risk for these diseases who have thrombocytopenia and testing for other infectious etiologies based on history and geographic region.

Treatment of the underlying infection will correct the thrombocytopenia which may take weeks to return to a normal count.

Myelodysplastic Syndrome

In less than 10 % of cases myelodysplastic syndrome (MDS) can present with isolated thrombocytopenia. It is more common for patients to present with leukopenia or anemia in addition to thrombocytopenia (Wong and Rose 2012).

Liver Disease with Hypersplenism

Chronic liver disease with portal hypertension leading to congestive splenomegaly can typically present with thrombocytopenia with anemia or leukopenia. Platelet counts are usually above 50,000/μL, the spleen is typically enlarged on palpation, and in most patients liver function is affected resulting in a prolonged PT (McCrae 2003; Afdhal et al. 2008). Most patients do not have spontaneous bleeding, and liver transplant provides cure in patients that are eligible.

Alcohol Abuse

Thrombocytopenia is the most common hematologic abnormality in those who abuse alcohol. Alcohol ingestion leads to acute thrombocytopenia, and patients are commonly seen with low platelets after being admitted for binge drinking. Prolonged heavy alcohol consumption has a direct toxic effect on the bone marrow and causes of reversible suppression of platelet production, anemia, and leukopenia (Cowan 1980).

With alcohol cessation and adequate folate and thiamine repletion, recovery of platelet and other blood counts occur. Platelet counts usually improve in 1–2 weeks and can even initially present as a rebound thrombocytosis.

Autoimmune Conditions

Patients with autoimmune disorders including systemic lupus erythematous (SLE) and antiphospholipid antibody syndrome can also present with thrombocytopenia with other cytopenias. In SLE, an ITP-like syndrome can form in the setting of a multi-organ lupus flare. Patients can also have bleeding tendencies. Treatment with corticosteroids as in ITP is standard first-line therapy.

In patients with antiphospholipid antibody syndrome, thrombocytopenia is usually mild and sporadic. Since these patients have mild thrombocytopenia and are usually at risk for thrombosis, specific therapy is geared towards preventing thrombosis and not treating the underlying mild thrombocytopenia (Miller et al. 1983; Mader et al. 2002; Krause et al. 2005).

Hematologic and Solid Tumor Malignancies

Patients with malignancy can have thrombocytopenia with other cytopenias secondary to the disease or to medications. Chemotherapeutic agents used in treatment of malignancies can also lead to multiple cytopenias. Disorders such as acute leukemia, myelodysplastic syndrome, myelofibrosis, multiple myeloma, and lymphoma commonly present with multiple cytopenias. Diagnosis should include a bone marrow biopsy.

Treatment of the underlying disorder can lead to improvement in the cytopenias in cases where the malignancy is causing the cytopenias. Dose-reducing or -stopping chemotherapeutic agents resolve cytopenias in those induced by chemotherapy.

Clinical Vignette 2

A 60-year-old male with hypertension and diabetes presents to his primary care physician with a nose bleed and purpura on his arms and legs. The patient states that 2 days prior he was feeling fine. He states that he has not been sick and denies any other complaints. He has no fever or chills. CBC done in the office is normal except for a platelet count of 5,000/μL, and the patient presents with petechiae on his chest and back but no mucosal bleeding.

Drug-Induced Thrombocytopenia

Drug-induced thrombocytopenia is a common presentation of isolated symptomatic thrombocytopenia because a patient usually presents with bleeding caused from a sudden drop in platelet count. Patients with drug-induced thrombocytopenia can also present with anemia or leukopenia secondary to the drug use. This diagnosis should be excluded in all patients with thrombocytopenia.

Medications that were started within the past 4–6 weeks are more likely to be the cause of thrombocytopenia than those taken for many years. Drug-induced thrombocytopenia is usually caused by a drug-dependent antibody that is created by drug binding to a platelet surface protein.

Quinine is the most common medication that is associated with drug-induced thrombocytopenia (Nguyen et al. 2011). History of quinine use is not always given by patients since it is found in over-the-counter treatments for muscle cramps and also in tonic water. Other common medications implicated in drug-induced thrombocytopenia include abciximab, carbamazepine, heparin (either unfractionated or low-molecular-weight heparin), phenytoin, trimethoprim/sulfamethoxazole, and vancomycin. Heparin-induced thrombocytopenia will be discussed under symptomatic isolated thrombocytopenia. Table 7.1 includes a list of common medications that may cause drug-induced thrombocytopenia (Schiavotto et al. 1993; Rizvi et al. 1999; Arepally and Ortel 2006; George and Aster 2009; Nguyen et al. 2011).

Treatment is to stabilize the patient and continue to monitor the platelet counts. Inciting drugs should be removed and added to the patient's allergy list. A systematic review showed median recovery of platelets to be between 5 and 7 days. In this review of 266 patients, 23 (9 %) had major hemorrhage including two patients who died from bleeding (Rizvi et al. 1999; George and Aster 2009; Nguyen et al. 2011; Gauer and Braun 2012). Supportive inpatient care with platelets, packed red blood cells, and close monitoring are essential until platelet counts recover.

Preeclampsia

Preeclampsia can present with isolated thrombocytopenia. Neutrophilia can be present, and a mild hemolytic anemia is sometimes seen from shearing of red blood cells. Patients with severe preeclampsia with worsening elevations in blood pressure and/or worsening thrombocytopenia should be induced for delivery if possible. Expert consultation with an obstetrical specialist is needed to ensure proper care and potential delivery of the fetus (Baron and Baron 2005; McCrae 2010; Kadir and McLintock 2011). Treatment is delivery of the fetus with resolutions of symptoms within 1–2 days of delivery.

Primary Immune Thrombocytopenia

ITP is a diagnosis of exclusion in those patients with isolated thrombocytopenia. All other etiologies should be excluded prior to the diagnosis of ITP. No further evaluation outside of routine history, physical examination, CBC, and examination of the peripheral blood smear is needed. In patients older than 60 years of age, a myelodysplastic disorder is the more prevalent diagnosis and a bone marrow biopsy can be considered.

Treatment of ITP is complex and should be done in conjunction with a hematologist. ITP should only be treated if the patient is symptomatic and if their platelet counts are below 50,000/μL. Initial treatment is steroids. For further treatment guidelines please refer to the 2011 American Society of Hematology and 2010 International Consensus report on the treatment and diagnosis of ITP (Cines and Bussel 2005; Provan 2009; Provan et al. 2010; McCrae 2011; Neunert et al. 2011).

Our patient was admitted to the hospital with a hematology consultation, and after full work-up including a bone marrow biopsy to rule out myelodysplastic syndrome a diagnosis of ITP was made. The patient was started on corticosteroids and was monitored closely. He had no further bleeding, and his platelet count improved to around 40,000/μL in 6 days. The patient was discharged to continue treatment on an outpatient basis with his hematologist

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is likely to present in a hospitalized setting and will be discussed further in another chapter in this book. DIC should be suspected in patients with an infection or a malignancy and abnormal PT and aPTT with a low fibrinogen and high-fibrin-split products. DIC is a medical emergency, and patients should be managed in a hospital setting.

Treating the underlying disorder will improve the thrombocytopenia. Supportive care including blood pressure support, fresh frozen plasma, packed red blood cells, antibiotics, and platelet transfusions are needed as indicated clinically (Taylor et al. 2001; Levi et al. 2009).

Heparin-Induced Thrombocytopenia

HIT should be suspected in patients with recent heparin exposures (up to 100 days). Platelet counts usually decline within 5–10 days after exposure to heparin and may decline within hours in patients with recent heparin exposure. Patients develop antibodies against platelet factor 4–heparin complexes causing platelet activation, thrombocytopenia, and thrombosis. Other characteristics include erythematous or necrotizing skin reactions at the site of injection, venous thrombosis, stroke, or myocardial infarction (Greinacher et al. 2005; Warkentin 2011).

A scoring system (4-T criteria) was developed utilizing the degree of thrombocytopenia, timing of thrombocytopenia after the initiation of heparin, thrombotic events, and exclusion of other causes of thrombocytopenia to aid in the diagnosis of HIT. In patients with a low score (0–3) HIT is unlikely. In those with a high score (6–8), HIT should be suspected and treatment should start immediately with a direct thrombin inhibitor. In those with an intermediate score (4–5) further testing is required to determine if the patient has HIT, but heparin should be discontinued and a direct thrombin inhibitor started until results are back (Lo et al. 2006). The most widely used test in suspected cases is an enzyme-linked immunosorbent assay with the platelet factor4/anion complex as the antigen (HIT ELISA). The test has 97 % sensitivity but a low specificity of 74–86 % (Arepally and Ortel 2006; Gauer and Braun 2012). A serotonin release assay can be used as a confirmatory test if there is a high suspicion of HIT, though in many institutions, it can take up to 7 days to result.

Treatment of HIT consists of immediately stopping any heparin products (unfractionated and low-molecular-weight heparin) including those given as in-line flushes. A heparin allergy should be added to the patient's medical record. A retrospective series of 62 patients with HIT showed that the 30-day risk of thrombosis was 53 % (Warkentin and Kelton 1996). For this reason patients should be started on a direct thrombin inhibitor (DTI) such as argatroban. Once the patient is stable on DTI therapy and their platelets are greater than 150,000/μL, the patient should be bridged to warfarin therapy. Anticoagulation should last at least between 2 and 3 months because of the high 30-day thrombosis risk, but no study has established the proper time course for anticoagulation (Warkentin 2011). HIT is a serious medical complication, and one study showed in-hospital mortality in patients who develop HIT to be as high as 20 % (Baroletti et al. 2008). HIT is discussed further later in this book (see Chap. 14).

Cardiac Surgery

Extracorporeal oxygenators lead to prolongation in the bleeding time and thrombocytopenia in patients who undergo cardiopulmonary bypass surgery. Platelet abnormalities are due to dilution by the priming solution and destruction of the platelets by the membrane of the machine. The platelet count usually drops by about 50 % and recovers within 4 days of surgery. HIT can also present in these patients as well and must be ruled out in any patients with cardiac surgery and a low platelet count (Wong and Rose 2012).

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome

TTP/hemolytic uremic syndrome (HUS) are disorders that should be suspected in any patient presenting with microangiopathic hemolytic

anemia and thrombocytopenia. The classic pentad of fever, microangiopathic anemia, thrombocytopenia, renal disease, and neurological changes occurs in less than 20 % of cases. A diagnosis of TTP can be made with microangiopathic anemia (schistocytes seen on peripheral blood smear) and thrombocytopenia. Incidence of TTP is 4–11 patients/1 million annually in the United States (George 2009; George 2010). The condition is often caused by an absence or a deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS 13) leading to ultra-long von Willebrand multimers that lead to microvascular aggregation of platelets resulting in ischemia and necrosis of tissue (Zheng et al. 2002; Sadler 2008; George 2010; Peyvandi et al. 2010). HUS is more likely to occur in children and can present with renal failure, bloody diarrhea, and/or abdominal pain. Shiga toxin-producing *Escherichia coli* is the most common causative organism in HUS (Hosler et al. 2003; George et al. 2008).

TTP is fatal without treatment. Patients should be admitted to the hospital if clinically suspected, and immediate daily plasma exchange should be started (Rock 2002; Michael et al. 2009; Nguyen and Han 2011). Corticosteroids and rituximab (off-label use) have also been used in the treatment of TTP, but plasma exchange remains the standard of care (George et al. 2006; Ling et al. 2009; George 2010). HUS in children related to infection can resolve on its own and may not require plasma exchange. Recently, eculizumab was shown to be effective in treatment of so called atypical HUS, which needs to be differentiate from a classic TTP (Legendre et al. 2010).

HELLP Syndrome

In patients who are pregnant with anemia, thrombocytopenia, and elevated liver enzymes the HELLP syndrome should be suspected. Many patients also present with right upper quadrant pain. Proteinuria is found with an elevated LDH.

Patients should be admitted and started on intravenous magnesium sulfate. Active management to deliver the fetus should be undertaken (McCrae et al. 1992; Martin et al. 2008; McCrae 2010; Gauer and Braun 2012).

Management of Patients with Chronic Thrombocytopenia

There is no consensus as to a time period when thrombocytopenic becomes chronic. In ITP, thrombocytopenia greater than 12 months is considered chronic ITP. Management of patients with chronic thrombocytopenia is aimed to prevent bleeding. In patients with thrombocytopenia and a multi-system disorder, the treatment of the primary disorder is the primary treatment goal. There is no evidence-based recommendations for a safe platelet count. Most experts agree that patients with platelet counts above >50,000/μL have levels adequate for hemostasis. Those with platelets between 30,000 and 50,000/μL rarely have purpura even with trauma. Those with platelet counts between 10,000 and 30,000/μL may be asymptomatic with everyday activities but can be at risk for excessive bleeding following more extensive trauma. Spontaneous bleeding typically does not occur unless platelet counts are <10,000/μL. Activity should only be restricted in patients with symptomatic thrombocytopenia or those with platelet counts <10,000/μL.

For invasive procedures, typically platelet counts greater than 40,000/μL provide safety for interventional procedures such as lumbar puncture, but this is controversial. In procedures at risk for complications even with minor bleeding such as neurosurgical procedures generally platelet counts greater than 80,000–100,000/μL are necessary. Commonly epidural anesthesia for obstetric delivery requires platelet counts of at least 80,000/μL (van Veen et al. 2010).

In patients with asymptomatic thrombocytopenia blood counts can be monitored monthly and then spaced out further as long as the platelet count is stable. In patients with symptomatic isolated thrombocytopenia, platelet counts should be checked daily to weekly depending on the causative reason until resolution of symptoms.

Thrombocytopenia in the clinic can become a challenge because of the many reasons that can lead to this laboratory finding. A good history and physical exam can help differentiate

life-threatening thrombocytopenia versus those cases that can be followed in the outpatient clinic. As more patients get complete blood counts on a routine basis it is essential that clinicians understand how to diagnosis and treat patients with thrombocytopenia.

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