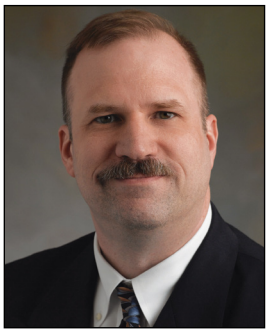
A Case-Based Approach to Thrombocytopenia in Adults

Part 1: Differential Diagnosis

Brennan



King

Matthew C. Brennan, MD
Hematologist/Oncologist
Ann B. Barshinger Cancer Institute
Penn Medicine Lancaster General Health

Bruce E. King, MD
Chair, Department of Pathology and Laboratory Medicine
Lancaster General Hospital

Thrombocytopenia is a vast topic ranging from lab artifacts like pseudothrombocytopenia to immediately life-threatening events such as microangiopathic hemolytic anemia. This case-based discussion demonstrates some key aspects of several common and uncommon causes of thrombocytopenia in adults and will be presented in two parts. The etiologies, which will be outlined in more detail in Part 2, can broadly be thought of as either decreased production or increased consumption.

Formulating the differential diagnosis necessitates keeping the acuity of the illness and the severity of the thrombocytopenia in mind (see Fig. 1). Once the provider has resolved that the thrombocytopenia is not emergent, the differential diagnosis can be focused using data from further lab and clinical studies.

Evaluation for new medications, recent illness, and travel are important. Chronic conditions such as cancer or chronic liver disease, as well as a history of gastric bypass surgery, can result in lower platelet counts. Lab testing often includes B_{12}, folate, HIV, and hepatitis C. If this workup is unrevealing, providers can consider using ultrasound to evaluate for splenomegaly, performing a bone marrow aspiration and biopsy for underlying hematologic malignancies, as well as checking serum copper (noting low serum copper levels can be seen in Wilson's disease, which is a copper overload state). Finally, if all testing is unremarkable, one could consider genetic testing for inherited platelet disorders in the right clinical context.

CASE 1: A 67-year-old male presents with a longstanding history of thrombocytopenia and the following labs.

WBC Count (4.8-10.8 10*3/µL)	**6.3**
RBC Count (4.60-6.20 10*6/µL)	**5.08**
Hgb (14.0-18.0 g/dL)	**14.9**
Hct (40.0-54.0%)	**43.3**
MCV (80.0-100.0 fL)	**85.2**
MCH (27.0-33.0 pg)	**29.3**
MCHC (32.0-36.0%)	**34.4**
RDW (12.2-14.6%)	**13.5**
Platelet Count (150-450 10*3/µL)	**83▼**
Neutrophils Absolute (2.20-8.00 10*3/µL)	**3.43**
Lymphocytes Absolute (0.90-5.00 10*3/µL)	**2.32**
Monocytes Absolute (0.20-1.10 10*3/µL)	**0.41**
Eosinophils Absolute (0.00-0.40 10*3/µL)	**0.07**
Basophils Absolute (0.00-0.40 10*3/µL)	**0.02**

On repeat, the following comment was made: "unable to perform accurate platelet count because platelets clump in ethylenediaminetetraacetic acid (EDTA)." Sending a sample in a sodium citrate tube results in a normal value.

Preanalytic variables can affect platelet counts and can create a clotted specimen (i.e., a collection that was not adequately mixed). This occurs when an antico-

	EVALUATION
• TTP (Thrombotic Thrombocytopenic Purpura) • HUS (Hemolytic Uremic Syndrome) shiga toxin or complement mediated	Normal coagulation studies Hemolysis ↑LDH ↑Reticulocytes ↑Indirect bilirubin ↓Haptoglobin
• HELLP (Hemolysis Elevated Liver enzymes Low Platelets)	
• DIC (Disseminated Intravascular Coagulopathy)	↓Fibrinogen; prolonged PT/PTT
• HIT (Heparin-Induced Thrombocytopenia)	Heparin exposure; anti-platelet 4 antibodies with reflex serotonin release assay
• Acute Leukemia	Bone marrow biopsy
• CAPS (Catastrophic Antiphospholipid Antibody Syndrome)	ACA, AB2gp1, LAC; history of autoimmune disorder
• ITP (Immune Thrombocytopenia Purpura)	Diagnosis of exclusion
• D-ITP (Drug-Induced ITP)	New medication
• PTP (Post Transfusion Purpura)	Platelet transfusion 5-10 days prior

Fig. 1. Differential diagnosis and associated evaluation for sick patients with thrombocytopenia.
ACA = anticardiolipin antibody, AB2gp1 = anti-beta 2 glycoprotein 1 antibody, LAC = lupus anticoagulant, LDH = lactate dehydrogenase.

agulant, typically EDTA, exposes a platelet membrane epitope, resulting in platelet clumping (see Fig. 2) due to immunoglobulin recognition (often to glycoprotein IIb/IIIa).[1] This clumping has no clinical significance, as it is purely an in vitro phenomenon causing erroneous automated platelet counts; clumps may be mistaken for white blood cells.

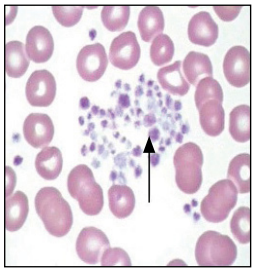


Fig. 2. Platelet clumping in EDTA in Case 1.

This phenomenon occurs in 0.1% of EDTA anticoagulated tubes.[2] It is recognized by reviewing a peripheral smear demonstrating the clumping and confirmed by switching to an alternative anticoagulant such as sodium citrate, heparin, or acid citrate dextrose, which results in a normal platelet count. If those attempts fail, however, providers can attempt running a fingerstick sample at bedside — making a peripheral smear without using an anticoagulated tube and estimating total values based on a manual count. Patients should be educated to inform health care professionals regarding this issue so that future tests are conducted using the appropriate anticoagulated sample.

Diagnosis: pseudothrombocytopenia

• If platelet clumping is noted, send a sample in a sodium citrate tube.

CASE 2: A 75-year-old male presents with a history of cirrhosis secondary to nonalcoholic steatohepatitis (NASH) complicated by portal hypertension and nonbleeding esophageal varices. He has the following labs and coronal CT abdominal imaging (see Fig. 3). The B_{12}, folate, and copper levels are unremarkable.

WBC Count (4.8-10.8 10*3/µL)	**4.7▼**
RBC Count (4.60-6.20 10*6/µL)	**4.37▼**
Hgb (14.0-18.0 g/dL)	**14.3**
Hct (42.0-52.0%)	**42.0**
MCV (80.0-100.0 fL)	**96.1**
MCH (27.0-33.0 pg)	**32.7**
MCHC (32.0-36.0%)	**34.0**
Platelet Count (150-450 10*3/µL)	**73▼**
Neutrophils Absolute (2.20-8.00 10*3/µL)	**2.82**
Lymphocytes Absolute (0.90-5.00 10*3/µL)	**1.08**
Monocytes Absolute (0.20-0.80 10*3/µL)	**0.56**
Eosinophils Absolute (0.00-0.40 10*3/µL)	**0.19**
Basophils Absolute (0.00-0.40 10*3/µL)	**0.03**
Immature Granulocyte Absolute (0.00-0.22 10*3/µL)	**0.01**

Splenic sequestration is a common finding among those with hypersplenism (normal spleen size is commonly defined as less than 12 cm, although taller individuals and men can be slightly larger than this and be normal).[3] Although the peripheral concentration of platelets is reduced, the total body platelet mass remains normal.[4] Therefore, bleeding does not typically correlate to the platelet concentration in hypersplenism, but rather some additional factor such as esophageal varices, coagulation factor derangements, or acquired platelet dysfunction in the setting of cirrhosis.

Two-thirds of those with cirrhosis will have thrombocytopenia, but only one in eight will have thrombocytopenia between 50,000/µL and 75,000/µL. Additional causes of thrombocytopenia can coexist and can include nutritional deficiencies, bone marrow suppression from medications, hepatitis C, reduced liver production of thrombopoietin (TPO), or underlying bone marrow disorders like myelodysplastic syndromes, among others.[5] Therefore, a platelet concentration <75,000/µL should raise suspicion for something beyond sequestration. Platelet transfusion in an acute setting or the use of TPO mimetics such as avatrombopag can be effective ways to raise platelet counts in cirrhosis and splenic sequestration.[6]

Diagnosis: splenic sequestration

• Thrombocytopenia <75,000/µL in cirrhosis should prompt consideration of alternative causes.

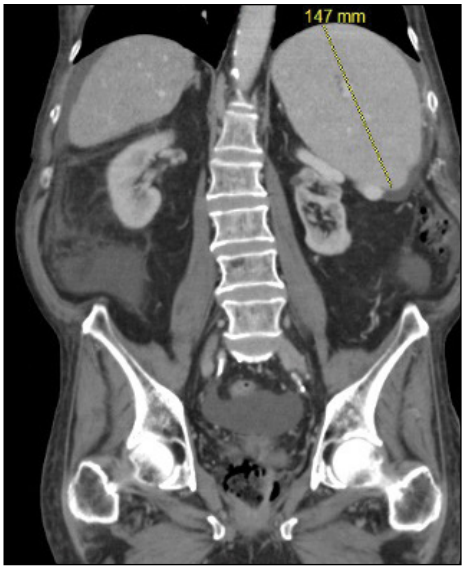


Fig. 3. Coronal reformatting of CT abdomen/pelvis with intravenous contrast demonstrating splenomegaly in Case 2.

CASE 3: A 55-year-old male with no recent medical care presents to the Emergency Department with severe sepsis due to *Streptococcus intermedius bacteremia.* CT imaging of the abdomen and pelvis demonstrates right hepatic and infrahepatic inferior venal canal thrombi as well as indeterminate hepatic masses, which

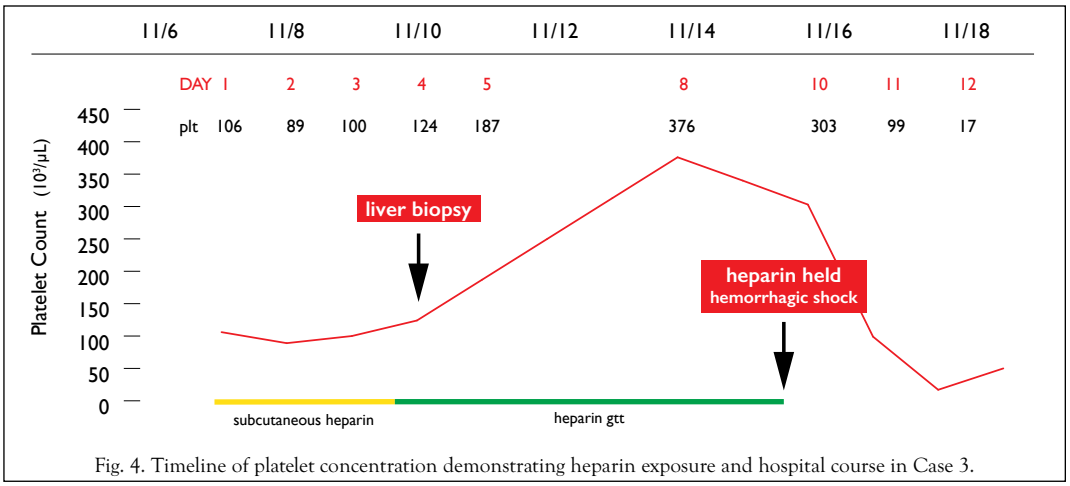


Fig. 4. Timeline of platelet concentration demonstrating heparin exposure and hospital course in Case 3.

are possibly abscesses. This prompts treatment with piperacillin/tazobactam and prophylactic heparin. The patient is started on a therapeutic heparin drip on day four after a liver biopsy was performed. On day nine, he develops shock secondary to hemorrhage into the liver, and heparin is held. Four doses of platelets and three units of packed red blood cells are transfused. At that time, the biopsy results determine the patient has an abscess.

Platelets at the time of admission are 106,000/μL. The time course of platelet concentrations is shown in Fig. 4, with a peak platelet on day eight at 376,000/μL; the platelet counts undergo a precipitous drop thereafter. Platelets did not recover despite appropriate measures, prompting the hematology consult on day 11.

This case illustrates that there should be a broad differential for thrombocytopenia. Timing of heparin exposure in relation to platelet drop should be considered when approaching all cases of thrombocytopenia. It is worth noting that platelets should recover about two or three days after an acute bleed or surgical procedure — that is, consumption should not last beyond two to three days of the acute event (provided bleeding has been controlled) and should alert the clinician to consider heparin-induced thrombocytopenia (HIT).

While critically ill patients may have more than one cause of thrombocytopenia, the pretest probability for HIT can be determined by using the 4T score (see Table 1).[7] A normal platelet count is not sufficient to rule out the possibility of HIT if there has been a 50% drop from baseline 5-10 days after heparin exposure (or within the first five days of exposure if there has been heparin exposure in the preceding 100 days). For example, a reactive thrombocytosis and a platelet count on admission of 500,000/μL may drop to 250,000/μL (still within the normal range) on day seven following heparin exposure. This scenario should prompt a consideration of HIT.

This patient had a drop in platelets between days nine and ten coinciding with hemorrhage. Furthermore, he was on broad-spectrum antibiotics, which can suppress the bone marrow production of platelets or cause drug-induced thrombocytopenia around day seven to ten of exposure. Thus, many possible etiolo-

Table 1. 4T Score

4Ts	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and nadir ≥20,000/μL	Platelet count fall 30% to 50% or nadir 10,000-19,000/μL	Platelet count fall <30% or nadir <10,000/μL
Timing of fall	Clear onset between days 5-10 or ≤1 day (prior heparin in last 30 days)	Consistent with days 5-10, but not clear (missing platelet counts): onset > day 10; or fall ≤1 day (prior heparin in last 30-100 days)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New proven thrombosis, skin necrosis, acute anaphylactoid reaction to heparin	Progressive/recurrent thrombosis, non-necrotizing (erythematous) skin lesions, suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

A score of 0-3 suggests low pretest probability for HIT, 4-5 suggests intermediate pretest probability, and 6 or more suggests a high pretest probability of HIT. Testing anti-platelet factor 4 antibodies with reflex serotonin release assay is indicated for intermediate or higher scores, and alternative anticoagulants are recommended. *Adapted from Lo et al.*[7]

gies could explain this thrombocytopenia. The 4T score, however, gave an intermediate pretest probability of HIT with four points: one point for nadir platelet count 10,000-19,000/µL, two points for timing within days five to ten and no recent heparin exposure, zero points for no attributed thrombotic event, and one point for possible other causes of thrombocytopenia. This prompted further testing.

An anti-platelet factor 4 antibody optical density was extremely high at 2.9, and a confirmatory serotonin release assay (SRA) was positive. Thus, the diagnosis of HIT was confirmed. Anti-platelet factor 4 antibody testing has a high sensitivity and thus a good negative predictive value if low, but there were many reasons for false positives; SRA is a more specific test and therefore can confirm the diagnosis.[8] Other testing platforms exist, but this approach is the most commonly used.

The incidence of HIT correlates with higher dosages of unfractionated heparin. It can occur in the setting of low molecular weight heparins, but it is less common with those agents than with unfractionated heparin. Orthopedic, surgical, and trauma patients are at higher risk of developing HIT compared to medical patients.[8] If one has had heparin exposure in the preceding 100 days, acute HIT can occur within the first 24 hours of repeat exposure. HIT should be a consideration even without concurrent thrombocytopenia in patients with necrotic skin reaction to the heparin product or anaphylactoid reaction to heparin administration.[8]

Stopping all heparin exposure is essential, including subcutaneous and intravenous doses as well as exposure from heparin flushes/locks and low molecular weight heparins. It is then critical to switch to an alternative anticoagulant (bivalirudin, argatroban, direct oral anticoagulants, warfarin, fondaparinux) unless medically contraindicated. HIT is extremely thrombogenic. Since it takes three months to clear platelet-activating antibodies, anticoagulation should be continued for at least three months.[9-11]

Direct oral anticoagulants (DOACs) are increasingly used due to their rapid onset and effectiveness, although they are not appropriate for all patients in the critically ill setting due to their longer half-lives compared to bivalirudin and argatroban. HIT can precipitate disseminated intravascular coagulation (DIC) and prolong partial thromboplastin time (PTT); bivalirudin and argatroban can confound PTT results. DOACs do not have this effect.[12]

Although warfarin can be used, one must be cautious due to its initial prothrombotic effects, and it should not be started until platelet recovery on an alternative agent.[13] For this reason, vitamin K reversal would be considered for those recently started on warfarin when diagnosed with HIT.

Heparin-independent anti-platelet 4 antibody disorders — autoimmune (heparin-independent) HIT and vaccine-induced immune thrombotic thrombocytopenia — are beyond the scope of this discussion; these may be considered in patients who have not received heparin products. Initial management is also similar, and intravenous immunoglobin (IVIG) may be useful for refractory cases.[12]

Diagnosis: heparin-induced thrombocytopenia

- If recent heparin exposure and a drop in platelet count, perform a 4T score. For intermediate/high-risk cases, send anti-platelet factor 4 antibody with reflex serotonin release assay and switch to alternative anticoagulant.
- A normal platelet count is not sufficient to rule out HIT if there is a 50% drop from peak.
- Anaphylactoid reaction to heparin raises suspicion of HIT.
- Platelets should start recovering two to three days after surgery; if not, consider HIT.
- HIT can be associated with DIC and prolonged PTT, which can affect titration of argatroban and bivalirudin.

CASE 4: A 36-year-old male presents with several weeks of bleeding gums and progressive lower extremity petechiae (see Fig. 5). His primary care physician finds he has severe thrombocytopenia.

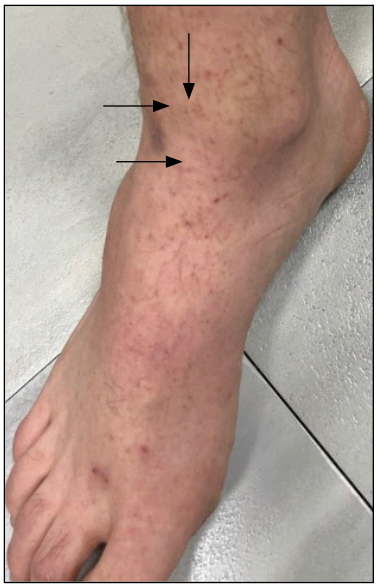


Fig. 5. Lower extremity petechiae, several identified by arrows, in Case 4.

He has the following labs.

WBC Count (4.8-10.8 10*3/µL)	6.3
RBC Count (4.60-6.20 10*6/µL)	4.17▼
Hgb (14.0-18.0 g/dL)	12.5▼
Hct (42.0-52.0%)	35.7▼
MCV (80.0-100.0 fL)	85.6
MCH (27.0-33.0 pg)	30.0
MCHC (32.0-36.0%)	35.0
Platelet Count (150-450 10*3/µL)	1.0▼
Immature Granulocyte (0.0-2.0%)	0.6
Neutrophils Absolute (2.20-8.00 10*3/µL)	4.48
Lymphocytes Absolute (0.90-5.00 10*3/µL)	1.27
Monocytes Absolute (0.20-0.80 10*3/µL)	0.31
Eosinophils Absolute (0.00-0.40 10*3/µL)	0.13
Basophils Absolute (0.00-0.40 10*3/µL)	0.03
Immature Granulocyte Absolute (0.00-0.22 10*3/µL)	0.04
Reticulocyte Count (0.5-2.5%)	3.9▲
INR (PT) (0.9-1.1)	1.0
PTT (23.0-31.6 s)	27.0
Vitamin B12	579
Folate Serum	16.7
GFR	>60
Glucose (serum)	104▲
Sodium	139
Potassium	3.9
Chloride	105
CO_2 Venous	27.5
Anion Gap	7
Blood Urea Nitrogen	12
Creatinine	1.1
BUN/Creatinine Ratio	11
Calcium	9.6
Calcium Corrected (Adj/Calc) Total	8.9
Protein Total Serum	7.5
Albumin	4.9
Globulin	2.6
A/G Ratio	1.9
Bilirubin Total	1.0
Alkaline Phosphatase	60
Lactate Dehydrogenase	293▲
AST (SGOT)	22
ALT (SGPT)	18
Haptoglobin	<30▼

He lives in the suburbs, has not recently traveled or gone hiking, and denies any known tick bites, recent viral illness, or diarrhea. He has no new medication or supplement exposure and denies illicit drug use. Labs done several years ago demonstrated a normal complete blood count and differential.

The anemia raises the possibility of a microangiopathic hemolytic anemia, which prompts additional lab evaluation. This reveals an elevated lactate dehydrogenase (LDH) and reticulocyte count, and a low haptoglobin consistent with hemolysis. Coagulation testing is normal, and direct antigen testing (DAT) is negative. A peripheral smear shows absolute thrombocytopenia with spherocytes, a normal white cell count, and an absence of schistocytes. Computed tomography of the chest, abdomen, and pelvis with intravenous dye shows splenomegaly (diameter = 17 cm) without adenopathy.

Spherocytes in the setting of hemolysis with thrombocytopenia raises the possibility of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). However, an ADAMTS13 activity level is normal, and the patient has no stigmata of TTP/HUS. On further questioning, he relates that his sister has a history of hereditary spherocytosis, which is likely the cause of his acute and mild hemolysis. Furthermore, DAT is negative, making Evan's syndrome — concurrent immune thrombocytopenia purpura (ITP) and warm autoimmune hemolytic anemia — unlikely.

A clinical diagnosis of ITP is made. The patient is started on dexamethasone 40 mg daily for four days, with intravenous immunoglobin for two days. He has an initial platelet response but subsequent relapse; thus, he is treated with weekly rituximab for four weeks and achieves ongoing remission for several years (see Fig. 6).

ITP is a diagnosis of exclusion that requires quickly evaluating for other severe and life-threatening causes of severe thrombocytopenia. TTP, HUS, DIC, HELLP (hemolysis, elevated liver enzymes and low platelets), CAPS (cryopyrin-associated autoinflammatory syndromes), acute leukemia, and tickborne illnesses should be included in the differential. ITP can be primary (autoimmune), secondary to another condition (e.g., viral infection, autoimmune disorder, chronic lymphocytic leukemia), or drug induced. The incidence is 100 per one million. In children, ITP is often self-limited, while in adults it can have a relapsing and chronic course.[14]

Evaluation for presumptive ITP should include a travel history and whether there has been exposure to

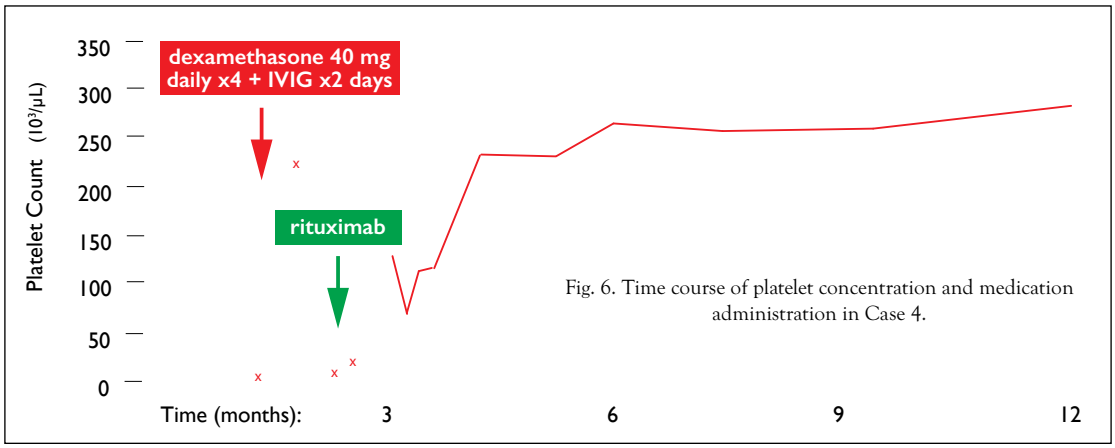


Fig. 6. Time course of platelet concentration and medication administration in Case 4.

ticks, recent viral infections, new medications, or herbal supplements. Workup should include testing for HIV, hepatitis C, and hepatitis B. Regarding the latter, it is critical to send hepatitis B core antibody (HBcAb) testing prior to administering IVIG, as passive antibody transfer will likely occur. Patients with HBcAb-positive serology need to undergo hepatitis B virus suppression if rituximab is ultimately needed, because CD20 depletion can result in fulminant hepatitis B.

Comparison to a patient's historic complete blood count if available will help to identify hereditary thrombocytopenia, which may help identify May-Hegglin anomaly or type 2B von Willebrand disease.

Treatment of ITP depends on the severity of the thrombocytopenia, as well as the clinical scenario. The goal platelet concentration is greater than 30,000/μL unless there is bleeding or the patient needs an invasive procedure. Therefore, some patients can be monitored without intervention as outpatients.

In those with newly diagnosed ITP and a platelet count <20,000/μL, admission to the hospital is recommended. If there is no urgent need to raise the platelets, steroids can be initiated — a dexamethasone pulse of 40 mg daily for four days or prednisone 0.5-2 mg/kg daily to be tapered off within six weeks should be initiated. It may take two to three days for platelets to begin responding. In those with active bleeding or bruising or platelet counts of <10,000/μL, IVIG may be more appropriate, as responses occur within 12-24 hours.

If there is life-threatening or serious bleeding, platelet transfusions may be considered; however, these may also be rapidly cleared by the immune process. Refractory or relapsing cases can be treated with rituximab or thrombopoietin receptor agonists such as eltrombopag or romiplostim. Some patients may experience a spontaneous remission within the first year, so splenectomy is reserved for refractory cases that last more than one year.[15] Additional evidence is emerging for anti CD38 monoclonal antibodies as well.[16]

Diagnosis: immune thrombocytopenia purpura with hereditary spherocytosis

- ITP is a diagnosis of exclusion.
- Initial treatment includes steroids +/- IVIG.
- Historical platelet count is helpful, as inherited thrombocytopenia can mimic ITP.

CONCLUSION

As these cases demonstrate, the differential diagnosis for thrombocytopenia can be broad and complex. Understanding the differential will allow a clinician to consider life-threatening etiologies and initiate the appropriate workup and treatment. In Part 2, we will present additional cases that illustrate the approach to thrombocytopenia in adults.

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Matthew C. Brennan, MD
Ann B. Barshinger Cancer Institute
2102 Harrisburg Pike, Lancaster, PA 17601
Matthew.Brennan@pennmedicine.upenn.edu

Bruce E. King, MD
LGH Pathology and Laboratory Medicine
555 N. Duke St., Lancaster, PA 17602
Bruce.King@pennmedicine.upenn.edu