Platelet Disorders

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Practice Gaps

Mucocutaneous bleeding and thrombocytopenia are commonly encountered in pediatric patients. It is important for pediatricians to recognize when these signs and symptoms warrant further investigation and subsequently what investigations are most helpful and when referral to pediatric hematology is necessary.

Objectives

After completing this article, readers should be able to:

1. Describe normal platelet function, including platelet adhesion, platelet activation, and platelet aggregation.
2. Identify laboratory tests helpful in evaluating a patient presenting with mucocutaneous bleeding.
3. Create a differential diagnosis for a patient presenting with mucocutaneous bleeding.
4. Describe the evaluation and initial treatment of someone with immune thrombocytopenia.
5. List at least 3 qualitative platelet disorders and their associated signs and symptoms.
6. Identify patient characteristics and laboratory findings of someone with or suggestive of a qualitative or quantitative platelet disorder who needs additional evaluation by a pediatric hematologist.

Abstract

After vascular injury and exposure of subendothelial matrix proteins to the intravascular space, mediators of hemostasis are triggered and allow for clot formation and restoration of vascular integrity. Platelets are the mediators of primary hemostasis, creating a platelet plug and allowing for initial cessation of bleeding. Platelet disorders, qualitative and quantitative, may result in bleeding signs and symptoms, particularly mucocutaneous bleeding such as epistaxis, bruising, petechiae, and heavy menstrual bleeding. Increasing evidence suggests that platelets have functional capabilities beyond hemostasis, but this review focuses solely on platelet hemostatic properties. Herein, normal platelet function as well as the effects of abnormal function and thrombocytopenia are reviewed.

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ABBREVIATIONS

BSS	Bernard-Soulier syndrome
CAMT	congenital amegakaryocytic thrombocytopenia
CBC	complete blood cell
CHS	Chediak-Higashi syndrome
COX-1	cyclooxygenase-1
DITP	drug-induced thrombocytopenia
FDA	Food and Drug Administration
FNAIT	fetal/neonatal alloimmune thrombocytopenia
GP	glycoprotein
GT	Glanzmann thrombasthenia
HIT	heparin-induced thrombocytopenia
HPA	human platelet antigen
HSCT	hematopoietic stem cell transplant
ICH	intracranial hemorrhage
IPF	immature platelet fraction
ITP	immune thrombocytopenia
IVIG	intravenous immunoglobulin
LTA	light transmission aggregometry
MPV	mean platelet volume
NSAID	nonsteroidal anti-inflammatory drug
TAR	thrombocytopenia with absent radii
TXA2	thromboxane A2
VWD	von Willebrand disease
VWF	von Willebrand factor
WAS	Wiskott-Aldrich syndrome

PLATELET PRODUCTION, STRUCTURE, AND FUNCTION

Platelets are tiny (2.5-μm) anuclear cell fragments that play complex and important roles in hemostasis, angiogenesis, inflammation, and immunity. (1)(2) Platelets are formed in the cytoplasm of megakaryocytes located in the bone marrow. (2) Differentiation of megakaryocytes from hematopoietic stem cells depends on transcription factors, including Runx1, Gata1, Fli1, and c-Myb. (3) The most important growth factor supporting megakaryopoiesis is thrombopoietin. (3) Megakaryocytes increase their ploidy through endomitosis and undergo cytoplasmic maturation to form an extensive membrane system and granules. (2)(3) Questions remain regarding the final steps of platelet production, but platelet formation likely occurs via a combination of 2 processes: 1) megakaryocytes enter the circulation and travel to the lung, where the forces of the pulmonary microcirculation cause fragmentation and platelet formation, (3) and 2) megakaryocytes develop processes that reach into the marrow sinusoids to release platelets into the circulation. (3)

Each megakaryocyte makes thousands of platelets, (4)(5) which then have a lifespan of approximately 7 to 10 days. (2) Approximately two-thirds of platelets circulate in the bloodstream, and the remainder are stored in the spleen. (5) The platelet membrane contains receptor and adhesive proteins and plays a crucial role in linking the events of primary and secondary hemostasis. (6) Glycoprotein (GP) Ib-IX-V complex, GPVI, and integrin αIIbβ3 (GPIIb/IIIa) mediate platelet adhesion and aggregation. (6) Additional surface receptors respond to platelet agonists such as thrombin to promote or amplify platelet function. Platelet cytoskeletal proteins mediate platelet shape change, and an inner platelet membrane system provides additional surface area for platelet spreading. (6) Platelet granules, alpha and dense, contain a variety of substances that mediate platelet function. Alpha granules contain von Willebrand factor (VWF), fibrinogen, GPIIb/IIIa, P-selection, factor V, factor XI, and factor XIII. (7) Dense granules contain adenosine diphosphate, adenosine triphosphate, serotonin, magnesium, and calcium. (7)

Platelets circulate, surveying for disruptions in the vascular endothelium. At sites of vascular injury, platelet surface GPIb-IX-V is captured by subendothelial VWF. Firm adhesion occurs through binding of GPVI to subendothelial collagen and through other integrin-ligand interactions. (8) Platelet activation is marked by a variety of events, which likely occur simultaneously after the initial step of calcium release (Fig) (9): 1) release of intracellular calcium from the dense tubular system, 2) exposure of phospholipid phosphatidylserine on the platelet surface to generate a negatively charged surface for interaction with the coagulation proteins, 3) release of storage granule contents, 4) GPIIb/IIIa undergoes a conformational change allowing for stable binding of fibrinogen and creation of platelet–fibrinogen–platelet aggregates, (8) 5) generation and release of thromboxane A2 (TXA2), and 6) platelet cytoskeletal rearrangement to increase surface area. (7) Release of granule contents and TXA2 results in autocrine and paracrine stimulation, amplifying platelet activation. As primary hemostasis begins, the coagulation proteins of secondary hemostasis are also activated, generating thrombin and fibrin to amplify the clotting cascade and seal the formed clot, respectively.

The normal number of platelets is 150 to $450\times10^3/\mu$L ($150–450\times10^9$/L). (10) Thrombocytopenia is defined as a platelet count of less than $150\times10^3/\mu$L ($<150\times10^9$/L). The number of platelets needed for hemostasis, though, is less than the lower limit of normal. The platelet count threshold at which bleeding signs and symptoms occur is not well-defined, but signs and symptoms associated with thrombocytopenia are frequently not clinically apparent until the platelet count is less than $50\times10^3/\mu$L ($<50\times10^9$/L), unless platelet dysfunction or medications affecting platelet function are also present. (11) Several studies of hospitalized patients have demonstrated that the risk of spontaneous clinically significant bleeding does not increase until platelet counts are less than $10\times10^3/\mu$L ($<10\times10^9$/L) and possibly even less than $5\times10^3/\mu$L ($<5\times10^9$/L). (12)

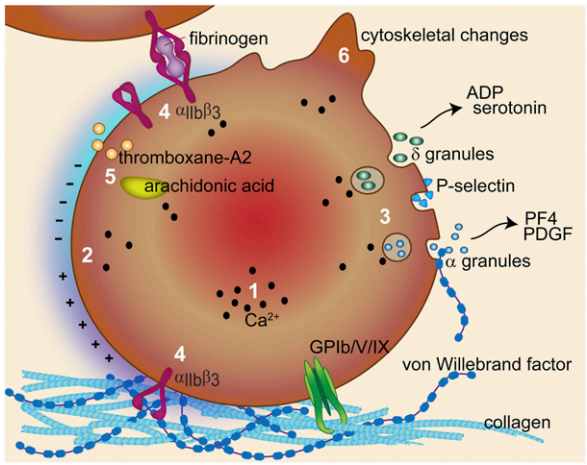

Figure. Platelet activation is marked by a variety of events that likely occur simultaneously after the initial step of calcium release and mediate platelet–platelet signaling and ultimately platelet–platelet aggregation. ADP=adenosine diphosphate, GP=glycoprotein, PDGF=platelet-derived growth factor, PF4=platelet factor 4. (Reprinted with permission from Haley KM, Recht M, McCarty OJ. Neonatal platelets: mediators of primary hemostasis in the developing hemostatic system. *Pediatr Res.* 2014;76(3):230–237.)

Clinical disorders of platelets can be due to deficiency or dysfunction, or a combination of the two, and can be congenital or acquired. Signs and symptoms related to thrombocytopenia and signs and symptoms related to platelet dysfunction overlap and can vary depending on the cause as well as confounding clinical factors. Platelet-related bleeding is typically mucocutaneous and unexpected or presents as excessive bleeding from trauma, surgery, or dental procedures. (13)(14) Muscle hematomas or joint hemorrhages are rare in patients with platelet problems. (13) Although the understanding of the interaction between primary and secondary hemostasis has evolved from a sequential series of events to a more coordinated simultaneous effort, thinking of platelets as the first line of defense to endothelial injury is helpful in connecting signs and symptoms to hemostatic defects.

The History

The most important part of an evaluation for a platelet disorder in a well-appearing child is the history, including family history, and physical examination. (15) Concern for an underlying bleeding disorder should arise when patients or parents report primarily mucocutaneous bleeding, including bruising, petechiae, epistaxis, or heavy menstrual bleeding. It can be difficult to determine normal versus abnormal bruising by questions alone. Photographs of bruising can be a helpful adjunct to the history, and images of large, deep, or raised hematomas can be more concerning for an underlying bleeding disorder. The lack of hemostatic challenges in a child at the time of evaluation can make determining a bleeding phenotype difficult. (16) Standardized bleeding tools can be helpful to assess the significance of bleeding signs and symptoms. (17) However, bleeding assessment tools can be cumbersome to administer. An abbreviated version of the International Society on Thrombosis and Haemostasis bleeding assessment tool is available online (https://bleedingscore.certe.nl) and can quickly generate a bleeding score, where a score of less than 3 is considered normal for pediatric patients. (18) Family history of bleeding symptoms, including heavy menstrual bleeding and postpartum hemorrhage in female relatives, is important. Other family history to elicit includes deafness, renal insufficiency or failure, albinism, or immunodeficiency because these signs may be present in association with platelet dysfunction and may be more prominent than the bleeding signs and symptoms (Table). (14)

The Examination

In evaluating a child with bleeding, an ill appearance, the presence of hepatosplenomegaly or adenopathy, or the presence of fever should raise concerns for a diagnosis that is separate from the platelet disorders reviewed herein. Bruising on the chest, abdomen, back, or buttocks is unusual unless associated with a very specific and memorable injury. The skin should be examined for petechiae, particularly around pressure areas such as bra straps, waistbands, backpack straps, and blood pressure cuffs. An assessment for hypermobility as seen in Ehlers-Danlos syndrome can also be helpful because patients with this syndrome can have similar bleeding signs and symptoms as those with platelet disorders. (19)(20) In addition, the patient and family members should be evaluated for telangiectasias in the nasal mucosa, which is a sign of hereditary hemorrhagic telangiectasia. (20)

CLINICAL TESTS TO EVALUATE PLATELETS

The cornerstone laboratory test is the complete blood cell (CBC) count. Individual laboratories may vary in their reference ranges for platelet count, but the normal range of platelet count remains 150 to $450\times10^3/\mu L$ ($150–450\times10^9/L$). Most automated CBC count machines will also provide the mean platelet volume (MPV). Similar to how the mean corpuscular volume can help differentiate causes of anemia, the MPV can help differentiate causes of thrombocytopenia because some types of thrombocytopenia are associated with small or large platelets, as in Wiskott-Aldrich syndrome and *MYH9* disorders, respectively. Review of the peripheral smear is a comparable method of determining platelet size to the MPV. (21) Platelets that are larger than a red blood cell are termed *giant platelets* and may indicate increased platelet turnover or an inherited macrothrombocytopenia. Many automated CBC count machines will also provide an immature platelet fraction (IPF), which measures young platelets in peripheral blood. (22) The IPF can be used to assess marrow response to thrombocytopenia. In diseases of peripheral platelet destruction, the IPF is expected to be increased, whereas in diseases of marrow failure, the IPF is expected to be normal or decreased. (23)

Review of the peripheral smear allows for assessment of platelet granularity as well as platelet clumping. Pseudothrombocytopenia occurs in some patients whose platelets clump when blood is obtained in the standard EDTA tube, and review of the blood smear to look for clumping can be helpful before pursuing further diagnostic evaluation. (24) Platelet clumping is not evident when blood is drawn into a citrated or heparinized tube in these patients.

Functional platelet testing is challenging owing to the sensitive nature of platelets to activation as well as the

TABLE. Acquired and Congenital Platelet Disorders, Including Qualitative, Quantitative, and Combination Disorders

DISEASE	ACQUIRED VS CONGENITAL	PATHOPHYSIOLOGY	EPIDEMIOLOGY	SYMPTOMS/ASSOCIATED FINDINGS	TESTING FOR PLATELET DISORDER DIAGNOSIS	TREATMENT
Thrombocytopenia						
Immune thrombocytopenia	Acquired	Autoimmune destruction of platelets plus impaired production	1.9–6.4 per 100,000 children per year	Severe thrombocytopenia, well-appearing, variable bleeding	Platelet count, marrow not necessary	Watch and wait, intravenous immunoglobulin or corticosteroid if bleeding
Drug-induced thrombocytopenia	Acquired	Antibodies to platelets induced by medication	Variable	Thrombocytopenia occurring 1–2 wk after starting a medication	History, can look for antidrug antibodies	Remove offending agent
Fetal/neonatal alloimmune thrombocytopenia	Acquired	Maternal antibodies form against paternal antigens present on fetal platelets	0.5–1.5 per 1,000 live births	Platelet count often $<50\times10^3$/μL ($<50\times10^9$/L), ICH in 1 of 10,000 births, high rate of recurrence	HPA genotyping of mother and father, alloantibody testing of maternal serum	Transfuse platelets (random donor until antigen-matched available)
Wiskott-Aldrich syndrome	Congenital	Mutations in the *WAS* gene, X-linked	1–10 cases per 1 million males	Eczema, small platelets, immune deficiency	Flow cytometry for WAS protein, *WAS* sequencing	Supportive care, HSCT
Thrombocytopenia with absent radii	Congenital	Unknown	0.42 per 100,000 live births	Absent radii, thumbs present, can have lower extremity anomalies	Radiographic findings plus thrombocytopenia	Supportive care, avoidance of milk protein
Congenital amegakaryocytic thrombocytopenia	Congenital	Mutations in the thrombopoietin receptor *c-Mpl*	Rare	Platelet count $\sim20\times10^3$/μL ($\sim20\times10^9$/L) at birth, no other anomalies	Bone marrow to demonstrate absent megakaryocytes	HSCT
Thrombocytopenia + dysfunction						
MYH9	Congenital	Mutations in the *MYH9* gene, autosomal dominant	Rare	Nephritis, high-frequency hearing loss, glaucoma, cataracts	Large platelets, Dohle-like bodies in neutrophils, mutation testing	Symptomatic, screen for associated symptoms
Bernard-Soulier syndrome	Congenital	Mutations in the genes that encode GPIb-IX-V	1 per 1 million	Isolated bleeding disorder with presentation typically at birth, large platelets	LTA demonstrates absent response to ristocetin, absent GPIb on flow cytometry	Platelet transfusion may cause alloantibody, consider recombinant factor VIIa
Paris-Trousseau syndrome	Congenital	Mutations in the *FLI-1* gene	Affects ~90% of patients heterozygous for the *FLI-1* gene	Thrombocytopenia at birth that may improve, associated with Jacobsen syndrome	Light or electron microscopy to assess alpha granule content of platelets	Supportive care with antifibrinolytics, rarely platelet transfusions

Continued

TABLE. (Continued)

DISEASE	ACQUIRED VS CONGENITAL	PATHOPHYSIOLOGY	EPIDEMIOLOGY	SYMPTOMS/ASSOCIATED FINDINGS	TESTING FOR PLATELET DISORDER DIAGNOSIS	TREATMENT
Platelet dysfunction						
Glanzmann thrombasthenia	Congenital	Mutations in the genes that encode GPIIb/IIIa	1 per 1 million	Isolated bleeding disorder with presentation typically at birth	LTA demonstrates absent response to all agonists except ristocetin, absent GPIIb/IIIa on flow cytometry	Platelet transfusion may cause alloantibody, recombinant factor VIIa is first-line
Storage pool disorder	Congenital	Deficiencies of platelet granules	Variable	Variable bleeding symptoms	Dense granule deficiency can be detected on electron microscopy	Supportive care with antifibrinolytics, rarely platelet transfusions
Hermansky Pudlak syndrome	Congenital	Dense granule deficiency, mutations in genes that encode components of lysosome-related organelles	Rare	Oculocutaneous albinism, colitis, pulmonary fibrosis	Electron microscopy shows absent dense granules	Supportive care with antifibrinolytics, rarely platelet transfusions, surveillance for colitis and pulmonary fibrosis
Chediak-Higashi syndrome	Congenital	Dense granule deficiency	Rare (<500 cases reported)	Oculocutaneous albinism, progressive neurologic dysfunction, immune deficiency	Electron microscopy shows absent or decreased dense granules	Immune deficiency and platelet dysfunction treated with HSCT
Secretion defects	Congenital	Granules are present but are not released on activation	Variable	Variable bleeding symptoms	Aggregation blunted or generally decreased on LTA	Supportive care with antifibrinolytics, rarely platelet transfusions
Drug induced	Acquired	Various effects depending on drug (eg, NSAIDs inhibit COX-1	Variable depending on drug	Typically minimal effect unless combined with underlying bleeding disorder, thrombocytopenia, comorbid conditions such as renal failure, or multiple medications with similar effect	Platelet function analysis will be abnormal for epinephrine only for NSAIDs and acetylsalicylic acid	Withdrawal of drug, limit drugs with overlapping platelet effects

COX-1=cyclooxygenase-1, GP=glycoprotein, HPA=human platelet antigen, HSCT=hematopoietic stem cell transplant, ICH=intracranial hemorrhage, LTA=light transmission aggregometry, NSAID=nonsteroidal anti-inflammatory drug, WAS=Wiskott-Aldrich syndrome.

influence of medications, diet, phlebotomy technique, and complex platelet function. In addition, the gold standard of platelet function assessment, light transmission aggregometry (LTA), is labor-intensive, requires large volumes of blood, and has limited availability. (25) LTA uses either purified platelets or whole blood and exposes the platelets to a series of agonists to interrogate signaling pathways. The response to the agonists varies between qualitative platelet disorders, and certain patterns of response are associated with specific platelet disorders. The platelet function analyzer is a whole-blood assay of platelet function that is more readily available than LTA. The instrument uses cartridges with either collagen/adenosine diphosphate- or collagen/epinephrine-coated membranes separated by a small aperture. Blood is aspirated under shear forces into the cartridge until aggregated platelets close the aperture, and the time until closure is recorded as the result. (25) The platelet function analyzer is sensitive to several variables, including platelet count (thrombocytopenia prolongs closure time), hematocrit value (anemia can prolong closure times), medications (nonsteroidal anti-inflammatory drugs [NSAIDs] prolong closure time), von Willebrand disease (VWD) (prolongs closure time), sample transport through vacuum systems, timing of sample collection, dietary factors, and platelet disorders. (25) A normal platelet function analyzer result is helpful to exclude severe platelet disorders such as Glanzmann thrombasthenia as well as more severe types of VWD. However, a normal platelet function analyzer result does not rule out a minor or moderate platelet disorder, such as a storage pool disorder or all types of VWD. (25) Prolonged closure times must be followed up with more extensive platelet testing as well as VWD testing if not previously performed. Bleeding time was historically used as a test of primary hemostasis, but this test has fallen out of favor because it is difficult to reproduce, is invasive, has low sensitivity, and cannot differentiate between types of primary hemostatic defects. (26)

Thromboelastography is a method developed to evaluate clot formation and strength in whole blood as a point-of-care test. (27) In this assay, whole blood is added to an oscillating cup, and a pin is suspended into the blood. As a clot forms, the motion of the pin changes in a characteristic pattern and is detected by a transducer, generating a visual representation of clot formation and strength. (27) Thromboelastography is primarily used in the actively bleeding patient in the emergency department, operating room, or ICU to guide transfusions rather than to diagnose bleeding disorders in the outpatient setting.

PLATELET DISORDERS: PROBLEMS OF NUMBER OR FUNCTION

Thrombocytopenia

The differential diagnosis for thrombocytopenia can be created based on the clinical features (well versus ill), timing (congenital versus acquired), age (infant versus older child), or size of platelet (normal versus small versus large). The differential diagnosis of a child presenting with thrombocytopenia as well as an additional cytopenia (such as anemia or neutropenia) is much different than that of isolated thrombocytopenia and is not reviewed herein.

Acquired Thrombocytopenias

A new finding of thrombocytopenia in a patient known to have a previously normal platelet count or signs and symptoms associated with thrombocytopenia in a patient who previously did not have such signs and symptoms should prompt evaluation for an acquired thrombocytopenia. The most common etiologies of acquired thrombocytopenia are reviewed herein.

Fetal/Neonatal Alloimmune Thrombocytopenia. Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of severe thrombocytopenia (platelet count $<50\times10^3/\mu L$ [$<50\times10^9/L$]) in neonates, occurring in 0.5 to 1.5 per 1,000 neonates, which is likely an underestimation. (28)(29)(30) FNAIT develops when fetal platelets have antigens inherited from the father that are absent in the mother, and the maternal immune system recognizes these antigens as foreign and mounts an immune response with antibodies to the paternally inherited platelet antigens. These antibodies cross the placenta, resulting in clearance of fetal platelets and thrombocytopenia. FNAIT can affect the first pregnancy. (31) The 2 most common antigens implicated in FNAIT in the white population are human platelet antigen (HPA)-1a and HPA-5a. (28) The International Society of Thrombosis and Haemostasis recommends that when FNAIT is suspected, testing should include HPA genotyping from the mother, the neonate, and/or the father; alloantibody testing of maternal serum; and a crossmatch with paternal platelets. (31) Thrombocytopenia can be severe (platelet count $<50\times10^3/\mu L$ [$<50\times10^9/L$]) and can lead to intracranial hemorrhage (ICH) in approximately 1 of 10,000 births, with a higher frequency in severe FNAIT. (32) Most ICH occurs in utero. (33) There is a very high rate of recurrent ICH in subsequent pregnancies if the first pregnancy was affected by ICH. (32) Because of the high rate of in utero ICH and recurrent FNAIT, several strategies for antenatal management have been developed and include

administration of intravenous immunoglobulin (IVIG) with or without corticosteroids to the mother during pregnancy. (33) In term infants with FNAIT and symptomatic thrombocytopenia or for platelet counts less than $30\times10^3/\mu L$ ($<30\times10^9/L$), platelet transfusions are indicated. (34) For pre-term infants, infants with ICH, or otherwise unwell infants, transfusion should be considered at a higher threshold. (34) The recommended transfusion product is compatible platelets. (30) If antigen-negative platelets are not available, then the newborn should be transfused with a random-donor type and matched platelets while antigen-matched platelets (for the antigen implicated in the FNAIT, eg, HPA-1a negative or HPA-5b negative) are obtained if possible. (30)(34) The role of IVIG in the treatment of FNAIT is not entirely clear, but IVIG is often combined with platelet transfusion therapy. (30)(32) All infants with FNAIT should have at least 1 cranial ultrasound, with repeated cranial ultrasonography as clinically indicated or if there is persistent thrombocytopenia. (32)(34) A critical aspect to management of FNAIT is preparing for future pregnancies that could be affected by FNAIT.

Immune Thrombocytopenia. Immune thrombocytopenia (ITP) is an autoimmune destruction of platelets that can be either primary, not associated with an underlying cause, or secondary, associated with other disorders, such as systemic lupus erythematous. (35) ITP is classified according to disease duration: newly diagnosed (diagnosis ≤3 months), persistent (3–12 months), and chronic (>12 months). (35) ITP develops due to immune dysregulation with development of autoantibodies to platelet antigens as well as megakaryocytes resulting in increased platelet clearance and impaired production. (36) The incidence of ITP in children is estimated to be 1.9 to 6.4 per 100,000 children per year, (37) but the incidence is difficult to determine due to variability in presentation and evaluation. (38) Pediatric patients with ITP are typically well-appearing and present with an acute onset of bruising, petechiae, and mucosal bleeding with isolated thrombocytopenia on CBC count. (39) A portion of children will have a preceding illness, vaccination, allergic reaction, or insect bite. (39) There is no specific diagnostic test for ITP, and other causes of thrombocytopenia must be eliminated either through the history and physical examination or additional laboratory evaluation. Current guidelines do not recommend routine bone marrow aspirate/biopsy evaluation in patients presenting with typical ITP. (40) Additional laboratory tests to consider at diagnosis include a metabolic panel to assess renal function, direct antiglobulin test, blood type, prothrombin time, partial thromboplastin time, and immunoglobulin G. (41) Severe bleeding, including ICH, is rare in pediatric ITP, with an overall incidence of ICH of 0.4% and a slightly higher incidence in patients with chronic ITP (1.3%). (41) The incidence of non-ICH severe bleeding is difficult to determine due to varying definitions but has been reported to be approximately 20% in pediatric patients. (41) Predictors of severe bleeding include a platelet count less than $10\times10^3/\mu L$ ($<10\times10^9/L$), newly diagnosed ITP, and previous minor bleeding. (41) Observation is recommended for patients presenting with no or mild (skin manifestations only) bleeding regardless of platelet count. (40) For children with bleeding, first-line treatment is either IVIG or a short course of corticosteroids. (40) Anti-D was previously used as a first-line treatment, but due to hemolytic anemia associated with anti-D used to treat newly diagnosed ITP, current guidelines advise against anti-D in children with anemia due to bleeding or with evidence of hemolysis. (40) Most children with ITP will have a self-limited course, regardless of treatment, but approximately 20% to 30% of children develop chronic ITP. (42) For patients with chronic ITP, current guidelines suggest treatment with rituximab or high-dose dexamethasone for patients with ongoing bleeding. (40) However, these guidelines were created before the introduction of thrombopoietin receptor agonists, which are increasingly used in the treatment of chronic ITP and are even being prescribed in persistent or newly diagnosed ITP. (43) The advantages of these medications lie in the avoidance of lifelong complications from other therapies, such as splenectomy or immunosuppression from rituximab, long-term corticosteroid use, or other immune-modulating medications. (43) Eltrombopag and romiplostim are the 2 Food and Drug Administration (FDA)-approved thrombopoietin receptor agonists for chronic ITP in pediatric patients. Eltrombopag is administered orally daily, and romiplostim is a weekly subcutaneous injection. Both are titrated based on platelet count. For persistent symptomatic ITP, treatment options include periodic IVIG or corticosteroid courses, or using one of the treatments listed previously herein for chronic ITP.

Drug-Induced Thrombocytopenia. Drug-induced thrombocytopenia (DITP) is an immune-mediated destruction of platelets that results in acute thrombocytopenia and presents with significant bleeding. (44) DITP typically develops within 1 to 2 weeks after starting a daily medication or within a few hours of taking a medication used on an intermittent basis.(44)(45) The thrombocytopenia occurs only in the presence of the drug, and the thrombocytopenia resolves within 1 week of drug removal. (45) However, on reexposure, the thrombocytopenia will recur. (44) A variety of medications have been implicated in DITP, including antibiotics,

antineoplastic agents, and antiseizure medications, as well as commonly used medications such as acetaminophen. (45) Some vaccines, herbs, foods, and supplements have also been implicated in DITP. Heparin-induced thrombocytopenia (HIT) is a unique form of drug-induced thrombocytopenia whereby antibodies are formed and attach to a novel epitope created by heparin binding to platelet factor-4. (46) HIT is associated with thrombocytopenia as well as a very high risk of thrombosis. The treatment of HIT requires immediate discontinuation of all forms of heparin, and a nonheparin anticoagulant is substituted. HIT is rare in the pediatric population and nearly nonexistent in the neonatal population. (46)(47)

Congenital Thrombocytopenias

Although rare, congenital thrombocytopenias may be more common than realized due to diagnostic uncertainty. Mild phenotypes, for example, patients with heavy menstrual bleeding or epistaxis, may not undergo a full investigation. (48) The causes of congenital thrombocytopenia that result in more significant bleeding are reviewed.

Small Platelets.

Wiskott-Aldrich Syndrome.

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by microthrombocytopenia, eczema, immunodeficiency, and an increased risk of lymphoid malignancies. (18)(49)(50) WAS develops secondary to mutations in the *WAS* gene, which lead to defects in or absence of the WAS protein. (51) When the protein is absent or truncated, the classic WAS phenotype develops. (51) However, missense mutations in *WAS* result in a milder phenotype, termed *X-linked thrombocytopenia*. (51)(52) The bleeding phenotype in WAS can be quite severe, including gastrointestinal and intracranial hemorrhages. (49) Hemorrhage is the cause of death in approximately 20% of patients with WAS. (49) Individuals with WAS have a higher rate of autoimmune disorders and malignancies. (49) Malignancies are associated with a high mortality rate. (49) The only curative therapy for WAS is hematopoietic stem cell transplant (HSCT). (49) The role of transplant in X-linked thrombocytopenia is more controversial, and disease phenotype and donor availability dictate intervention. (52) Gene therapy for WAS continues to be evaluated but has not yet replaced HSCT.

Normal-Sized Platelets.

Congenital Amegakaryocytic Thrombocytopenia.

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive disorder that presents at birth with severe thrombocytopenia. (53) Mean platelet counts at birth are $21\times10^3/\mu L$ ($21\times10^9/L$). (53) ICH can occur. Megakaryocytes are significantly reduced or absent in the bone marrow of patients with CAMT. (53) CAMT most commonly is a result of mutations of the thrombopoietin receptor *c-Mpl*. (53) Most children with CAMT will progress to trilineage marrow failure and are also at increased risk for myelodysplasia and acute myeloid leukemia. (53) The only curative therapy for CAMT is HSCT. (53)

Thrombocytopenia with Absent Radii.

Thrombocytopenia with absent radii (TAR) syndrome is characterized by thrombocytopenia and bilateral aplasia of the radii. (53)(54) Some family studies suggest that TAR overlaps with Roberts syndrome (a multiple congenital anomaly syndrome consisting of facial clefting, renal and genital anomalies, limb defects, and growth restriction) and is the compound heterozygote variant. (55) Platelet counts are typically less than $50\times10^3/\mu L$ ($<50\times10^9/L$) initially but improve with age and can reach near-normal ranges. (54)(56) Bleeding is common in the first year of life, and infants with TAR are at risk for ICH. (54) The thumbs are preserved in TAR, which differentiates it from Fanconi anemia. (56) Lower extremity abnormalities may also be present, as well as cardiac and facial anomalies. (54) Cow milk allergy is common, affecting a significant proportion of children with TAR, and may result in significant gastrointestinal bleeding. (54)(55) Treatment of TAR is supportive with platelet transfusions for bleeding or in preparation for procedures. (53) The rate of malignancy in TAR is lower than in other congenital marrow disorders. (53) (54)

Large Platelets.

MYH9-Related Diseases.

MYH9-related diseases include those previously termed *May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome,* and *Epstein syndrome*. (48) These disorders are due to mutations in the *MHY9* gene, are autosomal dominant, and are characterized by macrothrombocytopenia, neutrophil inclusions (Dohle-like bodies), and mild bleeding signs and symptoms. (57) Other clinical manifestations are variably present and may include nephritis with progression to end-stage renal failure, familial spastic paraplegia, pituitary growth hormone deficiency, high-frequency hearing loss, glaucoma, and cataracts. (57) The nonplatelet signs typically overshadow the bleeding phenotype. Because these are autosomal dominant conditions, eliciting a family history for renal failure, hearing loss, or early glaucoma or cataracts in a patient presenting with minimal bleeding and macrothrombocytopenia is vital

to diagnose the *MYH9*-related diseases and provide appropriate surveillance.

Velocardiofacial Syndrome.

Microdeletion of the proximal long arm of chromosome 22 results in a spectrum of developmental disorders, including velocardiofacial syndrome, which is characterized by velopharyngeal dysfunction, typical facial appearance, neurodevelopmental problems, and congenital heart defects. (58) One of the genes located on 22q11.2 is the gene that encodes one of the subunits of GPIb-IX-V. (58) Bernard-Soulier syndrome (BSS), as described later herein, results from a homozygous mutation in any one of the genes that encodes the GPIb-IX-V complex. Most children with velocardiofacial syndrome are obligate heterozygotes for mutations in GPIb and, thus, are at risk for having BSS if they inherit a variant in their other copy of the *GPIb* gene. (58) Patients with velocardiofacial syndrome frequently have a mild macrothrombocytopenia and a mild bleeding phenotype. (58)

Qualitative Platelet Disorders

The clinical phenotypes associated with platelet dysfunction range from minor (eg, limited bruising, epistaxis, heavy menstrual bleeding) to severe (eg, petechiae, purpura, gastrointestinal bleeding, intracranial bleeding, significant anemia). Functional platelet disorders can be acquired or congenital and associated with normal platelet counts or thrombocytopenia. Although the identified qualitative disorders are rare, it is possible that patients with a bleeding phenotype but no identified bleeding disorder have a platelet disorder that cannot be identified by current functional tests. (59) The most common and those with a severe bleeding phenotype are reviewed herein.

Congenital Platelet Dysfunction.

Disorders of Platelet Receptors.

Glanzmann Thrombasthenia.

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder caused by decreased expression or impaired function of the platelet GPIIb/IIIa, the mediator of platelet aggregation. (60) The platelet count in GT is normal, and the platelets are of normal size and granularity. The incidence is approximately 1 per 1 million but increases to 1 per 200,000 in populations with higher rates of consanguinity. (61)(62) Presentation in the neonatal period is common, and patients who present before age 5 years tend to have a more severe bleeding phenotype. (61) Heavy menstrual bleeding can result in significant anemia and be difficult to treat. The platelet surface in GT has deficient or absent GPIIb/IIIa when assessed by flow cytometry. (51) Because GPIIb/IIIa is diminished or absent, platelet–platelet aggregation cannot occur, and the LTA pattern for patients with GT is absent aggregation to all agonists except ristocetin. Ristocetin mediates platelet–platelet agglutination through GPIb and is, thus, unaffected by absent GPIIb/IIIa. Treatment with platelet transfusions can result in alloimmunization, yielding platelet transfusions ineffective. (63) Recombinant factor VIIa is an FDA-approved treatment for GT and is frequently used as first-line treatment for bleeding in GT, whereas platelet transfusions are reserved for major or life-threatening bleeding. (61)(64) HSCT is a curative therapy for patients with GT and may be considered for those with a severe bleeding phenotype or who have developed platelet antibodies. (61)(64)

Bernard-Soulier Syndrome.

BSS is an autosomal recessive disorder characterized by a moderate to severe macrothrombocytopenia ($20–100\times10^3/\mu L$ [$20–100\times10^9/L$]) (61) and a loss of VWF-dependent platelet adhesion to collagen with a moderate to severe bleeding phenotype. (63) It is also a rare disorder with an incidence of 1 per 1 million. (61) Genetic defects for any component of the GPIb-IX-V complex result in BSS. Presentation in infancy or early childhood is common with bruising and epistaxis. Other mucocutaneous bleeding, such as gastrointestinal bleeding and hematuria, can also occur. (61) Because ristocetin requires GPIb to mediate platelet–platelet interactions, LTA demonstrates normal aggregation to all agonists except ristocetin. Flow cytometry demonstrates deficient GPIb/IX/V. (61) Treatment of BSS is typically required before surgeries/procedures or in response to bleeding. Platelet transfusions are an effective therapy, however; similar to GT, patients can develop alloantibodies. (61) Recombinant factor VIIa has not been approved in BSS, but its use has been reported. (61) HSCT is not used as frequently in BSS as in GT. (61)

Disorders of Platelet Granules.

Storage Pool Disorders.

Storage pool disorders are the most commonly isolated deficiencies of dense granules, but rare patients with combined alpha and dense granule deficiencies are reported. (65)(66) In addition, as described later herein, dense granule deficiency can be associated with other clinical features. The bleeding in isolated dense granule deficiency is variable. Electron microscopy demonstrates decreased numbers of dense granules.

Hermansky-Pudlak Syndrome.

Hermansky-Pudlak syndrome is a very rare autosomal recessive disorder characterized by oculocutaneous albinism, a bleeding phenotype, granulomatous colitis, and pulmonary fibrosis. (67) Some areas of the world, such as Puerto Rico, have a higher incidence. (67) All 10 subtypes are characterized by oculocutaneous albinism

and platelet dysfunction, but the colitis and pulmonary fibrosis are variable. (67) The platelet dysfunction is secondary to absence (or near-absence) of dense granules, which can be detected by electron microscopy. Genetic testing should be performed due to implications regarding follow-up, surveillance, and prognosis for colitis and pulmonary fibrosis. (67) The presence of oculocutaneous albinism and a bleeding phenotype should prompt evaluation for Hermansky-Pudlak syndrome. (67).

Chediak-Higashi Syndrome.

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by variable oculocutaneous albinism, bleeding signs and symptoms due to platelet dense granule deficiency, (66) progressive neurologic dysfunction, and immune deficiency secondary to neutropenia and impaired natural killer cell function. (60)(68) CHS is also associated with a lymphoproliferative disorder, termed the *accelerated phase,* where lymphocytes and macrophages infiltrate the major organs in a manner similar to hemophagocytic lymphohistiocytosis. (68)(69) The accelerated phase occurs in approximately 85% of patients with CHS, and it is the most common cause of death in this population. (68) The immune defects and platelet disorder can be cured with HSCT, but the neurologic symptoms, which are progressive, cannot be cured. (68)(69).

Paris-Trousseau-Jacobsen Syndrome.

Paris-Trousseau-Jacobsen syndrome is characterized by thrombocytopenia in the neonatal period and platelet dysfunction. The thrombocytopenia may improve with time, but the platelet dysfunction persists. (70) Heterozygous mutations in the *FLI-1* gene, which is located on chromosome arm 11q, result in Paris-Trousseau syndrome. (70) Nearly 90% of patients with Jacobsen syndrome, a congenital syndrome characterized by bleeding signs and symptoms, congenital heart disease, intellectual disability, behavioral problems, and immunodeficiency secondary to variable deletions in the distal aspect of chromosome arm 11q, have Paris-Trousseau syndrome. (70).

Disorders of Platelet Signaling.

Secretion Defects.

The broad term *platelet secretion defects* can be applied to a heterogeneous group of platelet disorders with variable bleeding signs and symptoms. (60) In these disorders, there are normal numbers of granules, but the signaling that must occur for granule release is dysfunctional in some manner. (71) On LTA, aggregation is generally decreased or blunted, and the secondary aggregation wave is sometimes absent. (71) This ill-defined group of disorders likely represents a significant portion of patients with bleeding signs and symptoms and nonspecific findings on LTA. With improvement in detection of platelet molecular defects, this heterogeneous group will become better differentiated. (60)

Other inherited forms of platelet dysfunction that are rarer or more poorly defined than those listed previously herein exist. There is increasing use of genetic testing in the diagnostic evaluation of patients with bleeding disorders with unknown etiologies, with variable success at identifying a genetic change, which is related to the bleeding phenotype. (72)(73)

Acquired Platelet Dysfunction

Acquired causes of platelet dysfunction may result in mucocutaneous bleeding signs. Medications, foods, and supplements can affect platelet function. (74) The most well-known medications that affect platelet function are the NSAIDs. NSAIDs inhibit cyclooxygenase-1 (COX-1), which is an enzyme that converts arachidonic acid to TXA2 and promotes platelet activation. (74) NSAIDs reversibly inhibit COX-1, with effects lasting until the drug is out of the circulation. (74) Aspirin irreversibly inhibits COX-1, and its effect lasts the life of the platelet. (74) Other medications that may interfere with platelet function include selective serotonin reuptake inhibitors; however, the bleeding signs and symptoms associated with selective serotonin reuptake inhibitors are minimal and more common in elderly patients. (74) There are also several herbs and foods that can affect platelet function, such as garlic, ginkgo, and turmeric, and avoidance of these substances should be discussed with the patient's hematologist. (74) In addition to medications and foods, certain systemic illnesses can result in platelet dysfunction. Renal failure and subsequent uremia can affect platelet function and result in variable bleeding signs and symptoms due to impaired platelet aggregation. (75) Compounding the effect of uremia on platelet function is the anemia frequently present in patients with renal failure. (75) Chronic liver disease has also been associated with impaired platelet function as well as thrombocytopenia. (75) Although acquired conditions resulting in platelet dysfunction are likely more common in adult than pediatric patients, a thorough review of the medication list, supplements, and medical comorbidities is important when evaluating a patient with bleeding.

General Treatment Considerations

Treatment of platelet disorders is highly dependent on the etiology and the clinical scenario and should be coordinated with a pediatric hematologist in most cases. For inherited disorders of platelet function and thrombocytopenia, most do not require daily medications but rather require treatment in response to injury or in preparation for surgery. Standard first aid with application of pressure is critical to controlling bleeding in patients with platelet disorders. (76) In addition, antifibrinolytics (epsilon-aminocaproic acid and

tranexamic acid) can be helpful in treating and preventing mucocutaneous bleeding. (76) Desmopressin can also be used in some patients because it results in the release of VWF from endothelial cells and may augment platelet adhesion. (76) Platelet transfusions and recombinant factor VIIa are typically reserved for life-threatening bleeding, ICH, major surgeries, or bleeding resulting in significant anemia. Critical to the treatment of individuals with platelet disorders, though, is prevention and planning. Good oral hygiene is important to maintain dental health and avoid unnecessary dental procedures. (76) Patients should be instructed to alert their dentists and other health-care providers of their platelet disorder to ensure appropriate planning before procedures. Helmets and protective equipment should be worn during activities such as bike riding. Wearing helmets is generally unnecessary in everyday life except for patients with WAS. Care should be taken to avoid contact sports. Finally, medications known to affect platelet function should be avoided if possible.

When to Refer

An ill-appearing or febrile child with other cytopenias, with or without organomegaly or adenopathy, should be urgently evaluated to determine whether further evaluation for an underlying malignancy, marrow infiltrative disorder, serious systemic infection, or other life-threatening illness is present. For children who present to the office and are incidentally found to have mild thrombocytopenia and have a negative bleeding history and reassuring examination findings, the most likely outcome is resolution, with the most likely etiology being viral suppression. (77) Referral to pediatric hematology should be considered in the following circumstances:

- A positive bleeding history
- A patient who is scheduled for surgery and has limited bleeding signs and symptoms or no previous bleeding challenges but a family history of a bleeding disorder
- A patient with bleeding signs and symptoms and/or thrombocytopenia with a family history of hearing loss, nephritis, and glaucoma
- Diagnosis of a congenital syndrome associated with bleeding signs and symptoms (20)
- Persistent thrombocytopenia (platelet count $<150\times10^3/\mu L$ [$<150\times10^9/L$])
- For patients with ITP, consider referring to or contacting a pediatric hematologist when there is severe bleeding, when bleeding is not improving, if the patient or family or health-care professional is anxious
- If the family, patient, or health-care professional is concerned and requests further evaluation

A referral should consider the severity and chronicity of the signs and symptoms, family history, upcoming procedures, patient and parental anxiety, and distance to a specialist. The evaluation of a child with bleeding signs and symptoms with or without thrombocytopenia may require several trips to the hematologist and the laboratory. Coordination between the primary care provider and the hematologist is critical to ensure prompt, accurate, and efficient diagnosis or exclusion of a diagnosis.

Summary

- Based on research evidence, platelets are anucleate cell fragments that mediate hemostasis through adhesion to sites of endothelial injury, amplified activation, and aggregation. (5)(6)(7)
- Based on clinical studies, thrombocytopenia and platelet dysfunction both lead primarily to mucocutaneous bleeding signs and symptoms, which can range from mild to severe. Thrombocytopenia and platelet disorders can be acquired or congenital. (8)(9)(10)(11)
- Based on consensus, the evaluation of a child presenting with mucocutaneous bleeding signs and symptoms or thrombocytopenia requires careful history taking and laboratory investigations. Evaluation of platelet function should be conducted in coordination with a pediatric hematologist. (9)(10)(11)(13)
- Based on opinion, treatment of thrombocytopenia and platelet disorders is disease specific. In general, though, treatment is aimed at preventing complications by maintaining excellent dental hygiene, wearing appropriate protective equipment for activities, and planning for dental or surgical procedures. (75)
- Based on research and consensus, the treatment of immune thrombocytopenia is evolving, especially for those with chronic immune thrombocytopenia. (43)(35)(36)
- Research regarding the molecular drivers of platelet disorders is ongoing and is likely to help identify causes of mucocutaneous bleeding that have not previously been determined. (63)(64)

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1. You are giving a lecture to medical students about the mechanism of action of aspirin. You inform the students that aspirin causes irreversible inhibition of cyclooxygenase-1 for the life span of the platelets. Which of the following best describes the duration of the antithrombotic effect of aspirin on normal platelets?
   A. Less than 24 hours.
   B. 2 to 4 days.
   C. 7 to 10 days.
   D. 1 month.
   E. 3 months.
2. A 2-day-old term infant has prolonged bleeding from a heel stick. His platelet count is $12\times10^3/\mu$L (12×10^9/L). Evaluation is consistent with the diagnosis of fetal/neonatal alloimmune thrombocytopenia. Which of the following is the most appropriate next step in the management of this patient?
   A. Observation.
   B. Platelet transfusion.
   C. Prednisone therapy.
   D. Recombinant factor VIIa.
   E. Thrombopoietin receptor agonist.
3. A 3-year-old girl presents with easy bruising 2 weeks after an upper respiratory tract infection. Physical examination is notable only for petechiae and bruises on her face and body. Complete blood cell count showed a platelet count of $20\times10^3/\mu$L (20×10^9/L), with increased mean platelet volume, normal hemoglobin level, and normal white blood cell count. Her immature platelet fraction is elevated. Which of the following is the most appropriate next step in the management of this patient?
   A. Administer anti-D immunoglobulin.
   B. Administer thrombopoietin receptor agonist.
   C. Administer rituximab.
   D. Observe.
   E. Perform bone marrow examination.
4. A 6-year-old boy presents with a history of frequent and prolonged epistaxis. Which one of the following findings, if present, is most suggestive of a qualitative platelet disorder in this patient?
   A. Hemarthrosis.
   B. Joint hypermobility.
   C. Lymphadenopathy.
   D. Muscle hematoma.
   E. Nephritis.
5. A 2-month-old girl presents with bleeding from her oral mucosa and bruising on her face, trunk, and extremities. Platelet count and mean platelet volume are normal. Which of the following is the most likely diagnosis in this patient?
   A. Bernard-Soulier syndrome.
   B. Congenital amegakaryocytic thrombocytopenia.
   C. Glanzmann thrombasthenia.
   D. *MYH9*-related diseases.
   E. Wiskott-Aldrich syndrome.

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