ITP in Children: Pathophysiology and Current Treatment Approaches

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Summary: Primary immune thrombocytopenia (ITP) is one of the most common bleeding disorders of childhood. In most cases, it presents with sudden widespread bruising and petechiae in an otherwise well child. Thought to be mainly a disorder of antibody-mediated platelet destruction, ITP can be self-limited or develop into a chronic condition. In this review, we discuss current concepts of the pathophysiology and treatment approaches to pediatric ITP.

Key Words: thrombocytopenia, ITP, hematology, splenectomy

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CASE VIGNETTE

A 3-year-old child presented with easy bruising for 1 week. Aside from a viral upper respiratory infection 2 weeks before, her past medical history was unremarkable and she was otherwise well. There were no fevers, weight loss, pain, or changes in appetite or bowel/bladder habits. On examination, the child was covered with petechiae and purpurae in a generalized, nontraumatic distribution. She did not have lymphadenopathy, hepatosplenomegaly, or congenital deformities. A complete blood count and manual peripheral blood smear (Fig. 1A) showed profound thrombocytopenia (platelet count of 6000/μL) but was otherwise normal. Serum uric acid and lactate dehydrogenase were normal and Coombs testing was negative. We interpreted her history, physical examination, and laboratory studies to be most consistent with primary autoimmune thrombocytopenia (ITP). With an Rh-positive serotype, she was treated with 250 U/kg WinRho [Rh_o(D) intravenous immune globulin]. The infusion was well-tolerated and she was discharged after a period of observation. The child had a robust response to WinRho, with her platelet count increasing to 275,000/μL 1 week after the infusion. The platelet count dropped again (17,000/μL) 2 weeks later, and WinRho was readministered. The platelet response was less robust, peaking only to 57,000/μL and lasting only 2 weeks. She was treated with intravenous immunoglobulin (IVIg; 1 g/kg). Similar to WinRho, IVIg promoted only a modest "bump" in the platelet count (to 54,000/μL) and lasted only 2 weeks. The child was soon symptomatic again with widespread bruising and petechiae. With marginal responses to both WinRho and IVIg, it was decided to examine the bone marrow to ensure that underlying aplasia, leukemia, or other marrow pathology was not contributing to her thrombocytopenia. Bone marrow biopsy (Fig. 1B) and aspirate (Figs. 1C, D) showed normal cellularity (80% to 90%) and trilineage hematopoeisis with adequate numbers of megakaryocytes. Corresponding flow cytometry and cytogenetics were normal and screening tests for lupus and bone marrow failure syndromes (eg, Fanconi anemia, paroxysmal nocturnal hemoglobinuria) were negative. Confident in the diagnosis of immune thrombocytopenia (ITP), we prescribed a course of prednisone (2 mg/kg/d). The platelet count gradually increased to 72,000/μL after 10 days and we attempted to wean her dose to 1 mg/kg/d. The platelet count a week later was 3000/μL, thus the prednisone dose was raised again to 2 mg/kg/d. Unfortunately, the platelet count did not exceed 10,000/μL during the next 3 weeks of prednisone (2 mg/kg/d). Steroids were weaned, and the child was treated with rituximab (250 mg/m^2/wk for 4 consecutive weeks). The platelet count failed to rise > 14,000/μL for the following 2½ months despite intermittent dosing with WinRho. A repeat marrow examination was unremarkable. We prescribed immunosuppressive therapy with oral sirolimus and the patient's platelet count remained low (between 3000 and 13,000/μL) for the next 2 months. When her platelet count was found to be 0/μL, a dose of WinRho was given on top of sirolimus, and her platelet count rose unexpectedly to 106,000/μL, 5 days after the WinRho infusion and still on sirolimus. She maintained robust responses to WinRho administered every 3 weeks or so while on sirolimus. Roughly 5 months into sirolimus therapy and approximately 45 weeks after her initial presentation, her platelet count normalized. The child was treated with WinRho only twice more, each time with robust platelet responses. We gradually weaned the sirolimus, and she discontinued all ITP therapy 94 weeks after initial presentation. At the time of this writing, she is now approximately 1 year removed from her last dose of sirolimus and is clinically well. A graphical representation of her clinical course is included (Fig. 2).

PRIMARY IMMUNE THROMBOCYTOPENIA (ITP)

Thrombocytopenia caused by the production of autoantibodies directed against platelets is known as primary immune thrombocytopenia (ITP), previously termed idiopathic thrombocytopenic purpurae. ITP is defined as isolated thrombocytopenia (< 100,000 platelets/μL) in the absence of conditions known to reduce platelet count (Table 1). The pathophysiological basis for ITP is a misdirected humoral antibody response targeted against platelets resulting in a markedly shortened life span for platelets in circulation. Instead of lasting for 8 to 10 days,

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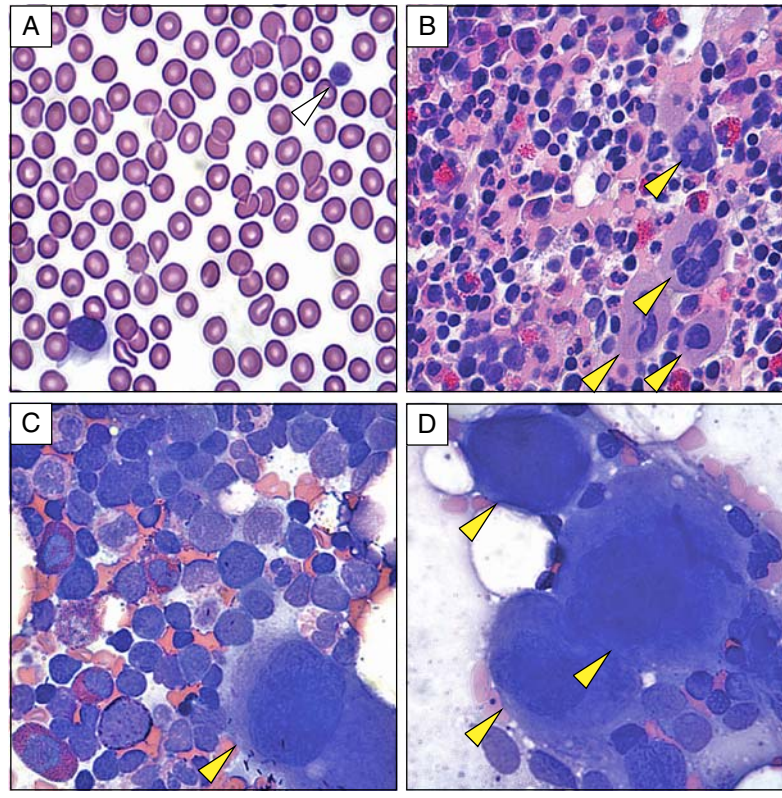

FIGURE 1. Representative hematologic images from the patient described in the clinical vignette. Shown are the peripheral blood smear (A), core bone marrow (BM) biopsy (B), and BM aspirates (C and D) from the patient 5 weeks into her clinical course. Note the paucity of platelets (white triangle in A) in the peripheral blood but adequate numbers of megakaryocytes (yellow triangles in B, C, and D) in a marrow of adequate cellularity and heterogeneity, consistent with peripheral destruction of mature platelets. All images are 400× magnification.

circulating platelets persist only for a few hours in patients with ITP because they are rapidly cleared once coated with antibody.[6] Interference with production of platelets may also occur in ITP through suppression of megakaryocyte production in the marrow,[7] therefore, ITP is a mixed disorder of destruction and production. As new platelet

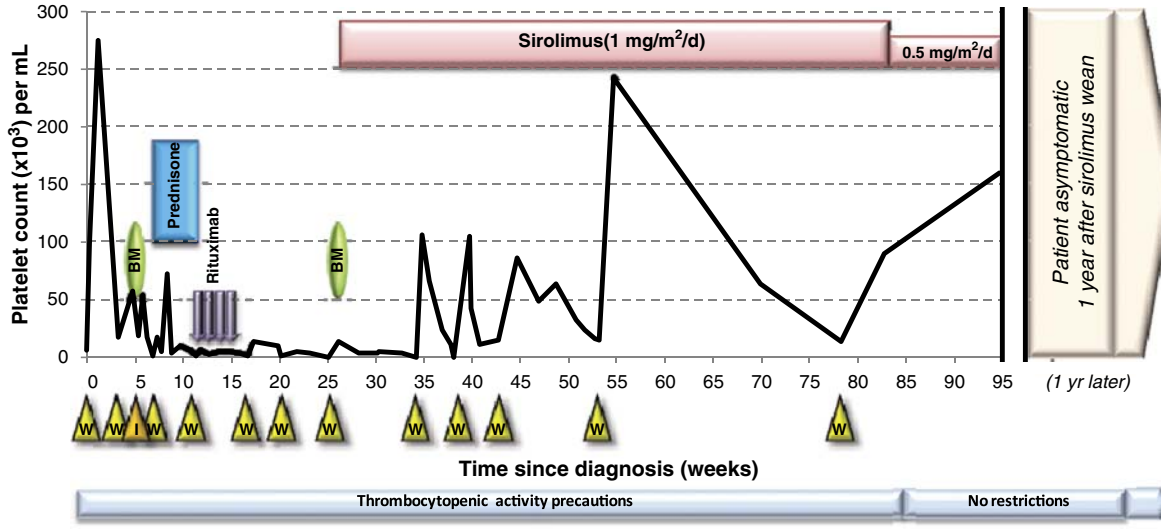

FIGURE 2. Clinical course of the patient in the vignette, shown as platelet count versus time since initial presentation with thrombocytopenia. Shown are various diagnostic and therapeutic interventions: bone marrow examination (BM), prednisone (2 mg/kg/d with taper), WinRho (W) (250 U/kg/dose) intravenous immunoglobulin (IVIg; 1 g/kg/dose), rituximab (250 U/kg/wk ×4 consecutive weeks).

TABLE 1. Differential Diagnosis of Thrombocytopenia in Children

Pseudothrombocytopenia	EDTA-induced platelet clumping
Gestational/neonatal causes	Maternal preeclampsia, HELLP syndrome
	Erythroblastosis fetalis
	Maternal drug ingestion (eg, thiazides)
	Neonatal alloimmune thrombocytopenia
Congenital or inherited disorders	Thrombocytopenia absent radius syndrome
	Amegakaryocytosis/congenital thrombocytopenia
	Wiskott-Aldrich syndrome; May-Hegglin anomaly
Infectious etiologies	Sepsis
	Congenital TORCH infection (especially rubella or CMV)
	Viral infection (EBV, VZV, influenza, rubella, CMV, HIV, hepatitis viruses, others)
	Rickettsial diseases
	Toxic shock syndrome
	Tuberculosis
	Helicobacter pylori [associated with immune thrombocytopenia (ITP)]
	Histoplasmosis, toxoplasmosis
Impaired thrombopoeisis (marrow failure)	Aplastic anemia
	Fanconi anemia
	Megakaryocytic aplasia
	Paroxysmal nocturnal hematuria
	Myelofibrosis
	Myelodysplastic syndromes
	Osteopetrosis
	Thrombocytopenia absent radius syndrome
	Wiskott-Aldrich syndrome
	Ionizing radiation exposure
	Cyclic thrombocytopenia
	Poststem cell transplantation
Giant platelet disorders	May-Hegglin anomaly
	Bernard-Soulier syndrome
Malignancy	Leukemias
	Lymphoproliferative disorders
	Myelophthisis (marrow infiltration)
Platelet sequestration	Hypersplenism (eg, lysosomal storage diseases)
	Sarcoidosis
Medication-induced	Chemotherapy-induced marrow suppression
	Heparin-induced thrombocytopenia
	Drug-induced ITP—valproic acid, chloramphenicol, quinidine, sulfonamides, indomethacin, thiazides, rifampin, estrogens, others
Nutritional (folic acid deficiency vitamin B_{12} deficiency)	Inadequate dietary intake
	Bacterial overgrowth
	Surgical resection of stomach or small bowel
	Short gut syndrome
	Crohn disease
	Pernicious anemia
Consumptive processes	Kassabach-Merritt syndrome (giant cavernous hemangioma)
	Disseminated intravascular coagulation
	Thrombotic thrombocytopenic purpurae (TTP)
	Hemolytic uremic syndrome
	Vasculitis
	Hemophagocytic syndromes
	Envenomation—snake bite, spider bite, scorpion sting, etc.
	Severe burn ($\geq$ 10% body surface area)
	Type 2B von Willebrand disease (mutant VWF with increased affinity for platelet glycoprotein Ib)
	Abnormal blood flow/shear (catheterization, prostheses, artificial valves)
	Purpura fulminans
Dilutional	Extracorporeal circulation
	Massive red cell transfusion
	Hemodialysis
Collagen Vascular disorders	Systemic lupus erythematosus
	Antiphospholipid syndrome
	Rheumatoid arthritis
Immune-mediated	Neonatal alloimmune thrombocytopenia
	Maternal ITP with trans-placental transfer of antiplatelet IgG to fetus
	Primary auto-ITP: acute or chronic
	Evans syndrome (concomitant ITP and autoimmune hemolytic anemia or autoimmune neutropenia)
	Post-transfusion purpurae
	Post-vaccination (especially MMR)
	Common variable immune deficiency
Other	Transfusion related
	Liver failure, thrombopoeitin deficiency
	Alport syndrome
	Hyperthermia, hypothermia

For primary ITP to be diagnosed, disorders known to be associated with secondary thrombocytopenia must first be reasonably excluded. Please note that this is an incomplete list and although diseases have been organized into broad categories, many can lower platelet count by $\geq$ 1 mechanism.[1–5]

CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; EDTA, ethylenediaminetetraacetic acid; HELLP, hemolysis, elevated Liver enzymes and low platelet count; HIV, human immunodeficiency virus; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus-2; VZV, varicella zoster virus.

production cannot keep pace with peripheral clearance, total number of circulating platelets drops and symptoms of thrombocytopenia ensue. Circulating platelets in ITP patients, although few in number, tend to be particularly effective at hemostasis, perhaps because most will have been recently released from the marrow and are fresh, large, and granular. As a result, ITP patients are far less likely to have serious bleeding than patients with similarly low platelet counts caused by other processes such as marrow failure. ITP can be diagnosed only when other causes of thrombocytopenias have been considered and reasonably excluded (Table 1). The marrow is typically normal in ITP,[8] reinforcing the concept that ITP is primarily a process of premature platelet destruction rather than one of insufficient or impaired platelet production. The American Society of Hematology suggests, however, that a bone marrow examination is not routinely indicated to establish the

diagnosis of ITP.[1] Likewise, testing for antiplatelet antibodies is not routinely helpful in diagnosing ITP.[1]

INCIDENCE

The peak age of diagnosis for childhood ITP is between 2 and 6 years of life and ITP affects roughly 1 in every 10,000 children.[9,10] Incidence in boys and girls is roughly the same.[11] Many patients give a history of a preceding viral infection within a few weeks of presenting with thrombocytopenia, raising the possibility that the aberrant autoimmune response of ITP may be triggered by infection. Indeed, seasonal fluctuation in ITP incidence has been described, highest in the spring and lowest in the autumn, perhaps reflecting seasonal variation in viral illnesses.[12] ITP is highly unusual below a year of life, probably due to the immaturity of the immune system in the very young patient. Neonatal immune-mediated thrombocytopenia is almost always due to maternally derived antibody either because of maternal ITP or because of neonatal alloimmune thrombocytopenia, an alloimmune maternal humoral response against "foreign" paternally-derived antigens on platelets.[13,14]

PRESENTATION AND WORK-UP

The typical presentation of ITP in children is acute widespread appearance of petechiae and purpurae most prominent on extensor surfaces of the skin and at sites where pressure was placed on an extremity, for example at sites of blood pressure measurement. Typically, the child will be completely well one day and then covered with petechiae and purpurae the next. It is not uncommon for patients to be referred because of suspicion of nonaccidental trauma (child abuse). In general, however, children with ITP appear well otherwise and usually are playful and interactive. Although some patients have "wet purpurae" inside the mouth, epistaxis or overt bleeding occurs in less than a third of patients.[11] ITP is a clinical diagnosis without a specific confirmatory test. To diagnose ITP, conditions known to be associated with thrombocytopenia must first be reasonably excluded (Table 1). A careful history and physical examination are mandatory. Constitutional symptoms (fever, weight loss), pallor, pain, lymphadenopathy, hepatosplenomegaly, or jaundice suggest diagnoses other than ITP.

Suggested aspects of the diagnostic work-up for ITP are shown in Table 2. Children with ITP generally have a completely normal complete blood count except for thrombocytopenia. The peripheral blood platelet count will typically be $< 100 \times 10^9$/L but in practice is often much lower at presentation. In 1 study, the platelet count in newly diagnosed children with ITP was found to be $< 20{,}000/\mu L$ in over 75% of cases.[20,21] Ironically, profound thrombocytopenia is actually reassuring as it points toward uncomplicated ITP rather than more serious diagnoses such as leukemia or bone marrow failure that usually feature more moderate platelet counts (40,000 to 90,000/μL). Serum lactate dehydrogenase and uric acid, if sent, are usually normal in ITP and may help allay concerns about leukemia or other lymphoproliferative diseases. The American Society of Hematology and several studies suggest that bone marrow examination is unnecessary for most children who present with classic features of ITP.[1,22–25] However, when atypical historical, physical, or laboratory features exist, then bone marrow examination is helpful to

TABLE 2. Diagnostic Work-Up of Immune Thrombocytopenia in Children

Patient history	Childhood ITP normally presents as abrupt onset of widespread bruising and petechiae
	Epistaxis and oral mucosal bleeding (gingivorrhea) occur in less than one third of patients
	Hematuria, hematemesis, hematochezia, or melena occur in $< 10\%$ of patients
	Symptoms of anemia (pallor, weakness, dizziness, etc.) or neutropenia (fevers, infections, etc.) are not typical in uncomplicated ITP
	Constitutional symptoms such as weight loss or unexplained fevers may indicate more sinister diagnoses such as cancer or systemic lupus erythematosus
Family history	ITP is normally a sporadic condition
	Family history of thrombocytopenia suggests inherited thrombocytopenia
Physical examination	Typical pediatric patients with ITP present with widespread cutaneous ecchymosis and petechiae
	As the presentation of ITP is normally acute, the bruises typically all are "fresh" rather than in various states of resolution
	In general, the pattern of bruising in ITP usually mimics that comes from activities of normal childhood (thus mainly on the extensor surfaces, especially, pretibial)
	Bruising on the face/head, buttocks, flexor surfaces of extremities, or specific patterns of bruising may indicate nonaccidental trauma
	Mucosal petechiae (gums or soft/hard palate) suggest more "symptomatic" thrombocytopenia and may warrant a more aggressive approach to treatment (in lieu of observation only)
	Unusual lymphadenopathy or organomegaly suggest a proliferative process (eg, acute leukemia) rather than ITP
	Forearm abnormalities or congenital deformities may indicate inherited conditions such as thrombocytopenia absent radius syndrome and warrant further investigation
	The height and weight should always be plotted out. Short stature may indicate an inherited marrow failure syndrome (eg, Fanconi anemia)
Complete blood count	ITP is almost always associated with isolated thrombocytopenia. Thus, the total white blood cell (WBC) count, WBC differential, absolute neutrophil count, hemoglobin, hematocrit, and red cell indices should be otherwise normal for age
	If other cytopenias exist, consider bone marrow failure syndromes and leukemias
	A slight anemia may be present if significant bleeding (eg, epistaxis) accompanied the presentation of ITP
	Significant anemia may reflect concomitant autoimmune hemolytic anemia (which would imply a diagnosis of Evans syndrome rather than uncomplicated ITP)
	The mean platelet volume is usually high normal or elevated in ITP (> 8 fL). If low, then other diagnoses (eg, Wiskott-Aldrich syndrome) should be considered

TABLE 2. (*continued*)

	Significant red cell macrocytosis may reflect stressed hematopoiesis (such as might occur in bone marrow failure) or indicate reticulocytosis (as might occur in Evans syndrome)
Reticulocyte count	The reticulocyte count should be normal in ITP
	If elevated, this may suggest a more widespread immune-mediated hematologic process (eg, Evans syndrome) or may simply reflect a compensatory marrow response to clinically significant bleeding caused by thrombocytopenia
Manual review of peripheral blood smear	Manual review of the peripheral blood smear should be performed for every new patient with ITP
	The peripheral blood smear in ITP will be notable for profound isolated thrombocytopenia (typically with ≤ 1 platelets found per high-power field)
	Besides thrombocytopenia, the peripheral blood smear should be normal
	Platelets that are found may appear large and with robust complexity/granularity
	The presence of red or white cell abnormalities (eg, schistocytes, nucleated red cells, neutropenia, blast forms) suggests diagnoses other than uncomplicated ITP and warrant further investigation
Blood typing	This is carried out to assess the patient's suitability for anti-D (WinRho) treatment. Only patients who are Rh + are eligible for WinRho therapy
Coombs (direct antiglobulin) testing	If positive, then a concomitant autoimmune hemolytic anemia may be at play and a diagnosis of Evans syndrome can be entertained
	WinRho should not be given to patients with evidence of autoimmune hemolytic anemia lest profound hemolysis result
Lactate dehydrogenase, uric acid	Serum lactate dehydrogenase and uric acid are typically normal in cases of ITP
	If either or both are elevated, then proliferative conditions (such as acute leukemia) should be ruled out (eg, by marrow examination)
Electrolytes, blood urea nitrogen, and creatinine	ITP is usually not associated with electrolyte or renal abnormalities
	Abnormalities warrant consideration of other diagnoses (eg, hemolytic uremia syndrome)
Diagnostic components/ tests that may be helpful but not always necessary	Bone marrow examination is generally not needed to make the diagnosis of ITP, but should be performed if atypical symptoms, signs, or laboratory features are present to rule out marrow failure syndromes, myelodysplastic syndromes, and leukemias. Many hematologists routinely perform confirmatory bone marrow examinations before starting patients on glucocorticoids to avoid partially treating undiagnosed acute lymphoblastic leukemia
	Antiplatelet antibodies. Although ITP is a humoral disease caused by antibodies directed against platelets and/or their precursors, testing for antiplatelet antibodies is generally not helpful in diagnosis. Antiplatelet antibody testing is notoriously nonspecific and insensitive
	Liver function studies: hepatic transaminases and bilirubin are normal in uncomplicated ITP
	Helicobacter pylori testing: active *H. pylori* infection has been associated with some cases of ITP in adults. In general, *H. pylori* testing is not recommended for most children who present with ITP
	Human immunodeficiency virus (HIV) testing: ITP can be part of the protean ways in which HIV infection can present. In general, HIV testing is not recommended for most children who present with ITP
	Antinuclear antibody: ITP can herald various autoimmune diseases such as lupus
	Peripheral blood flow cytometry can help detect clonal disorders such as leukemias
	Urinalysis: helpful to rule out occult hematuria. If urinalysis is positive for red blood cells or hemoglobin, consider systemic lupus erythematosus or Evans syndrome in the differential
	Quantitative Immunoglobulin testing. ITP can be part of immunodeficiency syndromes such as common variable immune deficiency

There is no "gold standard" test that could be used to diagnose ITP in children; ITP remains a diagnosis of exclusion. Most cases of ITP can be identified correctly based on history, physical findings, and targeted laboratory studies. In general, if the history, physical examination, and complete blood count are consistent with acute ITP, then the more esoteric studies may be excluded from the initial work-up and be reserved for cases of chronic or refractory thrombocytopenia or if the patient presents with atypical features.[1,4,15–19]

exclude other diagnoses, particularly leukemia and aplastic anemia. In practice, many pediatric hematologists elect to perform a bone marrow examination if a patient's thrombocytopenia is treatment-refractory or before starting glucocorticoids.

CLINICAL VARIANTS

ITP can be classified according to how long symptoms have persisted. Thus, ITP is referred to as "newly diagnosed" within 3 months of initial diagnosis, "persistent" from 3 to 12 months after diagnosis, and "chronic" if it persists beyond 12 months.[26,27]

Persistent or chronic ITP can manifest as a stuttering course of thrombocytopenia of variable severity or can simply be ITP that presented acutely but that has persisted over time. There is no way of knowing at diagnosis which clinical course a patient's ITP will take, however, patient age can be predictive. ITP affecting young children is more likely to be acute and resolving, whereas ITP in older children and adolescents has a higher risk of becoming chronic, similar to ITP in adults.[28–30] Insidious onset of symptoms or secondary ITP in association with other autoimmune disorders (such as collagen vascular disease) may also predict a chronic course.[31] Nonetheless, platelet counts will return to normal within 2 months of diagnosis in about half of children and within 3 months for almost two thirds.[32] Of those whose ITP persists for 6 months, up to a quarter will have normalization of their platelet within the next 6 months[20] and many will eventually resolve

beyond then with or without anti-immune–directed therapy.[33]

PATHOPHYSIOLOGY

A groundbreaking experiment performed in 1950 proved beyond doubt that ITP is a humoral disease associated with premature destruction of circulating platelets. In a clinical trial that could never be carried out today, Drs William Harrington and James Hollingsworth, 2 medical hematology fellows in St Louis, injected healthy subjects (including Harrington himself) with plasma derived from patients suffering from ITP. In each of 35 separate trials, plasma from patients with ITP (but not from normal controls) profoundly lowered the recipient's circulating platelet count within 30 to 60 minutes with persistence for up to 7 days. To be sure the humoral factor responsible for ITP caused destruction of platelets rather than inhibition of their formation, recipients also underwent bone marrow examinations—in each case no abnormalities in either the number or appearance of megakaryocytes was found.[34,35] We now know that the circulating factor responsible for ITP is IgG that binds platelets and leads to their premature destruction.[36] Platelet antigens recognized in ITP include membrane glycoproteins Ia/IIa, IIIa, Ib, IIb, and IX.[37–39] Regardless of the antigen targeted, binding of IgG to the platelets encourages opsonization and phagocytosis by reticuolendothelial cells primarily in the spleen. As a result, the life span of circulating platelets, normally 8 to 10 days, is profoundly reduced to a matter of a few hours.[35] Thus, ITP clearly is associated with premature clearance of platelets in the periphery. Recent evidence suggests that platelet underproduction may also contribute to ITP. Autoantibodies may bind megakaryocytes in the marrow and interfere with their survival or differentiation.[7,40] In addition, there is evidence that ITP is associated with impaired hepatic production of thrombopoeitin, the chief stimulant of megakaryocyte proliferation and platelet production.[41] This basic understanding of the various underlying mechanisms of disease at play in ITP explains our current treatment approaches to ITP: (1) interference with antibody production; (2) inhibition of F_c receptor-mediated opsonization by splenic macrophages; (3) immunosuppression; and (4) stimulation of thrombopoeisis in the marrow.

PSYCHOSOCIAL IMPACT OF THE DISEASE

The psychosocial burdens of ITP on patients and their families can be significant, especially when ITP is long-lasting. Parental concerns over serious bleeding, frequent blood testing, infusions, activity restrictions, and medication side effects are major stressors that accompany the diagnosis. Prolonged restriction of normal activities of childhood can have significant impact study by Klaassen et al[42] found that treating ITP patients with romiplostim, a thrombopoeitin agonist, significantly reduced parental psychological burden, presumably because parents were less stressed about potential bleeding in their children after platelet counts were raised. In 1 analysis of over 1000 adult ITP patients and over 1000 non-ITP controls, ITP patients scored significantly worse on a variety of lifestyle measures, including 7 of 8 SF (short form)-36 quality of life assessment domains, the Physical and Mental Summary score, and the EQ (EuroQol)-5D visual analog scale.[43] Another study found that the health-related quality of life in ITP patients was even worse than patients with cancer.[44] Therefore, although ITP can be considered to be a "benign" hematologic disorder, it is associated with significant psychological stress. To provide the most comprehensive care to children with ITP and their families, it is critical to explore the psychosocial impacts of the diagnosis on patients and their families.

THROMBOCYTOPENIC ACTIVITY PRECAUTIONS

One of the most challenging aspects to the management of a child with ITP is restricting participation in normal play and sports activities because of concerns over bleeding risk. Incidence of severe hemorrhage is actually rare in uncomplicated childhood ITP, and few internal bleeds occur unless a significant trauma or injury occurs while the patient is severely thrombocytopenic.[45] Intracranial hemorrhage occurs in only 1 in a thousand children diagnosed with ITP.[12] Nonetheless, many practitioners feel that a "common sense" approach should be adopted with regard to physical activities during periods of thrombocytopenia. In cases where the ITP persists for many weeks or months, activity limitations must be balanced with an appreciation of the many consequences of "sheltering" a child with chronic ITP, including deconditioning, weight gain, and sick child syndrome. There is great variation in how patients with ITP are counseled with respect to activity limitations. Some pediatric hematologists take the view that almost any supervised sports activity (with the possible exception of boxing) can be undertaken safely as long as proper precautions are taken (eg, wearing a helmet when batting or bicycling) and as long as the patient and parents clearly understand the risks of taking part in such activities. Other clinicians advise against participation in any activity associated with a significant risk of trauma (especially head injury) when platelet counts fall below 50,000 to 75,000/μL. For toddlers and preschool children, this might mean avoiding stairs and other climbing structures such as playground equipment or sleeping on the top bunk bed, etc.). For older children and adolescents, thrombocytopenia restrictions often involve avoiding certain sports and leisure activities (Table 3). Regardless of approach, medications that inhibit platelet function, most notably nonsteroidal anti-inflammatory drugs and aspirin, should be avoided while patients are thrombocytopenic.

THERAPEUTIC INTERVENTIONS

The ITP working group of the American Society of Hematology recently published updated evidenced-based practice guideline for the management of ITP. Regarding children, the committee suggested that observation alone is appropriate for pediatric ITP patients with skin manifestations (bruising and petechiae) only and no other bleeding, regardless of platelet count.[1] Recent data indicate that this "watch and wait" approach may be used in as many as 20% of children with ITP.[49] In practice, however, most hematologists and families opt to treat children with ITP, especially in the setting of a platelet count $< 10{,}000/\mu L$ or with active clinical bleeding (eg, epistaxis, menorrhagia, gingivorrhea).[50] Raising the platelet count reduces theoretical risk of serious bleeding, but importantly allows liberalization of physical activities and greatly relieves parental anxiety. Notably, neither platelet transfusions nor plasmapheresis have proven useful for treating ITP (except in situations of life-threatening or limb-threatening bleeds)

TABLE 3. Profile of Physical Activities and Their Risk of Trauma to Participants

Full contact sports	Physical activities in which either deliberate or incidental significant physical impact between or on participants is allowed for within the rules of the game and therefore can be expected to occur Most care providers would advise that thrombocytopenic patients avoid such activities	American football All-terrain vehicle or motorcycle racing Boxing Diving (competitive or high) Extreme sports Hang gliding or sky diving Hockey (either ice, field, or street) Horseback riding Kickboxing Lacrosse Martial arts, karate, tae kwondo Rock climbing Rugby Water polo Wrestling
Limited-contact sports	Activities in which the rules are specifically designed to prevent intentional or unintentional contact between participants, however, significant contact between players or between a player and sporting equipment can still occur during participation Many care providers would advise that their thrombocytopenic patients take precautions or abstain from participation to minimize risk of trauma and head injury	Baseball Basketball Cheerleading Cycling Dancing Gymnastics Racquetball Rollerblading Running Skiing Snowboarding Soccer Softball Squash Surfing Ultimate frisbee
Noncontact sports	Sports that limit the chances for trauma by separating participants Such activities include and are usually deemed as safe for thrombocytopenic patients	Aerobics Bowling Cricket Curling Golf Jogging Rowing Running Swimming Tennis Volleyball Walking Yoga

Physical activities can be divided into 3 groups based on the degree of interpersonal contact and/or risk of trauma involved. In general, thrombocytopenic patients should probably avoid those activities with significant risk of trauma.[18,46–48]

as transfused platelets are usually rapidly cleared from the circulation and autoantibodies rapidly reappear in the serum after plasmapheresis.[51–53]

MEDICAL MANAGEMENT

In general, therapy for children with chronic ITP tends to be individualized according to a variety of factors including efficacy, scheduling, toxicity, cost, and preferences of the patient, parents, and hematologist. Therapeutic interventions for ITP can be conceptualized as "front-line" or "second-line" approaches (Table 4). Each patient's ITP course is unique, and once therapy has begun, platelet counts are generally monitored overtime to assess response. Therapeutic response criteria have been standardized (Table 5). For some patients, only 1 treatment will be required before their ITP resolves, whereas for others (like our patient), repeated treatments may be needed over time. Presumably, the severity and course of thrombocytopenia will be determined by the strength and longevity of the antiplatelet immune response. In practice, practitioners must be somewhat flexible in their approach, and may turn from one therapy to another to optimize treatment for their particular patient. If platelets do not increase after an intervention, then either further therapy may be required (eg, a second dose of IVIg), or the diagnosis of ITP should be reevaluated. For the typical child who presents with acute ITP, front-line management includes IVIg, a short course of corticosteroids or WinRho (Anti-D) therapy in Rh-positive nonanemic children.[1] Each of these approaches interferes with antibody-mediated clearance of platelets, and most patients will respond to any of these treatments within days of administration. Although the infusion therapies (WinRho or IVIg) are more expensive, these are generally the preferred initial approach because of toxicity of glucocorticoids and theoretical concerns over partially treating unrecognized acute lymphoblastic leukemia.[25] Response to WinRho or IVIg can also help confirm the diagnosis of ITP. Antibody-based approaches such as IVIg or WinRho have a typical therapeutic window of roughly 3 weeks, coinciding with the normal half-life of IgG. The need for additional doses of IVIg or WinRho will be dictated by platelet count and how well the patient tolerated prior treatments. It should be noted that in 2010, the Food and Drug Administration issued a black box warning regarding WinRho and the potential for significant intravascular hemolysis and resultant severe anemia and multisystem organ failure. Risk seems highest in patients with preexisting hemolysis (eg, Evans syndrome), therefore screening with Coombs testing or reticulocyte count before WinRho administration seems reasonable. However, many children have been successfully treated with WinRho and severe hemolysis is a very rare adverse event.[54] Current guidelines for WinRho administration call for close monitoring of patients for at least 8 hours after infusion, with dipstick urinalysis checks for hematuria and hemoglobinuria. Glucocorticoids, the third recommended front-line therapy have long been used for ITP,[55] and platelet counts usually respond well to oral or intravenous steroids. Typically, steroids are prescribed at higher doses initially and then weaned as tolerated. Length of steroid therapy is typically for 1 to 2 weeks, but duration is often determined by platelet response. If steroids must be used chronically, then efforts should be made to find the lowest therapeutic dose to minimize toxicity.

Similar to acute ITP, children with chronic ITP may not require therapy in the absence of bleeding symptoms. However, in practice, being able to maintain a child's platelet count $>40{,}000$ to $50{,}000/\mu L$ allows significant liberalization of the patient's activities. It is estimated that $<10\%$ of

TABLE 4. Management Options for Immune Thrombocytopenia

Treatment	Dose	Mechanism of Action	Clinical Response	Toxicities
Front-line therapies				
Observation only with thrombocytopenic precautions	N/A	N/A	Symptoms and platelet counts can be expected to resolve spontaneously in most children within weeks to months	Persistence of symptoms (petechiae, purpurae, mucocutaneous bleeding)
Intravenous immunoglobulin (IVIg)	0.8-1 g/kg, IV over 4-6 h, may repeat dose if no response, consider premedication with diphenhydramine and acetaminophen	Antibody excess and F_c receptor competition F_c receptor downregulation on reticuolendothelial cells	Platelet count typically begins to rise in as little as 24 h Peak responses within a week Effect typically lasts roughly 3 wk	Headaches, abdominal pain not infrequent (leading to radiologic imaging) Fever Nausea/vomiting Infusion-related chills Hypersensitivity Anaphylaxis (particularly in IgA-deficient patients) Theoretical risk of infectious exposure (pooled plasma product)
WinRho (anti-D) (only for use in Rh + patients)	250 U/kg (50-75 μg/kg), IV over 30 min (with postinfusion monitoring (8 h) for hemolysis)	Induction of subclinical immune-mediated hemolytic anemia and F_c receptor competition F_c receptor downregulation on reticuolendothelial cells	Platelet count typically rich in 24-48 h Peak responses within a week Effect typically lasts roughly 3 wk	Headaches Fever, chills, Nausea/vomiting myalgia Risk of intravascular hemolysis, renal failure, multiorgan failure Do not use in patients with concurrent autoimmune hemolytic anemia, Evans syndrome or anemia
Glucocorticoids	Predinisone 1-2 mg/kg/d divided into bid dosing for at least 1-2 wk, followed by slow tapering wean High-dose dexamethasone pulses (20 mg/m^2/d in children or 40 mg/d in adults for 4 sequential days every 28 d typically through 6 cycles total) may be used for chronic or refractory immune thrombocytopenia (ITP)	Immunosuppressive; interference with antibody production impairment of antibody-coated platelet clearance by macrophages impairment of splenic function	Many clinicians prefer to perform a bone marrow aspirate before start of steroid therapy due to steroids efficacy in suppressing leukemic cells, and potentially masking a leukemia presenting with an isolated thrombocytopenia	Hypertension Mood disturbances Hyperphagia Weight gain, Cushingoid habitus Insulin resistance, hyperglycemia Osteoporosis Cataracts Cutaneous striae
Second-line approaches				
Observation only with thrombocytopenic precautions	N/A	N/A	Once ITP has persisted for 6-12 mo, it is likely to continue for some time	Prolonged activity restriction Persistence of symptoms (petechiae, purpurae, mucocutaneous bleeding)
Rituximab (anti-CD20)	Weekly infusional therapy (375 mg/m^2) for 4 consecutive weeks	Chimeric monoclonal antibody that targets mature B cells that manufacture immunoglobulin Goal is to eradicate the plasma cell clone making antiplatelet antibody.	Variable responsiveness Often a very delayed effect (weeks to months)	Hypersensitivity reactions Infusion reactions Hepatitis B reactivation Progressive multifocal leukoencephalopathy Pulmonary toxicity

TABLE 4. (*continued*)

Treatment	Dose	Mechanism of Action	Clinical Response	Toxicities
		Good second-line treatment of refractory or chronic ITP		
Other agents	Immunosuppressive agents (tacrolimus, sirolimus, cyclosporine) Chemotherapy (cyclophosphamide, mercaptopurine, vincristine, others) Thrombopoeitin agonists (eltrombopag, romiplostim)	Immunosuppression or stimulation of marrow platelet production	Variable responses Thrombopoeitin agonists being tested in children	See individual agent toxicities
Splenectomy	Complete removal of the spleen, usually with antecedent medical therapy to raise the platelet count preoperatively	Surgical removal of the organ responsible for the majority of clearance of antibody-bound platelets in ITP	Usually associated with rapid platelet increases Splenectomy restores adequate platelet counts in the majority of patients Relapses of thrombocytopenia possible after splenectomy in some patients	Chronic risk of infection (particularly encapsulated bacteria such as *Pneumococcus*, *Neisseria*, and *Haemophilus* (immunization, prophylactic antibiotics, fever management all critical) Chronic risk of thrombosis and pulmonary embolism

Front-line and second-line approaches are described.[1]

children with ITP will require regular platelet-enhancing therapy 1 year after diagnosis.[56] For those children whose ITP endures for many months or is refractory to treatment (like our patient), ITP truly becomes a nuisance. Regular clinic visits, frequent venipuncture, and continual activity restrictions interfere with family dynamics and with normal growth and development. If a patient's history, physical findings, and laboratory studies clearly have been consistent with ITP since diagnosis, and s/he has had robust increases in the peripheral blood platelet count with each antibody-based or steroid therapy, then his/her continued thrombocytopenia most likely represents chronic ITP. If, however, there are other features that call the diagnosis of ITP into question, then a bone marrow examination should be considered to rule out disorders of impaired marrow production.[57]

TABLE 5. Immune Thrombocytopenia Treatment Responses, as Defined by the International Working Group[26]

Complete response	No bleeding and Platelet count $\geq 100{,}000/\mu L$ measured twice ≥ 7 d apart
Response	No bleeding and Platelet count $\geq 30{,}000/\mu L$ and ≥ 2-fold increase from baseline measured twice ≥ 7 d apart
No response	Continued bleeding and/or Platelet count $< 30{,}000/\mu L$ or < 2-fold increase from baseline measured twice ≥ 1 d apart
Loss of complete response	Bleeding and/or Platelet count $< 100{,}000/\mu L$ measured twice ≥ 1 d apart in an immune thrombocytopenia (ITP) patient who previously had a complete response to therapy
Loss of response	Bleeding and/or Platelet count $< 30{,}000/\mu L$ or < 2-fold increase from baseline measured twice ≥ 1 d apart in an ITP patient who previously had a response to therapy

Various medical therapies are available to treat chronic or refractory ITP (Table 4) including rituximab (anti-CD20 therapy), immunosuppressive agents (such as the sirolimus used in our patient), chemotherapy (most notably 6-mercaptopurine), and most recently, thrombopoeitin agonists.[58] With the exception of the thrombopoeitin agonists, each of these therapies targets the wayward autoimmune response responsible for inappropriate production of antiplatelet antibodies. However, chronic immunosuppressive therapies all have significant side effects, most notably risk of severe infectious complications. The American Society of Hematology supports rituximab or high-dose dexamethasone as a preferred second-line medical approache.[1] With the development of effective noncytotoxic therapies for ITP, immunosuppressive approaches have become less popular. Rituximab, typically given as weekly infusional therapy ($375\ mg/m^2$) for 4 consecutive weeks, targets CD20-expressing plasma cells, the antibody-producing mature B cells that manufacture

the antibodies that perpetrate ITP. Anti-CD20 therapy, which has been used for over a decade, is generally well-tolerated with few side effects.[59–61] Although rituximab therapy can cause generalized decreases in antibody production, serious infections are rare after rituximab treatment.[62] For this reason, rituximab has emerged as a widespread therapy for chronic ITP either alone or in combination with other approaches.[63–67] However, rituximab produces durable treatment responses in only some patients, with response rates ranging from a less than a third of patients to just over three quarters of patients.[67–69] One recent large pediatric collaborative study found an association between steroid responsiveness and rituximab efficacy, with 87.5% of steroid-responsive chronic ITP patients having good therapeutic responses to rituximab.[70]

High-dose dexamethasone—typically 40 mg/d in adults (20 mg/m^2 in children) for 4 sequential days every 28 days—has been used with mixed success for chronic or refractory ITP. Although some studies reported good efficacy and low toxicity,[71,72] others found mixed responses and significant toxicity (such as hypertension with stroke or insulin-dependent diabetes).[73] More recent studies suggest that high-dose dexamethasone may be more useful as a front-line agent for ITP rather than second-line therapy[74,75] and that it may be worth trying before splenectomy in severe symptomatic chronic childhood ITP.[76,77]

Thrombopoeitin agonists are a novel class of ITP-selective drugs may decrease the need for immunosuppressive or cytotoxic therapies. Eltrombopag (an oral small molecule agonist) and romiplostim (an Fc-peptide fusion protein) both target and activate the thrombopoeitin receptor on megakaryocytes. Each serves as a positive signal to stimulate marrow production of platelets.[78] One French study of adult ITP patients found that romiplostim caused platelet counts to rise to at least 50,000/μL in 74% of patients and that long-term responses of at least 2 years were observed in 65% of patients.[79] In general, thrombopoeitin agonists seem to be well tolerated in adults, but their safety in children has not yet been established. These agents are now being studied in children with ITP.[42,78]

SURGICAL MANAGEMENT—SPLENECTOMY

Splenectomy has been recognized for nearly a century as being effective treatment for ITP.[80] As a reticuloendothelial organ rich with Fc receptor–expressing phagocytes, the spleen is the major site wherein antibody-coated (opsonized) platelets are actively removed from the circulation.[81] Thus, removal of the spleen leads to prolonged survival of opsonized platelets in the circulation. The spleen may also house plasma cells that produce antiplatelet antibodies, therefore, splenectomy may help eliminate the source of the errant autoantibodies that cause ITP. Although safer today because of better surgical (laparoscopic vs. open) and medical care, splenectomy is not without risk.[82,83] Splenectomized patients have life-long enhanced risk of thrombosis[84] and infection.[85,86] The spleen seems especially critical to the clearance of encapsulated organisms, therefore, asplenic patients are at risk of *Haemophilus*, *Neisseria*, and *Pneumococcus* sepsis[87–90] and incidence of overwhelming sepsis postsplenectomy is on the order of 1% to 2%.[91] Asplenic patients are also at heightened risk of certain protozoal infections, especially malaria and babesiosis.[92,93] As infectious risk is particularly high among very young children,[94] many practitioners defer splenectomy until a minimum of 5 years of age. Immunization against *Haemophilus influenza* type B, *Meningococcus*, and *Pneumococcus* is recommended preoperatively, and oral prophylactic antibiotic therapy (typically penicillin) is recommended postoperatively, as is appropriate sepsis evaluation for fever.[90,95] Splenectomy is definitive treatment for most children with ITP, raising their platelet counts to normal or at least to levels that support liberalization of physical activities. In one pediatric study, splenectomy resulted in significant platelet increases in 85% of patients with chronic ITP.[83] In comparison, 50% to 60% of adults with chronic ITP respond to splenectomy.[96] Nonetheless, some patients will fail to respond, and some initial responders may have recurrence of thrombocytopenia after splenectomy. In a retrospective analysis of over 400 patients with ITP, 23% of splenectomy-responsive patients relapsed, in most cases (80%) within 2 years of the procedure.[82] Some ITP relapses have correlated with the presence of accessory spleens.[97] Patients and their families must understand the unpredictable effectiveness and inherent risks of splenectomy for ITP. The American Society of Hematology suggests that splenectomy should be considered for patients with chronic or persistent ITP who have significant bleeding symptoms, intolerance of medical therapy, or the need for improved quality of life.[1]

MANAGEMENT OF SERIOUS BLEEDING

The presence of significant hemorrhage in the setting of ITP is a true medical emergency and life-threatening or limb-threatening bleeding is an indication for interventions aimed at quickly raising platelet count and achieving hemostasis. Intracranial hemorrhage, for example, carries a mortality rate of nearly 50% in ITP patients.[12,98] Medical management of serious bleeding will be dictated by clinical circumstances and may involve a variety of medical and surgical interventions tried alone or in combination. Massive or successive platelet transfusions, intravenous high-dose corticosteroids, IVIg/WinRho, and plasmapheresis have all been described.[99–101] Efforts aimed to interfere directly with splenic function may also be useful. Thus, emergency splenectomies under "cover" of serial platelet transfusion or medical therapies such as high-dose steroid or IVIg treatment have been described.[102,103] There is at least 1 case report of combination immunosuppressive therapy (cyclophosphamide, vincristine, and corticosteroids) in conjunction with frequent transfusions of platelets being used for life-threatening bleeding in a child with ITP.[104] Ligating or embolizing the splenic artery usually leads to profound increases in the circulating platelet counts, and may be performed before splenectomy to make resection of the spleen safer.[105] Fortunately, life-threatening bleeding is exceedingly rare in childhood ITP.

CONCLUSIONS

ITP is one of the most common hematologic disorders of childhood and adolescence. It is an autoimmune process characterized by the inappropriate production of antibodies directed against normal platelets and megakaryocytes. As a result of antibody binding, platelets and their precursors are destroyed, resulting in dramatic reductions in the numbers of circulating platelets. Clinically, this manifests as widespread appearance of cutaneous and mucosal petechiae and purpurae. A diagnosis of exclusion, most cases of ITP can be identified by a careful history, physical examination and

limited blood work. Although classified as a benign process, ITP can have a profound on quality of life and interfere with normal childhood. Our clinical case demonstrates the course of 1 particular patient with ITP whose disease initially responded to therapy but then became therapy-refractory and chronic. A variety of medical approaches were tested until 1 combination (sirolumus with intermittent WinRho administration) was found that maintained the platelet count at a reasonable level. This case also demonstrates the fact that ITP can resolve in children even when has persisted for a long time. The ITP working group of the American Society of Hematology suggests that front-line management for children with ITP includes IVIg, a short course of corticosteroids or WinRho (Anti-D) therapy in Rh-positive non-anemic children. Preferred second-line medical approaches are rituximab or high-dose dexamethasone. Splenectomy is a very effective therapy for most patients, but because of life-long risks of infection and thrombosis, should generally be considered only after medical interventions have proven inadequate.

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