When and how to treat childhood immune

Abstract: Childhood immune thrombocytopenia is an autoimmune process resulting in an isolated thrombocytopenia that puts the child at risk for bleeding and can negatively impact quality of life. Pharmacologic intervention aims to stabilize the platelet count, with the goal of achieving hemostasis and maximizing health-related quality of life.

By Jennifer D. Allen MSN, CPNP, CPHON

Immune thrombocytopenia (ITP) in childhood is generally a benign, self-limiting phenomenon characterized by an isolated, acquired thrombocytopenia with a platelet count less than 100,000/microliter (mcL).[1,2] Bleeding may or may not be present, but the possibility of serious bleeding can cause considerable distress for the child and family. Despite the relatively low incidence of serious bleeding events, the child with a precipitous drop in platelets must be managed appropriately to prevent hemorrhage.

Most cases resolve within the first year, though some children progress to a chronic form of ITP and require long-term intervention and follow-up. The decision to treat childhood ITP must be weighed carefully, using the most recent guidelines as a foundation, with the understanding that both treatment and observation affect the health-related quality of life (HRQoL) of the child. This article will aid the NP by reviewing the underlying mechanisms of ITP, discussing current treatment options, and reinforcing the importance of quality of life throughout management.

ITP is relatively rare, occurring in only 3 to 8 of every 100,000 children each year.[3] It has a peak incidence in children ages 4 to 6 and generally affects both genders equally.[4] It is categorized as primary or secondary and further categorized by its duration. Each category and stage of ITP necessitates a distinct approach to intervention (see *Standard categories and definitions of ITP*).

Pathophysiology

The recent name change from idiopathic to immune thrombocytopenia is linked to the realization that the body's loss of self-tolerance shortens the normal life span of circulating platelets to mere hours.[4] The exact mechanism for loss of self-tolerance and autoantibody production is not fully understood; however, the subsequent autoimmune reaction can be linked to an antecedent of preceding illness in 72% of newly diagnosed cases.[5] In the setting of a viral illness, antigen-presenting cells (APCs) confuse the viral epitope with that of the platelet epitope.[6]

An APC then presents the platelet antigen to B and T cells, triggering the autoimmune reaction and producing antibodies cross-reactive to platelets. Once the body recovers from the illness, the cross-reactive antibodies are generally cleared, leading to an increase in platelet counts.[6] In cases of persistent or chronic ITP, the cross-reactive antibodies remain, leading to prolonged thrombocytopenia that is often more difficult to manage.

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Keywords: health-related quality of life, immune thrombocytopenia, ITP, TPO receptor agonists

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thrombocytopenia

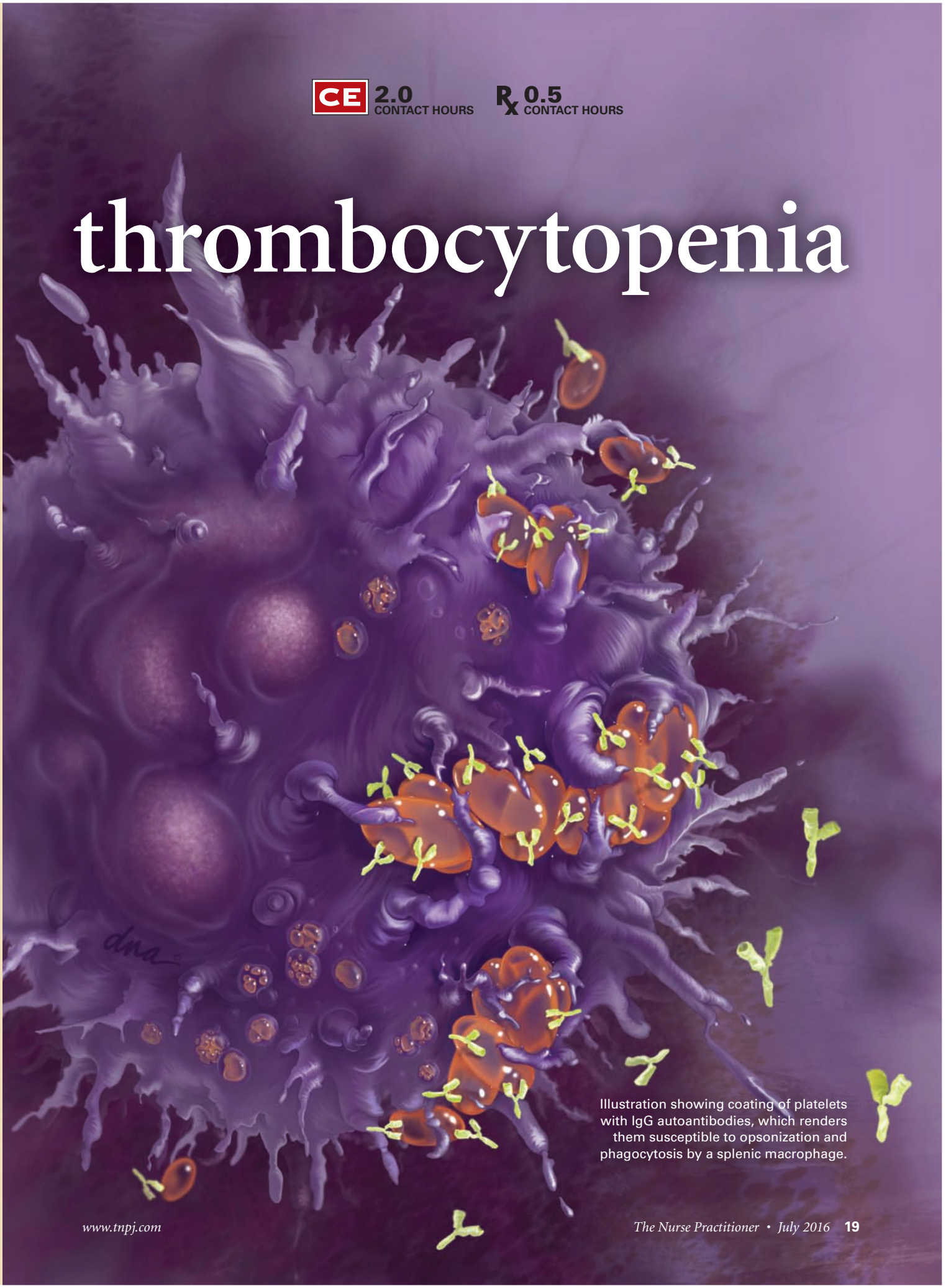
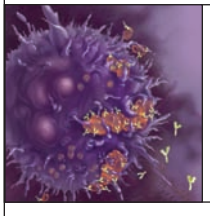


Illustration showing coating of platelets with IgG autoantibodies, which renders them susceptible to opsonization and phagocytosis by a splenic macrophage.

Mechanisms of platelet destruction

Understanding the pathophysiology surrounding thrombocytopenia in ITP is foundational to proper management. The immune dysregulation characteristic of ITP is the result of multiple aspects of the immune system, including the reticuloendothelial system and B and T cell lines.[7] The classic mechanism of platelet destruction in ITP occurs via immunoglobulin G (IgG) opsonization of circulating platelets.[6] B cell activation via the offending antigen leads to antigen-specific antibody production.

In ITP, plasma cell production of antiplatelet antibodies leads to antibody-platelet complexes that are then targeted by the liver, spleen, and complement cascade.[7] The spleen is responsible for normal degrees of platelet destruction; however, in ITP, platelets opsonized by IgG are cleared prematurely and at an accelerated rate by macrophages in the spleen.[6]



The eradication of* H. pylori *in children with secondary ITP allowed the thrombocytopenia to resolve.

T cell dysregulation is noted in ITP in a variety of ways. Decreased levels of CD4+CD25+ T-regulatory cells (Tregs) lead to T cell-mediated destruction of circulating platelets.[8] A decrease in circulating totals of Tregs correlates with loss of self-tolerance and is more indicative of severe disease.[7,8] Additionally, T cell-mediated attacks of megakaryocytes in the bone marrow affect platelet production.[8] The exact mechanisms of decreased platelet production are less well understood compared with platelet destruction, but stunted platelet production in the marrow may be explained by the presence of autoantibodies binding to megakaryocytes and preventing their maturation.[4]

Standard categories and definitions of ITP[18]

Category	Definition
Primary ITP	Autoimmune disorder characterized by an isolated thrombocytopenia, platelet count <100,000/mcL, with no other identifiable cause for the thrombocytopenia
Secondary ITP	All other forms of ITP not considered primary
Newly diagnosed ITP	First 3 months after diagnosis
Persistent ITP	Between 3 and 12 months after diagnosis
Chronic ITP	Lasting more than 12 months after diagnosis

Risk factors

The complete etiology of ITP is complex, with more than just acute onset of a viral illness triggering the disease process. An autoimmune process can also be launched after vaccinations, particularly after measles-mumps-rubella (MMR) in children ages 1 to 3.[9] An increased incidence of ITP was noted after receiving hepatitis A and varicella vaccinations in older children, which is particularly noteworthy, as most cases of ITP occur in early childhood.[9] However, complications resulting from vaccine-associated ITP are rare; children with a history of ITP who did not receive their MMR, or those whose titers show incomplete immunity, should still be immunized.[1,9]

Secondary ITP accounts for approximately 20% of cases with chronic infections, such as hepatitis C, HIV, or *Helicobacter pylori* (*H. pylori*) as the underlying problem.[6] Eradicating the infection removes the autoimmune trigger and allows platelet counts to normalize. Children found to have secondary ITP related to a chronic infection or autoimmune process should be managed by treating the underlying disease process. A 2008 study by Arnold and colleagues specifically showed that the eradication of *H. pylori* in children with secondary ITP allowed the thrombocytopenia to resolve, and that a normal platelet count was linked to the elimination of the bacteria, not the treatment itself.[10]

Clinical presentation

Proper recognition of a child with ITP can prevent unnecessary procedures and undue psychological stress for the child and family. The child presenting with ITP is well appearing and healthy except for the isolated thrombocytopenia. The history of the presenting illness for ITP differs from a thrombocytopenia related to malignancy or familial bleeding disorder.

Commonly, the family will report a recent viral illness, which should immediately raise the index of suspicion for ITP.[5] The onset of the disease is abrupt; the child and family with a history of multiple bleeding events should be considered for a hereditary bleeding disorder rather than ITP (see *Key components and findings in an ITP workup*).

Physical exam

The physical exam could be significant for petechiae, bruising, bleeding gums, melena, and commonly cutaneous bleeding and epistaxis.[1] It is important to differentiate between mucous membrane and cutaneous bleeding, as these relate to severity of disease. Patients presenting with mucous membrane bleeding, such as recurrent epistaxis or bleeding gums, are at a higher risk for complication than those presenting with petechiae or bruising and are thus more likely to require medical intervention.[11] There also appears to be a correlation between the age of presentation and the progression to severe bleeding, with average age at diagnosis impacting the bleeding severity as age increases.[11]

All other causes of thrombocytopenia should be considered before making the diagnosis of ITP. The patient's height and weight should be plotted to assess proper growth, as children with bone marrow failure syndromes will have fallen off their curve.[4]

Key components and findings in an ITP workup[4]

Components of workup and findings specific to ITP

History

- Generally healthy child
- No history of fever, fatigue, or weight loss
- No family history of bleeding disorders
- Acute onset of bleeding and bruising
- Recent "cold" or live attenuated vaccination

Physical exam

- Generally well-appearing child
- No organomegaly
- Bruising noted on extensor surfaces
- Petechiae
- Presence or absence of mucosal bleeding

Complete blood cell count with peripheral smear

- Platelet count <100,000/mcL
- Slight normocytic anemia if significant blood loss
- Isolated thrombocytopenia, no other cell lines affected
- Large, well-granulated platelets on peripheral smear

Complications

Active bleeding noted in the gums, nose, stool, or urine are red flags and should prompt immediate action in the child with ITP. Internal bleeding and intracranial hemorrhage (ICH) are the greatest concerns; those presenting with hematuria, head trauma, and platelet counts less than 10,000/mcL carry the highest incidence of hemorrhage.[12] ICH has a rare occurrence with an incidence of less than 1% in the first 4 weeks after new diagnosis.[11] Toddlers are at an increased risk for fatal bleeds, but outside of this age range, the incidence of severe bleeding and fatal hemorrhages drops until adulthood.[2]

Intervention: Goals of treatment

Management of ITP does not focus on a normal platelet count but rather on achieving a safe platelet count in order to maintain hemostasis.[2] While seeking to decrease the risk of hemorrhage, the provider should aim to maximize the HRQoL for the patient by considering the effects of treatment or observation on quality of life.[13,14] It should also be noted that the basis of treatment is expert consensus, and there are differences in recommendations—even in the published statements.

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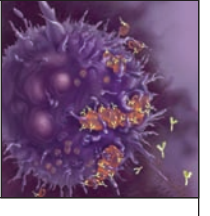


Managing newly diagnosed ITP

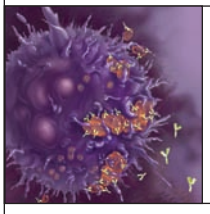
Correctly diagnosing the child and preventing complications is the priority in managing newly diagnosed ITP. Although ITP is a diagnosis of exclusion, a presumptive diagnosis can be made by history, physical exam, normal peripheral smear, and the presence of an isolated thrombocytopenia from a complete blood cell count.[15] Other diagnostics of value include Rh status, IgG level, and a direct antiglobulin test.[15]

Bone marrow aspirates are painful and generally not indicated. Although many providers evaluate the bone marrow aspirate before initiating corticosteroids for fear of misdiagnosing an acute leukemia, retrospective studies affirm current guidelines that bone marrow aspirates should only be performed if other hematologic abnormalities are present or later if the patient shows no response to treatment.[15,16]

The initial workup should include an assessment of the current HRQoL for the patient and family in order to assist in decision-making throughout therapy.[1] The Kids' ITP Tool was found to be reliable and valid in measuring HRQoL in children with ITP.[17] HRQoL does not linearly correlate with platelet counts; therefore, decreased HRQoL

can occur at any point during ITP management and should be included in each assessment.[14]

Providers should use an objective tool, such as the ITP Bleeding Assessment Tool, at the time of diagnosis and throughout therapy to assess the degree and risk of bleeding.[18] Currently, guidelines propose that children without bleeding or those presenting with only cutaneous manifestations, independent of a low platelet count, are managed with observation alone.[1] First-line treatment options for newly diagnosed ITP with active bleeding and a platelet count less than 10,000/mcL at diagnosis are candidates for treatment with one dose of I.V. immunoglobulin (IVIG), corticosteroids, or anti-D immunoglobulin in Rh positive, nonsplenectomized patients (see *Comparison of selected ITP interventions*).[1]



Children with chronic ITP are most likely to report both a decreased HRQoL and fatigue from their ongoing thrombocytopenia.

Treatment for persistent ITP

Children with persistent ITP who initially show a partial response to corticosteroids, IVIG, or anti-D immunoglobulin may continue intermittent treatment with these agents to maintain hemostasis in the first 12 months. If the disease is refractory to treatment, off-label, second-line treatments include rituximab or high-dose dexamethasone.[1] In one study, rituximab showed a complete response in 36% of patients who had previously failed first-line therapy.[19]

Additionally, 87.5% of patients who had a positive response to corticosteroid therapy showed a positive response to rituximab.[20] Although usually well tolerated, rituximab is associated with considerable adverse reactions, and its effects are temporary. Without a spontaneous remission, children would need multiple treatments.[21] High-dose dexamethasone is also an option for persistent ITP unresponsive to previous therapies and can be used in place of splenectomy in children in the first year of treatment.[1]

Treatment for chronic ITP

Chronic ITP in childhood is rare and has an even lower incidence of severe bleeding compatatively.[22,23] At diagnosis, common findings associated with chronic ITP include: initial age over 10; female gender; no preceding viral illness; platelet count greater than 20,000/mcL at initial diagnosis; and presence of other autoimmune diseases (such as Graves' disease or systemic lupus erythematosus).[24] Children will be characterized as having chronic ITP if their thrombocytopenia persists beyond 12 months, though the degree of thrombocytopenia may vary greatly from case to case.

Management of chronic ITP can be similar to persistent ITP, with the exception that splenectomy may be used to treat chronic ITP. Current guidelines recommend delaying splenectomy at least 12 months due to the high rate of spontaneous remission unless the patient's quality of life is so poor that intervention is necessary.[1] Splenectomy is the only known curative treatment for primary ITP but is utilized less in pediatrics due to the self-limiting nature of the disease.[25] Additionally, providers could consider evaluating the bone marrow with an aspirate and biopsy to rule out any underlying disease responsible for the ongoing thrombocytopenia in patients with chronic ITP.[3]

Children with chronic ITP are most likely to report both a decreased HRQoL and fatigue from their ongoing thrombocytopenia. One retrospective study showed 22% of children with chronic ITP experienced fatigue unrelated to other disease processes or treatments, but linked most closely with their disease.[21] With this in mind, the NP should consider what special allowances children might need for school, work, and physical activity.

New considerations in management

Newer options for management of persistent and chronic ITP include second-generation thrombopoietin (TPO) receptor agonists, which have been shown to be safe and effective methods of increasing platelet counts in children with chronic ITP. Most therapies in ITP aim to decrease the production of autoantibodies, but TPO receptor agonist therapy increases platelet production synergistically with the body without stunting endogenous TPO activity.[26]

In a recent multicenter study, romiplostim safely and effectively maintained platelet counts greater than 50,000/mcL for 7 weeks in 88% of children with persistent ITP.[27] Similarly, preliminary findings suggest eltrombopag to be a safe and effective means to increase platelet counts in children with persistent ITP.[28] Both show promising findings but should be further investigated in larger, longer studies. Romiplostim and eltrombopag are second-generation TPO receptor agonists and have been approved for adults with chronic ITP, but only eltrombopag is currently approved for use in children age 1 and older.[29,30]

Comparison of selected ITP interventions[1,4,13,16,19,24–26,30–34]

Intervention	Mechanism of action	Advantages	Disadvantages	Adverse reactions
Observation + thrombocytopenic precautions	Spontaneous resolution of disease	• Cost-effective • No adverse reactions from therapy	• Risk of bleeding • Activity restriction	None
Corticosteroids	Immunosuppression	Cost-effective	• Unwanted adverse reaction profile • Slower rise in platelet count compared with IVIG	• Immunosuppresion • Increased appetite and weight gain • Adrenal insufficiency • Gastrointestinal distress • Osteopenia and stress fractures • Hyperglycemia • Hypertension • Decreased vertical growth • Striae • Cataracts • Behavioral changes
IVIG	Binds to fragment crystallizable (Fc) receptor on macrophage, preventing circulating platelet destruction	Platelet counts increase in 1–2 days	Most expensive first-line therapy	• Severe headache • Hypersensitivity reactions • Fever • Chills during infusion • Nausea and vomiting • Hemolysis • Musculoskeletal aches
Anti-D immunoglobulin	Competitive interference with Fc receptor macrophages in the spleen by coating Rh+ red blood cells	Platelet counts increase in 1–2 days	• Not useful in patients with hemolysis • Not useful in Rh-negative patients	• Severe hemolysis • Disseminated intravascular coagulation • Acute kidney failure (rare) • Headache • Fever • Chills during infusion
Rituximab (off-label use)	Monoclonal antibody targets B cell to disrupt antibody production	Benefits up to 1 year after therapy	Delayed response of several weeks post infusion before rise in platelets	• Hypogammaglobulinemia • Hypersensitivity reactions • Hypotension • Arthralgia • Malaise • Serum sickness • Immunosupression • Risk of progressive multifocal leukoencephalopathy
Eltrombopag	Second-generation TPO receptor agonist binds to thrombopoietin receptors, increasing platelet production	Increases platelet production	Dietary restrictions	• Thromboembolic events • Nausea • Transient transaminitis • Epistaxis • Rebound thrombocytopenia
Romiplostim (not approved for use in children)	Second-generation TPO receptor agonist binds to thrombopoietin receptors, increasing platelet production	Increases platelet production	Weekly subcutaneous injection	• Headache • Nausea • Lacy rash • Arthralgia • Dizziness • Insomnia • Thromboembolic events
Splenectomy	Surgical removal of primary site of platelet destruction	Curative for primary ITP	• Surgery • Increased risk of infection by encapsulated bacteria	• Intraoperative hemorrhage • Immunosuppression

Discussion

Careful consideration is necessary when weighing the need for intervention. HRQoL is complicated to manage and measure. The treatment plan should be individualized by a responsible NP who is familiar with the disease process and the impact of treatment on HRQoL.[15] While managing platelet count and risk of hemorrhage, HRQoL should be a strong determinate in choosing a treatment modality; each intervention has associated adverse reactions and risks.

It should be understood, depending on the severity of bleeding at presentation, that most patients can be observed without intervention with no incidence of significant bleeding.[12] Providers should be cognizant that the cost of therapy and time commitments needed for treatment and follow-up add additional burdens on families.[23] Newer agents, such as TPO receptor agonists, are changing the landscape of managing chronic ITP and might be effective in improving HRQoL for children (more research is still needed).[17]

Implications for the NP

NPs operating in a variety of settings can benefit from a foundational knowledge base of ITP pathophysiology and treatment recommendations. An NP in the primary care setting is most likely to witness the initial presentation and can reduce anxiety and make the appropriate referral for continued management. With findings consistent of ITP (if the patient is stable and does not need immediate treatment), the NP should refer the family to the nearest hematologist rather than the ED only if the specialist can see the patient within the next day.

The primary care setting can also serve as a follow-up point for reliable patients and families who follow bleeding precautions—especially if the distance to reach a specialty center is too great. In specialty settings, the NP should use the current data while partnering with the family, child, and other providers to create patient-specific treatment plans based on the intervention guidelines.

Research is lacking in several areas related to childhood ITP, but providers could specifically target questions related to use of TPO receptor agonists in children, HRQoL throughout therapy, and continued research on use of standardized assessment tests for bleeding and HRQoL. Although more research is needed, improving the HRQoL and minimizing treatment and disease-related adverse reactions should be the goal of every provider caring for the child with ITP.

The goal of treating childhood ITP is hemostasis and protecting HRQoL. Providers should consider that the watch-and-wait option could be more distressing to the patient and family than active treatment, and newer agents could be used to allow for lifestyle normalcy. More research is needed on how to best protect HRQoL in children with ITP throughout their therapy. NP

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