Immune thrombocytopenia in children

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IMMUNE THROMBOCYTOPENIA IN CHILDREN

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Summary

Immune thrombocytopenia (ITP) of childhood is characterized by isolated, immune-mediated thrombocytopenia. ITP occurs most commonly in young children following a viral infection. It is usually a benign disorder with spontaneous recovery within following weeks or months. The optimal management including investigations, treatment, and follow-up of children with ITP is a matter of debate. Recent guidelines recommend that careful observation is appropriate for pediatric patients with no or mild bleeding regardless of platelet count. Pharmacologic intervention is required for children with severe bleeding.

Key words: immune thrombocytopenia, child, platelets

INTRODUCTION

Childhood immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count < 100 x 10^9/L). ITP is one of the most common bleeding disorders in children, with an incidence of approximately four per 100.000 per year [1,2]. ITP most frequently presents with acute onset of purpura and bruising in an otherwise healthy child, often after a preceding mild viral infection. A benign and self-limited course is common, and major bleeding complications are exceptional [1]. The management including diagnostic investigations, treatment and follow-up is controversial [3]. This review presents the current nomenclature, diagnosis, differential diagnosis, treatment options, and prognosis of children with ITP.

Nomenclature

The current nomenclature was proposed by International Working Group (IWG) of both pediatric and adult experts in ITP at the Vicenza Consensus Conference in 2009 [4]. IWG recommended term "immune thrombocytopenia", instead of previous "idiopathic thrombocytopenic purpura" or "immune thrombocytopenic purpura". Current term **I**mmune **T**hrombocyto**P**enia preserves its most widely accepted abbreviation "ITP", while underlying the immune-mediated nature of the disease. "Purpura" was proposed to be omitted since many patients have no or minimal bleeding symptoms. ITP in the absence of other causes or disorders known to reduce platelet count is known as primary ITP, while secondary ITP is characterized by the presence of an underlying disorder, including ITP that is drug-induced. IWG defined three different phases of ITP: "newly diagnosed ITP" (ITP within 3 months from diagnosis), "persistent ITP" (ongoing ITP between 3 and 12 months from diagnosis), and "chronic ITP" (ITP lasting more than 12 months). Severity of ITP is based on the presence of bleeding signs rather than the degree of thrombocytopenia. The term "severe ITP" should be used only in patients with clinically relevant bleeding, which is defined as bleeding at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention or increase in drug dose.

Pathophysiology

ITP is an immune-mediated disorder with complex pathophysiology. The key element in the pathogenesis is loss of self-tolerance leading to production of autoantibodies against platelet membrane antigens, in particular glycoprotein IIb/IIIa complex [1]. The antibody-coated platelets have a shortened half-life because of Fc receptor-mediated phagocytosis by tissue macrophages, predominantly those in the spleen. The same antibodies may inhibit platelet production. In addition to activated B-cells and increased phagocytic activity, cellular immunity is perturbed, and T-cell and cytokine profiles are significantly shifted toward a type 1 and Th17 proinflammatory immune response [5]. Further, a genetic predisposition to ITP likely plays a role in susceptibility to developing ITP in specific conditions. This finding is supported by rare reports of familial ITP, increased frequency of ITP in some genetic syndromes (common variable immunodeficiency, autoimmune lymphoproliferative syndrome, and hyper IgM syndrome), and evidence of an association between ITP and several candidate immune genes [5, 6]. Various underlying pathophysiological immune mechanisms are responsible for the clinical heterogeneity of ITP and different response to the treatment.

Epidemiology

Annual incidence of ITP is estimated to be between 1.9 and 6.4 cases per 100.000 children. This rate is probably an underestimate because it is based primarily on symptomatic and hospitalized patients [7]. Children with ITP can present at any age, but there is a peak between two and five years and a smaller peak in adolescence. There is a slight predominance of boys to girls, especially in infants. In a large study of the Intercontinental Childhood ITP Study Group (ICIS) that included 2540 pediatric patients, the mean age at presentation was 5.7 years. Seventy percent of children were between 1 and 10 years old, 10% were infants (older than 3 and less than 12 months old), and the remaining 20% were older (ages 10 to 16 years). Boys and girls were affected approximately equally. In infants, the male to female ratio was 1.7:1. The male predominance was minimal in older children, such that the overall male to female ratio in this study was 1.2:1 [8]. Seasonal occurrence has been reported, with the highest incidence in the spring and lowest in the autumn, most probably reflecting seasonal variations in viral illnesses.

Clinical manifestations

ITP in children typically presents with the sudden onset of a purpura or bruising in an otherwise healthy child. In almost two thirds of pediatric patients, there is a history of a prior viral infection, mainly an upper respiratory tract infection. The interval between the preceding infection and the onset of purpura varies from a few days to several weeks, with the most frequent interval about two weeks. In a minority of children, ITP occurs following MMR (measles, mumps and rubella) vaccination. MMR-associated ITP occurs rarely, in one to three cases per 100.000 doses of vaccine [2,9].

Approximately 60% of children with ITP have only skin bleeding at presentation that include petechial or purpuric rash or bruising, also referred to as “dry purpura”. Mucosal bleeding (“wet purpura”) may be present in as many as 40% of children with ITP. It involves epistaxis, buccal and gingival bleeding, and, much less frequently, hematuria, menorrhagia, or gastrointestinal bleeding. Other than the evidence of mucocutaneous bleeding, patients appear well and have no systemic symptoms such as fever, weight loss, or bone/joint pain. On physical examination, no significant lymphadenopathy or hepatosplenomegaly is present; if present, another diagnosis should be strongly considered. However, small cervical adenopathy is common in young children, and slightly palpable spleen may be present in 5% to 10% of children with ITP [10,11].

Severe hemorrhage requiring hospital admission and/or blood transfusions is rare, and occurs in about 3% of children with ITP (12). The most feared complication

of ITP is intracranial hemorrhage (ICH). The incidence of ICH is 0.1 to 0.8%, and is even lower in children with persistent thrombocytopenia. Patients with ICH and ITP are more likely to have a history of head trauma and wet purpura; in the majority of patients platelet count is less than 10 x 10^9/L [1,13].

Several attempts have been undertaken to establish a scoring system assessing the extent of bleeding in order to standardize treatment decisions and monitor the platelet response. Bolton-Meggs and Moon arbitrarily divided bleeding signs into four categories: none, mild, moderate, and severe [14]. Buchanan and Adix developed scoring system allowing semiquantitative assessment of hemorrhage based on physical examination and history of new bleeding during the previous 24 hours [15]. Edslev and co-workers proposed a clinical score predicting a brief and uneventful course of newly diagnosed ITP in children [16]. Pediatric bleeding score tools are summarized in Table 1.

Table 1. Grading and scoring systems in pediatric ITP

Bolton Maggs and Moon (14)	**Buchanan and Adix (15)**	**Edslev and co-workers (16)**
Asymptomatic No symptoms *Mild* Bruising and petechiae; occasional minor epistaxis, very little or no interference with daily living *Moderate* More severe skin manifestations with some mucosal lesions; more troublesome epistaxis and menorrhagia *Severe* Bleeding episodes (epistaxis, melena and / or menorrhagia) requiring hospital admission and / or blood transfusion; symptoms seriously interfering with quality of life	Grading of haemorrhage in children with ITP based upon history prior 24 hours and physical examination Grade 0-5 0 none 1 minor 2 mild 3 moderate 4 severe 5 life-threatening or fatal Skin bleeding (0-4) Epistaxis (0-4) Oral bleeding (0-4) Overall bleeding (0-5)	Scoring system based on 6 clinical features Six clinical features with prognostic information (weight) Abrupt onset (5) Age <10 years (3) Preceding infection (2) Platelet count <5 x 10^9 / L (1) Wet purpura (1) Male gender (1) High scores (10–14) identify low-risk patients

Laboratory findings

ITP is characterized by isolated thrombocytopenia. In most reports, presenting platelet count is less than 30 x 10^9/L, probably because patients with mild disease may not come to medical attention. About 80% of children with ITP have platelet count less than 20 x 10^9/L, and 44% less than 10 x 10^9/L [8,17]. Other hematologic abnormalities are consistent with the newly diagnosed ITP only if they can be explained easily, e.g. microcytic anemia in children with significant bleeding, or atypical lymphocytes in post-infectious cases. The exception is mild eosinophilia, which is a common finding.

For the typical cases of childhood ITP a complete blood count with a careful examination of the peripheral blood smear are the only necessary investigations. The blood smear shows normal morphology of all cell lines with platelets either normal in size or variably sized with some large platelets [1]. Antiplatelet antibodies, detected in 60% to 70% of cases, are not normally helpful as they are of no prognostic significance [18]. Besides, there is no evidence to recommend the routine testing of other autoimmune antibodies (antinuclear, antiphospholipid, antithyroid), platelet parameters (platelet volume, reticulated platelets), or serum thrombopoietin levels in the evaluation of children with suspected ITP [19]. The utility of measuring immunoglobulins in all patients to exclude common variable immune deficiency is equivocal [2]. Bone marrow examination is not routinely performed in children with typical ITP. According to the American Society of Hematology (ASH) guidelines, it is not necessary in children with typical features of ITP and in those who fail to respond intravenous immunoglobulin (IVIG). Important indications for bone marrow aspiration include atypical clinical or laboratory features at presentation that suggest malignancy or bone marrow failure, therapy-refractory ITP, and new findings that emerge during follow-up that are inconsistent with ITP [19].

Differential diagnosis

Primary ITP in children is a diagnosis of exclusion. The diagnosis of ITP is generally considered in well-appearing child with spontaneous abrupt onset of mucocutaneous bleeding and an isolated, often profound thrombocytopenia. For children with laboratory abnormalities other than thrombocytopenia or with atypical clinical findings, other conditions that can cause thrombocytopenia must be ruled out. The differential diagnosis of thrombocytopenia in pediatric population is very broad. It includes pseudothrombocytopenia (EDTA-induced platelet agglutination), active infection (e.g. infectious mononucleosis, hepatitis, HIV-1), autoimmune hemolytic anemia (Evans syndrome), systemic autoimmune diseases (e.g. systemic lupus

erythematosus, antiphospholipid syndrome), drug exposure (e.g. heparin, quinidine, phenytoin, sulfonamides, vancomycin), bone marrow failure syndromes (e.g. aplastic anemia, myelodysplastic syndrome), consumptive processes (e.g. hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation), immunodeficiency syndromes (e.g. common variable immunodeficiency, Wiscott Aldrich syndrome), and inherited thrombocytopenic disorders (e.g. inherited aplastic anemia, thrombocytopenia-absent radius syndrome, von Willebrand disease type 2B) [10,11].

Table 2 lists possible causes of thrombocytopenia, and suggested tests that are helpful in distinguishing between disorders.

Table 2. Differential diagnosis of thrombocytopenia and suggested tests

Condition	**Disorder**	**Suggested tests**
Analytical reasons	Pseudothrombocytopenia	Peripheral blood smear; alternative anticoagulant, e.g., heparin or citrate
Acquired peripheral destruction	Disseminated intravascular coagulation	Complete blood count, peripheral blood smear, coagulation tests
	Haemolytic uremic syndrome	
	Thrombotic thrombocytopenic purpura	
	Post-transfusion purpura	
	Splenic sequestration	
	Kassabach-Merrit syndrome	
	Cardiovascular disease	
	Neonatal alloimmune thrombocytopenia	HPA genotyping: maternal platelet antibody investigations
	Drug-induced thrombocytopenia	Antibodies against drugs
	Liver diseases	Liver function tests
	Infectious diseases	Serology (HIV, HBV, HCV, CMV)
	Systemic lupus erythematosus	Antinuclear antibodies, direct antiglobulin test
	Antiphospholipid autoantibodies	Lupus anticoagulant, anticardiolipin
Acquired production failure	Myelodysplastic syndrome	Bone marrow aspiration and biopsy
	Bone marrow infiltration	
	Aplastic anaemia	Genetic studies

Inherited thrombocytopenia	Thrombasthenia Glanzmann	Family history, complete blood count, peripheral blood smear (platelet morphology and size), platelet flow cytometry, bone marrow aspiration and biopsy, genetic studies
	Bernard–Soulier syndrome	
	Mediterranean thrombocytopenia	
	Gray platelet syndrome	
	Paris-Trousseau thrombocytopenia / Jacobsen syndrome	
	Velocardiofacial syndrome, DiGeorge syndrome	
	Wiskott–Aldrich syndrome	
	X-linked thrombocytopenia	
	Congenital amegakaryocytemia	
	Thrombocytopenia-absent radius syndrome	
	MYH-9-related disorders	
	GATA1 mutation	
	Von Willebrand disease type 2B	Von Willebrand factor, multimer analysis, Factor VIII
	Fanconi anaemia	Complete blood count, peripheral blood smear; karyotype/chromosomal breakage, genetic studies
	Autoimmune lymphoproliferative syndrome	Complete blood count, Fas protein, Fas ligand

Prognosis

Children with ITP have an excellent chance of recovery with or without treatment. Typically, bleeding signs subside within weeks, and the platelet count returns to normal in a few weeks to months. Overall, 70% to 80% of children diagnosed with ITP will go into complete remission within a few months [1]. Remission rate of 87%, achieved by watchful waiting without specific therapy 6 months after initial presentation, has been reported [20]. In ICIS Registry I involving 2031 subjects, an equal percentage of children had resolved their ITP at 6 months irrespective of whether they had been managed by observation only or had received platelet enhancing therapy. Moreover, 25% of children with thrombocytopenia lasting more than 6 months recovered over the next 6 months [21]. Data from ICIS

Registry II involving 1345 children supported that ITP is a benign condition for most affected children. Remission occurred in 37% of patients between 28 days and 6 months after the initial presentation, in 16% between 6 and 12 months, and in 24% between 12 and 24 months [22]. A recent systematic review and meta-analysis identified following predictors of chronic ITP in children: older age, insidious onset, no preceding infection or vaccination, mild bleeding, and higher platelet counts at presentation (> 20 x 10^9/L) [23]. Finally, two genetic biomarkers have been suggested as predictors of chronic disease: overexpression of vanin-1 (VNN-1), an oxidative stress sensor, and the Q63R missense variant of the gene encoding the cannabinoid receptor type 2 [24].

Management

Management of childhood ITP remains controversial. Besides bleeding manifestations and platelet count, pediatric hematologists should consider a number of factors when considering treatment decisions, such as age, physical activities, health-related quality of life, potential co-morbidities and co-medications, duration of the disease, geographic distance from a tertiary care center, patient's and parents preferences, time lost from school due to hospital visits, psychosocial impact and economic aspects [1,2].

In majority of pediatric cases ITP is a benign self-limited disorder that requires no or minimal therapy [1,25,26]. Universal supportive measure is the avoidance of medications that inhibit platelet function, including non-steroidal anti-inflammatory drugs, aspirin-containing preparations and anticoagulants. There is a great variation in how children with ITP are counseled with respect to activity restrictions. Most practitioners advice against participation in any activity associated with a significant risk of trauma (especially head injury) when platelet count is less than 30 x 10^9/L. For active toddlers and preschool children, protective helmets with close supervision are recommended. For older children and adolescents, restrictions often involve avoiding contact sports in the period of profound thrombocytopenia [1].

Depending on patient characteristics, appropriate initial management of a child with newly diagnosed ITP may be either observation or pharmacologic intervention. There is currently no consensus which therapeutic option is preferably used in a given situation.

Watchful waiting

The self-limited nature of childhood ITP and very low incidence of severe bleeding is the basis of a non-interventional strategy. Pharmacotherapy has proven to

be mostly effective in raising the platelet count in a short period of time, but it has never been demonstrated that the fast platelet response is of clinical significance [26]. ASH practice guidelines recommend that children with no bleeding or mild bleeding (defined as skin manifestations only), be managed with observation alone regardless of platelet count [22]. This "watch and see" strategy is now accepted by many experts.

Pharmacologic intervention

When platelet-enhancing therapy is indicated, the primary treatment options for a child with newly diagnosed ITP include IVIG or corticosteroids. Both of these pharmacologic approaches interfere with antibody-mediated clearance of platelets, and most patients respond within days of administration [1,28]. Selection of treatment and dosing/duration varies substantially among care providers. Platelet transfusion is generally contraindicated, with the exception of patients with life-threating hemorrhage or patients requiring urgent surgical procedures.

Corticosteroids

Different protocols of oral glucocorticoids have been used for decades to patients with ITP of all age groups. The most traditional regimen is oral prednisone in a daily dose of 2 mg/kg/day (60 mg maximum) for 2 weeks with tapering over 1 week [2]. There are observations that higher doses of steroids (intravenous methylprednisolone 30 mg/kg/day for 3 days, or oral methylprednisolone 30 mg/kg/day for 3 days followed by 20 mg/kg/d for 4 days) result in faster response, but without clinical benefit [29,30]. Data suggest that a short course of oral prednisone with 4 mg/kg/day for 4 days without tapering is effective and less toxic. Most common side effects of corticosteroid therapy include mood changes, sleep disturbance, hypertension, weight gain, and gastritis. Oral dexamethasone is not the first-line therapy in children, because of the predictable significant adverse events [1,2].

Immunoglobulins

IVIG raises the platelet count in more than 80% of children with newly diagnosed ITP. An increase in platelet count is usually observed within 24 hours. The original IVIG dose of 0.4 g/kg/day for 5 days has been superseded by shorter courses. It is generally administered in a single dose of 0.8 to 1 g/kg, with possible repeated treatment based on the short-term platelet response [31]. Transient side effects include headache, fever, nausea, and vomiting.

Anti-D immunoglobulin

Intravenous anti-D immunoglobulin (anti-D) as a single dose of 50 to 75 μg/kg can be effectively given to Rh-positive non-splenectomized children with ITP requiring treatment. Patients should be monitored for 8 hours after the infusion [1]. The use of anti-D as the first-line treatment remains controversial with respect to the risk of hemolysis. Besides, it is not currently licensed in European countries [31].

Life-threatening bleeding

On very rare occasions, children with ITP present with organ- or life-threatening bleeding. The goal of emergency treatment is to raise rapidly the platelet count to a level where the risk of severe bleeding is minimized. International consensus 2010 report recommends combination of therapies, including platelet transfusions (two- to three-fold larger-than-usual doses due to rapid platelet destruction, sometimes followed by continuous infusion), high doses of intravenous methylprednisolone (30 mg/kg over 20 to 30 minutes, maximum 1 g), and IVIG (1 g/kg/day for 2 days) [31,32]. Emergent splenectomy should be considered for patients with life-threatening bleeding refractory to medical management [1].

Treatment options for children with persistent or chronic ITP

The decision to treat a child who is unresponsive to initial treatment and /or who has persistent or chronic ITP should be individualized, relying largely on the frequency and severity of hemorrhage and the impact on quality of life. If previous treatments with steroids or IVIG have been successful, these drugs may be used as needed to prevent bleeding. Prolonged use of corticosteroid therapy should be avoided because of adverse effects, especially on growth [2]. Other treatments are preferred for pediatric patients with unresponsive persistent or chronic ITP and clinically significant bleeding. Rituximab (chimeric monoclonal anti-CD20 antibody) has been administered in case series, with response rate between 31% and 68% [31]. Several dosing regimens have been used, most frequently as a dose 375 mg/m^2 for 4 consecutive weeks. It has been demonstrated that response to corticosteroids strongly correlated with the response to rituximab, yet 48% of children unresponsive to steroids responded to rituximab [3]. Thrombopoietin-receptor agonists may have a role in the treatment of severe chronic ITP in children. Two randomized studies investigating romiplostin (given subcutaneously once a week) reported platelet increase in more than 80% of children; the response was maintained for a median of 7 weeks. Larger studies are needed in children, concerning efficacy and long-term safety. Numerous other medications interfering with the immune system have been used in a limi-

ted number of children. These include azathioprine, cyclosporine A, mycophenolate mofetil, danazol, and dapsone. Cytotoxic drugs (cyclophosphamide, vinca alkaloids) have been tried in severe refractory ITP, but should be used with extreme caution in children [34,35].

Splenectomy in children is generally deferred for as long as possible. Current guidelines agree that it should be postponed for at least 12 months after the initial diagnosis of ITP, due to the possible spontaneous remissions [36]. Although 60% to 80% of pediatric patients initially respond to splenectomy, it is associated with substantial risk of serious complications especially overwhelming sepsis [1]. ASH guidelines recommend splenectomy for children and adolescents with chronic or persistent ITP who have significant or persistent bleeding, and lack of responsiveness or intolerance of other therapies (corticosteroids, IVIG, and anti-D) and/or who have a need for improved quality of life. If elective splenectomy is planned, vaccinations against encapsulated bacteria should be completed preoperatively. Prophylactic antibiotic therapy (penicillin or alternatives in the case of penicillin allergy) is recommended [22,31]. Children with chronic severe ITP who fail to remit after splenectomy present very challenging management decisions for pediatric hematologists, that should be made in collaboration with the patient and the family.

CONCLUSION

Immune thrombocytopenia in children is a relatively uncommon and generally benign self-limited condition presenting as abrupt onset of bleeding tendency in an otherwise healthy child. Diagnostic approach includes history, clinical examination and full blood count with peripheral blood smear. Indications for treatment have not been standardized and include bleeding, quality of life and parental anxiety. Observation only should be considered in pediatric patients with mild disease. Intravenous immunoglobulin and steroids are the current frontline pharmacologic approaches for children at risk for severe bleeding.

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Sažetak

Imuna trombocitopenija u djece

Imuna trombocitopenija (ITP) u djetinjstvu je karakterizirana izoliranom, imunološki posredovanom trombocitopenijom. ITP se najčešće pojavljuje u male djece nakon virusne infekcije. U pravilu se radi o benignom poremećaju sa spontanim oporavkom unutar nekoliko tjedana ili mjeseci. Optimalan pristup pedijatrijskoj ITP, koji uključuje dijagnostičke postupke, liječenje i praćenje, nije usaglašen. Novije smjernice preporučuju pažljivo praćenje pedijatrijskih bolesnika s odsutnim ili blagim krvarenjem, bez obzira na broj trombocita. Farmakološko liječenje je indicirano u djece s ozbiljnim krvarenjem.

Ključne riječi: imuna trombocitopenija, dijete, trombociti

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