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Idiopathic thrombocytopenic purpura: laboratory diagnosis and management

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ABSTRACT

Idiopathic thrombocytopenic purpura (ITP) or immune thrombocytopenic purpura is a disease characterized by low platelet count (<150,000/ìL) caused by autoantibody-mediated platelet destruction and the absence of other causes of thrombocytopenia. Acute primary ITP is more common in children 2-6 years of age, with similar incidence between males and females, while the chronic form is usually encountered in adults with median age of 40-45 years. The clinical signs of ITP are purpura, ecchymosis, petechiae and gastrointestinal tract bleeding, gingival bleeding, epistaxis, and urinary tract bleeding. Spontaneous mucosal, intracranial, and gastrointestinal hemorrhage may occur at platelet counts of <10000/ìL. To date, the diagnosis of ITP is still arrived at by exclusion, i.e. by elimination of other causes of thrombocytopenia. The diagnosis of ITP also requires a medical history (anamnesis), physical examination, platelet count, and examination of a peripheral blood smear. The latter examination in ITP shows low numbers of normal-sized platelets, occasionally also giant platelets, while erythrocytes and leukocytes have a normal morphology. The bone marrow is usually normal or shows increased megakaryocytes. Assessment of antithrombocyte antibody may assist in establishing the diagnosis of ITP. Management of ITP is based on platelet count and severity of bleeding. Treatment is aimed at interfering with antibodies that damage the platelets, by inhibiting the functions of macrophage Fcã receptors and decreasing the production of antiplatelet antibodies. Thrombopoietin (TPO) receptor agonists including eltrombopag and romiplostim have offered an important new option in treating ITP.

Key words: Idiopathic thrombocytopenic purpura, antiplatelet, antibodies, splenectomy, thrombopoietin

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INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is an acquired disorder characterized by decreased numbers of circulating platelets, known as thrombocytopenia,[1] and resulting in subnormal platelet counts. Thrombocytopenia may be subdivided into four grades as follows:

Table 1. Causes of thrombocytopenia[2]

Decreased production	Increased destruction
Hematologic malignancies	Immune:
Aplastic anemia	ITP
MDS (Myelodysplasia)	HIV
Drugs: chemotherapy	Posttransfusion purpura
HIV	Non-immune:
Hereditary thrombocytopenia	DIC
Cancer metastases in bone marrow	Sepsis
	TTP-HUS

grade 1 with a platelet count of 75,000-150,000/μL; grade 2 with a platelet count of 50,000-<75,000/μL; grade 3 with a platelet count of 25,000-<50,000/μL; and grade 4 with a platelet count of <25,000/μL[2] The causative mechanisms of ITP are varied, making ITP a heterogeneous disorder.[3,4] Thrombocytopenia may be caused by failure of or reduction in platelet production or by increased platelet destruction (Table 1).[2]

In 1735 Paul Gottlieb Werlhof described a disorder, morbus maculosus hemorrhagicus, which became a recognized diagnostic entity at the turn of the twentieth century and is currently called idiopathic thrombocytopenic purpura (ITP) or immune thrombocytopenic purpura.[5] This disorder is characterized by a decrease in platelet count down to <150,000/μL, due to autoantibody-mediated platelet destruction, purpuric rash, normal bone marrow, in the absence of other causes of thrombocytopenia.[6,7] Although ITP has been known for a long time, there are still many unresolved issues regarding the pathogenetic mechanisms, epidemiology, diagnosis and management .

ITP is distinguished into primary and secondary types. Primary ITP comprises two forms, acute and chronic. The acute form is more common in children 2-6 years of age, with similar incidences between males and females, while the chronic form is usually encountered in adults with median age of 40-45 years, among whom the prevalence is higher in women, with a female to male ratio of 3:1. The chronic form is characterized by a thrombocytopenia persisting for more than 6 months,[8,9] typically has an insidious onset and often requires medical intervention to prevent bleeding.[10] The true incidence of ITP in adults remains unknown, but based on one study, the age adjusted prevalence of ITP was estimated to be 9.5 per 100,000 persons.[11] Thrombopoietin (TPO) is a naturally occurring hormonal growth factor that is primarily produced in the liver. It regulates megakaryocytopoiesis and stimulates platelet production in the bone marrow.[12]

Pathophysiology

ITP is caused by specific platelet autoantibodies binding to the platelets. The IgG autoantibody-coated platelets undergo accelerated clearing in the spleen and liver after binding Fc receptors expressed on tissue macrophages. Platelet destruction is presumably triggered by antibody, leading to the formation of neoantigens, thus resulting in the production of autoantibodies in amounts sufficient to cause thrombocytopenia.

Figure 1 gives an explanation about the trigger factors for autoantibody production, which to this date are still unknown.[13] In the initial stage, glycoproteins IIb/IIIa are recognized by autoantibodies, while antibodies recognizing glycoproteins Ib/IX have not been formed at this stage. Autoantibody-coated platelets will bind to antigen presenting cells (APCs), i.e. macrophages, through Fc receptors, and are then internalized and degraded. The APCs process not only glycoproteins IIb/IIIa, but also other glycoproteins. The activated

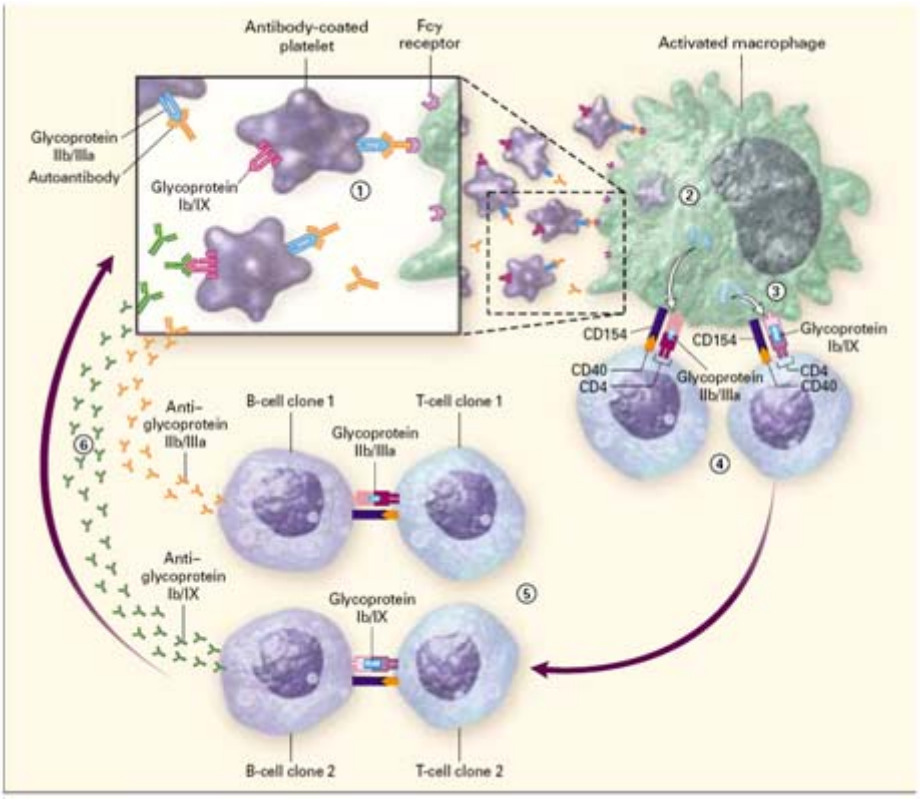

Figure 1. Pathogenesis of autoantibody production in ITP.[13]

APCs express new peptides on their surface, aided by costimulation (shown by interaction between CD154 and CD40). The new peptides subsequently are presented to T cells, whereupon these activated T cells produce cytokines and activate B cells to produce antibody against specific platelet glycoproteins.[14-16] In addition to autoantibody-mediated platelet destruction, ITP-associated thrombocytopenia may also be caused by suboptimal platelet production.[17]

Clinical manifestations

Bleeding in ITP is manifested by purpura, ecchymoses and petechiae, and mucosal hemorrhages. Hemorrhagic vesicles or bullae may be seen in the oral cavity and other mucosal surfaces. Gingival bleeding and epistaxis are the most frequent types of hemorrhage. Other types of bleeding may occur in the gastrointestinal tract as melena, and in the genitourinary tract as hematuria and menorrhagia.[9] Spontaneous mucosal, intracranial and gastrointestinal bleeding occur at a platelet count of <10,000/ìL.[2]

Diagnosis

To date the diagnosis of ITP is still arrived at by a process of exclusion, by eliminating other causes of thrombocytopenia, such as thrombocytopenia associated with autoimmune diseases, exposure to drugs such as heparin or quinine, and HIV or hepatitis C infection.[13,18] Thrombocytopenia associated with HIV or hepatitis C infection may be clinically indistinguishable from primary thrombocytopenia and may occur several years before the development of other symptoms.[19] The diagnosis of ITP also requires a medical history (anamnesis), physical examination, platelet count, and examination of a peripheral blood smear. The medical history may eliminate other causes of thrombocytopenia such as drugs or alcohol. On physical examination usually

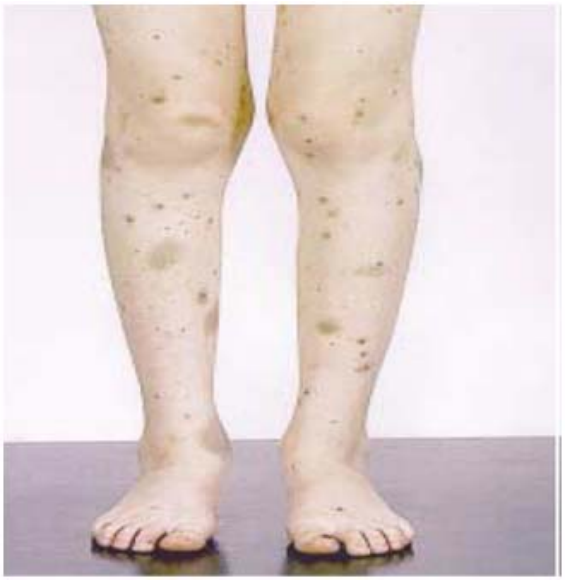

Figure 2. Petechiae and purpura in male patient with ITP.[13]

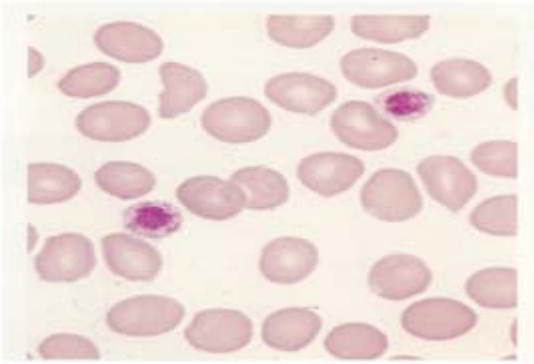

Figure 3. Peripheral blood smear with 2 giant platelets.[20]

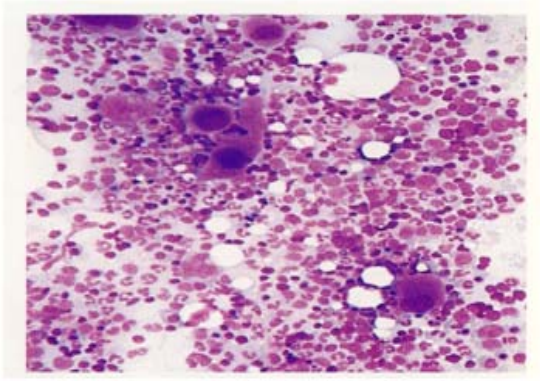

Figure 4. Bone marrow picture showing increased numbers of mega-karyocytes.[20]

signs of bleeding are encountered, such as petechiae, purpura, and conjunctival and mucosal hemorrhages (Figure 2).[13] Mild splenomegaly may also be found in young patients.[19]

Laboratory investigations

Laboratory examination of peripheral blood smears for ITP show low numbers of normal-sized platelets, occasionally also giant platelets, while erythrocytes and leukocytes have a normal morphology (Figure 3).[20] Anemia and iron deficiency from blood loss may also occur.[19] The bone marrow is usually normal or shows increased megakaryocytes (Figure 4).[20] In ITP patients with HIV infection the bone marrow shows pycnotic and dyspoetic megakaryocytes devoid of cytoplasm, termed naked megakaryocyte nuclei, of unknown etiology.[21,22] Bone marrow examination is performed in patients with poor therapeutic outcomes,[13] and may provide relatively significant information in patients aged over 60 years with systemic symptoms or abnormal signs. Details of platelet morphology may also be obtained by means of cytogenetic examination or flow cytometry.[19,23] The direct antiglobulin test (DAT) may also be used for ITP diagnosis. According to Aledort et al., DAT was positive in 22% of 205 patients with ITP, but its clinical significance is unclear.[19,24]

Assessment of antiplatelet antibodies may assist in establishing the diagnosis of ITP, although the results may not be positive in all patients with ITP, and negative results cannot always be taken as excluding ITP. Assays for detection of antiplatelet antibodies have been developed since 1950, involving three phases.[25,26] Initially indirect methods were developed to assess serum antiplatelet antibodies. Patients' sera were mixed with normal platelets, and the final outcome could be in the form of either platelet aggregation or lysis. This method is now obsolete, having low sensitivity and specificity due to the presence of many substances in serum, such as immune

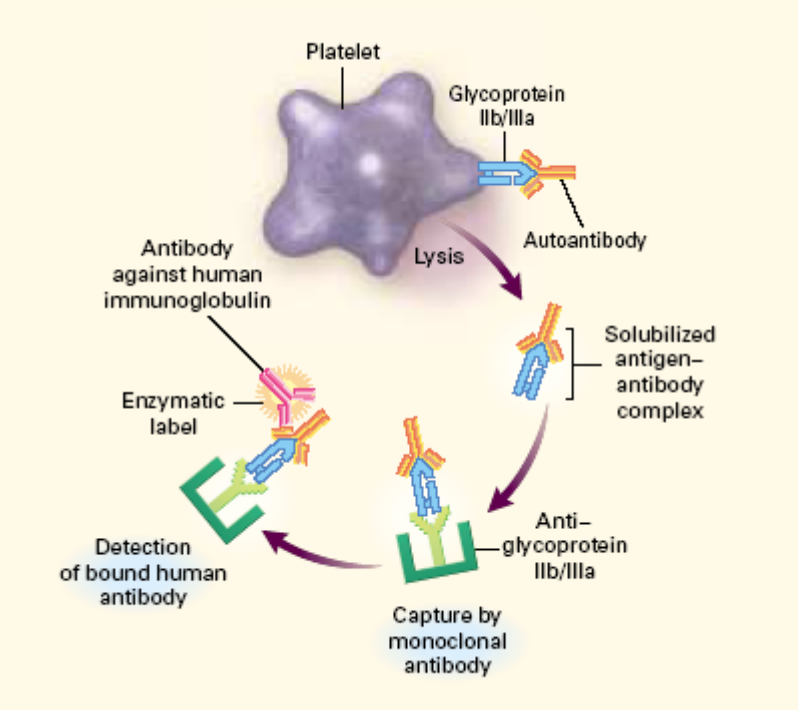

Figure 5. Detection of antiplatelet antibody by the monoclonal antigen capture assay.[13]

complexes and complement, that are capable of inducing platelet activation, thus leading to false positive results. In the next phase assays were developed for detection of platelet associated IgG (PA-IgG) and the most commonly used method was the enzyme linked immunosorbent assay (ELISA), for detecting platelet-bound immunoglobulin. This assay is sensitive as it is capable of detecting immunoglobulins bound to platelets but is less specific, because platelets from patients with immune as well as non-immune thrombocytopenia may increase PA-IgG levels. In the third phase specific antibodies against platelet glycoproteins were detected by means of a modified antigen capture enzyme linked immunosorbent assay (MACE), as illustrated in Figure 5,[13] one example of a MACE assay being the monoclonal antibody specific immobilization of platelet antigen assay (MAIPA).

In the MAIPA assay, mouse antiglycoprotein antibodies (anti-GPAb) bound to platelet glycoproteins (GP) initially form mouse antiGPAb-GP complexes, which upon addition of auto-antibody (autoAb) bearing platelets will form mouse antiGPAb-GP-autoAb complexes. These mouse anti-GPAb-GP-autoAb complexes are put into goat anti-mouse antibody-coated wells, to which enzyme-labeled anti-human Ig is added, which binds to the complexes (Figure 6).[26] The MAIPA assay has the advantage of preserving the platelet antigen (GP), as the antigen is presensitized with antibody before solubilization. Other antigen capture assays are the microtiter plate assay and the immunobead assay. In the microtiter plate assay, glycoprotein is added to wells coated with antiplatelet monoclonal antibody, then antibody-bearing platelets from the patient are added, followed by enzyme-labeled antihuman antibody (Figure 6).[26] In the immunobead assay, the following reagents are added to the wells, namely antiplatelet monoclonal antibody attached to beads, glycoprotein complexed with autoantibody-bearing platelets from the patient, and enzyme-labeled antihuman antibody (Figure 6).[26]

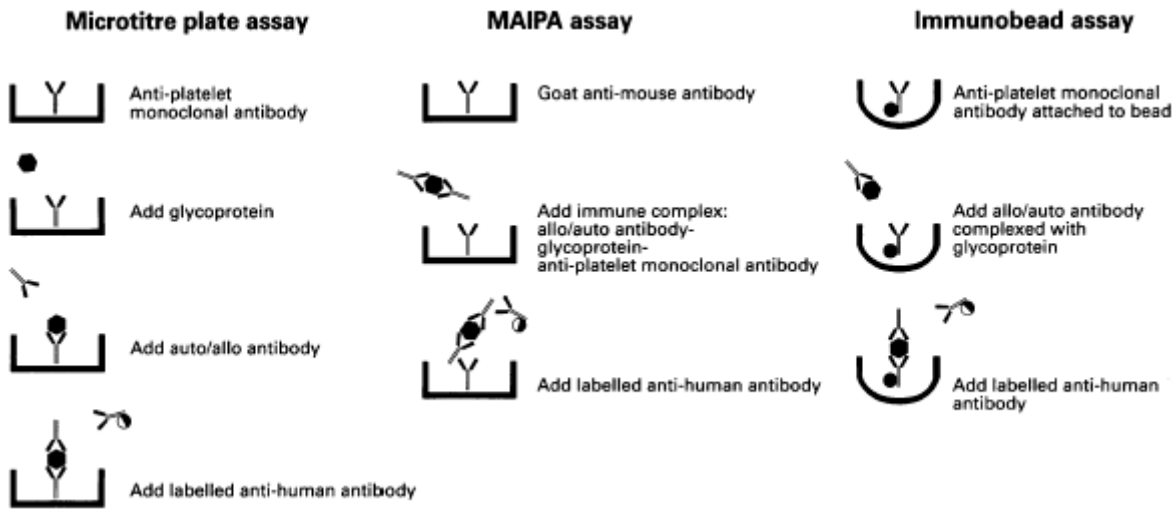

Figure 6 . Illustration of antigen capture assays.[26]

Management of ITP

Several factors playing a role in management of ITP are profuse bleeding, hemorrhagic comorbidity predisposition, complications of specific treatment, activities of living and life style, and tolerance to adverse effects.[19] Treatment is rarely indicated in patients with platelet counts above 50,000 per ìL, without bleeding associated with platelet dysfunction or other hemostatic defects, trauma, and surgery.[19,27] The management of ITP depends on platelet count and degree of bleeding. Treatment is aimed at interfering with antibodies capable of platelet destruction, by inhibiting the function of macrophage Fcã receptors and decreasing the production of antiplatelet antibodies.[28] First line treatment includes observation, corticosteroids, IVIg, or anti-D.[29]

Corticosteroid therapy in patients with ITP aims at increasing the platelet count through several mechanisms, i.e. reducing the platelet-destroying capability of macrophages, reducing autoantibody production, inhibiting platelet-autoantibody binding, and increasing levels of thrombopoeitin for stimulating megakaryocyte progenitors. Treatment with corticosteroids, such as prednisone at a dosage of 1-2 mg/kg/day may increase the platelet count by about 75%. Prednisone as initial firstline standard therapy for patients with ITP is usually administered at a dosage of 0.5-2 mg/kg/day, until the platelet count increases by ≥30,000-50,000/ìL, which takes several days to several weeks. To prevent complications from corticosteroid use, prednisone may be administered by tapering off and subsequently stopping, if there is no response after four weeks of therapy.[19] Parenteral administration of high-dose methylprednisone is indicated for treating patients who fail to respond to firstline treatment.[19] There are several studies on corticosteroid therapy in adult patients with ITP.[30,31] These studies found that 51.9%-80% of patients had a good response to dexamethasone, with the platelet count increasing after treatment. Anti-D immunoglobulin is one of the treatments for ITP, after the Food and Drug Administration (FDA) licensed the use of intravenous Rh (D) immunoglobulin (anti-D IVIg) in March 1995.[32] Anti-D immunoglobulin is only effective in non-splenectomized Rh (D) positive patients, where the antibodies are bound to the D antigen on red blood cells.[33] Anti-D immunoglobulin acts by clearance of anti-D coated red blood cells through macrophage Fc receptors in the reticuloendothelial system, thus

minimizing the clearance of antibody-coated platelets and increasing the platelet count.[32-34]

The standard dose of intravenous anti-D immunoglobulin is 50 mg/kg/day and the preparation takes 72 hours to produce a significant increase in platelet count. Treatment with anti-D immunoglobulin is not recommended as a firstline treatment to increase the platelet count in patients with advanced thrombocytopenia.[33]

The goal of secondline treatment, such as splenectomy in patients with ITP is to attain increased platelet counts. Splenectomy is indicated in patients failing to respond to corticosteroid therapy or requiring continuous platelet therapy. Splenectomy reduces interactions between T and B cells involved in antibody synthesis.[13] Indications for splenectomy after corticosteroid therapy are the following: a) platelet counts of less than 50,000 per ìL after 4 weeks of therapy; b) platelet counts remaining below normal after 6-8 weeks; and c) normal platelet counts, but decreasing upon reduction of corticosteroid dosage.[14] Around 80% of patients with ITP respond to splenectomy, with a five-year continuous response being encountered in 66% of patients without the need for additional therapy. Around 14% of patients are unresponsive to treatment and about 20% of patients relapse within weeks, months or years afterwards. Splenectomy also gives rise to complications, such as bleeding, infections, and thrombosis. Since ITP and splenectomy are both associated with a risk of thromboembolism, patients with ITP should receive appropriate thromboprophylaxis after surgery, and additionally long-term antibiotic prophylaxis, such as phenoxymethypenicillin 250-500 mg or erythromycin 500 mg twice daily.[19,29]

In secondline treatment, cyclosporine A may be administered, at a dosage of 2.5 - 3 mg/kg/day. The drug is effective as a single agent in patients with ITP, but its side effects may make some patients uncomfortable, particularly patients of advanced age.[19,35]

Immunosuppression with oral or intravenous cyclophosphamide is beneficial in patients who are difficult to treat with corticosteroids and/or splenectomy.[19] Mycophenolate mofetil (MMF) is an antiproliferative immunosuppressant useful in certain patients with ITP. It is administered at increasing dosages (250 mg up to the optimal dosage of 1,000 mg/day twice weekly), and increases platelet production in 39% of patients with refractory ITP.[19,36] However, according to 2011 Clinical Guidelines there are insufficient data for specific recommendations to use immunosuppressant therapy.[29]

A more recent development in ITP management is the use of TPO receptor agonists, such as romiplostim and eltrombopag, for stimulating platelet production through activation of TPO receptors. These preparations are second generation TPO receptor agonists which have been approved by the US Food and Drug Administration (FDA) since 2008. The first generation TPO to be studied for clinical application was recombinant human TPO (rhTPO), but this preparation had the disadvantage of inducing TPO autoantibody formation in healthy volunteers.[37,38] Romiplostim is injected subcutaneously once weekly at doses of 1–10 ìg/kg.[39] Eltrombopag is to be used at an initial oral dose of 50 mg once daily, but not exceeding 75 mg/day,[40] to achieve and maintain a platelet count $\geq$50 x 10^9/L necessary to reduce or prevent the risk of bleeding.[40,41] The drug has to be given on an empty stomach one hour before or two hours after a meal. Nplate and Promacta are brand names of romiplostim and eltrombopag, respectively, while Revolade is an eltrombopag-containing preparation that has been EU-approved since 2010 for adult chronic ITP.[41]

In emergency cases, such as patients requiring immediate surgery, or patients with uncontrolled gastrointestinal or urinary tract hemorrhages, where an increased platelet count is necessary, firstline combination therapy may

be given, such as prednisone and IVIg. High-dose methylprednisolone is also beneficial for emergencies, and platelet transfusion with or without IVIg will increase the platelet count by more than 20,000/ìL in 42% of ITP patients with hemorrhage and may possibly attenuate the hemorrhage. Administration of antifibrinolytics, such as oral or intravenous tranexamic acid and epsilon aminocaproic acid, may also be beneficial for prevention of recurrent hemorrhage in patients with severe thrombocytopenia, although their effectiveness has not been evaluated in patients with ITP.[19]

CONCLUSIONS

Idiopathic thrombocytopenic purpura is a disorder characterized by decreased platelet counts due to platelet-bound specific autoantibodies, accompanied by clinical signs of hemorrhage. Management of ITP depends on the platelet count and degree of bleeding. TPO receptor agonists including eltrombopag and romiplostim are an important new option in treating ITP.

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