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Immune Thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is a common hematologic disorder characterized by isolated thrombocytopenia. ITP presents as a primary form characterized by isolated thrombocytopenia (platelet count < 100×10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia, or a secondary form in which immune thrombocytopenia develops in association with another disorder that is usually immune or infectious. ITP may affect individuals of all ages, with peaks during childhood and in the elderly, in whom the age specific incidence of ITP is greatest. Bleeding is the most common clinical manifestation of ITP, with the risk of bleeding and related morbidity increased in elderly patients. The pathogenesis of ITP is complex, involving alterations in humoral and cellular immunity. Thrombocytopenia is caused by antibodies that react with glycoproteins expressed on platelets and megakaryocytes (glycoprotein IIb/IIIa, Ib/IX and others), causing shortened survival of circulating platelets and impairing platelet production. Diminished numbers and function of regulatory T cells, as well as the effects of cytotoxic T cells also contribute to the pathogenesis of ITP. Corticosteroids remain the most common first line therapy for ITP, occasionally in conjunction with intravenous immunoglobulin (IVIg) and anti-Rh(D). However, these agents do not lead to durable remissions in the majority of adults with ITP, and considerable heterogeneity exists in the use of second line approaches, which may include splenectomy, Rituximab, or thrombopoietin receptor agonists (TRAs). This review summarizes the classification and diagnosis of primary and secondary ITP, as well as the pathogenesis and options for treatment. Remarkable advances in the understanding and management of ITP have been achieved over the last decade, though many questions remain.

Keywords

immune; thrombocytopenia; ITP; platelets; thrombopoietin; splenectomy

Definition and history

ITP is a common hematologic disorder that affects patient of all ages, genders and races. Initially known as “idiopathic thrombocytopenic purpura”, an International Working Group (IWG) on ITP recently recommended that this disease be designated “Immune ThrombocytoPenia” (retaining the abbreviation ITP); this terminology recognizes the immune pathogenesis of ITP and the fact that patients with ITP may not uniformly exhibit

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purpura or bleeding manifestations[1]. The IWG also proposed terminology to allow standardized disease classification (Table 1). In this scheme, *primary* ITP is defined as isolated thrombocytopenia (platelet count < 100×10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia[1]. Secondary ITP is defined as any form of immune thrombocytopenia other than primary; these might include thrombocytopenia secondary to systemic lupus erythematosus, hepatitis C infection or lymphoproliferative disorders. The term "acute ITP" has been replaced by "newly-diagnosed ITP", which refers to ITP diagnosed within the preceding 3 months[1]. Immune thrombocytopenia of 3-12 months duration is designated as "persistent ITP", while "chronic ITP" is defined as disease of more than 12 months duration. "Severe ITP" refers to the presence of bleeding symptoms at presentation, or the development of new bleeding symptoms while on therapy, requiring additional intervention. "Refractory ITP" designates cases of immune thrombocytopenia that have not responded to splenectomy or have relapsed thereafter, and are severe or pose sufficient risk of bleeding to require ongoing therapy. Definitions to standardize criteria for responses to ITP therapy have also been proposed[1].

ITP has probably existed for centuries, and its history has recently been reviewed by Stasi and Newland[2]. Initial descriptions of purpura date to the Greco-Roman era and have been attributed to physicians such as Hippocrates and Galen. The most thorough early description of ITP was from Werhlof in 1735, who described a 16 year old girl with post-infectious bleeding symptoms including epistaxis and hematemesis. In 1808, Willan described "purpura simplex", characterized by diffuse petechiae in the absence of systemic symptoms and occurring primarily in women and children. The recognition of platelets as a distinct entity in the blood with an important role in hemostasis is attributed to Bizzozero in 1882, and led to the correlation between "purpura simplex" and thrombocytopenia, reported by Brohm in 1883[2]. Kaznelson, a medical student, hypothesized that ITP resulted from destruction of platelets in the spleen; this led to the first splenectomy for ITP, performed by Kaznelson's mentor, Professor Doktor Schoffler, in 1916, inducing complete resolution of severe thrombocytopenia in a 36 year old woman[2].

Etiology and Pathogenesis: Causes and mechanisms of primary and secondary ITP

The pathogenesis of ITP involves loss of tolerance to glycoproteins expressed on platelets and megakaryocytes [3-10]. ITP is not a single disorder, but a syndrome in which thrombocytopenia may be primary or occur secondary to underlying infectious or immune processes[7;8].

Cines et al have proposed that the immune tolerance defects in ITP can be divided into three categories that include 1) peripheral tolerance defects arising in the setting of immune stimulation 2) differentiation blocks with skewed peripheral B-cell subsets, and 3) central tolerance defects arising during development, or in the bone marrow[7]. Underlying mechanisms associated with each of these may explain the clinical characteristics of individual cases of ITP. ITP resulting from loss of peripheral tolerance is proposed to be platelet-specific, more amenable to therapy, and less likely to recur after treatment. In contrast, defects in central tolerance affect multiple cell types, and treated patients are more prone to relapse due to intrinsic autoreactivity.

Secondary ITP

Examples of secondary ITP related to loss of peripheral tolerance include *ITP of childhood*, which is preceded by a viral-like illness in 2/3 of affected children, and remits spontaneously in 80% of patients[11;12]. Loss of peripheral tolerance may also underlie the development of

secondary ITP due to vaccines or infectious exposures such as the *mumps-measles-rubella (MMR) vaccine* (incidence of 1 in 40,000 administrations), *Helicobacter pylori infection*, and infection with *cytomegalovirus* (CMV) or *Varicella-Zoster virus* (VZV)[13]. Perhaps the most common infection associated with ITP is *hepatitis C*, which is present in up to 20% of ITP cases, with a higher incidence in certain geographical areas[14]. The pathogenesis of HCV-associated ITP may involve activation of B cells, as well as antibodies cross-reactive with HCV and platelet GPIIIa[15]. *HIV* is another well-described cause of ITP; thrombocytopenia results from decreased platelet production due to infection of megakaryocytes as well as cross-reactive antibodies that react with viral proteins and a linear epitope on GPIIIa (amino acids 44-66)[16], causing platelet lysis through generation of reactive oxygen species[17]. The incidence of thrombocytopenia in patients infected with HIV increases with disease progression, and decreases in response to highly active anti-retroviral therapy (HAART).

Examples of ITP associated with blocks in differentiation with B cell skewing include *chronic lymphocytic leukemia* (CLL), in which thrombocytopenia develops in 1-5% of cases[18] and may correlate with poor prognostic markers and decreased survival. *Hodgkin's disease, non-Hodgkin's lymphomas and large granulocytic leukemia (LGL)* are associated with secondary ITP, though ITP develops in less than 1% of cases. ITP may develop in up to 10% of patients with *common variable immunodeficiency*. The pathogenesis of ITP or other immune disorders such as autoimmune hemolytic anemia that occurs in these patients may involve defects in B cell tolerance checkpoints and/or deficiencies of memory B cell subsets.

Examples of defects in central tolerance associated with secondary ITP include the *autoimmune lymphoproliferative syndrome (ALPS)*, a disorder linked to defective B and T cell apoptosis associated with mutations in genes encoding Fas, Fas-L or other apoptosis mediators such as caspases[19]. Patients develop hepatosplenomegaly and lymphadenopathy, and 20% develop immune thrombocytopenia, sometimes in association with autoimmune hemolytic anemia and/or neutropenia. *Evan's syndrome* is characterized by immune thrombocytopenia and autoimmune hemolytic anemia[20]. The *antiphospholipid syndrome* may be associated with immune thrombocytopenia in up to 1/3 of patients, while up to 40% of patients with ITP may have antiphospholipid antibodies. The role of antiphospholipid versus anti-platelet glycoprotein antibodies in the development of thrombocytopenia is uncertain, since anti-GPIIIa antibodies have been described in thrombocytopenic patients with antiphospholipid antibodies[21]. Immune thrombocytopenia develops in up to 1/3 of patients with *systemic lupus erythematosus* (SLE) which is associated with a broad array of autoantibodies. The management of thrombocytopenia in lupus patients is difficult, and corticosteroids and splenectomy are less effective than in primary immune thrombocytopenia[22]. Defects in central tolerance also develop *post-transplantation*; a number of mechanisms may be involved, including formation of alloantibodies against donor platelets in the setting of mixed chimerism.

Primary ITP

Like secondary ITP, diverse clinical features and responses to therapy in patients with primary ITP suggest that this apparently more defined disorder also derives from heterogeneous mechanisms. Most patients with primary ITP display a $CD4^+$ Th0/Th1 cytokine profile[4;23] (associated with increased levels of IFN-γ and IL-2) and decreased peripheral $Th2^+$ and T regulatory (Treg) cells[24]. The increased Th1/Th2 ratio may correlate inversely with the platelet count. Alterations in levels of apoptosis regulatory factors in T-cells from patients with ITP may influence T-cell subset expression and promote survival of autoreactive T-cell clones[4]. Reversions of Th1/Th2 ratios and normalization of T cell Vβ spectratyping may follow therapy with Rituximab or splenectomy[10]. Likewise, levels of regulatory T-cells improve with responses to Rituximab and other ITP therapies, including

thrombopoietic agents, suggesting a more complex mechanism for Rituximab than CD20+ B-cell depletion[25;26]. These findings are consistent with the hypothesis that autoantibodies in ITP develop as a consequence of T cell-dependent antigen-driven clonal expansion and somatic mutation[27]. $CD8^+$ Tc (cytotoxic) T cells may also contribute to the pathogenesis of primary ITP by causing platelet lysis through expression of granzymes A and B, Apo1/Fas and perforin[28]. Cytotoxic T cells from patients with ITP also mediate toxicity toward megakaryocytes, and increased numbers of $VLA4^+CD3^+CD8^+$ T cells expressing the homing receptor $CX3Cr1^+$ have been observed in the bone marrow of patients with ITP[29].

Antiplatelet antibodies—The observations of Katznelson and Schoffler provided evidence for a central role of the spleen in the pathogenesis of ITP. Other studies demonstrated that injection of an extract of splenic tissue from ITP patients into rabbits produced a rapid decrease in the platelet count. The studies of Harrington et al. in 1951 were the first to provide evidence of a circulating plasma component in the pathogenesis of human ITP[30]. Harrington arranged an exchange transfusion between himself and a woman with chronic ITP and a platelet count of 5×10^9/L. Afterwards, he developed severe thrombocytopenia that resolved over the next 7 days. Subsequent studies with additional volunteers yielded similar results, although the response to ITP plasma was variable and severe thrombocytopenia developed in only 16 of 26 recipients. In 1965, Schulman reported that the thrombocytopenic factor in ITP plasma was a platelet-reactive IgG antibody[31]. Studies performed in the 1970s demonstrated increased levels of platelet-associated IgG in 90% of patients with ITP[32], although subsequent work demonstrated that much of this material bound to platelets non-specifically or was contained within α-granules. The development of antigen-specific antiplatelet antibody assays in the 1980s identified IgG reactive with platelet surface glycoproteins, primarily GPIIbIIIa (integrin αIIbβ3) and GP Ib/IX, in 60% of patients with ITP[6;33]. Though antiplatelet antibodies may initially be directed toward a single platelet glycoprotein, following uptake of antibody-coated platelets and processing of antigenic peptides from originally non-targeted platelet glycoproteins, the production of antibodies against these new targets may ensue as a result of epitope spreading (Figure 1)[34].

Antibody-dependent mechanisms of platelet destruction—Platelet survival is decreased in patients with ITP, with the majority of platelets cleared in the spleen and liver[35-38]. Antibody-coated platelets are removed by splenic macrophages through Fcγ-receptor mediated phagocytosis[9]. Polymorphisms in the gene encoding FcγRIII (FcγRIIIA -581 V/V), a subtype of Fcγ receptor, are over-represented in adults and children with ITP; the V/V isoform of this receptor binds IgG1 and IgG3 with greater affinity than the F/F, or F/V isoforms. An important role for FcγRIII in humans is also suggested by the ability of a monoclonal antibody to this receptor (mAb 3G8) to increase the platelet count in patients with refractory ITP[39]. While one group has reported an essential role for FcγRIIa in the therapeutic effect of intravenous immunoglobulin (IVIg) in preclinical models, this finding has not been consistently reproduced.

Though uptake in the spleen is the primary mechanism by which antibody-coated platelets are cleared in patients with ITP, other mechanisms of platelet destruction exist. The failure of splenectomy in 1/3 of patients may reflect alternative mechanisms of platelet clearance and/or decreased platelet production[10]. Antiplatelet antibodies from more than half of a cohort of 240 patients with ITP were capable of fixing complement on platelets[40], and some anti-platelet antibodies induce complement-dependent lysis of platelets in vitro. In patients with HIV, antibodies to platelet GPIIIa amino acids 49-66 cause platelet lysis in a complement-independent manner by generation of peroxides through the NADH/NADPH oxidase system[17].

Evidence for decreased platelet production in patients with ITP—The concept of decreased platelet production as a cause of ITP was first suggested by Frank in 1915. Like platelets, megakaryocytes express GPIIb/IIIa and GPIb/IX, which are targets for platelet-reactive autoantibodies. Increased numbers of histologically abnormal megakaryocytes, specifically younger and more immature forms, were noted more than 70 years ago in patients with ITP. Similar abnormalities were observed in the megakaryocytes of healthy individuals infused with ITP plasma, and marked inhibition of megakaryopoiesis was observed in rats treated with antiplatelet serum. Electron microscopic studies have confirmed ultrastructural abnormalities in megakaryocytes in patients with ITP consistent with apoptosis and para-apoptosis; these include cytoplasmic vacuolization, mitochondrial swelling, abnormal chromatin condensation and increased staining for activated caspase-3[41].

Chang et al demonstrated that plasma from pediatric patients with ITP that contained anti-GPIb and/or anti-GPIIbIIIa antibodies inhibited the maturation of umbilical cord mononuclear cells into mature megakaryocytes in the presence of thrombopoietin[42]. McMillan et al extended this work, demonstrating that plasma from 12 of 18 adult ITP patients decreased the production of megakaryocytes from CD34 positive cells: these effects were mediated by IgG, and prevented by adsorption of IgG fractions with immobilized GPIIb/IIIa[43].

Measurement of platelet turnover rates provides convincing evidence that platelet production is impaired in patients with ITP. Since platelet production is equal to platelet destruction at stable platelet concentrations, and since platelet destruction can be measured through the use of ^{111}In-labeled platelets, platelet production rates can be estimated. Early thrombokinetic studies suggested that platelet production rates were increased in ITP, though these studies relied on allogeneic platelets labeled with Cr^{51}[35;44], a less effective platelet label. However, later studies in which allogeneic and autologous platelet survival were studied in the same individuals demonstrated significantly longer survival of autologous platelets[36;45;46], particularly in patients in whom autologous platelet survival exceeded 1 day[9]. Platelet production rates estimated based on these latter studies led to the conclusion that platelet production is normal or decreased in most patients with ITP.

Levels of plasma thrombopoietin are not elevated in patients with ITP, reflecting the fact that thrombopoietin production occurs in the liver and is largely constitutive[47]. Plasma thrombopoietin levels are regulated primarily via clearance, mediated through binding of thrombopoietin to the thrombopoietin receptor (c-Mpl) on circulating platelets and to bone marrow megakaryocytes. Accelerated clearance of platelets in ITP leads to enhanced metabolism of thrombopoietin, and thrombopoietin production rates do not increase proportionally [48].

Role of cellular immunity in platelet destruction and impaired platelet production—The maturation of antiplatelet antibodies is T-cell and antigen-dependent[27]. However, antiplatelet antibodies are only detectable in 60% of patients[33], and ITP may enter remission despite the continued presence of anti-platelet antibodies[10]; these observations suggest that antibody-independent mechanisms account for thrombocytopenia in some individuals. In one study, CD8+ cytotoxic T-cells from patients with active ITP but without detectable antiplatelet antibodies bound and lysed platelets in vitro, although CD8+ T-cells from patients with ITP in remission did not[28]. CD3+ T cells from patients with ITP also demonstrated increased expression of genes that mediate cell-dependent cytotoxicity, including perforin, TNF-α and granzyme A and B[28]. Li et al reported that CD8+ T cells also prevented apoptosis of autologous megakaryocytes [49], which is involved in budding and release of proplatelets.

Clinical Features of ITP

Epidemiology

ITP affects patients of all genders, races and ages [50]. Studies from Scandinavia suggest a prevalence of ITP ranging from 4.6 to 5.3 cases per 100,000 children[51]. In a study that analyzed data from the Maryland Health Care Commission, the prevalence of ITP was 9.5 per 100,000 children ages 1-5, 7.3 per 100,000 in children ages 6-10, and 4.1 per 100,000 in children of ages 11-14[52]. Analysis of the United Kingdom (UK) General Practice Research Database (GPRD) identified a higher incidence of ITP in boys between ages 2 and 5 (9.7 cases versus 4.7 cases in girls per 100,000 patient-years, respectively) compared to that in teenagers between ages 13-17 (2.4 cases per 100,000 patient-years, with equal sex distribution)[53].

The overall prevalence of ITP in adults is comparable to that in children[54]. A prospective, population-based study of patients greater than 16 years old with newly-diagnosed ITP demonstrated an annual incidence 1.6 cases per 100,000; the incidence was slightly higher in females between 45-49 years but otherwise no gender differences existed[55]. The highest age specific incidence of ITP was in individuals over 60 years. A Scandinavian study identified an ITP incidence of between 2.25 and 2.68 per 100,000 individuals/year; the incidence was greater in females (female:male ratio 1.7) and the elderly[56]. Other studies have suggested a prevalence of ITP in adults ranging from 4.0 to 23.6/100,000 patient years. A study based on queries of physician offices suggested a higher prevalence of ITP in females under 70 years, but a higher incidence in men above age 70[57].

Clinical manifestations of ITP

Since ITP is often secondary, a patient with newly-diagnosed thrombocytopenia should be evaluated for symptoms associated with disorders causing secondary ITP such as rashes, arthralgias or serositis associated with systemic lupus, hepatomegaly and elevated transaminase levels associated with hepatitis C or fever and lymphadenopathy associated with infection or lymphoid malignancy. A history of prescription and non-prescription drug intake, including herbs and supplements, is of critical importance.

In this section, we will focus on the manifestations of primary ITP, which may dominate even in cases of secondary ITP.

Bleeding—Bleeding is the most common clinical manifestation of ITP, presenting as mucocutaneous bleeding involving the skin, oral cavity and gastrointestinal tract. Purpura, usually on the extremities (“dry purpura”) may often appear without an obvious precipitating event. Mucosal bleeding include epistaxis, menorrhagia, and gingival and gastrointestinal bleeding[55]. Patients with severe thrombocytopenia may display oral hemorrhagic bullae (“wet purpura”), which may be a harbinger of more severe bleeding manifestations in the gastrointestinal tract or elsewhere. Bleeding from more distal sites in the GI tract may develop at the site of unsuspected preexisting lesions.

Intracranial hemorrhage is the most feared complication of ITP. The incidence of intracranial hemorrhage in children has been estimated to be less than 0.2%, almost always occurring at platelet counts $< 10 \times 10^9$/L [12;58]. A recent report from the International Cooperative Study demonstrates that this complication occurs more frequently in adults than children, occurring in 10 of 1784 children and 6 of 340 adults with newly diagnosed ITP[59]. In a natural history study that enrolled 152 patients, 4 patients died of ITP-related causes in the first two years (1 due to hemorrhage, 3 due to infection), and 2 died of ITP related causes during long-term follow up (1 with post-splenectomy sepsis, 1 with refractory

bleeding and a platelet count of 2×10^9/L)[60]. Patients with ITP may be at increased risk of hematologic malignancy[61], consistent with the demonstration of an increased frequency of CLL phenotype lymphocytes in patients with ITP[62].

Several risk factors for bleeding in ITP patients have been identified. Cohen et al identified 49 cases of fatal hemorrhage in 1718 patients from pooled ITP case series[63]. The overall risk of fatal hemorrhage was between 0.0162 and 0.0389 cases per patient-year, with a risk of 0.004 in patients below 40 years increasing to 0.130 for patients above age 60. Cortelazzo et al observed an overall incidence of hemorrhagic events of 3.2% per patient-year in patients with ITP. Hemorrhagic events at similar platelet counts occurred in 10.4% of patients > 60 years, compared to 0.4 percent in patients under age 40. A previous history of hemorrhage also predicted bleeding (relative risk 27.5)[64]. Michel et al compared the incidence of bleeding and other outcomes in 55 ITP patients older than 70 years (mean age 77.8 ± 6.1 years) with those of a younger cohort (mean age 40.3 ± 14.9 years)[65]. The median platelet count at diagnosis did not differ between the two groups, though bleeding symptoms were more frequent in the older (82%) versus the younger (62%).

In a prospective study of 245 patients greater than 16 years old with newly-diagnosed ITP, 30 (12%) presented with frank bleeding, 28% were asymptomatic, and the remainder displayed purpura[55]. Bleeding was uncommon at platelet counts above 30×10^9/L. However, in this and other studies a direct correlation between the platelet count and severity of bleeding was not uniformly demonstrated, reflecting the observation that occasional individuals with very low platelet counts exhibit little bleeding, while others with platelet counts > 30×10^9/L bleed frequently. This conundrum might be explained by binding of some antiplatelet antibodies to highly restricted regions in GP IIb β-propeller domain[66] near the ligand (fibrinogen) binding site, potentially interfering with platelet aggregation.

Fatigue—Fatigue is an underappreciated symptom in patients with ITP, occurring in approximately 22% of children, and 22 to 39% of adults[67]. Significant improvements in fatigue and several health-related quality of life measurements have been observed in successfully-treated patients[68]. In one study, univariate analyses demonstrated that the presence of fatigue correlated with a platelet count below 100×10^9/L, treatment with steroids, bleeding, and several other factors, but not with duration of ITP, age or gender[69]. Fatigue in ITP patients may reflect, in part, elevated levels of inflammatory cytokines, including IL-2 and IFN-γ, associated with the Th1 profile.

Thrombosis—Recent studies suggest that patients with ITP have an increased risk of thrombosis. Aledort et al initially reported 18 thromboembolic events in 186 adults with chronic ITP[70]. Sarpatwari et al observed that the adjusted hazard ratio for venous, arterial or combined thromboembolic events in patients with ITP mined from the UK General Practice Research Database were 1.58 (95% CI, 1.01-2.48), 1.37 (95% CI, 0.94-2.00) and 1.41 (95% CI 1.04-1.91), respectively[71]. The severity of thrombocytopenia correlated with the development of thrombosis. A study utilizing a matched ITP cohort from the Danish National Patient Registry observed an incidence rate ratio for venous thromboembolism in patients with ITP of 2.04 (95% CI: 1.45-2.87)[72].

The mechanisms underlying the paradoxical development of thrombosis in patients with ITP are uncertain. The incidence of antiphospholipid antibodies (APLA) is increased in patients with ITP, and ITP patients with APLA may develop thrombosis more frequently[73]. Though current guidelines do not recommend routine screening of ITP patients for APLA[74;75], this should be considered in patients who develop thrombosis. Other factors that may contribute

to the development of thrombosis include elevated levels of prothrombotic, platelet-derived microparticles and complement activation on antibody-coated platelets[76].

The management of thrombosis in thrombocytopenic patients with ITP is not addressed by current guidelines. Many experts consider anticoagulation to be justified at platelet counts above approximately 40×10^9L, though this should be individualized depending upon the severity of the thrombotic event and characteristics of the patient. Aggressive treatment of ITP is warranted during anticoagulation therapy.

Laboratory Studies

ITP is characterized by isolated thrombocytopenia without abnormalities in erythrocyte or leukocyte number or morphology. Platelet size may be normal or increased, though not usually to the degree observed in inherited causes of thrombocytopenia such as MYH9-related macrothrombocytopenias[77]. A careful examination of the peripheral blood smear is essential to exclude other causes of thrombocytopenia such as microangiopathic processes, platelet satellitism or pseudothrombocytopenia. Myelodysplastic syndromes or acute and chronic leukemias occasionally present with isolated thrombocytopenia, though in many cases review of the peripheral blood will reveal characteristic changes in other hematopoietic lineages. A recent report demonstrates decreases in the absolute immature platelet fraction (A-IPF) in patients with ITP. Treatment with eltrombopag increased the A-IPF[78].

Normal or increased numbers of megakaryocytes are present in the bone marrow of ITP patients, sometimes with an increase in immature megakaryocytes. Ultrastructural examination may demonstrate evidence of megakaryocyte apoptosis[41].

The sensitivity of measurements of platelet-associated IgG for the diagnosis of ITP is 91%, although the specificity is only 27%; thus, the positive predictive value is only 48% and the diagnostic utility of such assays is poor. Measurement of specific platelet glycoprotein antibodies offers greater specificity (78-92%), though their diagnostic value is limited by low sensitivity (49-66%) leading to a positive predictive value of only 80-83%[34;79].

A number of other laboratory parameters in the diagnostic evaluation of ITP have been recommended by the ITP IWG[75]; those considered to comprise the basic evaluation or to be of potential utility are listed in Table 2. A reticulocyte count and direct antiglobulin (Coombs) test are recommended to exclude concurrent autoimmune hemolytic anemia. Blood type may be useful in determining the utility of therapy with anti-Rh(D), while quantitative immunoglobulin levels may lead to the diagnosis of common variable immunodeficiency. Screening for HIV, HCV and H. Pylori is recommended regardless of geographic location, although the importance of H. Pylori in the development of ITP in North America is not well established.

Differential Diagnosis

The diagnosis of primary ITP is one of exclusion. Both non-immune causes of thrombocytopenia and secondary immune thrombocytopenia must be considered (Table 3). Non-immune causes of thrombocytopenia include exposure to drugs or toxins that suppress platelet production (alcohol, chemotherapeutic agents), splenic sequestration of platelets, primary bone marrow disorders, prior radiation exposure (therapeutic or incidental), and inherited thrombocytopenias.

Inherited thrombocytopenias may be misdiagnosed as ITP[80]. The diagnosis should be suspected in a patient with a family history of thrombocytopenia and in patients who do not

respond appropriately to standard ITP therapy. In some cases, characteristic findings such as absent radii (thrombocytopenia with absent radii, or TAR syndrome), right heart defects (DiGeorge syndrome) or specific laboratory features such as large platelets and Döhle bodies in neutrophils (*MYH9*-related disorders) support the diagnosis of familial thrombocytopenia[81].

The Bernard-Soulier syndrome is an autosomal recessive familial thrombocytopenic disorder characterized by the absence of the platelet GPIb-IX complex and associated with large platelets, lack of platelet aggregation by high-dose ristocetin, and bleeding[82]. Wiskott-Aldrich syndrome is an X-linked disorder characterized by severe immunodeficiency and small platelets. Congenital amegakaryocytic thrombocytopenia (CAMT) is an autosomal recessive disorder characterized by severe thrombocytopenia and absence of megakaryocytes, resulting from mutations in the c-Mpl. Inherited thrombocytopenias also occur in association with mutations in transcription factors that regulate megakaryocyte development, including GATA1 (sex-linked inheritance) and RUNX1 (autosomal dominant). Laboratories in Europe and the United States provide genetic testing for these disorders (see www.genetests.org).

Therapeutic Options and Prognosis

Management of ITP in children

Spontaneous recovery from ITP occurs in approximately 80% of children with ITP, usually within 6 months, but occasionally over a year or more [11;12]. Severe hemorrhage occurs in 1 in 200 children with newly-diagnosed ITP, and intracerebral hemorrhage occurs in less than 1 in 500, most often in the first month after diagnosis[83]. For those requiring treatment, a short course of corticosteroids, IVIg, or anti-D (in Rh-positive individuals) usually results in rapid improvement.

Several therapeutic approaches exist for the 20% of children who develop persistent thrombocytopenia. Rituximab has similar efficacy in children as in adults and is associated with a long term remission rate of 22% in retrospective analyses[84]. Romiplostim induces platelet responses in 83-88% of children with chronic ITP[85], although long-term safety in children is not established. Splenectomy is reserved for severe persistent thrombocytopenia and bleeding and results in complete remission in approximately 75% of children[11]. The risk of post-splenectomy sepsis is greater in children than in adults, and splenectomy is usually deferred until at least 5 years of age[86]. Vaccination against *S pneumoniae, N meningitidis*, and *H influenzae* type b should be administered prior to splenectomy in children and adults, and penicillin prophylaxis is recommended until adulthood.

Management of ITP in adults

Adult patients with ITP have increased morbidity and mortality (RR 2.3, 95% CI 1.8-3.0) compared to the general population, particularly those unable to maintain a hemostatic platelet count > 30×10^9/L despite therapy[60;61]. Bleeding and infection contribute equally to mortality[60].

The management of ITP in adults is more complex than children since most cases evolve into chronic disease, and the risk of bleeding is increased greater[55;61;64]. The goal of therapy is to achieve a hemostatic platelet count, generally considered to be at least 20-30×10^9/L[60], while causing the least toxicity. Treatment is rarely required above a platelet count of 50×10^9/L[75], and must be individualized to account for age, lifestyle, individual bleeding risk and patient preference.

There are no controlled studies demonstrating the superiority of any specific treatment algorithm in ITP, and hence no well-delineated "standard of care". The ITP IWG has divided therapies into first line treatments—consisting of corticosteroids, IVIg and IV anti-D, and second line therapies which consist of splenectomy and all other medical approaches[75] (Table 4).

First line therapy—*Corticosteroids* remain the most commonly used first line therapy for ITP. At least 80% of patients with ITP initially respond to corticosteroids, although most of these individuals relapse when steroids are tapered[75;87]. Several studies have examined whether more intensive dosing of steroids in newly-diagnosed ITP leads to more durable remissions. Cheng et al reported that treatment with a single course of dexamethasone (40 mg/day for four days) led to sustained responses (platelet count > 50×10^9/L at 6 months) in 50% of responders [88]. Mazzucconi et al observed that treatment of newly-diagnosed ITP with 4-6 cycles of dexamethasone given at two week intervals led to relapse-free survival of 80-90% at 15 months[87]. However, in a small, randomized study, a single course of high dose dexamethasone did not induce a greater percentage of sustained responses than standard doses of prednisolone[89]. Zaja et al compared a combination of dexamethasone and Rituximab with dexamethasone alone in the initial treatment of ITP, demonstrating a higher sustained response rate at 6 months in patients that received the combination (63% vs 36%, n = 52, P <0.004, 95% CI 0.079-0.455); however, these differences were lost on longer follow up[90].

Intravenous immunoglobulin is often used in conjunction with corticosteroids, particularly when a rapid rise in the platelet count is desired. IVIg is also used to support the platelet count until more definitive therapy can be delivered to patients whose platelets fall upon tapering of corticosteroids. IVIg increases the platelet count in 60-80% of treated patients, often within days, and is effective in both non-splenectomized and splenectomized patients, although responses are usually of short duration (1-3 weeks). Several IVIg regimens are employed, but many clinicians prefer the convenience of a 1 gm/kg/day infusion for 1 or 2 days[10]. The activity of IVIg is mediated through several mechanisms, including modulation of Fcγ receptor expression and activity, inhibition of cytotoxic T cell activation, complement neutralization, cytokine modulation and inhibition of megakaryocyte apoptosis[91;92]. Toxicities include aseptic meningitis, fluid overload, nephrotoxicity, thrombosis, and rarely, severe hemolytic anemia.

Anti-Rh(D) binds to the Rh(D) antigen on erythrocytes leading to clearance of antibody-coated cells and inhibiting the clearance of opsonized platelets by the reticuloendothelial system[92]; other mechanisms including reduction in antigen specific B cell priming and modulation of Fcγ receptor and inflammatory cytokine levels may contribute. Anti-D is effective only in Rh(D) positive individuals with an intact spleen. Anti-D causes a hemolytic response that results in a drop in hemoglobin of 0.5 to 2 gm/dl, though more severe hemolysis may occur in approximately 1 in 1000 patients, rarely accompanied by disseminated intravascular coagulation, renal failure and death[93]. Many of these toxicities can be avoided by appropriate patient selection[94]. At the approved dose of 50 μg/kg, anti-D raises platelet counts in 70% of treated patients, though higher doses (75 μg/kg) increase response rates. In a single arm study, repeated dosing of ITP patients with IVIg for recurring thrombocytopenia led to durable responses in 43% of patients [95].

Second-Line therapy—Several second line therapies exist for treatment of ITP resistant to corticosteroids, IVIg or anti-D. The use of older second-line agents has decreased significantly due to the emergence of Rituximab and thrombopoietin receptor agonists (TRAs), which offer greater efficacy with lower toxicity (Table 4). In this section we will

focus on the use of newer agents in ITP; excellent reviews on the safety and efficacy of older agents are available[96;97].

Rituximab is a chimeric anti-CD20 antibody approved for treatment of lymphoma that is often used for ITP in patients who fail first line therapy. Whether it is best positioned before or after splenectomy or thrombopoietin receptor agonists (TRAs) is not established. In a systematic review of 313 ITP patients, half of whom were not splenectomized, 62.5% (95% CI, 52.6%–72.5%) of patients treated with Rituximab achieved a platelet count response (platelet increment of 50×10^9/L), with a median time to response of 5.5 weeks (range, 2–18 weeks) and a median duration of response of 10.5 months[98]. In another systematic review that included 364 non-splenectomized patients, the complete response rate was 41.5% with a mean time to response of 6.34 weeks and a median duration of response of 49 weeks[99]. In a single-arm prospective study of 60 non-splenectomized ITP patients, 40% achieved a platelet count at or above 50×10^9/L with at least a doubling from baseline at 1 year, and 33.3% of these responses were sustained at two years[100]. However, a pilot, randomized, placebo-controlled trial that assessed a composite endpoint demonstrated only a non-significant trend toward superior responses to Rituximab within 6 months of therapy initiation[101]. An appealing aspect of Rituximab therapy is its ability to induce durable responses in approximately 21% of adults[84]. Rituximab is usually administered at a dose of 375 mg/m^2 weekly for four weeks, although a lower dose regimen of 100 mg/m^2 may have similar efficacy[102]. Despite targeting CD20 on B cells, the mechanism of Rituximab may involve more complex immunologic modulation. Successful therapy correlated in one report with normalization of T cell subset distribution[103], and in another with reappearance of normal numbers and function of regulatory T cells[26].

Adverse effects of Rituximab include infusion reactions, serum sickness, and cardiac arrhythmias. Fatal reactivation of hepatitis B infection has occurred; thus, Rituximab is contraindicated in hepatitis B infected patients. Reactivation of latent JC virus leading to progressive multifocal leukoencephalopathy occurred in several patients treated with Rituximab, one of whom had ITP, though most were heavily pretreated with other immunosuppressive agents[104].

Splenectomy was the first successful treatment for ITP, and is still considered by some to be the “gold standard” since it provides the greatest opportunity for a durable remission[105]. Splenectomy may be offered to patients who fail to achieve sustained responses after steroid therapy, or may be used before or after a trial of Rituximab or TRAs. In a systematic review of 135 case series between 1966 and 2004, complete responses to splenectomy were observed in 66% of patients, with a median duration of follow-up of 28 months (range 1 to 153 months)[106]. In another systematic review of 1223 patients with ITP undergoing laparoscopic splenectomy, a 5-year success rate of 72% was reported[107]; most relapses occurred within the first 2 years after splenectomy. The use of splenectomy, especially in the United States and some European countries, has decreased from 50-60% to 20-25% in recent years[108]. Laparoscopic splenectomy carries a mortality risk and complication rate of 0.2 and 9.6%, respectively (compared to 1.0 and 12.9% with open laparotomy)[106]. Splenectomy has been associated with an increased risk of infection and postsplenectomy sepsis, with an estimated mortality of 0.73 per 1000 patient years determined from a historical cohort undergoing splenectomy for hereditary spherocytosis[109]. However, whether patients with ITP experience an increased risk of postsplenectomy infection compared to other patients with ITP who have not undergone splenectomy has not been established. In a large Danish study, infection in patients splenectomized for ITP relative that in non-splenectomized individuals with a matched indication (ITP) was observed only within the first 90 days following splenectomy (RR 2.6, 95% CI 1.3-5.1). No significantly increased risk was seen thereafter, with relative risk of 1.0 between 91 and 365 days, and 1.4 (95% CI:

1.0-2.0) beyond the first year[110]. Early infections result primarily from enteric pathogens[110]. Nevertheless, immunization against encapsulated organisms and aggressive treatment of febrile illness may reduce long term infection-related morbidity and mortality post-splenectomy.

Current guidelines differ on the relative place of splenectomy in the management of ITP. While both the International Working Group[75] and revised ASH guidelines[74] consider splenectomy an acceptable second line option, the former group weights splenectomy similarly to several other options, while the ASH guidelines *recommend* splenectomy (Grade 1B evidence) for patients who fail corticosteroids, while only *suggesting* Rituximab or thrombopoietic agents (Grade 2C evidence). Given the lack of comparative data between splenectomy, Rituximab or TRA therapy, treatment decisions should be individualized and encompass both physician and patient preferences[111].

The position of *thrombopoietin receptor agonists* (TRAs) in ITP therapy continues to evolve. While some clinicians reserve these agents for patients with refractory ITP, others suggest their use in newly-diagnosed ITP with the goal of sustaining the platelet count for the first year after diagnosis in hopes of spontaneous remission[112]. Neither of the two approved TRAs, Romiplostim and Eltrombopag, have direct sequence homology with thrombopoietin (Figure 2). Both enhance platelet production following binding to the thrombopoietin receptor, c-Mpl, on megakaryocytes, stimulating megakaryocyte proliferation and differentiation[113].

Romiplostim (Nplate) is a fusion protein comprised of four thrombopoietin peptidomimetic regions linked to an IgG Fc domain that provides in vivo stability[114]. It is administered as a weekly subcutaneous injection, dosed according to the platelet count. After initial phase I dose finding trials, the efficacy of Romiplostim over a 6 month period was assessed in two placebo controlled, phase III trials that that enrolled 63 splenectomized and 62 non-splenectomized patients, respectively, with severe, chronic ITP[115]. A durable platelet response, defined as a platelet count $>50 \times 10^9$/L during 6 of the final 8 weeks of treatment, was achieved in 38% of splenectomized patients (vs. 0% in placebo) and 61% of non-splenectomized patients (vs. 5% in placebo) that received Romiplostim. Romiplostim-treated patients were more likely to reduce or discontinue concomitant treatment (usually corticosteroids) and less likely to require rescue medications[115]. Romiplostim was also compared to standard of care in a randomized study involving 234 adult patients with ITP who had not undergone splenectomy. Over a 12 month period, Romiplostim treated patients demonstrated a 2.3 fold higher incidence of platelet responses, a decreased incidence of treatment failure (11% vs 30%), a lower incidence of splenectomy (9% vs 36%), less bleeding and a better quality of life[112]. The efficacy and safety of Romiplostim over a longer treatment period has also been assessed in a single arm extension trial of 407 patients[116]. This revealed that 90% of patients achieved the platelet response definitions (doubling of the platelet count and platelet count $> 50 \times 10^9$/L, or platelets $> 20 \times 10^9$ from baseline) at a mean Romiplostim dose of 3.62 μg/kg.

Eltrombopag (Promacta) is an oral, small molecule TRA with a similar mechanism as Romiplostim, although Eltrombopag binds to the transmembrane portion of c-Mpl rather than the ligand (thrombopoietin) binding site[117] (Figure 2). Following phase I dose finding trials, the drug was tested in severe, chronic ITP patients in 6 week and 6 month[118](RAISE), randomized, placebo-controlled trials. Platelet responses were seen in 59-79% of patients, compared to 16-28% of placebo treated patients. Splenectomized and non-splenectomized patients responded similarly, and treated patients experienced less bleeding with many able to reduce concomitant ITP medications. The long term safety and efficacy of Eltrombopag has been studied in the EXTEND study, which enrolled 301 patients, with 84 and 28 patients

treated for at least 3 and 4 years[119]. Overall, 88% of patients achieved a platelet count > 50 × 10^9/L at least once during the study; the pretreatment platelet count, history of splenectomy or previous use of ITP medication was not predictive of response. Clinically significant bleeding decreased from 16% at baseline to 0% at week 156. A unique toxicity of Eltrombopag is the development of hepatobiliary abnormalities, which occurred in 34 (11%) of patients.

Both Romiplostim and Eltrombopag are well tolerated, although several class specific toxicities have been identified[120]. *Rebound thrombocytopenia* occurs in 8-10% of patients following discontinuation of TRAs and can lead to increased bleeding[120;121]. Platelet counts should be monitored closely for the first two weeks after discontinuation, and tapering of the medication may be considered. *Arterial and venous thrombosis* is a concern with elevated platelet counts in response to TRAs, but must be considered against the background of a potentially increased thrombosis risk in ITP[71]. In randomized Phase III studies, the incidence of thrombosis was not increased in patients treated with TRAs. Of 407 patients reported in the Romiplostim extension study, cerebrovascular accident, deep venous thrombosis and pulmonary embolism each occurred in 2 patients (0.5%)[116], while in 301 patients in the Eltrombopag extension study, 25 thromboembolic events developed in 19 patients for an incidence rate of 3.02/100 patient years[119]. In neither study did the development of thrombosis correlate with the platelet count. *Increased bone marrow reticulin* has been observed in approximately 5% of patients treated with TRAs[120]. In most cases, this process has been limited to reticulin, and not associated with clinical signs of bone marrow dysfunction[122]. Both the platelet count and peripheral blood film should be regularly monitored in patients on TRAs, and myelopthistic changes or loss of response to therapy should prompt consideration of discontinuation and bone marrow examination.

Special Situations

Emergency Treatment of ITP—Patients with severe thrombocytopenia, particularly those with newly-diagnosed ITP should be hospitalized. Therapy is directed at raising the platelet count as quickly as possible through the use of corticosteroids and IVIg. Platelet transfusion provides transient increases in the platelet count in emergent situations, and concurrent infusion of IVIg may prolong survival of transfused platelets in some patients[123]. Splenectomy offers the potential for increasing the platelet count most quickly, and has been used to treat immune thrombocytopenia in patients with acute intracranial hemorrhage. Recombinant factor VIIa has been used in anecdotal reports.

Pregnancy—ITP affects 0.1 - 1.0 of every 1000 pregnancies, and accounts for 3 - 5% of cases of pregnancy-associated thrombocytopenia; it is 50-100-fold less common than incidental thrombocytopenia of pregnancy. However, since incidental thrombocytopenia usually does not develop until the second or third trimester, ITP is the most common cause of isolated thrombocytopenia in the first trimester [124;125]. In the first and second trimesters, patients with no bleeding and a platelet count above 20-30 × 10^9/L do not require treatment[74;75]. As term approaches, a more aggressive approach is indicated to raise the platelet count to > 50-70 × 10^9/L, a level generally considered safe for epidural anesthesia and delivery[125]. Corticosteroids are effective in pregnant patients, but their association with toxicities such as pregnancy-induced hypertension, have led some to suggest that IVIg (2 gm/kg) should be considered as initial therapy[124]. Refractory patients may undergo splenectomy, which is optimally performed during the second trimester. Teratogenic agents such as danazol, cyclophosphamide or vinca alkaloids should be avoided [74;75]; azathioprine has been used in pregnant patients without teratogenicity, and Rituximab has also been used effectively though it may delay neonatal B-cell maturation.

Antiplatelet antibodies may cross the placenta and induce neonatal thrombocytopenia;approximately 10% of the offspring of mothers with ITP will be born with a platelet count $<50 \times 10^9$/L, and 1 - 5% will have platelet counts $<20 \times 10^9$/L. There is no effective means to predict neonatal thrombocytopenia, although it is more common in neonates with a sibling who was born thrombocytopenic. Although up to 50% of severely thrombocytopenic neonates experience bleeding during delivery, intracranial hemorrhage is rare (<1.0%)[126]. There is no evidence that the risk of fetal intracranial hemorrhage is reduced by caesarean section, thus the use of cesarean section should be dictated by maternal indications only[74;75]. In some offspring of patients with ITP thrombocytopenia may develop several days after delivery, thus careful monitoring of the neonate is indicated over this critical period.

Refractory ITP is often managed with a number of immunosuppressant and chemotherapeutic agents, such as azathioprine, cyclophosphamide, vinca alkaoids, danazol, cyclosporine, and mycophenylate mofitil, among others[97]. The efficacy of many of these agents has not been prospectively studied and estimates are derived from small series[96] (Table 5). The ITP IWG categorizes these agents as second line[75], though in the current era most patients with refractory ITP are managed with TRAs or Rituximab, with the approaches listed in Table 5 used less frequently[127]. Recent reports suggest, however, that the use of such approaches in combination with other agents listed in Table 4 may induce responses in patients with refractory ITP, and emerging data suggests that these agents may also be effective in combination with more contemporary treatment schemes.

Summary

- Primary ITP presents as isolated thrombocytopenia (platelet count $< 100 \times 10^9$/L) in the absence of other causes or disorders that may be associated with thrombocytopenia, or as a secondary disorder, most commonly associated with autoimmune disease, lymphoproliferative disorders or chronic infections.
- Primary ITP in children is usually self-limited, with approximately 80% of cases resolving within 6-12 months. In contrast, ITP evolves into a chronic disorder in 80% of adults.
- Bleeding is the most common clinical manifestation of ITP, occurring most commonly in the elderly, in whom the incidence of ITP is highest.
- The pathogenesis of ITP involves loss of tolerance to glycoproteins expressed on platelets and megakaryocytes. Epitope spreading may explain the fact that many patients have antibodies against more than one glycoprotein.
- Anti-platelet glycoprotein antibodies cause thrombocytopenia through two mechanisms: 1) reducing the survival of circulating platelets, and 2) inhibiting the production of new platelets by bone marrow megakaryocytes.
- Cellular immunity contributes significantly to the pathogenesis of ITP. Alterations in T cell subsets and decreased numbers and activity of regulatory T cells are common. Cytotoxic T cells may also mediate toxicity against platelets and megakaryocytes.
- The first line of therapy for ITP includes corticosteroids, sometimes in conjunction with IVIg or anti-Rh(D). While each of these are effective therapies, none reliably induce durable remission.
- The second line therapy for ITP may include Rituximab, splenectomy or thrombopoietin receptor agonists (TRAs). There is no consensus as to which is

superior, and no controlled data to support the preferential use of one over the other. Splenectomy provides the greatest chance for long term remission.

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Key Points

- Primary ITP presents as isolated thrombocytopenia (platelet count < 100×10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia, or as a secondary disorder, most commonly associated with autoimmune disease (such as systemic lupus erythematosus) or chronic infections (such as *H. Pylori* or Hepatitis C)
- Primary ITP in children is usually self-limited, with approximately 80% of cases resolving within 6-12 months. In contrast, ITP evolves into a chronic disorder in 80% of adults.
- Anti-platelet glycoprotein antibodies cause thrombocytopenia through two mechanisms: 1) reducing the survival of circulating platelets, and 2) inhibiting the production of new platelets by bone marrow megakaryocytes.
- The first line of therapy for ITP includes corticosteroids, sometimes in conjunction with IVIg or anti-Rh(D). While these are effective therapies, none reliably induce durable remission.
- The second line therapy for ITP may include Rituximab, splenectomy or thrombopoietin receptor agonists (TRAs). There is no consensus as to which is superior, and no controlled data to support the preferential use of one over the other. Splenectomy provides the greatest chance for long term remission, but its use is declining.

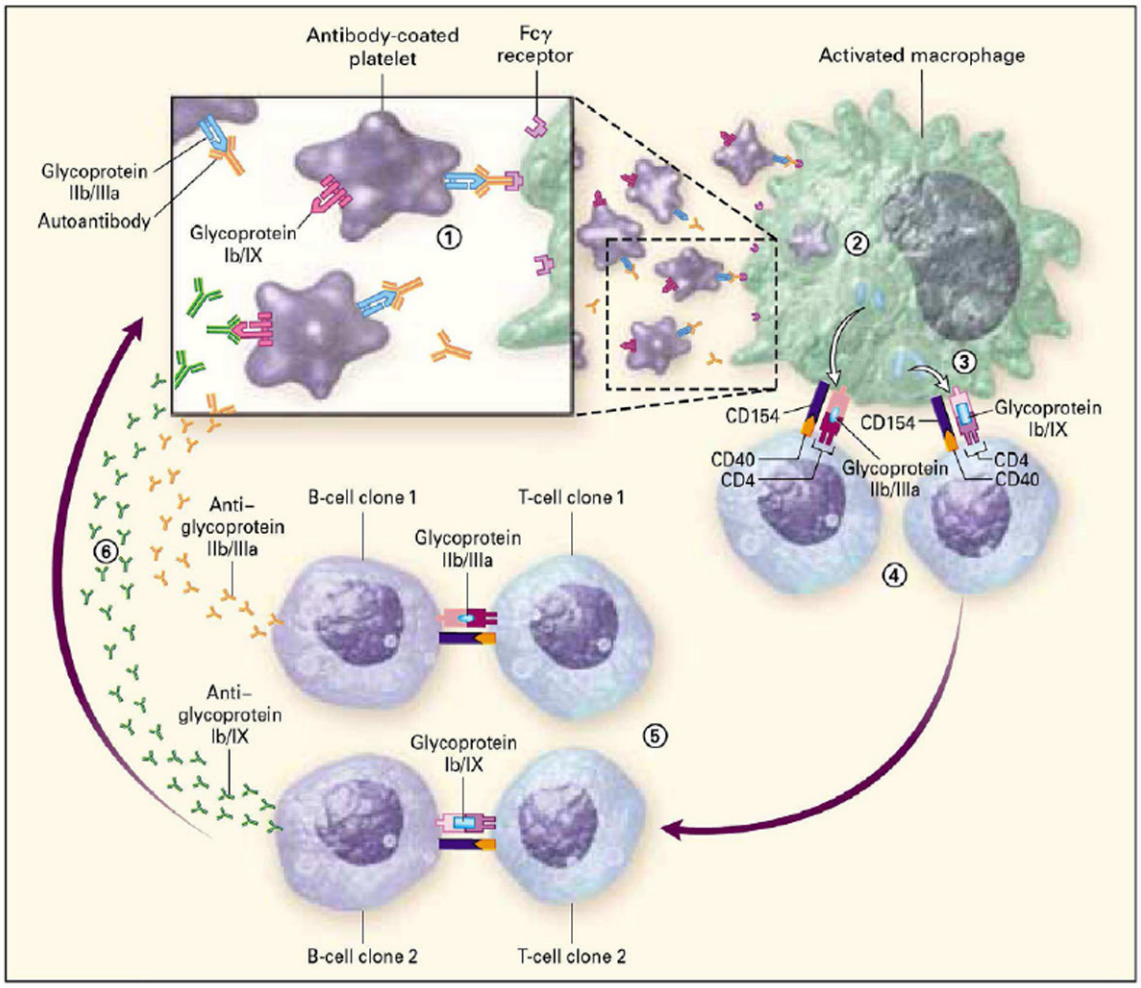

Figure 1. Pathogenesis of Epitope Spread in Immune Thrombocytopenia

The factors that initiate autoantibody production are unknown. Many patients have antibodies against several platelet surface glycoproteins at the time the disease becomes clinically evident. Here, glycoprotein IIb/IIIa is recognized by autoantibody (orange, inset), whereas antibodies that recognize the glycoprotein Ib/IX complex have not been generated at this stage (1). Antibody-coated platelets bind to antigen presenting cells (macrophages or dendritic cells) through Fcγ receptors and are then internalized and degraded (2). Antigen presenting cells not only degrade glycoprotein IIb/IIIa (light blue oval), thereby amplifying the initial immune response, but also may generate cryptic epitopes from other platelet glycoproteins (light blue cylinder) (3). Activated antigen-presenting cells (4) express these novel peptides on the cell surface along with costimulatory help (represented in part by the interaction between CD154 and CD40) and the relevant cytokines that facilitate the proliferation of the initiating CD4-positive T-cell clones (T-cell clone 1) and those with additional specificities (T-cell clone 2) (5). B-cell immunoglobulin receptors that recognize additional platelet antigens (B-cell clone 2) are thereby also induced to proliferate and synthesize anti-glycoprotein Ib/IX antibodies (green) in addition to amplifying the production of anti-glycoprotein IIb/IIIa antibodies (orange) by B-cell clone 1 (6). From Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:13-995, with permission.

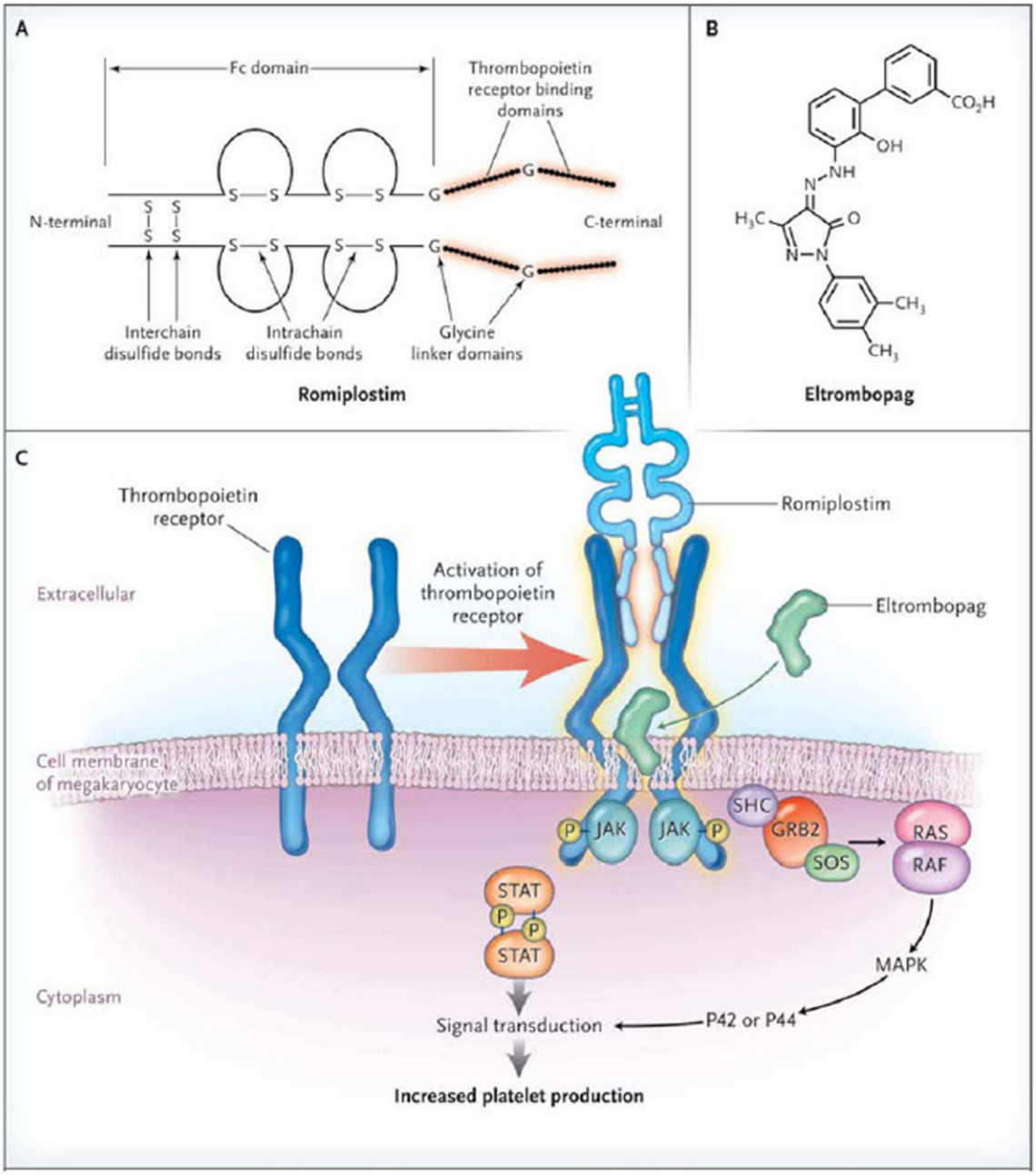

Figure 2. Structure of Romiplostim and Eltrombopag and the Cellular Mechanisms of Action

Panel A shows the chemical structure of romiplostim, which is composed of the Fc portion of IgG1, to which two thrombopoietin peptides consisting of 14 amino acids are coupled through glycine bridges at the C-terminal of each γ heavy chain. Panel B shows the chemical structure of eltrombopag. Panel C shows the cellular mechanisms of action of romiplostim, which binds to the thrombopoietin receptor, and of eltrombopag, which binds to the thrombopoietin receptor's transmembrane domain, thereby activating signaling that leads to increased platelet production. GRB2 denotes growth factor receptor-binding protein 2, JAK Janus kinase, MAPK mitogen-activated protein kinase, P phosphorylation, RAF rapidly accelerated fibrosarcoma kinase, RAS rat sarcoma GTPase, SHC Src homology

collagen protein, and STAT signal transducer and activator of transcription. From Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. *N Engl J Med* 2011;365(8):734-741, with permission.

Table 1

ITP International Working Group proposed definitions of disease

Primary ITP	**An autoimmune disorder characterized by isolated thrombocytopenia (platelet count < 100 × 10^9/L) in the absence of other causes and disorders that may be associated with thrombocytopenia. The diagnosis of primary ITP is one of exclusion, as no clinical or laboratory parameters are available to establish its diagnosis with accuracy. The main clinical problem in patients with primary ITP is an increased risk of bleeding, although bleeding symptoms are not always present.**
Secondary ITP	**All forms of immune-mediated thrombocytopenia other than primary ITP. The acronym ITP should be followed by the name of the associated disease, (e.g. secondary ITP-lupus associated, secondary ITP-drug-induced)**
Phases of the disease	**Newly diagnosed ITP: within 3 months of diagnosis**
	Persistent ITP: between 3-12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.
	Chronic ITP: lasting for more than 12 months
	Severe ITP: presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet enhancing agent or an increased dose.

*Adapted from Rodeghiero F, Stasi R, Gernsheimer T et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009;113:2386.

Table 2

Diagnostic recommendations (laboratory) of the ITP IWG*

Basic evaluation	**Potential utility**	**Uncertain or unproven benefit**
Complete blood count and reticulocyte count	Glycoprotein specific anti-platelet antibody	**Thrombopoietin level**
Peripheral blood film	Antiphospholipid antibodies	**Reticulated platelets**
Quantitative immunoglobulin level (consider in children, recommend in children with persistent or chronic ITP)	Thyroid function and anti-thyroid antibodies	**Platelet associated IgG**
Bone marrow examination (may be informative in pts > 60 years, with systemic symptoms, or before splenectomy)	Pregnancy test (women of childbearing potential)	**Platelet survival study**
Blood group (Rh)	Antinuclear antibodies	**Bleeding time**
Direct antiglobulin test	PCR for Parvovirus and CMV	**Serum complement**
H Pylori		
HCV		
HIV		

*adapted from Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168.

Table 3

Differential Diagnosis of Primary Immune Thrombocytopenia

Non-immunologic	**Immunologic (Secondary immune thrombocytopenia**
Decreased platelet production	**Autoimmune disorders**
• Acute or chronic leukemia	• **Systemic lupus erythematosus**
• Myelodysplasia	• **Evans syndrome**
• Aplastic anemia	• **Antiphospholipid antibodies**
• Congenital or acquired amegakaryocytic thrombocytopenia	**Drug induced thrombocytopenia**
• Toxic exposure (radiation, chemotherapy, alcohol)	• **Antibiotics (Bactrim, Vancomycin, etc)**
• Nutritional deficiency (B12, folate)	• **Quinine**
• Myelofibrosis	• **Valproic Acid**
• Myelopthistic processes	• **Heparin**
• Viral infection of hematopoietic precursors	• **Others (oxaliplatin, alemtuzumab, purine analogues)**
Enhanced platelet destruction	**Infection**
• Splenic sequestration	• **H pylori**
• Disseminated intravascular coagulation	• **HIV**
• Thrombotic thrombocytopenic purpura (no direct immune response to platelets)	• **HCV**
• Cardiopulmonary bypass	**Lymphoproliferative disorders**
• Infection/sepsis	**Immunodeficiency (ALPS, CVID)**
Inherited thrombocytopenia	**Post transfusion purpura**
	Vaccinations

Table 4

Treatment options for Immune Thrombocytopenia*

First line	Second line	Third line+
Corticosteroids	Rituximab	**Combination chemotherapy**
• Prednis(ol)one	Thrombopoietin receptor agonists	**Combination of first and second line therapies**
• Dexamethasone	Romiplostim	**Campath 1H (currently withdrawn from market)**
• Methylprednisolone	• Eltrombopag	**Hematopoietic stem cell transplantation**
IVIg	• Splenectomy	
Anti-Rh(D)	*Azathioprine†*	
	Cyclophosphamide	
	Danazol	
	Dapsone	
	Cyclosporine	
	Mycophenylate mofetil	

+considered to be treatment options supported by minimal data with the potential for inducing significant toxicity

†agents that are italicized are used less commonly in the current era of ITP therapy and might be considered “third line” by some clinicians

*adapted from Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168.

Table 5

Treatment options for refractory ITP*

Medication	Approximate response rate	Major toxicities
Azathioprine 1-2 mg/kg (maximum 150 mg/ day)	Up to two thirds, 40% in anecdotal reports	Infrequent and mild: weakness, sweating, transaminitis, severe neutropenia, pancreatitis
Cyclosporine A 5 mg/kg/day for 6 days then 2.5 -3.0 mg/kg/d (titrate to blood levels of 100-200 ng/ml)	Dose-dependent, up to 50-80% in small series	Moderate but transient in most patients: increased creatinine, hypertension, fatigue, paresthesias, myalgia, gingival hyperplasia, dyspepsia, hypertrichosis, tremor
Danazol 200 mg 2-4 times daily	67% CR or PR, 40% in anecdotal reports	Frequent: transaminitis, acne, hirsutism, increased cholesterol, amenorrhea
Cyclophosphamide 1-2 mg/kg orally daily for at least 16 wk, or IV 0.3-1 gm/m^2 for 1-3 doses every 2-4 wk	24-85%	Usually mild to moderate: neutropenia, DVT, nausea
Dapsone 75-100 mg	Up to 50%	Infrequent and reversible: anorexia, nausea, abdominal distention, methemoglobinuria, hemolytic anemia in G6PD deficiency Severe: skin rash, requires discontinuation
Vinca alkaloids: Vincristine 1-2 mg weekly- total 6 mg **Vinblastine: 10 mg weekly, total 30 mg**	Highly variable, 10-75%	Neuropathy, particularly in elderly, Neutropenia, fever Thrombophlebitis at infusion site

* adapted from Provan D, Stasi R, Newland AC et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168.