Overview of Adult Immune Thrombocytopenia

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INTRODUCTION

Primary Immune Thrombocytopenia (ITP)

There have been somewhat divergent criteria for making the diagnosis of immune thrombocytopenia (ITP). However, an attempt to standardize the definition of ITP has been made with the publication by the International Work Group (IWG) on ITP in 2009.[1] Despite this attempt to standardize those descriptions, many physicians do not conform to these definitions, so confusion in terminology persists. After publication of the IWG guideline, most use immune thrombocytopenia. Its various other names have included "idiopathic thrombocytopenic purpura", "autoimmune thrombocytopenic purpura", "immune thrombocytopenic purpura", "autoimmune thrombocytopenia", and "primary thrombocytopenic purpura". Despite what it is called, it represents an acquired autoimmune process and is no longer considered idiopathic. Autoantibodies are not only directed against the patient's own platelets, leading to their destruction by the spleen, but there may be humoral autoimmune processes involving the platelet progenitor, the megakaryocyte, resulting in decreased platelet production. In the 1st issue of *Blood*, published in 1946, Damasheck and Miller[2] reviewed the megakaryocyte counts and bone marrow morphology of patients with idiopathic thrombocytopenia and demonstrated most had an increase in the megakaryocyte count, however few platelets were produced. Multiple Fc receptor (FcRs) pathways are involved in the humoral immune response associated with ITP. It has also been discovered that cellular autoimmune disruption contributes to thrombocytopenia in ITP. The sole abnormality on the hemogram is a platelet count <100,000/μL (formerly <150,000/μL) in the setting of an otherwise normal peripheral blood with normal red cell and white cell morphology in a healthy person. The peripheral blood platelets can range from normal to large in size. The decrease in the platelet cut-off from 150,000 to 100,000/μL by the IWG was based on a long-term outcome study of healthy individuals, where it was found that those with platelet counts between 100,000 to 150,000/μL had a 10 year probability of developing ITP (a persistent platelet count below 100,000/μL) of only 6.9%.[1] Additionally, it was noted that platelet counts of 100,000 to 150,000/μL in non-Western populations are found with some frequency in healthy people. Immune thrombocytopenia remains the most common cause of isolated thrombocytopenia in clinical practice.[3]

Purpura was initially described by Hippocrates (c. 460 to c. 370 BC) as a sign associated with fever.[4] It is a non-specific clinical finding seen in a variety of medical conditions and infrequent in patients with ITP. The use of the term "purpura" has been discouraged, because few ITP patients demonstrate purpuric skin lesions.[1] The diagnosis of primary ITP is made through the process of exclusion of other possibilities. The IWG classifies ITP as primary, when there is no underlying cause or secondary, if it is associated with a disease. The group further categorizes ITP based on its duration: newly diagnosed for cases within 3 months of diagnosis; persistent ITP for cases from 3 to 12 months of diagnosis; chronic for cases greater

than 12 months in duration. Severe is reserved for cases presenting with bleeding sufficient enough to require treatment or for an already diagnosed ITP case demonstrating a new bleeding episode which requires an increased dosage of medication or an alternate platelet enhancing agent.[1] Note that the new definition of severe is no longer dependent on a platelet count. To some who resist the new terminology "severe ITP" was and still is diagnosed with a platelet count <30,000/μL (primarily because most fatal bleeding occurs below 30,000/μL). Still others define severe ITP with a platelet count less than 10,000/μL, without regard to bleeding.[1]

The IWG also says that in order to call ITP refractory, the patient should have failed splenectomy and have a risk of bleeding that requires treatment. Since the risk of bleeding and hemorrhagic fatality rate increases with advanced age (greater than 45 years old) treatment options should take into consideration the age of the patient.[1]

Historically, ITP has been classified as "acute" (less than 3 months) or "chronic" (anywhere from greater than 3 to 12 months) and these terms remain in common use today. The acute form is most often found in children, usually following a viral infection or a vaccination, and can spontaneously resolve in about 6 months.[3] A discussion of ITP in children is beyond the scope of this paper, but for those wanting details concerning this topic see the review by N. Cooper.[5] In contrast to the IWG definition, the traditional term chronic ITP refers to an adult who has primary ITP of at least 3 months duration. Chronic ITP is referred to as "refractory" in historical terms if the patient has failed treatment or has relapsed after conventional treatment including corticosteroids plus another form of therapy.

Primary ITP (IWG) or "chronic" ITP (traditional nomenclature) is the topic of this paper and occurs mainly in adults. It is not known to have a specific inciting event as in children with primary, newly diagnosed ("acute") ITP.

Secondary Immune Thrombocytopenia (ITP)

Primary ITP in adults is a diagnosis of exclusion and can be made only when secondary ITP is no longer a consideration. In the typical case of primary ITP, the patient is healthy and only thrombocytopenia is demonstrated with the rest of the medical workup being unremarkable. Rarely the manifestations of major or minor bleeding may be present. The term secondary ITP is used when ITP is found to be associated with a specific disorder or disease. Some causes of thrombocytopenia from secondary forms of ITP include autoantibodies to platelets produced in a variety of conditions, including drug-induced ITP, human immunodeficiency virus (HIV), hepatitis C virus (HCV), *Helicobacter pylori,* vaccinations, myelodysplastic syndrome, leukemia, lymphoproliferative disorders, aplastic anemia, systemic lupus erythematosus, antiphospholipid syndrome, and common variable immune deficiency (Table 1). The 2011 American Society of Hematologists (ASH) practice guideline for ITP states that only HCV and HIV tests should be routinely performed to rule out secondary ITP for newly diagnosed, adult ITP patients presenting in a typical fashion.[7] However, every effort should be made to rule out most secondary causes of ITP in the patient who is refractory to a variety of ITP medications because some of these diseases would preclude splenectomy. With splenectomy there could be immediate complications from the surgery resulting in excessive bleeding due to severe thrombocytopenia not to mention the risks associated from the surgery and the anesthesia.

Autoantibody-mediated thrombocytopenia:	Alloantibody-mediated thrombocytopenia:
-Medications/supplements	-Fetal/neonatal alloimmune thrombocytopenia
-Autoimmune diseases:	-Posttransfusion purpura
-Antiphospholipid syndrome (2%)	-Platelet alloimmunization after platelet transfusions
-Systemic lupus erythematosus (5%)	**Other causes**:
-Evans syndrome (2%)	-Cirrhosis
-Other connective tissue disorders	-Aplastic anemia
Infections:	-Thrombotic microangiopathic hemolytic anemia –TTP, HUS, aHUS, DIC
-Viruses-HCV (2%), HIV (1%), HBV	-Pregnancy - preeclampsia, abruptio placenta, HELLP syndrome
-Cytomegalovirus, varicella zoster	
-Other systemic infections (2%)	
-Helicobacter pylori (1%)	
-Vaccinations (1%)	
Malignancy:	
-Chronic Lymphocytic Leukemia (2%)	
-Lymphoproliferative disorders	
-Myelodysplastic syndrome	
-Bone marrow transplantation (1%)	
-Common variable immune deficiency (1%)	

Table 1: Causes of Secondary ITP – About 20% of ITP is secondary. The estimated percent of causes of total (primary and secondary) ITP is in parenthesis.[6]

Additionally, post-splenectomy patients have an increased long-term risk of bacterial septicemia. The 2011 ASH guidelines also mention that a bone marrow examination is not necessary in a typical case of primary ITP and that treatment is not necessary in those who are asymptomatic and have platelet counts >30,000/μL.[7]

About 20% of ITP cases are from secondary causes.[8] Immune drug-induced thrombocytopenia usually occurs after 5 to 7 days from initial exposure to the drug. Upon removal of the offending agent, the platelet count usually begins to rapidly rise within 1 to 2 days and is typically normalized within a week. On repeat exposure to the drug, the platelet count begins rapidly dropping within 3 days.[9] There are over 1000 drugs listed that induce thrombocytopenia, including over the counter medications, on the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database (www.ouhsc.edu/platelets). Some of the more established drugs linked to thrombocytopenia are listed in Table 2.

Abciximab	Nalidixic Acid
Acetaminophen	Naproxen
Acetazolamide	Oxaliplatin
Aminoglutethimide	Oxprenolol
Aminosalicylic Acid	Oxyphenbutazone
Amphotericin B	Phenytoin
Ampicillin	Piperacillin
Captopril	Procainamide
Carbamazepine	Quinidine
Chlordiazepoxide	Quinine
Chlorothiazide	Ranitidine
Chlorpropamide	Rifampin
Cimetidine	Rituximab
Danazol	Roxifiban
Diatrizoate meglumine	Simvastatin
Diclofenac	Sulfapyridine
Digoxin	Sulfamethoxypyridazine
Efalizumab	Sulfamethoxazole
Eptifibatide	Sulfisoxazole
Ethambutol	Sulindac
Etretinate	Tamoxifen
Fluconazole	Terbinafine
Glibenclamide	Ticlopidine
Gold	Tirofiban
Heparin Induced Thrombocytopenia (HIT)	Traztuzumab
Hydrochlorothiazide	Vancomycin
Ibuprofen	
Indinavir	
Interferon-α	
Levamisole	
Lotrafiban	
Meclofenamate	
Methicillin	
Methyldopa	

For a complete list of medications that can induce antibody-mediated drug-induced thrombocytopenia, see www.ouhsc.edu/platelets

Table 2: Medications reported to cause drug-induced thrombocytopenia. Two or more cases with definitive or probable clinical evidence.

About 40% of HIV patients develop thrombocytopenia during the course of the disease. Since HIV can initially present with only isolated thrombocytopenia, it may be hard to distinguish from primary ITP. Thrombocytopenia can result from molecular mimickry where antibodies directed against the HIV virus cross react with antigens on the platelet or megakaryocyte surface. The antibody coated platelets are removed by the spleen reticuloendothelial system (RES) as in primary ITP. Autoantibodies directed against megakaryocytes can inhibit platelet production. Additionally, HIV can directly infect megakaryocytes, disrupting the normal cellular biology, and resulting in decreased platelet production.[10] These same mechanisms are thought to be the cause of thrombocytopenia from HCV. Furthermore in severe liver disease associated with HCV, liver production of thrombopoietin may be diminished and result in decreased platelet production. The treatment for thrombocytopenia caused by these infectious agents is to administer the appropriate antiviral medication or antibiotics. It is important to remember that many of these therapeutic medications may contribute to thrombocytopenia.

Hypersplenism from cirrhosis or infiltration of the spleen by lymphoma or leukemia cells can lead to platelet sequestration in the spleen resulting in decreased circulating platelets and a relative thrombocytopenia. Anemia and abnormalities in the white blood cell (WBC) series may indicate other pathophysiologies such as leukemia, aplastic anemia or myelodysplastic syndrome (MDS). If giant platelets predominate, a diagnosis other than ITP should be considered such as Bernard-Soulier syndrome, MDS, or myelofibrosis.[9]

Some other causes of secondary thrombocytopenia which might also be confused with primary ITP in adults include thrombotic thrombocytopenic purpura (TTP), a condition in which high molecular weight von Willebrand factor (VWF), released from endothelial cells, is not cleaved to its functional form because of a decrease in the plasma metalloprotinase enzyme ADAMTS13 due to an autoantibody directed against this cleaving enzyme. Other examples inlcude hemolytic uremic syndrome (HUS) from *Escherichia coli* Shiga Toxin; atypical HUS from a genetic predilection resulting in a decrease in the production of complement inhibitors when the patient is exposed to stressful stimuli; thrombocytopenia in pregnancy (gestational thrombocytopenia, HELLP syndrome, preeclampsia); and pseudothrombocytopenia, in which patient antibodies agglutinate platelets only in the presence of the test tube anticoagulant, EDTA (ethylenediaminetetraacetic acid) during a complete blood count (CBC) leadng to an artificially low platelet count.[10,11]

In almost all secondary ITPs, except for pseudothrombocytopenia, the patient will generaly appear ill and eventually develop abnormal lab tests associated with this secondary condition, if not initially then as the disease progresses, in contradistinction to primary ITP where the sole abnormality in the patient remains a low platelet count with possibly associated manifesta-

tions of bleeding.

In general, the best therapy for thrombocytopenia from any secondary ITP is to treat the underlying disorder.

PATHOPHYSIOLOGY

Newly diagnosed ITP in children ("acute ITP" in older terminology) has been associated with a recent viral infection. The inciting event that causes primary ITP in adults is unknown.

ITP is caused by an imbalance between the production and destruction of platelets. The traditional explanation for the etiology of primary ITP is that platelets are coated with auto- antibodies made by B-lymphocytes and plasma cells. The theory of auto-antibodies to platelets was credited to Harrington in 1951 when normal volunteers including Dr. Harrington himself were infused plasma from patients with ITP and then themselves developed significant thrombocytopenia.[12] A platelet associated IgG antibody (PAIgG) was discovered in the 1970's which was thought to finally explain immune mediated thrombocytopenia.[13] These platelet auto-antibodies are mostly IgG, but occasionally IgM or IgA have been described. The antibody coated platelets are then removed from the circulation by Fc receptor-mediated phagocytosis conducted by mononuclear macrophages in the spleen, liver, or marrow.[11] Unfortunately, later evaluations including the discovery of PAIgG in patients without ITP declared these anti-platelet antibodies as non-specific.[14] Newer explanations for why thrombocytopenia occurs in ITP are more complex and additionally include autoantibodies directed against the bone marrow megakaryocyte resulting in decreased platelet production.[11] Cellular mechanisms of immunity are also involved in both of these processes. Disruption in antigen presenting cells and in T-helper and T-suppressor cells and reduction in T-regulatory (Treg) cells have been found in ITP and therefore favor the etiology of autoimmunity.[15] When bone marrow failure results in moderate to severe thrombocytopenia, serum thrombopoietin, produced by the liver, should be elevated. This is not the case for ITP. For the most part, thrombopoietin levels in ITP are in the normal range. It is postulated that this situation occurs because thrombopoietin is bound to the antibody coated platelets which are all rapidly removed from the circulation by the spleen.[11]

Most of the platelet autoantibodies in ITP are directed against the platelet membrane glycoproteins GPIIb/IIIa, GpIb/IX, and GPIa/IIa.[11] Eighty percentage of platelet associated antibodies are directed against GPIIb/IIIa (integrin $a_{IIB}b_3$).[16] The majority of ITP patients start with a single antibody targeting platelets, but after long standing disease these patients will develop antibodies directed against many platelet antigens probably through a process called epitope spreading. Once a single anti-platelet autoantibody is generated, the IgG coated platelets are cleared by the splenic reticuloendothelial system (RES) and in this process the proteolyzed platelet components are released and presented to macrophages and dendritic cells (antigen pre-

senting cells) as new antigens which may lead to the stimulation of specific T-cells that interact with B-cells to produce new, additional autoantibodies. This of course happens in an environment where there is disruption of the normal T-cell regulatory mechanisms involved with identify of self antigens.[10,11,15]

The spleen is the main organ involved in contributing to ITP, but also the liver and marrow may participate. Platelet autoantibodies are formed by lymphocytes and plasma cells in the white pulp while the red pulp contains the macrophages which remove the IgG antibody coated platelets. Removal of the spleen results in prompt increase of the platelet count in most cases, which points directly to the splenic macrophage system as being responsible for the rapid destruction of the antibody coated platelets. However in contemporary theory, decreased production of platelets is also thought to play a large role in producing thrombocytopenia in ITP. The decreased platelet life span cannot fully account for the degree of thrombocytopenia which suggests a concomitant decrease in platelet production.[17] In addition, most primary ITP patients treated with thrombopoietin receptor agonists (stimulants for platelet production) have a sustained increase in the platelet count above baseline while they are under treatment with these agents.[11] It is also postulated that T-cells may play a role in causing thrombocytopenia by directly lysing platelets and/or megakaryocytes, thereby inhibiting platelet production. This cellular killing mechanism may be the reason why those ITP patients remaining unresponsive to the usual humoral therapies sometimes may respond to T-cell directed agents such as cyclosporine, azathioprine and mycophenolate.[11]

CLINICAL FEATURES

Until age 65, there is a slight female preponderance of primary ITP in adults, but afterwards the rates are equal. ITP in the United States is seen in 9.5 to 23.6 cases per 100,000 of population.[11]

The practice of obtaining routine CBCs has led to the identification of many asymptomatic primary ITP patients because of the serendipitous finding of a low platelet count (<100,000/μL). However, a primary ITP patient can also present with hemorrhage due to severe thrombocytopenia. In the newer IWG terminology, the term severe is used only when profuse bleeding occurs regardless of the platelet count, but in the previous terminology severe thrombocytopenia is related to the platelet count and could mean a platelet count less than 30,000 per microliter or as little as 10,000 per microliter, as discussed previously. Severe hemorrhage is uncommon when the platelet count is greater than 30,000 per microliter.[15] The patient's age, activities, comorbidities such as uremia, and medications such as anticoagulants, will affect the potential risk for significant bleeding.

The clinical consequences of ITP are often related to severe thrombocytopenia with resulting minor spontaneous mi-

crovascular hemorrhages in the skin and mucous membranes (purpura, ecchymosis, petechiae), major spontaneous life-threatening bleeding from intracranial, gastrointestinal (GI), or genitourinary (GU) sources or from epistaxis or menorrhagia. The severity of bleeding correlates with the severity of thrombocytopenia with most life-threatening bleeding occurring either spontaneously or with minor trauma in patients with platelet counts less than 10,000/µL.[15] Cerebral hemorrhage has been reported at about 3% in patients with ITP whereas hemorrhagic death was reported at 4%.[18] Interestingly, there is an increased risk of thrombosis in ITP. In a review of 986 patients, arterial thrombotic disease was reported in 3.2% and venous thrombotic disease was seen in 1.4% of patients.[19]

Medical History and Physical Exam

It is important to initially obtain a detailed medical history (personal and family history) and physical exam in order to make the diagnosis of primary ITP, distinguish from secondary ITP, and to determine the best course of treatment. The medical history and physical exam should determine whether the patient has had any previous or current episodes of bleeding with petechiae, ecchymosis, and/or mucosal bleeding, or of a more serious nature such as GI, GU or intracranial bleeding, menorrhagia or epistaxis. Other areas of importance would be to determine if the patient is on anticoagulation for hypercoagulability conditions (stroke, myocardial infarction, atrial fibrillation, deep vein thrombosis) and if there are any other medical or social conditions (occupation, activities, and quality of life issues) that will affect the need for more rapid treatment of the thrombocytopenia. Is the patient taking antiplatelet therapy or other medications that increase the risk of bleeding in the presence of thrombocytopenia?

Concerning the possibility of secondary ITP, it is important to determine if the patient has fever, weight loss, night sweats, bone pain, joint pain, lymphadenopathy, hepatosplenomegaly, or a history of anemia or abnormal WBC count or morphology. Also is there a family history of platelet abnormalities or easy bruising.[1] Lifestyle is also important to determine. Those ITP patients with a highly active lifestyle that includes contact sports or places them in a high risk for injury might be considered for treatment at a platelet count above the traditional 30,000/µL threshold. Otherwise, they may have to consider discontinuation of such high risk activities.

At the end of the medical history and physical examination, the patient should be able to be categorized into one of 3 degrees of risk for bleeding: minor, intermediate, or major bleeding risk.

DIAGNOSIS

Primary ITP is a diagnosis of exclusion and needs to fulfill 2 criteria:

1. Thrombocytopenia showing a platelet count of less than 100,000/µL with an otherwise normal CBC and a normal peripheral smear;
2. No associated diseases/conditions (Table 1) or medications (Table 2) that can cause thrombocytopenia (secondary cause of low platelet count).

Testing for Immune Thrombocytopenia (ITP)

Primary ITP is a diagnosis of exclusion and the only tests indicated, initially, are a CBC and peripheral blood smear examination. In atypical case of primary ITP, the CBC and peripheral smear will show isolated thrombocytopenia with normal counts and normal morphology in the white cell and red cell series. The platelets may appear normal or slightly enlarged. Routine HIV and HCV antibody screening tests have also been recommended for the initial evaluation because treatment with antiviral agents will alter the course of these secondary ITPs.[1,15]

Several tests are available to detect antibodies on platelets as well as specific platelet autoantobodies.[20] However, there are no diagnostic tests to reliably confirm the diagnosis of primary ITP. American Society of Hematology (ASH) guidelines do not recommend performing such tests because of high interlaboratory variability and poor sensitivity.[15] Additionally, a negative test for platelet autoantibodies does not exclude the diagnosis of ITP. There is insufficient evidence in a typical primary ITP case to routinely order the following on initial presentation: antiphospholipid or antinuclear antibodies, lupus anticoagulant, thrombopoietin levels, platelet size/volume, platelet antigen-specific antibody, direct antiglobulin test, reticulocyte count, *H. pylori* infection testing or a CT scan.[1,10,15] However, a computed tomography (CT) scan should be promptly done if serious internal bleeding is suspected.

A bone marrow biopsy and aspiration in a typical case of primary ITP is unnecessary.[1,15] If performed, these bone marrow studies will show normal to increased numbers of megakaryocytes in a normal bone marrow setting. Should an atypical case of ITP be suspected or if primary persistent or chronic ITP occur, a bone marrow biopsy and aspirate are useful in excluding secondary causes of thrombocytopenia including leukemia, myelodysplastic syndrome, aplastic anemia, and myelofibrosis. Bone marrow studies should be performed prior to a splenectomy to rule out secondary causes of ITP which may be better treated with other forms of therapy.

Some would argue that a fasting comprehensive metabolic panel (CMP) should be ordered to verify the wellness of the patient and therefore confirm that many secondary causes of ITP are ruled out. These 14 tests (glucose, sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, total protein, albumin, total bilirubin, ALP, AST, ALT) measure electrolytes, fluid balance, renal and liver function. Of special importance is determining if significant uremia is noted (GFR<40 ml/min/1.73 m^2 or BUN>50 mg/dL). Platelet enhancing therapies might be considered for ITP patients with significant uremia even with a

platelet count above 30,000/μL because of the increased risk of uremic bleeding.

A more comprehensive lab investigation for the secondary causes of ITP is warranted if there is a change in the clinical or hematologic parameters from the initial diagnosis of ITP. These changes would include a first time significant bleeding episode, development of constitutional symptoms and notable changes on the CBC, peripheral blood smear or CMP.

INDICATIONS FOR TREATMENT

Treatment will be based on the initial evaluation of the patient including the personal history, family history, social history (job, activities, and quality of life issues), physical exam, CBC with platelet count, peripheral smear evaluation and lab screening tests for HIV and HCV.

The most important question to be determined in a patient with ITP is when to treat. If the patient has no evidence of bleeding or if only "mild bleeding" (defined as only skin such or mucous membrane microvascular bleeding manifesting as ecchymosis or petechiae) then no treatment is necessary and observation of the patient is recommended regardless of the platelet count as per the IWG.[1] Because in adults, only 9% of primary ITP patients undergo spontaneous remission, a long follow up is often necessary.[7]

The goal of treatment in primary ITP in adults is not to cure the ITP but to increase the platelet count to a level which will provide adequate hemostasis, thereby preventing major bleeding, with minimum toxicity from the treatment.[1] A safe platelet level varies from patient to patient and depends on the age, lifestyle, activities, type of job, requirement for antiplatelet or anticoagulant medications, the possibility of an upcoming major surgical procedure, side effects associated with platelet enhancing therapies, and the presence of comorbidities such as renal, cardiovascular, and pulmonary diseases and diabetes mellitus. The presence of significant uremia (GFR<40 ml/min/1.73 m^2 or BUN>50 mg/dL) increases the risk of platelet dysfunction from the inhibition of von Willebrand's factor platelet adhesion activities by uremic toxins. Of major concern is a previous history of bleeding and moreover how severe those bleeding episodes were in relation to the platelet count.[7] Most adult patients with primary ITP do not bleed severely until their platelet count is below 10,000/μL and most fatal bleeding occurs predominately in those patients with platelet counts below 30,000/μL.[1,7] For this reason not all adult patients with primary ITP need platelet enhancing therapy. If the platelet count is more than 30,000 and the patient is asymptomatic, platelet enhancing treatment should be avoided.

Young and active patients have a higher risk of spontaneous bleeding while frail, elderly patients are at a risk of both falling and having intracranial hemorrhage. Such patients, with a risk for major bleeding episodes, might be considered for platelet enhancing therapies at a platelet count of 30,000/μL by ASH standards,[7] while those who are at higher risk for bleeding (ITP patients with uremia or those who are on anticoagulation or antiplatelet medication) might have even a higher platelet threshold to receive treatment in order to prevent major spontaneous bleeding. However, all primary ITP patients with severe or life-threatening bleeding should be administered platelets and other hemostatic agents as well as some form of medical platelet enhancing treatment for ITP. The treatment should be aimed at reducing the risk of bleeding. The decision to treat needs to be determined for each patient individually and the possible benefits versus side effects should be discussed with the patient before starting on a specific therapy. Since, all patients with ITP are different there is not a single platelet value that should be incorporated for all patients.

Those primary adult ITP patients with platelet counts under 30,000 have a higher risk of fatal hemorrhage and of major bleeding.[7] One large study with 1,800 ITP patients in a series over 37 years found that fatal hemorrhage occurred in 1.6 to 3.9 cases per 100 patient years with a lower risk in patients less than 40 years old at 0.4% per year compared with patients greater than 60 years of age at 13% risk per year. The risk of non-fatal hemorrhage in the same series was estimated to be 3% per year in patients less than 40 years of age and 71% per year for patients greater than 60 years of age.[21]

The IWG has defined a complete response to therapy as attaining a platelet count ≥100,000/μL, a response as 30,000 to 100,000/μL plus at least doubling of the baseline platelet count, and no response as <30,000/μL and/or less than a doubling of the platelet count from baseline.

TREATMENT OPTIONS

Patients with platelet counts remaining above 30,000/μL probably do not need treatment and should be observed. However, ITP patients with a significant bleeding episode need immediate treatment with platelet concentrates and other hemostatic agents as well as longer term rapid platelet enhancing therapy, such as intravenous immunoglobulin (IVIG) or anti-D (see below), to raise the platelet count to hemostatic levels.

In the past, if an adult patient initially failed several courses of corticosteroid treatment for primary ITP or if the patient continued to have persistent ITP with the platelets count falling below 30,000 to 50,000, over a time frame of at least 6 months, splenectomy was the recommended second line treatment. Emergency splenectomies were even done in an effort to rapidly raise the platelet count in order to provide hemostasis. However, with the large increase in the classes of medications used to treat primary ITP in adults, the management of this disease has changed considerably so that many more medications can be tried and a period of at least a year, rather than 6 months, is used before splenectomy is even considered.[1] Since large randomized trials dealing with the treatment of ITP do not exist,

there is no true evidence based guideline on exactly how to manage these patients.[15] The choice depends mostly on the profile of the patient and the potential side effects of the treatment. The following order of medications used to treat ITP is arbitrarily divided into 1st, 2nd and 3rd line treatments. Most would agree that initial first line therapy should be with corticosteroids followed by intravenous immunoglobulin or anti-D (USA) and then rituximab. Combinations of these drugs, such as rituximab and dexamethasone, are usually considered part of the 2nd line category.

Corticosteroids

Corticosteroids are the preferred agents for 1st line therapy administered to support the platelet count, thereby minimizing the chance of bleeding.[1] Their mechanism of action is thought to be that corticosteroids act as a lympholytic agent against the more rapidly dividing lymphocytes, resulting in the decrease of the harmful autoantibodies targeting platelets and/or megakaryocytes. Sustained remission using corticosteroids occurs in only 10 to 30% of patients.[10] Once corticosteroids are tapered or discontinued the platelet count will often drift back to baseline or even lower. If this happens, corticosteroid treatment can be resumed until a decision about an alternate therapy is made. Complications from administering prolonged corticosteroids include immunosuppression resulting in infections with opportunistic organisms, diabetes mellitus, osteoporosis, cataracts, gastrointestinal ulcers, fluid and electrolyte imbalance resulting in fluid retention, hypertension, adrenal insufficiency from sudden cessation of this medication, and emotional liability. Because of these complications, many physicians will limit the use corticosteroids to several weeks rather than months and instead utilize other medications listed in the 1st line therapy discussion below after an ITP patient has failed 1 to 2 courses of corticosteroid treatment. The standard practice for initial treatment of ITP in adults has been to use oral prednisone at a daily dose of 0.5-2 mg/kg.[11,22] Most patients respond by increasing the platelet count to >30,000 to 50,000/μL within a few days to weeks from the start of therapy. Up to 85% of patients achieve an initial response within 7 to 10 days, but only 15% of these responders do not require further therapy over the next 6 to 12 months.[11] It is reasonable to begin rapidly tapering the prednisone as soon as a rise above 30,000/μL platelets occurs or at 4 weeks of prednisone therapy for non-responders.[22] Thirteen to 17% of primary adult ITP cases still relapse after one year of intermittent prednisone therapy.[22] Alternatively, high dose dexamethasone pulse therapy of 40 mg/day over 4 days, can be used if the patient is intolerant to prednisone and has resulted in a 50% sustained response in newly diagnosed cases.[22] This initial response rate has been increased to 86% with a lasting response rate in 74% at 8 months, by administering this same pulse dexamethasone, 4 day dosage every 2 weeks for 4 courses of therapy.[22]

Splenectomy

Splenectomy has been traditionally identified as the preferred choice for next treatment modality after corticosteroids in adults having primary, persistent or chronic ITP due to longer duration of response in patients who achieved a complete response after splenectomy; 80% respond initially with 66% requiring no further therapy for at least 5 years.[23] Also, about 60% of splenectomized primary ITP patients are relapse free at 10 years.[15,21] It should be noted that this was the case before rituximab became popular for the treatment of ITP. Splenectomy is the only therapy which is considered a cure for ITP. Patients less than 45 years of age seem to have a more favorable response to splenectomy than older patients. Accessory spleens are present in 12% and should be a consideration in those who relapse after splenectomy.[23] Complication rates and mortality rates from splenectomy are 13% and 1% respectively with laparotomy and 10% and 0.2% with laparoscopy.[23]

Today, splenectomy is probably not appropriate for patients with platelet counts >30,0000/μL who have at most minor bleeding, and should be deferred for at least 12 months after diagnosis of primary ITP because about 10% of patients can improve spontaneously, but moreover, there are numerous new medications that can be tried to raise the platelet count.[1,10,11,15] Splenectomy also has a high surgical risk in the presence of severe thrombocytopenia and also has a risk from the anesthetic. Additionally, splenectomized individuals are immunosuppressed because of the increased risk of infection with encapsulated bacteria and therefore need to be vaccinated at least 2 weeks before the splenectomy for *Streptococcus pneumoniae, Haemophilus influenzae b,* and *Neisseria meningitides.*[11] One study of patients with refractory ITP following splenectomy showed that only 3 patients out of 47 with platelet counts persistently below 100,000 μL after splenectomy died from hemorrhagic related events at a median of 7.5 years.[24]

Intravenous Immunoglobulin

In patients with contraindication to steroids or who are not responding to steroids even after treatment for 2 weeks, the platelet count can be increased rapidly, but only temporarily with intravenous immune globulin (IVIG) or by anti-D [Rho(D) immune globulin and WinRho].

IVIG is a viricidally treated blood derivative made from the gammaglobulin portion of plasma of 10,000 blood donors. It contains antibodies to many plasma proteins and circulating cells as well as to organs and tissues. Its mechanism of action may be related to the formation of many circulating intravascular antibody-antigen complexes which overwhelm the reticuloendothelial system (RES) of the spleen so that these macrophages can no longer remove the autoantibody coated platelets (also an antibody-antigen complex) from the circulation. Another theory is that the IVIG down regulates the phagocytic function of the RES by inhibiting Fc receptor expression.[8] IVIG is given as 1 g/kg per day, over 1-2 days, and the platelet count will rapidly rise above 30,000/μL in 65-80% of patients.[10] Unfortunately, this rise in platelet count is often short-lived and requires frequent administration of this expensive therapeutic

agent to keep the platelet counts in the desired range of 30,000 to 50,000 per microliter. Five-percent of patients receiving IVIG complain of various aches and pains–headaches, myalgia, arthralgia, and back pain. Rarely hypercoagulable events, renal failure and anaphylaxis can occur.[10]

Anti-D

Anti-D, also known as Rh immunoglobulin (RhIG), is a viricidally treated blood derivative made from the gammaglobulin portion of plasma of 10,000 blood donors. Anti-D is effective only in ITP patients who are Rh-positive, have a negative direct antiglobulin test (DAT) and who have a spleen. The IgG, anti-D binds to the D-positive RBCs of the patient and similar to IVIG, these antibody coated RBCs overwhelm the RES preventing it from clearing the IgG, autoantibody coated platelets.[10,11] Response rates of 70% have been reported with increased platelet counts lasting for 3 weeks.[10]

Rarely disseminated intravascular coagulation (DIC) reportedly 1/20,000 cases, as well as severe degrees of intravascular hemolysis and renal failure have been reported. Two cases resulting in fatalities have been described following use of anti-D and hence the FDA includes a black box warning.[1] Because of this rare complication, some European countries preclude the use of anti-D for treatment of ITP.[10]

Rituximab (Anti-CD20)

Rituximab is a chimeric, humanized monoclonal antibody directed against the CD20 determinant on B-cells and works by depleting these cells. Rituximab was originally developed for malignant B-cell lymphomas, but has been found to be effective in ITP and is a good option for patients who are not surgical candidates or who elect not to have a splenectomy. Rituximab has less response rates compared to splenectomy both in the complete remission and the duration of response. There is about a 63% response rate (platelet count >50,000/μL) to rituximab in ITP patients, with or without splenectomies, lasting for a median duration of 11 months.[10] There is apparently a sustained response rate of 40% at 1 year and 33% at 2 years.[10] Rituximab has less side effects than splenectomy and patients failing rituximab can proceed to splenectomy. Most physicians now consider rituximab a therapy that should be used prior to splenectomy.[25] Rituximab is associated with infusion reactions, prolonged immunosuppression and reactivation of viruses such hepatitis B and rarely with progressive multifocal leukoencephalopathy.[10,15]

Second Line Medications

Thrombopoiesis-stimulating agents (Thrombopoietin receptor agonists)

In 1958, Keleman theorized a hematopoietic growth factor that regulated platelet production and was termed thrombopoeitin.[26] Many endogenous chemicals were identified to increase mega-

karyocyte or platelet counts *in vivo* and *in vitro*, including interleukin-3 (IL-3), interleukin-6 (IL-6), interleukin-11 (IL-11), Granulocyte-Macrophage colony stimulating factor (GM-CSF), and c-Kit ligand.[27] Thrombopoeitin was characterized in 1994 and investigation into recombinant thrombopoietin began.[28] Because administration of recombinant thrombopoietin induced antibodies that cross-reacted with endogenous thrombopoietin resulted in severe thrombocytopenia, clinical trials taking place with this drug were halted in the 1990's.[10] Soon afterwards, thrombopoietin receptor agonists mimicking the effect of thrombopoietin were developed and found to be non-immunogenic in clinical trials since they lack sequence homology with human thrombopoietin.

Thrombopoietin receptor agonists were first approved by the FDA in 2008 for use in ITP in adults with insufficient response to corticosteroids, immunoglobulins (IVIG, anti-D), or splenectomy, and have been used as a second-line treatment.[10] The 2 drugs listed below in this category require repeated administration to maintain the platelet count above 30,000 per microliter and do not show an adequate platelet response for one week after initiation of therapy so that they are not effective in emergencies.[10] After long-term treatment, both of these medications can induce increased reticulin formation in the bone marrow and thromboembolism in a small percentage of patients. Additionally, rebound thrombocytopenia with platelet counts decreasing to less than pre-treatment baseline levels can occur within 2 weeks when treatment is stopped abruptly. Responders may require these drugs for years. Most patients taking thrombopoietin receptor agonists are able to decrease the dose of any other platelet enhancing agents that they are taking at the same time. Thrombopoietin receptor agonists are effective in patients with or without spleens.

Romiplostim is a thrombopoietin receptor agonist composed of an IgG Fc-peptide protein and is administered subcutaneously once weekly. Eighty-seven percentage (124) of 142 patients on this drug had a platelet count >50,000/μL at some time during the 156 week follow-up.[15]

Eltrombopag is an oral, nonapeptide, thrombopoietin receptor agonist administered daily. Platelet counts ≥50,000/μL are seen within 43 days of initiating therapy in up to 81% of the patients taking this drug.[15] Mild increases in alanine aminotransferase levels can occur in up to 7%. There is a black box warning concerning the possibility of hepatotoxicity.[15,29,30]

Most hematologists recommend thrombopoietin receptor agonist in patients who have failed multiple therapies such as 2 different classes of medical treatments like corticosteroids and rituximab and/or splenectomy.[7,15,31]

Third Line Medications

Multiple other drugs have been tried in refractory ITP, usually after splenectomy including azathioprine, cyclosporine, myco-

phenolate, cyclophosphamide, vinca alkaloids, androgens, and danazol.[11] These cytotoxic and extremely immunosuppressive agents mentioned in this discussion are used infrequently for the treatment of ITP because of their high toxicity profiles.[11]

Other Treatments

Hematopoietic stem cell transplant has induced remission in only 25-33% who had severe refractory ITP unresponsive to all other treatment. These patients have a high risk of morbidity and mortality from graft *versus* host disease and severe infection.[10,21] Plasmapheresis to remove the autoantibody directed against platelets has not been shown to be an effective treatment for symptomatic primary ITP in adults.[22] Plasmapheresis in theory would be only a temporary solution since it does not affect the production of the autoantibody.

SPECIAL SITUATIONS

ITP Patients on Anticoagulation Medications

Primary ITP patients may already be on anticoagulation for cardiovascular disease (MI, coronary stent, atrial fibrillation), stroke, deep vein thrombosis, or pulmonary embolism at the time of initial diagnosis. In such anticoagulated patients, very low platelet counts are associated with major spontaneous bleeding. It should be noted that patients with severe thrombocytopenia do not appear to be protected from thromboembolic events.[8] The risks of thromboembolic phenomena must be weighed against the risks of bleeding in primary ITP patients who are on anticoagulants to prevent thromboembolic events. For the most part it is recommended that those patients with platelet counts above 30,000 per microliter (the level at which spontaneous severe bleeding episodes usually do not occur) can receive venous (unfractionated heparin, low molecular weight heparin, and Coumadin) or arterial anticoagulation (platelet aggregation inhibitors–aspirin and clopidogrel) in the same way as patients without thrombocytopenia.[8] However if a major bleeding episode occurs, anticoagulant therapy should be withheld. Wherever possible, low molecular weight heparin with its much shorter half-life might be considered over Coumadin. Additionally, for those undergoing surgery with a high risk for thromboembolism (orthopedic or cancer surgery), if the platelet count is less than 30,000 per microliter, pneumatic leg devices might be considered over low molecular weight heparin.[8]

Life Threatening Bleeding and those ITP Patients who need Urgent Surgery

ITP patients with severe thrombocytopenia having a life-threatening bleed or those needing surgery should be hospitalized and stabilized. Life-threatening major bleeding can be seen in ITP patients with intracerebral, gastrointestinal (GI), genitourinary (GU) and gynecologic (GYN) bleeding or with epistaxis at any time during the course of their disease especially if the platelet count drops below 30,000 per microliter. Fatal hemorrhage occurs in 1 to 4% of primary adult ITP cases per adult patient-year.[22] Platelet concentrate infusion as well as IVIG with a corticosteroid have been used to rapidly increase the platelet count in urgent situations to provide hemostatic support.[22] Platelet transfusion with IVIG has been shown to increase platelets by more than 20,000/µL in 42% of ITP patients and was associated with resolution of bleeding.[22] A variety of other treatments have also been suggested for bleeding ITP patients with extremely low platelet counts and include recombinant factor VIIa, antifibrinolytic agents (tranexamic acid and epsilon amino caproic acid), DDAVP (promotes hemostasis in congenital platelet disorders), and vincristine.[8]

Minimally Invasive Procedures

Patients requiring minimally invasive interventional procedures like liver and kidney biopsies, lumbar puncture, central line placement, bronchoscopy, GI endoscopies, thoracentesis and paracentesis have traditionally been prophylactically transfused platelets to a count of at least 50,000/µL.[32] However, the practice and utility of prophylactic platelet transfusions for minimally invasive interventional procedures have recently been brought into question especially for those patients with platelet counts above 30,000/µL.[32]

The reason for this suggested change in transfusion practice is that about 1 to 2% of patients undergoing minimally invasive procedures will bleed whether or not prophylactic blood products are administered at a platelet count of 50,000/µL. The platelet count is not a good predictor of bleeding and the bleeding that occurs in these few cases is not due to the mild to moderate thrombocytopenia but to the experience of the person performing the procedure and/or to the possibility of inadvertently puncturing an arteriole or artery. Additionally, it is more efficacious to transfuse platelet concentrates to treat bleeding rather than to give them prophylactically.[32]

Thrombocytopenia in Pregnancy

For an excellent review of thrombocytopenia in pregnancy and for suggested treatments for this condition please see Quick-Reference Guides, The 2013 Clinical Practice Guide on Thrombocytopenia in Pregnancy on the American Society of Hematologists (ASH) website: http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx.

CONCLUSIONS

The definition, diagnosis, and treatment of immune thrombocytopenia has evolved over time. Although many causes of secondary ITP are identified, primary ITP is still the most prevalent cause of thrombocytopenia in clinical practice today. Recognizing the natural course of ITP and delineating the severity of the condition is paramount in appropriately treating patients with ITP. Emphasis is in treating only those patients in which clini-

cal implications demand therapy and avoiding unnecessary and potentially harmful treatment. With time, additional insight into the pathophysiology of immune thrombocytopenia may lead to the discovery of potential therapeutic targets, but the indications for treatment will need to be clearly defined as newer, expensive treatment modalities are developed.

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