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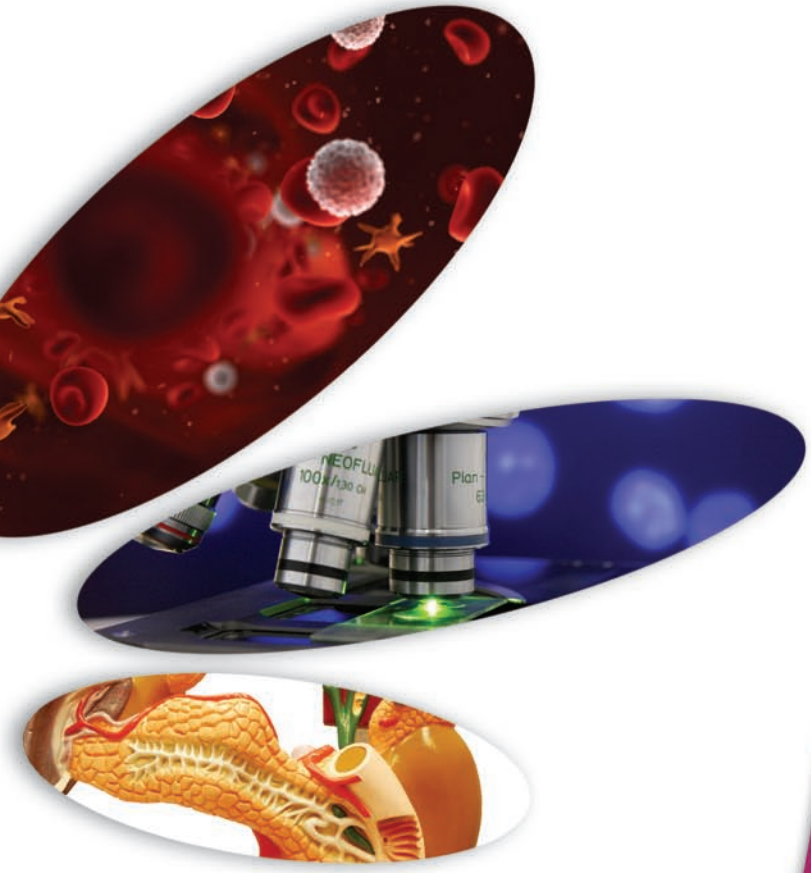
PLATELET DISORDER
SUPPORT ASSOCIATION

The Role and Function of Platelets in ITP

FREQUENTLY ASKED QUESTIONS



The Role and Function of Platelets in ITP

FREQUENTLY ASKED QUESTIONS

Q **What is ITP?**

A ITP is the abbreviation for a bleeding disorder called *immune (idiopathic) thrombocytopenic purpura*.

- **Immune** — meaning the immune system is involved
- **Thrombocytopenic** — meaning the blood doesn't have enough platelets
- **Purpura** — meaning there may be bleeding or bruising involving the skin or other parts of the body

When someone has ITP, they experience thrombocytopenia (low platelet count in their blood), which may lead to bleeding and bruising.

Q **Who gets ITP?**

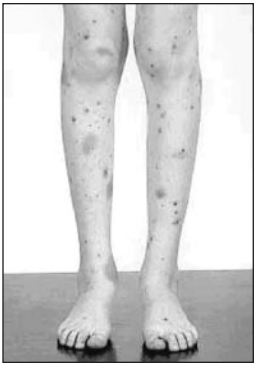
A Anyone can get ITP at any age. Children may get ITP at any age but it most commonly occurs in ages 1 to 6, with occurrence slightly more common in boys than girls. Adult men and women may get ITP at any age. Several newer studies indicate that there are more reported women than men with ITP only among ITP patients aged 45 to 59. In all the other adult age groups (age 44 and under and age 60 and older) there were more ITP cases reported in men than in women. These new studies also show that ITP increases as people age. See "Lessons from the Epidemiology of ITP," by Dr. Patrick F. Fogarty in *The Platelet News*, Vol. 9; No. 3, Fall 2007.

Q **Is ITP contagious? Can it be spread to family and others?**

A No, ITP is not a contagious disease and it cannot be spread to others like a cold.

Q **What is thrombocytopenia? What are the symptoms?**

A Thrombocytopenia is a condition of reduced or low platelets in the blood that has been defined as a platelet count of less than 150,000. Note: new international recommendations to be published soon may define thrombocytopenia as a platelet count of less than 100,000, but for this booklet we have relied on current standards. Symptoms associated with more profound reductions in the platelet count include: bleeding into the skin (thrombocytopenic purpura), red or purple spots on the skin (petechiae), spontaneous bruises, mucosal (mouth) and gingival (gum) bleeding, subconjunctival hemorrhage in the eye, and prolonged bleeding after a cut or injury, among others. There are many causes of reduced or low platelets in addition to ITP.



Petechiae on a child's legs.

Q **How is the severity of thrombocytopenia defined?**

A Mild thrombocytopenia is considered to encompass platelet counts of 50,000–150,000 and is not usually associated with an increased risk of bleeding. Moderate thrombocytopenia is often defined as platelet counts of 20,000–50,000 and may be associated with an increased risk of bleeding. Severe thrombocytopenia occurs with platelet counts of less than 20,000 and is often associated with an increased risk of bleeding. However, the platelet count provides only part of the story when it comes to estimating the risk of bleeding.

Q **Besides ITP, what other conditions cause low platelets?**

A In addition to ITP, many medical conditions can cause thrombocytopenia (low platelets) including congenital thrombocytopenia, bone marrow failure, leukemia, myelodysplasia, aplastic anemia, thrombotic thrombocytopenic purpura,

severe infection, enlargement of the spleen and pseudothrombocytopenia, among many others.

In addition, exposure to certain drugs, herbs, foods or other substances, such as quinine, may be associated with thrombocytopenia in some individuals.

Understanding ITP

Q **What is primary ITP? What is secondary ITP?**

A Doctors use the terms "primary ITP" and "secondary ITP" depending upon whether a coexisting disease may be present and responsible for the ITP symptoms. When there is no "coexisting" disease, then the ITP is considered Primary.

Secondary forms of ITP are those associated with medical conditions such as chronic lymphocytic lymphoma, systemic lupus erythematosus (SLE), thrombotic thrombocytopenic purpura, and HIV or Hepatitis C infection, among others.

Q **How is ITP an autoimmune disease?**

A In an autoimmune disease, the body mounts an attack on one or more of its seemingly normal organ systems. In ITP, platelets are the target of this attack and their destruction causes thrombocytopenia. Platelets are marked as foreign by the immune system and eliminated by phagocytosis (process of engulfment and digestion used normally to rid the body of bacteria or other foreign particles by white blood cells called macrophages) as they pass through the spleen and, sometimes, the liver. In addition to experiencing increased platelet destruction, most people with ITP also have impaired platelet production. Idiopathic means the cause is unknown.

Q **What is the natural history or progression of ITP in patients?**

A ITP can be either ***acute*** (sudden onset, often temporary, lasting for less than 6–12 months) or ***chronic*** (greater

than 6–12 months). Most children (80–90%) have acute ITP. The onset may be sudden and occur a week or so after a viral infection. These children usually recover within a few months whether they receive treatment or not. Late spontaneous recovery is possible even if a child is considered to have chronic ITP.

In contrast, ITP is chronic in the overwhelming majority of adults and requires medical treatment to restore normal platelet levels. Typically, the onset in adults is insidious, i.e., weeks or months of mild to moderate abnormal bleeding off and on before the patient seeks medical advice.

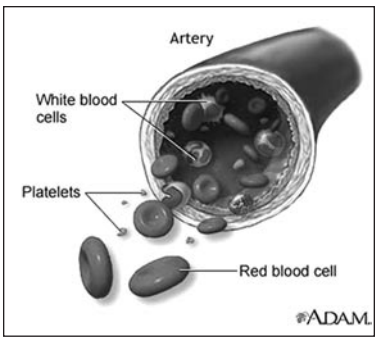
Q What is refractory ITP?

A *Refractory* ITP means the disorder is resistant to ordinary methods of treatment, including steroids, anti-D, IVIg, and splenectomy. The doctor caring for a patient with refractory ITP faces two treatment objectives: Emergency therapy and long-term treatment. The aim of the emergency therapy is to rapidly increase platelet count to safe levels. Long-term treatment aims to maintain safe platelet count and minimize bleeding symptoms.

Understanding Platelets

Q What are platelets? Why are they needed?

A Platelets are relatively small, somewhat disk-shaped cell fragments in the blood that are involved in blood clotting. Platelets are needed to maintain the integrity of our blood vessel walls and for our blood to clot when we are injured. If their platelet count is low, a person is subject to spontaneous bleeding or bruising.



Platelets and blood cells.

Q What is the role of platelets in hemostasis in the body?

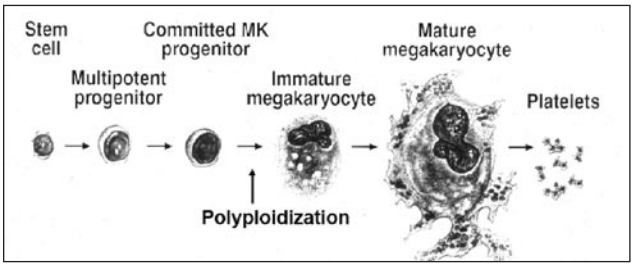
A Platelets are essential to helping the body maintain a state of hemostasis (the complex process of keeping the blood flowing smoothly under normal conditions and then stopping bleeding when blood vessels are injured). When an injury to a blood vessel causes bleeding, platelets stick to the site of damage where they release chemical substances that attract other platelets. Together, they form a temporary blood clot to stop the bleeding. Then, through a series of chemical reactions, the plasma protein fibrinogen is converted into fibrin. The fibrin molecules form threads that trap red blood cells and platelets, which produces a clot that seals the cut blood vessel. Thus, the role of platelets is to ensure the integrity (soundness) of blood vessel walls throughout the body.

Q What is a normal platelet count?

A Normal platelet count currently ranges from 150,000 to 400,000 per microliter of blood. A person with a platelet count of less than 10,000 per microliter of blood is at risk for spontaneous bleeding. For most people, 30,000–40,000 is a sufficient count to prevent most bleeding events. Certain medical procedures and situations, such as childbirth and surgery, require platelet counts higher than 50,000.

Q Where and how are platelets produced?

A Platelets are produced from special large cells called megakaryocytes found in the bone marrow (the soft tissue inside our bones). Proplatelets bud off from the megakaryocytes and enter the circulation. Through the

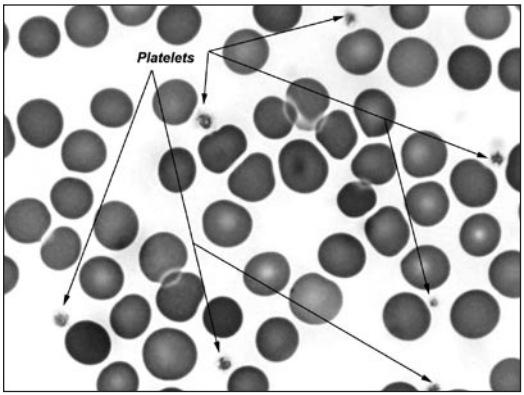


A megakaryoctye produces platelets.

process the entire cytoplasm of the megakaryocyte divides into many proplatelets. The process is regulated by cytokines and chemokines (types of signaling proteins that are needed in cellular communication). These proplatelets then become mature platelets in the circulation in the blood.

Q What is thrombopoietin and what is the process of thrombopoiesis?

A Thrombopoietin (TPO) is an important growth factor involved in the production of platelets in the bone marrow. It was first proposed in 1958 as a growth factor that raises platelet counts. However, it was not until 1994 that this hormone was isolated and identified. TPO is mainly synthesized in the liver. TPO is not stored but is produced and immediately secreted for use. TPO regulates platelet levels by binding to specific proteins called receptors (TPO-R) that are found on platelets and progenitors (parent cells) of platelets (megakaryocytes and hematopoietic stem cells).



Tiny platelets and red cells in the blood.

Q What is the normal buildup and breakdown in the lifespan of a healthy platelet?

A Under normal conditions, the human body makes 35,000 platelets per microliter of blood per day. A healthy, single megakaryocyte can produce 1,500–3,000 platelets. A normal platelet lives in the body on average 9–10 days. After that, it dies and is removed by many organs in the body (spleen, liver, lungs).

Q What happens to the lifespan of a platelet in ITP?

A In ITP, the breakdown of platelets filtering through the spleen occurs more rapidly than normal, reducing the lifespan of a platelet to as little as 6 hours in severe cases.

Causes of Low Platelets

Q What causes platelet counts to fall?

A The platelet count may fall because of destruction of platelets in the spleen causing a decrease of the platelets in circulation. Platelet counts may also fall because of a deficiency in platelet production in the bone marrow. Either can occur through inheritance or acquired as part of a disease. In the case of ITP, both platelet production and platelet destruction may be altered by auto (self-directed) antibodies.

Q What is the function of the immune system?

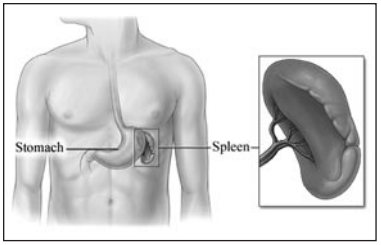
A The immune system is a network of cells, tissues and organs that protects the human body from various foreign invaders, called pathogens including bacteria, viruses, and parasites.

Q What are the parts of the immune system involved in ITP?

A The immune system contains B-lymphocytes, T-lymphocytes, antibodies, and the spleen, among other components. All these elements collaborate in the process of making both protective antibodies and autoantibodies. It is the B-cells that actually produce the antibodies that mark platelets for destruction.

Q What is the spleen?

A The spleen is an organ in the body that contains large numbers of B and T-cells and where macrophages devour/destroy foreign invaders (e.g., pathogens) and cellular debris (e.g., old blood cells). The spleen



is a spongy, soft organ about the size of a person's fist that is located just under the ribs in the upper left part of the abdomen. It helps "filter" the blood. The spleen contains two types of tissue: the white pulp and the red pulp.

The spleen and its body location.

Q What is the difference between the spleen's white and red pulp?

A White pulp is part of the body's infection-fighting (immune) system that produces white blood cells called lymphocytes. As mentioned, one type of lymphocyte, the B-cell produces antibodies that protect against invasion by foreign substances, such as bacteria.

Red pulp filters the blood, removing unwanted material. The red pulp contains white blood cells called phagocytes that ingest and digest microorganisms such as viruses, bacteria, and fungi. (Macrophages are one type of phagocyte.) The red pulp also monitors red blood cells and platelets, destroying those that are too old or damaged to function properly.

Q What is the spleen's role in ITP?

A Platelets that pass through the spleen are destroyed by special cells in the red pulp called phagocytes. If the platelets are marked with certain autoantibodies, the spleen destroys many otherwise healthy platelets quite efficiently as they pass through, causing a person to experience thrombocytopenia (low platelets).

Q What is the role of antiplatelet autoantibodies in ITP?

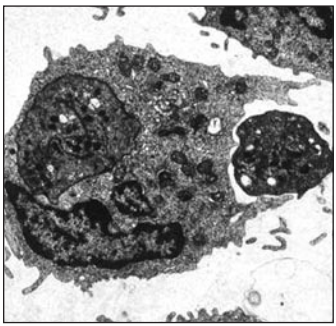
A Antibodies are proteins that are found in blood or other bodily fluids that are parts of the immune system used to identify and neutralize foreign invaders, such as bacteria and viruses. Antibodies are produced by a kind of white blood cell called a B cell.

Autoantibodies are antibodies that are manufactured by the immune system, and are, unfortunately, directed against one of the body's own proteins.

Antiplatelet autoantibodies, therefore, are antibodies that are directed against platelets.

Q What actually causes the platelet destruction in ITP?

A In ITP, abnormal autoantibodies, usually immunoglobulin G (IgG) with a specificity (reacting one specific way with one specific thing) for one or more platelet membrane glycoproteins (GPs), bind to the outer membrane of platelets circulating in the blood. These autoantibody-coated platelets are then recognized by special adaptor proteins on phagocytes such as macrophages, called Fc-gamma receptors (FcγR), which leads to the platelets' phagocytosis (ingestion) and destruction. This occurs mainly, but not exclusively, in the spleen.



A macrophage engulfing a platelet.

Karpatkin S. Autoimmune (idiopathic) thrombocytopenic purpura. *Lancet.* 1997; 349:1531–1536.

Q Are platelets destroyed anyplace else in the body?

A Yes, platelets are also destroyed in the liver.

Diagnosis of ITP

Q What happens when a person with low platelets sees the doctor?

A When a patient with low platelets first sees the doctor (usually a hematologist), a patient is asked to explain the reason why they made the appointment, the history of the present illness is discussed, the patient's general state of health is assessed, a physical exam is completed, and then blood tests are performed. Sometimes additional tests are needed.

Q What signs are usually found during physical exam of an ITP patient?

A The purpose of the physical exam generally is to reveal outward evidence of platelet-type bleeding (purpura, petechiae, conjunctival hemorrhage (in the eyes) or mucocutaneous (lining of the mouth) blisters. Evidence of other disorders, such as signs of weight loss, hypothyroidism, enlarged lymph nodes, or enlarged spleen, among many other potential findings will also be noted.

Q Which initial diagnostic tests are done to determine if a person has ITP?

A A *blood smear* and a *complete blood count* (CBC) are the first recommended diagnostic tests for evaluating a patient who might have ITP. Sometimes a bone marrow aspiration may be required as well.

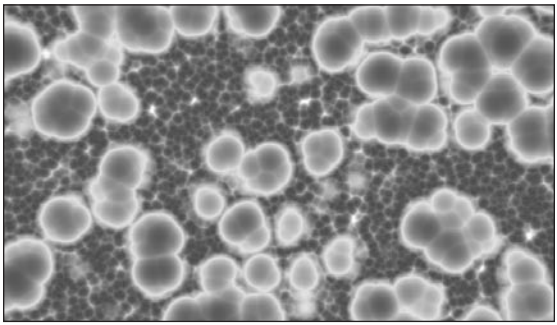
Q What is a CBC and why is important?

A A complete blood count (CBC) is a blood test that provides information about the severity of the thrombocytopenia. From a small sample of blood, an automated counter enumerates red cells, white cells, and platelets in a measured volume of blood (usually expressed as number of cells per microliter of blood). In ITP there is an isolated reduction in the number of circulating platelets. A normal platelet count ranges from 150,000 to 350,000 per microliter, with thrombocytopenia defined as a count below 150,000 platelets per microliter.

Q What does a blood smear show?

A A blood smear is also called a peripheral blood smear or blood film. Blood is placed ("smeared") on a glass microscope slide, stained (Wright stain), and examined under the microscope. A blood smear is a diagnostic tool that can show whether a platelet count is truly decreased and can detect any other blood abnormalities that might be present. The blood smear is, therefore, used to rule out pseudo (false)

thrombocytopenia due to platelet clumping outside the body, inherited giant platelet syndromes, or other hematologic (blood) disorders.



Blood smear showing platelets and blood cells.

The test provides information about platelet size. Giant platelets approaching or exceeding the size of red blood cells are more typical of congenital (from birth) thrombocytopenias such as Bernard-Soulier syndrome and May-Hegglin anomaly. Large, but not giant, platelets are often seen in patients with ITP. Very small platelets occur in Wiskott-Aldrich syndrome.

Q **What is a bone marrow aspiration? How is it done? When is it required?**

A Bone marrow aspiration is the removal by suction through an aspiration needle of fluid from the soft, spongy material that lines the inside of most bones.

A bone marrow aspiration may be done on an outpatient basis or in a hospital. The procedure takes about 30 minutes. The patient is sometimes given a sedative. Skin covering the sampling site (usually the rear bone of the hip or, rarely, the breastbone) is cleansed with an antiseptic. Then the injection area is numbed with a local anesthetic such as novocaine.

A special aspiration needle is inserted beneath the skin and rotated until it penetrates the hard outer covering of the bone and gets into the soft spongy inner portion of the bone. At least half a teaspoon of marrow is withdrawn from the bone by a syringe attached to the needle. The sample is transferred from the syringe to slides and vials, and then sent to a laboratory for analysis.

A bone marrow aspiration test may be helpful when the doctor wants to pinpoint the cause of abnormal blood test results, confirm the diagnosis of a blood disorder, or check the status of irregularities in the way blood cells are produced or mature. In older patients (age 60 and above) bone marrow aspiration is used to rule out causes of thrombocytopenia other than ITP as these tend to increase in prevalence as we age.

Q What is a bone marrow biopsy?

A A bone marrow biopsy is often done at the same time as a bone marrow aspiration. After performing the bone marrow aspiration, the biopsy needle is reinserted into the bone and a small piece of bone marrow (the "core") is removed and subjected to various microscopic tests.

Q What other tests might the doctor order to rule out non-immune causes of low platelets and secondary causes?

A A low platelet count raises the possibility of ITP. However, there are many other possible causes of thrombocytopenia, with clinical severity ranging from trivial to life threatening. ITP is a diagnosis of exclusion. This means that only after all other possible causes of low platelets have been ruled out, can a diagnosis of ITP be settled upon.

This makes it important to know or at least be aware of the other common causes of low platelets that may be mistaken for or misdiagnosed as ITP. These other causes are either platelet production problems centered in the bone marrow or platelet destruction problems often centered in the liver or spleen. Some low platelet conditions are characterized by both a low rate of production and a high rate of platelet destruction.

When thrombocytopenia is severe (i.e. platelet count less than 20–30,000/microliter) and no other cause of thrombocytopenia is apparent, a trial of agents that block destruction of antibody-coated platelets may be administered (prednisone, anti-D, IVIg). A rapid response (within a week) to these therapies helps confirm the diagnosis of ITP. Failure to respond

to these therapies should lead to an in-depth investigation of alternate causes for low platelets, which may include a bone marrow evaluation.

Treatment for ITP

Q **What are the therapies available to treat ITP?**

A There are two tiers of treatment for ITP, which are considered the initial or "first-line" treatments and the second-level or "second-line" treatments.

Q **What are the "first-line" medical treatments that doctors use initially to raise the platelet count in patients with ITP? What are the mechanisms of action, typical response rates, possible side effects and toxicities, and the pros and cons of these initial treatments?**

A Corticosteroids, IVIg, and IV-anti-D are the three most commonly used first line medical treatments for ITP. Examples of corticosteroids include prednisone and dexamethasone. Several different brands of IVIg are available, depending on the patient's needs. Some brands of IV-anti-D include WinRho SDF (from Cangene), Rhophylac (from CSL Behring), and RhoGAM (from Johnson & Johnson).

Corticosteroids (often referred to as steroids; not to be confused with sex steroids such as testosterone and estrogen) are anti-inflammatory by lessening swelling, redness, itching, and allergic reactions and they help to reduce the activity of the immune system. They are often used for asthma and other autoimmune diseases. Because corticosteroids help the body maintain the integrity of the walls of the veins and arteries, they are helpful in stopping or preventing unwanted bleeding.

For ITP, the drug is given by mouth in non-emergent settings. Typically, the initial dose is high dose and the dosage is gradually tapered depending on response and toxicity. Occasionally, the platelets remain elevated after the steroid is tapered. In most cases of ITP in

adults, the platelet count falls as the dose of steroid is reduced. Some patients with ITP are maintained for years on very low doses of steroids.

The mechanism of action of steroids is that they inhibit the destruction of autoantibody-coated platelets, lessening platelet destruction and, over time, decrease autoantibody production, which both reduces destruction and increases production.

The response rates for steroids vary from 50% to 90% depending on intensity and duration of therapy. However, only 10% to 30% of patients maintain sufficient numbers of platelets to prevent bleeding once therapy is tapered or stopped.

Corticosteroids are very strong medicines. In addition to their helpful effects, they have side effects that can be very serious. Be sure that you discuss the risks and benefits of this medicine with your doctor. Steroids may lower your resistance to infections and any infection you get may be more difficult to treat.

Some of the other possible problems that may occur with steroid use includes: glaucoma, cataracts, gastrointestinal bleeding, pancreatitis, aseptic bone necrosis, osteoporosis, peptic ulcers, myopathies (all types of diseases or damage to the muscles), obesity, edema, hypertension (high blood pressure), diabetic metabolism (increased blood sugar), sleep disturbances (insomnia), psychiatric syndromes (mood changes), delayed wound healing, atrophy (muscle wasting), potassium loss, and fragility of the skin.

Side effects of steroids can be uncomfortable and increase in severity as the treatment is continued for a long period of time. With prolonged use, the drug halts the communication between the pituitary gland and the adrenals, which are responsible for the normal production of steroids by the body. It can impair the body's response to stress for up to one to two years after cessation of the drug, requiring steroid replacement at the time of surgery, trauma or other stresses.

IVIg stands for intravenous immune globulin. IVIg is a plasma product that is formed by taking antibodies from about 20,000 donors and mixing them together. The product is purified and given as an intravenous

infusion over several hours. IVIg has proven effective in several autoimmune disorders in addition to ITP.

There are differences among the IVIg products and these differences are based on how the IVIg is prepared including their sodium and sugar content, how much immunoglobulin A (IgA) they contain, and types and amounts of certain chemicals used in their processing. Some patients who receive IVIg with higher amounts of sucrose may be at higher risk for renal failure. The patient's medical provider will determine the appropriate type of IVIg to be used in their treatment for ITP.

After their IVIg infusion, some patients may see a rise in the platelet count within 24–48 hours. Some may not see a response for up to eight days or more, and the drug is not effective in about 15% to 20% of patients.

Mechanism of action: With IVIg, the antibodies attach to the FCγR (Fc-gamma receptors) in the spleen, sparing the removal of antibody-coated platelets. IVIg is a temporary measure, i.e., it does not sustain an elevated platelet count, although a few adults will develop a spontaneous remission while under treatment.

Reported side effects of IVIg include post-infusion headaches, allergic reactions, or, less commonly, clotting and lung or renal injury. Because this product is developed from pooled blood samples of many different donors, it is theoretically possible that viruses or bacteria could be transmitted in the product. Since 1985, however, all products are tested for HIV and hepatitis and they undergo rigorous inactivation procedures during their manufacture.

Anti-D is the short term for Rho(D) Immune Globulin. Anti-D is a treatment available for ITP patients who are Rh+ and who have not undergone splenectomy. Intravenous anti-D rhesus (Rh)0 immunoglobulin (IV RhIG) is used to achieve a temporary elevation of platelet count. An advantage of anti-D over IVIg is that it can be administered intravenously over a few minutes vs. the several hours it takes to infuse IVIg. Anti-D-marked red cells are destroyed by macrophages in the spleen, sparing the antibody-marked platelets. Response rates are comparable to IVIg and somewhat faster than is seen with steroids.

Anti-D side effects of fever/chill reactions are common and preventable. A mild drop in the hemoglobin is typical and may last for several weeks. Severe red cell destruction (hemolysis), clotting, organ failure, and death are extremely rare complications.

Q **If "front-line" therapies are not effective what are the "second-line" medical treatments that the doctor is most likely to use to raise platelet counts?**

A If corticosteroids, IVIg, and anti-D are not effective in raising platelet counts to a safe level or the side effects pose problems, several "second-line" treatments may be tried. The two primary types of second-line treatment are either medical (drugs) or surgical (spleen removal). Second-line treatments include: the drugs Danazol, Dapsone, monocloncal antibodies (e.g, rituximab), and several immunosuppressant drugs; surgery to remove the spleen (splenectomy); and the newly approved thrombopoietin mimetics or platelet growth factors.

Danazol is a steroid-sparing agent. It is a synthetic androgen (male sex hormone) also known as 17alpha-ethinyl testosterone. Danazol was marketed as Danocrine in the United States. In the early 1970s it was approved by the U.S. FDA as the first drug to treat endometriosis. Danazol has also been used off-label for other disorders, including immune thrombocytopenic purpura (ITP).

Danazol's mechanism of action is that it disrupts the action of the pituitary gland by suppressing the output of some hormones, which causes the reduction of estrogen, which may increase androgens, halt menses, promote growth of facial hair, and cause acne. About 50% of patients who are treated will respond to danazol although responses may be slow (average response time is 2.7 months with 85% of responses occurring within 4 months). The reported response rate has been about 30%. Its main side effects are its masculinizing effects in sensitive women. Baseline and periodic liver function tests should be performed in all patients.

Dapsone (diamino-diphenyl sulfone) is an antibacterial drug commonly used in combination with rifampicin and clofazimine as multidrug therapy (MDT) for the

treatment of Mycobacterium leprae infections (leprosy). As an antibacterial, dapsone inhibits bacterial synthesis of dihydrofolic acid. Dapsone has also been used to treat chronic ITP. Several studies reported a response rate of 40% to 60%, with average response time of 3–5 months. Responses last for several months but relapse usually occurs unless therapy is continued. Dapsone may be considered as a substitute in patients whose platelet counts can be maintained with small doses of prednisone. It may be added to the prednisone and after a few weeks the prednisone would be slowly tapered.

Side effects include destruction of red blood cells (hemolysis) at higher doses and sometimes anemia. Hypersensitivity reactions occur in some patients and involve a rash and possibly fever, jaundice, and eosinophilia (increased white cell count).

Q What are monoclonal antibodies and how do they work? What are the side effects?

A **Monoclonal antibodies** are antibodies produced artificially from a cell clone and consist of a single type of immunoglobulin. Rituximab (trade name: Rituxan) is one type of monoclonal antibody that was approved by the FDA to treat lymphoma. There has been some success in its use to treat ITP. Clinical studies are in progress.

Mechanism of action: Rituxan (rituximab) destroys both normal and malignant B lymphocytes. It is used to treat diseases characterized by having too many B cells, dysfunctional B cells, or overactive B cells (as in ITP). Thus, Rituxan reduces the number of B cells in the body. B cells are a type of white blood cell that, when activated, multiply and produce antibodies. Since Rituxan reduces the number of B cells, it also reduces the number of cells that produce antibodies, including the antibodies that attack platelets, thereby enabling the platelet count to rise. Most recent reports from studies in the U.S. on the effects of Rituxan showed that after being given to patients for four weeks, 32% of patients had an increase in platelets lasting up to a year.

Side effects of Rituxan were reported in 87% of the patients. Ten percent of patients reported very serious

adverse effects that included fever, chills, weakness, nausea and headaches. Some hypersensitive patients may get serum sickness. Some rare cases of progressive multifocal leukoencephalopathy due to a specific virus have been reported to the FDA.

Q What are immunosuppressant drugs and how do they work?

A Immunosuppressants are a class of drugs that are capable of inhibiting the body's immune system. Many of the agents in this category are also cytotoxic (cell poisons) and are used in the treatment of cancer.

In ITP, the immune system is hyperactive and produces auto-antibodies at a rapid rate of growth. Chemotherapy medicines have their greatest effect against rapidly dividing cells and, therefore, can be beneficial in the treatment of ITP by suppressing the cells involved in the hyperactive immune response.

Immunosuppressant chemotherapy drugs have been used as an almost last resort for patients with chronic ITP. Vincristine and Cytoxan (cyclophosphamide) are those most frequently prescribed. Imuran (azathioprine) is used less frequently. Each drug has a slightly different profile of side effects. These effects include hair loss, decreased immunity, gastrointestinal symptoms, bleeding from the bladder, damage to the central and peripheral nervous systems, bone marrow suppression, liver toxicity and risk of developing leukemia.

SPLENECTOMY

Q If ITP patients do not respond to "second-line" drug therapies what else can be done?

A Another second-line treatment for ITP is surgery to remove the spleen (splenectomy) in patients whose platelet count remains below 30,000 and who have serious bleeding. The decision as to whether to undergo a splenectomy is a complex issue that each patient must consider carefully depending on their personal medical situation and medical history. The issues are

too complex to fully cover in this brochure. Please consult with your doctors and get a second opinion.

On the positive side, the medical community has considerable experience with splenectomy. It has been used on thousands of published patients over the decades in countries throughout the world. It has a reasonable cure rate and benefit to risk ratio. Patients and their doctors may wish to defer splenectomy until the sometimes irreversible toxicity of Cytoxan and Vincristine and other immunosuppressant agents has manifested. In other cases, there are patients who do not wish to take the risks associated with rituximab and other drugs. In these cases, splenectomy is a valid second-line treatment to consider for ITP.

Q What is a splenectomy?

A Splenectomy is the surgical removal of the spleen, an organ that filters and stores blood, destroys old red blood cells and platelets, and produces antibodies to fight infections. Removing the spleen may raise the platelet count by removing the site of platelet destruction. The spleen is also an important site of antibody production. The procedure is effective in approximately two-thirds of patients with ITP and most responses are durable. Surgery is performed in a hospital with the patient under general anesthesia (asleep). Many patients are able to have laparoscopic surgery, which uses small incisions and has faster recovery time.

Q How can a splenectomy stop platelet destruction?

A Surgically removing the spleen should significantly reduce platelet destruction because the spleen acts as the primary site of platelet removal and of antiplatelet autoantibody production.

Q What are the short and long-term side effects of having a splenectomy?

A Possible short-term complications of splenectomy immediately following surgery may include infection, incisional bleeding, pneumonia, incisional hernia, pancreatic inflammation, deep vein blood clots, and

pulmonary embolism (blood clot that travels to the lungs). While general anesthesia prevents pain during the surgery, there may be incisional pain for several days after surgery.

Because the spleen filters the blood and produces antibodies to help fight infections, having a splenectomy may result in impaired immune system functions, which may increase a person's susceptibility to three bacterial infections that may be life-threatening in some cases. Vaccinations are available for these three bacteria (*S. Pneumoniae, N. meningitides,* and *H. influenzae*). Fortunately, the immune system is well developed in adults. The risk of overwhelming infection in adult patients who have been properly vaccinated (see below) and receive appropriate antibiotic therapy for infection is approximately 1% over a life-time.

Over the long term, patients who have had a splenectomy should seek timely medical attention for any illness with fever (temperature over 101°F). These illnesses, such as sinus infection or severe sore throat may require antibiotics to prevent a more serious infection. Patients should always tell doctors and medical staff that they do not have a spleen. When travelling outside the U.S., they should take special precautions against malaria and other infections that may cause a threat.

Also, patients should talk to their health care provider about immunizations they may need prior to splenectomy. In particular, at least two weeks prior to splenectomy patients should receive immunizations including *Haemophilus influenzae* type B vaccine, Pneumococcal vaccine, and *Neisseria mennigitid* vaccine. The patient should also be familiar with the schedule for booster shots. Patients who have had splenectomy are advised to wear a medical alert bracelet to identify their condition to emergency and medical staff. They need to be sure all doctors treating them know they have had a splenectomy.

Q What percent of ITP patients are cured by having a splenectomy?

A This is a complex question to answer because it depends upon what is meant by "cured" and for how long the patients were followed to see that they remained cured. Patients want to know the likely outcome of having a splenectomy.

A representative study is, "Splenectomy for Adult Patients with Idiopathic Thrombocytopenic Purpura: A Systematic Review to Assess Long-term Platelet Count Responses, Prediction of Response, and Surgical Complications," by Kiarash Kojouri, M.D., M.P.H., Sara K. Vesely, Ph.D., Deirdra R. Terrell, M.P.H., James N. George, M.D., *Blood,* First Edition Paper. It was prepublished online June 24, 2004.

In this important meta-study the authors identified and reviewed 135 case series, 1966–2004, that described 15 or more consecutive patients who had undergone splenectomy for ITP and that had data for one of three outcomes of interest: (1) platelet count response, (2) predictors of response, or (3) surgical complications. A complete response was defined as a normal platelet count following splenectomy and for the duration of follow-up with no additional treatment.

Forty-seven case series of the 135 case series studied, reported complete response in 1,731 of 2,623 adult patients (i.e., 66%) with follow up for a range of 1–153 months (0.1–12.7 years) over all the case series. The median follow-up was 29 months (2.4 years).

Mortality rate was 1.0% (48/4955 patients) with laparotomy and 0.2% (3/1301 patients) with laparoscopy. Complication rates were 12.9% (318/2465) with laparotomy and 9.6% (88/921 patients) with laparoscopic splenectomy.

This study concludes that although the risk of surgery is an important consideration, splenectomy provides a high frequency of durable responses for adult patients with ITP.

At present, there is no way to reliably predict, prior to surgery, who will respond to splenectomy, or how long the response will last.

Q What about the platelet growth factors?

A **Platelet Growth Factors** are the newest approved form of treatment for patients with chronic ITP. Nplate™/romiplostim (from Amgen), has completed all clinical testing and was approved in August 2008 by the Food and Drug Administration (FDA) for use in the U.S. for chronic ITP in splenectomized and non-splenectomized patients. Another platelet growth factor, PROMACATA®/eltrombopag (from GlaxoSmithKline/ Ligand), has completed all clinical testing and received FDA approval in November 2008 for use in the U.S. for chronic ITP. Both of these new treatments have been found effective for raising platelets in ITP. Nplate™ is given by weekly subcutaneous injections at a doctor's office. PROMACTA® is a pill taken once a day.

Mechanism of action: Most previous treatments for ITP have focused on stopping destruction of platelets in the spleen and elsewhere. The platelet growth factors or thrombopoietin (TPO) receptor agonists are a new class of treatments that stimulate the megakaryocytes in the bone marrow to produce more platelets. TPO, a protein made in the liver, naturally stimulates platelet production in the bone marrow. TPO receptor agonists bind to the same receptor as the TPO produced in the body. This then prompts the megakaryocytes in the bone marrow to produce more platelets than they would otherwise.

While ITP is often considered a disease characterized by platelet destruction, recent research has shown that many people with ITP also have unusually low platelet production. The additional bone marrow stimulation prompted by the TPO receptor agonists (e.g., Nplate™ or PROMACTA®) creates a sufficient number of platelets to overcome the platelet production and destruction problems in most people who receive these treatments. The result is a safe level of platelets with minimal side effects.

Nplate™/romiplostim (Approval for use in other countries is expected in 2009) Recent studies of romiplositm indicated an initial response rate of 78% in splenectomized patients, and 87% in non-splenectomized patients, with 0% response to placebo.

More than 60% of the non-splenectomized patients achieved a durable response rate, compared to 38% of splenectomized patients. Durable response was defined as platelet counts of 50,000 or higher for at least six weeks, without rescue medications, such as steroids. Nplate™ dose depends on the patient's weight and response to previous doses. The initial dose is 1 mcg/kg. The dose is reduced or discontinued if the platelet count rises too high or the patient doesn't respond.

The most commonly reported romiplostim side effect was headaches (35% in those taking romiplostim, 32% in those taking the placebo). Other reported adverse events included dizziness, insomnia, pain in an extremity, abdominal pain, shoulder pain, indigestion, and paresthesia (feeling of pins and needles, usually in an extremity). Serious adverse events included bone reticulin deposition and worsening thrombocytopenia after discontinuation of romiplostim therapy. Other risks include blood clots from excessive platelet formation and potential for leukemia in patients with myelodysplasia.

Because of these risks, Nplate™/romiplostim is available only through a restricted distribution program called Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. This is part of a risk evaluation program that provides patient support and education and collects safety data. For questions regarding the Nplate™ NEXUS Program, call 1-877-NPLATE1 (1-877-675-2831) or visit the Web site at http://www.nplatenexus.com/

PROMACTA®/eltrombopag — In the most recent clinical studies the response rate where patients achieved a platelet count higher than 50,000 up to six weeks after treatment was 59% for eltrombopag treated patients on the 50 mg dose and 16% for placebo treated. There was a significantly lower incidence of bleeding during treatment with eltrombopag compared to placebo. Significant serious bleeding was observed in fewer eltrombopag patients (16%) than in placebo patients (36%). In earlier studies, after six weeks of treatment, the response rate was 70% in those receiving the 50 mg dose and 81% in those receiving the 75 mg dose, compared with only 11% in those getting

the placebo. After 15 days on the study, more than 80% of patients getting the 50 mg and 75 mg doses of eltrombopag responded with platelet counts in the normal range of 150,000–400,000.

The most common adverse event reported was headaches, in 8% and 11% of patients receiving eltrombopag and placebo, respectively. Other common adverse events occurring in at least 5% of eltrombopag patients included nausea, nasopharyngitis, diarrhea, and vomiting.

PROMACTA® may cause hepatotoxicity (chemical-driven liver damage). Patients receiving therapy with PROMACTA® must have regular monitoring of serum liver tests. Because of the risk for hepatotoxicity and other risks, PROMACTA®/eltrombopag is available only through a restricted distribution program called PROMACTA® Cares. Under the PROMACTA® Cares Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive PROMACTA®. To enroll in the PROMACTA® Cares Program, call 1-877-9-PROMACTA.

Other Factors Affecting ITP

Q **What is the role of the bacteria *H. pylori* in ITP?**

A Some studies from Italy and Japan have shown if the bacteria *Helicobacter pylori* (*H. pylori*) was present in the stomach and was treated and eradicated with antibiotics, many (37% Japan; 68% Italy) patients increased their platelet counts and recovered from ITP. However, studies performed in Spain, France, England and the U.S. showed less benefit. Indeed, in the United States, tests for *H. pylori* are not routinely performed when ITP is being diagnosed in the absence of gastrointestinal symptoms but the testing may be useful in some cases of chronic ITP.

Q What is the role of thyroid disease in ITP?

A A small percentage of patients with ITP have or will develop immune thyroid disorders (hyper- or hypothyroidism). Platelet survival is reduced in patients with hyperthyroidism (which may also impair response to ITP-directed therapy) and platelet production may be impaired in those with hypothyroidism, with platelet values returning to normal as the thyroid condition is corrected.

Q What is done to manage the bleeding of ITP?

A The initial goal of treatment in ITP is to attain a hemostatic platelet count greater than 20,000–30,000, while minimizing side effects and toxicity of treatments. Therapy is generally indicated in all patients who present with bleeding and platelet counts that are less than 20,000. This is because in adults, fewer than 10% attain spontaneous remission.

Patients who have platelet counts above 50,000 can generally be observed (unless there is a special reason such as surgery or trauma or need for anti-platelet or anticoagulant drugs), although some may require treatment later on. For patients in the range between 20,000 and 50,000 platelets, immediate therapy is not required if there are no bleeding symptoms or other complicating factors such as uncontrolled high blood pressure, diabetes, recent surgery, or active peptic ulcer disease. However, higher platelet counts may be desirable based on lifestyle and risk of bleeding.

Q When are ITP patients usually hospitalized?

A Hospitalization may be required for ITP patients with serious mucocutaneous or internal bleeding and who have a platelet count of less than 20,000, those who have a history of significant bleeding, or those at risk for trauma or incapable of caring for themselves.

Q What is the goal of therapy in patients with ITP?

A Therapy for ITP patients must be individualized based on the patient's signs and symptoms, tolerance of

treatment side effects, lifestyle, and patient preference. What works for an active 46-year-old man who is a hard hat construction worker, a 63-year-old retired female nurse with a family history of heart disease, a 5-year-old child, and for a 22-year-old male college student who is also a competitive athlete is very different in each case. In ITP, there is no "one size fits all" approach to therapy.

Q What are the risks of severe, life-threatening bleeding in ITP?

A When ITP patients have platelet counts less than 30,000 they face a risk of serious bleeding. The results of a meta-analysis of 17 studies indicated that the risk of fatal hemorrhage at platelet counts less than 30,000 is 0.4% for those under age 40, 1.2% for those ages 40 to 60, and 13% for those older than 60. Major bleeding complications, including intracerebral (within the brain) hemorrhage, rarely occur in patients with platelet counts above 20,000 and it should be emphasized that survival is essentially normal in those whose platelet counts can be maintained above 30,000 without excessive medication.

Q Is ITP inherited? Will my children develop ITP?

A ITP is not passed from one generation to another. However, there are some rare examples where several family members were diagnosed with ITP. Most of these cases represent another form of familial thrombocytopenia rather than ITP, e.g., the rare disease Bernard-Soulier syndrome. ITP is unlikely to affect other members of your family.

Q Where can I find additional information about ITP?

A The Platelet Disorder Support Association provides a wide variety of information about ITP and all the topics in this booklet. There are hundreds of pages on the PDSA Web site. Visit the PDSA website and join PDSA! Navigate to **www.pdsa.org**. PDSA publishes a monthly e-newsletter and a quarterly newsletter, and makes available many other publications. PDSA holds an annual conference, several regional meetings, and has established support groups around the U.S.

Notes

Thank you to our PDSA medical advisors for their valuable assistance and contribution of information for this free educational booklet.

Depending on your circumstances, one of our other booklets may also be helpful:

ITP in Adults — Frequently Asked Questions
ITP in Teens — Frequently Asked Questions
ITP in Children — Frequently Asked Questions
Coping with ITP — Frequently Asked Questions
ITP and Pregnancy — Frequently Asked Questions
PTI Infantil — Preguntas Frecuentes
PTI en la Adultez —Preguntas Frecuentes

For more information about ITP, additional copies of this booklet, or to become a member of PDSA, please contact us:

Platelet Disorder Support Association
133 Rollins Avenue, Suite 5
Rockville, MD 20852

tel 1-87-PLATELET (1-877-528-3538)
fax 301-770-6638

pdsa@pdsa.org
www.pdsa.org

The Platelet Disorder Support Association is dedicated to enhancing the lives of people with ITP and other platelet disorders through education, advocacy and research.

Membership benefits include a newsletter, discounts to the ITP Annual Conference, optional participation in the Name Exchange Program, and the good feeling of helping others.

PDSA is a 501(c)3 organization. All contributions are tax deductible.

PDSA would like to thank **Amgen** for their assistance in printing this educational booklet.

The information in this booklet is for educational purposes only. For your unique medical condition, please seek the care of a qualified medical doctor and/or other health care provider.

PDSA

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Rockville, MD 20852

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