IMMUNE THROMBOCYTOPENIA PURPURA:

A GUIDE THAT WON'T CLOT YOUR UNDERSTANDING

By

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Abstract

Approximately 50 million Americans, 20 percent of the population or one in five people, suffer from autoimmune diseases (How many Americans have an autoimmune disease?, n.d.). Autoimmunity is when the immune system (which usually protects individuals from infection) begins attacking cells and tissues within the body. Autoimmune disorders can be particularly difficult to deal with because in many cases there are no definite cures. Additionally, many fail to understand how the body system that is supposed to protect them from illness is the exact system causing them problems. When the immune system begins attacking the body's cells and tissues, an immune response is mounted and resulting damage occurs. The overall goal of this research on Immune (also sometimes referred to as Idiopathic) Thrombocytopenia Purpura (ITP) is to make a more comprehensible guide to the autoimmune disorder and the various treatment options available without over complicating an individual's understanding.

Introduction

In Immune (or Idiopathic) Thrombocytopenia Purpura (ITP), the body recognizes platelets as foreign causing them to be inappropriately destroyed. This can lead to excess bleeding issues. Luckily, there are several different treatment options available, including those that suppress the immune system, stimulate the bone marrow to increase the production of platelets, or stop the destruction of platelets from happening. Although there are several treatment options available, ITP tends to call for lifestyle changes that can range from lowering exercise/physical activity to altering diet patterns for medication to changing medication types and more. Many individuals that don't have severely low platelet counts are able to continue their lives with minor adjustments, but it is relative to each patient and their condition severity. Overall, it is critical that a diagnosed patient be aware of their diagnosis and what it means in

terms of lifestyle, treatment, and what the disorder is actually doing to cause their low platelet counts.

There is immense importance in understanding one's condition or diagnosis. If there is no basic understanding of the human body, one cannot hope to understand what is actually going on. It might make sense to a doctor to diagnose someone with "cardiac ischemia", but if a patient has no idea that the term refers to the heart or that it means their heart isn't receiving the proper blood flow, they will not have an understanding of their condition or its severity. Thus, it's truly important one understands the human anatomy and concept of an autoimmune disorder because otherwise, a diagnostic term might not mean anything to them. As mentioned previously, ITP is an autoimmune disorder in which the immune system destroys platelets. After the cardiovascular and immune systems are introduced, there will be an explanation as to how and why the destruction takes place. In general, there are a vast variety of treatments available to those diagnosed with the condition, and they all work with a relatively high efficacy rates for various individuals. Different individuals might be better suited for various treatments (i.e., an individual that works in a laboratory full of bacteria or in a hospital may want to first try a treatment form that does not suppress their immune system). In general, this compilation of research from textbooks and various studies should help to break down the jargon and technicalities of ITP in order to create a better overall understanding of the disorder and the various aspects that accompany it.

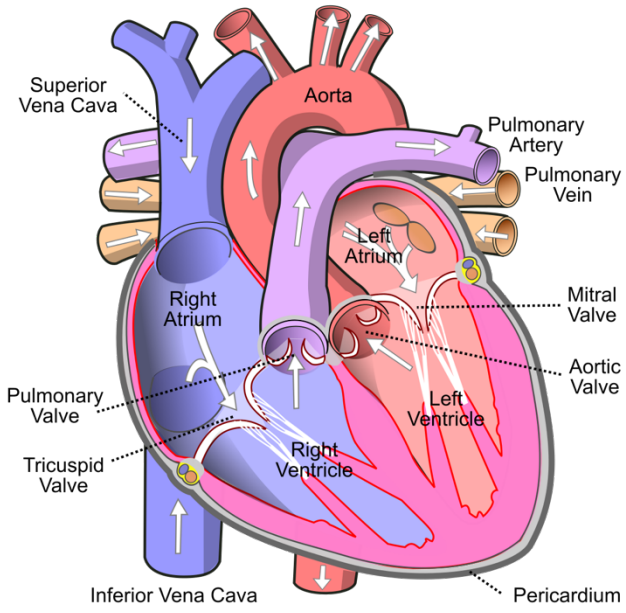
Cardiovascular System

In order to begin to comprehend the various components of immune thrombocytopenia purpura, an understanding of the body systems it encompasses is necessary. Since it is an autoimmune disorder, it clearly involves the immune system, but because it involves platelets

(which are a type of blood cell), it also has to do with the cardiovascular system. The cardiovascular system is made up of three main components: the heart, blood vessels, and blood itself.

The heart is an undeniably important organ as it pumps blood to the entire body. General anatomy of the heart is important to understand the physiology behind it. The heart is located in the mediastinum which is anatomical region in the body between the lungs from the sternum (the bone in the center of the chest) to the back near the vertebral column; it extends from the first rib to the diaphragm (Tortora and Derrickson, 2014). Most of the heart (approximately two-thirds of its mass) lies to the left of the midline of the body (Tortora and Derrickson, 2014). The heart itself is made up of four chambers on the inside: the right atrium, the right ventricle, the left atrium, and the left ventricle. The atria are the upper two chambers of the heart, and the ventricles are the lower two chambers. Figure 1 to the left reveals the anatomical structure of the heart. The right atrium and ventricle sit on the patient's right side of the body, and the left atrium and ventricle sit on the patient's left side of the body (so, if an individual was to directly face a patient, a patient's right side would be the other individual's left and the patient's left would be the other individual's right).

Figure 1

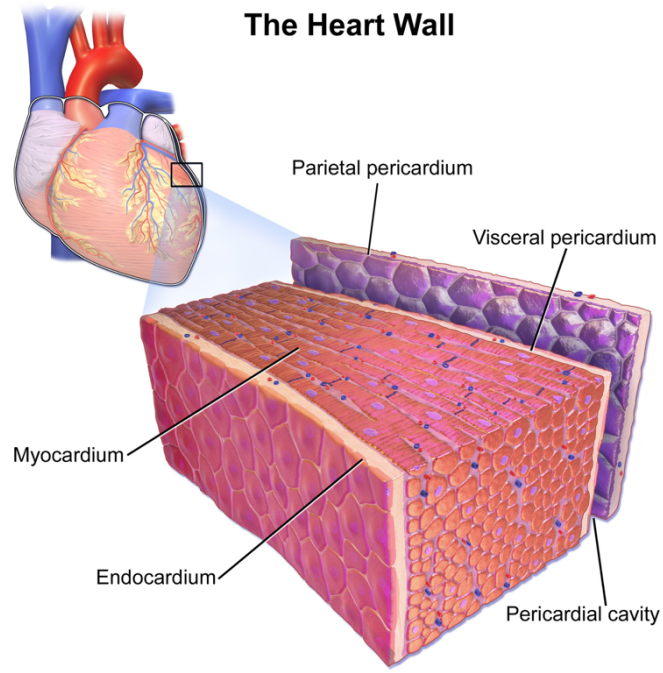


Additionally, the apex of the heart is the pointed portion of the heart that is formed by the tip of the left ventricle and rests on the diaphragm; it points forward, down, and to the left of the

body (Tortora and Derrickson, 2014). The base of the heart is at the top (and towards the back) of the heart. The base consists of both of the atria, but the left atria makes up a more significant portion (Tortora and Derrickson, 2014). There is also a membranous sac known as the pericardium that surrounds the heart which makes sure to keep the heart stable in its general position. It also allows the heart to perform regular pumping functions necessary for survival (Tortora and Derrickson, 2014). See Figure 1 to reveal the location of the pericardium. The pericardium is made up of both the fibrous and serous pericardium. The fibrous pericardium stabilizes the heart in its position and protects the outer layer, while the serous pericardium is located below the fibrous layer (Tortora and Derrickson, 2014). The serous pericardium has a parietal and visceral layer (see Figure 2 below). The parietal layer of the pericardium (also known as epicardium) is fused to the outer fibrous pericardium, and the visceral layer is attached to the heart wall (Tortora and Derrickson, 2014). Between the two layers is a fluid known as pericardial fluid which lubricates the layers of the pericardium and reduces friction between them as the heart pumps (Tortora and Derrickson, 2014).

There are also three layers of the heart wall. The outer most layer is known as the epicardium, which was mentioned above. The middle layer of the heart is known as the myocardium. This layer contains the muscle that is responsible for the pumping function of the heart and it makes up about 95% of the heart wall tissue (Tortora and Derrickson, 2014). Finally, the inner most layer of the heart is known as the endocardium; it consists of a thin layer of endothelial tissue that covers connective tissue beneath it (Tortora and Derrickson, 2014). It gives the chambers of the heart a smooth lining, minimizing friction as blood passes through the heart (Tortora and Derrickson, 2014). Figure 2 above is a cartoon describing the structure of the wall of the heart.

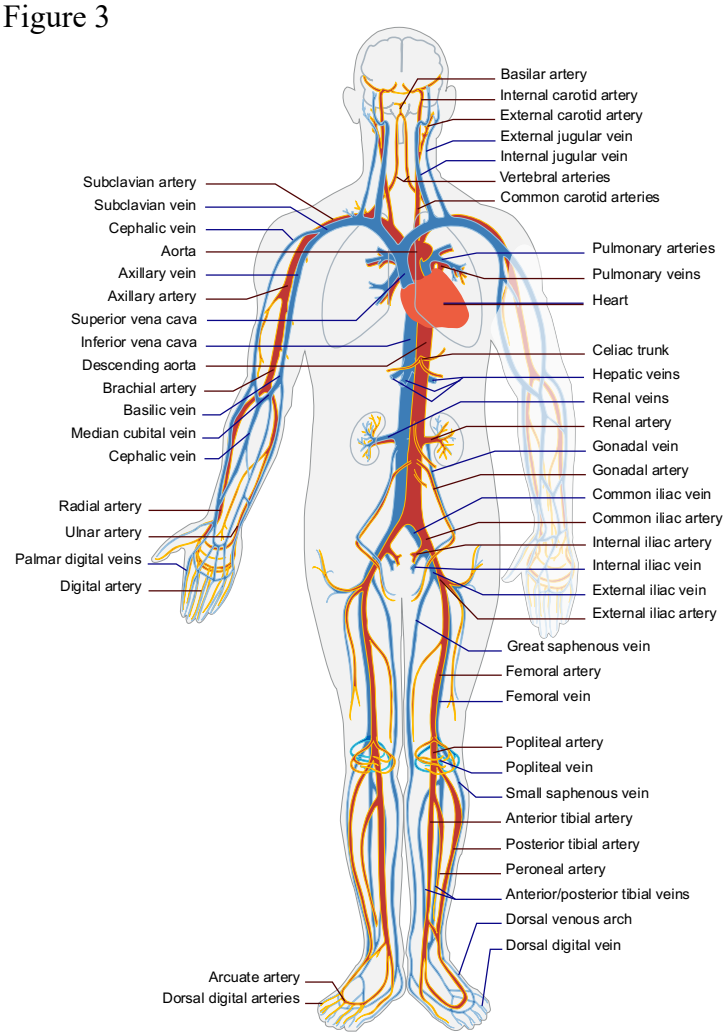
Figure 2



Each chamber of the heart serves a specific function. To begin, the two atria are known as "receiving chambers" and the ventricles are the "pumping chambers" (Tortora and Derrickson, 2014). Both the left and right atrium receive blood that are returning to the heart through veins. The right atrium receives deoxygenated blood from the entire body (i.e., blood that has passed through tissues and dropped off oxygen and other nutrients), and the left atrium receives oxygenated blood from the lungs or pulmonary circuit of the body. After deoxygenated blood comes back to the right atrium of the heart (through three major veins which will be discussed further below), it flows into the right ventricle through the tricuspid or right atrioventricular valve (the valve separates the right atrium and ventricle) (Tortora and Derrickson, 2014). Blood

then passes from the right ventricle through the pulmonary valve into a large artery known as the pulmonary trunk which divides into the two pulmonary arteries, which then continue to carry the blood to the lungs. After the blood passes through the lungs and becomes oxygenated, it returns to the left atrium through pulmonary veins. Once in the left atrium, the blood passes through the bicuspid valve (also known as mitral or left atrioventricular valve), and into the left ventricle (Tortora and Derrickson, 2014). From there, blood is pumped into the aorta (passing through the aortic valve) and out to the rest of the body. Refer back to Figure 1 to clarify structures and pathways.

Figure 3



When discussing blood flow to and from the heart, it is important to understand the vessels that carry the blood. There are five major classes of blood vessels and they are arteries, arterioles, capillaries, venules, and veins (Tortora and Derrickson, 2014). Arteries carry blood away from the heart and to other organs. The largest and most elastic artery begins at the heart and divides into more medium-sized arteries further away from the heart (Tortora and Derrickson, 2014). Moreover, the medium arteries keep dividing into smaller arteries, and the smaller arteries then

divide into even smaller arteries which are known as arterioles (Tortora and Derrickson, 2014). These arterioles enter tissue and branch into the smallest vessels known as capillaries. Capillaries have specialized thinner walls that allow for exchange of oxygen, nutrients, and more to occur between blood and tissue (Tortora and Derrickson, 2014). Groups of capillaries in tissue join together to form venules, which are the smallest division of veins; these venules form together to make larger veins that eventually help blood flow back into the heart (Tortora and Derrickson, 2014). Some of the major veins that feed blood back into the heart include the superior vena cava, inferior vena cava, and the major coronary vein. The major arteries that pump blood from the left ventricle to the body include the ascending aorta, descending aorta, and the coronary arteries. Figure 3 maps out the major arteries and veins found throughout the body (not including those that supply blood to the heart).

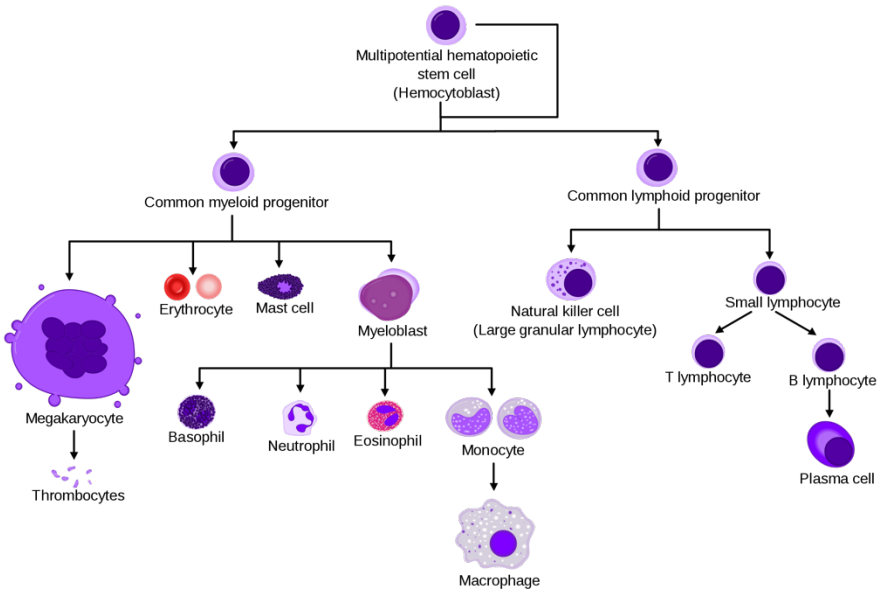
Having a basic understanding of the heart and the vessels that bring blood to and from the heart helps create a basic understanding of how critical a fluid blood is to the body's homeostasis. The function of blood in the body is transportation, regulation, and protection (Tortora and Derrickson, 2014). Blood is an important transportation medium that helps the body transport oxygen from the lungs to the body while returning carbon dioxide back to the lungs so that it may be removed from the body (Tortora and Derrickson, 2014). Additionally, blood carries nutrients, hormones, heat, and waste products to and from different portions of the body (Tortora and Derrickson, 2014). Blood also helps maintain homeostasis of all of the rest of the body's fluids, body temperature, and influences osmotic pressure and water content of cells (Tortora and Derrickson, 2014). Lastly, blood provides protection because the cells within it can assist during injuries or infections.

Whole blood has two main components known as blood plasma and formed elements. Blood plasma is a watery liquid that forms about 55% of blood and contains dissolved substances; formed elements make up approximately 45% of blood and they are cells and their fragments (Tortora and Derrickson, 2014). If one were to take a sample of blood and put it in a centrifuge, they would find that the denser components of blood (the cells) sink to the bottom while the plasma would be found at the top. The densest cells that sink to the bottom are the erythrocytes, or red blood cells. The cells that are less dense than red blood cells such as white blood cells and platelets form the middle layer known as the buffy coat, and the plasma is at the top as mentioned (Tortora and Derrickson, 2014) .

Blood plasma is made up of about 91.5% water and 8.5% solutes (most of which are proteins) (Tortora and Derrickson, 2014). Some plasma proteins include albumins, globulins (some of which are gamma globulins, otherwise known as antibodies), and fibrinogens (Tortora and Derrickson, 2014). Other solutes that can be found in plasma include hormones, gases, creatinine, electrolytes, and more.

The formed elements of blood that were mentioned earlier are erythrocytes (RBCs/red blood cells), leukocytes (WBCs/white blood cells), and thrombocytes (platelets). RBCs are the cells that help the blood transport oxygen and carbon dioxide to and from tissues. WBCs

Figure 4



form part of the body's immune system as they are the cells that protect the body from foreign substances. There are many different types of white blood cells including T and B lymphocytes, monocytes, neutrophils, and more which will be discussed in further detail once the immune system has been introduced. The final cellular component of blood includes platelets which are non-nucleated fragmented parts of larger cells (megakaryocytes) that help blood clot (Tortora and Derrickson, 2014). Platelets are the cells that are affected by the autoimmune disorder of Immune Thrombocytopenia Purpura (ITP), the focus of this paper. Figure 4 above illustrates some of the cells that can be found in the blood and their general appearance (note: mast cells and other stem cells are found in the tissue and bone marrow respectively, not blood).

All blood cells are formed by a pluripotent stem cell in the bone marrow. Once a pluripotent cell becomes a myeloid stem cell and then a progenitor cells known as CFU-Meg, it can become a megakaryocyte (Tortora and Derrickson, 2014). Platelets are fragmented pieces of huge megakaryocytes that can be broken up into 2000 or more fragments (Tortora and Derrickson, 2014). Figure 4 reveals this process. Platelets contain granules which hold chemicals that promote blood clotting to prevent blood loss from damaged vessels. Thus, without these important cells, blood clotting becomes more difficult and might be altogether impossible depending on the levels present in blood. Lack of any cells are critical, but if the body is not able to clot to keep damage contained and prevent blood loss, one is left at a serious disadvantage.

Immune System

In order to understand ITP, it is important to know about the cardiovascular system since that is where the blood (and platelets) circulate, but there also needs to be a general understanding of the immune system. The immune system's job is to help maintain homeostasis by fighting off harmful agents inside and outside of our bodies (Tortora and Derrickson, 2014).

These harmful agents can be a variety of entities including ultraviolet rays, toxins, pathogens, and more (Tortora and Derrickson, 2014). Pathogens are microbes such as viruses and bacteria that cause disease and they are usually the most common agent that affects our immune system because we are constantly being exposed to them. Essentially, the immune system utilizes all of its various components to combat these pathogens or other entities in order to maintain homeostasis.

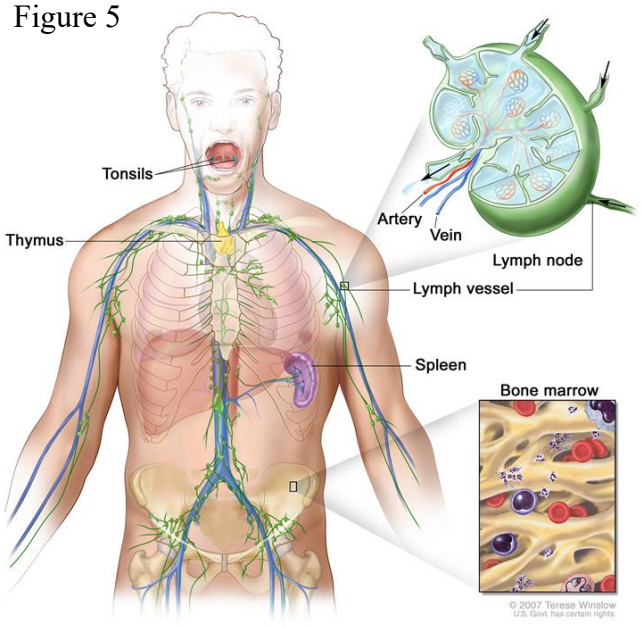
To begin, the human body has two types of immunity— innate and adaptive immunity. Immunity refers to "all the mechanisms used by the body as protection against environmental agents that are foreign to the body" (Coico and Sunshine, 2015). Innate immunity is essentially all the elements that we are born with and is a fast and non-specific response. Components of the innate immune system include the skin, mucous membranes, the pH levels in the stomach, phagocytes, natural killer cells, complement, and pattern recognition receptors (Coico and Sunshine, 2015). The skin and mucous membranes are barriers that help defend the body from invaders. If the invaders make it past these barriers, the pH levels in the stomach and other cells such as phagocytes and natural killer cells step in. Additionally, pattern recognition receptors bind to various microorganisms and recognize things such as bacterial cell walls or other pathogen associated molecular patterns (PAMP) or damage associated molecular patterns (DAMP) on damaged cells. Once this binding occurs, inflammation ensues which attracts phagocytic cells (cells that eat foreign objects), or it can lead to the activation of complement (which will be discussed later in further detail) (Cohen notes, Innate to Adaptive, 2018). While the innate immune system is important because of how fast it is, adaptability is also critical.

Adaptive immunity is different than innate immunity because it allows the immune system to adapt to pathogens by creating memory. There are two classes of cells that work under

the adaptive immune system and they are lymphocytes and phagocytes. Lymphocytes help recognize foreign or damaged material while phagocytes eat and digest (Cohen notes, Innate to Adaptive, 2018). There are two types of lymphocytes known as T lymphocytes (T cells) and B lymphocytes (B cells). However, there is a wide variety of T cells and B cells leading to immense diversity in the cells, further allowing them to target massive amounts of different pathogens. These cells create memory by duplicating themselves when they respond to specific pathogens. Those duplicated cells circulate throughout the body in case the body ever encounters that same pathogen again and the memory cells will lead to a stronger and faster response. Essentially, an antigen (foreign substance) binds to either a T or B cell which activates them and leads to two different types of immune responses— humoral or cell mediated immunity (more on this later) (Cohen notes, Innate to Adaptive, 2018).

While it is important to know the different kinds of immunity and the physiology behind them, there needs to be a basic understanding of the anatomy and physiology of the entire immune system first. The main components of the immune system include lymph, lymphatic vessels, organs that are made up of lymphatic tissue and lymphatic cells, and other various white blood cells. Lymph is formed from the interstitial fluid that filters through blood capillary walls. Lymph contains a variety of components including proteins and salts, but the main cellular constituents include lymphocytes and macrophages. This fluid and its

Figure 5



constituents are moved throughout the body by means of lymphatic vessels much the same way blood is moved throughout the body by arteries and veins. Figure 5 above illustrates how closely lymphatic vessels (in green) are intertwined with veins from the cardiovascular system (blue). After lymph has been delivered and filtered through various lymphatic organs by means of smaller lymphatic vessels, it begins to drain into larger vessels known as lymph trunks (Tortora and Derrickson, 2014). There are five lymph trunks located throughout the body and they drain lymph from the general area of the body they are located near. These trunks then deliver lymph to either the thoracic duct or right lymphatic duct, which then return the lymph back to the cardiovascular system (Tortora and Derrickson, 2014).

In addition to lymph and lymphatic vessels, there are various organs that compose the immune system. These organs fall into two primary categories, central and peripheral lymphoid organs. Central organs are where lymphocytes develop, and these include the thymus and red bone marrow (Cohen notes, Anatomy and Physiology of the Immune System, 2018). On the other hand, the secondary (or peripheral) lymphoid organs are where mature cells are arranged in a certain way in order to contain and deal with anything the immune system deems to be dangerous (Cohen notes, Anatomy and Physiology of the Immune System, 2018). These organs include lymph nodes, the spleen, gut-associated lymphoid tissue (referred to as GALT) found in Peyer's patches, tonsils, and adenoids (Cohen notes, Anatomy and Physiology of the Immune System, 2018).

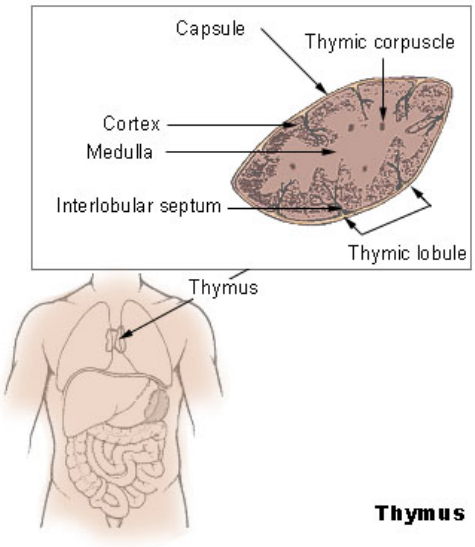
As mentioned, the bone marrow is where blood cells are formed and this includes white blood cells (also known as leukocytes) such as T cells, B cells, neutrophils, and more. B cells mature in both the bone marrow and a secondary lymphoid organ. When a common lymphoid progenitor begins synthesizing immunoglobulin (antibody) components (particularly the mu

heavy chain in the cytoplasm), it is officially a “pro-B cell” (Cohen notes, Ontogeny, 2018). This “pro-B cell” continues to progress to a “Pre-B cell” after synthesizing some more immunoglobulin components until it reaches immature B cell status (Cohen notes, Ontogeny, 2018). Once the B cell becomes an immature B cell, it contains surface IgM antibody (antibody classes discussed later) and undergoes B cell selection to help filter out autoreactive B cells.

Blood that passes through the bone marrow has a fair amount of free-floating self-antigen. If the B cells bind to antigen that enters the bone marrow, the bone marrow determines the cell has the potential to be autoreactive if it were to be released into the periphery (Cohen notes, Ontogeny, 2018). Since the B cell was constructed with one of two possible alleles found in the cell, the B cell tries to undergo “receptor editing”. If the B cell continues to bind to self-antigen, it is marked as a risky cell and will undergo apoptosis (programmed cell suicide); if the cell does not recognize self-antigen, it is allowed to pass on to a secondary lymphoid organ where it will finish its maturation (Cohen notes, Ontogeny, 2018). T cells also do some developing in the red bone marrow, but unlike B cells they undergo T cell differentiation and selection in the thymus.

The thymus is both an endocrine and a lymphoid organ, but for the purposes of this paper, we will focus on its lymphoid aspects. As Figure 6 shows, the thymus sits in about the center of the chest behind the sternum. The thymus has two lobes, each of which are wrapped by a layer of connective tissue known as the capsule (Tortora and Derrickson, 2014). Trabeculae are extensions of the capsule and extend into the thymus in order to further divide each lobe into smaller lobules (Tortora and Derrickson, 2014). Each of these lobules contains two major sections known as the cortex and the medulla. When T cells first enter the thymus, they are found in the cortex along with other dendritic cells, macrophages, and epithelial cells (Tortora and Derrickson, 2014). More mature T cells can be found in the medulla (as can some of the other cells that are also found in the cortex). The thymus is the place where T cells undergo differentiation and testing. Essentially, by the time a T cell has left the thymus, it has become either a helper T cell or cytotoxic T cell. However, only about 2% of all T cells that enter the thymus ever actually make it to being circulated in the blood and to a secondary lymphoid organ (Tortora and Derrickson, 2014) and this has to do with the testing mentioned earlier. T cells undergo testing in order to minimize their chances or recognizing the wrong things as foreign (such as ourselves) when they are in circulation. The testing is very strict-- T cells must not bind too strongly or loosely to any proteins that we produce, otherwise they are marked for destruction (Cohen notes, T cells, 2018). T cell selection is even more accurate and strict than B cell selection.

Figure 6



Thymus

In addition to the primary lymphoid organs, we have secondary lymphoid organs which include lymph nodes. Lymph nodes help to filter out bacteria and other harmful substances from the lymph in order for an immune reaction to take place. Fluid from lymph vessels enter the node through the afferent lymphatic vessel and exit the node through the efferent lymphatic vessel in order to pass onto the next lymph node (see Figure 7). After a dendritic cell has ingested an antigen in the periphery, the dendritic cell will migrate to the lymph node, where it will present itself to T cells. Then, certain T cells enlist B cells for additional help. The lymph node is organized into three sections known as the cortex, the paracortex, and the medulla. The cortex (yellow region and yellow circles in Figure 7) is the outer region of the lymph node and it contains motile but densely packed lymphocytes known as follicles (Cohen notes, Anatomy and Physiology of the Immune System, 2018). Additionally, there are germinal centers in the cortex which are areas full of dividing cells. The cortex is mostly composed of B cells that come from the bone marrow. The paracortex (the blue area in Figure 7) is mostly composed of T cells that come from the thymus, and dendritic cells are arranged between the cortex and paracortex (Cohen notes, Anatomy and Physiology of the Immune System, 2018). The medulla of a lymph node contains B cells, antibody producing cells, and macrophages (Tortora and Derrickson, 2014).

Figure 7

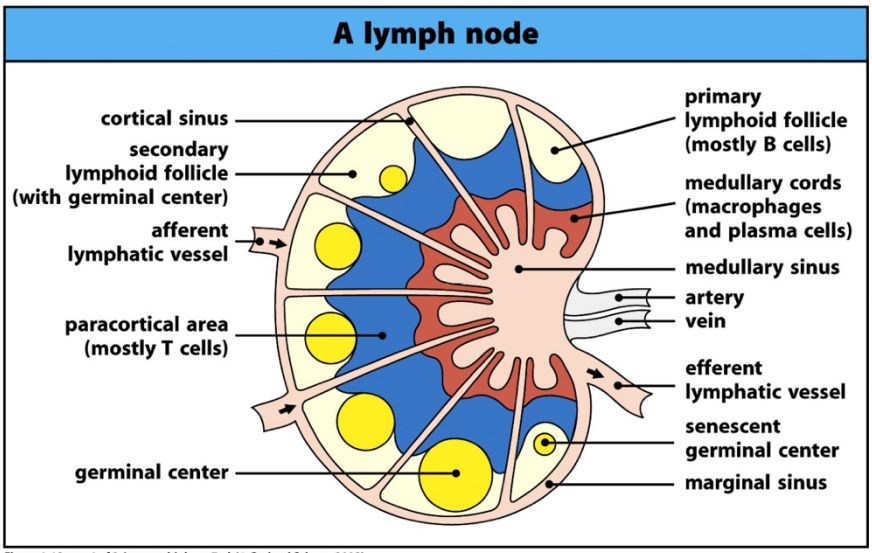
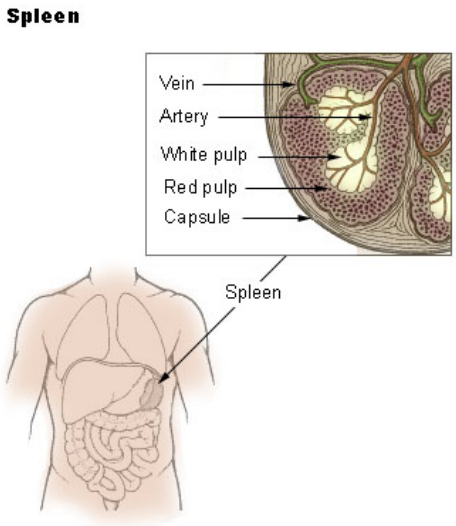


Figure 1-18 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)

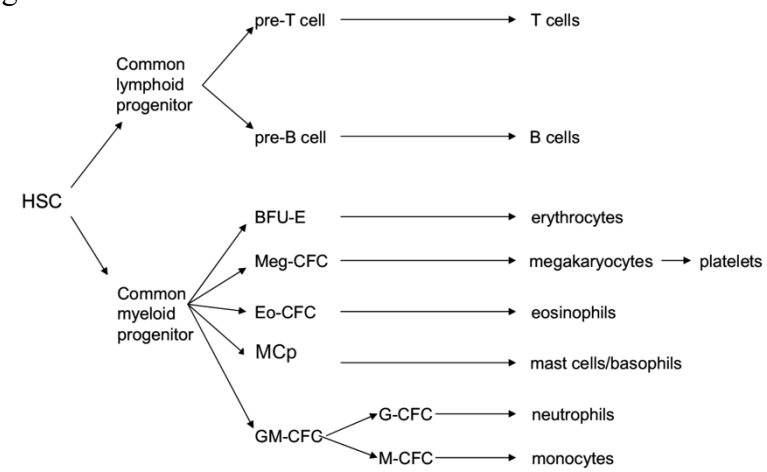
Another important secondary lymphoid organ is the spleen. As Figure 8 shows, the spleen is located on an individual's left side of the body near the stomach and large intestine (see Figure 8). The spleen is the "largest single mass of lymphatic tissue in the body" (Tortora and Derrickson, 2014). The portions of the spleen that are of most importance include the red and white pulp. The red pulp is filled with phagocytes and is where red blood cells are filtered out of blood while the white pulp is similarly structured to our lymph nodes (Cohen notes, Anatomy and Physiology of the Immune System, 2018). The T cells tend to collect around arterioles in the white pulp, and the B cells are a little further away from them, which is again similar to the set-up of B cells in the cortex and T cells in the paracortex of the lymph nodes. As mentioned previously, there is also lymphoid tissue in the tonsils and the intestinal linings, but they aren't as critical for understanding ITP.

Figure 8



Now that there is a basic understanding of the organs within the lymphatic system, it is important that we understand the cells that comprise the immune system in more detail. Throughout the course of this paper, it has been clear that the leukocytes in the immune system are created in the bone marrow. All blood cells begin as a hematopoietic stem cell before they differentiate into either a common lymphoid progenitor or a common myeloid

Figure 9



progenitor (see Figure 9). Common lymphoid progenitors go on to become T lymphocytes or B lymphocytes. Common myeloid progenitors go through a few extra steps before either becoming red blood cells, platelets, eosinophils, mast cells/basophils, neutrophils, and monocytes.

In general, leukocytes can be split up into two categories based on the shapes of their nuclei. Mononuclear cells are cells that have one large nucleus; these include monocytes, macrophages and lymphocytes. Polymorphonuclear cells have a nucleus that is separated into many different lobes; these cells include eosinophils, basophils, and neutrophils. Mast cells and dendritic cells still play a role in immune responses, but they are not found in the blood as they stay in the tissue (Cohen notes, Anatomy and Physiology of the Immune System, 2018).

Monocytes initially start out as blood cells. Once they are signaled by other cells and chemicals in the immune system, they travel to the site of infection where they enter tissue and differentiate into macrophages (Cohen notes, Anatomy and Physiology of the Immune System, 2018). Macrophages are a type of phagocyte, which means they digest cellular and foreign debris. Essentially, once these macrophages have been activated by their surrounding area, they become cells that eat foreign objects and even present them on their receptors to other cells of the immune system. Unfortunately, macrophages are not as “smart” as fellow leukocytes, and once they become activated, they will eat whatever is in their way, including healthy tissue (Cohen notes, Anatomy and Physiology of the Immune System, 2018). Neutrophils are similar to macrophages in the sense that they are phagocytes, but they are not as vicious. Other immune cells found in the blood include eosinophils and basophils. Eosinophils aid in the killing of parasites, whereas the true function of basophils remains unknown (Cohen notes, Anatomy and Physiology of the Immune System, 2018).

These cells are all important in the immune system, but perhaps the most critical cells in terms of ITP are T and B lymphocytes. The function of these cells is the same as other leukocytes- recognize and remove foreign substances (Cohen notes, Anatomy and Physiology of the Immune System, 2018). However, each type of lymphocyte does this differently. There are two classes of T cells known as helper T cells or cytotoxic T cells, broken into a total of seven T cells. Helper T cells include: Th1 and Th2, Th_{17} (similar to Th1 cells but stronger), Tfh (help B cells), Treg (regulate other T cells). There other group of T cells is known as cytotoxic or killer T cells (CTLs) and they directly kill infected cells. In general, T cells participate in cell-mediated immunity because they are more interested in the cells of our body. They scan the surface of the cells in our body, looking for cells that have either mutated or contain viruses and parasites. Cytotoxic T cells do this by attaching their T cell receptors to structures on other cells in the body to determine whether or not those other cells are displaying normal proteins on their receptors or something that is abnormal. In other words, they want to see if the cells are making what they should be, or if they are making mutated products or products of viruses (Cohen notes, Anatomy and Physiology of the Immune System, 2018). On the other hand, helper T cells scan the antigen presenting cells (dendritic cells, B cells or macrophages) to see whether what they have ingested is alright, so that they might determine the appropriate course of action (they will attack or help B cells get activated if the antigen is deemed dangerous, or they will do nothing if the antigen presented was harmless).

Table 1

Type of T Cell	Products Released from T Cell/Function of T cell (Once they encounter antigen)
Th1	• IFNγ- Calls for blood monocytes that then become macrophages in tissue. Macrophages become classically-activated "M1" that ingest and kill bacteria/foreign invaders. • IL-2- Once CTLs bind to/recognize antigen, IL-2 helps fully activate the CTL.
Th2	• IL-4- Calls for blood monocytes that become alternatively activated "M2" macrophages that are more involved with healing by scar formation, removing debris, etc. IL-4 can also call in eosinophils in cases of parasitic infections.
Th17	• IL-17- Similar to the function of IFNγ but initiates a stronger response.
Tfh	• These cells help B cells that have recognized antigen become activated and differentiate into plasma cells as well as help the cells switch classes of the antibodies they are producing. They secrete a variety of cytokines.
Treg	• Produce TGFβ and IL-10. This cell suppresses the function and activation of other helper T cells.
CTL	• Signal cells to undergo apoptosis through either the Fas ligand on CTL/death receptor on target cell or through the release of perforins that penetrate the cell and granzymes that can enter the cell and trigger apoptosis.

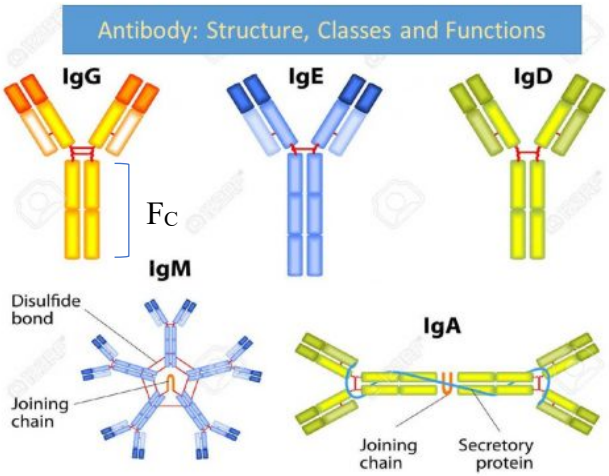
Table 1 helps to categorize and explain the function of various T cells. Information for this table was obtained from Dr. Cohen's lecture notes on T cells.

B cells are involved with humoral immunity, meaning that B cells protect the fluids and extracellular spaces of the body by releasing antibodies. In some cases, they can do this without T cell help, but because we have different antibodies that are useful in different cases, B cells need help "class switching" between the different types of antibodies, and the Tfh cells help them do this. Once these B cells are told what to do, they differentiate into plasma cells and produce antibodies that bind to bacteria or other foreign objects. These mark pathogens or other foreign objects for destruction or neutralizes them, rendering them useless. Another very critical cell that works with T and B cells is known as a dendritic cell. Dendritic cells can ingest

microorganisms or other foreign objects, digest them, and then present them on their receptors to T and B cells. Macrophages, B cells, and dendritic cells are known as antigen presenting cells.

As mentioned, B cells produce antibodies (or immunoglobulins). Something that not everybody might be familiar with is that there are actually several different types of antibodies. There are five classes of antibodies known as IgG, IgM, IgE, IgA, and IgD. Refer to Figure 10 to see the differences between the structures of each type of antibody. IgG antibodies are the most common antibody in the blood and tissue fluids. They neutralize toxins and have the ability to bind to bacteria, activate complement, or they can call in phagocytic cells like neutrophils or macrophages to eat the bacteria (Cohen notes, Antibody Structure, 2015). IgA is similar to IgG but is less likely to be found in the blood than it is to be found in the mucous membranes. It has a special structure known as secretory component that keeps it from being degraded from the secretions in the mucous membranes (Cohen notes, Antibody Structure, 2015). IgM is similar in function to IgG but is much larger. In fact, because IgM is so big, it is typically only found in the blood and not in any tissues because it cannot be filtered through capillaries. It is also the first antibody to show up in the serum post immunization and is even better at activating complement than IgG (Cohen notes, Antibody Structure, 2015). Lastly, IgD mainly functions as a receptor on

Figure 10



B cells and IgE helps in combatting parasites, but it is also the antibody that causes allergies (Cohen notes, Antibody Structure, 2015).

Table 2

Class of Antibody	Typical Location of the Antibody	Function of the Antibody
IgG	Blood and tissue fluids	Neutralizes toxins/brings about destruction of bacteria through binding to phagocytic cells or activating complement.
IgM	Blood; size prevents it from easily entering tissues	IgM function is similar to IgG. It's the first antibody to appear in blood after serum and is much more effective at activating complement due to its 5 Fc regions (discussed in greater detail below).
IgA	Mucous membranes	Similar to IgG but mainly functions in dimer form in secretions.
IgE	Mostly found in conjunction with a mast cell, some can be found in serum.	Helps with parasitic infections and is the antibody that causes allergies.
IgD	Mostly found as receptors on B cells	Its role in the blood is uncertain but it functions as a receptor on the surface of B cells.

Table 2 lists out the different antibody classes and their functions/characteristics. The information in this table was summarized from Dr. Cohen's Antibody Structure notes.

It has been noted that IgG and IgM antibodies activate a system known as complement. In order to activate complement (or at least one of the three potential pathways), a portion of the antibody known as F_C must be in close proximity to another F_C (refer to Figure 10 again) (Cohen notes, Antibody Structure, 2015). IgG antibodies only have one F_C whereas IgM has five, so it is easier for it to activate complement. In general, once an antibody has bound its antigen and has come into contact with another F_C, complement activation takes place. The complement system uses serum enzymes in order to rid the body of a pathogen either by means of lysis of the pathogen or enhanced phagocytosis by phagocytic cells like macrophages and neutrophils (Coico and Sunshine, 2015). It is a very complex and intertwined process, but the important aspect to

retain is that the complement system leads to the destruction of whatever the immune system deems as foreign through lysis of the object or digestion of the object by a phagocytic cell. This is a critical component of ITP.

Overall, the immune system is wonderful when it works properly, but once it begins to malfunction, there can be huge repercussions for those that are affected. There are four types of immunopathologies in which there is some type of dysfunction that is occurring in the immune system. They are known as Type I, Type II, Type III, and Type IV immunopathologies. Type I Hypersensitivity is actually very common in society and is better referred to as allergies. IgE antibodies bind to mast cells. When some antigen, whatever the individual is allergic to, attaches to the antibody that is on the surface of the cell, it initiates a response in which mast cells are activated. Mast cells release both histamine (immediately) and other products that are formed by mast cells (later on) (Cohen notes, Type I Immunopathology, 2018) leading to the symptoms we typically deem as an allergic reaction.

The second type of immunopathology, and the most critical for ITP, is known as antibody-mediated autoimmunity. Type II hypersensitivity occurs when IgM or IgG antibodies "bind inappropriately to antigen on the surface of cells…" (Coico and Sunshine, 2015), which can lead to a variety of effects. One way in which this becomes a problem for the cell is if the antibody binds to the receptor on the surface of the cell and either acts as an agonist or antagonist for the hormone that typically acts at that cell (Cohen notes, Type II Immunopathology Notes, 2018). In other words, the antibody could cause an over or underproduction of hormone. An example of this is Grave's disease where antibody binds to receptors on the thyroid gland, leading to an overproduction of thyroid hormone. Another mechanism of tissue damage is complement-mediated damage. Cells or tissues that have antibody made against them can be

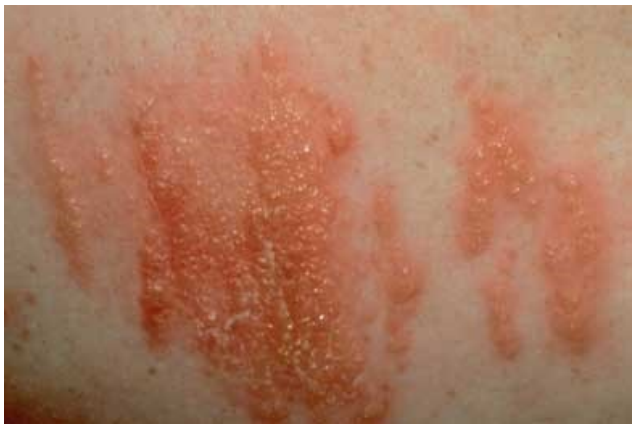
damaged through complement by means of lysis, phagocytosis, or by the release of phagocytic enzymes and reactive oxygen species (Cohen notes, Type II Immunopathology Notes, 2018). The current mechanism for ITP suggests that platelets are destructed by phagocytosis, meaning they are marked by auto-antibodies which attracts phagocytes which then consume the platelets.

The third type of immunopathology (Type III Hypersensitivity) is known as an immune-complex reaction. When antigens form complexes with IgG antibodies or IgM antibodies, they can begin to accumulate in tissues of the body or in circulation (Coico and Sunshine, 2015). Once these complexes accumulate, they activate the complement cascade, attracting leukocytes with granules that release lytic enzymes, leading to destruction (Coico and Sunshine, 2015). An example of a Type III hypersensitivity is when an individual is bitten by a rattlesnake and they have to go to the hospital to receive an excess of antibodies in order to bind up the venom. The antibodies individuals usually receive is horse anti-venom antibodies. Since horse antigen (which comes along with the antibody) is foreign, our own body begins to produce additional antibodies that will bind the horse antigen (Cohen notes, Type III Immunopathology Notes, 2018).

Finally, Type IV Hypersensitivity is more commonly referred to as delayed-type hypersensitivity (DTH) and is a cell-mediated rather than antibody-mediated reaction (Coico and Sunshine, 2015). With DTH, there is usually an initiation phase and then an elicitation phase. The initiation phase is when the body first comes into contact with the substance. An example of this is with poison ivy. People don't have the typical poison ivy reaction the first time they encounter poison ivy because the body requires a long time to complete its cell signaling that would lead to proliferation of T cells that recognize the pathogen (Cohen notes, Type IV Immunopathology Notes, 2018). Usually, people have showered or wiped their skin by this time. The second time however, there are memory cells mentioned earlier that are floating in

circulation. It only takes a small number of memory T cells (Th1 in the case of DTH) to call in and activate macrophages, and it does so much more quickly (Cohen notes, Type IV Immunopathology Notes, 2018). Thus, the typical poison ivy rash and blisters result from macrophages eating up the urushiol (the chemical compound in poison ivy that leads to this reaction) and healthy skin tissue. Figure 11 shows the typical damage macrophages cause after they begin to eat healthy skin tissue. This reaction can be rather mild like in Figure 11 or can be much more extensive with huge blisters. Overall, it is critical to understand the immune system and the ways it can be destructive against an individual in order to be able to understand what causes ITP and how it is best (and most safely) treated.

Figure 11



Immune Thrombocytopenia Purpura

Immune (or Idiopathic) Thrombocytopenia Purpura (ITP) is an autoimmune disorder involving both the cardiovascular and immune systems in which the immune system destroys platelets. The normal range for platelets is about 150,000-450,000 platelets/microliter (μL) of circulating blood (Mayo Clinic, n.d. a). ITP is characterized by a low platelet count of less than 150,000 platelets per microliter of circulating blood (hereafter referred to as thrombocytopenia) (Zainal et al., 2019). Bruising is a common symptom of ITP that helps with diagnosis. Furthermore, the disorder can be labeled as primary or secondary. If the disorder is primary, there is no associated illness or direct known cause of the disease. If the diagnosis is secondary, it is likely due to an underlying disorder which would make it a more acute diagnosis as opposed to chronic like the primary classification (Cines and Blanchette, 2002). Moreover, the disorder

can occur in both adults and children. Childhood-onset ITP tends to have a more sudden onset noted by bruising a few weeks following an illness and typically clears up on its own within a few months (Cines and Blanchette, 2002). On the other hand, adult-onset ITP is more chronic, but adults can also experience spontaneous remission (Zainal et al., 2019). ITP can be considered a diagnosis of exclusion (Zainal et al., 2019), so it is critical that all other possibilities have been ruled out such as drug-induced thrombocytopenia or other underlying illnesses including leukemia, Hepatitis C infection, heavy alcohol consumption, etc. (Mayo Clinic, n.d. b).

Lastly, women are about two to three times more likely as men to develop ITP (Badulescu et al., 2017). There is no definitive reason for this, but there is some speculation. In one 1985 study, researchers noted that healthy women (in comparison to healthy men), had a higher ratio of helper T cells to cytotoxic T cells (Mylvaganam et al., 1985). When they examined cohorts of ITP individuals, they noticed there was in imbalance in T cells in both genders but that the imbalance was more severe in women. In fact, women experienced a drastic decrease in helper T cells and an increased level of cytotoxic T cells whereas men only experienced a decrease in helper T cells (Mylvaganam et al., 1985). When they compared these values in remission patients, they noticed that while helper T cell counts were still low in both genders, the cytotoxic T cell levels returned to normal in women who were in remission suggesting women had a higher immune imbalance before and during ITP (Mylvaganam et al., 1985). Another general theory that has been noted in research is women are more susceptible to autoimmune disorders than men and sex hormones are increasingly being linked to their role in B-cell-mediated autoimmune diseases and immune effector cells (Andres, 2016).

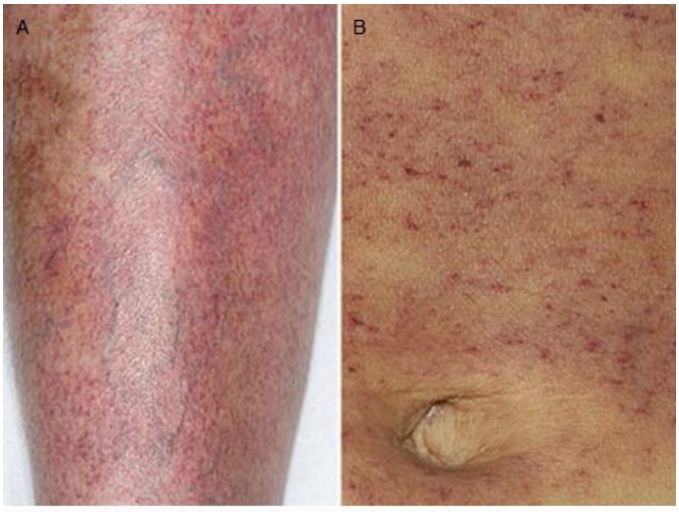
As mentioned earlier, platelets are extremely important for blood clotting. A lack of them leaves individuals susceptible to excess bleeding which can lead to fatal outcomes, including

accidents and injuries that lead to open wounds with profuse bleeding and/or internal bleeding. Individuals that are diagnosed with this disorder typically have to undergo some sort of lifestyle changes that depends on the treatment course they follow. Additionally, because treatments can vary in duration, cost, type, and relapses, the cost of treating ITP may end up being extremely expensive, especially to those who lack insurance. A study in France found that when a subgroup of patients that received a treatment known as IVIG (explained in detail in treatments section) was chosen from another subgroup of patients that had been admitted to the hospital during the study, they had an average cost of €26,581 each which is equivalent to $30,100.48 (Khellaf et al., 2009). The group that had been hospitalized at least once but did not receive IVIG as a treatment had an average treatment cost of €15,334 which is approximately $17,249.98 (Khellaf et al., 2009). Furthermore, cost was even lower for those that were not hospitalized, but still ended up being thousands of dollars. Overall, ITP can be a debilitating disorder when taking into account the physical issues, lifestyle changes, as well as overall cost of treatment.

Symptoms of ITP

ITP may present itself with or without symptoms. Those without symptoms are referred to as asymptomatic and in these cases, ITP may just be accidentally discovered by doing routine bloodwork (Badulescu et al., 2017). In a Romanian study, they found that nearly 15.4% of the male participants and 22.2% of the female participants were asymptomatic (Badulescu et al., 2017). However, if the patient does experience symptoms, they tend to include easy or

Figure 12



excessive bruising (often referred to as purpura), blood in urine or stools, bleeding from the gums or nose, unusually heavy menstrual flow (for women), and superficial bleeding into the skin resulting in petechiae which looks like a rash or reddish purple spots (usually on the lower legs) (Mayo Clinic, n.d. a). Figure 12 shows petechiae on the legs and the one on the right shows it on the abdomen.

Whether or not a patient experiences symptoms has been linked to the severity of their thrombocytopenia. To illustrate, the Romanian study mentioned previously recognized a connection between ITP severity and the intensity of the clinical symptoms that patients experience (Badulsecu et al., 2017). The study found that the intensity of symptoms was stronger in those with lower platelet counts. As the study points out, asymptomatic patients had significantly higher mean platelet values, suggesting symptoms are correlated with decreasing platelet counts (Badulsecu et al., 2017). Furthermore, those with lower platelet counts experienced a range of symptoms, including small lesions in either the mucosa of the mouth or nose, or a greater number of massive bleeds (Badulsecu et al., 2017). The massive bleeds (which can include intracranial or retinal hemorrhage) tended to present themselves in patients who had less than 10,000 platelets/μL of blood (Badulsecu et al., 2017). It may seem less worrisome if there are not hemorrhagic symptoms, but this can lead to a false sense of security. In the event an accident occurs, the patient may not have enough platelets to help their blood clot and control bleeding. Thus, understanding the symptoms of ITP is a critical aspect of being able to identify the disorder and its overall severity.

Diagnosis of ITP

Since ITP is considered a diagnosis of exclusion, physicians typically begin by recording patient history including medications, symptoms, history of autoimmune disorders, etc. to rule out secondary causes of ITP including drugs that induce thrombocytopenia, leukemia, Hepatitis C, and more. After this initial information is recorded, the physician can then begin testing the individual to determine if the diagnosis of exclusion will be ITP. The first common test that is used is a blood test known as a Complete Blood Count (CBC) (Mayo Clinic, n.d. a). Essentially, this is a very common blood test that is used to count the number of various blood cells (white blood cells, red blood cells, and of course, platelets). Typically, ITP patients have normal counts of white and red blood cells, but lowered platelet counts (Mayo Clinic, n.d. a). Normal platelet counts vary by laboratory or institution, but the normal reference range that is listed by Mayo Clinic, n.d. for platelet counts is 150,000 to 450,000 platelets per micro liter of circulating blood. Patients with ITP have platelet counts below 150,000/μL, but this can drop to 20,000/μL or below. Figure 13 below shows a comparison between a normal CBC (on the top) and a CBC of a patient diagnosed with ITP (on the bottom). The platelet count is significantly lower in the ITP patient.

Figure 13

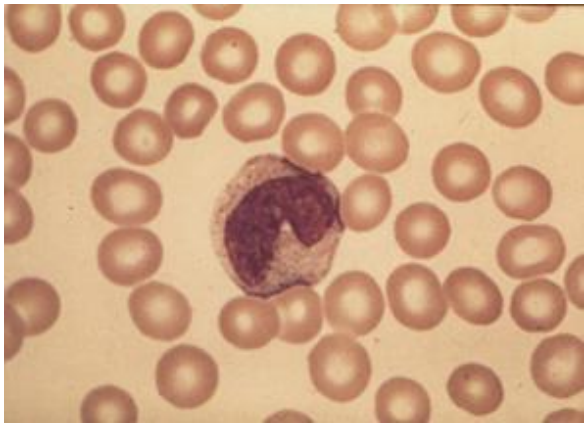
TEST	RESULTS	REFERENCE RANGES	UNITS	PL
HEMATOLOGY				
CBC w/ Differential, w/ Platelet				
WBC	6.6	4.0 - 11.0	k/mm3	TC
RBC	4.80	3.70 - 5.40	m/mm3	TC
Hemoglobin	13.5	11.5 - 16.0	g/dL	TC
Hematocrit	42.7	35.0 - 48.0	%	TC
MCV	89.0	78.0 - 100.0	fL	TC
MCH	28.1	27.0 - 34.0	pg	TC
MCHC	31.6	31.0 - 37.0	g/dL	TC
Platelet Count	261	130 - 450	k/mm3	TC
RDW(sd)	41.5	38.0 - 49.0	fL	TC
RDW(cv)	12.7	11.0 - 15.0	%	TC
MPV	10.3	7.5 - 14.0	fL	TC
Segmented Neutrophils	57.8*		%	TC
Lymphocytes	32.5		%	TC
Monocytes	7.9		%	TC
Eosinophils	1.1		%	TC
Basophils	0.5		%	TC
Absolute Neutrophil	3.83	1.60 - 9.30	k/uL	TC
Absolute Lymphocyte	2.15	0.60 - 5.50	k/uL	TC
Absolute Monocyte	0.52	0.10 - 1.60	k/uL	TC
Absolute Eosinophil	0.07	0.00 - 0.70	k/uL	TC
Absolute Basophil	0.03	0.00 - 0.20	k/uL	TC
Immature Granulocytes	0.2		%	TC
Absolute Immature Granulocytes	0.01	0.00 - 0.10	k/uL	TC
NRBC RE, Nucleated Red Blood Cell Percent	0.0	0.0 - 1.0	%	TC

*Segmented Neutrophils: Automated Diff

Component	Your Value	Standard Range
WBC	**11.3** K/UL	*3.5 - 10.5 K/UL*
RBC	**5.71** M/UL	*4.20 - 5.80 M/UL*
HGB	**16.6** GM/DL	*13.0 - 17.5 GM/DL*
HCT	**49.1** %	*38.0 - 54.0 %*
MCV	**86.0** FL	*82.0 - 99.0 FL*
MCH	**29.1** PG	*27.0 - 34.0 PG*
MCHC	**33.9** GM/DL	*32.0 - 36.0 GM/DL*
RDW	**12.6** %	*11.0 - 15.0 %*
PLT CNT	**62** K/UL	*150 - 400 K/UL*
Testing performed at Cancer Center Lab		
MPV	**9.6** FL	*7.0 - 11.0 FL*
ABS NEUTROPHIL COUNT	**8.9** K/MM3	*1.5 - 7.0 K/MM3*
PRELIMINARY RESULT. CONFIRM WITH REVIEWED/MANUAL DIFF.		
DIFF TYPE	**AUTOMATED**	
LYMPH #	**1.5** K/MM3	*1.0 - 4.0 K/MM3*
MONO #	**0.8** K/MM3	*0.0 - 1.0 K/MM3*
GRAN #	**8.9** K/MM3	*1.5 - 7.0 K/MM3*
EO #	**0.1** K/MM3	*0.0 - 0.7 K/MM3*
BASO #	**0.0** K/MM3	*0.0 - 0.2 K/MM3*
LYMPH %	**13**	
MONO %	**7**	

Another test that is used to help exclude other diagnoses and come to the conclusion of ITP is a blood smear. Peripheral blood smears are used to confirm the platelet count observed in the CBC (Mayo Clinic, n.d. a) as well as to help rule out other causes of thrombocytopenia. Blood is smeared onto a slide and stained with two dyes referred to as hematoxylin and eosin (H&E) and examined under a microscope; the cell types are identified and counted. As mentioned previously, other disorders or diseases can lead to ITP through an indirect route, so it is important that the blood count and smear does not reveal other cell abnormalities that can be better explained by another diagnosis such as leukemia, Hepatitis C, etc. An image of a typical blood smear of an ITP patient is shown to the side (Figure 14). The photo shows normal red blood cells (red circles) and a normal looking neutrophil (larger circle with purple in the middle), and a lack of platelets. Abnormal looking cells would suggest a diagnosis other than ITP.

Figure 14



A third test that is now less common (but is still performed on some individuals suspected of having ITP) is a bone marrow biopsy. It is important to note that the American Society of Hematology does not recommend this exam be performed on children, but the test can be used to help determine the cause of the low platelet counts (Mayo Clinic, n.d. a). In fact, the American Society of Hematology even suggests that “A bone marrow examination is not necessary irrespective of age in patients presenting with typical ITP” (Neunert et.al, 2011). During a bone marrow biopsy, samples of bone tissue and bone marrow (the soft sponge-like tissues in the center of large bones) is removed and tested. Physicians can also do a bone marrow aspiration in which they take a sample of the liquid portion of the marrow. The most common

site for a bone marrow biopsy is the hip bones, and the physicians typically enter through a patient's back. The reason this test is performed is because the bone marrow is where blood cells are produced. By sampling and examining the bone marrow, physicians can ensure that they rule out other diagnoses such as cancer. Mayo Clinic, n.d. reveals that patients that have ITP tend to have normal bone marrow biopsy results because the mechanism of ITP involves destruction of platelets in the blood or the spleen rather than issues stemming from the bone marrow.

In addition to these three major testing methods, there a few other minor tests that are sometimes done on a patient's blood, but they are not always helpful when determining a diagnosis. For instance, there are tests that examine the blood and determine whether the patient has antinuclear or antiplatelet antibodies. An Antinuclear Antibody (ANA) test simply reveals whether or not a patient has antibodies that recognize normal proteins or tissue in the body as foreign (autoantibodies); however, a positive ANA test does not indicate the presence of an autoimmune disorder (Wesselman, 2017). On the other hand, antiplatelet antibodies are antibodies that specifically recognize platelets as foreign and mark them for destruction. There are some studies that have found the detection of antiplatelet antibodies to be useful when it comes to diagnosing ITP. For instance, a Meta-Analysis on the sensitivity and specificity of platelet autoantibody testing came to the conclusion that "A positive autoantibody test can be useful for ruling in ITP, but a negative test does not rule out ITP" (Vrbensky et al., 2019). Another study concerning the screening for platelet antibodies in ITP also suggested that the detection of the antibodies can be helpful when trying to convey the mechanism of ITP which will be discussed below (Lin, 2006). In general, the American Society of Hematology suggests that there is insufficient evidence to advise the regular use of antiplatelet or antinuclear antibody testing (along with some other tests/parameters) in order to diagnose patients with ITP.

Mechanism of ITP

Autoantibodies and B cells

Immune Thrombocytopenia Purpura is an autoimmune disorder in which the body mistakenly attacks platelets. The ways in which this occurs may be a result of a variety of different mechanisms. The mechanism that is most often recognized concerns platelet destruction by means of autoantibodies. In this case, destruction of platelets is brought about by complement or phagocytic cells with Fc or Cb3 receptors (Coico and Sunshine, 2015). (A quick side note: Fc receptors are receptors on cells that recognize the Fc portion of an antibody—see Figure 10). Individuals with ITP typically produce IgG antibodies that attack their platelets; however, under more rare circumstances, patients may produce anti-platelet IgM or IgA (Zufferey et al., 2017). These anti-platelet antibodies will bind to special proteins on platelets (most commonly GPαIIbβ3 or GPIb-IX-V) which in turn makes them more susceptible to phagocytosis (Zufferey et al., 2017). Once the platelets have been opsonized (made more susceptible), they travel to the spleen or liver where they undergo destruction by phagocytosis. The conclusion drawn by the Zufferey et al. review suggests that ITP patients have impaired B cells that lead to a production of the autoreactive antibodies. Furthermore, these antibodies can bind to both platelets and megakaryocytes (platelet precursors) in order to destroy these cells or interfere with the production of additional megakaryocytes. This mechanism incorporates the adaptive immune system along with both cellular and humoral mediated immunities. This is because both the antibodies and the cells that produce and/or regulate them are involved. This is thought to be the main mechanism of platelet destruction in ITP, but it cannot be the only one because antiplatelet antibodies have not been found in all ITP patients (Zufferey et al., 2017).

T-Cell Imbalance

Since not all patients present with autoantibodies in the blood stream, there must be additional alternative mechanisms that ITP may undergo. It has been noted that some patients with ITP have abnormal T cells which includes higher T helper cell reactivity against platelets, a lower frequency of a certain type of circulating T regulatory cell and CD4+ Th0 cells, and Th1 activation patterns (Zufferey et al., 2017). CD8+ T cells are also found in higher quantities in the circulation of ITP patients. This is significant as CD8+ T cells (or cytotoxic T cells) can directly kill platelets or can be found aggregating in the bone marrow where they can inhibit production of platelets (Zufferey et al., 2017). T regulatory cells are also a crucial component in potential T cell mechanisms of ITP. T regulatory cells are in charge of regulating helper T cells (such as Th1, Th2, Tfh, etc.). Thus, issues with this class of T cell can lead to dysregulation of other T cells and by extension B cells (since B cells are typically influenced by T cells, especially Tfh). Without the regulation of T cells, B cells that are autoreactive are more likely to be activated and thus create autoreactive plasma cells and antibodies.

As the review by Zufferey et al. describes, T cells have critical responsibilities in terms of self-tolerance through their interactions with antigen presenting cells and down regulating the B and T cell responses. If T regulatory cells lack the ability to regulate cellular immunity, it becomes feasible for autoreactive cells in the body to become more active and lead to autoimmunity. Additionally, when T regulatory cells are unable to do their jobs, other T cells begin to secrete various cytokines that are usually found in the body but are now found in unbalanced levels. ITP patients have been found to have increased levels of IL-2, TNF-α, IL-22, and INF-γ (Zufferey et al., 2017). These cytokines are all extremely important in regulating various immune mechanisms and complement, so an imbalance in quantities can lead to critical

consequences in the body. Thus, the lower amounts of T regulatory and imbalance of other T cells help form the other potential adaptive cellular immunity mechanism for ITP.

Dendritic Cells

In addition to the mechanisms presented above, there has been some evidence linking malfunction of antigen presenting cells to ITP. Antigen presenting cells, especially dendritic cells, continuously ingest and present foreign antigens to cells such as T cells. During certain scenarios like inflammation, the function of antigen presenting cells can be altered so that abnormal processing and enhanced self-antigen production is noted (Zufferey et al., 2017). This malfunction can lead to the evolution of autoimmunity. Zufferey et al., 2017 shares a study from Catani et al. in which dendritic cells (DC) from ITP patients were able to trigger T cell proliferation outside of a living organism (in vitro) when the DC came into contact with platelet antigens. There have also been studies showing lower numbers of certain types of dendritic cells in ITP patients (Zufferey et al., 2017). In addition to dendritic cell action, there has also been some noted innate immune responses in ITP patients where Toll-like receptors (TLR) are involved in certain induced ITPs (Zufferey et al., 2017). Overall, it seems that dendritic cells may be affected in some ITP patients allowing for abnormal self-antigen presentation to lead to abnormal T and B cell reactions.

Megakaryocytes

In addition to mechanisms affecting antibodies, B cells, T cells, and dendritic cells, there is one last potential mechanism in which ITP may occur involving megakaryocytes (MK). As mentioned previously, megakaryocytes are the precursors to platelets; they are produced in the bone marrow which is a specialized environment for cell growth and maturation. A study by McMillan et al. (2004) showed that once healthy cells from a donor were cultured in a medium

containing plasma from ITP patients there was a significant decrease in megakaryocyte production and maturation. This study suggests this might also be occurring within the body of ITP patients. It has also been mentioned earlier that anti-platelet antibodies have an effect on the creation of megakaryocytes. Other studies have also found that "megakaryocytes [MKs] have been directly cleared by neutrophils and macrophages despite normal or slightly elevated plasma levels of TPO" (Zufferey et al., 2017). (Note: TPO is thrombopoietin, which is a hormone that helps with the stimulation and production of megakaryocytes and by extension, platelets).

This information suggests the precursors of platelets are being destroyed before they are able to mature because the anti-platelet antibodies bind to the megakaryocytes, leading to morphological and physiological changes in the MKs (Zufferey et al., 2017). Additionally, MKs help contribute to the specialized environment in the bone marrow by regulating other cells like plasma cells and may indirectly contribute to ITP that way (Zufferey et al., 2017). Zufferey et al. also suggests that patients with ITP might have a defective vascular niche in the bone marrow, reducing the regulatory effect of MKs, contributing to the progression of ITP.

Table 3

Components Involved in Mechanism of ITP	How Mechanism Leads to ITP
Autoantibodies/B cells	• Autoantibodies bind to platelets or megakaryocytes. • Platelets travel to spleen or liver and are destroyed. • Dysregulation of faulty B cells lead to production of plasma cells and autoreactive antibodies.
T cells	• Abnormal T cells lead to a downregulation or lack of T regulatory cells. • T regulatory cells are unable to regulate other T cells or B cells. The dysregulation of B cells allows for production of autoantibodies, and the upregulation of cytotoxic T cells allows for direct killing of platelets. • Abnormal cytokine secretions due to dysregulation of T cells may also play a role in progression of ITP.
Dendritic Cells	• Abnormal self-antigen presentation that allows autoreactive antibodies to be produced.
Megakaryocytes	• MKs destroyed or impaired by autoantibodies and T cells. Maturation of them is also impaired.

Table 3 is shown here in order to summarize the different mechanism that may contribute to ITP.

Treatments: Options, Safety, and Efficacy

Corticosteroids

As discussed, there are several different mechanisms that can take place in the body that lead to the development of ITP. Thus, it would make logical sense that there are several treatment options that can target these mechanisms. The most common form of first line-treatment for those diagnosed with ITP is corticosteroids. Prednisone is a commonly prescribed oral corticosteroid for ITP and may help raise platelet counts by means of suppressing or decreasing the activity of auto-antibody producing B cells. If the platelet counts go up and stabilize, it is possible to stop taking the steroids; however, this needs to be done by the careful process known as tapering. Once the physician feels the patient is ready, they will slowly wean the patient off the medication by providing smaller and smaller doses until there are no doses left

to give. This can take anywhere from 2 to 6 weeks or even longer for certain patients (Mayo Clinic, n.d. a). There have been several studies detailing the safety and efficacy of corticosteroids in treating ITP.

According to one study by Pizzuto and Ambriz, 373 out of the total 934 ITP patients were labeled as acute, subacute, or chronic and were given corticosteroids as a treatment (additional patients were given corticosteroids, but the most detailed information in the study came from these three groups). The study revealed that Prolonged Complete Remission (PCR) (defined as a normal platelet count sixth month after all treatment was discontinued) was observed in only 14% of the chronic ITP patients, 40% of the acute patients, and 35% of subacute patients (Pizzuto and Ambriz, 1984). Many patients underwent several additional treatments if the steroids failed such as splenectomy or immunosuppressive agents, so it was slightly difficult to determine the response rates of patients that solely used the corticosteroids as a treatment.

A more recent study that was done in 2001 also examined the efficacy of corticosteroids. In this study, there were 17 patients (7 men and 10 women) that were examined for the effects of prednisone on a platelet kinetic study. The researchers found that 13 of these 17 patients responded to prednisone treatment while 4 other individuals did not (Louwes et al., 2001). Of those 13 individuals, 6 demonstrated a full response while the other 7 only had a partial response. The study found that prednisone increased platelet production in the responsive patients from $138 \pm 126 \times 10^9$ platelets per day to $321 \pm 152 \times 10^9$ platelets per day. However, the increase in platelet production was not considered statistically different from the increase non-responders experienced (non-responders are individuals whose platelets may have risen but remained lower than 50×10^9 platelets/L) (Louwes et al., 2001). Instead, the study found that the mean platelet life

increased in responding patients, and that difference was statistically significant when compared to the mean platelet life for non-responders (Louwes et al., 2001). This suggests that the response to steroids might have more do to with its effect on mean platelet life-span rather than platelet production (Louwes et al., 2001).

There aren't many studies that focus on the safety of corticosteroids in ITP, but perhaps that is because the side effects of the drug are relatively well known. One study concerning the side effects of corticosteroids took into account the perspectives of both hematologists and patients. The study surveyed 80 ITP patients from the Oklahoma ITP registry as well as 83 hematologists in order to evaluate the severity and occurrence of 18 side-effects of the steroids. The results showed that the responses from the two groups were very different from one another; of the people that responded, patients reported a greater occurrence and severity of symptoms than hematologists did for 13 of the 18 side effects (Guidry et al., 2009). The study also identified about 65 corticosteroid side-effects including bruising, purpura, bloating, stretch markers, weight gain, acne, hair loss, nervousness, insomnia, sweating, and much, much more (Guidry et al., 2009). Furthermore, the same study showed that the longer the amount of time the patient was on the medication, the greater the mean number of side effects they tended to experience.

Mayo Clinic does not recommend corticosteroids as a long-term treatment because many patients will experience some sort of relapse when they have been tapered off the steroids. Additionally, there is a greater risk of serious side effects in the long-term including the thinning of the bones/osteoporosis, cataracts, high blood sugar, increased risk of infection. In general, it seems that corticosteroids are a decent first line treatment option for ITP. There are mixed results on efficacy and plenty of undesirable side effects, but it can be an effective cure or lead to

remission for many ITP patients. If prednisone or other forms of corticosteroids don't work on an ITP patient, physicians and hematologists begin to look at the other options for treating ITP.

IVIG

Another line of treatment that is typically tried after corticosteroids is Intravenous Immunoglobulin (henceforth referred to as IVIG). During this treatment, patients receive immunoglobulins (or antibodies) that could act in a manner of potential mechanisms in order to help booster platelet counts for those with ITP. Many recent reviews tend to focus on the thought that IVIG effects occur through the inhibition of the Fc-receptor mediated platelet phagocytosis, anti-idiotypic inhibition of anti-platelet antibodies, or the suppression of anti-platelet antibody production (Hansen and Balthasar, 2004). Mayo Clinic mentions that IVIG may also be used if an individual is experiencing critical bleeding or needs a rapid increase in blood count for a surgery. They also mention that the effects of IVIG tend to wear off within a couple of weeks and potential side effects include vomiting, headache, and low blood pressure.

The safety and efficacy of IVIG has been investigated in several different studies. In a study conducted by several Serbian scientists, they found that 22 out of 24 patients responded to a novel IVIG (BT681) treatment making for a response rate of 91.7% (Colovic et al., 2003). Furthermore, the study had split the patients into two groups; 15 patients were placed in the group that received a higher dosage for two days and 9 patients were placed in the group that received a smaller dose for 5 days. The total mean duration of the desired platelet response (greater than or equal to 50/nl) was 19.8 ± 7.8 days. More specifically, the mean for the two-day group was 17.6 ± 8.0 days and the mean for the 5-day group was 23.6 ± 6.3 days. The study also found that in most patients, platelet counts would rise until day 7 or 14 respectively and fell on days 21 and 28; moreover, they saw a reduction in various clinical symptoms of the patients

(Colovic et al., 2003). While these results may seem promising, the study noted that 62.5% of patients experienced some of the 38 adverse events recorded. There were 27 adverse events in 66.7% of the patients in the two-day group and 11 adverse events in 55.6% of patients in the five-day group (Colovic et al., 2003). Headache, fever, nausea, and destruction of red blood cells were mentioned in more than two patients. Most of the adverse events reported were of mild intensity, but there were still some moderate intensity and one severe intensity event (hypertension).

Another study examined the safety and efficacy of Gammaplex® (a 5% concentrated IVIG preparation). In this study, 35 patients (predominantly female) between the age of 6-70 that had ITP for at least six months with a platelet count of less than $20x10^9$ platelets per liter were evaluated for their response to Gammaplex®. The patients were given 1g/kg of Gammaplex on two consecutive days and then evaluated several times over 87 days. Patients were considered to have "responded" to treatment if they reached $50x10^9$ platelets per liter on or before the ninth day after their first dose of Gammaplex. According to the study, 29 of the study's 35 patients responded to Gammaplex (Dash et al., 2014). The response rate was also higher in patients that had not had a splenectomy, but it wasn't a statistically significant difference (Dash et al., 2014). Furthermore, the mean platelet count increased from $5.95x10^9$ to $36.43x10^9$ platelets/L before the second day of infusions and even up to $158.3x10^9$ platelets/L on Day 9; eventually however, platelet counts declined (Dash et al., 2014). In this study, 42.9% of the participants reported 63 adverse drug reactions. 10 patients experienced headache, 6 vomiting, and 5 developed a fever (Dash et al., 2014). Additionally, five of the reactions were considered serious because the patients became dehydrated, had a headache, and was vomiting. In general, the effect of IVIG seemed to be the same in this clinical trial as the first study mentioned regarding IVIG.

One final study that will be mentioned regarding IVIG is one done on a new IVIG formulation named Panzyga®. Panzyga is a novel human normal IVIG 10% concentrated preparation. Forty patients were enrolled in this study and the analysis was done on 36 patients. 29 out of the 36 achieved a response (greater than $50x10^9$ platelets/L as in previous studies) (Arbach et al., 2017). The study also found that the median time to a response and the response duration were 2 days and 14 days respectively. It seemed that platelet counts rose in individuals up until day 7 but began to decline near day 8. As far as safety, at least one treatment-emergent adverse (TEAE) effect occurred in 75% of participants, and 122 TEAE were recorded (Arbach et al., 2017). Most of these were mild or moderate responses, but 15 of them were classified as severe reactions. The most common TEAEs were headaches and fever, but three patients experienced an adverse effect that led to them withdrawing from the study (Arbach et al., 2017). Additionally, two patients passed away during the study, but they were determined to be unrelated to the treatment method.

In general, IVIG is a relatively effective treatment method for many, but tends to be a short-term solution as counts end up rescinding back to baseline after some amount of time. Furthermore, there are some immediately noticeable side effects/adverse reactions that many patients may end up being uncomfortable with. Thus, they might search for other treatment options.

Thrombopoietin receptor agonists

If neither corticosteroids nor IVIG seem to help the patient, a second line of therapy known as thrombopoietin receptor agonists may be considered. Unlike the previous two drugs which are thought to operate by suppressing the immune system, these drugs work by stimulating the bone marrow to produce more platelets. The two most frequent options for

thrombopoietin receptor agonists include eltrombopag (Promacta) and romiplostim (Nplate). These drugs also have side effects and they include headache, increased risk of blood clots, dizziness, and nausea or vomiting (Mayo Clinic, n.d. a).

There has been much research on this "newer" type of treatment option. The first treatment option that will be discussed is eltrombopag which is the drug that goes by Promacta. Interesting results were found in a Korean study assessing the efficacy and safety of eltrombopag in 18 adults with ITP. The study states that 16 out of its 18 participants began receiving eltrombopag at a dose of 25 mg/d and the other two patients received 25 mg every other day. The target platelet count was greater than or equal to 50,000 platelets/μL (Kim et al., 2015). Among the 18 patients, only 12 of them achieved complete remission where platelet counts were greater than 100,000 platelets/μL. 27.8% of the 18 however failed to reach the target platelet count (Kim et al., 2015). Moreover, the study revealed that in patients who had received 4 or more previous treatments for ITP, 57.1% of those individuals achieved the target platelet count. It was more likely for non-splenectomized patients to achieve the target goal than it was for splenectomized patients to achieve it. Additionally, the doses required to achieve the target platelet count and the amount of time it took for patients to reach the count varied from patient to patient. Moreover, 12 patients achieved complete remission during the treatment and stopped treatment, yet 83% of the patients experienced a relapse where their platelet counts returned to baseline level.

In terms of safety, this study found that seven of the patients experienced hepatobiliary laboratory abnormalities (henceforth referred to as HBLA) (Kim et al., 2015). Essentially, they had abnormal liver tests. If the treatment was discontinued for a short amount of time and then restored, there didn't seem to be a reoccurrence of HBLA. Other adverse events that occurred during treatment included back pain, some bleeding (no severe bleeding episodes though), some

cellulitis, coughing, epigastric pain, and even a case of bone marrow fibrosis (Kim et al., 2015). The epigastric pain didn't show any causal links upon examination, and the individual that developed grade 1 fibrosis after a year of treatment didn't have definitive abnormal immature cell clusters and the peripheral blood smear came back as normal. A follow up of the fibrosis patient after 2 years of treatment revealed the same results. However, the study concluded that eltrombopag is relatively well tolerated (Kim et al., 2015).

Another study conducted on the safety and efficacy of eltrombopag found that 79% of their patients (159/201) achieved a platelet count of greater than or equal to 50,000 platelets/μL (Bussel et al., 2008a). Furthermore, this study found that 18 out of the 75 patients who received eltrombopag for at least 25 weeks were able to maintain the target platelet count for greater than or equal to 25 weeks. In terms of safety, this study found adverse events in 150 patients, but most of these were mild to moderate in terms of severity (Bussel et al., 2008a). Headache was the most common adverse effect, but there were also upper respiratory tract infections, diarrhea, and nasopharyngitis reported (Bussel et al., 2008a). Additionally, six thromboembolic events were reported, but no clinically relevant effects of eltrombopag on bone marrow were found. Lastly, 39 serious adverse events were reported in 17 patients while on therapy and four deaths were reported, but none of the deaths were considered to be related to the medication (Bussel et al., 2008a).

The last study that will be mentioned on eltrombopag was done by Wong et al. and published in 2017. This study was also done to determine the safety and efficacy of eltrombopag; they found similar results to the previously mentioned studies. Specifically, 259 of 302 patients achieved a platelet response of at least $50x10^9$ platelets per liter of blood (Wong et al., 2017). Additionally, they found that the platelets had increased to this target level by week 2 of

treatment and remained at least at that level throughout the 250 weeks of treatment. This study found the same general mild adverse effects (i.e. headaches, upper respiratory infections, nasopharyngitis). On the other hand, some of the more severe effects included HBLA, anemia, hypertension, cataracts, diarrhea, migraine, dyspnea, pain in extremities, pneumonia, fatigue, and back pain (Wong et al., 2017). This study certainly went into more depth on the safety of eltrombopag and they were able to explain in depth why the adverse events occurred or whether or not they were associated with the medication or not.

The other thrombopoietin receptor agonist mentioned was romiplostim (referred to as Nplate). This form of treatment also helps to stimulate the bone marrow to increase platelet production but is administered through a once-a-week injection instead of an oral pill in the case of Promacta. It is also slightly different than eltrombopag as it is a peptide whereas eltrombopag is a non-peptide drug. There have also been several studies detailing the safety and efficacy of Nplate and it is often used for more resistant ITP cases.

One study on 142 patients found that median platelet counts increased drastically within the first 4 weeks of treatment and then continued to increase at a slower rate through week 16 of treatment (Bussel et al., 2008b). According to Bussel et al., platelet responses (the same one defined for all previous studies) were observed in 87% of all patients. Additionally, 77% of patients were able to keep their romiplostim dose within 2μg/kg of their most frequent dose 90% of the time, and many subjects were able to self-administer their treatment (Bussel et al., 2008b). When evaluating safety, it was found that 95% of patients reported at least one adverse side effect. As usual, the most common was headache, but there were instances of nasopharyngitis, contusions (bruises), and fatigue. There were also serious side effects reported in 31% of patients and the events that were reported in 3 or more individuals were thrombocytopenia, increased

bone marrow reticulin (associated with many benign and malignant cancers), and congestive cardiac failure (Bussel et al., 2008b). It should also be noted that bone marrow biopsies were not routinely performed throughout the study, so it is possible that more individuals were afflicted with similar problems. In general, this study showed that many adverse reactions seem to occur with romiplostim.

According to other studies done by Vishnu and Aboulafia (2016) found that 16 of 42 patients who received romiplostim and had their spleen removed experienced a durable platelet response, and 25 of the 41 patients with their spleens had a durable response to romiplostim. Patients with placebos experienced no significant increases in their platelet counts. This study found that adverse events occurred in all 83 of their treatment patients, but again, most of these were mild or moderate (Vishnu and Aboulafia 2016). There were however serious treatment-related adverse effects reported in two of the treated patients. One of these patients had an increase in bone marrow reticulin (discontinuation of treatment eventually led to a return to normal levels) and another patient with peripheral vascular disease and atrial fibrillation ended up being diagnosed with a right popliteal artery embolism (Vishnu and Aboulafia 2016). This study seems to match information in the previous study.

One final study that will be mentioned regarding safety and efficacy of romiplostim was conducted by Khellaf et al in 2011. In this study, 72 patients were evaluated for their responses to romiplostim. According to the results, a platelet response was observed at least once in 74% of the patients (53 out of 72). 45 patients continued to receive treatment at the two-year mark, and the mean time to a dose stabilization was two months. Long-term responses were present in 47 patients and 37 of them had achieved and maintained platelet responses with a median platelet count of $106x10^9$ platelets/L (Khellaf et al., 2011). The most common adverse side effects

reported in this study was joint pain, fatigue, and nausea. Unfortunately, this study did not retrieve any bone marrow biopsies, so it is difficult to assess some of the more severe adverse events seen in the other studies. Overall though, the study claimed that they found romiplostim to be both safe and effective in treating patients with chronic ITP.

Rituximab

Another treatment option for ITP is known as Rituximab, a monoclonal anti-CD20 antibody (CD20 is a marker found on B cells, thus the antibody targets B lymphocytes). Once attached to the B cell, the antibody causes Fc-mediated cell lysis (Arnold et al., 2007). Essentially, Rituximab (or Rituxan) helps reduce the immune system response that's actually causing the damage to the platelets (Mayo Clinic, n.d. a). Rituxan seems to help because it is able to reduce autoantibody-producing B lymphocytes (Arnold et al., 2007).

The use of Rituximab in treating ITP has increased in popularity, but there seems to be a smaller amount of studies or evidence surrounding it. According to one systematic review by Arnold et al., they found about 599 citations but only retrieved 60 for detailed review, and ultimately 31 were selected for inclusion in their final report. According to the review, rituximab is given to patients as a weekly infusion for 4 consecutive weeks (this applied in 16 of 19 studies). The review concluded that rituximab resulted in complete response (greater than $150x10^9$ platelets/L) in 46.3% of patients and an overall response (greater than $50x10^9$ platelets/L) in 62.5% of patients (Arnold et al., 2007). For most of these studies, the median response time was 10.5 months and many patients had received other treatments or had been unresponsive to previous treatments. The review found that among the 29 reports 66 patients experienced mild or moderate effects in response to rituximab, ten patients experienced severe or life-threatening events, and 9 patients had died (Arnold et al., 2007). It should be noted that the

authors of the review believe deaths were more attributable to lengthy courses of complex treatments or patients that had more advanced cases. None of the studies examined seemed to use a control group.

A more recent study done by Khellaf et al. in 2014 examined both the safety and efficacy of rituximab as a treatment for ITP. This study consisted of 248 patients and they noted a total of 87 adverse events in 44 patients; 66 of the 87 reactions were possibly rituximab related (Khellaf et al., 2014). The most frequent adverse event recorded was intolerance to the rituximab infusion and most of them were only of mild severity; however, there were 3 more severe events requiring the treatment be stopped which included hypotension (low blood pressure), dyspnea with laryngeal discomfort, and reversible serum sickness (Khellaf et al., 2014). The less serious adverse events included skin rash, digestive discomfort, chills and fever, headache, and some others. There were also 11 cases of infection in 7 patients and infection occurred 2 to 28 months after the first transfusion of rituximab. 8 of the 11 cases recovered, but 3 patients died of infection (these patients also were older than 70 years and had comorbidities/other issues) (Khellaf et al., 2014). In terms of efficacy, 61% of patients has a general initial response at median time of 2 months; furthermore, of the 152 initial patients, 39% showed a lasting response at a two-year follow-up (76 of them had a complete response). The study also found the median relapse time to be 35 months (Khellaf et al., 2014). The study came to a final conclusion that treatment with rituximab had an acceptable safety trial and that the treatment leads to an overall response rate of 39% at 2 years (Khellaf et al., 2014).

Splenectomy

Many of the above treatments may be intimidating in terms of efficacy and safety, but they are worth trying before resorting to surgical options. In general, splenectomy involves the

removal of the spleen. This treatment option is typically recommended for those that have a severe, chronic, and persistent condition (Mayo Clinic, n.d. a). The surgical removal of the spleen is done in order to "quickly eliminate the main source of platelet destruction" in the body and has been found to improve platelets count; unfortunately, the treatment does not work for everyone (Mayo Clinic, n.d. a). Moreover, whenever a surgery is performed, there is a risk for post-operational complications and while living without a spleen is possible, it is not ideal since it increases the risk of infection (Mayo Clinic, n.d. a). This treatment type is almost never recommended for children as it has been noted that children that are diagnosed with ITP usually have the acute rather than chronic version and will get better without such harsh treatment.

Research performed by Zoghlami-Rintelen et al. shows that 38 of the 48 patients that received a splenectomy in their study were considered to be in complete remission, 8 to be in partial remission, and finally, 2 individuals did not have a response. Three patients experienced a local hematoma which needed to be punctured in two cases and no patients died during the postoperative period (Zoghlami-Rinteelen et al., 2003). After a median post-surgical observation time of 3.5 years, 7 of the 38 patients that had a complete response were found to be in a relapse (platelet count was less than $100x10^9$ platelets/L), and 4 of the eight who were in partial remission had a relapse (Zoghlami-Rinteelen et al., 2003). All of these relapses were noted to have occurred within about 1 year. Long-term analysis on safety revealed that three patients had been hospitalized due to infections (one with pneumonia and two fevers of unknown origin) (Zoghlami-Rinteelen et al., 2003). All of the infections seemed to be easily controlled.

Another study examining the safety and efficacy of splenectomy found that 345 out of 402 patients were able to achieve a "good" response. 66% of the 402 achieved a complete response (greater than $150x10^9$ platelets/L) and 20% achieved a partial response (greater than

$50x10^9$ platelets/L) (Vianelli et al., 2005). The remaining 57 individuals seemed to be resistant to the effects of splenectomy. Additionally, the study found that 79 of the 345 responsive patients faced relapses, most of which occurred within the first two years post-splenectomy (Vianelli et al., 2005). The study also mentioned that 6 patients experienced perioperative infections including pneumonia, but infections were able to be cleared up. Unfortunately, 12 patients experienced thrombosis and it was fatal in 3 individuals. Three patients died of intracranial hemorrhage and only one of them was under 60 years-old; all patients had resistant severe thrombocytopenia. The researchers in the study concluded based on their experience that splenectomy seems to be the only treatment capable of producing a sustained response in 66% of cases. The group also noted than splenectomy failed in 40% of their cohort, causing them to have to seek other treatments (Vianelli et al., 2005).

In general, splenectomy is often times considered a more long-term solution as it is removing the organ that is responsible for a majority of platelet destruction. However, splenectomy is a permanent solution. While individuals can live without a spleen, it leaves them more vulnerable to future infections. Furthermore, splenectomy does not work in all patients. Those patients then require additional forms of treatment that might also have to further suppress immune responses. Thus, while splenectomy can be effective for many, it might be saved for a last resort option for those that have resistant ITP.

Fostamatinib

A newer treatment option known as fostamatinib is an orally administered option that uses a completely different mechanism than all the previously mentioned treatments. This drug contains a small molecule spleen tyrosine kinase (SYK) inhibitor (McKeage and Lyseng-Williamson 2018). According to McKeage and Lyseng-Williamson, fostamatinib's "active

metabolite targets the SYK-mediated pathway of platelet destruction." The two also list the most common adverse events during clinical trials with the drug to be diarrhea, hypertension, nausea, and increased transaminase levels (McKeage and Lyseng-Williamson, 2018).

Since fostamatinib is a newer drug, there are fewer studies evaluating its safety and efficacy. The main study was performed by Bussel et al. and it was published in 2018. The study displayed the results of two phase-three randomized, placebo-controlled trials. According to their trial results, more patients had achieved a stable response (greater than 50,000 platelets/μL at 4 or more of 6 biweekly visits and weeks 14-24 without rescue therapy) than patients that had received the placebo (Bussel et al., 2018). Stable responses occurred in 18% of patients on the drug versus 2% of the people that were on the placebo. The study also had a category of responses known as overall responses where a patient had one or more platelet counts at greater than 50,000 platelets/μL within the first 12 weeks of treatment; this allowed 43% of treatment patients vs 14% of placebo patients to achieve overall responses (Bussel et al., 2018). It typically took patients around 15 days to respond to the medication when they received 100 mg doses and 83% of the patients had achieved a response within 8 weeks of starting the trial (Bussel et al., 2018).

As previously mentioned, the study found the most common adverse effects to be diarrhea (31% of treatment patients), hypertension (28% of treatment patients), nausea (19% of treatment patients), dizziness (11% of treatment patients), and an increase in transaminase levels (11% of treatment patients) (Bussel et al., 2018). The study noticed that treatment patients were slightly more likely to encounter mild infections than placebo patients, but moderate and severe infections were about equally likely in both groups (Bussel et al., 2018). Bussel et al. also said that most adverse events were mild to moderate in nature, but 13% of fostamatinib patients had

experienced severe adverse events (only 3 events were experienced in more than 1 patient in either group and they were epistaxis, thrombocytopenia and menorrhagia) (Bussel et al., 2018).

Overall, fostamatinib was determined to have produced clinically-meaningful responses in patients that had been chronically afflicted by ITP and had undergone multiple different treatments in the past. It seems that there aren't as many adverse side effects as in other treatment options (such as splenectomy), but the efficacy results weren't as high as other treatments. It is important to note that this clinical trial had higher standards for a stable response than previous studies and took on patients that had been afflicted for far longer than many other studies (median duration was 8.5 years) (Bussel et al., 2018). In general, fostamatinib seems to be a promising new drug.

Azathioprine

One final treatment option that will be discussed for ITP patients is azathioprine. Azathioprine is an oral immunosuppressive drug that has been used in various autoimmune diseases and organ transplant patients (Poudyal et al., 2016). Azathioprine is typically used as a second line treatment after treatment with corticosteroids has failed. It has also been noted to be a relatively inexpensive drug when compared to other treatments and thus works better for those in countries where individuals cannot afford as expensive of treatment options (Poudyal et al., 2016). According to Mayo Clinic however, even though azathioprine has been used to treat ITP, it can cause significant side effects (fever, headache, nausea/vomiting, and muscle pain, and increased risk of infection) and its effectiveness has yet to be proven.

The main study that will be examined discussed the role of azathioprine in ITP treatment; it found that azathioprine gives a relatively high incidence of durable responses with low side effects and is useful as a second line treatment option (Quiquandon et al., 1990). In this study, a

complete response was considered a platelet count greater than $150x10^9$ platelets/L for more than 3 months, a partial response was a platelet count between 100-$150x10^9$ platelets/L for 3 months, and a minor response was a count greater than $50x10^9$ platelets/L for 3 months (Quiquandon et al., 1990). The study found that 24 of 53 patients (45%) achieved a complete response, 3 patients a partial response, seven patients had a minor response, and 19 patients had no response (Quiquandon et al., 1990). The time range to meet these responses and duration of treatment varied, but it was noted that all responders had a significant increase in their platelet counts within the first 4 months of the start of their treatments. The study also mentioned that 7 of the 24 complete response patients relapsed at various times for various reasons. Two out of the three partial responses also relapsed but those two still met criteria for a minor response as long as they kept taking their medication. Lastly, six of the 7 that had seen a minor response also relapsed. This study did not examine safety, but they mentioned a few deaths of patients that had been in the trial, none of which they directly linked to the patient themselves, rather their extremely low platelet counts.

Treatments: Comparison

Table 4

Treatment Name/Option	Mechanism of Action	Efficacy (Response rates listed in order of studies presented)	Side Effects
Cortico-steroids (1st line option)	Suppressing/decreasing activity of immune system.	65%, 76.5%	Increased risk of infections, thinning of bones, cataracts, high blood pressure, potential for adrenal insufficiency if steroids are discontinued
IVIG (1st line option)	Inhibition of the Fc-receptor mediated platelet phagocytosis or the suppression of anti-platelet antibody production.	91.7%, 82.9%, 80.6%	Headache, vomiting, low blood pressure
Thrombo-poietin receptor agonists (2nd line option)	Stimulate platelet production.	Eltrombopag: 66.7%, 79%, 85.8% Nplate: 87%, 49.4%, 74%	Headache, dizziness, nausea or vomiting, increased risk of blood clots, bone marrow fibrosis (Nplate)
Rituximab (2nd line option)	Fc-mediated cell lysis leading to reduction in immune system response.	62.5%, 61%	Low blood pressure, fever, sore throat, rash
Splenectomy (2nd line option)	Removal of spleen to decrease platelet destruction.	95.8%, 83.5%	Post-surgical complications, increased risk of infections.
Fostamatinib (2nd line option)	SYK inhibitor disrupts the pathway in the spleen that leads to the destruction of platelets.	43%	Diarrhea, hypertension, nausea, increased transaminase levels, respiratory infection, dizziness, rash, abdominal/chest pain, fatigue, neutropenia
Azathioprine (2nd line option)	Suppresses the immune system.	64.2%	Increased risk of infections, fever, headache, nausea and vomiting, muscle pain

Table 4 can be used to help distinguish the differences between treatment options.

It is important to keep in mind that ITP has many mechanisms. It is impossible to know which treatment will work for which individual. The above table is a way to guide a patient into understanding the different options available to them. It is also critical to note that different studies can produce different rates depending on the experimental set-ups, the patients chosen, and the sample size. It is also difficult to determine which exact treatment leads to the greatest remission rates as ITP patients tend to have gone through several different types of treatment and some can even obtain spontaneous remission. Through the compilation of research, it seems that those that have been afflicted with ITP longer (i.e., have had ITP for a longer period time) seem to have a harder time obtaining target responses or achieving longer periods of remission. For instance, the first study mentioned under corticosteroids stated that the steroid treatment worked most often in those that had been diagnosed within the last six months. Additionally, many of the studies showed that patients were often taking two treatments at once to help them achieve target levels or to get a response if they were initially unresponsive to the treatment provided to them.

Another important factor that plays into treatment is side effects. For many individuals, side effects can be the determining factor in a treatment. If a patient experiences the rarest of side effects for one treatment, they will likely never return to the treatment even it has the potential to help them because the cost outweighs the potential benefit. It seems that one of the more severe effects comes from Nplate in which an individual could experience an increase in bone marrow reticulin which could be benign or malignant. Many ITP treatment options also involve suppressing the immune system, which leaves individuals vulnerable to other infections as well. Some side effects may be more tolerable than others to various individuals depending on their lifestyles, so treatment with ITP is truly individualized. Lastly, based on the research, it seems corticosteroids (when used for as short a time as possible), splenectomy, and rituximab might be

along the best lines for longer-term treatment; however, it is possible that all patients that experience remission may fall into a relapse. Again, treatment will always vary from person to person.

Conclusion

Immune (or sometimes Idiopathic) Thrombocytopenia Purpura is an autoimmune disorder in which the body's immune system recognizes platelets as foreign objects which leads to the destruction of those platelets (typically in the spleen). ITP is important to understand because it can lead to serious unfortunate consequences for an individual diagnosed if they have no idea of their condition or how they can treat it. Having low platelet counts leads to a lack of blood clotting which can be critical in accidents or injuries. While there are several recognized mechanisms that could lead to the presence on ITP in a patient, the most frequently recognized (and the one certain treatments like IVIG may target) involve autoantibodies that attach to platelets and lead to their destruction by complement, phagocytic cells, or destruction in the spleen. ITP is most frequently discovered through routine blood tests and is typically a diagnosis of exclusion. Blood smears, antibody tests, and sometimes bone marrow examinations can help to ensure the proper diagnosis.

Symptoms typically are more prominent at lower platelet counts and can include petechiae, bruising, blood in urine/stool, bleeding from the gums and/or nose, and heavy menstrual cycles for women. As mentioned, there are several treatment types and they range from oral medication (corticosteroids, eltrombopag, fostamatinib, azathioprine), to injections (Nplate), to infusions (IVIG, rituximab), to organ removal (splenectomy). These treatments have all been deemed safe to use in the treatment of ITP; however, some of them can have more severe common side effects or severe rare side effects that can lead to people choosing various

treatments in order to minimize side effects. The first line of treatment is usually corticosteroids which can be followed by IVIG if the tapering off of steroids leads to relapse. The rest of the other options are considered second-line, but they can be used in combination to produce the best possible effects for the patient. It seems that there are plentiful amounts of research concerning thrombopoietin receptor agonists, but less for azathioprine and fostamatinib (though this is likely due to the fact that the latter is a much newer drug and azathioprine is typically used to treat other conditions). Overall, it seems that even if no one option is 100% effective, patients have a multitude of different options when it comes to choosing their treatment plans and can even combine treatments in order to help them achieve remission. Now that newer drugs and continuing research is being conducted on treatments for ITP, there is a chance that treatment options and outcomes could become even more effective in the future.

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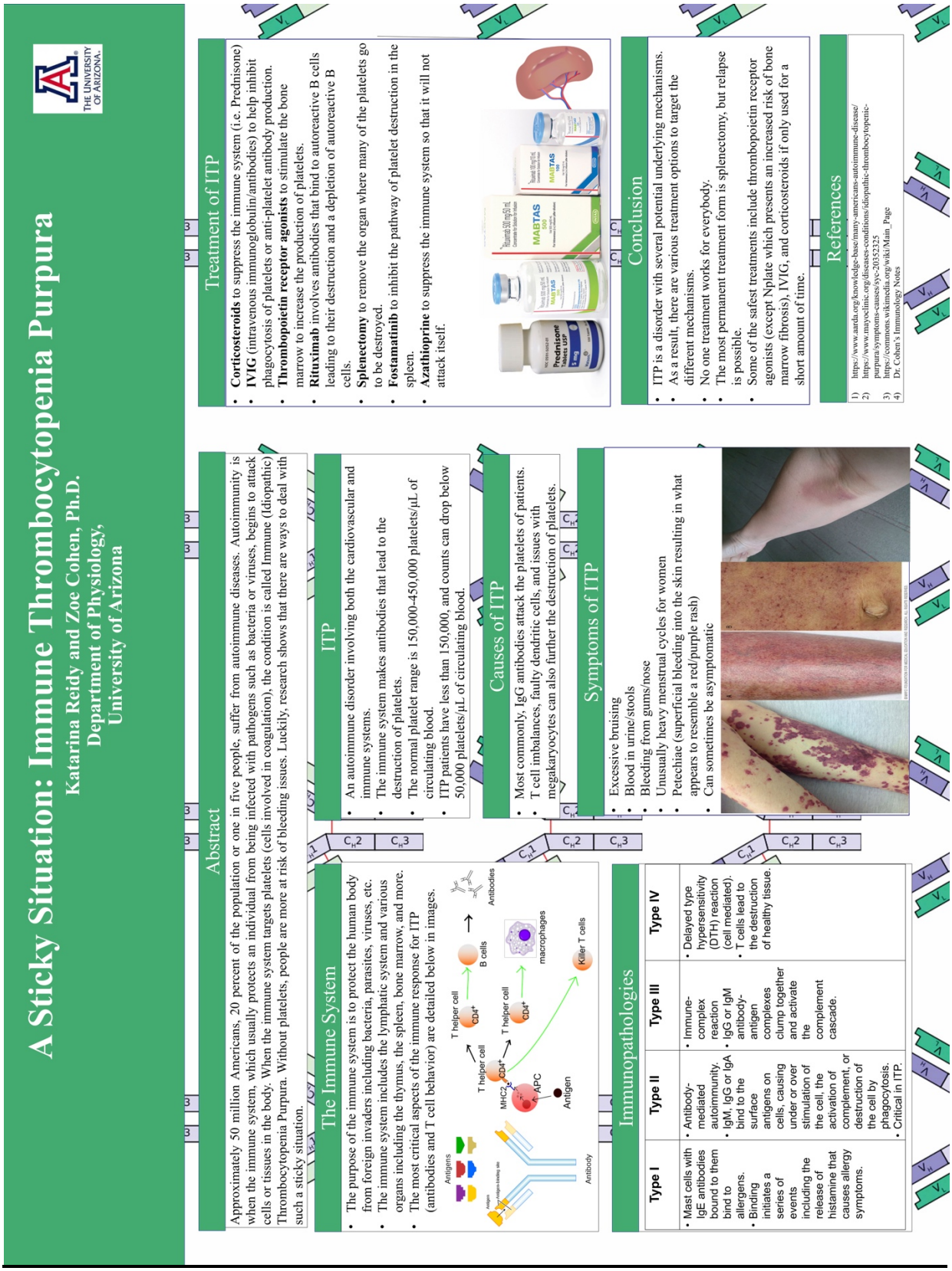
Appendix A


A Sticky Situation: Immune Thrombocytopenia Purpura
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Abstract
Approximately 50 million Americans, 20 percent of the population or one in five people, suffer from autoimmune diseases. Autoimmunity is when the immune system, which usually protects an individual from being infected with pathogens such as bacteria or viruses, begins to attack cells or tissues in the body. When the immune system targets platelets (cells involved in coagulation), the condition is called Immune (Idiopathic) Thrombocytopenia Purpura. Without platelets, people are more at risk of bleeding issues. Luckily, research shows that there are ways to deal with such a sticky situation.
The Immune System
The purpose of the immune system is to protect the human body from foreign invaders including bacteria, parasites, viruses, etc.
The immune system includes the lymphatic system and various organs including the thymus, the spleen, bone marrow, and more.
The most critical aspects of the immune response for ITP (antibodies and T cell behavior) are detailed below in images.
Antigens
Antibody
APC
Antigen
MHC2
T helper cell
CD4+
B cells
Antibodies
macrophages
Killer T cells
ITP
An autoimmune disorder involving both the cardiovascular and immune systems.
The immune system makes antibodies that lead to the destruction of platelets.
The normal platelet range is 150,000-450,000 platelets/µL of circulating blood.
ITP patients have less than 150,000, and counts can drop below 50,000 platelets/µL of circulating blood.
Causes of ITP
Most commonly, IgG antibodies attack the platelets of patients.
T cell imbalances, faulty dendritic cells, and issues with megakaryocytes can also further the destruction of platelets.
Symptoms of ITP
Excessive bruising
Blood in urine/stools
Bleeding from gums/nose
Unusually heavy menstrual cycles for women
Petechiae (superficial bleeding into the skin resulting in what appears to resemble a red/purple rash)
Can sometimes be asymptomatic
Immunopathologies
Type I
Mast cells with IgE antibodies bound to them bind to allergens.
Binding initiates a series of events including the release of histamine that causes allergy symptoms.
Type II
Antibody-mediated autoimmunity.
IgM, IgG or IgA bind to the surface antigens on cells, causing under or over stimulation of the cell, the activation of complement, or destruction of the cell by phagocytosis.
Critical in ITP.
Type III
Immune-complex reaction
IgG or IgM antibody-antigen complexes clump together and activate the complement cascade.
Type IV
Delayed type hypersensitivity (DTH) reaction (cell mediated).
T cells lead to the destruction of healthy tissue.
Treatment of ITP
Corticosteroids to suppress the immune system (i.e. Prednisone)
IVIG (intravenous immunoglobulin/antibodies) to help inhibit phagocytosis of platelets or anti-platelet antibody production.
Thrombopoietin receptor agonists to stimulate the bone marrow to increase the production of platelets.
Rituximab involves antibodies that bind to autoreactive B cells leading to their destruction and a depletion of autoreactive B cells.
Splenectomy to remove the organ where many of the platelets go to be destroyed.
Fostamatinib to inhibit the pathway of platelet destruction in the spleen.
Azathioprine to suppress the immune system so that it will not attack itself.
Prednisone
MABTAS
Conclusion
ITP is a disorder with several potential underlying mechanisms.
As a result, there are various treatment options to target the different mechanisms.
No one treatment works for everybody.
The most permanent treatment form is splenectomy, but relapse is possible.
Some of the safest treatments include thrombopoietin receptor agonists (except Nplate which presents an increased risk of bone marrow fibrosis), IVIG, and corticosteroids if only used for a short amount of time.
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4) Dr. Cohen's Immunology Notes

Appendix B

My thesis was inspired by my significant other. A little over two years ago, my boyfriend was diagnosed with ITP. The hardest thing for me as a physiology student and someone that wanted to go into the medical field was watching him struggle with doctors and mass amounts of misinformation. Both he and his family struggled to understand what exactly he was diagnosed with, and the research they had on ITP was solely research that was available to the general public. Some of the more thoughtful and more credible research was blocked behind pay walls that only I could access because of the University libraries. Additionally, there was no real communication by the doctors to him or his family of what he was really dealing with. He had no fundamental understanding of mechanisms of the disorder, the reasons why certain tests were being run on him, or why certain treatments weren't working for him. All of these factors inspired me to write this thesis. Too often in the medical field, patients either don't follow doctor orders, or follow them blindly. Both have negative consequences. I thought it would be useful to create a general guide to ITP that would be easier for an individual who doesn't have a Ph.D. or M.D. to understand their diagnosis and treatment options.