Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Immune Deficiency Foundation

This book contains general medical information which cannot be applied safely to any individual case. Medical knowledge and practice can change rapidly. Therefore, this book should not be used as a substitute for professional medical advice.

SIXTH EDITION

Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

6th Edition

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Preface

The Immune Deficiency Foundation (IDF) is dedicated to improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiencies (PI) through fostering a community empowered by advocacy, education, and research. Since it was founded in 1980, one of the ways IDF has advanced these aims is through its publications, such as this IDF Patient & Family Handbook, to provide reliable information about the often unfamiliar diseases to individuals with PI, their families and their healthcare providers. The first edition of the Handbook was published in 1987, and since then tens of thousands of copies have been distributed and it has been translated in part or in whole into at least 13 different languages.

The first edition was composed of nine chapters covering five types of PI. By the time the 5th edition was produced, the content of the Handbook by 33 chapters and featured 100 different PIs. This new 6th edition has 46 chapters and includes expanded information on more than 350 types of PI. The Handbook includes an overview of The Immune System and Primary Immunodeficiency Diseases to provide a basic description of the components of the immune system and how its defects lead to disease. There are 24 chapters covering the specific details of many of the individual PIs themselves. There are additional chapters with general information relevant to the inheritance, laboratory diagnosis, general care and specific medical treatments of PI, as well as chapters on life management issues for individuals of different ages.

Since the previous edition was released, there have been many important breakthroughs and discoveries regarding PI. All of the existing chapters have been revised and updated with new information and many have been completely rewritten.

The authors and editors have tried to condense the often highly technical information available into a form that is informative yet still understandable to a reader not trained in medicine or immunology. We hope that you find the Handbook to be a useful source of information about primary immunodeficiency diseases and would appreciate your feedback so that we can continue to make improvements in future editions. In addition, all the information that is found in the IDF Patient & Family Handbook can be found on the IDF website (www.primaryimmune.org).

It is important to recognize that a regular dialogue between the individual with PI, their family, and their healthcare provider team is essential to facilitate the highest quality care. This Handbook is not intended to be a substitute for those critical interactions, but it should be used as a tool for patients and their families. Our goal is to help them understand the information that they receive from their providers and arm them with background information so that they can better communicate with their healthcare team. Each situation is unique and the management of illness and its treatment must be customized to meet their individual needs. The development of a partnership between the individual and family and the healthcare provider is critically important for success in the management of life-long challenges like those presented by PI.

The Editors
2019

Letter from the President & CEO

Since the Immune Deficiency Foundation was founded in 1980, a central focus of ours has been to provide information to those affected by primary immunodeficiency diseases (PI) so they can live life on their own terms. To thrive, not just survive.

The problem is that for most, that doesn't happen organically. Many within our community are simply grateful to have a diagnosis, and ultimately find themselves settling for a life with some significant burdens. They don't realize that – in many cases – their care could be optimized. Their lives could be better.

And, maybe when I say "they," I should actually be saying "you."

It's you that we have in mind when we talk about an improved quality of life, and you that we want to thrive. To get to that point of optimized care and living your best possible life, you have to be armed: armed with knowledge. You need to have a good, broad-spectrum understanding of your form of PI. You need to know enough to be able to ask the right questions, specifically the life-changing kind.

With that in mind, we offer you this, the sixth edition of the IDF Patient & Family Handbook for Primary Immunodeficiency Diseases. Written and edited by leading immunologists, nurses, and life management specialists, this publication focuses on what's important to our community: information to advance the diagnosis and treatment of PI, as well as healthcare and life management skills that can make a difference in the lives of those living with PI. Simply put, it was written for you.

You'll likely notice that some of the information in this publication is diagnosis-specific, and some is applicable to all forms of PI. These two aspects of your life with PI – diagnosis-specific and general – are reflective of all of IDF's efforts. We focus on issues and needs that transcend individual diagnoses: educating families, providing support, creating connections, and helping you fight your fights. But we also focus on the issues that make each diagnosis unique.

What we've captured here in this publication is only the tip of the iceberg. If we were to try to write up all of what's known, this publication would weigh a ton. Literally. But that's why we have our website: www.primaryimmune.org. And as much as we have in this book and on our website, there's even more that we don't know. And again, that's where you come in.

We intend to continue to provide better and more complete diagnosis-specific information for future versions of this Handbook, but we need your involvement. By sharing your experiences, participating in research, and being part of our community, you can help us deepen the information available about each diagnosis. You can help us literally rewrite the book (this book) on what's known about PI.

I know that this is possible, because I've seen it. I've seen the field of immunology evolve from when I was diagnosed with PI in 1978. I've lived through an evolution of better and more efficacious Ig treatments, greater survival outcomes, and a myriad of other ways in which our world has improved.

While we work together to rewrite what's known about PI, we hope that you'll find this expanded and updated version of the Handbook to be a critical starting point for understanding and living with PI. IDF has many other resources and services that are meant to help you when you need it, so in this book and beyond, just know that IDF has your back. We're here to help you lead the life that you want to live.

John G. Boyle
President & CEO
Immune Deficiency Foundation

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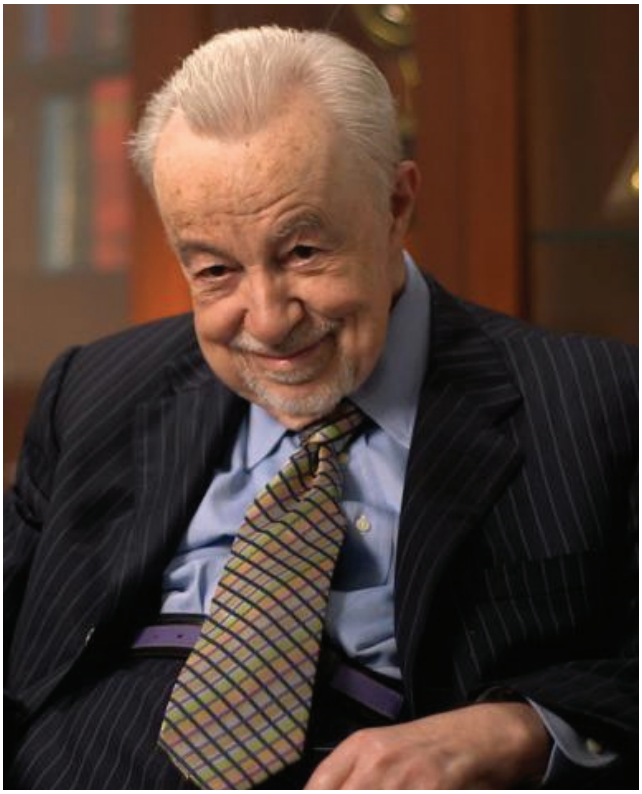
This book is dedicated in memory of

William T. Shearer, MD, PhD

One of the greatest champions of the primary immunodeficiency community.



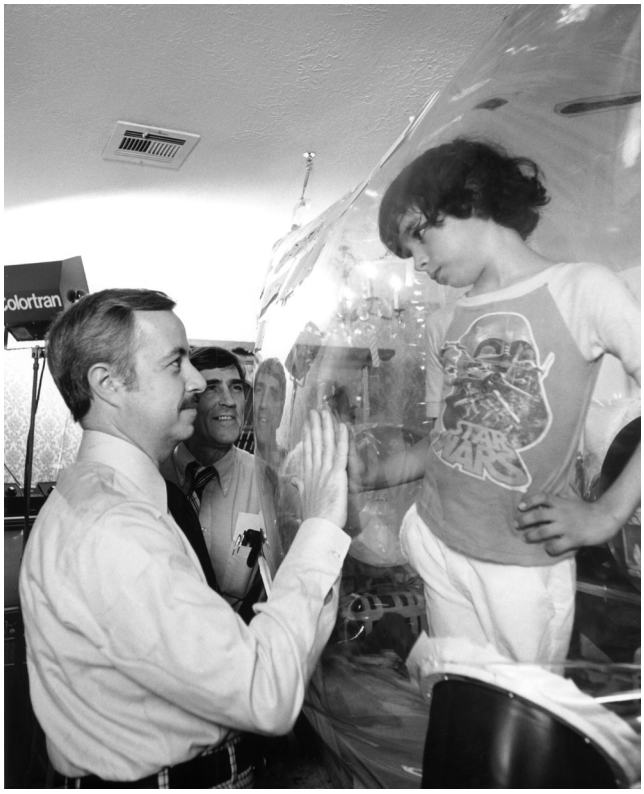


Photo Credit: Texas Children's Hospital

Chapter 1

The Immune System and Primary Immunodeficiency Diseases

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The immune system is composed of a variety of different cell types and proteins. Each element performs a specific task aimed at recognizing and/or reacting against foreign material (germs).

Organization and Development of the Immune System

The immune system is a wonderful collaboration between cells and proteins that work together to provide defense against infection. These cells and proteins do not form a single organ like the heart or liver. Instead, the immune system is dispersed throughout the body to provide rapid responses to infection (Figure 1:1). Cells travel through the bloodstream or in specialized vessels called lymphatics. Lymph nodes and the spleen provide structures that facilitate cell-to-cell communication. The proteins may be made by immune cells or other organs such as the liver. Some immune proteins circulate in the bloodstream, while others are made by immune cells and act on the organs and tissues near where the proteins are produced.

Primary immunodeficiency diseases (PI) can affect a single component of the immune system or multiple cells and proteins. To better understand the forms of PI, it's helpful to know about the organization and maturation of the immune system. It is typical to consider two broad categories of immune responses: the innate immune system and the adaptive immune system.

Innate immune responses are those that rely on cells that require no additional training to do their jobs. These cells include neutrophils, monocytes, natural killer (NK) cells, and a set of proteins known as the complement proteins. Innate responses to infection occur rapidly and reliably. Even infants have excellent innate immune responses.

Adaptive immune responses comprise the second category. These responses involve T cells and B cells, two cell types that require training or education to learn how to fight invaders (antigens) and not to attack our own cells. The advantages of the adaptive responses are their long-lived memories and the ability to adapt to new types of infections.

The bone marrow and thymus represent training grounds for two cells of the adaptive immune system (B cells and T cells, respectively). The development of all cells of the immune system begins in the bone marrow with a hematopoietic (blood-forming) stem cell (Figure 1:2). This cell is called a stem cell because all the other specialized cells arise from it. Because of its ability to generate an entire immune system, this is the cell that is most important in a bone marrow or hematopoietic stem cell transplantation. It is related to embryonic stem cells, but it is a distinct cell type, capable of developing into any type of blood cell but not other organs such as brain or muscle.

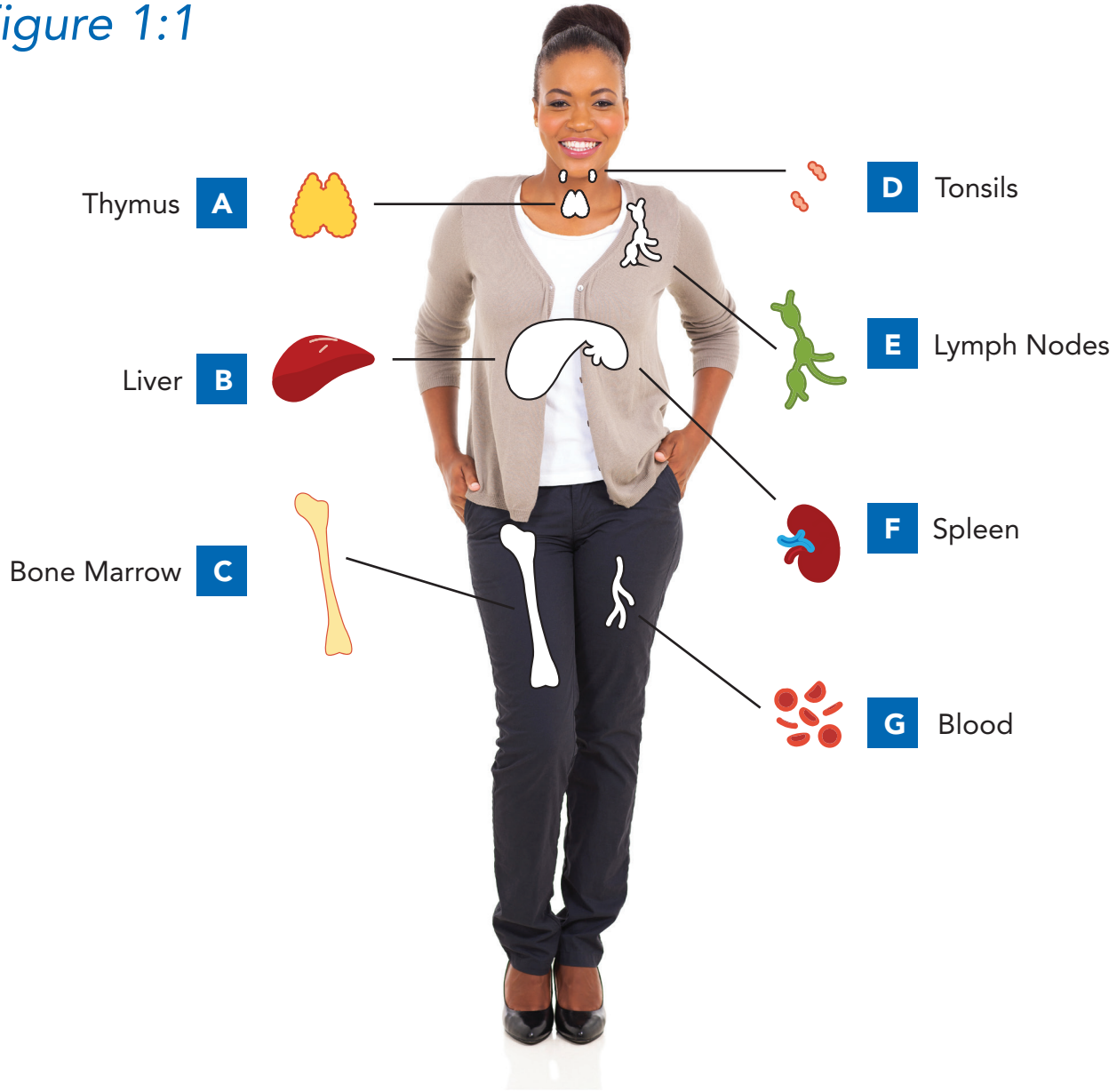
Central to both categories of immune responses is the ability to distinguish foreign invaders (germs), which need to be attacked, versus our own tissues, which need to be protected. Because of their ability to respond rapidly, the innate responses are usually the first to respond to an invasion. This initial response serves to alert and trigger the adaptive response, which can take several days to fully activate.

Early in life, the innate responses are most prominent. Newborn infants do have antibodies received from their mothers but do not make their own antibodies for several weeks. Maternal antibodies are passed to the baby through the placenta and protect the baby for the first few months of life, until babies should be able to make adequate amounts of antibodies on their own.

The adaptive immune system is functional at birth, but it has not gained the experience necessary for optimal memory responses. Although this formation of memory occurs throughout life, the most rapid gain in immunologic experience is between birth and three years of age. Each infectious exposure leads to training of the cells so that a response to a second exposure to the same infection is more rapid and greater in magnitude.

Major Organs of the Immune System

Figure 1:1



A. Thymus: The thymus is an organ located in the upper chest where T cells mature. First, lymphocytes (a type of white blood cell) that are destined to become T cells leave the bone marrow and find their way to the thymus where they are then "educated" to become mature T cells.

B. Liver: The liver is the major organ responsible for producing proteins of the complement system. In addition, it contains large numbers of phagocytic cells (a specific type of white blood cell) that ingest bacteria in the blood as it passes through the liver.

C. Bone Marrow: The bone marrow is the location where all cells of the immune system begin their development from stem cells.

D. Tonsils: Tonsils are collections of lymphocytes in the throat.

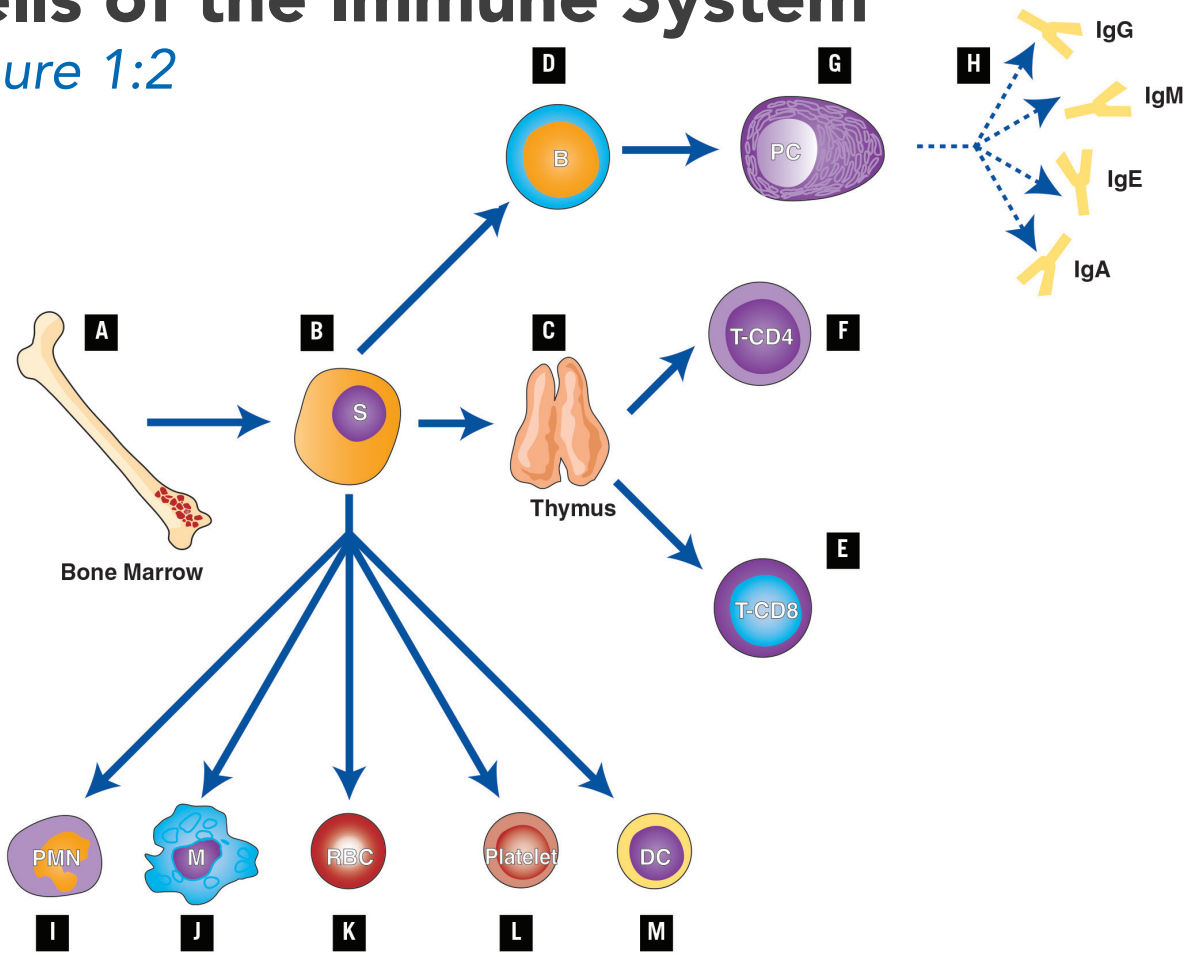
E. Lymph Nodes: Lymph nodes are collections of B cells and T cells throughout the body. Cells congregate in lymph nodes to communicate with each other. Lymph nodes can become swollen when they are fighting an infection.

F. Spleen: The spleen is a collection of B cells, T cells, and monocytes. It serves to filter the blood and provide a site for invaders/germs and cells of the immune system to interact.

G. Blood: Blood is contained within the circulatory system that carries cells and proteins of the immune system from one part of the body to another.

Cells of the Immune System

Figure 1:2



A. Bone marrow: The site in the body where most of the cells of the immune system develop from hematopoietic stem cells.

B. Stem cells: These cells have the potential to develop and mature into the different cells of the immune system.

C. Thymus: An organ located in the chest which instructs immature lymphocytes to become mature T cells.

D. B cells: These lymphocytes arise in the bone marrow and differentiate into plasma cells which in turn produce immunoglobulins (antibodies).

E. Cytotoxic T cells: These lymphocytes mature in the thymus and are responsible for killing cells infected with viruses.

F. Helper T cells: These specialized lymphocytes help other T cells and B cells to perform their functions.

G. Plasma Cells: These cells develop from B cells and are the cells that make immunoglobulin (antibodies).

H. Immunoglobulins: These highly specialized protein molecules, also known as antibodies, fit foreign antigens, such as polio, like a lock and key. Their variety is so extensive that they can be produced to match almost all possible microorganisms in our environment.

I. Neutrophils (also known as polymorphonuclear cells or PMN) are a type of white blood cell found in the blood stream that rapidly ingest microorganisms and kills them through a process called phagocytosis.

J. Monocytes: These white blood cells are cells found in the blood stream that develop into cells called macrophages when they migrate into tissues. Like neutrophils, macrophages also ingest and kill germs via phagocytosis.

K. Red Blood Cells: The red cells in the blood stream that carry oxygen from the lungs to the tissues.

L. Platelets: Small cells in the blood stream that are important for blood clotting.

M. Dendritic Cells: These cells instruct T cells on what to attack, also known as antigen presenting cells.

Over the first few years of life, most children are exposed to a wide variety of infections and produce antibodies directed at those specific infections. The B cells producing the antibodies remember the infection (germ) and provide long-lasting immunity to it. Similarly, T cells can remember viruses that the body has encountered and can make a more vigorous response when they encounter the same virus again. This rapid maturation of the adaptive immune system in early childhood makes testing young children a challenge since the expectations for what is normal change with age. In contrast to the adaptive immune system, the innate immune system is largely intact at birth.

Components of the Immune System

Each major component of the immune system will be discussed separately. PI can affect a single component or multiple components. The manifestations can be a single type of infection or a more global susceptibility to infections. Because of the many interactions between the cells and proteins of the immune system, some forms of PI can be associated with a very limited range of infections. For these forms, there are other elements that can compensate at least partly for the missing piece. In other cases, the ability to defend against infection is very weak overall, and the person may have significant problems with many types of infections.

The most common cells of the immune system can be categorized as lymphocytes (T cells, B cells, and NK cells), neutrophils, and monocytes/macrophages. These are all types of white blood cells. The major proteins of the immune system are predominantly cytokines (a type of hormone responsible for communication between cells of the immune system), antibodies (immunoglobulins), and complement proteins.

Lymphocytes of the Immune System

B cells

B cells (sometimes called B-lymphocytes and often named on lab reports as CD19 or CD20 cells) are specialized cells of the immune system whose major function is to produce antibodies (also known as immunoglobulins or gamma-globulins). B cells develop in the bone marrow from stem cells. As part of their normal maturation in the bone marrow, B cells are trained or educated so that they do not produce antibodies to healthy tissues. When mature, B cells can be found in the bone marrow, lymph nodes, spleen, some areas of the intestine, and the bloodstream.

When B cells encounter foreign germs (antigens), they respond by maturing into another cell type called plasma cells. B cells can also mature into memory cells, which allows a rapid response if the same infection is encountered again. Plasma cells are the mature cells that actually produce the antibodies and are located in the spleen and lymph nodes throughout the body. Antibodies are highly specialized serum protein molecules that find their way into the bloodstream, tissues, respiratory secretions, intestinal secretions, and even tears. Collectively, plasma cells have the ability to produce antibodies against virtually all microbes in our environment. Each plasma cell, however, produces only one kind of antibody.

In fact, antibodies are actually specifically designed to recognize practically every germ that can cause infection. For every foreign antigen, there are antibodies molecules specially designed to fit that antigen, like a lock and key. The variety of different antibody molecules found in a healthy immune system is vast. For example, there are specific antibody molecules that can recognize poliovirus, bacteria like diphtheria, the common cold virus, or the measles virus.

When antibody molecules recognize a microorganism as foreign, they physically attach to it and set off a complex chain of events involving other components of the immune system that work to eventually destroy the infection. Antibodies vary with respect to their specialized functions in the body. These variations are determined by the antibody's chemical structure, which in turn determines the class of the antibody (or immunoglobulin).

There are five major classes of antibodies (IgG, IgA, IgM, IgD, and IgE). IgG has four different subclasses (IgG1, IgG2, IgG3, IgG4). IgA has two subclasses (IgA1 and IgA2).

Each immunoglobulin class has distinct chemical characteristics that provide it with specific functions (Figure1:3). For example, IgG antibodies are formed in large quantities, last in the circulation for a few weeks, and travel from the blood stream to the tissues easily. Only IgG crosses the placenta and passes some immunity from the mother to the newborn. Antibodies of the IgA class are produced near mucus membranes and find their way into

secretions such as tears, intestines, bile, saliva and mucus, where they protect against infection in the respiratory tract and intestines. Some of the IgA also appears in the circulation. Antibodies of the IgM class are the first antibodies formed in response to infection. They are important in protection during the early days of an infection. Antibodies of the IgE class are responsible for allergic reactions. IgD is an immunoglobulin isotype that only makes up 0.25% of the serum immunoglobulins. IgD is expressed on mature B cells along with IgM and may play some role in helping B cells differentiate into plasma cells. Recently, studies have suggested that IgD may be important in the gut homeostasis by binding to mast cells and basophils to react against pathogenic bacteria in the gut.

Antibodies protect the body against infection in a number of different ways. For example, some microorganisms, such as viruses, must attach to body cells before they can cause an infection, but antibodies bound to the surface of a virus can interfere with the virus' ability to attach to the host cell. In addition, antibodies attached to the surface of some microorganisms can cause the activation of a group of proteins called the complement system that can directly kill some bacteria. Antibody-coated bacteria are also much easier for neutrophils to ingest and kill than bacteria that are not coated with antibodies. All of these actions of antibodies prevent microorganisms from successfully invading body tissues and causing serious infections.

The long life of plasma cells enables us to retain immunity to viruses and bacteria that infected us many years ago. For example, once people have been fully immunized with live vaccine strains of measles virus, they will almost never catch it because they retain the plasma cells and antibodies for many years and these antibodies prevent infection.

T cells

T cells (sometimes called T lymphocytes and often named in lab reports as CD3 cells) are another type of immune cell. Some T cells directly attack cells infected with viruses, and others act as regulators of the immune system.

T cells develop from hematopoietic stem cells in the bone marrow but complete their development in the thymus. The thymus is a specialized organ of the immune system in the chest. Within the thymus, immature lymphocytes develop into mature T cells (the "T" stands for the thymus) and T cells with the potential to attack normal tissues are eliminated. The thymus is essential for this process, and T cells cannot develop if the fetus does not have a thymus. It is in the thymus that T cell receptor excision circles (TRECs) are made as a by-product of T cell maturation. (TRECs are measured in blood spots from newborn screening cards to identify infants with Severe Combined Immunodeficiency (SCID), before they become sick with infections). Mature T cells leave the thymus as naïve T cells, ready to meet new antigens and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow, and blood as memory T cells after these exposures to antigen.

Each T cell reacts with one specific antigen, just as each antibody molecule reacts with one specific antigen. In fact, T cells have molecules on their surfaces that are similar to antibodies. The variety of different T cells is also so extensive that the body has T cells that can react against virtually any antigen.

T cells have different abilities to recognize antigen and are varied in their function. There are killer or cytotoxic T cells (often denoted in lab reports as CD8 T cells), helper T cells (often denoted in lab reports as CD4 T cells), and regulatory T cells. Each has a different role to play in the immune system.

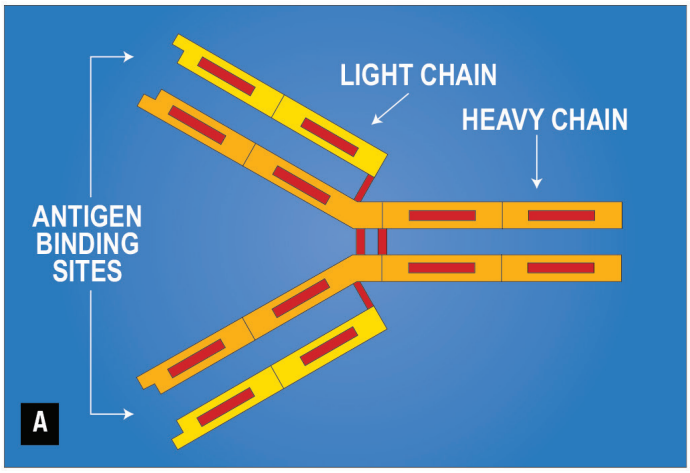
Killer, or cytotoxic T cells perform the actual destruction of cells infected with viruses. Killer T cells protect the body from certain bacteria and viruses that have the ability to survive and even reproduce within the body's own cells. In addition to fighting germs, killer T cells also recognize and respond to foreign tissues in the body, such as a transplanted kidney.

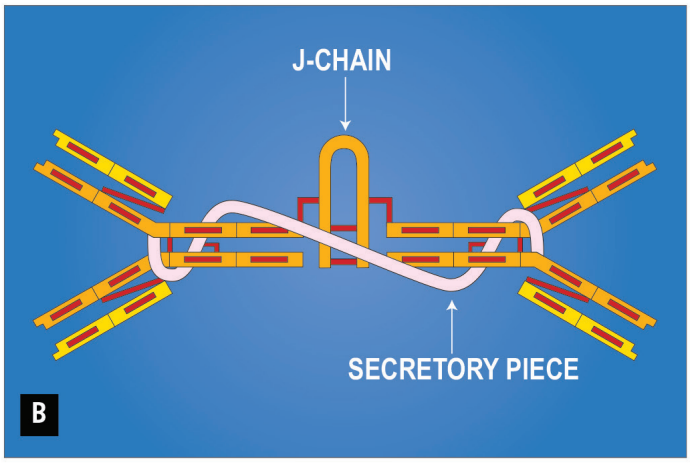
Helper T cells assist B cells to produce antibodies and assist killer T cells in their attack on foreign substances. The killer T cell must migrate to the site of infection and directly bind to its target to ensure its destruction.

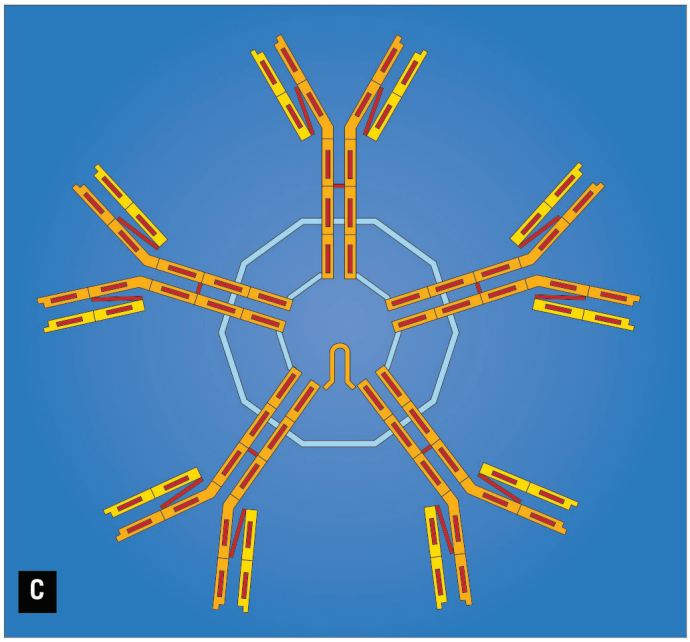
When T cells are fighting infections, they grow and divide, making more T cells. Regulatory T cells suppress or turn off the T cells when an infection is controlled and they are no longer needed. Without regulatory cells, the immune system would keep working even after an infection has been treated. Without regulatory T cells, there is the potential for the body to overreact to the infection. Regulatory T cells act as the thermostat of the lymphocyte system to keep it turned on just enough—not too much and not too little.

Immunoglobulin Structure

Figure 1:3







Each class or type of immunoglobulin shares properties in common with the others. They all have antigen binding sites which combine specifically with the foreign antigen.

A. IgG: IgG is the major immunoglobulin class in the body and is found in the blood stream as well as in tissues and secretions. Immunoglobulin replacement therapy contains primarily IgG.

B. Secretory IgA: Secretory IgA is composed of two IgA molecules joined by a J-chain and attached to a secretory piece. These modifications allow the secretory IgA to be secreted into mucus, intestines and tears where it protects those areas from infection.

C. IgM: IgM is composed of five immunoglobulin molecules attached to each other. It is formed very early in infection and activates complement very easily.

NK Cells

Natural killer (NK) cells are so named because they easily kill cells infected with viruses. They are said to be natural killer cells as they are always ready to fight and do not require the same thymic education that T cells require. NK cells are derived from the bone marrow and are present in relatively low numbers in the bloodstream and in tissues. They are important in defending against viruses and possibly preventing cancer as well.

NK cells kill virus-infected cells by injecting them with a killer potion of chemicals called cytotoxic granules. They are particularly important in the defense against herpes viruses. This family of viruses includes the traditional cold sore form of herpes (herpes simplex) as well as Epstein-Barr virus (the cause of infectious mononucleosis or mono) and the varicella virus (the cause of chickenpox and shingles).

Neutrophils

Neutrophils or polymorphonuclear leukocytes (polys or PMNs) are the most numerous of all the types of white blood cells, making up about half or more of the total. They are also called granulocytes and appear on lab reports as part of a complete blood count (named in lab reports as CBC with differential). They are found in the bloodstream and can migrate into sites of infection within a matter of minutes. These cells, like the other cells in the immune system, develop from hematopoietic stem cells in the bone marrow.

Neutrophils increase in number in the bloodstream during infection and are in large part responsible for the elevated white blood cell count seen with some infections. They are the cells that leave the bloodstream and accumulate in the tissues during the first few hours of an infection and are responsible for the formation of pus. Their major role is to ingest bacteria or fungi and kill them. Their killing strategy relies on ingesting the infecting organisms in specialized pockets within the cell. Neutrophils contain toxic chemicals that fuse with the bacteria-containing pockets to kill the bacteria. Neutrophils have little role in the defense against viruses.

Monocytes

Monocytes are closely related to neutrophils and are found circulating in the bloodstream. They make up 5 to 10% of the white blood cells. They also line the walls of blood vessels in organs like the liver and spleen where they capture microorganisms in the blood as they pass by. When monocytes leave the bloodstream and enter the tissues, they change shape and size and become macrophages.

Macrophages are essential for killing fungi and the class of bacteria to which tuberculosis belongs (mycobacteria). Like neutrophils, macrophages ingest microbes and deliver toxic chemicals directly to the foreign invader to kill it.

Macrophages live longer than neutrophils and are especially important for slow growing or chronic infections. Macrophages can be influenced by T cells and often collaborate with T cells in killing microorganisms.

Cytokines

Cytokines are a very important set of proteins in the body. These small proteins serve as messengers for the immune system. They are produced in response to a threat and represent the communication network for the immune system. In some cases, cells of the immune system communicate by directly touching each other, but often cells communicate by secreting cytokines that can then act on other cells either locally or at a distance.

This clever system allows very precise information to be delivered rapidly to alert the body as to the status of the threat. Cytokines are not often measured clinically but can appear on lab slips as IL-2, IL-4, IL-6, etc. Some cytokines were named before the interleukin (IL) numbering convention was started and have different names.

Complement

The complement system is composed of 30 blood proteins that function in an ordered fashion to defend against infection. Most proteins in the complement system are produced in the liver. Some of the proteins of the complement system coat bacteria to make them more easily taken up by neutrophils. Other complement components act to send out chemical signals to attract neutrophils to sites of infection. Complement proteins can also assemble on the surface of microorganisms forming a complex. This complex can then puncture the cell wall of the microorganism and destroy it.

Examples of How the Immune System Fights Infections

Bacteria

Our bodies are covered with bacteria and our environment contains bacteria on most surfaces. Our skin and internal mucous membranes act as physical barriers to help prevent and protect us from infection by these bacteria. When the skin or mucous membranes are broken due to disease, inflammation

or injury, bacteria can enter the body. Infecting bacteria are usually coated with complement and antibodies once they enter the tissues, and this allows neutrophils to easily recognize the bacteria as something foreign. Neutrophils then engulf the bacteria and destroy them (Figure 1:4).

When the antibodies, complement, and neutrophils are all functioning normally, this process effectively kills the bacteria. Recurrent bacterial infections, however, can occur and even damage tissues and organs when the number of bacteria is overwhelming or there are defects in antibody production, complement, and/or neutrophils.

Viruses

Most of us are exposed to viruses frequently. The way our bodies defend against viruses is different than how we fight bacteria. Viruses can only survive and multiply inside our cells. This allows them to hide from our immune system. When a virus infects a cell, the cell releases cytokines to alert other cells to the infection. This alert generally prevents other cells from becoming infected. Unfortunately, many viruses can outsmart this protective strategy, and they continue to spread the infection.

Circulating T cells and NK cells become alerted to a viral invasion and migrate to the site where they kill the particular cells that are harboring the virus. This is a very destructive mechanism to kill the virus because many of our own cells can be sacrificed in the process. Nevertheless, it is an efficient process to eradicate the virus.

At the same time the T cells are killing the virus, they are also instructing the B cells to make antibodies. When we are exposed to the same virus a second time, the antibodies help prevent the infection. Memory T cells are also produced and rapidly respond to a second infection, which also leads to a milder course of the infection.

The Immune System and Primary Immunodeficiency Diseases

Immunodeficiencies are categorized as primary or secondary. Primary immunodeficiency diseases are primary because an inherent defect in the immune system is the primary cause. Most are caused by genetic defects that may be inherited. Secondary immunodeficiencies are so called because they have been caused by other conditions including certain diseases or medications affecting the immune system.

The most common secondary immunodeficiencies are caused by aging, malnutrition, certain medications and some infections, such as human immunodeficiency virus or HIV. The most common medications associated with secondary immunodeficiencies are chemotherapy agents and immune suppressive medications, cancer, transplanted organ rejection, or autoimmune diseases. Other secondary immunodeficiencies include protein losses in the intestines or the kidneys. When proteins are lost, antibodies are also lost, leading to low immunoglobulins or low antibody levels. These conditions are important to recognize because, if the underlying cause can be corrected, the function of the immune system can be improved and/or restored. Regardless of the root cause, recognition of the secondary immunodeficiency and provision of immunologic support can be helpful. The types of support offered are comparable to what is used for primary immunodeficiencies.

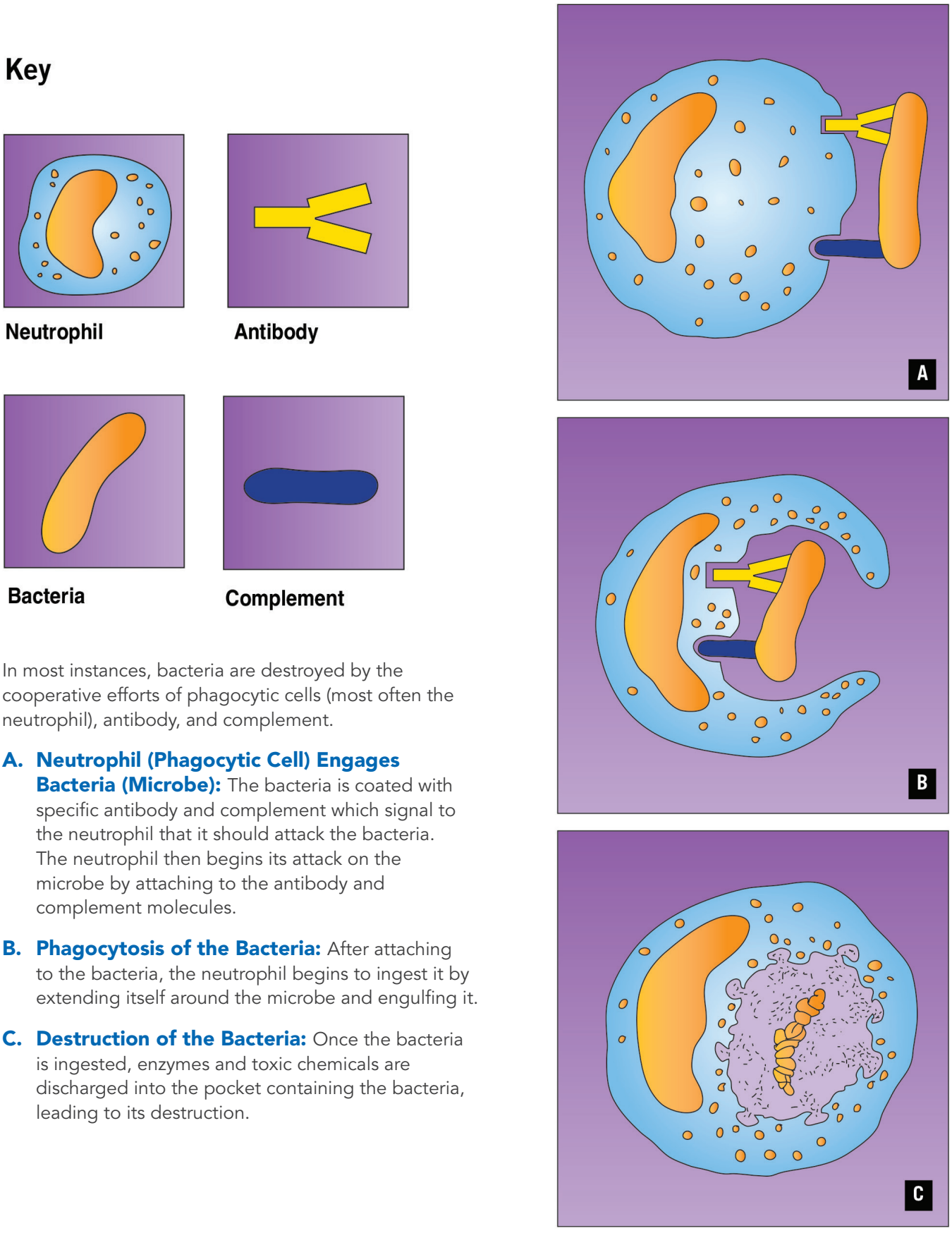
Primary immunodeficiency, or PI, are a group of disorders caused by basic defects in immune function that are inherent to the cells and proteins of the immune system. There are more than 350 forms of PI. Some are relatively common, while others are quite rare. Some affect a single cell or protein of the immune system, and others may affect two or more components of the immune system.

Although forms of PI may differ from one another in many ways, they share one important feature. They all result from a defect in one or more of the elements or functions of the normal immune system, such as T cells, B cells, NK cells, neutrophils, monocytes, antibodies, cytokines, or the complement system. Most of them are inherited diseases and may run in families, such as X-Linked Agammaglobulinemia (XLA) or SCID. Other primary immunodeficiencies, such as Common Variable Immune Deficiency (CVID) and Selective IgA Deficiency are not always inherited in a clear-cut or predictable fashion. In these disorders, the cause is unknown, but it is believed that the interaction of genetic and environmental factors may play a role in their causation.

Because the most important function of the immune system is to protect against infection, people with PI have an increased susceptibility to infection. This may include too many infections, infections that are difficult to treat, unusually severe infections, or infections with unusual organisms. The infections may be located anywhere in the body. Common sites are the sinuses (sinusitis), the bronchi (bronchitis), the

Normal Anti-Bacterial Action

Figure 1:4



In most instances, bacteria are destroyed by the cooperative efforts of phagocytic cells (most often the neutrophil), antibody, and complement.

A. Neutrophil (Phagocytic Cell) Engages Bacteria (Microbe): The bacteria is coated with specific antibody and complement which signal to the neutrophil that it should attack the bacteria. The neutrophil then begins its attack on the microbe by attaching to the antibody and complement molecules.

B. Phagocytosis of the Bacteria: After attaching to the bacteria, the neutrophil begins to ingest it by extending itself around the microbe and engulfing it.

C. Destruction of the Bacteria: Once the bacteria is ingested, enzymes and toxic chemicals are discharged into the pocket containing the bacteria, leading to its destruction.

lung (pneumonia), or the intestinal tract (infectious diarrhea).

Another function of the immune system is to discriminate between the healthy tissue ("self") and foreign material ("non-self"). Examples of foreign material can be microorganisms, pollen or even a transplanted kidney from another individual. In some immunodeficiency diseases, the immune system is unable to discriminate between self and non-self. In these cases, in addition to an increased susceptibility to infection, people with PI may also have autoimmune diseases in which the immune system attacks their own cells or tissues as if these cells were foreign, or non-self.

There are also a few types of PI in which the ability to respond to an infection is largely intact, but the ability to regulate that response is abnormal. Examples of this are autoimmune lymphoproliferative syndrome (ALPS) and IPEX (X-linked syndrome of immunodeficiency, polyendocrinopathy and enteropathy). These conditions are characterized by prominent autoimmunity where the body attacks itself.

PI can occur in individuals of any age. The original descriptions of these diseases were in children. As medical experience has grown, however, many adolescents and adults have been diagnosed with PI. This is partly due to the fact that some of the disorders, such as CVID and Selective IgA Deficiency (SAD), may have their initial clinical presentation in adult life.

Effective therapy exists for many forms of PI, and many people with these disorders can live relatively normal lives. PI was initially thought to be very rare. Recent research, however, has indicated that as a group they are more common than originally thought. It is estimated that as many as 1 in every 1,200 to 2,000 people may have some form of PI.

Adapted from: Chapter 1 The Immune System and Primary Immunodeficiency Diseases. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 2
Antibody Deficiency with Absent B Cells

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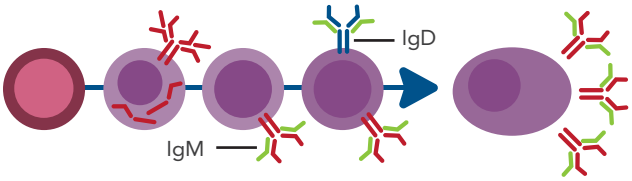
Some people with primary immunodeficiency diseases (PI) lack the cells that are responsible for producing antibodies (immunoglobulins). They have very low or absent levels of all types of antibodies and an increased risk of infection. People with genetic causes of low or absent antibodies (agammaglobulinemia) have a severe form of antibody deficiency with absent B cells. This results from the failure of precursor-B cells to develop into mature B cells and plasma cells.

Definition

The basic defect in agammaglobulinemia is an inability of the patient to produce antibodies. Antibodies are an integral part of the body's defense mechanism against germs. When a germ, such as bacteria, lands on a mucous membrane, or enters the body, antibody molecules that recognize the germ stick to its surface. Antibodies bound to the surface of a germ can have one or more effects that are beneficial. For example, some germs must attach to body cells before they can cause an infection and antibodies prevent the germs from sticking to the body's cells. Antibody on the surface of some germs will also activate other body defenses, such as a group of blood proteins called serum complement, which can directly kill the bacteria or viruses. Finally, antibody coated bacteria are much easier for white blood cells (phagocytes) to ingest and kill than are bacteria that are not coated with antibody. All of these actions prevent germs from invading body tissues where they may cause serious infections. Antibodies are also important in the recovery from infections and to protect against getting certain infections more than once. (See The Immune System and Primary Immunodeficiency Diseases Chapter.)

Antibodies are produced by specialized cells in the body, called plasma cells. Plasma cells are derived from B lymphocytes (a type of white cell) that develop in an orderly sequence of steps beginning with stem cells located in the bone marrow. The stem cells give rise to immature lymphocytes that eventually develop into mature lymphocytes including T cells, B cells, or NK cells. A subset of these immature lymphocytes called pro-B lymphocytes next develop into pre-B lymphocytes, which then give rise to mature B lymphocytes (Figure 2:1). Each B lymphocyte has antibodies on its cell surface. Each B cell makes a slightly different antibody, or immunoglobulin, to allow the body to respond to millions of different foreign substances (also known as antigens), like vaccines or parts of bacteria or viruses. There are specific antibodies designed to recognize each unique antigen. When the B lymphocyte comes into contact with its antigen, it is triggered to mature into a plasma cell. Plasma cells specialize in making and secreting large amounts of specific antibodies.

Figure 2:1 Agammaglobulinemia



The first form of agammaglobulinemia to be recognized, X-Linked Agammaglobulinemia (XLA), was described in 1952 by Colonel Ogden Bruton, MD. This disease, sometimes called Bruton's Agammaglobulinemia or Congenital Agammaglobulinemia, typically affecting boys, was the first type of PI to be identified. Most individuals with XLA have normal numbers of B cell precursors, but very few of these are able to go on to become mature B cells. People with XLA have mutations, or changes, in a gene that is necessary for the normal development of B cells. This gene, discovered in 1993, is named Bruton's Tyrosine Kinase (BTK) in honor of Dr. Bruton.

After BTK was identified as the cause of XLA, it became clear that only about 85% of children with agammaglobulinemia and absent B cells had mutations in BTK. In addition, it had been known for several years that there were girls who had an immunodeficiency that looked just like XLA with agammaglobulinemia and absent B cells, but which could not be explained by X-linked inheritance of BTK mutations.

Since 1996, several genes that can cause agammaglobulinemia with autosomal recessive inheritance (ARA) have been identified. The following genes (and their official gene symbol) have been reported to cause ARA:

- μ heavy chain (IGHM)
- λ5 (IGLL1)
- Igα (CD79A)
- Igß (CD79B)
- BLNK (BLNK)
- PI3K p85α (PIK3R1)

In addition, more recently, autosomal dominant forms of agammaglobulinemia have been described due to mutations in LRRC8 (LRRC8A) and E2A (TCF3).

All of these genes code for proteins involved in the maturation of B cells. Individuals with mutations in any of these genes have clinical and laboratory findings that are very similar to those seen in those with mutations in BTK.

Clinical Presentation

Individuals with any form of antibody deficiency with absent B cells are prone to develop infections. These infections frequently occur at or near the surfaces of the mucus membranes, such as the middle ear (otitis), sinuses (sinusitis), lungs (pneumonia), and gastrointestinal tract (infection causing diarrhea). In some instances infections can involve the skin, bloodstream, or internal organs.

In people without antibodies, any of these infections may invade the bloodstream and spread to other areas deep within the body, such as the bones, joints, or brain. Germs that are usually killed or inactivated very effectively by antibodies in healthy people cause infections in people with agammaglobulinemia. The most common bacteria that cause infections are pneumococcus, streptococcus, staphylococcus, and Hemophilus influenzae. Enterovirus infections (Echovirus, Coxsackie, Polio, etc.) are particularly troublesome for someone with agammaglobulinemia and can be associated with serious central nervous system infections.

The deficiency of antibody production is present at birth, and infections may begin at any age. Nevertheless, frequent infections often do not occur until sometime between 6-18 months of age because, until then, babies are protected by antibodies they received from their mother during the third trimester of pregnancy.

On physical examination, most individuals with agammaglobulinemia have very small tonsils and lymph nodes, which are the glands in the neck. This is because these tissues are made up of mostly B cells. In the absence of B cells, these tissues are much smaller. In more rare cases of agammaglobulinemia, like LRRC8A, individuals may have uncommon facial features.

In addition to lacking B cells, some people with XLA may also have low neutrophil counts and may develop a rare form of arthritis. Although infrequent, some with antibody deficiency with absent B cells may develop autoimmune or central nervous system disease.

Diagnosis

The diagnosis of agammaglobulinemia should be considered in any individual (male or female) with recurrent or severe bacterial infections, particularly if they have small or absent tonsils and lymph nodes.

The first screening test should be an evaluation of serum immunoglobulins. In most individuals with agammaglobulinemia, all of the immunoglobulins (IgG, IgM, IgA, IgE) are low or absent. In addition, healthy babies make only small quantities of immunoglobulins, particularly IgA and IgE, in the first few months of life, making it difficult to distinguish a healthy baby with a delay in immunoglobulin production from a baby with true immunodeficiency.

If the serum immunoglobulins are low or if the healthcare provider strongly suspects the diagnosis of agammaglobulinemia, the number of B cells in the blood should be measured. A low percentage of B cells (1% or less of the lymphocytes) in the blood is the most characteristic and reliable laboratory finding in someone with agammaglobulinemia.

If a newborn baby has a parent, sibling, maternal cousin, or maternal uncle with agammaglobulinemia, the baby is at risk to have a similar immunodeficiency, and the family and healthcare providers should

immediately determine the percentage of B cells in the blood so that treatment can be started before an affected infant gets sick.

The diagnosis of XLA can be confirmed by demonstrating the absence of BTK protein in monocytes or platelets or by the detection of a mutation in BTK in DNA. Almost every family has a different mutation in BTK; members of the same family, however, usually have the same mutation. The specific gene that causes ARA can be identified by genetic testing.

Inheritance

Antibody deficiency with absent B cells are a group of genetic diseases, and can be inherited or passed on in a family. It is important to know the type of inheritance so the family can better understand why a child has been affected, the risk that subsequent children may be affected, and the implications for other members of the family.

As the name XLA suggests, the BTK gene (which is mutated in XLA) is located on the X chromosome. Since XLA is an X-linked disorder, typically only boys are affected because they have only one X chromosome (XY). Girls can be carriers of the disorder because they have two X chromosomes. Carriers of XLA typically have no symptoms, but they have a 50% chance of transmitting the disease to each of their sons.

Now that the precise gene that causes XLA has been identified, it is possible to test the female siblings (sisters) of a male with XLA, and other female relatives, such as the child's maternal aunts, to determine if they are carriers of the disease and could transmit it to their sons. It is also possible to determine if a fetus of a carrier female will be born with XLA. (See Inheritance Chapter.)

ARA occurs when an individual inherits two copies of a gene (typically one from each parent), each of which has a mutation that makes the gene not function. This is more likely when parents are related in some way to one another, or come from a small, isolated geographic region or close-knit community. In autosomal recessive forms of agammaglobulinemia, an individual who inherits only one gene with a mutation and has one normal gene will not be affected. Individuals with autosomal dominant forms of agammaglobulinemia need to only inherit one copy of the gene mutation to be affected.

Treatment

At this time, the only treatment for individuals with agammaglobulinemia is immunoglobulin (Ig) replacement therapy. There currently is no cure for XLA, but there has been promising research regarding gene therapy for XLA, which is still in the pre-clinical stage. Ig replacement therapy for those with agammaglobulinemia replenishes some of the antibodies that they are lacking. The antibodies are supplied in the form of Ig, also known as gamma globulins or IgG. This Ig replacement therapy can be given directly into the blood stream (intravenously) or under the skin (subcutaneously). (See Immunoglobulin Replacement Therapy Chapter.)

The varying types of Ig replacement therapy contain antibodies that substitute for the antibodies that the individual cannot make themselves. These products contain antibodies to a wide variety of germs and is purified from the blood of healthy donors. Ig is particularly effective in preventing the spread of infections into the bloodstream and to deep body tissues or organs. Some people may also need daily oral antibiotics to protect them from infection or to treat chronic sinusitis or chronic bronchitis.

People with antibody deficiency with absent B cells should not receive any live viral vaccines, such as live polio, the measles, mumps, rubella (MMR) vaccine, the chicken pox vaccine, the rotavirus vaccine, yellow fever, live typhoid, or the live shingles vaccine. Although uncommon, it is possible that live vaccines, particularly the oral polio vaccine, in people with agammaglobulinemia can transmit the diseases that they were designed to prevent.

Individuals with antibody deficiency with absent B cells should receive the yearly influenza (flu) vaccine. Ig replacement therapy may interfere with the response to a vaccine; therefore, individuals should contact their healthcare provider prior to receiving any vaccination. It is also important for family members and close contacts of people with antibody deficiency with absent B cells to be vaccinated in order to provide them with a level of protection called herd immunity or community immunity.

Expectations

Most individuals with antibody deficiency with absent B cells, who receive Ig replacement therapy on a regular basis, will be able to lead relatively normal lives. They do not need to be isolated or limited in their activities. Children with agammaglobulinemia can participate in all regular school and

extracurricular activities, and active participation in team sports should be encouraged. Infections may require some extra attention from time to time, but many with antibody deficiency with absent B cells can go on to become adults with productive careers and families. A full active lifestyle is to be encouraged and expected.

Adapted from: Chapter 2 Agammaglobulinemia: X-Linked and Autosomal Recessive. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 3

Common Variable Immune Deficiency Phenotypes

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Common Variable Immune Deficiency (CVID) is one of the most frequently diagnosed forms of primary immunodeficiency diseases (PI). While children may have this immune defect, it is usually diagnosed in adults. CVID is characterized by low levels of serum immunoglobulins and also lack of specific antibodies in response to vaccines. Lack of antibody protection leads to increased susceptibility to infections. Genetic causes are found in some (approximately 30%), but for a large majority the causes are not well understood.

Overview

CVID is a relatively frequent form of primary immunodeficiency, found in about 1 in 25,000 persons; this is the reason it is called common. The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from person to person, hence, the word variable. An additional characteristic is a decreased IgA and/or IgM level, or a low level of all three major types of immunoglobulins (IgG, IgA, and IgM). In some individuals, there are defects of the T cells, and this may also contribute to increased susceptibility to infections as well as autoimmunity, granulomatous disease, and cancer.

To be sure that CVID is the correct diagnosis, there must be evidence of a lack of specific antibodies (measured antibodies in response to vaccines) and other possible causes of these immunologic abnormalities must be excluded, such as loss in the gastrointestinal tract or urine. Frequent and/or unusual infections may first occur during early childhood, adolescence or adult life. As mentioned earlier, some people with CVID also have an increased incidence of autoimmune or inflammatory conditions, granulomas and an increased susceptibility to cancer when compared to the general population. Sometimes it is the presence of one of these other conditions that prompts an evaluation for CVID.

Although CVID is a distinct diagnosis, some may confuse it with other antibody deficiencies. The medical terms for absent or low blood immunoglobulins are agammaglobulinemia and hypogammaglobulinemia, respectively. Due to the late onset of symptoms and diagnosis, other names that have been used in the past include acquired agammaglobulinemia, adult onset agammaglobulinemia, or late onset hypogammaglobulinemia. The term "acquired immunodeficiency" refers to a syndrome caused by the human immunodeficiency virus (HIV) and should not be used for individuals with CVID, as these disorders are very different.

Clinical Features

Both males and females may have CVID. In many, the diagnosis is not made until the third or fourth decade of life. About 20% of people with CVID, however, have symptoms of the disease or are found to be immunodeficient in childhood. Because the antibody arm of defense (the humoral immune system) is slow to mature, the diagnosis of CVID is generally not made until after the age of 4.

The usual presenting features of CVID are recurrent infections involving the ears, sinuses, bronchi (breathing tubes), and lungs (respiratory tract). When the lung infections are severe and occur repeatedly, permanent damage with widening and scarring of the airways, a condition termed bronchiectasis, may develop.

The organisms most commonly found in sinus and lung infections are bacteria that are widespread in the population and that often cause pneumonia (Haemophilus influenzae, Streptococcus pneumoniae) even in people who do not have CVID. The purpose of treatment of lung infections is to prevent their recurrence and to prevent the accompanying chronic and progressive damage to lung tissue. A regular cough in the morning and the production of yellow or green sputum (a mixture of saliva and mucus) may suggest the presence of chronic bronchitis or bronchiectasis.

Individuals with CVID may also develop enlarged lymph nodes in the neck, chest, or abdomen. Enlarged lymph nodes may be caused by infection, an abnormal immune response, or both. Similarly, enlargement of the spleen is relatively common, as is enlargement of Peyer's patches, which are collections of lymphocytes in the walls of the intestine.

In some cases, other collections of inflammatory cells called granuloma (comprised of white blood cells including monocytes and macrophages) can be found in the lungs, lymph nodes, liver, skin, or other organs. Granuloma may form in response to an infection, but the cause of their collection in tissues in CVID is not really known.

Although people with CVID have depressed antibody responses and low levels of immunoglobulins in their blood, some of the antibodies they produce may attack their own tissues (autoantibodies). These autoantibodies may attack and destroy blood cells, like red cells, white cells, or platelets. Although, most individuals with CVID present first with recurrent bacterial infections, in about 20% of cases, the first manifestation of the immune deficiency is a finding of very low platelets in the blood or less commonly, severe anemia due to destruction of red cells. Autoantibodies may also cause other diseases such as arthritis or endocrine disorders, like thyroid disease.

Gastrointestinal (GI) complaints, such as abdominal pain, bloating, nausea, vomiting, diarrhea, and weight loss, can also be associated with CVID. Approximately 21% of people with CVID may have significant GI problems. Careful evaluation of the digestive organs may reveal a reduced ability to absorb fat and certain sugars or inflammatory bowel disease. If a small biopsy (sample) of the bowel mucosa (tissue) is obtained, characteristic changes may be seen. These changes are helpful in diagnosing the problem and treating it. In some people with digestive problems, the detection and eradication of infections due to bacteria, parasites, or viruses may help eliminate the GI symptoms.

Some people with CVID, particularly those who have not received the ideal immunoglobulin (Ig) replacement therapy, may also develop a painful inflammation of one or more joints. This condition is called polyarthritis. In the majority of these cases, the joint fluid, if tested, does not contain bacteria. To be certain that the arthritis is not caused by a treatable infection, the joint fluid may be removed by needle aspiration and studied for the presence of bacteria. In some instances, a bacterium called Mycoplasma may be the cause and can be difficult to diagnose. The typical arthritis associated with CVID may involve the larger joints such as knees, ankles, elbows, and wrists. The smaller joints, like the finger joints, are more rarely affected. Symptoms of joint inflammation may disappear with adequate Ig replacement therapy and appropriate antibiotics. In some, however, arthritis may occur even when the individual is receiving adequate Ig replacement therapy.

Finally, people with CVID may have an increased risk of cancer, especially cancer of the lymphoid system or possibly the gastrointestinal tract. However in a recent study of cancer incidence of people with PI enrolled in the United States Immunodeficiency Network (USIDNET) patient registry, of the four most common malignancies in men and women (lung, colon, breast, and prostate cancers), there was no significant increase of these cancers in people with PI versus the age-adjusted population.

Diagnosis

CVID should be suspected in children or adults who have a history of recurrent bacterial infections involving ears, sinuses, bronchi, and lungs. The characteristic laboratory features include low levels of serum immunoglobulins, including IgG, often IgA and sometimes IgM. Another part of the diagnosis of CVID is to determine if there is a lack of functional antibody. This is done by measuring serum levels of antibody that are specific to vaccine antigens such as Tetanus/ Diphtheria, or pneumococcal polysaccharide. People with CVID have very low or absent antibody levels to most of these vaccines.

Immunization with killed vaccines is used to measure antibody function, and this functional testing is crucial prior to beginning treatment. These tests also help the healthcare providers decide if the individual will benefit from Ig replacement therapy and are

often essential in obtaining insurance authorization for this therapy. The number of B and T lymphocytes may also be determined and their function can be tested in laboratories. Recent studies have also shown that examining the maturity of the B cells in the blood by looking at the surface receptors (B cell memory markers) can help in predicting the relative severity of the immune deficiency.

Genetics and Inheritance

People with CVID usually have normal numbers of the cells that produce antibody (B cells), but these cells fail to undergo normal maturation into plasma cells, the cells capable of making the different types of immunoglobulins and antibodies for the blood stream and secretions.

The genetic causes of CVID are largely unknown, although recent studies have shown the involvement of an increasing number of genes in select people. These include genes that regulate immune functions, B cell surface proteins that help cells signal properly when a foreign substance is identified, and genes important in B cells activation. Until recently, the majority of the genes identified caused autosomal recessive CVID (See Inheritance Chapter), but increasingly autosomal dominant inheritance has been reported (one copy of an abnormal gene leading to variable expression). In these cases, other family members with the same genetic abnormality may not have any medical symptoms. As these are very rare gene defects for the most part, genetic testing is not required for most individuals with CVID. Particularly in those with inflammatory or autoimmune complications, however, genetic studies have been helpful in guiding additional individualized therapies.

Treatment

The treatment of CVID is similar to that of other disorders with low levels of serum immunoglobulins. In the absence of a significant T lymphocyte defect or organ damage, Ig replacement therapy almost always brings improvement of symptoms. Immunoglobulin is extracted from a large pool of human plasma; it consists mostly of IgG and contains all the important antibodies present in the normal population. (See Immunoglobulin Replacement Therapy Chapter.)

People with chronic sinusitis or chronic lung disease may also require long-term treatment with broad-spectrum antibiotics. If mycoplasma or other chronic infections are suspected, antibiotics specific for those organisms may be indicated. If bronchiectasis has developed, a daily pulmonary regimen (chest physiotherapy and postural drainage) may be needed to mobilize the secretions from the lungs and bronchi and make them easier to cough up.

When individuals with CVID are on Ig replacement therapy, routine immunizations are not required because the Ig solutions contain protective antibodies against these. Exceptions may be the new killed shingles vaccine, the human papilloma virus vaccine (HPV), and the annual viral influenza vaccine.

Those with GI symptoms and malabsorption should be evaluated for the presence of *Giardia lamblia*, rotavirus, Campylobacter, norovirus, bacterial overgrowth, and other GI infections. In some cases, inflammatory bowel disease is found. This is an autoimmune condition that can be treated by the medications normally prescribed for individuals who are not immunodeficient, including the newer biologic drugs. Maintaining a balance between the immunosuppression used to control the autoimmune process while avoiding compounding the defects of the underlying PI requires close cooperation between the individual and the various specialists involved in their care. (See Autoimmunity in Primary Immunodeficiency Chapter.)

If autoimmune or inflammatory disease, granulomas, or tumors develop, the treatment is usually the same as would be given to a person with a normal immune system. When people with CVID, however, have these complications, there is a tendency for them to be less responsive to therapy. Regular checkups including lung function are recommended.

Most individuals with CVID carry out most if not all normal activities. Regularly scheduled and careful follow-up is still mandatory as new problems may arise or evolve over time. In general, those who are stable are seen at least yearly, but with added questions or when other conditions arise, shorter intervals such as three to six months are needed. In addition to addressing routine questions and checking blood counts, metabolic panels, and Ig levels, monitoring for weight changes is important, as Ig doses may need to be adjusted. There is no current consensus on how best to monitor for lung disease. Chest X-rays are not able to show the same level of detail as a CT scan, but there is a lower radiation exposure with a chest x-ray. For more frequent follow-up of those with chronic cough and/or known lung damage, complete lung

functions including carbon monoxide (CO) diffusion is useful, with possible chest CT at 3-4 year intervals. Monitoring for autoimmunity is usually accomplished through routine blood counts and general medical oversight which will reveal characteristic symptoms. GI diseases will be similarly evident with complaints of diarrhea and, often, weight loss. Routine endoscopy is not required although people with suggestive GI symptoms should have appropriate upper and/or lower endoscopy (colonoscopy) with examination for H pylori, pathogenic bacteria or viruses, or other mucosal changes. Loss of height may reflect loss of bone density; this requires attention to vitamin D, calcium, and other standard therapies. Evaluation of enlarged lymph nodes is not simple. When new lymph nodes appear and persist, biopsy may be required, but most commonly these reflect simply reactive changes that are not clinically significant.

Expectations

Ig replacement therapy combined with antibiotic therapy has greatly improved the outlook of people with CVID. The aim of the treatment is to keep the individual free of infections and to prevent the development of chronic inflammatory changes in tissues. The outlook for people with CVID depends on how much damage has occurred to lungs or other organs before the diagnosis is made and treatment Ig replacement therapy started, as well as how successfully infections can be prevented in the future by using these therapies. The development of autoimmune disease, inflammatory problems, granulomas, and/or malignancy can have a significant impact on the quality of life. These diagnoses often require additional therapies.

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Chapter 4

Selective Immunoglobulin Deficiency: IgA and IgM

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Selective IgA Deficiency

Individuals with Selective IgA Deficiency (SIgAD) lack immunoglobulin A (IgA), but they usually have normal amounts of IgG and IgM. SIgAD is relatively common in people of Caucasian descent and rare in people of Asian descent. In North America, it is the most common form of primary immunodeficiency disease (PI), estimated to affect 1 in 500 people. Many affected have no symptoms and do not even know they have a deficiency until the lack of IgA is noted when they are being evaluated for another condition, such as celiac disease. Those people who are symptomatic may develop a variety of significant clinical problems, including infections, allergies, and autoimmune diseases. It is important to know that, with the exception of an undetectable level of IgA, all other components of the immune system function are usually normal.

Overview

SIgAD is defined as a primary immunodeficiency characterized by an undetectable level of IgA in the blood and secretions but normal IgG and IgM in an individual age 4 and older. IgM and IgG mainly protect people from infections inside body tissues, organs, and blood. While IgA is present in the blood, most of the IgA in the body is in the secretions of the mucosal surfaces, including tears, saliva, and colostrum, as well as genital, respiratory, and gastrointestinal secretions. The IgA antibodies in these secretions play a role in protecting people from infections in the respiratory tract, gastrointestinal tract, and genitourinary tract.

Immunobiology

Individuals with SIgAD lack serum (IgA <7 mg/dl) and secretory IgA, but they do make all the other immunoglobulin classes. Some of the individuals with SIgAD also have IgG subclass deficiency. Among the four IgG subclasses, low IgG2 levels are most commonly observed. In those who have associated allergic diseases serum IgE levels may be increased. In those with SIgAD who have autoimmune disease, a variety of autoantibodies (like ANA, Rheumatoid factor) may be positive. In most people with SIgAD, there are no problems with cellular immunity, the complement system, or white blood cell function.

Secretory IgA has some differences compared to the IgA present in the blood. Secretory IgA is made of two IgA antibody molecules joined together by a protein called the J chain—J for joining. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) In order for this unit to be secreted, it is attached to another protein called the secretory piece. Therefore, the final secretory IgA unit that protects the mucosal surfaces is actually composed of two IgA molecules joined by the J chain and attached to the secretory piece. The secretory IgA is able to exist in the gastrointestinal tract because it is resistant to gastrointestinal enzymes.

IgA promotes health by regulating the composition and function of microbiota, which regulates metabolism, epithelial barrier integrity, and the immune system.

Clinical Presentation

A common problem in SIgAD is susceptibility to infections. Problems with infections are seen in about half of the individuals with SIgAD. Recurrent ear infections, sinusitis, bronchitis, and pneumonia are the most common infections. Some individuals may develop gastrointestinal infections and other gastrointestinal disorders, such as chronic diarrhea. Another problem in SIgAD is the occurrence of autoimmune diseases. These are found in about one third of individuals who seek medical help. Some of the more frequent autoimmune diseases associated with SIgAD include rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Idiopathic Thrombocytopenic Purpura (ITP) (low platelet counts). Other kinds of autoimmune disease may affect the endocrine system and/or the gastrointestinal system. Allergic disorders are more common among individuals with SIgAD than among the general population. The types of allergies associated with SIgAD include allergic rhinitis, allergic conjunctivitis, eczema, and asthma. Food allergy may also be associated with SIgAD.

Diagnosis

The diagnosis of SIgAD is usually suspected because of chronic or recurrent ear infections, sinusitis, respiratory tract infections, chronic diarrhea, or some combination of these problems. Other individuals are identified when immunoglobulins are ordered for some non-immunologic problem, for example when a person is being evaluated for possible celiac disease. The diagnosis is established when blood tests demonstrate undetectable levels of IgA (reported usually as >7 mg/dl), with normal levels of the other major classes of immunoglobulins (IgG and IgM). The healthcare provider may order several other tests including autoantibodies.

Prevalence and Inheritance

Genetic susceptibility in IgA deficiency is not well defined, but familial inheritance of SIgAD may occur in approximately 20% of cases. SIgAD can be observed in families with Common Variable Immune Deficiency (CVID). There are reports of some individuals with SIgAD being later diagnosed with CVID.

Treatment

Ideal treatment for SIgAD would be to replace IgA. However, no IgA-enriched immunoglobulin (Ig) preparation is available in the U.S. Treatment should be directed toward a specific illness. For example, individuals with chronic or recurrent infections need treatment with appropriate antibiotics. Ideally, antibiotic therapy should be targeted at the specific organism causing the infection. It is not always possible, however, to identify these organisms and their antibiotic sensitivities precisely, and therefore, the use of broad-spectrum antibiotics may be indicated. Certain individuals who have chronic sinusitis or chronic bronchitis may need to stay on long-term preventive antibiotic therapy (antibiotic prophylaxis). In these cases, the healthcare provider and person with SIgAD need to discuss the benefits and risks of the various possibilities and reach mutual agreement regarding treatment.

People with SIgAD (>7 mg/DL) are often considered to be at increased risk of life-threatening allergic reactions, also known as an anaphylactic reaction, to blood and blood products including immunoglobulin (Ig) replacement therapy that may contain traces of IgA. This is thought to be due to antibodies (IgE) against the IgA antibody, which may be found in some IgA-deficient individuals. These reactions, however, are very rare overall. If individuals with SIgAD and IgG2 subclass deficiency have a history of recurrent serious infections, a trial of Ig replacement therapy may be used to prevent infections. If there is a concern about the risk of adverse reactions because of the small amounts of IgA in intravenous immunoglobulin (IVIG) preparations, then it is advised to use subcutaneous immunoglobulin (SCIG). The latter is preferred over low IgA containing preparations administered intravenously because of the following reasons: there is only one IVIG preparation with extremely low IgA, infusions need to be given in a hospital setting and under medical supervision, and anaphylactic reaction to SCIG has not been reported. Individuals with SIgAD who need a blood transfusion should receive washed red cells to remove the plasma that contains the IgA that may cause a transfusion reaction.

As for autoimmune diseases, a variety of therapeutic options exist such as anti-inflammatory drugs, steroids, or biological drugs. As with every treatment, the individual and/or caregiver and their healthcare provider should discuss the treatment plan and best treatment options.

Expectations

Although SIgAD is usually one of the milder forms of immunodeficiency, it may result in severe disease in a subset of people. Therefore, it is difficult to predict the long-term outcome in an individual with SIgAD, although generally the prognosis is considered to be very good. It is important for healthcare providers to continually assess and re-evaluate individuals with SIgAD for the existence of associated diseases and to consider the possibility of diagnosing later with a more extensive immunodeficiency, for example CVID.

Individuals need to inform their healthcare providers of anything unusual, especially fever, productive cough, skin rash, or sore joints. The importance of good communication with the healthcare provider and the initiation of appropriate therapy as soon as necessary cannot be overstated.

Selective IgM Deficiency

Individuals with Selective IgM Deficiency have low levels or lack immunoglobulin M (IgM) but have normal levels of IgA, and IgG. These individuals may have no illness, whereas others develop a variety of illnesses including infections, allergy, and autoimmunity.

Overview

IgM is the largest in size of all immunoglobulins. It is predominantly present in the circulating blood as compared to IgG, which is present both in the circulation and in the tissues, and IgA, which is present predominantly in secretions. IgM is the first immunoglobulin secreted during an initial exposure to infectious organisms or to a vaccine. IgM is also different from other immunoglobulins in that it contains five antibody molecules held together by the J chain. IgM antibodies serve as a first line of defense against bacteria, viruses, and fungi, and in protection against autoimmune diseases and inflammation.

Although described more than 50 years ago, it is only recently that Selective IgM Deficiency is included in the list of forms of PI. It is characterized by low (partial) to absent IgM (complete) in the blood but normal IgG and IgA levels. It occurs equally both in children and adults, and in men and women. Partial Selective IgM Deficiency is more common than previously realized, whereas complete Selective IgM Deficiency is rare. Individuals with Selective IgM Deficiency, partial or complete, may not have any symptoms, and therefore, are unrecognized or undiagnosed. Those individuals who do have symptoms commonly suffer from infections, allergies, and autoimmune diseases. There is no specific treatment to correct low IgM levels; however, individuals who have this condition and also have impaired responses to vaccines antigens, particularly pneumococcal polysaccharide vaccines, may require Ig replacement therapy.

Immunobiology

Blood levels of IgM are low or absent, but IgA and IgG are normal. In some cases, IgG subclass deficiency may also be seen. One third to one half of individuals with Selective IgM Deficiency make poor response to Pneumovax-23 vaccine. Cellular immunity is normal. Phagocytic cell system and complement system are also normal.

Clinical Presentation

Individuals with Selective IgM Deficiency may be asymptomatic or symptomatic. Of those who are symptomatic, approximately 80% present with predominant bacterial infections. Among infections, most common are chronic sinusitis, upper respiratory tract infections, bronchitis, and pneumonia. Occasionally cellulitis, sepsis and meningitis have been observed. Almost 40% of individuals with Selective IgM Deficiency have allergic diseases including hay fever and asthma. Autoimmune diseases are observed in

about one third of all individuals with Selective IgM Deficiency. Autoimmune diseases are more common in adults than children with Selective IgM Deficiency. Some common autoimmune diseases associated with Selective IgM Deficiency are systemic lupus erythematosus, rheumatoid arthritis, and autoimmune thrombocytopenia. Autoimmune diseases of endocrine glands, like Hashimoto's thyroiditis and Addison's disease, have also been seen in Selective IgM Deficiency.

Diagnosis

Since the symptoms of Selective IgM Deficiency are similar to other antibody deficiencies, such as CVID and SIgAD. Selective IgM Deficiency may be discovered when immunoglobulins are obtained to evaluate someone who is suspected of having a PI. Individuals are also identified when immunoglobulins are ordered for illnesses other than PI. The diagnosis of partial Selective IgM Deficiency is made if the serum IgM level is below 2 standard deviations of the mean for age-matched controls. Complete Selective IgM Deficiency is diagnosed with serum IgM levels less than 5mg/dl. A definitive diagnosis of Selective IgM Deficiency, especially in children, should only be established after months of follow-up. Finally, in order to confirm a diagnosis of primary Selective IgM Deficiency, other possible causes of IgM deficiency must be excluded, such as leukemia, lymphoma, and immune suppressive medications, such as Clozapine.

Prevalence and Inheritance

Inheritance of Selective IgM Deficiency is not known because family studies have not been done. Only a few families with Selective IgM Deficiency have been described. A prevalence of 3 in 10,000 for complete Selective IgM Deficiency, and 3 in 1,000 for partial Selective IgM Deficiency in adults has been reported. However, large-scale and several generation family studies are needed in order to determine the true inheritance and prevalence of Selective IgM Deficiency.

Treatment

Ideal treatment for Selective IgM Deficiency would be to replace IgM. However, no IgM-enriched immunoglobulin preparation is available in the U.S. Approximately one third of individuals with Selective IgM Deficiency who have recurrent infections also have impaired IgG antibody response to vaccines. In such cases, Ig replacement therapy has been used and found to be beneficial. Recommendations for treating infections are similar to SIgAD; however, prophylactic use of antibiotics in Selective IgM Deficiency is generally not recommended. Allergic and autoimmune diseases are generally treated in a similar manner as those diseases in people without a PI.

Expectations

In the majority of reported cases clinical presentation is mild; however, in some cases meningitis and sepsis have been reported. Therefore, it is difficult to predict long-term outcomes for individuals with Selective IgM Deficiency. Serious complications are rare. Although progression to other immunodeficiencies such as CVID have not been reported, long-term follow-up with individuals is still needed. Therefore, even people with mild symptoms should be followed every six months or annually, and assessed to determine if there has been a progression to another immunodeficiency, as well as for the development of any complications such as autoimmune diseases.

Adapted from: Chapter 4 Selective IgA Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 5
Hyper IgM Syndromes

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The Hyper-IgM Syndromes (HIGM) are rare inherited primary immunodeficiency diseases (PI) characterized by decreased blood levels of immunoglobulin G (IgG) and normal or elevated levels of IgM. Most individuals with HIGM are susceptible to recurrent and severe infections including opportunistic infections, which are infections by organisms that do not normally infect healthy individuals, and are susceptible to an increased risk of cancer. A number of different genetic defects can cause HIGM. The most common form is inherited as an X-linked disease affecting boys. The other forms of HIGM are inherited as autosomal recessive traits affecting both boys and girls. (See Inheritance Chapter.)

Overview

When B cells, which are the cells that make antibodies, develop, the first type of antibody they make is IgM. IgM is responsible for the immune system's initial response to an infection. Once healthy B cells make IgM, they can receive signals from T cells that tell them to switch from making IgM to IgG, IgA, or IgE depending on which type is needed to continue to fight infection. B cells from individuals with HIGM are unable to switch from the production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE type due to several different genetic defects in the signaling pathways between T cells and B cells. As a result, people with this disease have decreased levels of IgG, IgA, and IgE but normal or elevated levels of IgM in their blood. These different types of antibodies perform different functions and are all important in fighting infections. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) Since most individuals with HIGM are identified early and usually do not have elevated IgM levels, the name HIGM is not always accurate. Nevertheless, HIGM is used to denote that these diseases are characterized by the inability to switch antibody type--the B cells can only make IgM. Depending on the genetic defect causing HIGM, individuals may also be susceptible to opportunistic infections [such as *Pneumocystic jirovecii (carinii)*], cryptosporidium, certain forms of cancer, and autoimmune disease. Therefore, HIGM are severe immunodeficiency diseases and in the past have a guarded long-term outcome with few individuals surviving beyond the third or fourth decade of life. In recent years, hematopoietic stem cell transplantation (bone marrow, peripheral blood stem cells or umbilical cord blood stem cells) has been performed successfully in individuals with the X-linked form of XHIGM. (See Hematopoietic Stem Cell Transplantation Chapter.)

Immunobiology

People with HIGM have an inability to switch from the production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE types. As a result, individuals with this disease have absent or decreased levels of IgG, IgA, and IgE but normal or elevated levels of IgM in their blood. B cells, the cells that make antibodies, can produce IgM antibodies on their own, but they require interactive help from T cells in order to switch from IgM to IgG, IgA or IgE. HIGM syndromes result from a variety of genetic defects that affect this interaction between T cells and B cells, as well as cell signaling events that occur within B cells that are necessary for antibody switching.

The most common form of HIGM results from a defect or deficiency of a protein that is found on the surface of activated T cells. The affected protein is called CD40 ligand because it binds (ligates) to a protein on B cells called CD40. The interaction between CD40 and CD40 ligand signals the B cell to switch from production of IgM to other types of antibodies like IgG or IgA.

Some individuals with HIGM due to CD40 ligand deficiency have normal IgA levels, and the mechanism for this is not clear. It appears to occur via a CD40 ligand independent pathway. CD40 ligand is made by a gene on the X chromosome. Therefore, this form of PI is inherited as an X-linked recessive trait. X-linked recessive trait means that mothers can be carriers and boys are affected if they inherit the affected X chromosome from their mother. (See Inheritance Chapter.) CD40 ligand is also important for other functions carried out by T cells, so individuals with XHIGM have defective cellular immunity and thus are also susceptible to opportunistic infections and to some types of cancer.

Other forms of HIGM are inherited as autosomal recessive traits and have been observed in both girls and boys. (See Inheritance Chapter.) One of these forms results from a defect in CD40 and is clinically identical to XHIGM (the disease with the defect in CD40 ligand). Other autosomal recessive forms of HIGM result from defects in proteins that are involved in antibody class switching through the CD40 signaling pathway, these are known as Uracil-DNA glycosylase (UNG) deficiency and activation-induced cytidine deaminase (AID) deficiency. Autosomal recessive inherited genetic defects in two other proteins involved in antibody class switching, INO80 and MSH6 have also been seen in individuals with clinical HIGM.

The function of these genes is limited to antibody switching (after the B cell has received the signal to switch from the interaction of CD40 and CD40 ligand), so the other T cell functions of CD40 ligand are not affected and these patients are less likely to have opportunistic infections or cancer. Unlike individuals with defects in CD40 or CD40 ligand whose B cells cannot receive the signal to switch due to faulty communication with the T cells, B cells from individuals with defects in AID or UNG do receive an activating signal, and this may lead to the development of enlarged lymph nodes (where B cells and T cells are found). Individuals with AID or UNG defects may be more susceptible to develop autoimmune disease.

Finally, since switching antibody types in B cells involves breaks and subsequent repair in DNA, defects in genes that are important for DNA repair may also present with HIGM. The main features of these diseases are related to the defect in DNA repair, but some have immunoglobulin levels similar to HIGM. These diseases include Ataxia-Telangiectasia, Nijmegen breakage syndrome, and PMS2 deficiency.

Clinical Presentation

Most individuals with HIGM develop clinical symptoms during their first or second year of life. The most common problem in all forms of HIGM is an increased susceptibility to infection including recurrent upper and lower respiratory tract infections. The most frequent serious infective agents are bacteria, but viral illnesses are also more frequent and severe.

In people with XHIGM and autosomal recessive HIGM due to a CD40 defect, a variety of other microorganisms can also cause serious infections. For example, *Pneumocystis jiroveci (carinii)* pneumonia, an opportunistic infection, is relatively common during the first year of life, and its presence may be the first clue that a child has HIGM.

Gastrointestinal complaints, most commonly diarrhea and malabsorption, also occur commonly in XHIGM and CD40 deficiency. One of the major organisms causing gastrointestinal symptoms in XHIGM is Cryptosporidium. A Cryptosporidium infection may cause sclerosing cholangitis—a severe, often fatal, disease of the liver.

Approximately half of the individuals with XHIGM or CD40 deficiency develop neutropenia (low count of granulocyte white blood cells), either transiently or persistently. The cause of the neutropenia is unknown, although most individuals respond to treatment with colony stimulating factor, G-CSF. Severe neutropenia is often associated with oral ulcers, inflammation, ulceration of the rectum (proctitis), and skin infections.

Autoimmune disorders may also occur in individuals with HIGM especially in those with defects in AID or UNG. Autoimmune manifestations may include chronic arthritis, low platelet counts (thrombocytopenia), hemolytic anemia, hypothyroidism and kidney disease.

Enlargement of the lymph nodes and the spleen is seen frequently in those with autosomal recessive HIGM due to defects of AID or UNG. As a result, they often have enlarged tonsils and adenoids that may cause snoring and obstructive sleep apnea.

Finally, the risk for cancer, particularly liver cancer, is increased in individuals with XHIGM or CD40 deficiency. A few individuals with HIGM have developed a rapidly progressive neuroendocrine carcinoma.

Diagnosis

XHIGM should be considered in any boy presenting with severe recurrent respiratory infections or an opportunistic infection who has low or absent IgG and normal or elevated IgM levels with normal T cell and B cell numbers. The presence of neutropenia in addition to the above features increases the likelihood of having XHIGM.

Failure to express CD40 ligand on activated T cells is a characteristic finding. Some express a defective CD40 ligand protein that may be detected by the antibody used in the test (falsely normal test result) but will not bind to a soluble form of CD40. Confirming the diagnosis of XHIGM depends on the identification of a mutation affecting the CD40 ligand gene. Carriers of XHIGM can be identified by finding decreased expression of CD40 ligand on activated CD4 T-lymphocytes (on average 50% of the cells will be normal) and confirmed by genetic testing.

The autosomal recessive forms of HIGM can be suspected if an individual has the characteristics of XHIGM but is either a female or is a male who has a normal CD40 ligand gene with normal expression on activated T cells. The diagnosis of the different forms of autosomal recessive HIGM can also be confirmed by mutation analysis of the genes known to cause these disorders.

Inheritance

X-linked Hyper IgM (XHIGM) is inherited as an X-linked recessive disorder, and typically only boys are affected. In girls, all cells randomly inactivate one of the X chromosomes. Very rarely, female carriers of XHIGM (or NEMO) may have markedly skewed X chromosome inactivation such that most of their cells (>95%) have the X chromosome with the defective CD40 ligand gene active in their cells and may present with a milder form of the disease.

Since the autosomal recessive forms of HIGM require that the gene on both chromosomes be affected, by inheriting one mutation from each parent, they are less frequent than the X-linked conditions. The likelihood of having an autosomal recessive form of HIGM is increased if the parents are related prior to marriage.

If the precise mutation in the affected gene is known in a given family, it is possible to make a prenatal diagnosis or test family members to see if they are carriers of the mutation. Early diagnosis of any HIGM will allow initiation of treatment prior to the development of long-term consequences of serious infections.

Treatment

Since individuals with all forms of HIGM have a severe IgG deficiency, they require immunoglobulin (Ig) replacement therapy. The Ig replaces the missing IgG and often results in a reduction or normalization of the serum IgM level, if it was elevated. Ig replacement therapy can be given intravenously or subcutaneously. (See Immunoglobulin Therapy Chapter.)

Since individuals with XHIGM or CD40 deficiency also have a marked susceptibility to *Pneumocystis jiroveci (carinii)* pneumonia (PJP, or PCP), they should be started on prophylactic treatment with the antibiotic trimethoprim-sulfamethoxazole (orally) as soon as the diagnosis of XHIGM is made. Other drugs for PJP prophylaxis are available if the individual is allergic to sulfa drugs.

When present, neutropenia may also improve during Ig replacement therapy. Individuals with persistent neutropenia may also require granulocyte colony stimulating factor (G-CSF) therapy, especially if they have infections, mouth sores or other complications associated with the neutropenia. G-CSF treatment, however, is only necessary in select individuals and long-term treatment with G-CSF is usually not recommended.

Individuals with XHIGM or CD40 defects should not receive live virus vaccines since there is a remote possibility that the vaccine strain of the virus may cause disease. Bottled water should be used to avoid exposure to Cryptosporidium if using well water or water outside the U.S.

Individuals with XHIGM or CD40 deficiency have defects in T cell function in addition to their antibody deficiency, and treatment with Ig replacement therapy may not fully protect them against all infections and does not protect them from some opportunistic infections or cancer. Hematopoietic stem cell transplantation (bone marrow, peripheral blood stem cells, or cord blood stem cells) has been performed successfully in individuals with XHIGM. (See Hematopoietic Stem Cell Transplantation Chapter.) While a permanent resolution of the PI is anticipated after successful stem cell transplantation, the long-term prognosis for these individuals is not yet known. Earlier transplant is associated with improved survival.

Since individuals with autosomal recessive HIGM caused by mutations in AID or UNG only have defects of antibody production with no defect in T cell function, stem cell transplantation is not recommended at this time.

While gene therapy has been effective in treating some severe forms of PI, there are a number of issues that make it difficult for HIGM:

- The genetic defect in HIGM does not affect the development of T cells or B cells, and thus gene therapy will have to be very efficient to correct a sufficient percentage of stem cells.
- CD40 ligand is expressed only transiently on activated T cells, and thus gene therapy will have to mimic the regulation of expression of normal CD40 ligand, which remains a difficult task.
- Dysregulated expression of CD40 ligand is associated with autoimmune diseases and lymphoproliferation (increased numbers of lymphocytes with enlarged lymphoid tissues).

Gene therapy researchers are testing new approaches to correct the defect in the CD40 ligand gene in its location on the X chromosome in order to provide normally regulated expression of a normal CD40 ligand gene. Efficiency of correction in stem cells remains an obstacle currently.

Expectations

There is a broad range of severity seen amongst individuals with different genetic forms of HIGM. Those with defects primarily involving antibody switching can be effectively treated by Ig replacement therapy and can live long, productive lives. Those with associated defects in T cell activation characteristically have more significant immune deficits and may encounter additional problems including susceptibility to more dangerous types of infections as well as the development of cancer as further challenges. The experience with hematopoietic stem cell transplantation (HSCT) is encouraging for those with more severe diseases. A recent study looking at the outcome of individuals treated with HSCT as compared to those who were not did not show an overall decrease in mortality. When the data was examined over time, however, there was a trend for decreased mortality if the transplant was done more recently. In addition, those who had survived HSCT had a better quality of life and none had developed cancer at the time of the study. Further studies are needed to evaluate the long-term outcomes of HSCT.

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Chapter 6

IgG Subclass Deficiency and Specific Antibody Deficiency

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IgG Subclass Deficiency

*The main immunoglobulin (Ig) in human blood is IgG. This is the second most abundant circulating protein and contains long-term protective antibodies against many infectious agents. IgG is a combination of four slightly different types of immunoglobulin called IgG subclasses: IgG1, IgG2, IgG3 and IgG4. When one or more of these subclasses is persistently low and total IgG is normal, a subclass deficiency is present. IgG subclass deficiencies are clinically relevant **only** when the levels are absent or very low **and** when they are detected in people with recurrent upper and/or lower respiratory infections. In individuals without frequent or severe infections, low levels of IgG subclasses may be a clinically irrelevant finding. In the absence of infections, mild or moderately decreased subclass concentrations should not lead to unnecessary long-term use of immunoglobulin (Ig) replacement therapy. A subclass deficiency needs to be considered and looked for only under special circumstances discussed in this chapter.*

Definition

Most of the antibodies (also known as immunoglobulins) in the blood and the fluid that surround the tissues and cells of the body are of the IgG class. This class of antibodies is composed of four different subtypes designated IgG1, IgG2, IgG3, and IgG4. Each subclass is present in different concentrations in the blood and also varies with age. The IgG in the bloodstream is 60 to 70% IgG1, 20 to 30% IgG2, 5 to 8% IgG3, and 1 to 3% IgG4. IgG1 and IgG3 reach normal adult levels by 5 to 7 years of age; while IgG2 and IgG4 levels rise more slowly, reaching adult levels at about 10 years of age.

Each subclass serves predominantly (but not exclusively) a slightly different function in protecting the body against infection. For example, IgG1 and IgG3 subclasses play a role in protection against toxins from bacteria such as diphtheria and tetanus and also viral infections. In contrast, IgG2 predominantly aids in protection against the polysaccharide (complex sugar) capsule of certain disease-producing bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Individuals with IgG Subclass Deficiency are defined as having recurrent infections, persistently low levels of one or more IgG subclasses, and normal concentrations of total IgG, IgM, and IgA. IgG2 or IgG3 deficiencies are the most common IgG subclass deficiencies. Since IgG1 comprises 60% of the total IgG level, having a deficiency of IgG1 usually drops the total IgG level below the normal range, resulting in hypogammaglobulinemia. Because IgG4 does not reach adult levels until the age of 10 years, a diagnosis of IgG4 deficiency should not be made in young children. In addition, it may also be undetectable in the serum of many normal adult individuals, and therefore low IgG4 alone is insufficient evidence of an antibody deficiency disorder.

All individuals with IgG subclass deficiency require additional diagnostic evaluation. This evaluation must include the demonstration of a poor antibody response to vaccine challenge and careful documentation of recurrent infection. If these are **both** present, then the individual can be diagnosed with a clinically significant IgG subclass deficiency necessitating specific treatment.

Clinical Presentations

Most individuals with IgG Subclass Deficiency are completely asymptomatic. They may present, however, to a healthcare provider with recurrent ear and/or sinus infections; bronchitis and pneumonia may also have occurred. These infections are commonly caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, infections common in other people with antibody deficiencies. These types of infections are seen most commonly among those with IgG2 deficiency with or without IgG4 deficiency. Infections occurring in those with selective IgG subclass deficiency may not be as severe as infections in individuals with more significant antibody deficiencies, such as agammaglobulinemia or Common Variable Immune Deficiency (CVID). Individuals with IgG subclass deficiencies may have other types of invasive infections such as episodes of bacterial meningitis or infections of the bloodstream (sepsis), but these are extraordinarily rare. Frequent viral infections have been associated with IgG3 subclass deficiencies.

As in people with Selective IgA Deficiency, allergic diseases and autoimmune diseases are more common in those with IgG subclass deficiency.

Diagnosis

Measurement of IgG subclass levels is not universally recommended as part of the evaluation of antibody mediated immunity in individuals with recurrent or severe infections. Assessing IgG subclasses adds cost and may not add clinical value when total immunoglobulins and specific antibodies are measured. Most clinical immunologist do not obtain or measure IgG subclasses.

When IgG subclasses are measured, all four should be measured at the same time. An abnormal level should be confirmed at least one month after the first measurement. It is important to consider that IgG subclasses vary over time and among different laboratories. In addition, normal range values are usually defined as those values found in 95% of normal individuals of that person's age. This means that 2.5% of normal individuals will be considered deficient, and 2.5% of normal individuals will have values above that range. (See Laboratory Tests Chapter.)

Measurement of IgG subclasses can be recommended in the presence of known associated abnormalities, particularly if recurrent infections are also present. These circumstances include individuals with:

- Selective IgA Deficiency with recurrent infections to determine if there is an associated IgG2 and IgG4 subclass deficiency
- Wiskott-Aldrich Syndrome or Ataxia-Telangiectasia at the onset of recurrent infections
- Specific Antibody Deficiency with normal total immunoglobulins

Inheritance

No clear-cut pattern of inheritance has been observed in the IgG subclass deficiencies. Both males and females may be affected. Occasionally, two individuals with IgG subclass deficiency may be found in the same family. In some families, IgG subclass deficiencies have been found in some family members while other family members may have Selective IgA Deficiency or CVID. A partial gene deletion has been found in a few individuals with IgG subclass deficiency. Rarely individuals with complete absence of IgG2 due to deletion of the gene coding for its production have been described.

Treatment

The mainstay of treatment includes appropriate use of antibiotics to treat and to prevent infections. The type and severity of infection usually determines the type of antibiotic used and the length of treatment. Additional immunization with pneumococcal vaccines may also be used to enhance immunity. It is important to encourage patients to continue normal activities of daily living, such as school or work.

A trial (6 months) of immunoglobulin replacement therapy may be considered in patients with recurrent infections affecting quality of life, who have failed antibiotic therapy. (See Immunoglobulin Replacement Therapy Chapter.) At minimum, most insurers before they will approve Ig therapy will require documentation demonstrating failure of such conservative treatment in addition to persistently low IgG subclass levels and deficient antibody responses to vaccines. Children diagnosed with IgG subclass deficiency should be reevaluated with increasing age, as many appear to outgrow their IgG subclass deficiencies.

Expectations

The natural history of individuals with a clinically significant IgG subclass deficiency is not completely understood, but the outlook is generally good. Many children appear to outgrow their deficiency as they get older. For those with a persistent deficiency and impaired antibody responses, the use of prophylactic antibiotics and, in certain circumstances, the use of Ig replacement therapy may prevent serious infections and complications, such as impaired lung function, hearing loss, or injury to other organ systems.

Recent studies have shown that many children with a subclass deficiency in early childhood (younger than 5 years of age) develop normal subclass levels and the ability to make antibodies to polysaccharide vaccines as they get older. IgG subclass deficiencies, however, may persist in some children and adults. In some instances, a selective IgG subclass deficiency may evolve into a more serious antibody deficiency, such as Common Variable Immune Deficiency (CVID). (See Common Variable Immune Deficiency.) At this time, it is not possible to determine which individuals will have the transient type of subclass deficiency and which individuals may later evolve into a more significant immunodeficiency. For these reasons, regular reevaluation of immunoglobulin levels and function, as well as IgG subclass levels, is necessary.

Specific Antibody Deficiency

Among the five classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE, IgG has the predominant role in protection against infection. Some people have normal levels of immunoglobulins and all subclasses of IgG, but they do not produce sufficient specific IgG antibodies that protect them from some viruses and bacteria. People who produce normal immunoglobulin levels but who lack the ability to produce protective IgG antibodies against the types of organisms that cause upper and lower respiratory infections are said to have Specific Antibody Deficiency (SAD). SAD is sometimes termed partial antibody deficiency or impaired polysaccharide responsiveness.

Definition

Each individual IgG molecule is uniquely designed to protect against a specific pathogen. We call these molecules specific antibodies, and they are usually formed in response to natural exposure to bacteria and viruses, or through exposure to vaccines. Some of these antibodies can be measured in the laboratory, and these levels (or titers) are used to help diagnose problems with immunity.

Children less than 2 years of age often do not have a robust response to infections with bacteria such as *Streptococcus pneumoniae, Moraxella catarrhalis,* or *Haemophilus influenzae*. This is primarily due to an inability to make antibodies against the polysaccharide (sugar) coat that covers these bacteria. Children in this age group typically acquire protection against these microbes through the use of certain vaccines in which a protein is added to elicit an immunologic response (conjugate vaccines). Most children begin to naturally make stronger immune responses to these bacteria around 2 years of age, and they can then fight off these infections more effectively. Children and adults who fail to develop the immune response to the polysaccharide coating on bacteria (and therefore lack protection to these microbes) but who otherwise have normal antibody levels are diagnosed with having SAD.

Specific IgG antibodies are important in fighting off infections; however, other components of our immune system also work to eradicate bacteria and viruses. T cells, complement proteins, IgM and IgA antibodies (to name a few) are parts of our immune system that work together during a complete immune response. If these other components work well, some individuals with low specific antibody levels may rarely get sick. Antibodies of certain IgG

subclasses interact readily with the complement system, while others interact poorly, if at all, with the complement proteins. Thus, an inability to produce antibodies of a specific subclass or mild deficiencies of other arms of the immune system may render the individual susceptible to certain kinds of infections but not others. These factors must be taken into account before an individual's immune system is considered to be abnormal, either by virtue of having a low IgG subclass level or an inability to make a specific type of antibody.

Clinical Presentation

Recurrent ear infections, sinusitis, bronchitis, and pneumonia are the most frequently observed illnesses in people with SAD. Some individuals will show an increased frequency of infection beginning in the first years of life. In others, the onset of infections may occur later. In general, the infections in individuals with SAD are not as severe as those who have combined deficiencies of IgG, IgA, and IgM, like X-linked Agammaglobulinemia (XLA) or CVID. Some, however, may present with a single severe pneumonia or other infection at the time of diagnosis.

Diagnosis

Problems with specific antibody production may be suspected in children and adults who have a history of recurrent infections of the ears, sinuses, bronchi, and/or lungs. The recommended evaluation usually includes measurement of total immunoglobulins, and antibody levels to specific bacteria such as tetanus, diphtheria, and/or *Streptococcus pneumoniae*. When total immunoglobulins are low, a more profound immunodeficiency may be present. If isolated low antibody levels to *Streptococcus pneumoniae* are found during the initial evaluation, a Pneumococcal vaccine (Pneumovax) is administered and follow-up levels are measured. Individuals older than 1 year of age may be immunized with the pneumococcal polysaccharide vaccine (Pneumovax 23 or Pnu-immune 23). These vaccines have the ability to induce protective levels to 23 strains (serotypes) of *Streptococcus pneumoniae*. Antibody levels are measured again four to six weeks later to determine if adequate protective antibody levels were produced. It is felt that normal individuals respond to a majority of the serotypes in these vaccines and retain those protective levels for years after receiving them. Antibody responses may not last as long in young children. For therapy, it is also possible to re-immunize with Prevnar 13, a conjugate type of pneumococcal vaccine, which, for most, may be more immunogenic than Pneumovax. This vaccine, however, cannot be used to diagnose SAD.

A classification for mild, moderate, and severe forms of SAD exists which factors in the individual's age and number of normal post-immunization serotypes to define immunologic severity. Responses in which children respond to less than 50% of serotypes and adults respond to <70% have a moderate form of SAD with an increased risk of upper/lower respiratory tract infections that may warrant treatment. In the experience of many clinical immunologists, however, a normal vaccine response for an individual consists of producing protective titers of antibodies to at least 50% of the serotypes present in the vaccine. Furthermore, there are individuals who may fall into a response zone between 50 to 70% that have significant infections that may warrant a trial of replacement Ig therapy.

An additional subset of people are defined as having a memory phenotype meaning they respond normally initially and subsequently lose protective levels within 6 months.

When interpreting pneumococcal levels, it is important to recognize the variability in testing methodology and subsequent results that may occur among different labs. This highlights the importance of utilizing a detailed clinical history in addition to laboratory findings to guide the immunologic evaluation when considering a diagnosis of SAD.

Inheritance

No clear-cut pattern of inheritance has been observed with SAD.

Treatment

Individuals with SAD frequently have recurrent or chronic infections of the ears, sinuses, bronchi and lungs. Treatment of these infections usually requires antibiotics. One goal of treatment is to prevent permanent damage to the ears and lungs that might result in hearing loss or chronic lung disease with scarring. Another goal is to maintain individuals with SAD as symptom-free as possible so that they may pursue the activities of daily living such as school or work. Sometimes antibiotics may be used for prevention (prophylaxis) of infections.

As in IgG subclass deficiency, the use of Ig replacement therapy for SAD is not as clear-cut as it is for those with XLA or CVID. For individuals

with SAD in whom infections and symptoms can be controlled with antibiotics, Ig replacement therapy is usually not necessary. However, for those with more severe clinical phenotypes whose infections cannot be readily controlled with antibiotics or who have more frequent and severe infections, Ig replacement therapy may be considered.

Since many young children appear to outgrow SAD as they get older, it is important to reevaluate them to determine if the deficiency is still present. If Ig replacement therapy has been previously initiated, reevaluation after a period of time is recommended with discontinuation of Ig therapy for 4 to 6 months before repeat immune testing, and re-immunization with pneumococcal vaccines (if needed) is performed. If the response to vaccination is adequate, Ig replacement therapy may be discontinued and the individual observed. It is reasonable to reevaluate antibody levels periodically to document retention of protective antibody levels. If the diagnosis of SAD is made in teenagers or adults, resolution of the deficiency is less likely.

Expectations

The outlook for individuals with SAD is generally good. Many children appear to outgrow their deficiency as they get older, usually by age 6. For those for whom the deficiency persists, the use of prophylactic antibiotics and, in certain circumstances, the use of Ig therapy may prevent serious infections and the development of impaired lung function, hearing loss or injury to other organ systems.

The natural history of individuals with SAD is not completely understood. SAD seems to occur more often in children, probably due to a delay in the natural maturation of the immune response. Children may outgrow SAD over time. Adults with similar symptoms and poor response to vaccination are less likely to improve over time. Similar to IgG subclass deficiencies, SAD may evolve into CVID. (See Common Variable Immune Deficiency Chapter.) At the present time, it is not possible to determine which individuals will have the transient type of deficiency and in which individuals the deficiency may be permanent or the forerunner of a more wide-ranging immunodeficiency, such as CVID. For these reasons, periodic reevaluation of immunoglobulin levels and specific antibody levels is necessary.

Adapted from: Chapter 5 IgG Subclass Deficiency and Chapter 6 Specific Antibody Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 7

Transient Hypogammaglobulinemia of Infancy

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Immunoglobulin or Ig, also known as gamma globulin or immune globulin, refers to the liquid plasma component of blood that contains immunoglobulins or antibodies. These antibodies have the important role in the immune system of neutralizing bacteria and viruses, and enhancing the phagocytosis and destruction of bacteria, certain viruses, and other pathogens.

When antibody molecules recognize a microorganism as foreign, they physically attach to it and set off a complex chain of events involving other components of the immune system that work to eventually destroy the infection. Antibodies vary with respect to their specialized functions in the body. These variations are determined by the antibody's chemical structure, which in turn determines the class of the antibody (or immunoglobulin). There are five major classes of antibodies (IgG, IgA, IgM, IgD and IgE). IgG has four different subclasses (IgG1, IgG2, IgG3, IgG4). IgA has two subclasses (IgA1 and IgA2).

Overview

Newborn babies are unable to make their own IgG. Instead, babies rely on the IgG that passes through the placenta to them from their mother during the last three months of pregnancy. This IgG is important in protecting babies against infections. The other immunoglobulins, IgA, IgM, and IgE, do not cross the placenta. When IgG levels are checked in a newborn, the levels reflect the IgG received from the mother. Babies born early, or prematurely, have less time to receive IgG from their mothers, so they may have lower IgG levels. Gradually, the baby's humoral immune system matures and begins to make its own IgG. Sometimes it takes longer than expected for children to make their own sufficient levels of IgG. This is called Transient Hypogammaglobulinemia of Infancy (THI).

All babies have a period of physiologic low IgG, or hypogammaglobulinemia, when the levels of the mother's IgG are decreasing and the baby's production of IgG is increasing. This generally occurs when babies are 3 to 6 months of age and may be more pronounced in premature infants. When low IgG levels persist past 6 months of age, THI may be suspected. It has been estimated that as many as one in 1,000 children have THI. The true frequency of THI is unknown because immunoglobulins are not routinely checked in healthy children. For this reason, THI may be underdiagnosed. THI has been reported around the world. Both males and females are affected, though males appear to be more frequently affected, about twice as often as females.

Cause

The cause of THI is unknown, but it is thought to be due to B cells (the cells that make antibodies) taking longer to mature than normal.

Clinical Features

Some children with THI have no symptoms at all while others have recurrent infections beginning in infancy. Asymptomatic children with THI may come to medical attention due to a family history of immune system problems. In children with symptoms, recurrent upper respiratory tract infections are commonly seen, especially ear infections. Lower respiratory tract infections, such as bronchitis and pneumonia, can also occur. More severe infections affecting the bloodstream, brain, and gastrointestinal (GI) tract have been reported but are rare. If severe infections occur, it is important to consider other types of immunodeficiency as a possible cause. Infections in children with THI usually start to improve by age 2. Most children with THI have normal growth and development.

Diagnosis

While THI may be suspected in an infant, the diagnosis can only be made once IgG levels have normalized, showing that the low level was temporary. In other words, THI can only be officially diagnosed looking back over time.

The criteria for diagnosing THI includes an IgG level that is found to be lower than 95% of children of similar age (two standard deviations below the average level or lower) when measured on at least two separate occasions. The other immunoglobulins including IgA and IgM might be normal or low in infants with THI. Other immunodeficiencies must be ruled out prior to making the diagnosis. When the IgG is very low, or when all immunoglobulins are low, an alternate diagnosis may be suspected. There are no specific findings on physical examination that help make the diagnosis of THI.

The evaluation should include checking antibody levels (titers) to things against which the child has been previously vaccinated, such as tetanus and pneumococcal vaccine. Most children with THI are able to make antibodies to vaccines. However, if vaccine titers are low, a booster dose of the vaccine may be given and measurement of the antibody levels repeated after four to six weeks, to evaluate the immune response. Immune memory may be evaluated by rechecking the vaccine antibody levels again in six months. If a child does not make antibodies to vaccines, consultation with an immunologist is indicated.

A complete blood count to check the numbers of white blood cells, especially the lymphocytes, is important in the work-up of THI. If lymphopenia, a low number or percent of lymphocytes, is present along with low IgG levels, additional studies will be necessary and consultation with an immunologist is warranted. This is because low lymphocyte numbers are not typically seen in THI and may be a sign of another type of PI. Additional reasons for consultation with an immunologist are severe or persistent infections, unusual infections, poor growth, chronic diarrhea, or IgG levels that do not improve over time.

It is important to rule out other causes of low IgG during the evaluation, including B cell defects (such as X-linked Agammaglobulinemia) and combined T and B cell defects (such as Severe Combined Immunodeficiency). In addition, it is important to rule out loss of IgG as a possible cause of a low IgG level. In THI, the IgG is low because the infant has trouble making IgG, a production problem. In contrast, some infants make normal levels of IgG but quickly lose it, such as those infants with some gastrointestinal, heart, or kidney diseases.

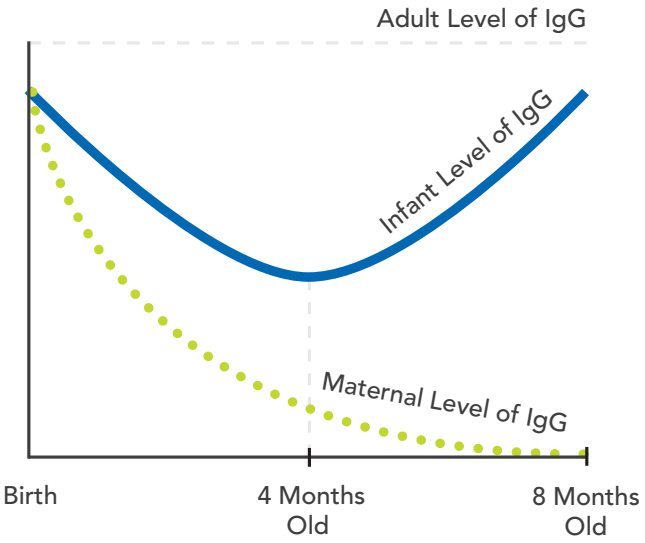
Treatment

Asymptomatic children with THI do not require treatment, but they still require monitoring until it is demonstrated that the IgG level is normal and the child can make and maintain protective responses to vaccinations. For children with symptoms, the goal of treatment is to prevent infection. It is important to adhere to good hand hygiene and limit sick contacts to reduce the risk for infection transmission.

In children who have frequent or severe bacterial infections, antibiotics are sometimes given prophylactically for prevention. Rarely, in those with recurrent or severe infections who continue to have infections even while receiving antibiotic prophylaxis, IgG replacement has been selectively used. Based on studies, it does not appear that using IgG replacement prolongs the natural course of THI, but it is important to note it will delay further work-up. This is because when immunoglobulins and specific antibody levels are measured in someone receiving immunoglobulin replacement therapy, the IgG and antibody response levels measured reflect the amount of antibody in the Ig product as well as that the child's immune system is

making. A period off IgG replacement for 4-6 months is necessary before the child's own immunoglobulin levels and vaccine titers can be checked accurately. Generally this assessment off of Ig replacement is done during the spring and summer months, after the flu and respiratory virus season. However the vast majority of children with THI do not require Ig replacement therapy.

Figure 7:1: Immunoglobulin G (IgG) Levels



Expectations

Children who have low IgG levels should be closely followed, because low IgG can increase the risk for infections. Monitoring includes checking immunoglobulin and specific antibody levels, tracking growth, and evaluating for other possible causes of low IgG. The expectation is that IgG levels will normalize between 2 to 5 years of age.

If monitoring reveals persistently low immunoglobulin levels and/or low responses to vaccines, a different diagnosis should be considered. Some children initially suspected to have THI are later diagnosed with another antibody disorder such as Common Variable Immune Deficiency or Specific Antibody Deficiency when their THI does not resolve. Careful monitoring is important for this reason.

Until it is demonstrated that the child has normal humoral immune function, live viral vaccines (Varivax®) should be held. If a child has an impaired response to these vaccines, it is possible to contract the illness after vaccination.

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Chapter 8

Classic Severe Combined Immunodeficiency

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Overview

Severe Combined Immunodeficiency (SCID, pronounced "skid") is a serious primary immunodeficiency disease (PI) in which there is combined absence of T lymphocyte and B lymphocyte function. SCID is fatal without a stem cell transplant or corrective gene therapy. There are at least 13 different genetic defects that can cause SCID. These defects lead to extreme susceptibility to very serious infections. This condition is generally considered to be one of the most serious forms of PI. Fortunately, effective treatments, such as hematopoietic stem cell transplantation (bone marrow transplant), exist that can treat the disorder, and the future holds the promise of gene therapy for some types.

Definition

SCID is a rare and fatal syndrome of diverse genetic causes in which there is combined absence of T lymphocyte and B lymphocyte function and in many cases also natural killer (NK) lymphocyte function. These defects lead to extreme susceptibility to serious infections. There are currently at least thirteen different genes that, when mutated (changed), cause SCID. Although they vary with respect to the genetic type that causes the immunodeficiency, some of their laboratory findings and their pattern of inheritance, these infants all have an absence of T cells and severe deficiencies in both T cell and B cell function. Recently, leaky or atypical (hypomorphic) SCID was described. In these patients, there are low numbers of T cells with reduced but not absent function. While these patients can be diagnosed in infancy, particularly if SCID newborn screening is available, many are diagnosed later in life.

Deficiency of the Common Gamma Chain of the T Cell Receptor

The most common form of SCID, affecting nearly 30% of all cases, is due to a mutation in a gene on the X chromosome that encodes a component (or chain) called IL2RG shared by the T cell growth factor receptor and other growth factor receptors. This component is referred to as the common gamma chain (γc). Changes in this gene result in very low T lymphocyte and NK lymphocyte numbers, but the B lymphocyte count is normal or high (a so-called T-, B+, NK- phenotype). Despite the presence of B lymphocytes, there is no B lymphocyte function, since the B cells have abnormal receptors for growth factors on their cell surfaces. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) This deficiency is inherited as an X-linked recessive trait. (See Inheritance Chapter.) Only males have this type of SCID, but females may carry the gene and have a 1 in 2 chance (50%) of passing it on to each son as well as a 1 in 2 chance of passing the carrier state on to each daughter.

Deficiency of Recombinase Activating Gene 1 and 2

With the advent of newborn screening, improved access to genetic testing and recognition of leaky SCID as a clinical entity, there has been increased diagnosis of SCID caused by autosomal recessive mutations in Recombinase Activating Gene 1 and 2 (RAG1 and RAG2). RAG1 and RAG2 are enzymes critical to development of T and B cells, but not NK cells. Babies with this type of SCID will present with low or absent T and B cells, but typically have normal or high NK cells. RAG1 and RAG2 mutations are seen in 40% of those with leaky SCID and about 19% of those with SCID overall. Both boys and girls can be affected.

Adenosine Deaminase Deficiency

Another common type of SCID is caused by mutations in a gene that encodes an enzyme called adenosine deaminase (ADA). ADA is essential for the metabolic function of a variety of body cells but especially T cells. The absence of this enzyme leads to an accumulation of toxic metabolic by-products within lymphocytes that cause the cells to die. ADA deficiency is the second most common cause of SCID, accounting for about 15% of cases. Babies with this type of SCID can have the lowest total lymphocyte counts of all because T, B, and NK lymphocyte counts are all very low. This form of SCID is inherited as an autosomal recessive trait. (See Inheritance Chapter.) Both boys and girls can be affected.

Deficiency of the Alpha Chain of the IL-7 Receptor

Another form of SCID is due to mutations in a gene on chromosome 5 that encodes another growth factor receptor component, the alpha chain of the IL-7 receptor (IL-7Rα). Infants with this type of SCID have B and NK cells, but no T cells. However, the B cells don't work because of the lack of T cells. The B cells and NK cells are intrinsically normal; however, so after T cell reconstitution through transplantation, the function of all cell lineages is normal. IL-7Rα deficiency accounts for less than 10% of SCID cases. It is inherited as an autosomal recessive trait. (See Inheritance Chapter.) Both boys and girls can be affected.

Deficiency of Janus Kinase 3

Another type of SCID is caused by a mutation in a gene on chromosome 19 that encodes an enzyme found in lymphocytes called Janus kinase 3 (Jak3). This enzyme is necessary for function of the above-mentioned common gamma chain (γc). Infants with this type look very similar to those with X-linked SCID, so they are T-, B+, NK-. However, since this form of SCID is inherited as an autosomal recessive trait, both boys and girls can be affected. (See Inheritance Chapter.) Jak3 deficiency accounts for less than 10% of cases of SCID.

Deficiencies of CD3 Chains

Three other forms of SCID are due to mutations in the genes that encode three of the individual protein chains that make up another component of the T cell receptor complex, CD3. These SCID-causing gene mutations result in deficiencies of CD3Aσ, ε or ζ chains (CD3 delta, epsilon or zeta). These deficiencies are also inherited as autosomal recessive traits and account for less than 5% of individuals with SCID. Both boys and girls can be affected.

Deficiency of Artemis and Other Radiosensitive Forms of SCID

There are a group of other autosomal recessively inherited forms of SCID associated with a lack of T and B cells, but presence of NK cells as well as sensitivity to ionizing radiation. These are due to mutations in genes necessary for DNA repair, including DCLRE1C (encoding the ARTEMIS protein), PRKEDC, NHEJ1, and LIG4. In addition to radio sensitivity and absence of T and B cells, individuals with PRKEDC, NHEJ1, and LIG4 commonly exhibit microcephaly, when the brain does not develop properly resulting in a smaller than normal head. The radiosensitive forms of SCID comprise less than 5% of those with SCID, but they require special consideration in selection of conditioning agents to minimize the risk of late effects.

Other Causes of SCID

There are several other genetic defects associated with autosomal recessive inheritance of SCID, including mutations in the genes that encode CD45, Coronin 1A, and LAT. In a recent study, in about 6-10% of individuals with SCID, there was not an identifiable genetic defect to explain their clinical and laboratory features.

Clinical Presentation

The presentation of SCID is changing rapidly in the U.S. because of the introduction of nationwide newborn screening for SCID using the detection of T cell receptor excision circles (TREC) to identify infants at risk before the onset of infections. This allows for earlier intervention and improved survival. Infants with SCID have no outward physical findings to distinguish them from normal newborns and are usually clinically well until the onset of infections. For those not detected by newborn screening, an excessive number of infections is the most common presenting symptom of infants with typical SCID. These infections are not usually the same sorts of infections that normal children have, such as frequent colds. The infections of the infant with SCID can be much more serious and even life threatening, and they may include pneumonia, severe viral respiratory

infections, meningitis, and/or bloodstream infections. The widespread use of antibiotics, even for minimal infections, has changed the pattern of presentation of SCID, so the doctor seeing the infant must have a high index of suspicion in order to detect this condition.

Infants with SCID are susceptible to routine infections seen in healthy babies, but they are also at increased risk for infections caused by organisms or live vaccines which are usually not harmful in children with normal immunity. Among the most dangerous is an organism called *Pneumocystis jiroveci* that can cause a rapidly fatal pneumonia (PJP) if not diagnosed and treated promptly. Another very dangerous organism is the chickenpox virus (varicella). Although chickenpox is annoying and causes much discomfort in healthy children, it usually is limited to the skin and mucous membranes and resolves in a matter of days. In the infant with SCID, chickenpox can be fatal because it doesn't resolve and can then infect the lungs, liver, and brain. Cytomegalovirus (CMV), which nearly all of us carry in our salivary glands, may cause fatal pneumonia in infants with SCID. Other dangerous viruses for infants with SCID are the cold sore virus (Herpes simplex), adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza 3, Epstein-Barr virus (EBV or the infectious mononucleosis virus), polioviruses, the measles virus (rubeola), and rotavirus.

Since vaccines that infants receive for chickenpox, measles and rotavirus are live virus vaccines, infants with SCID can contract infections from those viruses through these immunizations. If the newborn screen for SCID is abnormal or it is known that someone in the family has had SCID in the past, or currently has SCID, these vaccines should not be given to new babies born into the family until SCID has been ruled out in those babies. This is especially a problem for the rotavirus vaccine, which is routinely given when babies are 6 to 8 weeks old, and the baby with SCID may not have had any infections by that time, so would not be diagnosed except by newborn screening.

Fungal (yeast) infections may be very difficult to treat. As an example, candida infections of the mouth (thrush) are common in most babies but usually disappear spontaneously or with oral medication. In contrast, for the child with SCID, oral thrush may improve, but it either doesn't go completely away or recurs as soon as the medication is stopped. The diaper area may also be involved. Occasionally, candida pneumonia, abscesses, esophageal infection or even meningitis may develop in infants with SCID.

Persistent diarrhea resulting in failure to thrive is a common problem in children with SCID. It can lead to severe weight loss and malnutrition. Diarrhea may be caused by the same bacteria, viruses or parasites that affect normal children. However, in the case of SCID, the organisms are very difficult to get rid of once they become established.

The skin may be involved in children with SCID. The skin may become chronically infected with the same fungus (candida) that infects the mouth and causes thrush. Infants with SCID may also have a rash that is mistakenly diagnosed as eczema, but it is actually caused by a reaction of the mother's T cells (that entered the SCID baby's circulation before birth) against the baby's tissues. This reaction is called graft-versus-host disease (GVHD) due to maternal engraftment.

In individuals with leaky SCID, the clinical presentation may be later in life, if they are not diagnosed due to an abnormal newborn screen. In these individuals, the symptoms can be highly variable signs and symptoms of combined immunodeficiency, with autoimmunity and invasive granulomatous lesions being common as the individual ages.

Diagnosis

The diagnosis of SCID currently and in the future is most likely going to be made after an abnormal newborn screen and while the newborn is clinically well. If newborn screening is not available, SCID is usually first suspected because of the above clinical features. In some instances, there has been a previous child with SCID in the family, and this positive family history may prompt the diagnosis even before the child develops any symptoms. One of the easiest ways to diagnose this condition is to count the peripheral blood lymphocytes in the child (or those in the cord blood). This is done by two tests; the complete blood count and the manual differential (or a count of the percentage of each *different* type of white cell in the blood), from which the doctor can calculate the absolute lymphocyte count (or total number of lymphocytes in the blood). There are usually more than 4,000 lymphocytes (per cubic millimeter) in normal infant blood in the first few months of life, 70% of which are T cells. Since infants with SCID have no T cells, they usually have many fewer lymphocytes than this. The average for all types of SCID is around 1,500 lymphocytes (per cubic millimeter). If a low lymphocyte count is found, this should be confirmed by repeating the test once

more. If the count is still low, then tests that count T cells and measure T cell function should be done promptly to confirm or exclude the diagnosis.

The different types of lymphocytes can be identified with special stains and counted in a technique called flow cytometry. In this way, the number of total T lymphocytes (including new T cells that have markers indicating they are made in the baby's thymus), helper T lymphocytes, killer T lymphocytes, B lymphocytes and NK lymphocytes can be counted. Since there are other conditions that can result in lower than normal numbers of the different types of lymphocytes, the most important tests are those that detect new T cells that have just come out of the baby's thymus and tests of T cell function. The most definitive test to examine the function of the lymphocytes is to place blood lymphocytes in culture tubes, treat them with various stimulants and then, incubate them for several days. Normal T lymphocytes react to these stimulants by undergoing cell division. In contrast, lymphocytes from individuals with SCID do not react to these stimuli.

Since IgG from the mother passes into the baby's blood through the placenta, it will be present in the newborn's and young infant's blood at nearly normal levels. Therefore, IgG deficiency may not be present for several months until the transferred maternal IgG has been metabolized away. However, other immunoglobulin levels (IgA and IgM) are usually very low in SCID. IgE may be elevated, particularly in those with leaky SCID.

The diagnosis of SCID can also be made in utero (before the baby is born) if there has been a previously affected infant in the family and if the molecular defect has been identified. If genetic analysis had been completed on the previously affected infant, a diagnosis can be determined for the conceptus (an embryo or fetus with surrounding tissues). This can be done by molecular testing of cells from a chorionic villous sampling (CVS) or from an amniocentesis, where a small amount of fluid (that contains fetal cells) is removed from the uterine cavity. Even if the molecular abnormality has not been fully characterized in the family, there are tests that can rule out certain defects. For example, adenosine deaminase deficiency can be ruled in or out by enzyme analyses on the above-mentioned CVS or amnion cells. If there is documentation that the form of SCID is inherited as an X-linked recessive trait and the conceptus is a female, she would not be affected.

Early diagnosis, before the infant has had a chance to develop any infections, is extremely valuable since bone marrow transplants given in the first three and a half months of life have a 96% success rate prior to the onset of infection. As noted earlier, screening of all newborns to detect SCID soon after birth is possible through the use of TREC based newborn screening. As of 2018, all babies born in the U.S. are now being screened for this condition.

Inheritance

All types of SCID are due to genetic defects. These defects can be inherited from the parents or can be due to new mutations that arise in the affected infant. As already noted, the defect can be inherited either as an X-linked (sex-linked) defect where the gene is inherited from the mother or as one of multiple types of autosomal recessive defects (see previous section on the causes SCID) where both parents carry a defective gene. See Inheritance Chapter to more fully understand how autosomal recessive and sex-linked recessive diseases are inherited, the risks for having other children with the disease, and how these patterns of inheritance affect other family members. Parents of children with SCID should seek genetic counseling so that they are aware of the risks for future pregnancies.

It should be emphasized that there is no right or wrong decision about having more children. The decision must be made in light of the special factors involved in the family structure; the basic philosophy of the parents; their religious beliefs and background; their perception of the impact of the illness upon their lives; and the lives of all the members of the family. There are countless factors that may be different for each family.

General Treatment

Infants with this life-threatening condition need all the support and love that parents can provide. They may have to tolerate repeated hospitalizations that, in turn, may be associated with painful procedures. Parents need to call upon all of their inner resources to learn to handle the anxiety and stress of this devastating problem. They must have well-defined and useful coping mechanisms and support groups. The demands on the time and energies of the parents caring for someone with SCID can be overwhelming. If there are siblings, parents must remember that they need to share their love and care with them. Parents also need to spend energy in maintaining their own relationship with

each other. Family counseling may be necessary to keep relationships together, even with a successful therapeutic outcome for the child with SCID.

The infant with SCID needs to be isolated, especially from young children. If there are siblings who attend daycare, religious school, kindergarten, or grade school, the possibility of bringing infections, particularly those of viral origin, into the home represents the greatest danger. Cytomegalovirus (CMV), is currently the most common viral illness seen in newborns with SCID. This infection can lead to devastating long-term complications such as chronic lung disease and neurologic impairment, particularly blindness. It is for this reason that screening of mothers for serologic positivity to CMV is commonly done prior to allowing the child to breastfeed by many but not all immunology and transplant centers.

The infant with SCID should not be taken to public places, such as group child care settings, stores, doctors' offices, etc., where they are likely to be exposed to other young children who could be harboring infectious agents. Contact with relatives should also be limited, especially those with young children. Neither elaborate isolation procedures nor the wearing of masks or gowns by the parents is necessary at home. Frequent hand-washing is essential, however.

Although no special diets are helpful, nutrition is nevertheless very important. In some instances, the child with SCID cannot absorb food normally, which in turn can lead to poor nutrition. As a result, in some instances the child may need continuous intravenous feedings to maintain normal nutrition. Sick children generally have poor appetites, so maintaining good nutrition may not be possible in the usual fashion. (See General Care Chapter.)

Death from infection with *Pneumocystis jiroveci*, a widespread organism which rarely causes infection in normal individuals but causes pneumonia in individuals with SCID, used to be a common occurrence in this syndrome. This type of infection has become less common with early diagnosis and prophylactic treatment with trimethoprim-sulfamethoxazole. All infants with SCID should receive this preventive treatment until their T cell defect has been corrected.

LIVE VIRUS VACCINES AND NON-IRRADIATED BLOOD OR PLATELET TRANSFUSIONS ARE DANGEROUS. If you or your healthcare provider suspect that your child has a serious immunodeficiency, you should not allow rotavirus, chickenpox, mumps, measles, **live** virus polio, or BCG vaccinations to be given to your child until their immune status has been evaluated. As mentioned above, the child's siblings should not receive the rotavirus vaccine. If viruses in the other live virus vaccines are given to the child's siblings, they are not likely to be shed or transmitted from the sibling to the patient. The exception to this could be the chickenpox vaccine if the sibling develops a rash with blisters around the vaccine site.

If your infant with SCID needs to have a blood or platelet transfusion, your infant should always get irradiated (CMV-negative, leukocyte-depleted) blood or platelets. This precaution is necessary in order to prevent fatal GVHD from T cells in blood products and to prevent your infant from contracting an infection with CMV.

Specific Therapy

Immunoglobulin (Ig) replacement therapy, given either intravenously or subcutaneously, should be given to infants with SCID when they are diagnosed and continued on an ongoing basis until they have been transplanted and demonstrate recovery of B cell function. Even after transplantation, individuals with SCID who do not develop B cell function will need to continue to receive this indefinitely. Although Ig replacement therapy will not restore the function of the deficient T cells, it does replace the missing antibodies resulting from the B cell defect and is, therefore, of benefit.

For individuals with SCID due to ADA deficiency, enzyme replacement therapy (elapegademase-lvlr) has been used with some success, particularly as a bridge or temporary treatment before transplant or gene therapy. The immune reconstitution effected by enzyme replacement therapy is not as good as with a transplant or gene therapy and is not a permanent cure; it requires regular injections for the rest of the child’s life.

Currently, the most successful therapy for SCID is immune reconstitution by hematopoietic stem cell transplantation (HSCT). HSCT for SCID is best performed at medical centers that have had experience with SCID and its optimal treatment, and where there are pediatric immunologists overseeing the transplant. In a HSCT, bone marrow cells, peripheral stem cells, or umbilical cord stem cells from a normal healthy donor are given to the individual with SCID to replace the defective lymphocytes of their immune system with the normal cells of the donor's immune system. The goal of

transplantation in SCID is to correct the immune dysfunction. This contrasts with transplantation in people with cancer, where the goal is to eradicate the cancer cells and drugs suppressing the immune system are used heavily in that type of transplant.

The ideal donor for an infant with SCID is a perfectly HLA-type matched normal brother or sister. Lacking that, techniques have been developed over the past four decades that permit good success with matched unrelated donors or half-matched related donors (such as a mother or a father). Several hundred marrow transplants have been performed in infants with SCID over the past 30 years, with an overall survival rate of 70% at 10 years from HSCT. However, the outcomes are better if the donor is a matched sibling (>94% success rate) and if the transplant can be performed soon after birth or less than three and a half months of life. There is controversy in the field regarding the use of pre-transplant chemotherapy based conditioning, and there does not appear to be an impact on survival with the use of conditioning. However, the use of conditioning does appear to be associated with improved immune function, particularly recovery of B cell function in certain genetic forms of SCID. The decisions regarding donor source and conditioning regimen choices should be discussed with the immunologist and the transplant team at the center to decide the best available treatment option for a particular person with SCID.

There does not appear to be any advantage to *in utero* marrow stem cell transplantation over transplantation performed immediately after birth.

Finally, another type of treatment that has been explored over the past three decades is gene therapy. There have been successful cases of gene therapy in both X-linked and ADA-deficient SCID leading to correction of the immunodeficiency. Unfortunately, in one of the clinical trials for X-linked SCID, there was a high rate of later development of blood born cancers in the treated individuals. This has led to the development of safer ways to administer gene therapy. Gene therapy for ADA SCID has been commercially available in Europe as Strimvelis since 2016. This gene therapy product has demonstrated similar efficacy to non-sibling donor HSCT. There are currently clinical trials underway to explore new gene therapy options for x-linked (IL2RG) and ARTEMIS forms of SCID. One cannot perform gene therapy, however, unless the abnormal gene is known; hence the importance of making a specific molecular diagnosis.

Expectations

SCID is generally considered to be one of the most serious forms of PI. Without a successful HSCT, enzyme replacement therapy, and/or gene therapy, the individual with SCID is at constant risk for a severe or fatal infection. With a successful HSCT, the individual's own defective immune system is replaced with a normal immune system, and normal T lymphocyte function is restored. The first bone marrow transplantation for SCID was performed in 1968. That patient is alive and well today!

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Chapter 9

Combined Immune Deficiency

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Combined Immune Deficiencies (CID) are a group of primary immunodeficiency diseases (PI) in which both the T lymphocytes and B lymphocytes of the adaptive immune system function poorly. There are many different genetic defects that can cause CID. These defects lead to moderate to severe susceptibility to infections, and they can sometimes also cause inflammatory disease or autoimmune manifestations due to immune dysregulation. Preventative treatments such as immunoglobulin (Ig) replacement therapy and prophylactic antibiotics can be helpful, and immunosuppressive and anti-inflammatory drugs may be needed to control immune dysregulation. However, several forms of CID require definitive therapy with hematopoietic stem cell transplantation (HSCT).

Definition

CID is a group of rare genetic disorders of the immune system that results in impaired immunity. CID is referred to as combined because both T lymphocytes and B lymphocytes are affected. Unlike Severe Combined Immunodeficiency (SCID), T lymphocytes are usually detectable in CID, and their function can be variably affected. The clinical spectrum of CID is wide, with some disorders causing mild to moderate disease and others causing severe susceptibility to infections as well as inflammatory complications due to immune dysregulation (dysfunction of the immune system in which lymphocytes may be present but not work well, allowing for the development of excessive autoreactivity and resultant autoimmune disease and inflammation). Unfortunately, the prognosis of CID is not always easy to determine at the level of the affected individual. This becomes important when considering the relative potential risks vs. the potential benefits of a particular treatment strategy.

Fortunately, the success rate of HSCT, particularly for those without an HLA-matched sibling donor, has improved substantially over the past few years so that the risk of this treatment has become much more acceptable for less severely affected individuals.

Clinical Features

Individuals with CID often present in the first two years of life with recurrent infections and/or immune dysregulation and specific findings associated with the different syndromes. Individuals with milder defects, however, may not present until later in childhood or even early adulthood. An increased incidence of hematologic malignancy and solid tumors has also been reported, especially in adulthood.

Individuals with CID may present with infections that are typical of deficits of cellular immunity, like chronic viral infections (CMV, HPV, EBV), mycobacterial disease, fungal, parasitic, or other

opportunistic infections. However, many instead may be uniquely affected by infections characteristic of a deficit of humoral immunity, such as recurrent bacterial sinopulmonary infections. The spectrum of severity is variable, ranging from life-threatening and disseminated infections characteristic of SCID to milder infections that respond to conventional therapy and do not require hospitalization. Diarrhea and failure to thrive are present in only half of those affected.

Interestingly, some individuals with CID may not present with infections but rather with autoimmunity, tissue inflammation, and allergic disorders as consequence of immune dysregulation. Multiple autoimmune manifestations in the same individual, with typical patterns of presentation upon specific genetic defects, have been documented in CID. Autoimmune manifestations are due to different mechanisms including T cell dysfunction leading to self-reactivity against the subject's own tissues, or B cell dysfunction with consequent autoantibody production and organ damage. In many forms of CID, functional impairment of regulatory T cells (a subgroup of T cells that are able to control and suppress self-reactive lymphocytes) has also been documented.

Autoimmune diseases frequently seen are: autoimmune cytopenias (autoimmune hemolytic anemia, thrombocytopenia and neutropenia), enteropathy, endocrinopathies, liver disease, vitiligo, alopecia, nephritis, and CNS autoimmunity. Endocrine glands are often affected leading to high rates of hypo- and hyperthyroidism, diabetes, hypoparathyroidism, and adrenal insufficiency. Granuloma formation is another manifestation of immune dysregulation. Granulomas are mainly localized in the skin, but the mucosa, lymphoid tissue, and internal organs may also be affected. Individuals with early onset multiple autoimmunity and/or granulomas should be investigated for possible immune defects. Neutralizing autoantibodies against specific cytokines, important molecules that help fight infections, may be present in those patients leading to a significant increase in infection rate. Specific syndromes, particularly hyper-IgE, predispose individuals with CID to severe eczema and allergies.

Finally, individuals with CID are at higher risk of developing malignancies as a consequence of uncontrolled cellular proliferation and/or altered immune-surveillance. The most common forms of cancer in CID are hematologic malignancies including lymphomas, lymphoproliferative disease and leukemias, that are often (but not always) associated with EBV infection. An increased frequency of solid tumors has also been documented. Those who develop HPV-associated warts are at high risk of squamous cell carcinoma of the skin. Basal cell carcinoma of the skin is also more frequent. Furthermore, increased incidence of carcinomas of the liver, pancreas and gut has been documented.

Diagnosis

CID is often first suspected due to clinical symptoms as described above, including frequent or unusual infections, autoimmune disease, and severe allergic disease. Sometimes it may be diagnosed due to a known family history of immunodeficiency. The diagnosis of CID can be very challenging, as lab results may vary widely between the different types of CID. General immunologic blood testing may demonstrate low T and/or B lymphocyte numbers, and altered distribution of lymphocyte subsets. In some cases, lymphocyte numbers may be normal in spite of poor cellular function. Poor B lymphocyte function is often reflected by low immunoglobulins and/or poor vaccine responses.

Newborn screening for Severe Combined Immunodeficiency (SCID) is routinely done in the U.S. Although newborn screening, which looks for a lack of T lymphocytes, is very sensitive for SCID, it does not uncover the majority of the forms of CID (See Newborn Screening Chapter). This is because T cells are often present in many forms of CID. Therefore, a normal newborn screen does not eliminate the possibility of CID.

Genetic testing is considered to be the most definitive method of diagnosing CID. Genetic testing involves sequencing (reading) genes that cause CID to look for mutations (changes). Most current genetic tests involve sequencing using a panel of genes known to be related and disease-causing for SCID and CID, or providers may opt to sequence all the protein-encoding regions of the genome (whole exome sequencing). This test is often performed on blood but may also be done using a cheek swab. Sequencing may show mutations that have been described in other individuals with CID or mutations that are entirely new. Predictive analysis can provide some assistance in interpreting new changes, though specialist interpretation and additional testing is

often needed to determine if a new mutation is likely disease-causing. Sequencing of additional family members can often help in this regard as well. (See Inheritance and Laboratory Testing Chapters.)

Inheritance

There are many different forms of CID, and they are inherited in several different ways. See Inheritance Chapter for a more detailed description of how genes are passed along generations. Most (but not all) forms of CID are inherited in an autosomal recessive manner. Some forms of CID are caused by a mutation in only one copy of a gene, which is known as autosomal dominant inheritance. Since males only have a single X chromosome, a single mutation in a gene located on the X chromosome may result in disease. This is known as X-linked inheritance.

Treatment

Prophylaxis against infections is indicated for CID, depending on the degree of immunodeficiency. If a humoral deficiency is present (see Clinical Features section above), then Ig replacement therapy should be started. Similarly, depending on the degree of cellular dysfunction, prophylaxis against opportunistic infections, such as herpetic viruses, fungi and *Pneumocystis jirovecii*, may be indicated. Use of immunosuppressive drugs may be necessary in individuals with significant manifestations of immune dysregulation.

Specific treatment varies but will likely be based on the underlying genetic defect. Our ability to genetically diagnose diseases has transformed treatment for these disorders, as specific inhibitors or promoters of the poorly functioning proteins may be available. Recent publications show beneficial effects of specific inhibitors in certain diseases, although it remains to be proven whether these medications will sustain long-term remission of symptoms.

If the condition is very severe and not amenable to prophylaxis or medications, then a referral for HSCT may be considered. As many of these disorders are newly described, the collective experience with transplantation for any specific type of CID may be limited. It will be important to discuss with the affected individual's healthcare team how effective transplantation has been in this disease, as well as what the long-term outcome is expected to be with prophylaxis alone or if specific medications for the disease are available. It is likely that indications for transplant or for new medications will continue to change as more is learned about these disorders.

Expectations

CID is a growing group of disorders, and within many of these disorders, there is a great deal of variability in the disease findings. Supportive therapies are often helpful in reducing complications, and as more is known about these disorders, the recommendations regarding which individuals should be referred for HSCT as well as best methods of transplantation are likely to change.

Known Forms of CID (A-Z)

A list of several forms of CID follows, although there may be additional syndromes that qualify for inclusion that are not listed. Sometimes a child with clinical CID is found to have a mutation in a gene that would be expected to result in SCID but does not have the typically severe disease as anticipated. This situation is often called "leaky" SCID (See Severe Combined Immunodeficiency Chapter).

Activated PI3-Kinase Disorder (APDS)

Genes: PIK3CD, PIK3R1
Inheritance pattern: AD
Activated PI3-Kinase Disorder (APDS) is also known as PI3K-p110δ activating mutation and is characterized by senescent T cells, lymphadenopathy, and immunodeficiency (PASLI). It is an autosomal dominant disease associated with a higher risk of bacterial and viral infections, as well as a predisposition to lymphoma. Most affected individuals develop multiple respiratory infections, which cause progressive lung damage. They also accumulate lymphocytes through life, although they do not work well, leading to significant lymphadenopathy. EBV and CMV infections are commonly described. Using medications to block the protein that stimulates PI3k, mTOR, has recently been shown to improve most symptoms, though we do not yet know if this response if sustained long term. HSCT has also been reported to be successful.

Bare Lymphocyte Syndrome (class I & II)

Genes: TAP1, TAP2, TAPBP, RFXANK, RFXAP, RFX5, CIITA
Inheritance pattern: AR
MHC (HLA) class I deficiency: MHC molecules are important to present self and foreign protein to the cells of the immune system. Individuals with severe reduction of class I MHC expression are usually healthy during the first year of life. However, by late childhood they can develop frequent upper and lower respiratory tract bacterial infections leading to lung damage and hearing loss. Granulomatous skin lesions are also a typical feature. A less-well-characterized group of affected individuals has an earlier presentation of symptoms, with recurrent bacterial, fungal, and parasitic infections in the first year of life. Most individuals with class I MHC deficiency have low CD8+ T cells and decreased NK cell killing activity. The definite diagnosis can be made by looking for class I MHC expression on the surface of peripheral blood mononuclear cells. Further genetic testing is then undertaken. Treatment is aimed at infection control with prompt antimicrobial therapy. Some individuals can benefit from Ig replacement therapy. HSCT is not routinely used for class I MHC deficiency because class I MHC expression is not restricted to hematopoietic stem cells, and, therefore, HSCT may not correct all disease manifestations.

MHC (HLA) class II deficiency: Class II major histocompatibility complex (MHC) deficiency (bare lymphocyte syndrome type II) is an autosomal-recessive disease. MHC class II deficiency generally results in a clinical picture of CID since class II MHC plays a pivotal role in the maturation and function of both T and B cells. However, milder cases have been described. Most individuals present with viral, bacterial, fungal, and/or protozoal infections. Common disorders include pneumonitis, bronchitis, gastroenteritis, and septicemia. Infections usually start in the first year of life and are associated with failure to thrive, diarrhea, and malabsorption. The following abnormal laboratory findings are commonly observed: low CD4 T cell count, low levels of immunoglobulin, and/or poor specific antibody responses to vaccines. Decreased T cell response to stimulation in the lab with stimulants like tetanus. There is a complete absence of class II MHC expression on B cells, and slight decrease in class I MHC expression.

An attempt should be made to identify the exact genetic defect once an absence of MHC class II is observed. Therapy is supportive and is aimed at reducing infections with the administration of antibiotics and Ig therapy. HSCT can resolve the immune deficiency. The chances for success are higher if the transplant is performed in the first two years of life. Individuals with MHC (HLA) class II deficiency generally die before five years of age without HSCT.

BCL10 deficiency

Gene: BCL10
Inheritance pattern: AR
Deficiency of BCL10 is a rare immunodeficiency that has been associated with severe recurrent infections and autoimmunity. This disorder has been described to result in decreased memory T cells and B cells, and absence of regulatory T cells. Best treatment for this disorder is unclear, though Ig replacement therapy and preventative antibiotics are likely warranted, and HSCT should be considered given the severity of this disorder.

BCL11A deficiency

Gene: BCL11A
Inheritance pattern: AD
BCL11A deficiency is a rare disorder that has been described to cause profound T cell lymphocytopenia and risk of invasive infections akin to SCID. Other described features include neonatal teeth, umbilical hernia, skeletal, and brain abnormalities. The immunologic features of this disorder are correctable by HSCT. This disorder is autosomal dominant but occurred due to a spontaneous mutation in the first described affected individual.

Bloom syndrome

Gene: BLM
Inheritance pattern: AR
A DNA repair defect, Bloom syndrome is an autosomal recessive rare disease primarily described in the Ashkenazi Jewish population. These children develop repeated lung and ear infections, and may have decreased immunoglobulin levels. Due to the DNA repair problems, they are very sensitive to sunlight and tend to be small in size. Other associated complications are distinctive facial features, an increased risk for diabetes and obstructive pulmonary disease, and a high lifetime risk of developing cancer. Ig replacement therapy may be indicated.

CARD11 deficiency or gain of function

Gene: CARD11
Inheritance pattern: AR/AD
Mutations in CARD11 are associated with a spectrum of PI. Complete absence of CARD11, which is a rare autosomal recessive condition, causes hypogammaglobulinemia and T cell dysfunction in spite of normal T cell numbers. Ig replacement therapy and preventative antibiotics are indicated. CARD11 deficiency has been successfully treated by HSCT.

Dominant gain-of-function mutations in CARD11 (in which the protein is present but altered) has been shown to cause a B cell lymphoproliferative disorder known as B cell expansion with NF-κB and T cell anergy, lack of response by T cells in which the T cells are unable to mount a normal response to certain antigens (BENTA), which is seemingly benign, though its long-term implications are not yet understood. Other dominant negative mutations in CARD11 have been found in children with severe allergies, eczema, and variable antibody deficiency with risk of recurrent infections.

Cartilage Hair Hypoplasia

Gene: RMRP
Inheritance pattern: AR
Cartilage-hair hypoplasia is a skeletal dysplasia inherited as an autosomal recessive trait. CHH is sometimes also referred to as immunodeficiency with short-limbed dwarfism. It is caused by mutations in the ribonuclease mitochondrial RNA-processing (RMRP) gene. Common features of the disorder include short stature with short limbs; fine, sparse, fragile hair; varying degrees of immunodeficiency; Hirschsprung disease (HD) with associated enterocolitis; increased risk of bone marrow failure; and susceptibility to hematologic malignancies. Individuals with CHH have normal intelligence and achieve normal developmental milestones throughout childhood. Impairment of immune function is the greatest health risk among persons with CHH. Cell-mediated immunodeficiency is most commonly reported. Individuals may develop severe infections like *Pneumocystis jirovecii* pneumonia, cytomegalovirus pneumonitis, or severe oropharyngeal candidiasis. Sinopulmonary infections suggestive of humoral immune deficiency are also common requiring Ig replacement therapy. Among adults there is higher incidence of hematologic malignancy including lymphoma, squamous cell carcinoma, and leukemia. Autoimmune disease, like autoimmune hemolytic anemia, immune thrombocytopenia, and juvenile idiopathic arthritis, is also reported in the disease. Granulomatous inflammation of the skin and visceral organ is present and responsive to various immune-suppressive medications. There is not a clear pattern of immunodeficiency among people with CHH, and they may have variable cellular and humoral deficiency. Surveillance for immunodeficiency, malignancy, and autoimmune disease is important for all with CHH. Administration of live, attenuated vaccines is not recommended without first demonstrating normal T cell responses. HSCT reverses the immune defect for SCID in the setting of CHH, and associated autoimmunity also resolves after transplantation. However, HSCT does not improve the musculoskeletal or growth features of the syndrome. Transplantation before the development of serious infections, significant organ damage, and/or malignancy improves survival for those individuals.

CD3G deficiency

Genes: CD3G, CD3D, CD3E
Inheritance pattern: AR
CD3 chains are important components of the TCR/CD3 complex and have a crucial role in T cell signaling and function. While CD3 delta, CD3 epsilon, or CD3 zeta deficiencies lead to a SCID phenotype with absent T cells and present but non-functional B cells, individuals with CD3 gamma deficiency have residual T cell function and numbers, and a broad spectrum of clinical phenotypes ranging from immune deficiency to immune dysregulation with autoimmunity. The onset is usually delayed, in childhood and young adulthood; however few have been reported with early onset SCID phenotype. Features include recurrent lung and urinary tract infections, intractable diarrhea, and failure to thrive. Chronic CMV infection has also been reported. Multiple autoimmune phenomena can affect those including autoimmune cytopenias, autoantibody positive severe colitis, cardiomyopathy, thyroiditis, nephritis, alopecia, and vitiligo. Laboratory data show T cell lymphopenia with low TCR-alpha-beta expression and CD3 on T cell, low immunoglobulin, and poor vaccination responses. Ig replacement therapy with antimicrobial and immunosuppressive therapy are supportive measures; however in the most severe cases HSCT is required.

CD70 deficiency

Gene: CD70
Inheritance pattern: AR
CD70 deficiency is a rare form of immunodeficiency that has been described in individuals with hypogammaglobulinemia and low CD8+ T cells, with particular susceptibility to chronic Epstein-Barr virus (EBV) and high risk of EBV-associated lymphoma. Severe varicella infections have also been described. Ig replacement therapy and prophylactic antibiotics are recommended in this disorder, and HSCT should also be strongly considered given the high risk of malignancies.

CD8 deficiency

Gene: CD8A
Inheritance pattern: AR
CD8 deficiency is an extremely rare autosomal recessive disorder due to homozygous mutation of CD8 gene. CD8 is a T cell receptor (TCR) accessory molecule that interacts with major histocompatibility complex (MHC). CD8 is found on cytotoxic T cells and NK cells. CD8 deficiency clinical phenotype ranges from recurrent sinopulmonary infections beginning later in childhood to asymptomatic. CD4+ T cell, B cell, and NK cell percentages and absolute counts are normal, but CD8+ T cells are absent. There is no published data regarding therapy for these patients and management is directed toward infectious complications and may include Ig replacement therapy.

Combined Immunodeficiency with Intestinal Atresias

Gene: TTC7A
Inheritance pattern: AR
Combined Immunodeficiency with Intestinal atresias (CID-IA) is a rare, severe disorder in which parts of the small intestine fail to develop properly. It presents in early infancy due to inability to feed as well as profound susceptibility to illnesses, most notably due to enteric bacteria. Surgical intervention and parenteral nutrition have been helpful in some cases. Ig replacement therapy and preventative antibiotics are often indicated, and in the setting of profound lymphopenia, HSCT has been successful in some cases in correcting the immunodeficiency associated with CID-IA. Though reported cases are very limited, outcomes have been guarded in this disorder due to extreme difficulty in correcting the intestinal abnormalities and preventing life-threatening infections.

Coronin 1A deficiency

Gene: CORO1A
Inheritance pattern: AR
Coronin 1A deficiency is associated with very low number of T cells, with impaired function, similar to SCID. However, unlike in SCID, affected individuals have a thymus. They can also produce antibodies, though they are non-specific and do not function well. They have severe, early predisposition to infections, as well as early lymphomas. Most have also had neurological complications, though this may be due to confounding factors. HSCT has been shown to improve the immunodeficiency aspect of the disease.

DOCK2 deficiency

Gene: DOCK2
Inheritance pattern: AR
DOCK2 deficiency is an autosomal recessive disorder associated with early-onset invasive bacterial and viral infections, lymphopenia, and defective T, B, and NK cell function. DOCK2 protein is important not only for the cytoskeletal structure of peripheral blood leukocytes but also for thymus, spleen, and liver function. DOCK2 deficiency causes defective actin polymerization and migration in T, B, and NK cells; impaired NK cell killing ability, diminished cytokines (interferons) production in peripheral blood mononuclear cells in response to viral infections and consequent increase in viral replication. Most of known individuals with DOCK2 deficiency presented in the first four months of life with recurrent viral and bacterial respiratory tract infections as well as chronic diarrhea and failure to thrive. Affected individuals may be susceptible to disseminated vaccine-strain varicella, oral thrush, and severe infections with nontuberculous mycobacteria, human herpesvirus-6, mumps, parainfluenza virus, adenovirus, cytomegalovirus (CMV), and *Klebsiella pneumoniae*. Additional clinical features include thrombocytopenia, hepatomegaly, and colitis. Treatment with interferons is under investigations while HSCT may be curative for the disease.

EXTL3 deficiency

Gene: EXTL3
Inheritance pattern: AR
Individuals with this condition can present with severe T cell defects that may mimic SCID at birth. Additionally, they present with significant bone deformities, such as early fused cranial bones (craniosynostosis) with a small cervical canal, short

stature and abnormally shaped digits. While very rare, all described patients have had neurological complications, including developmental delay. Liver and kidney cysts have been described in several affected individuals. It is inherited in an autosomal recessive pattern. Ig replacement therapy and prophylactic medication against infections is indicated. Many have died early in life, but prolonged survival, with spontaneous improvement of the lymphocyte count, has been reported in others.

ICF syndrome

Genes: ZBTB24, DNMT3B, CDCA7, HELLS
Inheritance pattern: AR
Short for immunodeficiency-centromeric instability-facial anomalies syndrome, ICF syndrome is an autosomal recessive disorder that may be due to defects in the ZBTB24, DNMT3B, CDCA7, or HELLS genes. Recurrent infections, mostly respiratory, are the usual presenting symptom, though it is also associated with mild facial dysmorphism, growth retardation, failure to thrive, and psychomotor retardation. Although poor production of antibodies is most often described, some affected children also have severe cellular dysfunction, as evidenced by PJP or invasive fungal infection. Ig replacement therapy is standard treatment. HSCT has been curative for those with severe cellular dysfunction, and may be considered in these cases.

IL21 pathway deficiency

Gene: IL21, IL21R
Inheritance pattern: AR
Deficiencies of the cytokine IL-21 and IL21 receptor are a rare category of PI that has been described in children with very early onset inflammatory bowel disease, liver disease, and immunodeficiency with T cell and B cell defects. Ig replacement therapy and preventative measure to prevent infections with *Cryptosporidium* are warranted. HSCT may be warranted for treatment of this disorder.

Kabuki Syndrome

Genes: KMT2D, KDM6A
Inheritance pattern: AR
Kabuki syndrome is a multisystem genetic disorder involving facial dysmorphisms, growth and developmental delay, and skeletal abnormalities. Immune findings have been described including antibody deficiency and autoimmune cytopenias. Ig replacement therapy and immunosuppressive therapy may be indicated for treatment of these manifestations when present.

LCK deficiency

Gene: LCK
Inheritance pattern: AR
Autosomal recessive disorder due to deficiency of lymphocyte-specific protein-tyrosine kinase (Lck or p56lck), one of the proteins that are activated upon engagement of the TCR/CD3 complex. Depending on the mutation, individuals may present within the first year of life with variable features. While some have a SCID phenotype others presented with Common Variable Immune Deficiency (CVID) or idiopathic CD4 lymphopenia. Clinical features include failure to thrive, oral candidiasis, sepsis, diarrhea, and hypogammaglobulinemia combined immunodeficiency, recurrent sinopulmonary infections, and inflammatory/autoimmune manifestations even without immune-deficiency. Treatment is supportive with the administration of antibiotics and Ig replacement therapy. Indication to treat with HSCT is still controversial.

LICS syndrome

Gene: NSMCE3
Inheritance pattern: AR
An autosomal recessive condition, a lack of this protein causes a type of DNA repair defect called Lung disease, immunodeficiency, and chromosome breakage syndrome (LICS). Children with this condition have severe lung disease very early in life, and have a high predisposition to viral pneumonias. Distinctive facial features have been reported. Ig replacement therapy may be indicated.

Ligase I deficiency

Gene: LIG1
Inheritance pattern: AR
An autosomal recessive condition, it is thought to present very similar to Bloom syndrome (see previously mentioned). This includes a high sensitivity to sunlight, stunted growth, developmental delay, and high predisposition to cancer. Similarly, they can present with repeated ear and lung infections, for which Ig replacement therapy may be indicated.

MALT1 deficiency

Gene: MALT1
Inheritance pattern: AR
The mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALT1) is important to control inflammation. MALT1 deficiency has an autosomal recessive transmission pattern. Clinical presentations include failure to thrive, severe eczema, recurrent bacterial and viral skin and lung infections with resultant chronic inflammatory lung disease, meningitis, inflammatory gastrointestinal disease, long bone fractures, recurrent production of granulation tissue, severe periodontal disease and persistent cytomegalovirus (CMV) infection. These individuals have normal newborn screening for SCID. Lymphocyte numbers are normal, with normal T and NK cell numbers. IgG, IgA, and IgM levels and production of protective antibody titers are normal. B cell phenotype may present abnormalities.

Moesin deficiency

Gene: MSN
Inheritance pattern: XL
Moesin deficiency is an X-linked immunodeficiency associated with lymphopenia, neutropenia, and recurrent bacterial infections. Prolonged or severe varicella infections have been described in several affected individuals. Eczema and autoimmune manifestations including thrombocytopenia have been described. Use of antibiotic prophylaxis, Ig replacement therapy, and use of granulocyte colony stimulating factor (GCSF) should be strongly considered. HSCT may also be a consideration.

Nijmegen Breakage syndrome

Gene: NBN
Inheritance pattern: AR
Mutations in the NBN gene cause the syndrome, which is autosomal recessive and codes for a protein called nibrin. Deficiency leads to poor ability to repair DNA. As a result, affected individuals are highly sensitive to the effects of radiation, or any substance that can cause breaks in DNA. Inability to repair DNA has many associated complications, including short stature, small head size (microcephaly), distinctive facial features, recurrent respiratory tract infections, an increased risk of cancer, and intellectual disability. Ig replacement therapy can help with the recurrent infections.

NIK deficiency

Gene: NIK
Inheritance pattern: AR
NIK deficiency is a rare immunodeficiency resulting in impaired function of T cells, B cells, and Natural Killer (NK) cells. T cells are generally normal in number, whereas B cells and NK cells are decreased. Affected individuals are susceptible to a wide range of infections, including opportunistic parasites such as *Cryptosporidium*. Development of secondary lymphatics may be impaired. NIK deficiency may be amenable to HSCT, though the ideal methods remain unclear.

OX40 deficiency

Gene: TNFRSF4
Inheritance pattern: AR
OX40 deficiency is a rare immunodeficiency that was first uncovered in a young woman with childhood onset Kaposi's sarcoma, which is a rare skin cancer that is occurs in immunocompromised individuals after infection with human herpesvirus 8. CD4+ T cells appear to be dysfunctional in this disorder, whereas antibody production is still intact.

Partial RAG1/2 deficiency

Gene: RAG1, RAG2
Inheritance pattern: AR
Recombination activating genes 1 and 2 (RAG1 and 2) are important for generation of T cell receptor on T cells and immunoglobulin on B cells. This process is essential for adequate immune response to the vast majority of infectious microorganisms. Severe mutations in *RAG1* and *RAG2* can cause SCID. However, "leaky" mutations with residual protein function and T cell production can have a variable presentation, including Omenn syndrome in the newborn with T cells that infiltrate the skin, liver, and spleen, but also CID manifesting later in life with granulomatous disease and/or autoimmunity. Granulomas may affect the skin and multiple organs while autoimmune disease include autoimmune cytopenias and multi-organ autoimmunity. Disseminated infection with viruses like varicella and nontuberculous mycobacteria can also be present. Individuals with RAG deficiencies sometimes can have isolated low T cell counts with delayed onset of infections, or manifest as a Hyper IgM Syndrome, Common Variable Immune Deficiency (CVID) or sterile chronic multifocal osteomyelitis (CRMO). Presentation can be beyond early childhood with autoimmune and autoinflammatory complications

with or without chronic recurrent sinopulmonary infections. Most of individuals require Ig replacement therapy and antibiotic prophylaxis as standard treatment but also immunosuppressive therapy may be indicated to control granulomas and autoimmunity. HSCT has been curative and should be considered in these cases.

POLE/POLE2 deficiency

Gene: POLE, POLE2
Inheritance pattern: AR
This is inherited in an autosomal recessive manner. Affected individuals have a high predisposition to infections, and decreased numbers of both T and B cells. Additionally, those with POLE deficiency may manifest autoimmune problems (including type I diabetes and thyroid disease), short stature, and livedo of the skin. It is thought this may also represent a cancer predisposition syndrome, as this mutation has been described in adults with early onset colon cancer.

Purine Nucleoside Phosphorylase Deficiency

Gene: PNP
Inheritance pattern: AR
Purine nucleotide phosphorylase (PNP) deficiency is a rare recessive disorder resulting in moderate to severe immunodeficiency with reduced T cell numbers and risk of recurrent infections as well as autoimmune disease. Autoimmune hemolytic anemia is particularly frequent in this condition. Ig replacement therapy and prophylactic antibiotics are warranted for treatment. HSCT can be curative for the immunologic features of PNP deficiency. Neurologic disease is also frequently described in individuals with PNP deficiency, including neurodevelopmental delay, tremors, spasticity, and ataxia.

RelB deficiency

Gene: RELB
Inheritance pattern: AR
RelB deficiency has been found in a small number of individuals with poor T cell and B cell function in spite of normal lymphocyte numbers. Recurrent bacterial infections have been described beginning in the first year of life. Rheumatoid arthritis was described in one child with RelB deficiency. HSCT has been utilized successfully to treat the immunodeficiency, but it is unclear if arthritis resolves after transplantation.

RHOH deficiency

Gene: RHOH
Inheritance pattern: AR
This is an autosomal recessive disease due to mutations in the Ras homolog gene family member H (RHOH) gene leading to a defect of T cell function. Affected individuals present in childhood with persistent epidermodysplasia verruciformis (flat warts like lesions) due to persistent human papillomavirus (EV-HPV) infection. The disease is also associated with recurrent bronchopulmonary infections and lymphoma. While the total T cell counts are normal, those with this deficiency have impaired TCR signaling, profound peripheral naive T cell lymphopenia with increased memory T cells. Management is directed toward medical and surgical treatment of the epidermodysplasia verruciformis lesions and prompt prevention/early diagnosis of skin cancer resulting from the malignant evolution of the skin disease.

RIDDLE syndrome

Gene: TNF168
Inheritance pattern: AR
RIDDLE is short for Radiosensitivity, ImmunoDeficiency, Dysmorphic features and LEarning difficulties. It is an autosomal recessive disorder, in which individuals have difficulty repairing DNA damage sustained by the cells. Individuals can have recurrent sinopulmonary infections due to low production of immunoglobulin and may require Ig replacement therapy. They also share a high risk of developing cancer during their lifetime.

Schimke's Immuno-osseous Dysplasia

Gene: SMARCAL1
Inheritance pattern: AR
In this condition, flattened vertebrae (the bones in the spine) lead to short neck and trunk; average adult height is 3 to 5 feet. Affected individuals usually present kidney disease that often becomes severe early in life, as well as hyperpigmented skin. A low number of T cells or and/or lymphocytes is frequently seen. In cases in which the lymphopenia is severe, HSCT has been attempted, with mixed results. It is inherited in an autosomal recessive pattern.

STK4 deficiency

Gene: STK4
Inheritance pattern: AR
An autosomal recessive disease due to mutations in the serine/threonine protein kinase 4 *(STK4)* gene. The clinical phenotype include persistent viral infections, like HPV-associated epidermodysplasia verruciformis, EBV, molluscum contagiosum and bacterial infections. Other reported features include fungal infections, mild eczema, autoimmune cytopenias, and lymphopenia. The immunological phenotype is characterized by reduced number of T cells and B cells and increased number of immunoglobulin G. Leukocyte have impaired migration and adhesion. Management is directed toward medical and surgical treatment of the epidermodysplasia verruciformis lesions. Affected individuals often require targeted antimicrobial therapy for infections and immunosuppression if autoimmunity is present.

TFR1 deficiency

Gene: TFRC
Inheritance pattern: AR
Deficiency of Transferrin receptor 1 (TFR1) is a rare recessive immunodeficiency, which has been associated with hypogammaglobulinemia, defective T cell function in spite of normal quantities, intermittent neutropenia and thrombocytopenia, and mild anemia. TFR1 deficiency has been successfully treated via HSCT with resolution of all abnormalities.

TCRa deficiency

Gene: TRAC
Inheritance pattern: AR
This is an autosomal recessive disease due to mutation in the TCR alpha subunit constant *(TRAC)* gene that cause markedly reduced surface expression of the T cell receptor alpha-beta (TCR-alpha-beta) complex. Such complex is crucial for T cell signaling and function. Those affected have absent numbers of TCR-alpha-beta+ T cells but increased TCR-gamma-delta+ T cells together with hypereosinophilia, and sometimes elevated immunoglobulin E (IgE) but normal IgG levels. Patients present within the first two years of life suffering from recurrent respiratory tract infections, candidiasis, and gastroenteritis (*Salmonella, Cryptosporidium*, rotavirus) that respond to conventional treatment. Susceptibility to Herpesviridae infections is also reported. Additional clinical features included failure to thrive, immune dysregulation (e.g., vitiligo, alopecia, eczema, and autoimmune hemolytic anemia), lymphadenopathy, and hepatomegaly. HSCT has been curative in this disease.

Tricho-hepato-enteric syndrome

Genes: TTC37, SKIV2L
Inheritance pattern: AR
Tricho-hepato-enteric syndrome (THES) is a rare recessive disorder characterized by chronic diarrhea with poor growth, liver disease, hair and facial abnormalities, and immunodeficiency with impaired antibody function and lymphopenia. Ig replacement therapy is indicated for treatment of this disorder. Gastrointestinal disease in THES requires intensive nutritional therapy but seemingly improves with age. Transplantation is, therefore, not generally recommended for THES.

X-linked Immunodeficiency with Magnesium defect, EBV infection, and neoplasia (XMEN)

Gene: MAGT1
Inheritance pattern: XL
XMEN is seen in boys, and is characterized by CD4 T cell lymphopenia, chronic EBV infections, and lymphoproliferative disorders related to the EBV. All have decreased cytolytic function, and may have decreased antibody responses due to their low CD4 T cells. Oral magnesium supplementation has been proposed in the treatment of this condition, but it is not clear whether it is clinically helpful. HSCT may be curative, though there is limited experience.

ZAP-70 deficiency

Gene: ZAP-70
Inheritance pattern: AR
ZAP-70 deficiency is a rare autosomal recessive combined immunodeficiency. ZAP-70 plays a crucial role in T cell development and function, and is crucial for CD8 T cell selection. Peripheral T cells from individuals with ZAP-70 deficiency demonstrate defective T cell signaling and have an autoreactive phenotype. Indeed, several individuals have presented with autoimmune disorders. Some children with ZAP-70 deficiency present within the first two years of life with a history of life-threatening infections, similar to infants with SCID. However, those with ZAP-70 deficiency may present later in childhood with palpable lymph nodes, visible tonsils and thymus. While most of the mutations cause

decreased ZAP-70 activity, one mutation led to increased ZAP-70 function and a unique constellation of autoimmune phenotypes including bullous pemphigoid associated with autoantibodies and ulcerative colitis. Unlike those with SCID, individuals with ZAP-70 deficiency may have *Pneumocystis jirovecii* pneumonia, and cytomegalovirus (CMV) pneumonitis after 6 months of age. Autoimmunity or manifestations of immune dysregulation such as ulcerative colitis and blood cytopenias are reported. Unique presentations, such as pustular skin lesions from birth, subcutaneous nodules, lymphoma, and multisystem autoantibody disease, are also seen. In addition, cases with inflammatory features like Omenn syndrome and hemophagocytic lymphohistiocytosis (HLH) have been described. Individuals with ZAP-70 deficiency may have a normal number of circulating lymphocytes. They have normal CD3 and CD4 T cells but lack CD8 T cells. Typically, their T cells display impaired proliferation *in vitro*. All individuals have normal B cell and NK cell numbers. They may have reduced immunoglobulin G levels. The diagnosis of ZAP-70 deficiency should be considered in infants and young children with recurrent bacterial or opportunistic infections but also in those with early-onset autoimmunity and lymphoma. Those individuals require general management like an individual with CID, including infection avoidance; vaccination with killed, but not live, vaccines; antibiotic prophylaxis; and Ig replacement therapy. Most individuals with ZAP-70 deficiency die within the first two years of life from infection if they do not undergo HSCT.

Adapted from: Chapter 9 Severe Combined Immune Deficiency and Combined Immune Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 10
DiGeorge Syndrome

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Introduction

DiGeorge Syndrome (DGS) was first described by Dr. Angelo DiGeorge who described the syndrome consisting of low T cells, recurrent infections, and heart defects. DGS is a form of primary immunodeficiency disease (PI) characterized by:

- Heart defects,
- Small or absent parathyroid glands that control calcium levels, and
- Small or absent thymus gland that makes T cells (a type of white blood cell that fights infections).

Infants born with heart defects may require surgery. If the parathyroid glands are small, calcium levels in the blood can be dangerously low resulting in seizures (patients require treatment with calcium supplements). If the thymus size is small, infants may have lower T cell numbers than normal. In the rare situation in which the thymus is absent at birth (1% of cases), the infant will not have any T cells to fight infections and have a life-threatening immunodeficiency.

DGS most commonly occurs in children with 22q11.2 deletion syndrome, CHARGE syndrome, and infants of diabetic mothers. Other names for DGS include:

- Velocardiofacial syndrome
- 22q11.2 deletion syndrome
- Shprintzen syndrome
- Conotruncal anomaly face syndrome.

Some children, however, do not have any genetic syndromes or mothers with diabetes.

Overview

Children with DGS can have a wide range of presentations and can range from having mild to severe immunodeficiency. The term DGS is used most commonly for individuals with T cells below the 10th percentile for age. DGS occurs in four main groups of children:

1. The most common cause is due to a genetic defect called 22q11.2 deletion syndrome (22q11.2DS). In children with 22q11.2DS, a piece of chromosome 22 is missing.
2. Patients with CHARGE syndrome. CHARGE syndrome is usually caused by mutations (changes) in the gene CHD7. Children with CHARGE have many of the same problems as those with 22q11.2DS, but they have additional problems, especially involving the eyes, nose, and ears. Children with CHARGE syndrome who have low T cells are said to also have DGS. Developmental delay is found in both 22q11.2DS and CHARGE syndrome.
3. Infants of diabetic mothers who do not have any genetic defects.
4. Infants without any genetic defects or whose mothers do not have diabetes.

Of children with DGS, only 1% have no thymus and thus no T cells. These patients are said to have Complete DGS. These children have life-threatening infections and need a transplant to give them T cells. The transplant can be a hematopoietic stem cell transplantation (bone marrow transplantation) or an experimental thymus transplant.

Immunobiology

It is helpful to understand how the thymus works. The thymus acts as a schoolhouse for developing T cells (the students). First, white blood cells called stem cells leave the bone marrow and go to the thymus to learn to become T cells. The developing T cells have to learn two key lessons and pass a final test in order to graduate and leave the thymus. The first lesson is how to fight infections. The second lesson is to how not to attack the body and cause autoimmune disease. The majority of T cells (90%) fail the final test and die without leaving the thymus. The 10% that pass the test leave the thymus as mature T cells. They are able to protect the body from infection but also do not attack the body.

Clinical Presentation

Infants with DGS do not all present in the exact same way. For example, some have severe heart problems; some have none at all. Some have parathyroid disease; some do not. To be called DGS, most people would say that the T cell counts in the blood should be low (in the bottom 10th percentile for age). Individuals with DGS due to 22q11.2 deletion may have many other findings. They may have a unique facial appearance such as a small chin, eyes with hooded eyelids, and ears that are rotated back with small upper portions of the ear lobes, cleft palate, and floppy outer part of the ear (the pinna). Infants with DGS secondary to CHARGE syndrome may have additional defects beyond those found in 22q11.2DS. Parts of the eye may be missing leading to partial blindness. The inner ear area (semicircular canals) may not be properly formed leading to balance problems and deafness. Individuals with DGS can have autoimmune disease resulting in low platelets (which causes bleeding problems), low neutrophils (white blood cells that also fight infection), and low red blood cells that carry oxygen in the blood. Individuals can also develop thyroid disease (and need to take thyroid medication). Some develop arthritis. Individuals with DGS may have a variety of other abnormalities including cleft palate, delayed speech, and difficulty in feeding and swallowing. Some have learning disabilities, behavioral problems, psychiatric disorders (such as schizophrenia), and hyperactivity.

Diagnosis

The diagnosis of DGS is made on the basis of findings that are present at birth, or develop soon after birth, in particular, heart defects and low calcium. Babies with heart defects are often screened for 22q11.2DS by a blood test, commonly a FISH assay, a method using a fluorescent signal to visualize the presence of the genetic region on one of two copies on chromosome 22. Other newer tests are available to analyze gene mutations and chromosome deletions to make a diagnosis of DGS. Children with CHARGE are usually identified at birth because of their physical findings. Even though children with 22q11.2DS or CHARGE often have normal T cell numbers, these children should be followed by a geneticist who can provide guidance for the other issues that are common problems for children with DGS.

Newborn screening (a drop of blood from a heel stick) for Severe Combined Immunodeficiency (SCID) may identify a child as having low T cells. If the test indicates that a child has low T cells, an additional blood test is done to determine the actual number of T cells. An immunologist reviews the data and lets the parents know if the T cell numbers are low and if the child needs additional follow up.

Inheritance

Most cases of 22q11.2 DS occur spontaneously. DGS is caused by a large deletion from chromosome 22. This deletion means that several genes from this region are not present in those with DGS. It appears that the variation in the symptoms of the disease is related to the amount of genetic material lost in the chromosomal deletion. Many of the manifestations of DGS have been linked to deletion of the T-box transcription factor 1 *(TBX1)* gene on chromosome 22q11, which plays a role in neural crest cell migration, pharyngeal arch (PA) development and formation of the pharyngeal pouches. *TBX1* interacts with many genetic molecular pathways leading to craniofacial defects and aberrant neural crest cell migration and survival.

Once a child is found to have 22q11.2 deletion, it is recommended that all parents be tested to determine if they or their other children are at risk. Affected parents or siblings may not have obvious symptoms of DGS.

All described cases of CHARGE syndrome due to CHD7 mutation have occurred spontaneously. There are no known parents with CHARGE syndrome. It is extremely unlikely for any couple to have more than one baby with CHARGE syndrome.

Treatment

The treatment of a child with DGS varies depending on the infant's immune status and the medical problems that the child has. For the 1% of infants with DGS who on newborn screening are found to have no T cells, transplant of thymus is recommended because of the high risk of infection and death. Because the defect in T cell development is due to a lack of thymus, hematopoietic stem cell transplantation (bone marrow transplantation) is not effective. These infants should be kept in strict isolation to avoid infection until T cells develop after thymus transplantation.

For all infants with DGS, a multidisciplinary team is the preferred form of care. One example of such a team would be a clinic specializing in 22q11.2DS with multiple medical specialists needed for any child with DGS (whether or not the child has 22q11.2DS). The table below lists specialists who may be needed to care for infants with DGS. When a team is not available, the pediatrician, geneticist, or immunologist caring for the child should be asked to arrange for the appropriate doctors to be consulted for care for the child.

Team Member	Medical Focus
Geneticist, genetic counselor	Counseling for the child and other family member and coordination of care
Immunologist	T cell counts, immunization schedule
Speech therapist	Speech therapy and feeding
Physical and occupational therapist	Physical skills such as rolling over, sitting, crawling, walking and activities of daily living
Cardiologist	Heart abnormality if present and blood pressure
Kidney doctor	High blood pressure, single kidneys, abnormalities of the urine system
Pulmonology	Treatment of breathing problems, tracheostomy care if necessary
Gastroenterologist and nutritionist	Tube feeding, growth, constipation management
Ears/nose/throat doctors	Cleft palate, tubes in ears
Orthopedic surgeons	Scoliosis (curved spine)
Endocrinologists	Calcium management, thyroid disease
Pediatric psychologists or psychiatrists	Behavioral problems and psychiatric disease

Expectations

For the 99% of infants with DGS who have T cells, the immune system is not a major problem. An immunologist will determine if the T cells are high enough for administration of live vaccines such as the rotavirus vaccine; the measles, mumps, rubella virus vaccine; and the varicella (chickenpox) vaccine. An immunologist should assess each child periodically to confirm that the T cell numbers remain adequate.

T cells help another white blood cell called the B cell make antibody responses to vaccines. In about 10% of individuals with 22q11.2 DS, they have difficulty with production of immunoglobulins or vaccine responses. Some of these individuals require immunoglobulin replacement therapy. (See Immunoglobulin Replacement Therapy Chapter.)

There is great variability in the other problems that a child with 22q11.2 DS may have.

Some children with very mild forms of DGS are diagnosed later in life due to speech abnormalities or other subtle findings, while others have varying degrees of impairment in any combination of the following aspects of DGS.

The heart defects at birth often need to be repaired by heart surgery. Cardiac follow up will be needed depending on the type of heart defect. The cardiologist may also provide guidance for high blood pressure (if present.)

Low calcium levels from a poorly functioning parathyroid gland usually improve, and most children do not need calcium replacement for more than one year. The exception is the group born with no T cells—these children often remain on calcium for life. It is important that calcium levels be followed by the pediatrician because on rare occasions the calcium levels may drop in a child who previously had been able to come off of calcium replacement.

The thyroid should be checked annually in children with DGS because thyroid disease is very common. By the time an individual with DGS is 40 years old, 1 of 5 have thyroid disease and are treated with thyroid medication.

Learning disabilities are common. Most children with DGS take longer than usual to learn to talk. Math is particularly difficult. Working with school officials, including the school nurse, to develop an Individualized Education Program (IEP) and/or an Individual Healthcare Plan (IHP) can be very helpful.

Psychiatric disease can develop in adolescents and adults. Two common conditions are schizophrenia and bipolar disorder in individuals with 22q11.2DS. Family and school support are very important for children with DGS to enhance their development as best as possible. Staying connected to others through the Immune Deficiency Foundation, the 22q11.2 Society, and the CHARGE Syndrome Foundation can be helpful for families.

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Chapter 11
Wiskott-Aldrich Syndrome

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Wiskott-Aldrich Syndrome (WAS) is unique among primary immunodeficiency diseases (PI) because, in addition to being susceptible to infections, individuals may have a bleeding problem, develop eczema, and have an increased incidence of autoimmunity and malignancies.

The bleeding tendency is the result of markedly reduced numbers of unusually small, dysfunctional platelets (blood cell fragments that play an important role in the formation of blood clots). These additional complications lead to unique health challenges for individuals with WAS that are not typically seen in other forms of PI. WAS is a rare X-linked genetic disorder with an estimated incidence of approximately 1 in 100,000 male live births. Milder forms of the disease that have some, but not all of the usual WAS symptoms, also exist, which can sometimes cause delays in making a correct diagnosis.

Clinical Presentation

WAS was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia) and small platelets, bloody diarrhea, skin rash (eczema), and recurrent ear infections. All three died at an early age from complications of bleeding or infection. Notably, their sisters did not have symptoms. Seventeen years later, by studying a large six-generation Dutch family with boys who had similar symptoms to the individuals described by Wiskott, Dr. Robert Aldrich, an American pediatrician, was able to clarify that the disease was passed down from generation to generation in an X-linked recessive manner. (See Inheritance Chapter.) In 1994, the gene that is defective in individuals with WAS was identified, and this discovery led to the understanding that milder forms of this disease, such as X-linked thrombocytopenia (XLT), exist and that individuals with XLT have mutations in the same gene.

In its classic form, WAS is characterized by three basic clinical features:

1. Increased tendency to bleed, caused by a significantly reduced number of very small platelets
2. Recurrent bacterial, viral, and fungal infections
3. Eczema affecting various regions of the skin

In addition to this basic triad of symptoms, individuals with WAS also have an increased risk of developing severe autoimmune diseases and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See Autoimmunity in Primary Immunodeficiency Chapter.)

Bleeding Tendency

Thrombocytopenia is a common feature of individuals with WAS. In addition to being decreased in number, the platelets themselves are small, less than half the size of normal platelets and dysfunctional. As a result, individuals with WAS may bleed easily, even if they have not had an injury. Bleeding into the skin may cause pinhead sized bluish-red spots, called petechiae, or they

may be larger and resemble bruises. Affected boys may also have bloody bowel movements (especially during infancy), bleeding gums, and prolonged nose bleeds. Hemorrhage into the brain is a dangerous complication, and some clinicians recommend that toddlers with WAS/XLT wear a helmet to protect them from head injuries. Since WAS is the only disorder where small (micro-) platelets are found, their presence is a useful diagnostic test for the disease.

Infections

The combined immunodeficiency associated with WAS affects the function of both B and T cells. As a result, infections are common in the classic form of WAS and include bacteria, viruses and fungi. The most common infections consist of upper and lower respiratory infections, such as ear infections, sinus infections, and pneumonia. More severe bacterial infections, such as sepsis (bloodstream infection or "blood poisoning") and meningitis (infection of the brain and spinal cord tissues), or severe viral infections, are less frequent but can occur. Occasionally, individuals with the classic form of WAS may develop pneumonia caused by the fungus *Pneumocystis jirovecii*. The skin may become infected with bacteria such as Staphylococcus in areas where individuals have scratched their eczema. In addition, a viral skin infection called molluscum contagiosum is commonly seen in WAS. Vaccination to prevent infections is often not effective in WAS since individuals do not make normal amounts of protective antibody responses to certain vaccines.

Eczema

An eczema rash is common in individuals with classic WAS. In infants, the eczema may occur on the face or scalp and can resemble cradle cap. The rash can also have the appearance of a severe diaper rash, or it can be more generalized, involving the arms and legs. In older boys, eczema is often limited to the skin creases around the front of the elbows or behind the knees, behind the ears, or to the wrist. Since eczema can be extremely itchy, individuals often scratch themselves until they bleed, even while asleep. When the skin barrier is broken, the lesions serve as entry points for bacteria that can cause skin and blood stream infections.

Autoimmune Manifestations

The term autoimmunity describes a situation in which one's own immune system turns against itself and attacks specific cells or organs of the body. Clinical problems caused by autoimmunity are common in WAS, affecting almost half of all individuals. Among the most frequently observed autoimmune manifestations is the destruction of red blood cells by auto-reactive antibodies generated inappropriately by the dysregulated immune system. Red blood cell destruction is called autoimmune hemolytic anemia. Antibody-related platelet destruction in WAS is rare and is called idiopathic thrombocytopenic purpura (ITP). ITP, if it occurs, decreases further the platelet count and makes platelet transfusions difficult or ineffective. Another common autoimmune disorder in WAS is a type of blood vessel inflammation (vasculitis) that typically causes fever and skin rash on the extremities. Occasionally, vasculitis may affect the kidneys, muscles, heart, brain or other internal organs, which can cause a range of symptoms. Some individuals have a more generalized autoimmune disorder in which there may be high fevers in the absence of infection, associated with swollen joints, tender lymph glands, kidney inflammation, and gastrointestinal symptoms, such as diarrhea or colitis. Each of these autoimmune features may last only a few days or may occur in waves over a period of many years, and each may be difficult to treat.

Malignancies

Individuals with WAS have an increased risk of malignancies (cancer) compared to unaffected individuals. Overall, it has been estimated that 15 to 20% of individuals with WAS eventually develop malignancies. Lymphomas or leukemias that arise from B cells are the most common, with Non-Hodgkin lymphoma making up the majority of cases. Malignancies can occur in young children but are more common as individuals age.

Milder Forms of Disease

The clinical presentation of WAS varies from person to person. Some individuals have all three classic manifestations, including low platelet counts, immunodeficiency, and eczema while others have only low platelet counts and bleeding. Initially, the latter disorder was called X-linked thrombocytopenia (XLT). It was not until the gene that causes WAS was identified that it became evident that both disorders are caused by mutations in the same gene. Typically, individuals with XLT do not have

significant immunodeficiency and only few episodes of infections, but they do have an increased risk of autoimmunity and malignancy, although the risk is not as high as in classic WAS. Another very rare disorder associated with a mutation in the WAS gene causes a form of congenital neutropenia called X-linked neutropenia (XLN).

Diagnosis

A diagnosis of Wiskott-Aldrich syndrome (WAS) should be considered in any boy who has unusual bleeding and bruises at an early age associated with thrombocytopenia. The characteristic platelet abnormalities including low numbers and small size are almost always present, even in the cord blood of newborns. The simplest and most rapid test to determine if an individual may have WAS is to obtain a platelet count and to determine the platelet size.

The immune problems typically begin to manifest themselves in toddlers and older children when individuals begin to develop frequent infections. Evaluation of the immune system typically shows that individuals are not able to make good antibody responses to certain types of vaccines, particularly those that contain polysaccharides or complex sugars, such as the vaccine against *streptococcus pneumoniae* (Pneumovax). IgE levels are usually elevated and B and T cell function is often abnormal.

A definitive diagnosis of WAS can be made by sequencing the WAS gene to identify a mutation and by studying the individual's blood cells to determine if the Wiskott-Alrdrich Syndrome protein (WASp) is expressed at normal levels. These tests are done in a few specialized laboratories, and they require blood or other tissue.

Inheritance

WAS is caused by mutations (variations) in the WASp. The WAS gene is located on the short arm of the X chromosome, so the disease is inherited in an X-linked recessive manner. (See Inheritance Chapter.) This means that boys develop the disease, but their mothers or sisters, who may carry one copy of the disease gene, do not generally have symptoms. Because of the X-linked recessive inheritance, boys with WAS may also have brothers or maternal uncles (mother's brothers) who have the disease. It is estimated that approximately 1/3 of newly diagnosed individuals with WAS have no identifiable family history and, instead, are the result of new gene mutations. Identification of the precise gene mutation of an individual with WAS can help immunologists predict how severe their symptoms may be. In general, if the mutation is severe and interferes almost completely with the gene's ability to produce the WAS protein, the individual has the classic, more severe form of WAS. In contrast, if there is some production of mutated WAS protein, a milder form of the disorder may result. Identification of the mutation that causes WAS in a particular family not only allows the diagnosis of WAS in a specific individual but also makes it possible to identify females in the family who carry a mutant copy of the gene, and to perform prenatal DNA diagnosis for male pregnancies using cells obtained by amniocentesis or chorionic villus sampling.

Treatments

Vaccines

Because individuals with WAS have abnormal B and T cell function, they should not receive live virus vaccines since there is a possibility that a vaccine strain of the virus may cause disease. Complications of chicken pox infection occur occasionally and may be helped by early treatment following exposure with antiviral drugs, high dose immunoglobulin (Ig) replacement therapy or Varicella Zoster Immune Globulin (VZIG). Other non-live vaccinations can be given safely to individuals with WAS but may not generate protective levels of antibody.

Infections

Since individuals with WAS have abnormal antibody responses to vaccines and to invading microorganisms, most are treated with Ig replacement therapy to prevent infections. Because of the bleeding tendency in WAS, subcutaneous immunoglobulin replacement therapy (SCIG) is used with caution, but most individuals tolerate SCIG very well. Individuals who have had a splenectomy are particularly susceptible to rapidly progressing severe bacterial blood stream infections, so Ig replacement therapy combined with prophylactic antibiotics is particularly important in these individuals. When there are symptoms of infection, a thorough search for bacterial, viral, and fungal infections is necessary to determine the most effective antimicrobial treatment.

Bleeding Problems

Because the benefit is short-lived, preventative platelet transfusions are not recommended in WAS to increase the platelet count in an attempt to prevent bleeding episodes. In cases of active bleeding or injury especially if affecting the brain

or the gut, it may be necessary to stabilize the individual and prevent organ damage. For example, if serious bleeding cannot be stopped by usual measures, platelet transfusions are indicated. Due to constant increased blood loss, iron deficiency anemia is common among individuals with WAS, and iron supplementation is often necessary.

The spleen is an organ in the abdomen that serves as a sort of "filter" for the blood. Abnormal platelets or platelets that have been coated with autoantibodies are often trapped by the spleen where they are destroyed. For individuals with WAS, this may become a significant problem. Surgical removal of the spleen (splenectomy) has been performed in selected individuals with WAS/XLT in an attempt to correct thrombocytopenia, and in many cases, did increase platelet counts. Since the spleen also filters bacteria out of the blood stream, splenectomy significantly increases the susceptibility of individuals with WAS to blood stream infections (sepsis) and meningitis caused by encapsulated bacteria like *Streptococcus pneumoniae, Hemophilus influenzae*, and others. In the absence of a spleen, these infections can be rapidly fatal, so it is imperative that splenectomized individuals receive prophylactic antibiotics on a daily basis for the remainder of their lives. Splenectomy does not prevent the other features of WAS and should only be used to control particularly severe thrombocytopenia and potential lethal bleeding.

Eczema

The eczema in WAS can be severe and persistent, requiring constant care. Consultation with an allergist or dermatologist is often helpful for these individuals. At a minimum, regular application of a thick moisturizing ointment, not a lotion, at least twice a day is recommended. Excessive bathing may dry the skin further and worsen the eczema. Steroid ointments should be used to control inflammation in areas that are more significantly affected, but they may thin the skin with chronic use so should be used sparingly and in consultation with an allergist or dermatologist.

Allergic Disease

IgE mediated food allergy manifesting with anaphylaxis is common in WAS. Consultation with an allergist to assist in diagnosis and management of food allergies, including potential food challenges is recommended. Epinephrine should be prescribed to those with IgE mediated food allergy.

Autoimmune Disease

Autoimmune complications may require treatment with drugs that further suppress the individual's immune system. Systemic steroids (such as prednisone) are often the first immunosuppressant medication used to treat autoimmune disease and are often helpful in individuals with WAS. Since long-term use of high-dose steroid is associated with many undesired side effects, the dose should be reduced to the lowest level required to control symptoms and stopped if no longer needed. High dose Ig replacement therapy may also be beneficial in treating autoimmune disease in some cases. Rituximab, a B cell specific immunosuppressant, is effective in antibody mediated autoimmune diseases, such as autoimmune hemolytic anemia.

Hematopoietic Stem Cell Transplantation (HSCT)

Until recently, before gene therapy was introduced, the only long-lasting treatment for WAS was transplantation of hematopoietic stem cells present in bone marrow, peripheral blood, or cord blood. (See Immunoglobulin Replacement Therapy and Hematopoietic Stem Cell Transplantation Chapter.) Individuals with WAS have some residual T cell and NK cell function despite having an immune deficiency, and this has the potential to cause rejection of transplanted donor cells. To prevent this, individuals must undergo conditioning, or treatment with chemotherapy drugs, to destroy their own immune cells before the donor stem cells are infused. There are four potential donor types for any transplant:

1. Matched sibling donor
2. Matched unrelated donor
3. Haploidentical donor (half-matched, typically a parent)
4. Cord blood donor

In general, the risks of transplant rejection and Graft Versus Host Disease (GVHD) are decreased when the HLA-types match between the donor and recipient are closest. In WAS, the outcomes using an HLA-identical sibling donor bone marrow are excellent with an overall success rate approaching 90%-100% in most centers. With improvements in conditioning regimens and supportive care, the outcome using cells from an HLA-matched unrelated donor approach those obtained with matched sibling donors. Transplants using fully or partially

matched cord blood stem cells have also been quite successful. Before the year 2000, transplantation with cells from a haploidentical (half-matched) donor was successful in only approximately 50% of cases. However, in more recent clinical trials, the success rate of haploidentical transplantation increased to 90% following the introduction of novel techniques to prevent graft versus host disease. There remains a slight, but significant survival advantage if transplantation is performed in individuals less than age 5. After transplant, most individuals remain on immunosuppressant medications for a short period of time in order to decrease the risk of GVHD.

Gene Therapy

Gene therapy is an approach whereby a normal copy of the WAS gene is delivered into the individual's own bone marrow stem cells using a virus so the blood cells derived from the individual's bone marrow are then able to make normal WASp protein. (See Gene Therapy Chapter.) Since the individual's own cells are being modified, there is no risk for graft versus host disease like that observed after HSCT. The major risk of gene therapy is that the virus may insert a copy of the WAS gene randomly into one of the individual's chromosomes and cause increased production of one or more proteins that can cause cancer. Several years ago, gene therapy was used to successfully treat a small number of individuals with WAS, correcting their bleeding problems and immune deficiency. Unfortunately, most individuals participating in this trial developed leukemia as a result of the gene therapy virus inserting its DNA into a sensitive region of the individual's chromosomes. Subsequent clinical trials used new viral vectors demonstrating excellent long-term outcomes without resulting in leukemia. The success of more recent gene therapy trials for WAS is very encouraging, but a number of problems remain to be solved before it becomes more broadly applicable.

Expectations

Thirty years ago, WAS was considered to be a fatal disorder with a life expectancy of only two to three years. Even though WAS remains a serious disease with potentially life-threatening bleeding and infectious complications, advances in Ig supplementation, antimicrobials, and other supportive care have improved quality of life and significantly prolonged the survival of individuals. In addition, improvements in HSCT protocols and the development of additional drugs to treat infectious complications have substantially improved the outcomes of HSCT to an overall survival of close to 100%. The recent success of gene therapy for WAS holds promise for being the treatment of choice for this disease in the future.

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Chapter 12

Ataxia-Telangiectasia (A-T) and Related Disorders

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Ataxia Telangiectasia (A-T), Bloom Syndrome (BS), and Nijmegan Breakage Syndrome (NBS) are examples of a group of disorders called DNA breakage (or chromosomal instability) syndromes. They are characterized by chromosomal instability and breakage as well as a defect in the DNA repair mechanism. These syndromes are inherited in an autosomal recessive fashion. Affected individuals have varying degrees of delays in mental and physical development, organ system dysfunction, combined immunodeficiencies, and they are at high risk for various types of cancers.

Ataxia Telangiectasia

Clinical Features

Individuals with A-T have an unsteady, wobbly gait (ataxia), dilated corkscrew-shaped blood vessels (telangiectasia) on the white part of the eyes and sun exposed areas of the skin, immunodeficiency involving both B cells and T cells, and high rates of cancers. The neurologic symptoms worsen as individuals get older.

Some individuals with A-T are identified before they have any symptoms, because they have an abnormal newborn screen (TREC) test for Severe Combined Immunodeficiency. The first symptom of A-T is generally ataxia. When children start walking, they tend to sway, stagger, or wobble, and do not improve as they get older. They are usually unstable when sitting unsupported or standing in one place, for example, when standing in front of the sink to brush their hair or teeth. The ataxia is caused by abnormalities in the cerebellum, the part of the brain that controls balance and movement. Often these children are initially thought to have some other neurologic condition, such as cerebral palsy. When ataxia is the only symptom present, it is sometimes hard to make a diagnosis.

A-T causes a progressive decline in motor function, which may not become apparent until children are 4 to 8 years old. It is this deterioration, in addition to ataxia, which often leads to a correct diagnosis as deterioration does not occur in children with cerebral palsy. As they get older, children with A-T develop abnormalities in eye movements (delayed onset of eye movements, jerky movements, and difficulty in eye/head coordination when tracking moving objects or following a single line of print in a book). They also develop problems with fine motor control and have problems feeding and dressing themselves. Most have enough difficulty walking so that they need to use a wheel chair for at least part of the day by the time they are 10 or 12 years old. They develop an intention tremor (shaking when trying to use the hands), and difficulties with speaking (dysarthria) and swallowing (dysphagia). While this progressive deterioration occurs in all children, the rate of progression and severity vary widely from individual to individual.

Telangiectasia cause the whites of the eyes to look bloodshot. It can appear as though they have pink eye (conjunctivitis) or an allergy. Telangiectasia can also develop on sun-exposed skin such as the ears, neck, arms and legs. Most individuals with A-T

have these telangiectasia but some do not, and telangiectasia are rare in infants and very young children. This is another reason why the diagnosis of A-T is sometimes delayed.

Individuals with A-T have an increased susceptibility to infections, particularly in the lungs and/or sinuses. The reason for this susceptibility can be related to a humoral (B cell) immunodeficiency causing low immunoglobulin levels and impaired antibody responses. Approximately 2/3 of individuals with A-T have low levels or a complete absence of IgA, the immunoglobulin that protects individuals from infections on mucosal surfaces like the linings of the nose, airway, and intestines.

Individuals with A-T can also have reduced numbers of T cells, giving them a combined (B cell and T cell) immunodeficiency. They may have problems with chronic or recurrent warts or molluscum. A small number of individuals develop chronic inflammation of the skin (granulomas) that appears to be caused by a defective response to the rubella virus in the MMR vaccine. They do not usually get opportunistic infections like pneumocystis pneumonia. However, if they are treated with steroids at high doses or over a long period of time or if they need chemotherapy to treat cancer, the T cell counts may become low enough to make individuals susceptible to opportunistic infections.

The immunodeficiency in individuals with A-T generally remains stable over time but does worsen in approximately 15% of individuals. A thorough evaluation of humoral immune function is necessary in order to determine if there is a need for immunoglobulin (Ig) replacement therapy.

Immunodeficiency is not the only reason for susceptibility to infection. Individuals with A-T often have neurologic problems with swallowing (dysphagia), which can cause aspiration (solid food or liquids go down the trachea and into the lungs instead of into the esophagus and stomach). They also have an ineffective cough so that they have difficulty clearing mucus and aspirated material from the airways. The ineffective clearance can lead to chronic lung infections. The use of a vibrating vest or a cough assist device several times a day may be useful to shake mucus loose and make secretions easier to cough up. Sometimes infections related to aspiration can only be prevented by bypassing the mouth and esophagus and putting calories and nutrients directly in to the stomach through a gastrostomy tube (G-tube), thereby decreasing the amount of food and liquid taken by mouth.

Individuals with A-T are at an increased risk for developing cancers. For individuals under the age of 20 years, most cancers are lymphomas or leukemias. For individuals over the age of 20 years, there is also a considerable problem with solid organ cancers including the breasts, esophagus, colon, liver, and intestines. Treatment of the cancer must be modified to account for sensitivity to radiation and certain types of chemotherapy. Cancer occurs in approximately 25% of individuals with A-T.

Diagnosis

The diagnosis of A-T is based on detection of the features of the syndrome and supported by the following laboratory tests:

- Elevated alpha fetoprotein in the blood
- Mutation (abnormal DNA sequencing) in the A-T gene (ATM)
- Increased cell death or chromosomal breakage after the exposure of blood cells to x-rays in the laboratory
- Absence of the ATM protein on Western blot

Inheritance

A-T is an autosomal recessive disorder, which means that two copies of the abnormal gene (one from each parent) are required to cause the condition. The ATM gene controls the production of the ATM protein, an essential enzyme involved in cellular responses to DNA damage and other forms of cellular stress. For example, if there is a break in the double strand structure of the DNA, ATM signals the cell to stop growing and dividing, and then signals the DNA repair machinery to start working. The identification of this gene has made carrier testing and prenatal diagnosis possible.

Treatment

There is no cure for A-T or any of the specific features of the syndrome. Treatment is supportive. A team of care providers, including the affected individual, family members, primary care providers, immunologists, pulmonologists, neurologists, nutritionists, and ancillary therapy providers, is key in managing the disease. Other providers such as geneticists and oncologists may also be part of the team.

Treatment should be proactive as well as supportive. While the timing of the progression of the disease is unpredictable, the progression of the disease is not. For example, feeding problems will inevitably develop as dysphagia, and tremors can make

meals take a long time and become very fatiguing. Nutrition can be compromised and aspiration can occur. Early placement of a G-tube can supply nutrition that will allow growth, improve stamina, and decrease the risk of aspiration associated problems.

Infection management is another important part of treatment. Preventing infection is the first step. Prevention includes handwashing and avoiding individuals who are ill. Unless they are receiving Ig replacement therapy, individuals with A-T should receive all standard immunizations, including an annual influenza vaccine and a pneumococcal vaccine every 5-10 years. The MMR vaccine should be avoided because of the risk of developing cutaneous granulomas. Close contacts and family members should also receive all recommended immunizations, including an annual influenza vaccine.

Respiratory problems can be serious for individuals with A-T. They often have problems taking deep breaths and effectively coughing. They may benefit from a regular program of chest physiotherapy and daily use of a therapy vest. The key is to establish a pulmonary care regimen before serious, irreversible lung problems develop. If chronic lung disease develops, individuals may benefit from antibiotic prophylaxis to prevent infection and inhaled corticosteroids to decrease inflammation. Supplemental oxygen may also be beneficial.

Diagnostic A-T is a disorder of DNA breakage, and thus, there is a theoretical risk of chromosomal damage from radiation. Certain types of imaging tests pose a threat to individuals for chromosomal damage. For example, X-rays should be limited in individuals with A-T. It is generally accepted that x-rays should be done only if the results will have an impact on diagnosis and treatment. It is also important to limit the amount of radiation delivered in a routine CT scan by limiting the number of images taken. Individuals with A-T can have diagnostic MRIs and ultrasound exams, without problems since their imaging procedures are different than X-rays and CT scans. Consultation with a radiologist will help determine the best way to get imaging if it is necessary.

Expectations

Unfortunately, there is not a cure for A-T, and there are no specific therapies for the neurologic problems associated with the disease. The key to treatment is to anticipate that problems will occur and progress, and to deal with them proactively. For example, putting in a G-tube and getting at least part of needed calories and nutrients via G-tube feedings can prevent problems associated with malnourishment and decrease the risk of lung problems caused by aspiration. Diagnosing and treating an associated antibody disorder and instituting a regimen for airway clearance and other pulmonary care can help with infection prevention. Using a wheelchair when ambulation becomes difficult can help prevent exhaustion and other related difficulties. Addressing issues proactively will improve the quality and length of lives for individuals with A-T.

Children with A-T can and should attend school, although most will need assistive devices and full-time aides to assist with activities of daily living while the children are at school. Some academic difficulties are to be expected as progressively impaired eye movements make reading difficult. Delayed initiation of speech and problems with writing or using a computer may make it seem that there is cognitive impairment. However, cognitive function and hearing are not impaired in individuals with A-T. Early introduction and use of adaptive devices and technologies will help to mitigate some of the challenges children with A-T face at school. These children should always have an Individualized Education Program (IEP) and school personnel should be an integral part of the care team.

A-T is a progressive disease, but the timetable of progression is not the same for all individuals. It cannot be predicted in an individual. There is great variability between affected individuals, even individuals within the same family. The key is to assemble a care team knowledgeable about the disease, tuned in to potential problems, and dealing proactively with them. For example:

- A chronic cough may indicate a lung or sinus infection or demonstrate the need for a more effective airways clearance regimen.
- Choking when eating or drinking may indicate aspiration.
- Failure to grow or a child falling off their growth curve may indicate insufficient caloric intake.
- Daily fevers, pallor, and fatigue may indicate a malignancy.
- Infections that recur or fail to resolve when treated appropriately may indicate an immunodeficiency.

Even if problems are addressed proactively and promptly, the reality is that there will still be neurologic deterioration. It is important to note that as research and knowledge about A-T increases, so does the hope for changing the course of the disease. In the recent past, children with A-T seldom lived to adulthood. Currently there are individuals with A-T who are college students and able to live independently. Some individuals are living into their 50's. The goal of ongoing research is to make this the norm for individuals with A-T, rather than the exception.

Bloom Syndrome

Bloom Syndrome (BS) is a chromosomal damage syndrome, with some of the same features as A-T. The disease is caused by a mutation in the BLM gene that encodes a protein important in repairing malfunctioning DNS strands during DNA replication. BS is characterized by short stature, learning disability, dermatologic problems, immunodeficiency, obstructive lung disease, infertility, and increased risk of all types of cancers. As with all syndromes, not every affected individual has all of these characteristics, so there is great variability and degree of severity among individuals.

Individuals with BS often have high-pitched voices, narrow facial features, and long arms and legs. They tend to have normal muscle development but reduced amounts of subcutaneous fat tissue. The dermatologic problems associated with BS include significant sun sensitivity and poikiloderma, a skin condition characterized by areas of abnormal pigmentation and telangiectasias. The diagnosis of BS is made when individuals present with characteristic features of the syndrome and is confirmed with genetic testing.

The potential for cancer is the greatest concern for individuals with BS. Often individuals have multiple malignancies. Leukemia is the most common cancer in individuals less than 20 years and solid organ tumors are more common in individuals older than 20 years. Colon cancer can present at any age, as can skin cancers.

As with A-T, proactive care is key to improve the quality of life. Affected individuals should have all routine cancer screenings including colonoscopy and skin surveillance. In this population, symptoms, such as fatigue, night sweats, bruising, and swollen glands, should be assumed to be signs of malignancy until they are proven otherwise.

Nijmagen Breakage Syndrome

Nijmagen Breakage Syndrome (NBS) is a chromosomal instability condition. Affected individuals generally have small heads (microcephaly), a combined B and T cell immunodeficiency, and predisposition for cancers. Individuals with NBS often have mild growth retardation and cognitive disability. They have a propensity for infections, particularly sinopulmonary infections, because of the combined immunodeficiency. Individuals with NBS require the same types of care as do those with other DNA breakage syndromes. Health maintenance and cancer surveillance are critically important, as is aggressive management of infection and related problems.

Summary

DNA breakage syndromes are a rare group of disorders characterized by radiation sensitivity, and varying degrees of immunodeficiency as well as cognitive and/or physical developmental problems. All share an increased risk for malignancies. While there is no cure for these illnesses, symptoms can be alleviated by proactive medical management and surveillance by a knowledgeable healthcare team. Early diagnosis is important to allow for optimal management of the affected child, as well as genetic counselling for the parents and extended family members.

Adapted from: Chapter 12 Ataxia-Telangiectasia. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 13

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) Syndrome

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Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome is an inherited immunodeficiency in which individuals develop severe, early-onset autoimmune disease because of a problem with how the immune system is controlled and regulated. Unlike most immunodeficiencies that are very susceptible to frequent or severe infections, infections are not a major problem for most individuals with IPEX. Rather, severe autoimmunity causes a poor quality of life and leads to early death in most individuals.

Overview

IPEX is an X-linked disorder (See Inheritance Chapter) in which affected boys develop severe autoimmunity that can target any organ. The gut, skin, and endocrine organs — particularly the pancreas and thyroid gland — are the most common targets. Usually, the autoimmunity begins early in life and can be very severe. It tends to worsen and spread as individuals age, leading to a poor quality of life and early death in virtually all cases. Treatment for IPEX is a combination of supportive care and immune suppression. Hematopoietic stem cell transplantation (HSCT), also referred to as bone marrow transplantation, is the only treatment where improvement is seen for this condition and should be considered early in most cases.

Immunobiology

A variety of mechanisms are used by the immune system to restrain autoimmune reactions. One of the key mechanisms is generation of a group of T cells known as regulatory T cells, sometimes referred to by immunologists as Treg cells. These Tregs make up only a small portion of the total T cells in the human immune system, but they play a powerful role in controlling or restraining the actions of other immune cells. In fact, they might be considered to be like a small police force that has the job of monitoring the responses of other immune cells to make sure that they don't react longer than necessary, respond too strongly, or inappropriately target other cells or organs of the host's body.

The problem in IPEX is that this small population of regulatory T cells is missing or not working effectively so the immune system is unrestrained in its responses. Essentially, the immune system can be activated normally but has no brakes. Once threats like infectious organisms have been attacked and cleared, the activated immune system will turn its assault on the host if it is not controlled by regulatory T cells using a variety of tools that they have for this purpose. One of the key proteins that is required for regulatory T cells to develop and function normally is called FOXP3. Mutations that damage or destroy the FOXP3 protein are the cause of IPEX.

Using animal models of IPEX, it has been determined that when Tregs are absent, the remaining T cells become highly activated and play a major role in driving the autoimmunity and inflammation that are characteristic of the disease. Since T cells have the ability to guide and direct the activities of other immune cells, these highly activated T cells attract other immune cells into the inflammatory process leading to an overwhelming, uncontrolled immune response.

Clinical Presentation

Most individuals with IPEX develop autoimmune problems when they are very young, often when they are infants. There are four autoimmune disorders that are most common in individuals with IPEX. Most individuals have at least two of these:

Enteropathy: This is an autoimmune attack on the gastrointestinal tract that often presents with severe, watery diarrhea that makes it difficult for individuals to absorb nutrients. As a result, it is very common for individuals to have problems gaining weight and growing. Individuals often lose weight after the diarrhea starts. Occasionally, there may also be blood in the diarrhea although this is less common. More than one-third of individuals complain of food allergies that may cause worsening of the diarrhea or may lead to full-fledged allergic reactions with breathing problems, hives, and other complications.

Rashes: Inflammatory rashes of the skin are present in most individuals, with eczema being the most common. Other rashes may also occur including psoriasis, characterized by itchy, red, scaly patches of skin, or pemphigus, a rash in which inflamed blister-like patches develop on the skin.

Diabetes: Autoimmune diabetes, sometimes referred to as type 1 diabetes, leads to high blood sugar levels that develop because the cells in the pancreas that are supposed to be making insulin are under attack by the immune system so their capacity to produce insulin is destroyed. As a result, individuals may need to be treated with insulin shots to control their blood sugar levels.

Thyroid disease: Autoimmune attack of the thyroid gland leads to problems with normal production of thyroid hormone. In most cases this causes hypothyroidism or a decreased level of thyroid hormone production. As a result, individuals may feel cold, have low energy, etc. In some individuals the autoimmune attack may cause hyperthyroidism or increased thyroid hormone levels that can cause them to feel hot, overly energetic, lose weight, and have thinning hair.

In addition to these four autoimmune disorders, other autoimmune problems are also quite common in IPEX. Approximately half of individuals develop problems with destruction of blood cells by autoimmune attack leading to anemia (low red blood cell numbers), thrombocytopenia (low platelet numbers), or neutropenia (low neutrophil numbers). Autoimmune liver disease and autoimmune kidney disease are also present in some individuals. IgE levels are highly elevated in virtually all individuals with IPEX, and this is often accompanied by allergies to foods or medications but severe asthma is not particularly common.

Milder forms of the disease have now been diagnosed in some older individuals (> 20 years old) who only have inflammatory bowel disease, severe allergies, eczema, or early-onset type 1 diabetes, and it is likely that other clinical presentations will become evident as more individuals are diagnosed by genetic testing.

Diagnosis

IPEX is usually suspected in individuals that have the characteristic clinical findings of early-onset diarrhea, endocrine problems (particularly early-onset type I diabetes), and rash. A diagnosis of IPEX is confirmed by identification of a mutation in the FOXP3 gene sequencing. Almost all individuals have highly elevated levels of Immunoglobulin E (IgE), but this can be seen in other immune deficiencies or in some individuals with allergies, so is not diagnostic. Many individuals have a decreased number of regulatory T cells circulating in blood. Some individuals with IPEX have a normal or increased number of regulatory T cells. These cells however, do not function appropriately to suppress other immune cells. Since there is no reliable clinical test for assessing the function of regulatory T cells, the measurement of Treg numbers or function is inadequate as a diagnostic test for IPEX.

Inheritance

The FOXP3 gene is on the X-chromosome, and inheritance of IPEX occurs in an X-linked recessive pattern. Females that carry a mutation of FOXP3 on one chromosome do not exhibit symptoms of IPEX because they have a second X-chromosome that has a normal copy of the FOXP3 gene that compensates for any problems. Boys of carrier mothers have a 50% chance of being born with IPEX since they inherit one X-chromosome from their mother. If they receive the X-chromosome that has a mutation in the FOXP3 gene, they develop IPEX because the Y chromosome received from their father does not have a copy of the FOXP3 gene on it.

Treatment

Because of the severe autoimmunity in IPEX, initial treatment typically involves a combination of supportive care and aggressive immune suppression. Supportive care needs vary among individuals depending on their major clinical symptoms.

Supportive care: Most individuals with IPEX have had at least some degree of nutritional compromise due to chronic diarrhea and malabsorption, often leading to significant weight loss and poor growth so nutritional support is very important. Some individuals can improve by receiving supplemental oral feeding using elemental formulas made up of basic nutrients. Often these need to be given by nasogastric tube (NG-tube) or gastrostomy tube (G-tube) so they can be delivered at a slow, steady rate throughout the day. In some individuals, even this slow, gentle approach of delivering nutrients to the bowel leads to worsening of the diarrhea. In these individuals, a central venous catheter is placed, and nutrition is delivered intravenously in the form of Total Parenteral Nutrition (TPN). Little or no food is given into the bowel. This allows the individual to receive much needed nutrition without making the diarrhea worse.

The severity of skin disease in IPEX varies widely with some individuals having only mild eczema and other individuals having severe psoriasis-like rashes that are associated with skin fissuring and ulceration. Aggressive treatment of the skin using a combination of moisturizers, steroid ointments, ointments containing other immunosuppressants, like tacrolimus, and wet wraps can help to control skin disease. Often referral to dermatology, and in severe cases, consultation with wound care specialists is very helpful.

All individuals with IPEX need to be screened for diabetes and thyroid disease. Individuals diagnosed with diabetes or hypothyroidism should be evaluated by an endocrinologist and treated with insulin and/or thyroid hormone as appropriate. Individuals who have autoimmune disease causing anemia or low platelet counts may require transfusions with red blood cells or platelets. Supportive treatments to counteract the effects of autoimmunity on other organs should also be provided as needed.

Immune suppression: As described above, previous research in the animal model of IPEX has determined that T cells play a major role in driving the immune attack that is characteristic of the disease. Initial immunosuppressive treatments therefore focus on decreasing the activity of T cells with drugs like tacrolimus, cyclosporine, or rapamycin. Steroids like prednisone are often used initially when individuals have very active disease but as they improve, the steroids can often be discontinued and individuals can be maintained on tacrolimus, cyclosporine or rapamycin alone. In individuals who have autoantibodies that target specific organs and make the autoimmunity worse, treatment with rituximab or similar drugs that deplete the B cells can be helpful. Since anything that activates the immune system like vaccination or severe infection may cause disease symptoms and autoimmunity to worsen, individuals who have not been vaccinated may be started on intravenous or subcutaneous immunoglobulin replacement (See Immunoglobulin Replacement Therapy Chapter) to try to prevent infections and avoid the need for further vaccination. Often, individuals require progressively increasing immune suppression over time, which leads to a need for other treatments such as Hematopoietic Stem Cell Transplantation (HSCT).

Hematopoietic stem cell transplantation: The only transformative treatment for IPEX at the present time is HSCT, also referred to as bone marrow transplantation. There are a variety of approaches used to perform the transplants in individuals with IPEX, and the approach used often varies by transplant center. Often, HSCT in IPEX is complicated because individuals are ill and pre-existing organ damage caused by autoimmunity or side effects of medications can increase the risk of transplant. Aggressive supportive care to stabilize individuals and improve their clinical status prior to initiating transplant is critical. Overall survival after transplant has been reported to be 60-85% in most studies. Gene therapy and gene editing approaches to treat IPEX are under development and may be available in the future but neither are clinically available at the present time.

Expectations

Historically, individuals with the most severe forms of IPEX died within the first two years of life from complications associated with autoimmunity. With increased recognition of the disease by pediatricians and pediatric subspecialists along with initiation of appropriate supportive care and immune suppression, most individuals with severe disease can be stabilized until they can undergo HSCT. Individuals with milder forms of IPEX can survive much longer even without ideal management. That said, most individuals with milder forms of

the disease still have multiple and severe clinical complications. As a result, it is unusual for individuals to survive beyond 30 years of age without a HSCT. HSCT can potentially treat the clinical problems associated with the disease except for diabetes or thyroid disease. If these develop prior to transplant, it is usually the result of significant damage to the pancreas or thyroid gland. This damage is typically permanent and does not recover after transplant. This suggests that evaluation for early transplant after the diagnosis is made is an important consideration. The earliest transplants for IPEX were done more than 20 years ago, and those individuals who have had successful transplants have continued to do well although some individuals have had transplant-related complications or recurrence of some autoimmune problems.

Chapter 14

CTLA-4 Haploinsufficiency and LRBA Deficiency

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Mutations in the genes encoding cytotoxic T lymphocytic antigen-4 (CTLA-4) and lipopolysaccharide responsive beige-like anchor (LRBA) can cause immune dysregulation. This means the components of the immune system regulating inflammation, autoimmunity, and cancer lose their proper function, leading to an array of autoimmune disorders and infections.

Overview

CTLA-4 Haploinsufficiency is a genetic condition in which one copy of the gene is lost leaving a single functional copy of the gene. However, having only one copy of the good gene is not sufficient to produce normal function for the CTLA-4 gene in question. LRBA Deficiency causes poor immune function that results from uncontrolled activation and inadequate regulation of some of their immune cells. This results in both immune deficiency and immune dysregulation, the latter leading to a variety of autoimmune disorders. As a result, individuals with either of these diseases may have recurrent respiratory infections that start early in childhood, significant immune inflammation of their organs, and may have a number of autoimmune conditions. Autoimmune conditions occur when the immune system creates antibodies that attack the body's own tissues and cells. There may also be invasion of tissues with lymphocytes that result in the destruction or dysfunction of the targeted organs. The lungs, brain, intestines, liver and kidneys are the organs most commonly affected. Uncontrolled aggregation of immune cells can lead to an enlarged spleen or lymph nodes. Additionally, because of immune dysfunction, these conditions increase the risk of developing some cancers, like lymphoma.

Immunobiology

The CTLA-4 protein, found on the surface of T cells, is critical for the immune system, particularly in the role of regulating and keeping the immune cells in check. The LRBA protein is important for the control and transport of CTLA-4 from inside the cell to back on the surface. Mutations in either CTLA-4 or LRBA genes may lead to significantly diminished or absent CTLA-4 protein and function, ultimately causing uncontrolled inflammation and autoimmunity.

Clinical Presentation

Because mutations in CTLA-4 and LRBA can both result in decreased CTLA-4 protein and function, there are many similarities in the clinical presentation of these two conditions. The hallmark feature of both is uncontrolled immune activation, inflammation and often immunodeficiency (Table 14:1A). The immunodeficiency is similar to Common Variable Immune Deficiency (CVID) as individuals have hypogammaglobulinemia and impaired antibody responses. In fact, some individuals with these conditions are initially diagnosed with CVID. Like individuals with CVID, they are prone to developing recurrent sinus and lung infections. These infections often start in childhood and can become more severe with age. Individuals with LRBA Deficiency usually

present in their pre-school age years while those with CTLA-4 Haploinsufficiency may not present until young adulthood. In both diseases, individuals also have increased susceptibility to infections caused by Epstein Barr virus (EBV, the mono virus) and cytomegalovirus (CMV). These infections may recur frequently and may lead to the development of certain lymphomas.

The degree of immune dysregulation, such as autoimmunity and inflammation seen in individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency, is clinically quite variable (Figure 14:1B). Both diseases may present with chronic diarrhea caused by inflammation of the intestine, also called enteropathy. An individual may present with failure to thrive, weight loss, or nutritional deficiencies because of their chronic gastrointestinal losses. Almost all individuals will develop an autoimmune condition as part of their immune dysregulation at some time in their life; some individuals develop multiple autoimmune problems. Autoimmune conditions result from the body making antibodies that attack the body's own tissues and cells. Autoimmune cytopenias (low white blood cells, red blood cells, or platelets) are the most common issue. Individuals can also form antibodies that attack their own organs (such as thyroid, pancreas, joints) and result in destruction and altered function of those organs or tissues. This may present in the form of thyroid disease, diabetes, arthritis, psoriasis, vitiligo, or alopecia (hair loss). Similarly, some individuals can develop aggregates of immune cells or lymphocytes that appear as localized areas of inflammation in their vital organs that leads to organ dysfunction. In CTLA-4 and LRBA, the most often seen type of inflammation occurs in the lung, brain, intestines, bone marrow, and—to a lesser degree—in kidneys.

On clinical exam, individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency may have a big spleen, liver or sometimes enlarged lymph nodes.

Individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency are at increased risk for developing cancers and lymphoma. Because of this, their health status needs to be closely monitored.

Diagnosis

CTLA-4 Haploinsufficiency or LRBA Deficiency should be considered in any individual who presents with early onset recurrent sinopulmonary infections and autoimmune conditions. The symptoms can include chronic diarrhea, weight loss or failure to gain weight, an enlarged spleen, and/or enlarged lymph nodes. White blood cell infiltration of certain body parts (such as lung, brain, kidney, intestines, or bone marrow) is also a distinguishing feature of both diseases.

When considering CTLA-4 or LRBA mutations as a potential cause of disease in an individual, an initial immune evaluation should include a complete blood count (CBC) with differential to look for low blood counts, serum immunoglobulins (IgG and IgA are usually low, while IgM can be normal or low), and flow cytometry to look at the numbers of different kinds of lymphocytes. Individuals may not have protective levels of antibodies, even to diseases against which they have been vaccinated. Autoimmune conditions are often diagnosed by detecting auto-antibodies, or antibodies targeted at the body's own tissues and cells. When there is a clinical concern for lymphocytic infiltration of organs, imaging studies (usually CT scans or MRIs) or even biopsies of these tissues may be necessary.

Ultimately the diagnosis of CTLA-4 Haploinsufficiency or LRBA Deficiency is confirmed after identifying a gene mutation with genetic testing.

Inheritance

Both CTLA-4 Haploinsufficiency and LRBA Deficiency are rare immunologic diseases that can be inherited or passed on to family members, or they can occur spontaneously. CTLA-4 Haploinsufficiency is caused by a mutation in one copy of the CTLA-4 gene that results in decreased protein and function. The inheritance pattern for CTLA-4 Haploinsufficiency is known as autosomal dominant, which means that if a child inherits the gene mutation the child can have the disease. The chance of a child inheriting the mutation is 50% if one of the parents is carrying the mutation. Some individuals with CTLA-4 Haploinsufficiency appear to be asymptomatic, meaning they have the mutation but have no clinical signs of the disease. This is because CTLA-4 Haploinsufficiency is considered to have variable penetrance. As a result, multiple members of the family may carry the gene mutation but only some may be sick and some may not be sick at all. Nonetheless, all family members identified with the mutation need to be counseled of their risks, as disease signs and symptoms can present later in life. LRBA Deficiency is usually caused by two mutations in the LRBA gene causing decreased protein. The inheritance pattern for LRBA Deficiency is known

as autosomal recessive, which means that both genes for the protein must have the mutation for the condition to develop. The chance of a child inheriting the condition is 25% if each parent is a carrier of one mutation. Unlike CTLA-4 Haploinsufficiency, LRBA Deficiency has shown near complete penetrance, meaning that people with the two mutations (one in each copy of the gene) almost always have clinical signs of disease.

Treatment

Individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency who have recurrent infections because of an antibody deficiency require immunoglobulin (Ig) replacement therapy. They may be treated with prophylactic antibiotics, which are antibiotics given to prevent the development of disease or infection. The goal of these therapies is to prevent organ damage that can happen when infections occur frequently.

Individuals with evidence of significant immune dysregulation and resulting decreased organ function should be treated with immune suppression. These therapies work to turn off the dysregulated immune system. There is now an injectable drug, abatacept, a medication approved by the FDA for use in rheumatoid arthritis and certain types of psoriasis, which can act as a CTLA-4 replacement, and has shown promising results in improving the immune dysregulation in both individuals with CTLA-4 Haploinsufficiency and LRBA Deficiency. Other immunosuppressants often used to treat these diseases include systemic steroids (such as prednisone, methylprednisolone), sirolimus, and rituximab. Sirolimus is an immune suppressant that inhibits the activation of T cells and B cells, useful in preventing the rejection of kidney transplants. Rituximab is a monoclonal antibody directed at B cells and is used to treat a number of autoimmune diseases and certain cancers. As with many primary immunodeficiency diseases, hematopoietic stem cell transplantation (HSCT) is an option in treating CTLA-4 Haploinsufficiency and LRBA Deficiency but is not without significant risk.

Expectations

Some people carrying the mutations in CTLA-4 do not have signs or symptoms of disease, or may be minimally affected (for example, they may only have thyroid disease or vitiligo). Still they must be followed closely by doctors because they are at risk for developing more signs and symptoms of disease later in life.

Once on appropriate management to reduce infections, inflammation and autoimmunity, many individuals with CTLA-4 Haploinsufficiency or LRBA Deficiency are able to lead relatively normal lives. They do not need to be isolated or limited in their daily activities. Because the types and extent of immune dysregulation seen in both CTLA-4 Haploinsufficiency and LRBA Deficiency is quite variable, individuals often are followed by many subspecialty doctors and need close monitoring.

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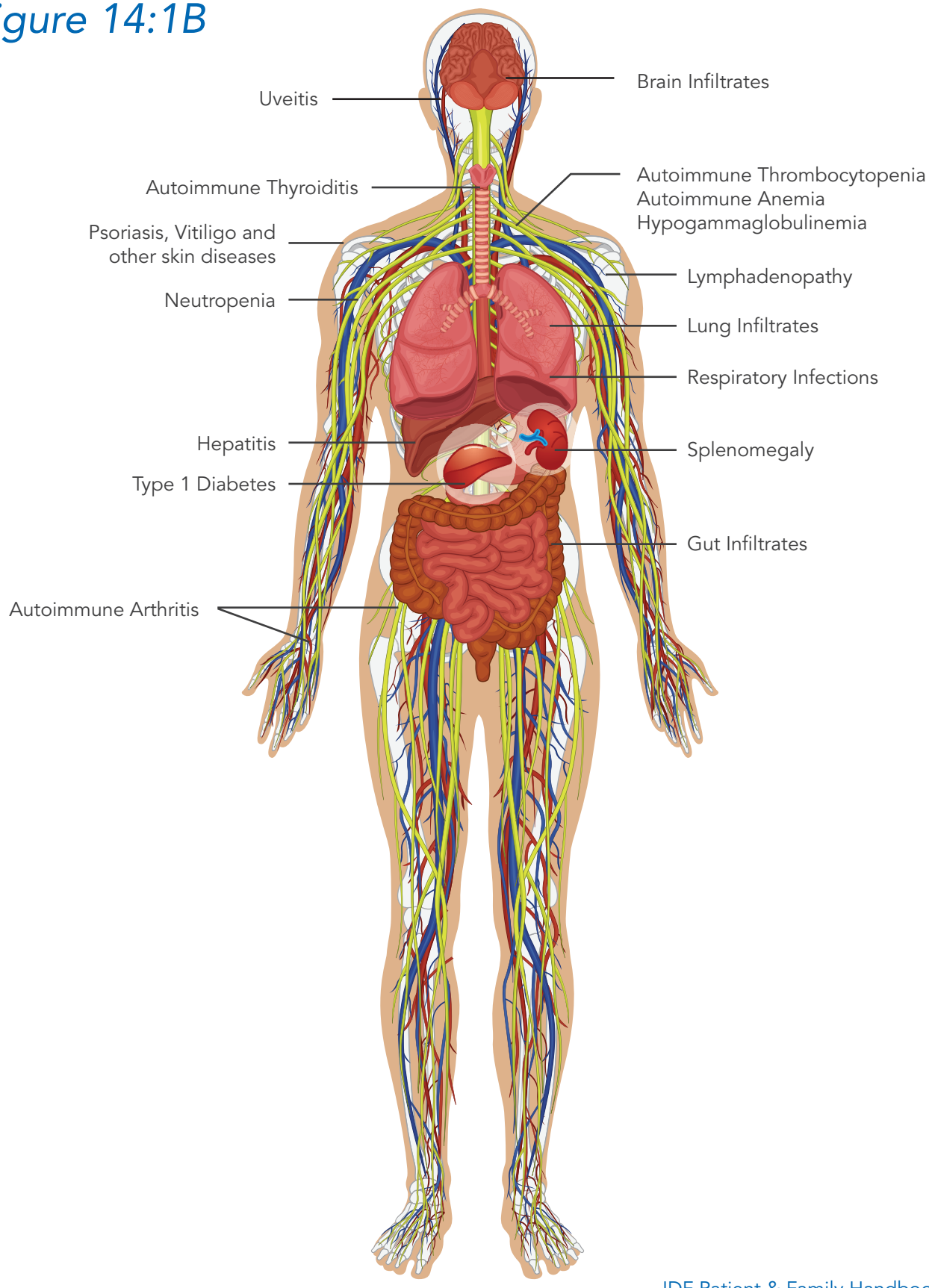
Common Clinical and Laboratory Findings Associated CTLA-4 Haploinsufficiency and LRBA Deficiency

Table 14:1A

Infection Susceptibility
Recurrent otitis media
Recurrent viral upper respiratory infections
Recurrent bronchitis, sinusitis and/or pneumonia
Epstein-Barr virus or Cytomegalovirus in the blood
Autoimmunity
Thyroiditis
Type I Diabetes mellitus
Hepatitis
Psoriasis, vitiligo, and other skin diseases
Uveitis (inflammation of the eye)
Lymphoproliferation, White Blood Cell Organ Infiltration and Inflammation
Chronic lymphadenopathy
Splenomegaly
Inflammatory bowel disease, enteropathy
Lung infiltrates
Brain infiltrates
Liver disease
Immune Laboratory Abnormalities
Hypogammaglobulinemia (most commonly low IgG and low IgA)
Poor vaccine response
Low circulating lymphocyte numbers - many with low T and B cells
Low NK cells
Low number of Treg cells

Widespread Immune Dysfunction Seen in CTLA-4 Haploinsufficiency and LRBA Deficiency

Figure 14:1B



Chapter 15

Diseases of Immune Dysregulation: STAT1 and STAT3 Gain of Function

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Introduction

Immune dysregulation occurs when the immune system cannot regulate normal control over inflammation, leading to severe inflammatory complications. Two of these diseases are called STAT1 Gain of Function (GOF) Disease and STAT3 Gain of Function (GOF) Disease. STAT stands for: signal transducer and activator of transcription. There are six STAT proteins. STATs are important proteins that enhance immune responses, particularly the production of interferon gamma, another protein that is crucial for defense against certain infections and for the control of inflammation. Mutations in STAT proteins can lead to:

- Loss of function of the protein where it does not function at all, or
- Gain of function of the protein where the protein functions too much and cannot be turned off.
- Gain of function of the STAT1 and STAT3 proteins cause diseases of immune dysregulation, autoimmunity, and increased risk of infections.

Definition

STAT1 and STAT3 GOF Diseases are genetic disorders in which immune cells are over activated. STAT1 and STAT3 are proteins found inside most immune cells that are activated after the immune cell itself is activated by other signaling proteins called cytokines, such as interferon gamma and IL-6, respectively. Once the cell is stimulated, the STAT protein activates and encourages other immune responses to help the cell to kill bacterial, viral, and fungal infections. Overactive STAT1 and STAT3 lead to dysfunction of both STAT1 and STAT3, and it places individuals at increased risk of infections and autoimmune disease.

Clinical Presentation

STAT1 GOF

Individuals with STAT1 GOF will present to a healthcare provider because of chronic or unusual infections or severe autoimmune disease that is not easily controlled with standard immune suppressing medications.

One of the most common manifestations in individuals with STAT1 GOF is chronic infections with a fungus that are mostly limited to mucosal surfaces, skin, and nails, also known as mucocutaneous candidiasis (CMC). This occurs in more than 90% of individuals. CMC is an infection of the mucus membranes of the mouth (called thrush), gastrointestinal tract, skin, and nails with *Candida* or other common skin fungus. Presentation of CMC is usually in childhood, with some as young as age of 1 at the time the infections start. CMC can often be difficult to treat, requiring oral anti-fungal medication, and likely will return when anti-fungal medications are stopped. More rarely, individuals with STAT1 GOF can be susceptible to severe invasive fungal infections. These infections include *Aspergilllus, Histoplasma, Coccidiomycosis*, and *Cryptococcus*. Pneumonia, an infection of the lungs, is the most common site of invasive fungal infection.

Bacterial infections with common community acquired bacterial organisms also occur in individuals with STAT1 GOF. The infections have a tendency to occur in the lungs as lower respiratory tract infections, bronchitis, or pneumonia. Bacterial infection of the eye, skin, and nail beds are also common. Individuals with STAT1 GOF are also susceptible to Mycobacterial infections. Mycobacterium is a class of bacteria that typically only infect individuals with immunodeficiency or those that are immune suppressed.

Viral infections are also a source of concern in these individuals. The most common viruses causing infection are Herpes family viruses such as herpes simplex virus, the cause of cold sores; varicella zoster virus, the virus that causes chickenpox and shingles; Epstein Barr virus (EBV), the cause of mononucleosis; human papilloma virus (HPV), the cause of warts; and cytomegalovirus (CMV), a virus that typically goes unnoticed by people with competent immune systems but causes severe disease in individuals with immune deficiency. These viruses can cause skin infection, pneumonia, or enter the blood stream where they cause widespread infection and dysfunction of different organ systems.

Most individuals develop some form of autoimmunity by the third decade of life. The autoimmunity that occurs in STAT1 GOF often affects the endocrine and hematologic systems. Hypothyroidism and early onset diabetes are common. Autoimmune hemolytic anemia and autoimmune thrombocytopenia (autoimmune destruction of red blood cells or platelets) can be life threatening and may require blood or platelet transfusions. A subset of individuals with STAT1 GOF have symptoms very similar to Immunodysregulation-Polyendocrinopathy-Enteropathy-X-linked (IPEX). (See IPEX Chapter.) These individuals will have early onset autoimmunity, such as diabetes mellitus and hypothyroidism as well. In addition, individuals with STAT1 GOF with similar symptoms to IPEX can have severe enteropathy. Enteropathy is destruction of the small and large intestine's absorptive surface. Individuals with enteropathy have substantial difficulty in absorbing nutrients and have very frequent diarrhea with weight loss and malnutrition. Because of poor nutrition, individuals will have growth failure.

Other clinical features include a susceptibility to the development of aneurysms in the brain. An aneurysm is an abnormal out-pouching of a blood vessel that causes the blood vessel wall to become weak. Small numbers of individuals have learning disabilities. Some individuals also demonstrate susceptibility to skin, gastrointestinal tract, and throat cancer.

The immune features in individuals with STAT1 GOF can be very variable. Individuals may have low lymphocyte counts and function including low T cell, B cell, and NK cells. Some individuals may also have hypogammaglobulinemia (low IgG, low IgA, or low IgM). Susceptibility to infections, particularly viruses and Mycobacterium, occurs when there are abnormal lymphocyte counts and/or function.

Clinical Presentation

STAT3 GOF

Individuals with STAT3 GOF most commonly present with severe early onset autoimmunity. Individuals often have more than one autoimmune disease and the symptoms of autoimmunity are severe and hard to control. The most common types of autoimmunity involve the endocrine (hormone) system, the hematologic system (blood cells and platelets), gastrointestinal tract, lungs, and liver. Thyroid disease is the most common autoimmune endocrine disorder, treated with thyroid replacement. Hematologic autoimmune disorders include autoimmune destruction of the blood cells and platelets that can be life threatening and require transfusions of blood or platelets. Enteropathy due to autoimmune destruction of the lining of the intestinal tract as chronic diarrhea can cause severe malabsorption of nutrients and failure to thrive. In addition, some individuals may have inflammation of the intestine or colon, termed colitis, that can also lead to poor weight gain, abdominal pain, chronic diarrhea, and blood in the stool. Autoimmune destruction of the liver or lung can lead to organ dysfunction or failure respectively. Other autoimmune disorders, including eczema, rheumatoid arthritis, and eye disease, can also occur.

A major feature of individuals with STAT3 GOF is the presence of lymphoproliferative disease. In lymphoproliferative disease, immune cells in lymph organs grow at an abnormal rate. Lymphoid organs include the spleen, liver, and lymph nodes and when this growth occurs, these organs will expand causing abnormally large lymph nodes, liver, and/or spleen. Lymphoproliferation, which is growth of lymphocytes in increased quantities, can ultimately impact the function of the affected organ, and it can prevent the lymph cells from responding appropriately when there is infection.

Acute short stature is another common feature in individuals with STAT3 GOF. The height of individuals is often substantially lower than the expected normal for age, and this persists to adulthood. Individuals often are treated with growth hormone replacement, but this is controversial as to whether there is any benefit.

Immune abnormalities also are very variable in individuals with STAT3 GOF. Low T cell and B cell quantities can occur as can hypogammaglobulinemia (low IgG). It is often hard to differentiate if the

immune abnormalities are secondary to treatment of the autoimmune features. Infections can occur in STAT3 GOF, but the autoimmune features are the more common presentation. Infections, including bacterial, viral, mycobacterial, and fungal, can be severe, invasive, and life threatening. Prophylaxis against infections is often used especially if a substantial number of immune suppressing medications are used for treatment of autoimmunity.

Diagnosis

The definitive diagnosis for both STAT1 and STAT3 GOF Diseases currently consists of genetic testing and confirmation with functional tests. Thus far, the functional tests are only available on a research basis. However, it is critically important to perform a comprehensive immune evaluation to understand how the disease has affected the immune system.

Inheritance

Mutations in STAT1 and STAT3 that cause gain of function are inherited in an autosomal dominant manner. With autosomal dominant inheritance, one parent is affected. However, STAT1 and STAT3 GOF mutations can also occur spontaneously in individuals in which a parent is not affected.

Treatment

Treatment of individuals with STAT1 GOF and STAT3 GOF Diseases concentrates on suppressing the immune system to treat autoimmunity, treating infection, and preventing further infection. Treatment of the autoimmunity is challenging. If there is hypothyroidism or diabetes, hormone replacement with thyroid hormone or insulin is indicated. Treatment of other autoimmune features, including autoimmune anemia or thrombocytopenia (low platelet count), often is treated with corticosteroids or other immune suppressing medications. In some cases, the autoimmune features fail standard therapy and require the addition of several immunosuppressing agents. In these cases, risk of infection increases as these medications suppress the immune system.

Treatment of CMC in STAT1 GOF often requires oral or IV anti-fungal medications, and individuals should remain on anti-fungal prophylaxis to prevent CMC. Depending on the effects of immunologic evaluation – whether there is low lymphocyte counts or function and whether there is hypogammaglobulinemia will dictate whether an individual may need to receive prophylaxis against bacterial, fungal, or viral infections. Some individuals receive immunoglobulin (Ig) replacement therapy when there is low IgG.

The biology that leads to STAT1 and STAT3 activation has afforded the opportunity to use specific therapeutic agents that interfere with the mechanism of disease at the cell level. In STAT3 GOF, there is a strong signature with the inflammatory cytokine IL-6. IL-6 is a cytokine that is associated with the development of specific autoimmune diseases, particularly rheumatoid arthritis. Blockage of IL-6 with medications such as tocilizumab has been effective in a small number of STAT3 GOF individuals that have autoimmunity. Both STAT1 and STAT3 are activated in the cell after activation of specific proteins called janus kinases. Two medications are available that block janus kinase induced activation of STAT proteins: tofacitinib and ruxolitinib. These janus kinase inhibitors have been used off-label (in a non-FDA approved treatment regimen) in a small number of individuals and have been extremely successful at improving or resolving autoimmunity and in treating CMC. Tocilizumab, ruxolitinib, and tofacitinib are all FDA approved medications for treatment of other diseases and are not approved for use in STAT1 or STAT3 GOF. Therefore, these medications should be used cautiously, only when other methods of treatment have failed and used in consultation with an immunologist or rheumatologist. Clinical trials to understand how best to use these medications in individuals with STAT1 and STAT3 GOF are forthcoming.

Lastly, hematopoietic stem cell transplantation (HSCT) has been used successfully as a form of treatment in a small number of individuals with STAT1 and STAT3 GOF. In all cases, the transplantation was performed as a lifesaving procedure. Overall survival was disappointing at 40% and 56% in STAT1 and STAT3 GOF respectfully. Determining the optimal transplant strategy needs further study before HSCT is more widely and routinely used.

Expectations

Individuals with both diseases must take caution with infection exposures. Inflammation from infection can trigger or worsen inflammatory and autoimmune manifestations especially those in the lung and intestines. Individuals with STAT1 GOF are especially susceptible to fungal disease and viral disease with herpes family viruses. Individuals with STAT3

GOF are susceptible to progressive autoimmune disease. With early diagnosis and treatment of infections and autoimmunity with targeted therapy, individuals can have stable disease. For the more severe presentations, HSCT can be considered after a thoughtful discussion between the family and the immunology provider in order to weigh the risks and benefits on an individual basis. Genetic counseling is important for individuals and their families.

Chapter 16

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) and Autoimmune Polyglandular Syndrome Type-1 (APS-1)

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Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type-1 (APS-1) or polyglandular autoimmune (PGA) syndrome type-1, is a primary immunodeficiency disease caused by mutations in the autoimmune regulator (AIRE) gene.

Overview

Without a functional AIRE gene, self-reactive T cells in the thymus are not removed, whereupon they leave the thymus gland leading to multi-organ autoimmune diseases and Candida infections of the mouth, skin, vaginal mucosa, and potentially other areas of the body. APECED affects individuals worldwide with an estimated frequency of 1 in 100,000 to 1 in 500,000. It occurs more frequently (1 in 9,000 to 1 in 25,000 individuals) among certain populations, such as the people of Finnish, Sardinian, and Iranian Jewish decent.

Immunobiology

APECED is caused by mutations in the gene AIRE. AIRE provides instructions for making a protein called the **a**uto**i**mmune **re**gulator (AIRE), which helps control when other genes get turned on or expressed. The AIRE protein is expressed predominantly in the thymus, a key immune organ located behind the breastbone. T cells migrate to the thymus where they are taught to distinguish the body's own healthy cells from foreign material called antigens. AIRE plays an important role directing this process. Mutations in the AIRE gene reduce or eliminate the function of the AIRE protein, making it more likely that T cells will attack the body's own healthy tissues. Autoimmunity can affect several organs and results in inflammation that over time can cause irreversible tissue damage.

There are many types of mutations occurring in multiple locations along the AIRE gene. Interestingly, different mutations have been found to be enriched and somewhat specific to certain populations, such as in Finnish, Sardinian, and Iranian Jewish populations, and certain populations in Britain, Norway, and North America.

Clinical Presentation

APECED is characterized by chronic or recurrent *Candida* yeast infections and autoimmunity affecting several endocrine and non-endocrine organs in varied frequency (Table 16:1, Figure 16:1). Most individuals with an APECED begin having symptoms in early childhood, although the time between onset of symptoms an APECED diagnosis can be frustratingly long for many families. APECED is a disorder with striking clinical presentation variability, even within affected

siblings in the same family. This suggests that there are complex interactions between genetic, epigenetic (influences on gene expression not explained by the DNA sequence), and environmental factors contributing to the development of APECED manifestations.

Oral Manifestations

Candida infections develop early in life and are often the first symptom to appear, usually in the form of oral candidiasis, commonly known as thrush. Thrush can range in severity from redness and soreness at the corners of the mouth to whole-mouth involvement; it can interfere with eating spicy or acidic foods. Chronic inflammation of the mouth and throat makes some individuals with APECED (approximately 5%) susceptible to developing oral squamous cell carcinoma, a type of cancer. Candidiasis can also affect the esophageal, intestinal, or vaginal mucosal surfaces as well as the nails. People with APECED are not susceptible to developing systemic *Candida* infections that would involve the blood or deep organs, like the liver, lungs, or bone.

In addition to oral candidiasis, individuals with APECED commonly have reduced tooth enamel (the outer covering of the teeth) beginning early in childhood, resulting in frequent cavities and need for dental procedures. Other individuals may develop symptoms of dry mouth and decreased salivary production with or without accompanying dry eye symptoms.

Skin and Nail Manifestations

A characteristic rash called an urticarial eruption typically appears as early as the first year of life and before the age of 3 in the majority of North American individuals with APECED. The rash appears as many individual, pink-red spots on the trunk of the body, face, arms, and legs. The spots may be flat or raised and, they are sometimes accompanied by a high fever. The rash may recur many times over months to years before resolving without any treatment. No apparent trigger, such as a viral illness or prior vaccination, is identified in the majority of individuals. Other skin manifestations may include loss of skin pigmentation (vitiligo) and hair loss (alopecia). Abnormal nail growth called nail dystrophy may also occur in the absence of nail fungal infection.

Endocrine Manifestations

As the acronym APECED indicates, endocrine problems are a very common feature of the syndrome. Hypoparathyroidism and adrenal insufficiency are the most frequent endocrine manifestations. Hypoparathyroidism typically occurs earlier than any other endocrinopathy and causes low calcium levels in the blood resulting in muscle cramping and seizures if not treated. Adrenal insufficiency causes low blood pressure, called hypotension, which can lead to adrenal crisis, a dangerous and potentially fatal complication. Salt craving is an early clinical observation in individuals with subclinical adrenal insufficiency. Darkening of the skin can also be seen. Other endocrine manifestations, which occur less often than hypoparathyroidism and adrenal insufficiency, include hypothyroidism, growth hormone deficiency, and ovarian failure or testicular failure that may affect puberty and childbearing. Type-1 diabetes is a relatively uncommon feature of APECED.

Intra-abdominal Manifestations

There are several intra-abdominal manifestations seen in APECED. The most common are intestinal symptoms presenting as chronic diarrhea, chronic constipation, or an alternating pattern of both, frequently causing malabsorption of fat. This causes abdominal bloating, distention, and excessive flatulence. The cause of fat malabsorption is indefinable in most individuals, but in a small proportion of them, it is caused by exocrine pancreatic insufficiency, a condition where there is a lack of or decreased pancreatic enzymes that are important for digestion and responds clinically to pancreatic enzyme replacement therapy. Inflammation of the liver (autoimmune hepatitis), the stomach (autoimmune gastritis), and rarely the small intestines (autoimmune enteritis) may occur and are diagnosed by biopsy where cells are seen invading the corresponding tissue. Lastly, some individuals with APECED develop pernicious anemia that is caused by an inability to absorb vitamin B12 in the gut. Autoimmune gastritis and B12 deficiency increase the risk for development of gastric cancer in individuals with APECED.

Other Manifestations

Autoimmunity affecting the lung and causing inflammation (pneumonitis) presents with symptoms of chronic cough (particularly prolonged after a viral illness and often occurring at night) and shortness of breath. Often, pneumonitis in APECED is misdiagnosed as asthma or bronchitis. Without immunosuppressive treatment, prolonged inflammation can cause damage to the airways (called bronchiectasis) and lead to recurrent bacterial respiratory infections and eventual respiratory failure. Inflammation is visible on computed tomography (CT) of the chest and in lung tissue biopsies.

Autoimmune attack against the spleen over time reduces its size and function. This makes the immune system weak at fighting certain types of bacteria, such as *Streptococcus pneumoniae*, and can result in serious bloodstream infections. Those individuals without a spleen require vaccinations against pneumococcus and meningococcus and prophylactic antibiotic therapy to protect against these bacteria.

There are several eye problems that may occur in individuals with APECED. Inflammation affecting the cornea and conjunctiva (keratoconjunctivitis) is the most common. Other individuals may develop inflammation of the retina (retinitis) and/or along the eyelid (blepharitis).

The most common kidney problem in APECED results from taking calcium supplementation for hypoparathyroidism for many years. Calcium is excreted from the blood into the kidneys, and it can accumulate in the kidney tissue and form kidney stones (nephrolithiasis). Rarely (less than 10%), inflammation can occur in the tubules of the kidneys (tubulointerstitial nephritis); if this condition is untreated, it may result in kidney failure.

Diagnosis

Diagnosis of APECED is based on clinical symptoms with confirmatory genetic testing of the AIRE gene. Detection of autoantibodies against interferon-omega is a useful diagnostic tool as it is seen early in the course of the disease and is highly sensitive and specific for APECED (less than 90 to 95%). A clinical diagnosis of APECED is made based on the presence of at least two of the three classic components of the syndrome: chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency, or having one of these three components and a sibling with confirmed APECED. However, these criteria are imperfect and do not capture a substantial proportion of affected individuals early on during the course of the disease. Some individuals have other syndrome components, such as urticarial eruption, reduced tooth enamel, or malabsorption, for years before the classic APECED manifestations become apparent. Therefore, a high index of suspicion is required by clinicians to make the diagnosis early.

Inheritance

APECED is inherited in an autosomal recessive manner. In autosomal recessive inheritance, an affected person has a mutation on each of their two copies of the AIRE gene—one inherited from the mother and one from the father. Typically, both parents of an affected person carry one abnormal AIRE gene and are unaffected by the disease. When both parents are carriers, each child has a 25%, or one in four, chance of being affected by the disease. Sometimes the two copies of the AIRE gene that a child inherits have identical, or homozygous, mutations. Most North American individuals with APECED have different mutations on the two copies of AIRE, called compound heterozygous mutations. In either case, they are not able to produce functional AIRE protein.

Recent evidence suggests that in some individuals who present with APECED-like clinical manifestations, the disease is inherited in an autosomal dominant manner. In autosomal dominant inheritance, an affected person has a mutation on one of their two copies of the AIRE gene. The mutation is inherited from a parent who is also affected by the syndrome. The other parent does not carry a mutation in the AIRE gene and is healthy. In this situation, each child has a 50% chance of being affected by the disease. Such mutations have been reported in European individuals, but so far have not been observed in North American individuals with APECED. The individuals do not typically present with the full-blown APECED syndrome but instead develop organ-specific autoimmune manifestations that are seen in APECED such as vitiligo, B12 deficiency, or an endocrine disorder.

About 15% of North American individuals with a clinical APECED diagnosis do not have detectable mutations or deletions in both copies of the coding regions of the AIRE gene, suggesting that other undiscovered genetic factors may be involved in the syndrome. Further research is needed to understand the genetic factors (non-coding AIRE elements

or non-AIRE genes) that contribute to APECED in families without biallelic AIRE gene mutations; a biallelic mutation is a mutation but not necessarily the same mutation in both copies of a particular gene (a paternal and a maternal mutation).

Treatment

Therapy is based on an individual's clinical condition and includes a combination of medications to treat specific components of the disease as well as autoimmunity. Individuals with APECED may take antifungal drugs to treat Candida infections; calcium and hormone replacement for corresponding endocrine problems; and immunosuppressive drugs to control autoimmunity in the lungs, liver, intestine, or kidney. Because APECED affects many of the body's organs and tissues, optimal care requires a team of specialists working closely with each other.

Expectations

The variability in the number and severity of manifestations makes it difficult to predict an individual's clinical course. Moreover, individuals with APECED often develop new manifestations over the course of their life, and it is difficult to predict who is at risk of developing specific manifestations at any given time. Generally, most individuals can expect normal life expectancy. It is important to be aware of the full spectrum of potential manifestations in APECED syndrome and to perform periodic systematic screening for manifestations that have not yet developed. With early recognition, new manifestations can be treated promptly and appropriately to preserve organ function and quality of life.

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Prevalence of Disease Manifestations in American and European Individuals with APECED

Table 16:1

Shown are approximate average percentages of corresponding manifestations pooled from various published studies from the Americas and Europe.

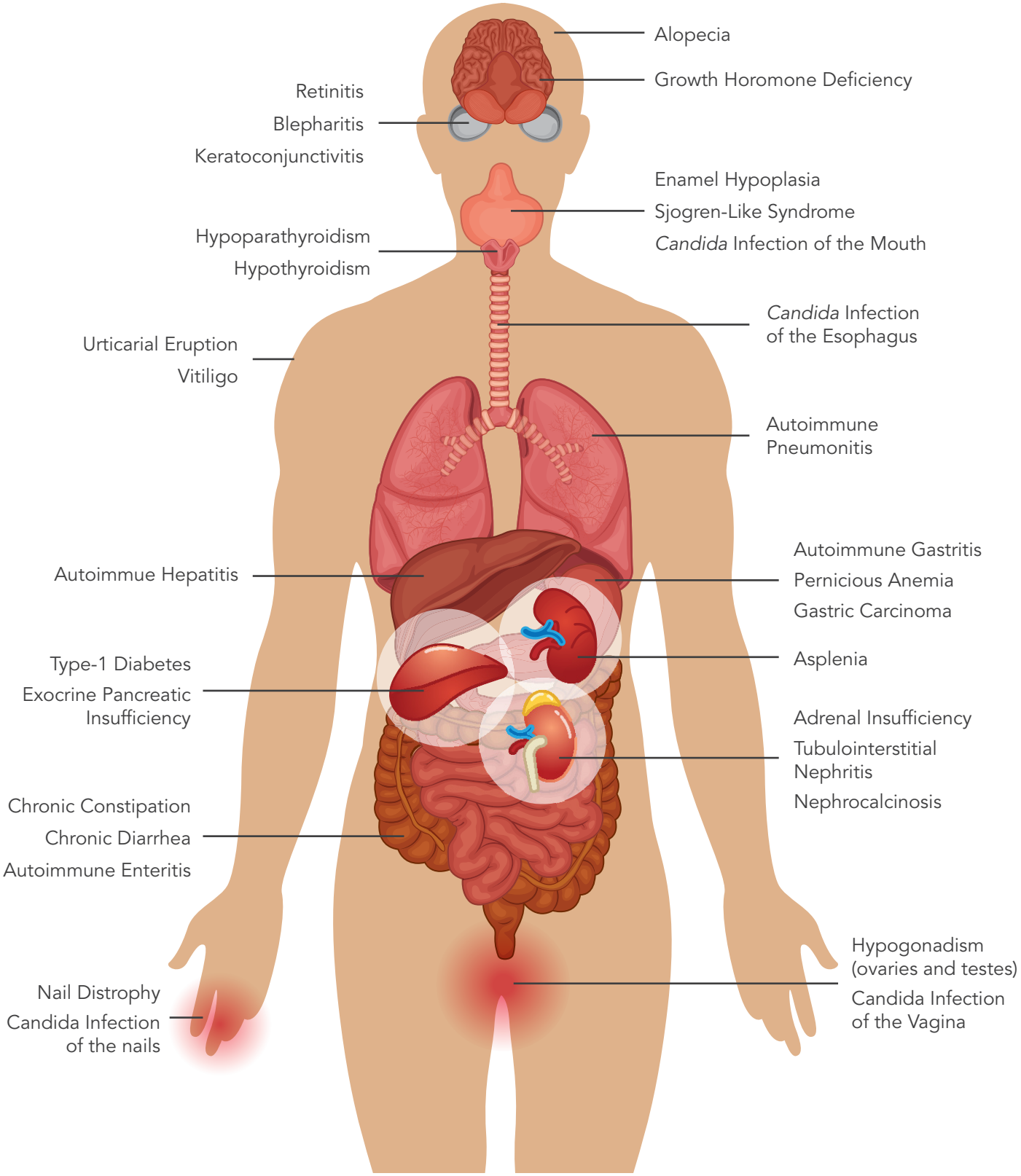
	North/South America (%)	Europe (%)
Oral Disorders		
Chronic mucocutaneous candidiasis	86#	87
Enamel hypoplasia	86#	52
Endocrine Disorders		
Hypoparathyroidism	91#	83
Adrenal insufficiency	83	71
Hypothyroidism	23	15
Growth hormone deficiency	17	17
Type-1 diabetes	11	12
Testicular failure	21	21
Ovarian failure	38	46
Intra-Abdominal Disorders		
Intestinal dysfunction	80*#	29
Hepatitis	43*	13
Gastritits	49*	20
B12 deficiency	29	20
Skin/Nail Disorders		
Urticarial eruption	66*#	10
Alopecia	17	30
Vitiligo	37	19
Nail dystrophy	17	23
Other		
Pneumonitis	40*	7
Sjogren's-like syndrome	43*	12
Keratoconjunctivitis	29	17
Asplenia	9	9
Tubulointersititial nephritis	6	4
Early-onset hypertension	17	15

**Disease manifestations that appear more prevalent in American APECED individuals relative to reported frequencies in European APECED individuals.*

#Disease manifestations that typically present early in the course of the syndrome.

Common APECED Symptoms and the Organs They Affect

Figure 16:1



Chapter 17

Autoimmune Lymphoproliferative Syndrome (ALPS) and Related Disorders

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Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare genetic disorder in which lymphocytes, a type of white blood cell, increase and accumulate in the spleen and lymph nodes. This is due to the failure of the mechanism that normally causes lymphocytes to die naturally. The disease was also known as the Canale-Smith syndrome before its genetic causes were discovered and inheritance patterns were understood.

ALPS is due to genetic defects in a gene coding for a specific protein called FAS. It is associated with childhood onset increases in the size of lymph nodes (lymphadenopathy) and spleen (splenomegaly) as well as decreases in red blood cells, platelets and, occasionally, neutrophils as well as an increased lifetime risk of lymphoma. More than 1,000 individuals with ALPS-FAS and their relatives have been identified and followed worldwide.

Overview

The normal response to infection by a pathogen is the multiplication of lymphocytes in the lymph nodes. When the rapid growth of these cells in the lymph nodes and spleen is uncontrolled, excessive, and harmful, it is described as a lymphoproliferative syndrome.

Lymphocytes are normally subject to programmed cell death (known as apoptosis), controlled by the FAS gene. If there is a change in the genetic code in the FAS gene, also known as a genetic mutation or variant, because the lymphocyte control pathway no longer functions normally, there is an uncontrolled expansion of certain lymphocytes. This is the cause of most ALPS cases and, hence, the condition is known currently as ALPS-FAS. In very rare cases, the defect in lymphocytes is caused by mutations in other genes involved in the lymphocyte control pathway.

Initial Presentation

ALPS can be diagnosed early in childhood, when the child presents with chronically enlarged lymph nodes in neck, groin, and armpits. ALPS is also often associated with an enlarged spleen. Other early presentations include fatigue, pallor, or jaundice (all the result anemia), unusual bruising, frequent nosebleeds (due to low platelets), and frequent infections (due to low neutrophils).

Diagnosis

ALPS can be difficult to diagnose because its symptoms and laboratory results overlap with a number of other common childhood diseases including childhood cancers, such as lymphoma and leukemia, and chronic viral infections, such as infectious mononucleosis, commonly known as mono.

ALPS is diagnosed when manifestations of autoimmunity are present along with two other factors: low blood cell counts including low hemoglobin, low platelets, and/or low neutrophils, and enlarged lymph nodes and/or spleen. The lymph nodes and spleen become enlarged because they are key lymphocyte storage and production sites. An enlarged liver (hepatomegaly) is also seen in 30% to 40% of individuals with ALPS.

Because ALPS is a genetic disorder, a family history of ALPS or other lymphoproliferative disease is also considered when making the diagnosis.

Failure of FAS-mediated cell death (apoptosis) can sometimes be detected with specialized laboratory tests, but very few laboratories are equipped to run these tests and the results are subject to some degree of uncertainty. Instead, certain biomarkers in the blood are strongly associated with ALPS, such as increased immunoglobulins, elevated serum vitamin B12 levels, and particular proteins including interleukin 10 (IL-10) and soluble FAS ligand (sFASL).

In many cases, antibodies that attack the individual's own body (known as autoantibodies), such as antibodies to normal red blood cells, may also be present. Various forms of autoimmune cytopenias (low blood cell count) lead to anemia (low red blood cells that carry oxygen), thrombocytopenia (low platelets that normally help blood to clot at sites of injury), and/or neutropenia (low neutrophils that fight bacteria) can be a serious and continuous problem for individuals with ALPS, especially young children.

Other autoimmune complications that are less common but possible with ALPS include glomerulonephritis (inflammation of the kidneys); autoimmune hepatitis (inflammation of the liver caused by immune attack); vasculitis (inflammation and destruction of blood vessels); uveitis (inflammation of the colored part of the eye); and, rarely, chronic pancreatitis (inflammation of the pancreas).

Treatment

Two of the key manifestations of the disease, lymphoproliferation and splenomegaly, are especially difficult to treat but may not always cause severe harm without treatment. Treatments for ALPS usually focus on the complications due to autoimmune conditions associated with ALPS, especially severe autoimmune cytopenias, which can be life threatening.

Splenectomy (removal of spleen by surgery) was often used to treat the autoimmune cytopenias until the early 2000s. However, since then, spleen-sparing immunomodulatory regimens have become the mainstay of long-term therapy for these complications in individuals with ALPS. The shift away from splenectomy was driven by the observation that individuals with ALPS had a greater than normal risk of suffering a severe and potentially life-threatening infection after splenectomy.

The drugs used to treat autoimmune cytopenias include corticosteroids, mycophenolate mofetil (MMF), and rapamycin (also known as sirolimus). Rapamycin has been shown to reduce spleen and lymph node size over the long term. MMF does not reduce lymph node or spleen size and can cause hypogammaglobulinemia, which is a condition of a low level of immunoglobulins and may require immunoglobulin (Ig) replacement therapy.

Rapamycin has been used to resolve 90% of autoimmune symptoms as well as enlargement of lymph nodes and spleen. This drug may cause immune suppression leading to an increased risk for infections; though it has not been reported to cause hypogammaglobulinemia. Individuals taking rapamycin require careful monitoring as the drug can increase the risk of various cancers, cause mucositis (painful inflammation and ulceration of the digestive tract), diarrhea, hyperlipidemia (increased lipid/fat levels in blood), and slow the healing of wounds.

Corticosteroids can and should be used only as a short-term pulse therapy to address cytopenias and organ enlargement, and overall they have been met with limited success. Hematopoietic stem cell transplantation (HSCT) has also been used for some individuals. However, generally HSCT is not advised because the good prognosis of most individuals with ALPS usually doesn't warrant the challenges and risks associated with HSCT.

The spleen plays a critical role in fighting a common bacteria called pneumococci. If ALPS-related splenomegaly becomes severe enough, long-term rapamycin and short-term corticosteroids should be used to shrink the spleen. As noted above, splenectomy can result in a significant risk of sepsis with encapsulated bacteria, which is a life-threatening condition in which tissues and organs are infected by bacteria and damaged by the body's response to it. Therefore, individuals whose spleens have been removed should employ long-term antibiotic treatment and consult a healthcare

provider immediately upon developing a fever. More individuals with ALPS-FAS have died due to infection developed many years after splenectomy far more than from any other cause including lymphoma.

Management

Unlike many forms of primary immunodeficiency diseases, ALPS does not significantly raise the risk of severe or frequent infection. Individuals that have undergone splenectomy should wear a medical alert bracelet, take prophylactic antibiotics, and seek immediate medical care for any fevers.

Complications associated with ALPS, including autoimmune hepatitis, vasculitis, uveitis, and others, should be managed just as they would be in people who do not have ALPS.

Because of its genetic nature, ALPS often affects more than one family member. Prompt recognition and treatment of any symptoms is important for optimal outcomes. Symptoms associated with ALPS are sometimes most severe in early childhood, when the lymphatic system is expanding, but may improve during adolescence and adulthood.

Individuals with ALPS have a higher risk of developing B cell lymphomas (Hodgkin and non-Hodgkin lymphoma), and they require frequent screening and monitoring for these cancers on a lifelong basis. Whenever individuals with ALPS develop systemic symptoms (like fever, night sweats, weight loss, or loss of appetite) and/or sudden focal enlargement of a group of their lymph nodes beyond their norm of clinical and seasonal variability, they should undergo further medical evaluations. These may include radiological imaging with computerized tomography (CT) and/or positron emission tomography (PET) scans followed by a biopsy of an appropriate lymph node(s). Routine frequent whole body imaging on a yearly basis only for monitoring lymph nodes for lymphoma yields little benefit, and it is not recommended for individuals with ALPS.

In children, the enlargement of lymph nodes can be severe enough to be visible, resulting in potential anxiety and embarrassment. Shrinkage of the nodes for cosmetic reasons is not recommended, although attention to the child or young adult's overall well-being and emotional concerns is equally vital. The nodes should be carefully watched for any sudden and significant changes in size, which should be promptly reported to the healthcare provider. The size of the lymph nodes and the spleen should also be regularly monitored through measurement by the medical team.

Although there are reports of successful use of rapamycin and MMF, the long-term toxicities of these therapies remains unknown. Through proper care, ALPS is usually manageable, and most individuals can have a relatively normal lifestyle and life span. However, this does not preclude the need for careful lifelong monitoring for possible progression to autoimmune and malignant diseases particularly in children and young adults.

More recently additional genetic defects have been discovered that also mimic ALPS with similar clinical findings. For the sake of this material, they will be referred as ALPS related disorders (Table 17:1). Knowing the genetic basis of many of these lymphoproliferative disorders with autoimmune problems may facilitate better and more targeted treatment of these individuals.

ALPS Related Disorders

Table 17:1

ALPS Classification	Chronic LPD/ Splenomegaly	Recurrent Infections
ALPS-FAS (germline mutation)	+	-
ALPS-sFAS (somatic mutation)	+	-
ALPS-FASLG	+	-
ALPS-CASP10	+	-
ALPS-U	+	-
ALPS-related apoptosis disorders		
Caspase-8 deficiency state	+	+
RALD	+	+ -
BENTA disease	+	+ -
FADD deficiency	-	+
PRKCD deficiency	-	+

ALPS-FAS, ALPS caused by germline FAS mutations; ALPS-sFAS, ALPS caused by somatic mutations; ALPS-FASLG, ALPS caused by mutations in FAS ligand; ALPS-CASP10 caused by caspase-10 mutations; ALPS-U, ALPS that fulfills criteria but lacks any identifiable mutation; RALD, RAS-associated autoimmune leukoproliferative disorder; BENTA, B cell expansion with NF-κB and T cell anergy.

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Chapter 18
Hemophagocytic Lymphohistiocytosis and EBV Susceptibility

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe systemic inflammatory syndrome that can be fatal. HLH occurs when histiocytes and lymphocytes become overactive, and they attack the body instead of bacteria and viruses. Histiocytes, like macrophages, are phagocytes—cells that ingest and destroy pathogens, as well as cellular debris. When histiocytes and lymphocytes are overactive in HLH, they overproduce cytokines which can lead to a cytokine storm. These cytokines also attack blood cells and bone marrow in particular, as well as the spleen, liver, lymph nodes, skin, and even the brain. Initial clinical features are typically high and unremitting fever, rash, hepatitis (liver inflammation), jaundice, an enlarged liver and spleen, pancytopenia (low counts of all blood types), and lymphadenopathy (enlarged lymph nodes). Neurological components such as confusion, seizures, and even coma may also occur.

HLH occurs in someone because they have specific genetic defects that directly cause HLH, in which case it is called Primary HLH. Primary HLH is also sometimes called Familial HLH. The genetic mutations that cause Primary HLH are present at birth. Individuals with Primary HLH often become ill in the first few years of life, and if not diagnosed and treated, this condition is usually fatal. For Primary HLH, treatment typically includes hematopoietic stem cell transplantation (HSCT).

HLH sometimes occurs in people with other medical problems that cause a strong activation of the immune system, such as infection or cancer. HLH in these settings is called Secondary HLH. Secondary HLH may also be associated with medical conditions such as autoimmune diseases, in which HLH is often called Macrophage Activation Syndrome (MAS). It can also be associated with primary immunodeficiency diseases (PI). If secondary HLH and its underlying medical condition are detected promptly and then treated aggressively, the prognosis is improved.

Causes of Primary HLH

Primary HLH is a rare disease, reported in about 1 per 50,000 births worldwide per year. These numbers seem to be increasing slightly, possibly due to increased success in detecting the disease. It is caused by defects in several genes, including *PRF1, UNC13D, STXBP2, STX11, RAB27A, LYST, AP3B1, SH2D1A, MAGT1* and *XIAP/BIRC4*. Individuals have mutations in RAB27A, are said to have Griscelli syndrome, while individuals with mutations in *LYST* are said to have Chediak-Higashi syndrome. When individuals have mutations in *SH2D1A*, and *XIAP/BIRC4*, they are usually classified as having X-linked Lymphoproliferative Disease Type 1 or 2, respectively (XLP1 and XLP2). XLP1 and XLP2 usually occur only in boys as they are X-linked disorders, as is HLH due to *MAGT1* mutations (Table 18:1). All of these genes normally produce proteins that regulate immune cells, but when these are absent or don't work correctly, the cells of the immune system become overactive, expand unchecked, and create the harmful cytokine storm.

Susceptibility to Epstein-Barr virus (EBV) infection

EBV is one of the most common human viruses, infecting most people at some point in their lives. EBV infections in children usually do not cause symptoms, or the symptoms are not distinguishable from other mild, brief childhood illnesses. People who get symptoms from EBV infection, usually teenagers or adults, have

infectious mononucleosis ("Mono"), which usually improves in two to four weeks. However, EBV can cause serious complications in individuals with PI. In particular, for individuals who have genetic defects which predispose them to HLH, EBV infection can become a life-threatening problem due to the development of EBV-driven HLH. Additionally, XLP1 is characterized by extreme vulnerability to EBV infection, and HLH in these individuals is nearly always associated with EBV. Male individuals with *MAGT1* mutations are also highly susceptible to developing HLH from EBV infection.

EBV is also a major triggering factor for Secondary HLH. In this setting, individuals have often been disease-free for most of their lives, but then HLH manifests when EBV infection triggers an immune response that cannot be shut off. In other words, what started as infectious mononucleosis progresses into HLH. Individuals with XLP1, *MAGT1* mutations and other select forms of PI are also prone to develop lymphoma (cancer involving lymph nodes) as a result of EBV infection, and this can occur with or without the development of HLH.

Chronic active EBV infection (CAEBV)

EBV typically infects B cells (the lymphocytes that develop into plasma cells, the antibody producing cells). In individuals without PI, T cells and NK cells mount an immune response against EBV infected B cells thereby controlling EBV infection. In some individuals, EBV predominantly infects T cells or NK cells, causing an EBV related illness lasting less than 3 months known as chronic active EBV (CAEBV) that is characterized by high levels of EBV in the blood. CAEBV occurs in apparently healthy children and adolescents and has been most commonly described in individuals of East Asian or Hispanic origin. In CAEBV, EBV infection causes T cells or NK cells to multiply rapidly and overproduce cytokines, leading to the development of HLH and a lymphoproliferative disorder that can be detected with specialized imaging (e.g., CAT scans). This lymphoproliferative disorder can progress into (EBV-driven) lymphoma. In terms of treatment, special measures are required to control the cytokine storm generated by EBV and to suppress proliferating EBV-containing T or NK cells, because the clinical course often results in a poor outcome, unless HSCT is successful.

Diagnosis of HLH

When most of the typical clinical signs are present and HLH is suspected, blood tests can help confirm the diagnosis by measuring the levels of blood cells, as well as various markers that indicate excessive immune activity. A bone marrow biopsy may be done to look for evidence of hemophagocytosis (bone marrow phagocytic cells that ingest red cells), and a spinal tap may also be performed. Once the diagnosis of HLH is made, it is important to determine whether HLH is Primary or Secondary, because Primary HLH will eventually need HSCT. Genetic testing can look for mutations in genes known to be involved in Primary HLH. There are also special screening tests that can be done to evaluate for genetic causes of HLH. In addition to causing Secondary HLH, infections, particularly viral infections, can also trigger primary HLH. Hence, it is important to screen for viral infections, including EBV. Blood tests can help detect an active infection. In boys with EBV infections, special screening tests can be done to look for XLP1 and XLP2. In individuals of East Asian or Hispanic ethnicity, CAEBV should be considered, and special tests can help determine if EBV is in the T cells or NK cells. Primary HLH often presents very early in life or in in very young children. If HLH occurs for the first time in older children, it is important to consider Secondary HLH due to infection, cancer or autoimmune causes e.g. rheumatologic, but one should not discard the possibility of Primary HLH in older children, or even young adults. In some cases, it may be necessary to complete detailed evaluations for lymphoma or leukemia before starting treatment for HLH.

Treatment of HLH

Once HLH has been diagnosed, therapy should start as soon as possible. HLH therapy includes aggressive courses of immunosuppressants and anti-inflammatory agents such as corticosteroids, chemotherapeutic agents, and anti-cytokine agents. High doses of dexamethasone (corticosteroid) and etoposide (a chemotherapy drug) are the mainstay of treatment for HLH. The cytokine storm can be targeted with drugs such as anakinra or emapalumab, an anti-interferon gamma antibody. If individuals have EBV related HLH, rituximab may be used to deplete B-cells, which are the cells commonly infected with EBV. Other agents used against HLH might include anti-thymocyte globulin (ATG), a T cell depleting antibody, or alemtuzumab, a lymphocyte depleting antibody. In CAEBV, treatment with rituximab is not effective as EBV infects T cells or NK

cells and rituximab targets only the B cells. Special measures that include combinations of the above drugs are required to control the cytokine storm generated by EBV, and to suppress EBV containing T cells or NK cells. Antibiotics, antiviral drugs, anti-fungal drugs, as well as immunoglobulin replacement therapy are often administered to combat infections and provide protection during HLH therapy that invariably is immunosuppressive.

Despite effective treatment of HLH with the above immune suppressive and anti-inflammatory agents, recurrence of HLH is to be expected in individuals who have Primary HLH. HSCT is the only therapy with a possibility of permanently restoring normal immune function. If a genetic defect is identified, curative treatment with HSCT should be considered. The earlier a transplant can be done, the better are its chances of success. In the absence of a genetic defect, HSCT should also be considered for young individuals, those with a family history of bad inflammation or death, recurrent HLH, or laboratory data suggesting an inherited defect in NK cell and T cell cytotoxic function. Individuals with CAEBV also have recurrent episodes of HLH, are at risk for developing lymphoma and invariably need to undergo stem cell transplant to get rid of EBV infection. Without HSCT, CAEBV is often fatal. EBV-driven lymphoma typically responds well to standard lymphoma (chemo) therapy, but depending if an underlying PI is present, may require curative HSCT (timed in conjunction with lymphoma therapy) as well.

Expectations

Primary HLH and HLH related to EBV or other infections remain a life-threatening problem, particularly for individuals with genetic disorders that cause HLH. Understanding of HLH and the role of EBV infection have significantly improved in the past couple of decades. Early recognition and initiation of treatment for HLH is essential for favorable outcome. The next decade promises to yield even further advances in diagnostics and treatment breakthroughs that will continue to improve outcomes. Increased knowledge regarding genetic defects that underlie HLH and PI may help with better separation between Primary and Secondary forms of HLH. Advances in HSCT also make possible transformative treatments for individuals with both Primary and Secondary forms of HLH.

Genetic Defects Associated with Primary HLH

Table 18:1

Primary Immune Deficiency	Gene Mutation	Clinical Features
Familial HLH 2	PRF1	Onset of HLH at a very early age Blacks most likely (98%) to have mutations in PRF1
Familial HLH 3	UNC13D	Neurologic involvement common
Familial HLH 4	STX11	More common in Kurdish, Turkish, and Lebanese ethnic background
Familial HLH 5	STXBP2	Severe diarrhea, bleeding, low Immunoglobulin levels
Chediak-Higashi Syndrome	LYST	Albinism Frequent bacterial infections Progressive neurologic dysfunction that is not corrected by HSCT
Griscelli Syndrome type 2	RAB27A	Partial albinism Silvery grey hair Variable neurological involvement
Hermanski-Pudlak syndrome types 2 and 9	AP3B1 BLOC1S6	Albinism, platelet function defect Bleeding due to defect in platelet function
X-linked lymphoproliferative disease type 1	SH2D1A	Extreme vulnerability to EBV infection Lymphoproliferative disease, including lymphoma Low immunoglobulin levels
X-linked lymphoproliferative disease type 2	BIRC4	Inflammatory bowel disease
XMEN (**X**-linked immunodeficiency with **m**agnesium defect, **E**BV infection, and **n**eoplasia) Disease	MAGT1	Persistent high level EBV infection Frequent sinus/ear/lung infections EBV associated lymphoma
Lysinuric Protein Intolerance	SLC7A7	Episodes of vomiting, diarrhea, stupor or coma after a protein-rich meal, muscle weakness

Chapter 19

Immune Dysregulation, Enteropathy, and Colitis

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Primary immune regulatory disorders (PIRD) are characterized by a disturbance of immune tolerance (See Autoimmunity Chapter) and excessive inflammation. Inflammation in the gastrointestinal (GI) tract presenting as colitis (inflammation and ulcers of the bowel wall of the colon) and enteropathy (inflammation of the bowel especially the small bowel) is a common presentation of PIRD that can significantly affect the quality of life in individuals with PIRD. Colitis can be the presenting manifestation of an underlying broader immune dysregulation (abnormality or impairment in the regulation of some part of the immune system), or it could develop later in the disease course. Other types of broader immune dysregulation include multi-system autoimmune conditions, such as low blood cell counts, thyroid failure, pancreatic failure, and arthritis. Lymphoproliferation (excessive lymphocyte production) and susceptibility to infections can co-exist or develop later in the disease course. It is important to identify individuals who have colitis or enteropathy as the presenting manifestation of PIRD as it can help in both early identification and initiation of treatment. This approach can result in better control of disease. Very early onset inflammatory bowel disease (VEO-IBD) is common in this population, but the age of onset should not be the only reason for initiation of immune and genetic evaluation to identify underlying PIRD in individuals with inflammatory bowel disease.

Immunobiology

A healthy gastrointestinal tract needs robust interaction between the gut, skin barrier function, the immune system, and the microscopic living organisms of the gut. Dysregulation or deficiency in any compartment of the immune system, such as neutrophils, T and B cells, and macrophages, can cause colitis and enteropathy in children. While colitis is associated with inflammation in the GI tract and is associated with painful often bloody bowel movements, enteropathy is associated with an autoimmune response that leads to large volume watery bowel movements. Both can be associated with poor weight gain and failure to thrive.

Depending on what causes the underlying immune dysregulation and inflammation, GI tract colitis in PIRD can be classified as:

- **Colitis due to defects in neutrophil function:** Chronic Granulomatous Disease (CGD), which is a form of primary immunodeficiency disease characterized by defect in neutrophil function, is a prototype of this group. (See Chronic Granulomatous Disease Chapter.) Individuals with CGD can present with varying severity of colitis and perianal disease.

- **Autoimmune enteropathy due to defects in T cell immune tolerance:** This group has a genetic defect that results in either decreased T regulatory cell numbers or function; T regulatory cells are a subpopulation of T cells that can control the immune system by maintaining tolerance to self-tissues and prevent autoimmune disease. IPEX syndrome due to FOXP3 mutation is the prototype of this group. IPEX is a syndrome of immune dysregulation, endocrine failure and enteropathy in an X-linked inheritance pattern. (See IPEX Chapter.) Several other immunodeficiencies (IPEX-like) with functional T regulatory cell defects are also associated with autoimmune enteropathy. In all these conditions, the functional deficiency of T regulatory cells leads to unchecked T cell activation. This results in autoimmune disease against cells in the intestines as well as other parts of the body.
- **Colitis due to defects in IL-10 and IL-10R signaling:** GI inflammation due to excess pro-inflammatory signals from the macrophages has been proposed to be the primary driver of inflammatory bowel disease (IBD) in infants and children with genetic defects in IL-10 and IL-10R.
- **Colitis due to hyper-inflammatory disorders:** Excess inflammation due to defects in critical proteins involved in the inflammatory cascade can also lead to GI inflammation and colitis.
- **Colitis due to isolated or combined T and B cell defects:** Varying degree of T and B cell immune defects can present with colitis. Classical examples are Wiskott-Aldrich Syndrome (See Wiskott-Aldrich Syndrome Chapter), Common Variable Immune Deficiency (CVID), and genetic defects that present with CVID-like illness. A significant percentage of these individuals have associated colitis (See Common Variable Immune Deficiency Chapter.)

Clinical Presentation

Colitis as a presentation of underlying immune dysregulation can have a varied presentation with regard to age of onset, severity, and pathology findings. Though several of them present at a younger age with infantile onset (less than two years) or VEO-IBD (less than six years), a significant proportion of them will present with colitis after age 6. Colitis in these individuals can have a slow, gradual onset with frequent small volume bloody and mucousy diarrhea. Due to the slow onset, it is common for these infants to have been evaluated for allergic colitis and to have had multiple formula changes for presumed allergic colitis. GI inflammation resulting in perianal fistula can be seen in individuals with IL-10 and IL-10R signaling defects, XIAP deficiency (X-linked inhibitor of apoptosis protein), and CGD.

On the contrary, clinical presentation of severe enterocolitis in infants is usually much more dramatic. There is typically explosive large volume watery diarrhea. This presentation is common in infants with IPEX and IPEX-like disorders. Biopsy findings include villous atrophy and apoptotic enterocolitis.

In addition to colitis, other autoimmune symptoms of PIRD include autoimmune endocrinopathy (such as type 1 diabetes), autoimmune cytopenia (such as immune thrombocytopenia), and lymphoproliferation (generally manifests as enlarged lymph nodes, liver or spleen). Furthermore, the presence of unusual or difficult to treat infections can be another associated symptom of PIRD. Evaluation of underlying PIRD should be considered if colitis or enteropathy is associated with early onset colitis or enteropathy, especially associated with autoimmune disease or lymphoproliferative disorders, fistula formation, non-responsiveness to first and second line IBD therapy, recurrent fevers, or difficult to treat eczema.

Diagnosis

To diagnose underlying PIRD with colitis, a combination of immune and genetic testing is warranted in most individuals. Immune studies to look at the number, proportion, activation status, and functional status of the different immune cells might be done. Immune studies could give a clue to the nature of immune dysregulation and in some cases clues to possible underlying genetic defects. Increasingly, genetic studies are being done upfront for most individuals. Instead of testing one gene at a time most physicians now rely on gene panels (usually ten to several hundred genes) that include the genes that are likely to result in immune dysregulation. If the gene panel is negative, several clinical centers will proceed to whole exome sequencing, wherein all the genes that are known to cause disease in humans are looked at. When whole exome sequencing is done, samples from the parents are often requested to improve the diagnostic accuracy.

Inheritance

The genetics and mode of inheritance of PIRD presenting with colitis is varied, and summarized in the table below (Table 19:1). It is important to realize, especially with autosomal dominant inheritance that more than one family member might be affected with the same genetic defect. Severity and the age of onset is variable with family members with the same genetic defect. De-novo mutations (neither of the parents are carriers of the defective genes) are known to be the cause of genetic defect in some PIRD.

Known Causes of Genetic Defect in Some PIRD

Table 19:1

Mode of Inheritance	Gene Mutation
Autosomal recessive (both copies of gene affected)	LRBA
Autosomal dominant (only one affected copy needed to cause disease by several mechanisms)	One defective copy/one normal copy (CTLA4, NFKB1, NFKB2) Gain of function (GOF)-defective copy is over active: STAT1 GOF, STAT3 GOF
X linked (males are affected, females can be carriers)	FOXP3, IKBKG, WAS

Treatment

It is important to understand there is not a defined protocol for management of colitis in individuals with broader immune dysregulation. The underlying genetics and immune defect will often guide the immunologist in the selection of medicines that are likely to be most effective for the management of colitis as well as the other manifestations of immune dysregulation. Individuals with underlying broader immune dysregulation and colitis may not respond adequately to medications, such as anti-TNF agents including infliximab or adalimumab.

Treatment with other biologic drugs, such as vedolizumab or ustekinumab, may be considered early in the management. Also, non-conventional targeted treatments might be tried; these agents might include immune suppression with tacrolimus, cyclosporine, sirolimus, abatacept, ruxolitinib or anakinra. However, in some of these individuals, multiple trials of different medications are needed to find the best combination.

Allogeneic hematopoietic stem cell transplantation (HSCT) is being increasingly considered in the management of genetically defined immune dysregulation disorders with colitis. Though the disease might be well controlled medically, long-term quality of life may not be good with medical management alone. Disease flares, loss of response to therapy, and other autoimmune manifestations, infections or lymphoproliferative complications are common findings in these individuals. If matched sibling or matched unrelated donor options are available the role of HSCT should be discussed. Usually, HSCT in these disorders is not an emergency; efforts are made to control colitis and other autoimmune complications, and to nutritionally rehabilitate as aggressively as possible before HSCT. The outcome is improved if the overall immune dysregulation and colitis are better controlled before HSCT. HSCT gives a possible definitive treatment option of the immune system defect. However, careful consideration regarding the long-term risks from chemotherapy before HSCT, the risk of graft vs. host disease after transplant, the risk of infection, and the small but significant risk of graft failure need to be considered (See Hematopoietic Stem Cell Transplantation Chapter).

Expectations

The process of diagnostic immune and genetic evaluation is time-consuming. In some individuals, there is development of more autoimmune or infectious symptoms over months to years. Colitis can be an early presenting symptom of underlying immune dysregulation or a late presentation that follows other autoimmune complications. Despite extensive immune and genetic evaluation, a significant majority of individuals with immune dysregulation might not have a genetic diagnosis. However, every year new genes are being identified that cause immune dysregulation; in the future we expect a higher percentage might have a recognized genetic basis.

Additionally, since the GI inflammation in these individuals might be different, they may not have a positive response to traditional first and second line IBD therapy (anti-TNF agents). In some non-classical IBD, treatment addressing broader immune dysregulation might be a better approach. If the immune and genetic basis is identified and medical management alone results in a poor response or if the treatment has significant side effects limiting the long-term options, HSCT to correct the underlying immune defect might be an option.

If an underlying genetic defect is identified, genetic counseling to identify other family members with carrier or disease state might be recommended. Additionally, for parents who are carriers of genetic defects, genetic counseling and techniques such as in-vitro fertilization and pre-implantation genetics could give an option of having a healthy child.

Chapter 20

Hyper IgE Syndromes (HIES): STAT3 Loss of Function, DOCK8 Deficiency and Others

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Hyper IgE Syndromes (HIES) are rare forms of primary immunodeficiency diseases (PI) characterized by recurrent eczema, skin abscesses, lung infections, eosinophilia (high numbers of eosinophils in the blood), and high serum levels of immunoglobulin E (IgE). Although initially described as two forms, with autosomal dominant (AD) and autosomal recessive (AR) inheritance, we now recognize that these are two distinct diseases caused by different genetic causes, with the two most common being from harmful mutations in STAT3 causing loss of function (STAT3-LOF) and DOCK8. These diseases share overlapping clinical and laboratory features; however, they also exhibit distinct clinical symptoms, disease courses, and outcomes. In addition, several other genetic variants have since been described to present with similar symptoms.

History

STAT3-LOF was described first as Job Syndrome in 1966 in two girls with many episodes of pneumonia, eczema-like rashes, and recurrent skin boils. These boils were remarkable for their lack of surrounding warmth, redness or tenderness, and were so called cold abscesses. In 1972, the syndrome was refined and clarified upon. It found similar infectious problems in two boys who also had a distinctive facial appearance and extremely elevated IgE levels. Following this report, elevated IgE was found in the two girls from the initial report, showing that Job Syndrome and Buckley Syndrome represented the same condition. In 2007, a heterozygous mutation in the gene encoding the transcription factor STAT3 was found to underlie most cases of AD-HIES. In 2009 mutations and deletions in the DOCK8 gene were found to underlie many patients with similar symptoms inherited in an AR fashion.

Clinical Presentation

STAT3 Deficiency

STAT3 Deficiency, is associated with heterozygous loss of function mutations in the transcription factor STAT3. This is the more common form of HIES in the U.S. It commonly presents with skin findings including newborn rash, eczema, and recurrent staphylococcal skin abscesses as well as ear, sinus, and lung infections. The lung infections often result in cavitary lesions in the lungs (pneumatoceles). Other common infections in STAT3 deficiency include mucocutaneous candidiasis (Candida fungus on mucous membranes and/or skin), manifesting typically as thrush, vaginal candidiasis or candidal nail infection (onychomycosis), and recurrent shingles outbreaks. Additional findings include connective tissue and skeletal abnormalities, such as a typical facial appearance, hyper-extensibility of joints, retained primary teeth, recurrent bone fractures with minimal trauma, and

Forms of HIES

Table 20:1

Syndrome	Causative Gene	Symptoms
"Autosomal dominant HIES" (Job's Syndrome)	STAT3 Deficiency	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
ZNF341 Deficiency	ZNF341	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive GP130 deficiency	IL6ST	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive IL-6 receptor deficiency	IL6R	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils). Mucocutaneous Candidiasis. Minimal Trauma Fractures, Retained Primary Teeth, Scoliosis
Autosomal recessive HIES DOCK8 deficiency	DOCK8	High IgE, High Eosinophils, Severe Eczema, Skin infections (boils), Mucocutaneous Candidiasis, Warts, Herpes Viridae infections, Malignancy, Severe Food Allergies
Autosomal recessive PGM3 deficiency	PGM3	High IgE, Severe Eczema, Sinopulmonary Infections, Herpes Viridae infections, Malignancy, Severe Food Allergies, Asthma, Neurocognitive Delays, Scoliosis
Dominant negative CARD11 deficiency	CARD11	High IgE, High Eosinophils, Severe Eczema, Pulmonary Infections, Molluscum, Food allergies and Asthma
Comel-Netherton Syndrome	SPINK5	High IgE, High Eosinophils, Severe Eczema, "Bamboo Hair", Recurrent sinopulmonary infections, Enteropathy, Allergies (Food Allergy, asthma, allergic rhinitis)
CARMIL2 Deficiency	CARMIL2	High IgE, High Eosinophils, Severe Eczema, Warts (HPV and molluscum), Herpes Viridae infections, Eosinophilic GI Disease, Inflammatory Bowel Disease, Asthma/Bronchiectasis, EBV associated malignancy

a propensity to aneurysm formation of brain and cardiac blood vessels. Severe allergic diseases, such as food allergies, are not common in individuals with STAT3 Deficiency. However, they often have positive skin prick tests making it appear that they have significant allergies.

A newborn rash or eczema is frequently the first manifestation of AD-HIES. Pustular and eczema-like rashes usually begin within the first month of life, first affecting the face and scalp. Skin abscesses are a classic finding in this disorder, caused by a particular susceptibility to infections with Staphylococcus aureus. The degree of inflammatory symptoms, such as tenderness and warmth, often is quite variable. The term cold abscesses is applied to those lesions that lack external signs of inflammation despite the presence of pus. The occurrence and severity of these abscesses is substantially decreased with prophylactic therapy with antibiotics against Staphylococcus aureus. Deep tissue abscesses, such as liver or bone infections, are much less common in AD-HIES.

Recurrent bacterial pneumonias are often encountered in individuals with AD-HIES. Pneumonias typically start in childhood and are most frequently caused by Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae. Similar to the occurrence of cold skin abscesses, these pneumonias may present with fewer symptoms than would be expected in a person with intact immunity. This relative lack of symptoms and subsequent delay in clinical presentation may contribute to advanced disease and significant tissue damage before identification and initiation of appropriate therapy. Infection-induced tissue destruction in individuals with AD-HIES may give rise to pneumatocele formation, large cavities in the lung, which is a distinguishing feature of AD-HIES due to STAT3 deficiency. When pneumatoceles or bronchiectasis are present in the lungs, the individuals are more susceptible to lung infections with other bacteria such as Pseudomonas and molds such as Aspergillus.

Involvement of both the connective and skeletal tissues is an important feature of STAT3 deficiency. An asymmetrical facial appearance with prominent forehead and chin, deep-set eyes, broad nose, thickened facial skin, and a high arched palate are typical of this disease. These features evolve during childhood and become more established by adolescence. Individuals with AD-HIES exhibit hyper-extensibility of the joints. They frequently suffer bone fractures from seemingly insignificant trauma, and bone density may be reduced. Scoliosis is common and typically emerges during adolescence or later in life. Craniosynostosis, fused skull bones, and extra/abnormally formed ribs or vertebrae are also found more often in those with AD-HIES than in the general population. These skeletal abnormalities are not usually seen in individuals with DOCK8 deficiency.

Abnormalities affecting dentition are another common feature of AD-HIES with STAT3 mutations. Retention of primary teeth even after the permanent teeth have erupted is a consistent finding. This abnormality is revealed on panoramic x-ray views as double rows of retained primary teeth overlaying the permanent ones. Surgical extraction of the retained primary teeth is often necessary for healthy dentition. Children who have had their retained primary teeth extracted will have normal eruption of their permanent teeth.

DOCK8 Deficiency

Individuals with AR-HIES due to DOCK8 deficiency have characteristics similar to STAT3 deficiency in that they have eczema, skin abscesses caused by Staphylococcus aureus, recurrent respiratory infections, mucocutaneous candidiasis and other fungal infections. However, those with DOCK8 deficiency are distinguished from those with AD-HIES by the lack of joint, bone, and teeth changes. They tend to have frequent occurrence of severe, recurrent viral infections not seen in those individuals with STAT3-LOF. Individuals with DOCK8 deficiency often have frequent outbreaks from Herpes simplex (cold sores or other skin lesions) and Herpes zoster (shingles), and difficult to treat warts, like Human Papillomavirus (HPV), and Molluscum contagiosum a viral skin infection that causes round, firm, painless bumps that can occur on any part of the body.

Recurrent lung infections are common in DOCK8 deficiency, and they may also lead to chronic lung disease with damage to the airways (bronchiectasis) and lung tissues. However, cavitary lesions are not commonly seen in DOCK8 deficiency. DOCK8 deficiency is also associated with a higher incidence of pneumonia caused by the bacteria Pneumocystis jirovecii. Liver disease can result from chronic infection with the parasite Cryptosporidia.

Asthma and allergies can be more severe in DOCK8 deficiency, including food allergies manifesting with anaphylaxis.

Vasculitis, inflammation within blood vessels, may occur in the brain blood vessels and in the main body vessels, such as the aorta. This may lead to a stroke, resulting in neurologic impairments.

Risk of Cancer

Both individuals with STAT3-LOF and DOCK8 deficiency are at increased risk for malignancies, especially lymphomas. Individuals with DOCK8 deficiency are susceptible to papilloma virus-induced squamous cell carcinoma as well as lymphomas, particularly Epstein-Barr virus (EBV) induced lymphoma.

Laboratory Findings

Both STAT3 and DOCK8 deficiency impact the immune system and lead to immunological abnormalities. Increased serum IgE concentrations and eosinophil numbers are present in both forms of the disease.

In those with STAT 3 Deficiency, total white blood cell counts are typically normal and may not increase appropriately during acute infection. Neutropenia, low blood numbers of white blood cells called neutrophils, are seen in some people, but is not severe. A special type of T cell called Th17 cells are very low. Antibody levels, including IgG, IgA and IgM levels, are usually normal, but the ability to respond to vaccines is sometimes abnormal. Some may require immunoglobulin (Ig) replacement therapy.

Individuals with DOCK8 deficiency typically have low numbers of T cells, which often decrease further with age. They also tend to have low serum IgM levels and the antibody responses to vaccines are often poor.

Diagnosis

The diagnosis of HIES can be made based on a combination of clinical and laboratory findings for both AD- and AR-HIES. An elevated level of serum IgE is a virtually universal finding in these individuals. However, it is not sufficient on its own to make the diagnosis as people with other conditions, such as severe eczema, may also have very high IgE levels.

An HIES scoring system has been previously developed at the National Institutes of Health (NIH) that can help with the diagnosis of STAT3-LOF. In this system, individuals are evaluated for the existence and severity of the following clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper respiratory infections, pneumonia, lung cavities, candidiasis, other severe infections, fatal infections, characteristic facial appearance, increased nasal width, high palate, retained primary dentition, joint hyper-extensibility, fractures with minor trauma, scoliosis, midline anatomic abnormalities, lymphoma, high serum IgE level, and eosinophilia. The score correlates with the presence of the disease and higher scores reflect a more severe presentation. In addition, a recent study demonstrated that scoring five features: eosinophilia, parenchymal lung disease, frequency of sinusitis/otitis, retained primary teeth and minimal trauma fractures allowed differentiation between defects in STAT3 versus DOCK8.

A definitive diagnosis can be established with genetic analysis of the STAT3 and/or DOCK8 genes.

Inheritance

STAT3 Deficiency

STAT3-LOF occurs in both males and females of all ethnic groups with apparently equal frequency. In many, the disease occurs sporadically but then can be passed down to children in an autosomal dominant manner with each child have a 50% chance of having the mutation. Mutational analysis of the STAT3 gene would enable definitive diagnosis and genetic counseling.

DOCK8 Deficiency

Some individuals with AR-HIES are from families that are consanguineous, where parents are related or descended from the same ancestor. Deletions and mutations occur in the DOCK8 gene on chromosome 9. Mutational analysis of the DOCK8 gene is important for diagnosis and genetic counseling.

Treatment

Antibiotic prophylaxis with trimethoprim-sulfamethoxasole is frequently used as prophylaxis against recurrent respiratory infections, and Staphylococcal abscesses. Treatment for these infections, when they occur, should be started promptly.

Given that most individuals with HIES suffer from significant eczema and skin infections that come from having open lesions on the skin, skin care and prompt treatment of skin infections is an important component of HIES management. When the eczema is severe, topical moisturizing creams, non-steroidal topical creams and limited use of topical steroids can

help achieve healing. Cleaning the skin by bathing with chlorhexidine or dilute bleach baths helps to reduce the amount of bacteria that are on the skin. Skin abscesses may require incision and drainage but can largely be prevented with prophylactic oral antibiotics.

A remarkable feature of STAT3 Deficiency is how well the individuals may feel (and appear) when they have an infection. For example, even with evidence of a significant infection on physical examination and x-ray corroboration of pneumonia, the individual may deny feeling sick and may not feel the need for invasive diagnostic testing or prolonged therapy. Moreover, doctors unfamiliar with the diagnosis can be hesitant to believe that individuals who do not appear very ill can really be quite sick. Therefore, it is always important for individuals with this diagnosis to see their healthcare providers when there are even mild symptoms. Lung infections need to be diagnosed and treated promptly to prevent formation of pulmonary cavities. Once lung cavities are present, antifungal prophylaxis is often recommended to prevent mold infections. In those with structural lung disease, pulmonology consultation is recommended to assist with development of a regimen to improve airway clearance and decrease risk of further damage.

Frequent Candidiasis of the fingernails, mouth, or vagina may lead to consideration of antifungal prophylaxis. Also, individuals with this disease are more susceptible to some environmental fungi that are more common in certain part of the country, such as Histoplasmosis and Coccidiodes. Discussing with your healthcare provider any precautions based on location is important.

Those with DOCK8 deficiency with Herpes infections or shingles may benefit from prophylaxis with an antiviral agent such as acyclovir. Since those with DOCK8 deficiency have a higher incidence of Pneumocystis jirovecii, pneumonia prophylaxis for this disease is often recommended. These individuals are also more susceptible to the parasite Cryptosporidia that can be found in water. Depending on the water supply, bottled or filtered water may be recommended. Individuals with this diagnosis may be counseled to avoid water parks and swimming in fresh water lakes, ponds or rivers.

Hematopoietic stem cell transplantation (HSCT) is generally recommended for people with DOCK8 deficiency given the severity of the disease and the risk of developing fatal complications, including infections and malignancies early in life. In STAT3 deficiency, the role for HSCT is less clear, but it has been effective in select individuals with severe symptoms of the disease early in life.

In individuals with STAT3 deficiency who have demonstrated fractures, use of DEXA scan and consultation with an endocrinologist focused on bone health is recommended. Calcium and Vitamin D supplementation can also be considered. Collaboration with a dentist is essential in children to determine the optimal age to remove baby teeth. Adults should be monitored for high blood pressure as well as heart and brain aneurysms.

Expectations

Individuals with both types of HIES require constant vigilance with regard to infections and development of chronic lung disease.

With early diagnosis and treatment of infections, most individuals with STAT3 deficiency do fairly well. DOCK8 deficiency is associated with much higher risk of death by age 30 without HSCT. The more severe nature of DOCK8 deficiency should prompt early consideration of HSCT.

Genetic counseling is advised for families with HIES children and is especially important for those families where consanguinity is involved.

Adapted from: Chapter 1 The Immune System and Primary Immunodeficiency Diseases. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 21

Chronic Granulomatous Disease (CGD) and Other Phagocyte Disorders, Leukocyte Adhesion Deficiency and Neutropenia

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Chronic Granulomatous Disease (CGD) is a genetic (inherited) disease in which the body's cells that eat certain invaders (also called phagocytes) do not make superoxide, hydrogen peroxide, and other chemicals needed to kill certain bacteria and molds. As a result of this defect, individuals with CGD have severe infections from bacteria, molds, and other environmental pathogens that do not typically cause infections in healthy people. Individuals with CGD can also have difficulty with immune cells forming knots called granulomas, hence the name of the disease. Additionally, individuals with CGD can get excessive inflammation even when there is not an infection, and that inflammation can cause intestinal and urinary problems.

Definition

CGD is due to mutations in the NADPH oxidase complex. The NADPH complex is a made up of a group of molecules inside certain types of white blood cells known as phagocytes (from Greek, phagein, to eat). The NADPH complex usually functions to make chemicals that kill invaders and control inflammation. Individuals with CGD typically get recurrent infections and inflammation. There are two main types of phagocytes, neutrophils and monocytes, that travel from the bloodstream to sites of infection. They surround invading microorganisms and then ingest them into tiny compartments within the cells. These compartments, known as phagosomes, generate high levels of oxygen free radical chemicals (also called superoxides), such as hydrogen peroxide and bleach, that help kill the microorganisms. Phagocytes from individuals with CGD go to the sites of infection and ingest the microorganisms normally. However, once the microorganisms are ingested, phagocytes in those with CGD cannot effectively kill the microorganisms because they are missing key proteins required to make the necessary chemicals.

The production of superoxide inside the cell is required for killing of a specific set of invaders known as bacteria and fungi, which explains why individuals with CGD are susceptible to only those specific infections (*Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia and Aspergillus*). However, individuals with CGD have normal defense against many common infections, which is why the infections in CGD are so specific and unusual. Individuals with CGD make normal antibodies, so unlike individuals with lymphocyte problems, they are not particularly susceptible to viruses (such as, common cold, flu, chicken pox, measles, etc). Individuals may go months or years without infections and then have a severe one.

Clinical Presentation

Children with CGD usually appear healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria *Serratia marcescens*, so any infant with this particular infection should be tested for CGD. In fact, any infant or child with a significant infection with any of the organisms previously listed should be tested for CGD.

Infections in CGD may involve any organ or tissue, but the skin, lungs, lymph nodes, liver and bones are the usual sites of infection. Infections may rupture and drain with delayed healing and residual scarring. Infection of lymph nodes (under the arm, in the groin, in the neck) is a common problem in CGD, often requiring drainage or surgery along with antibiotics.

Pneumonia (infection of the lungs) is a common problem in CGD. Pneumonias due to the fungus *Aspergillus* may come on very slowly, initially only causing fatigue, and only later causing cough or chest pain. Fungal pneumonias often do not cause fever. In contrast, bacterial infections (*Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia*) usually come on with fever and cough. Nocardia, in particular, can cause high fevers and lung abscesses that can destroy parts of the lung. It is important to identify the presence and specific cause of infections early and to treat the infection completely, usually for long periods of time, to ensure infection stops and prevent relapse. Chest X-rays and computerized tomography (CT) scans of the chest are the best ways to look for lung infections. When they are seen, it is very important to figure out exactly which infection it is and that may require a biopsy (usually done with a needle or a bronchoscope) or sometimes even surgery. Treatment may require many weeks.

Liver abscesses occur in about one third of individuals with CGD. A liver abscess can start out as fever and fatigue, but it may also cause pain over the right upper abdomen. Some sort of scan is required for diagnosis, such as magnetic resonance imaging (MRI), CT scan, or ultrasound, and needle biopsy is necessary to determine the specific cause of the infection. *Staphylococcus aureus* causes most liver abscesses in CGD. Liver abscesses are hard to drain and may need surgery, but treatment with a combination antibiotics and steroids reduces the inflammation and lets the antibiotics work better even without surgery.

Bone infection (osteomyelitis) can involve the hands and feet, and can also involve the spine, particularly if there is a fungal infection in the lungs that spreads to the spine.

Newer antibiotics and antifungals are very active when administered by mouth. Managing infections and improving quality of life in individuals with CGD can be greatly improved with early diagnosis and appropriate therapy.

Inflammation is also a significant problem in people with CGD, both with and without infection. Granulomas can cause trouble with intestinal or urinary function, and can also form in the lung, the eye, or the skin.

One of the most difficult aspects of living with CGD is bowel inflammation. About 40 to 50% of individuals with CGD develop inflammation in the intestine that is not clearly due to a specific infection. Individuals with CGD can have severe abdominal pain, diarrhea, weight loss, and sometimes abnormal narrowing in parts of the intestines. Inflammation in the gastrointestinal (GI) tract can present as colitis (inflammation and ulcers of the bowl wall of the colon) (See Immune Dysregulation, Enteropathy, and Colitis Chapter). Commonly called inflammatory bowel disease (IBD), this inflammation is similar in clinical appearance to Crohn's disease. In addition, mouth sores, frequent vomiting, problems with urination and sometimes damage to the kidneys can be seen due to the inflammation associated with CGD. Treatment of this is similar to that applied to other forms of IBD, with steroids having good effect to control symptoms, but other immunosuppressive drugs are often used as steroid sparing agents. It is important to note that, injectable drugs that block the action of inflammatory molecule tumor necrosis factor alpha (TNFα), although very effective to reduce the IBD symptoms, can lead to severe infections in individuals with CGD and are not recommended.

Diagnosis

There are five different genetic kinds of CGD. The most common form in North America is called X-linked because the affected gene for part of the NADPH complex is on the X chromosome (70% of cases in the U.S.) and affects almost only males. The other types of CGD are due to autosomal recessive mutations where two abnormal copies of the gene for other parts of the NADPH complex lead to symptoms of CGD, therefore males and females are equally affected. In addition, girls carrying the X-linked gene may have autoimmune problems, like lupus of the skin, and sometimes may have serious infections. It is important to follow the neutrophil function in females carrying the abnormal x-linked gene, since this can change over time and lead to increased risk of CGD symptoms including infections and IBD. (See Inheritance Chapter.)

Usually infections begin in childhood leading to the diagnosis. However, some individuals with CGD may not have infections until late adolescence or adulthood. Pediatricians and internists must consider the possibility of CGD in any person with pneumonia with a characteristic CGD organism, such as *Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia* and *Aspergillus*.

The most accurate test for CGD, called the dihydrorhodamine reduction (DHR), measures the ability of phagocytes to produce oxygen free radicals in phagocytes using a chemical called dihydrorhodamine. In the past, the Nitroblue Tetrazolium (NBT) slide test was used to diagnose CGD, but this is less commonly used now since it is more prone to incorrect reading.

Once the diagnosis of CGD is made, it is valuable to determine the specific gene and mutation involved for purposes of prognosis and genetic counseling. The severity of CGD can partly be determined from the specific mutation in the gene and it's impact on the DHR result.

Treatment

All individuals with CGD should be on antibiotics for prevention (prophylaxis) of bacterial infection. The first line therapy is usually trimethoprim/sulfamethoxazole, also know as cotrimoxazole and septra. In addition, itraconazole, voriconazole, or posaconazole should be used for prevention of fungal infections. Use of these medications reduces infections dramatically. Interferon gamma is an injectable pro-inflammatory molecule that can be used together with antibacterial and antifungal prophylaxis to reduce infection. Since the infections that are important in CGD are found in the environment and not carried in our bodies normally, the effect of prophylaxis is to build a wall around the individual: it can still be jumped over but prophylaxis makes it harder for infections to get in. Maximum infection prophylaxis for CGD involves treatment with twice-daily oral doses of cotrimoxazole and once daily itraconazole, plus three times weekly injections of interferon gamma. With these prophylactic treatments, the average incidence of severe infections in CGD is less than once every four years.

Early diagnosis of infection and prompt, aggressive use of appropriate antibiotics and antifungal agents are the best ways to treat acute CGD infections. Initial therapy with antibiotics aimed at the usual suspects makes sense while waiting for results of infection test results, but it is important to try to identify the specific infection and not just guess all the way along. Intravenous antibiotics may be needed for serious CGD infections. Phagocyte transfusions are sometimes used when an infection is especially life threatening or slow to resolve such as can be the case with deep tissue fungal infections.

Steroid medications, such as prednisone or methylprednisolone, may sometimes be required to control inflammation. Individuals on steroids need close monitoring for side effects such as high blood pressure and high sugar levels.

Side effects of both antibiotics and antifungals may include nausea, vomiting diarrhea, loss of appetite, or rash. Interferon gamma injections may cause fever, fatigue, and depression. Acetaminophen taken before the injection may help. Flu-like side effects are usually related to the dose and may be decreased by lowering the dose or how often it is given. Even doses lower than the standard recommendation may provide some protection against infection. Individuals with CGD should consult their healthcare provider if they experience side effects. The risks and benefits of any treatment should be carefully considered.

Managing Exposures

Fungal and bacterial exposures are prevalent in every day life, but there are some precautions that can be taken to avoid exposures and reduce infection risk.

Many physicians suggest that swimming should be confined to well-chlorinated pools. Brackish water in particular, like bays and rivers near the ocean, may contain organisms that are specifically dangerous in CGD, such as *Francisella philomiragia, Chromobacterium violaceum*.

Individuals with CGD should avoid handling of dirt, as well as grass cuttings, decaying leaves, garden mulch (shredded moldy tree bark), and potting soil because they contain high levels of fungi and bacteria. These exposures can cause severe pneumonias. Individuals with CGD should remain indoors during mulching in neighboring yards. Once the mulch is settled firmly on the ground and is not being spread or raked, it is much less of a danger to individuals with CGD. Individuals with CGD should also avoid turning manure or compost piles, repotting house plants, cleaning cellars or garages, removing carpets, performing demolition, digging

in dirt, dusty conditions, cutting grass, raking leaves, hay rides, and barns. *Aspergillus* is also present in marijuana, so individuals with CGD should avoid smoking it. Individuals should see their doctors about even minor infections and colds to avoid life-threatening infections.

Hematopoietic Stem Cell Transplantation and Gene Therapy

Individuals with CGD can be treated with hematopoeitic stem cell transplantation (HSCT), which, in those with CGD, essentially replaces the defective phagocytes with working ones. HSCT outcomes are generally good for people with CGD. HSCT has been associated with improved long-term survival, approximately greater than 90%, and improved quality of life, particularly in individuals with X-linked CGD when compared to those individuals who are managed with medications. HSCT is also quite effective for the treatment of inflammatory colitis associated with CGD. HSCT is not indicated for all individuals with CGD, as many do well on medical management. The risks and benefits of the procedure must always be carefully weighed. (See Hematopoietic Stem Cell Transplantation Chapter.)

Replacement of only the defective gene, called gene therapy, is currently available in clinical trials for X-linked CGD. In this therapy, some of the individual's own hematopoietic stem cells are harvested (removed) from the individual, and a healthly copy of the abnormal gene is added to the individual's own stem cells. These corrected cells are then transfused back into the individual, similar to the procedure used for HSCT. As with HSCT and any treatment, the risks and benefits of the procedure must always be carefully weighed. (See Gene Therapy Chapter.)

Expectations

The long-term outcome for individuals with CGD is highly dependent upon how much superoxide the phagocytes are able to make. Particularly for individuals with X-linked CGD and minimal superoxide production, the survival after 20 years of age is poor with medical management alone. In contrast, survival is better for individuals with autosomal recessive forms of CGD or X-linked CGD associated with higher levels of residual superoxide production. Individuals should talk with their immunologist to understand the predicted long-term outcome based on their genetic testing and DHR results.

Hospitalizations may be required for individuals with CGD to locate sites and causes of infections. Intravenous antibiotics may be needed for serious infections. Prophylactic antibiotics and treatment with interferon gamma increase healthy periods. The vast majority of individuals reach adulthood, when serious infections tend to occur less frequently.

Leukocyte Adhesion Deficiencies

The chief phagocytic white blood cell is the polymorphonuclear granulocyte (PMN), also known as neutrophil. The neutrophil's job is to move to sites of infection, ingest the invader and kill it. (See The Immune System and Primary Immunodeficiency Diseases Chapter.)

In order for neutrophils to remove invaders, they must be able to get into the tissues. To do this they need to stick to the walls of the blood vessel and squeeze their way between the vessel cells to get out into the tissues. There are several specific defects that impair this process, all grouped together as Leukocyte Adhesion Deficiencies (LADs). LADs are characterized by recurrent life-threatening infections, delayed separation of the belly button (umbilical) stump, infection of the umbilical stump, skin infections without pus formation, and elevated white blood cell counts. LAD type 1 (LAD1) is due to mutations that cause failure of the tight sticking of neutrophils to the blood vessel, which allows the neutrophil to go out into the tissue. LAD1 is by far the most common cause of LAD and, it is usually corrected by HSCT. However, milder forms of LAD1 can sometimes be managed with antibiotics alone. LAD type 2 (LAD2) causes trouble with the gentle sticking of neutrophils to the vessel wall. LAD type 3 (LAD3) causes problems with how neutrophils sense when attachment is happening.

Neutropenias

Neutropenias are disorders with less than 500 neutrophils/microliter; normal is more than 2,000 cells/microliter. Depending on its severity and duration, neutropenia can lead to serious infections or intermittent infections of the skin or other tissues. Therefore, not all neutropenias are severe and some do not require therapy (benign neutropenia).

Neutropenia can be recognized at birth or later and can be either chronic and constant or intermittent. One form, termed severe congenital neutropenia (Kostmann syndrome), is an autosomal recessive disorder due to mutations in the gene *HAX1*. These individuals require treatment with granulocyte colony stimulating factor (G-CSF), a medication that stimulates the body's production of granulocytes, and HSCT should be considered since there are risks associated with long term use of G-CSF.

The intermittent form of neutropenia is called cyclic neutropenia, an autosomal dominant disorder in which the neutropenia occurs every two to four weeks and lasts about a week. In between periods of neutropenia, the individual typically has a low normal neutrophil count. Cyclic neutropenia is caused by mutations in a gene termed *ELANE*.

Autoimmune neutropenia can present at any time of life. In this condition, an antibody against the neutrophils causes their destruction. This can occur on its own but may also be one of the first symptoms of Common Variable Immune Deficiency (CVID). (See Common Variable Immune Deficiency Chapter.) In children autoimmune neutropenia most commonly resolves on it's own.

Treatment for neutropenias may include antibiotics for infections, prophylactic antibiotics, immunoglobulin (Ig) replacement therapy, G-CSF injections or HSCT.

Several other forms of primary immunodeficiency diseases (PI) may have associated neutropenia. These include X-linked Hyper IgM Syndrome (CD40 ligand deficiency), CVID, X-linked Agammaglobulinemia (XLA), WHIM Syndrome, Wiskott-Aldrich Syndrome, and GATA2 deficiency. Not all neutropenias result from genetic defects. Neutropenia can be acquired secondary to severe infections as well as treatment with certain medications and is seen in lupus.

Other Neutrophil Disorders

Specific Granule Deficiency: Specific granule deficiency is extremely rare and is associated with decreased granules within the neutrophils that help with killing of invaders. Individuals with this condition are at risk for bacterial infections.

Glycogen Storage Disease Type Ib: Glycogen storage disease type Ib is a disorder with neutropenia, poor neutrophil killing of invaders, a large liver, and low blood sugar. It is due to a defect of the enzyme glucose-6 phosphate transporter 1 with accumulation of glycogen in the liver. Individuals with this condition are at risk for bacterial infections and are often treated with G-CSF.

Beta-actin Deficiency: Beta-actin Deficiency is associated with poor granulocyte movement (chemotaxis) and recurrent infections. Other chemotactic disorders which are associated with severe periodontitis and early tooth loss include Papillon-Lefebre syndrome, prepubertal periodontitis, and juvenile periodontitis.

Chediak Higashi: Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder in which granules in the neutrophil inappropriately fuse causing impaired bacterial killing. People with CHS have partial albinism (light skin and silvery hair), and they have problems with sun sensitivity and photophobia. These individuals also have problems with lymphocytes and may develop an accelerated phase, in which fever and cell destruction can require chemotherapy treatments. Progressive periperhal nerve damage neuropathy are common and increase with age. Bacterial infections involve mucous membranes, skin, and the respiratory tract. Infections are treated with antibiotics and abscesses are surgically drained when appropriate. HSCT fixes the accelerated phase and the infections but does not change the neuropathy.

Griscelli Syndrome: Griscelli syndrome (GS) is a rare autosomal recessive disorder that results in low amounts of pigment in the skin and hair. There are three different forms of GS and only GS type 2 (caused by mutation in the RAB27A gene) is a form of PI. Individuals have partial albinism, frequent bacterial infections, and neutropenia, and low platelets. Individuals also have low immunoglobulins. Individuals with GS2, like those with CHS can develop the accelerated phase, which is fatal if not treated aggressively. Early HSCT is strongly recommended for GS2.

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Chapter 22
Complement Deficiencies

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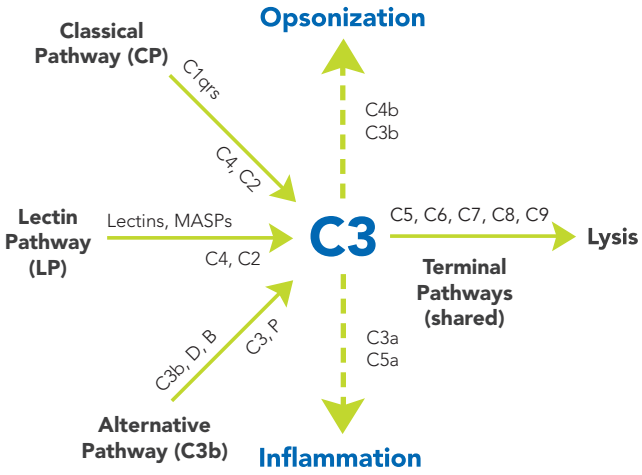
The complement system consists of more than 40 proteins, present in fluids (blood) and tissues, and other proteins anchored on the surfaces of cells. Most of the blood complement proteins are made in the liver, though a few of them are made by cells outside the liver, including neutrophils and fat cells (adipocytes). The primary functions of the complement system are to protect the body from infection, to remove particulate substances (like damaged or dying cells, microbes or immune complexes), and to initiate and modulate (change) immune responses. As part of the innate immune system, complement acts immediately to start the process of removal and resolution of the problem, such as an infection. Complement works with cells of the immune system and proteins of the coagulation pathway to control an infection. There can be deficiencies in any one of the many individual complement proteins. Individuals with a complement deficiency can have clinical problems that are a result of the role that the specific complement protein plays in the normal function of the human body.

Activation of the Complement System and Its Pathways

Complement activation is designed to eliminate invading microbes while producing minimal collateral damage. Complement proteins in the circulation are generally not activated until triggered by an encounter with a bacterial cell, a virus, an immune complex (antibody attached to a foreign material), or damaged tissue.

Complement activation is a cascading event with tremendous amplification potential. It must follow a specific order if the result is to be achieved. The circulating proteins have been grouped into three major activation pathways, based on the types of substances and proteins that initiate the activation. If you visualize a trident, the three tines (teeth) represent the different initiation routes of the complement system, while the handle represents the mechanism by which this cascade ultimately destroys the threat, no matter which activation pathway started the response. The diagram in Figure 22:1 depicts the activation pathways.

Figure 22:1 Complement System and Its Pathway



The **Alternative Pathway (AP)** is the most evolutionarily primitive of the complement pathways. It is initiated by fragments of the complement component C3. These are always being generated at a low level in our body but get rapidly amplified when they encounter a

pathogen or abnormal cells. Other elements of the AP are Factor B, Factor D and properdin. A unique feature of the AP is the presence of the only positive regulator in the complement system, properdin. Properdin makes it possible for the amplification loop of the AP to efficiently put lots of C3b onto the surface of the activating cells, bacteria, protein complexes, or particles in the immediate vicinity of the activation site. Because the ability of C3b to bind to these surfaces decays rapidly, the activation is limited to just the region around the C3 cleavage (activation) site. This time-limitation is another control mechanism for the complement pathway.

The **Classical Pathway (CP)** is activated primarily by immunoglobulins (antibodies, including autoantibodies) that are bound to antigens, either in the fluid phase as soluble immune complexes or on the surfaces of cells. Components of the CP are C1q, C1r, C1s, C2 and C4. The CP was the first to be discovered, but is the most recent in evolutionary terms.

The **Lectin Pathway (LP)** is similar to the CP except for the first two steps. Mannose binding lectin (MBL), the ficolins and collectins initiate the LP. These are often present on surfaces of pathogens or altered host cells (such as dead cells). C2 and C4 also participate in the LP.

The **Terminal Pathway (TP)** is the final set of steps in the complement activation process that forms a membrane lesion or hole (membrane attack complex, MAC), thus killing susceptible pathogens (bacteria) or other cells that activate complement on their surfaces. The TP is dependent upon at least one of the other pathways, such as AP, CP or LP for activation. The components of the TP are C5, C6, C7, C8 and C9, and they form the MAC (C5bC6C7C8C9, or C5b-9).

Regulatory proteins to prevent unregulated activity (and tissue damage) are present as control mechanisms for each pathway. These can be present in the fluid phase, such as blood, or on the cell surface. **C1-esterase inhibitor** (C1-INH) is a serine protease inhibitor (SERPIN) in the blood and acts by forming a complex with active enzymes to trap and inactivate them. It is important in controlling the C1r and C1s activation in the classical pathway and the MBL-associated serine proteases in the lectin pathway along with enzymes in the coagulation system. **Factor H and Factor I** are also fluid-phase proteins that help to regulate the amplification of the complement system. Their deficiency can result in a condition known as atypical hemolytic uremic syndrome (aHUS), which is associated with red blood cell damage and kidney dysfunction. CD46 and CD55 are proteins present on the cell surface, that also limit complement activation on the cell from which they are expressed. CD59 deficiency is associated with lysis of red blood cells and kidney damage, seen in paroxysmal nocturnal hemoglobinuria (PNH).

The dynamic interplay among the different complement pathways and their control processes involves other plasma protein systems such as enzymes of the coagulation system, enzymes from inflammatory cells, and substances such as histamine and elastase released from cells in the local environment. All of these participants affect the outcome of an activation event. Most of the time, the outcome is favorable to the host. The diseases that accompany uncontrolled activation or a defect in the function of complement are often the result of an inherited deficiency or subtle impairment of one or more of its regulators.

Complement Deficiencies and Their Diagnosis

General Features

Over 50% of people who have deficiency in complement proteins develop infections. An even higher percentage of individuals with a deficiency in the CP develop autoimmunity, primarily systemic lupus erythematosus (SLE). Deficiency of C3, the most abundant complement protein, results in severe, recurrent infections (especially those of the respiratory tract) that begin soon after birth. As the age increases, infections are primarily due to a bacterial species, *Neisseria*, which can cause meningitis. Hence, the typical clinical symptoms of complement deficiencies include recurrent mild or serious bacterial infections and autoimmune disease. In C1 inhibitor deficiency, episodes of angioedema (a swelling under the skin or in the intestines) occur. The list of potential complement-related health problems includes renal disease, vasculitis (blood vessel inflammation), and age-related macular degeneration. A history of family members having the same presentation should increase the suspicion of an inherited complement deficiency.

The initial tests done to evaluate an individual's complement system can identify an inherited defect and indicate what further testing must be done to make the diagnosis. The aim of the evaluation process is to define the complement component deficiency, while ruling out acquired causes of low

complement values. Several screening blood tests are available that make it easier to find the answers. These include **CH50**, which is a useful tool to screen for classical pathway deficiencies, and **AH50**, which is used to screen for alternative pathway deficiencies. Individual complement levels can also be tested. It is important to know as much as possible about the reason(s) for low or absent complement so that decisions regarding appropriate treatment can be made, including when to use antibiotics and immunizations as well as for decisions about genetic counseling for inherited deficiencies.

Therapies specific for complement deficiencies are still in the developmental stage for most components, but in some cases, such as C1-INH deficiency, there are currently a number of medications available. For poorly controlled complement activation, especially that occurring due to deficiencies in regulatory proteins as in aHUS or PNH, there are certain drugs available to treat acute episodes or to prevent recurrence. Additionally, a monoclonal antibody to C5 (eculizumab) is used to block complement-induced damage. Additional therapeutic agents may become available in the next decade.

Deficiencies in the Alternative Pathway: C3, Factors D, B and Properdin

Inherited C3 deficiency results in repeated, severe infections starting from birth, especially those of the respiratory tract. Organisms such as *Streptococcus pneumoniae* and *Hemophilus influenzae* are the most frequent causes of infection. These infections have decreased in frequency and severity due to use of antibiotics and vaccines.

Properdin is the only complement protein that is X-linked, so its deficiency only affects males. The protein is synthesized by immune cells such as monocytes, granulocytes, and T cells. Properdin deficiency increases the susceptibility to bacterial infections of the *Neisseria* family of organisms. The most prominent in the group is *Neisseria meningitidis*, which can cause a serious form of meningitis. Typical family histories include male relatives who have had or died from *Neisserial* infections.

Factor D deficiency is very rare and has only been described in two families. Both of these families had multiple members with a history of serious infections.

Deficiencies in the Classical Pathway: C1, C4, C2, C1-INH

Rapid clearance of immune complexes, dying cells and debris from damaged tissues is a job that is efficiently performed by a normal **classical pathway**. The C1 protein is made up of C1q, C1r, and C1s. Complete deficiency of C1, C2, or C4 is closely linked to development of systemic lupus erythematosus (SLE). This is thought to be due in part to the inability of complement to clear immune complexes and debris from dying cells, especially DNA and RNA.

C2 deficiency is the most common complement deficiency in Caucasian populations, with frequency estimates between 1 in 10,000 to 1 in 20,000 individuals are homozygous C2-deficient. In primary immunodeficiency diseases (PI), C2 deficiency is found in young children who have recurrent infections, mainly upper respiratory tract or ear infections due to *Streptococcus pneumoniae and Hemophilus influenzae*. Many adults with C2-deficiency also have SLE.

Hereditary angioedema (HAE) is a disease caused by deficiency of the CP control protein, C1-INH. Symptoms generally begin around puberty but can occur earlier. These individuals have recurrent moderate to severe swelling in the extremities, face, lips, larynx (vocal cords), and gastrointestinal tract (intestines) that is frequently painful and debilitating. Intestinal swelling can cause acute severe abdominal pain, and the acute intestinal swelling can result in obstruction, which may need acute surgical intervention Swelling the vocal cords can be concerning because of the possibility of airway obstruction leading to suffocation. These episodes typically last three-five days if not treated with effective medication.

Acute treatments for HAE include C1 inhibitor, a replacement therapy [both plasma derived (concentrate) and recombinant products are available]; ecallantide, a kallikrein inhibitor (available in the U.S. only) and icatibant, a bradykinin-2 receptor antagonist. Note that steroids and antihistamines are not effective to treat HAE or prevent attacks. Prophylactic treatments include androgens, C1 inhibitor concentrates, and lanadelumab.

Deficiencies in the Lectin Pathway: MBL, M-ficolin, L-ficolin, H-ficolin, CL-11, MASPs

Deficiencies in the lectin pathway are fairly common, affecting approximately 5-30% of individuals. There is some controversy over the importance of the lectins to overall immunity. Most experts agree that the lectin pathway is important to fight bacterial infections during the early months of a baby's life when maternal antibodies decrease and the child's own antibody production is not fully functional. In certain cases, the deficiency may be severe. [For example, a homozygous mutation in the ficolin-3 gene leads to severe, recurrent pulmonary infections in children that can result in severe lung disease, including bronchiectasis (damage to the lungs), later in life. Other studies have shown increased susceptibility to HSV-2 (Herpes Simplex Virus-2), influenza A, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Homozygous mutations in either the collectin-11 gene or MASP-1 gene can result in developmental abnormalities (including facial irregularities, cleft lip and palate, and cognitive defects).]

Manose Binding Lectin Deficiency

Manose Binding Lectin Deficiency (MBL) is a part of the lectin pathway of the complement system, one of several different components of our immune defense. The lectin pathway may be first to react before a traditional immune response occurs. It was thought that deficiency of MBL might explain some cases of increased susceptibility to bacterial infection. However, when a test was developed to measure MBL in the blood, it was determined that low or absent MBL is very common, affecting approximately 5-30% of all individuals. Therefore, its absence alone cannot be a cause of serious immunodeficiency or a large portion of the world's population would suffer from frequent major recurrent and potentially fatal infections. The MBL test is occasionally still ordered during an evaluation for immunodeficiency and, when the results show MBL to be low or absent, it is wrongly interpreted as indicating the presence of a PI. By contrast, expert immunologists experienced in caring for people with PI believe that low or absent components of this lectin system, including low or absent MBL, do not cause immunodeficiency by themselves. There is no recommended treatment for low or absent MBL, and immunoglobulin replacement therapy is clearly not indicated for that purpose. It is important to stress that the finding of low or absent MBL does not indicate that the cause for an individual's infections has been found and that the diagnostic process must continue until the correct diagnosis is determined.

Deficiencies in the Regulatory Proteins: Factor H, Factor I, CD46, CD55 and CD59

Complete deficiency of Factor H leads to uncontrolled activation of the alternative pathway and C3 consumption. Recent data has been published that demonstrates how critical the role for this complement control protein is in maintaining health in a number of tissues. In addition to bacterial infections, deficiency or dysfunction of factor H is associated with various forms of kidney disease including atypical hemolytic uremic syndrome (aHUS), as well as age-related macular degeneration (AMD). Heterozygous variants in Factor I and CD46 can also result in aHUS. These diseases are examples of control processes gone awry on the surfaces of the organs affected. An acquired deficiency of CD59 is seen in paroxysmal nocturnal hemoglobinuria, which is associated with hemolytic anemia and renal failure. More recently, genetic sequencing has identified mutations in CD55 that are associated with CHAPLE syndrome (complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy), which often presents as abdominal pain or diarrhea, recurrent infections, and thromboembolic disease (blood clots).

Treatment of Complement Deficiencies

Any complement deficiency should be treated as a form of PI, and the individual should be immunized against the bacteria that are most likely to infect them (see above). For example, boys with properdin deficiency should be immunized against *Neisseria meningitidis*, meningococcal vaccines in addition to the usual childhood vaccinations. People with deficiencies of the other alternative pathway components and the terminal pathway proteins are also susceptible to *Neisseria meningitidis* and should be immunized. Antibody responses should be checked after vaccination, since the inability to activate complement may impair response to the vaccine.

Currently, there is no single treatment for complement deficiencies. Appropriate prevention and treatment of infections (usually with antibiotics) is key. Fresh frozen plasma infusions have been tried in some cases but carry a risk that the individual may make antibody to the missing complement component, so prolonged use is not advised. In case of HAE, effective medications to treat or prevent angioedema episodes are available. In aHUS or PNH, eculizumab, a complement-inhibitory antibody may help. Prophylactic antibiotics can be used if the individual experiences repeated infections. Most of these individuals who are presdisposed to infections

eventually make antibodies against the offending bacteria and do not get sick as often.

Summary

The inherited deficiency of various complement proteins results in diseases due to the inability to perform primary immune functions, such as protection from infection or clearance of cellular debris. Additionally, in most situations where autoantibodies are present (such as SLE), these antibodies can engage complement, consume it and result in tissue damage. Thus, there are certain acquired deficiencies of complement that are not inherited but can lead to disease. Both children and adults can be affected by complement deficiencies so it is important to recognize the typical presenting symptoms of specific deficiencies as outlined above. Knowledge of the role of each complement component in the body and how it is regulated can help in understanding the effect of the specific deficiency and its treatment.

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Chapter 23

Innate Immune Defects

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Introduction

The immune system is in charge of protecting us from unwelcome invaders. Primary immunodeficiency diseases (PI), in which part of the body's immune system is missing or does not function properly, can be divided into two groups:

1. Those less common conditions with defects in innate immunity, a system of cells and mechanisms that defend the host from infection in a non-specific manner.
2. Those conditions due to defects of adaptive immunity in which defense is carried out in a more specific manner by T cells and antibody producing B cells.

The innate immune system represents our first line of defense. It comprises our physical barriers (such as skin and the mucosa in the gastrointestinal tract, sinuses, and lungs), immune cells (neutrophils, monocytes, macrophages, natural killer cells, and mast cells, among others), and complement proteins. The name innate comes from being naturally present prior to any microbial encounter and for not requiring additional training to do its job.

Innate immune disorders include: Myd88 and IRAK-4 deficiencies, TLR3 deficiency, NF-kappa-B Essential Modulator (NEMO) deficiency syndrome, natural killer (NK) cell deficiency, and defects in interferon-γ (IFN-γ) and interleukin (IL)-12/23 signaling pathways.

Overview

Every time we face a new microbe, several questions need to be addressed in a timely manner. Is it a threat? Is any immediate action required? If yes, of which kind? The innate immune system answers these questions, in a quick and reliable way. Even very specialized cells, like T and B cells, rely on these initial steps to know who the enemy is, when it is time to attack, and what to do.

Innate immune cells deal with the first challenge of identifying which organisms are potentially harmful by using danger sensors known as pattern-recognition receptors (PRRs). These receptors recognize certain structures that are present in pathogens but not in human cells, named pathogen-associated molecular patterns (PAMPs). This way of detecting threats proves to be a very smart strategy. PAMPs are shared by groups of microbes, and they are essential for their survival. This means that a single receptor is able to recognize several pathogens, and, even if mutations occur, the sensing system will remain functional because these structures are so important that they are unlikely to change.

Some of the best-known and widely present PRRs are the Toll-like receptors (TLR) family. In humans, there are 10 different TLRs, termed TLR1 to TLR10. TLR1, -2, -4, -5, -6, and -10 are located on the surface of the cell, where they sense extracellular molecules, while TLR-3, -7,-8, and -9 stay in the cytoplasm inside the cell to recognize intracellular products, such as viral nucleic acids. The binding of certain molecules, like RNA and DNA from viruses to these receptors, initiates a cascade of chemical reactions that will ultimately deliver a message to the nucleus, where genes will be activated to mount an immune response that is appropriate to the type of signal sensed by the TLR.

Innate Immune Deficiencies

Myd88 and IRAK-4 Deficiencies

Several intermediate proteins take part in the process of sending signals sensed by TLRs to the nucleus. Two of these proteins are of importance here, as inherited defects that are known causes of PI.

All TLRs except TLR3 use myeloid differentiation primary response protein 88 (or simply Myd88) as an adaptor (partner) protein. Since Myd88 recruits and interacts with interleukin-1 receptor-associated kinase 4 (IRAK-4) in the signaling pathway, genetic

defects in either Myd88 or IRAK-4 result in the same clinical manifestation of invasive pyogenic infections, which means that pus-inducing bacteria (pyogenic) infect areas that are normally germ free. *Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa* are the most common bacteria to cause infections in these individuals. Infections are usually severe (sepsis, meningitis, arthritis, osteomyelitis, abscesses) particularly during the first years of life. Of note, immune responses to other types of bacteria, viruses, fungi, and parasites are unaffected.

Despite having severe infections, individuals with defects in Myd88 or IRAK 4 commonly present only with low-grade fever and slightly abnormal inflammatory markers like a sedimentation rate or CRP. Diagnosing these defects can be tricky as most routine immunological tests are normal. Some individuals show abnormal antibody responses to polysaccharide antigens and elevated serum levels of IgE. Specialized laboratories can run specific tests to evaluate TLR function, but a definitive diagnosis relies on gene sequencing.

Infection severity for these individuals decreases with age, once other arms of the immune system mature and take control of the troublesome pathogens. However, early-life infections can be life threatening and require careful management. Caregivers and healthcare professionals must be prepared to provide immediate and aggressive treatment to infections, in spite of mild symptoms. Most of these individuals benefit from prophylactic antibiotics, and some individuals might need immunoglobulin (Ig) replacement therapy temporarily.

TLR3 Deficiency

Individuals with defective TLR3, the only TLR that does not signal through Myd88, are at increased risk of developing herpes simplex virus (HSV-1) encephalitis, a severe viral infection of the brain and central nervous system. It typically occurs in childhood, when individuals first encounter this virus (HSV-1 is the most common cause of cold sores). Infection susceptibility is restricted to HSV-1, as individuals are able to mount effective responses against other viruses, bacteria, and fungi. HSV-1 encephalitis is a rare infection and should prompt investigation for immunodeficiency. Other genes related to TLR3 signaling, such as *UNC93B1, TRIF, TRAF*, and *TBK1*, also need to be screened. Mortality rates associated with these diseases are high (around 70%) when they are untreated. However, outcomes can improve with the use of antivirals, interferons, and supportive care.

NEMO Deficiency Syndrome

In the chain of chemical reactions after TLR activation, NF-kappa-B Essential Modulator (NEMO) is an important protein downstream of Myd88 and IRAK-4. NEMO is required for the activation of the NF-kappa-B family of transcription factors. These factors ultimately regulate lymphocyte development and proliferation, inflammation, and immune responses.

Besides TLRs, other signaling pathways also recruit NEMO. For this reason, in NEMO deficiency, many cellular processes are affected and individuals tend to have more clinical manifestations compared to TLR deficiencies. One of these pathways starts with the ectodysplasin-A receptor, which is important for the development of ectodermal tissues, such as hair, skin, nails, etc. Malfunction of this pathway results in anhidrotic ectodermal dysplasia (EDA), a condition characterized by dry and thickened skin, conical teeth, absence of sweat glands, and thin, sparse hair. Several different defects can cause EDA, but the association of EDA and immune defects (EDA-ID) is highly suggestive of NEMO deficiency.

From the immunological standpoint, individuals with NEMO deficiency syndrome have a range of infections with pyogenic organisms. *Streptococcus pneumonia and Staphylococcus aureus* are the most common pathogens, but individuals with NEMO can also have viral and fungal infections. Infections can be severe and may be found virtually anywhere in the body, including the lungs, skin, central nervous system, liver, abdomen, urinary tract, bones and gastrointestinal tract. Many individuals have humoral immunity problems with a complete lack of antibody response against certain bacteria, such as pneumococcus, despite vaccination. A subset of these individuals presents with high serum levels of IgM. Other individuals exhibit defects in additional arms of the immune system that cause increased susceptibility to mycobacteria. These individuals may develop disseminated infection if they receive BCG (the live vaccine against tuberculosis, which is commonly given in countries other than the U.S.).

About 90% of individuals with NEMO deficiency have EDA. A small group of individuals have a more severe disease course presenting with two additional conditions: osteopetrosis (a disorder in which bones are denser, prone to fractures and the bone marrow fails to produce blood cells) and lymphedema (fluid retention due to defects in lymphatic vessels), known as OL-EDA-ID syndrome.

NEMO deficiency is inherited in an X-linked manner; hence, almost all cases occur in boys. Female carriers are normally free of immune symptoms, but some might have a condition called incontinentia pigmenti, mostly affecting the skin.

Diagnosis of NEMO deficiency is based on clinical manifestations. The presence of EDA is usually a hint but can be absent in 10% of the individuals. Almost all individuals with NEMO deficiency lack protective levels of pneumococcal antibodies following pneumococcal vaccination. Routine immunological tests are variable among individuals, and normal results do not rule out the diagnosis. Diagnostic confirmation requires genetic testing.

Therapy for NEMO deficiency is aimed at preventing infections and complications stemming from infection. Individuals with antibody defects receive Ig replacement therapy. While this therapy is a cornerstone of treatment, it is insufficient alone to control infections given the broad-based immune defects in these individuals. Therefore, individuals also receive a series of prophylactic antibiotics as part of their infection preventive regimen.

Individuals with NEMO deficiency should see their primary care physician and immunologist regularly as problems and complications can be frequent. Treatment should be started promptly whenever an infection is suspected. Hematopoietic stem cell transplantation (HSCT) has been used for some individuals with NEMO deficiency. Outcomes after transplantation have been variable. Transplantation is able to correct the immunological defects of NEMO deficiency but does not improve the other complications of the syndrome.

Natural Killer (NK) Cell Deficiency

NK cells are innate immune cells important in the killing of cancer cells or cells that have been infected by viruses. NK cells are so named because they are able to kill cells without the need of any pre-training. They are present in relatively low numbers in the bloodstream and in tissues.

NK cells kill virus-infected cells by poking holes on the cells' membranes and injecting toxic proteins into the viral infected cells. NK cells are particularly important in the defense against herpes viruses. This family of viruses includes herpes simplex virus (HSV) that causes cold sores and genital herpes; Epstein-Barr virus (EBV) that causes infectious mononucleosis; cytomegalovirus (CMV); and varicella-zoster virus (VZV) the cause of chicken pox and shingles. Individuals with NK cell deficiency present with severe or recurrent infections caused by herpes viruses and papilloma viruses that can cause warts and cancer.

Human NK cell deficiencies have been divided into two categories:

1. Quantitative defects: with absent or very low numbers of NK cells in the peripheral blood
2. Qualitative defects: with normal numbers of NK cells but abnormal NK cell function

NK cell deficiencies in the first category have been labeled as classical NK cell deficiencies and those in the second functional NK cell deficiencies.

Diagnosis includes quantification of NK cells, as well as assessment of function (ability to kill target cells). Several medications and disease processes may have an impact on NK cell numbers and activity. Therefore, abnormal tests should be repeated on separate occasions to establish the diagnosis. Genetic causes of NK cell deficiency have been identified including autosomal recessive and dominant forms.

Vaccination against human papillomavirus (HPV) is recommended. Some individuals might need continuous use of antiviral agents and may benefit from Ig replacement therapy. More specific therapies are under study. For individuals with severe disease, HSCT might be considered.

Defects in Interferon-γ (IFN-γ) and Interleukin (IL)-12/23 Signaling Pathways

Macrophages ("big eaters" in Greek) are innate immune cells found in all human tissues. They are able to kill microbes by eating and subsequently digesting them. However, some pathogens, such as *Mycobacteria* and *Salmonella*, learned how to escape from destruction and became capable of surviving and growing within macrophages. To overcome this, macrophages produce IL-12 to activate specialized T and NK cells and stimulate interferon-γ (IFN-γ) production that will act on macrophages leading to the killing of intracellular microbes. This cooperation represents the IFN-γ/IL-12 pathway. Rare genetic defects affecting this pathway have been described and are collectively called Mendelian susceptibility to mycobacterial disease (MSMD).

The hallmark of MSMD is susceptibility to mycobacteria (the family of bacteria that causes tuberculosis and related infections) and salmonella infections, with some individuals also suffering from viral, fungal, and parasitic infections. Many of the affected individuals become ill in infancy after

receiving the live anti-tuberculosis BCG vaccine. Other individuals have skin infections, swollen lymph nodes or blood stream infections later in life, upon encountering *Mycobacterium tuberculosis* or other environmental nontuberculous mycobacteria (NTM) that are not harmful to healthy individuals.

In about half of the cases, the genetic cause of MSMD is not known. Some individuals presenting with adult-onset infections resembling MSMD do not have genetic defects in the IFN-γ/IL-12 pathway but rather have autoantibodies directed against interferon-γ.

Once MSMD is suspected, diagnosis can be sought by investigating whether the components (proteins) involved in the IFN-γ/IL-12 pathway are present and/or functionally adequate. For that reason, sometimes, specific tests to assess function are needed. Genetic testing can confirm the diagnosis.

Individuals with MSMD should not receive BCG or live Salmonella vaccines, as complications can be life threatening. Treatment of infections consists of prolonged courses of antibiotics, and surgical procedures are sometimes required. Depending on their defect, IFN-γ replacement can benefit some, but not all individuals with MSMD. Once infections are cleared, prophylactic antibiotics are usually prescribed. HSCT is restricted to severe cases, given that rejection rates after transplant in these individuals are high.

Adapted from: Chapter 18 Innate Immune Defects. IDF Individual & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 24
Inheritance

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Primary immunodeficiency diseases (PI) are mostly caused by genetic abnormalities that lead to weaknesses in the immune system. To understand the inheritance in PI, it's good to understand a few basic concepts in genetics.

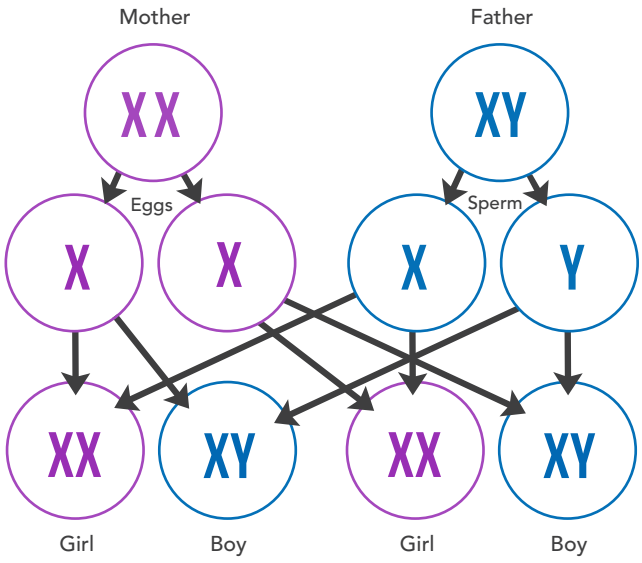
Inheritance of Primary Immunodeficiency Diseases

Every cell in the human body contains genetic material that instructs the job of that cell. This genetic material is packaged into 23 pairs of chromosomes (22 numbered chromosomes, and one pair of sex chromosomes (XX for females and XY for males). Children inherit one chromosome in each pair from their mother, and one chromosome of each pair from their father.

During fertilization, the egg which consists of 23 chromosomes (haploid) fuses with 23 chromosomes of the sperm and the resulting zygote has 46 chromosomes (diploid). This way each parent contributes half of their genetic information and physical characteristics, such as hair color, eye color, blood type, etc., onto the offspring. The sex of the offspring is determined by which chromosome (X or Y) of the sperm (X or Y) fuses with the egg (only X). An X chromosome results in a female offspring and a Y chromosome in a male offspring. (Figure 24:1)

The genetic material packaged in these chromosomes is made up of DNA, which is composed of individual molecules called nucleotides. Four nucleotides make up the DNA, these are Adenine (A), Thymidine (T), Guanine (G), and Cytosine (C). The DNA is made up of long chains of codons comprised of three nucleotides (letters) that are arranged in a specific way, similar to the arrangement of alphabetical letters to form words and sentences. Errors in the spelling of the words (because of misplacement of one or more letters) lead to genetic mutations, now called variants. Some spelling errors might not lead to a significant change in the word, and those variants do not cause disease, while other spelling errors can cause diseases, such as PI. If these errors occur in the egg or sperm of one of the parents, it can cause disease in the child. Occasionally, the errors occur in the fertilized egg, and neither of the parents actually carry that variant.

Figure 24:1 X-Linked Recessive Inheritance - Carrier Mother



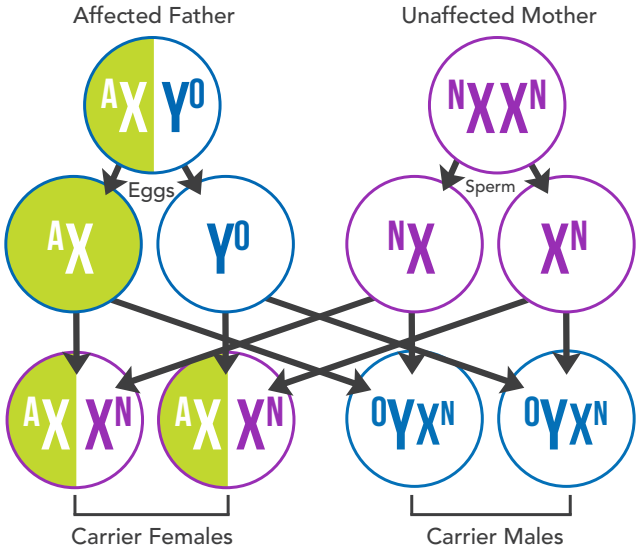
Types of Inheritance

PI can be inherited in one of three different ways: X-linked recessive, autosomal recessive or autosomal dominant. Family history and laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular PI and may be useful to identify a particular pattern of inheritance.

X-linked Recessive Inheritance

X-linked recessive is a mode of inheritance where the gene causing disease is present on the X chromosome, mainly affecting males. Males have only one X chromosome. If the inherited X chromosome carries the mutated gene in a male, this will lead to disease expression, as there is no additional X chromosome to compensate and the Y chromosome does not carry information that duplicates that of the X chromosome. An affected male will pass on the defective gene to all his female offspring. All of his daughters will be carriers, and all of his sons will carry the healthy Y chromosome and will therefore not be affected by the disease. Females have two X chromosomes and must inherit both mutated genes – one from each parent to develop the disorder. Therefore, females are carriers if they inherit one faulty X gene, while the second normal X gene continues to carry out its function and consequently prevents the abnormal gene from expression. Females with one affected X and one healthy X appear to be a healthy carriers. However, at times, female carriers could present with symptoms similar to males with X-linked disease due to a process called X-inactivation. In this process, some cells shut down (inactivate) the X chromosome coming from the mother, and other cells inactivate the X chromosome from the father. In the case of X-linked disease carrier, if the inactivation happened to the X chromosome coming from the mother, then the only active chromosome will be the X chromosome coming from the father, which carries the disease-causing variant, leading to symptoms similar to the affected males. Carriers can pass on the mutated gene to their children.

Figure 24:2 X-Linked Recessive Inheritance - Affected Father



Mothers who are carriers can pass on the disease to their sons if the sons inherit the affected X, and in this type of inheritance, a family history may show multiple males affected with the disease. Mothers who are carriers can also pass on the affected X to their daughters, who then become carriers of the disease themselves.

Mutations in X chromosomes may occur spontaneously and may occur in individuals with no previous family history.

The following are examples of PI with X-linked recessive inheritance:

- Bruton's or X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome
- Severe Combined Immunodeficiency (SCID), caused by mutations in the common gamma chain
- Hyper IgM Syndrome, due to mutations in CD40 ligand
- X-linked Lymphoproliferative Disease, two forms
- Chronic Granulomatous Disease (CGD), the most common form
- Properdin Deficiency
- Dyskeratosis Congenita

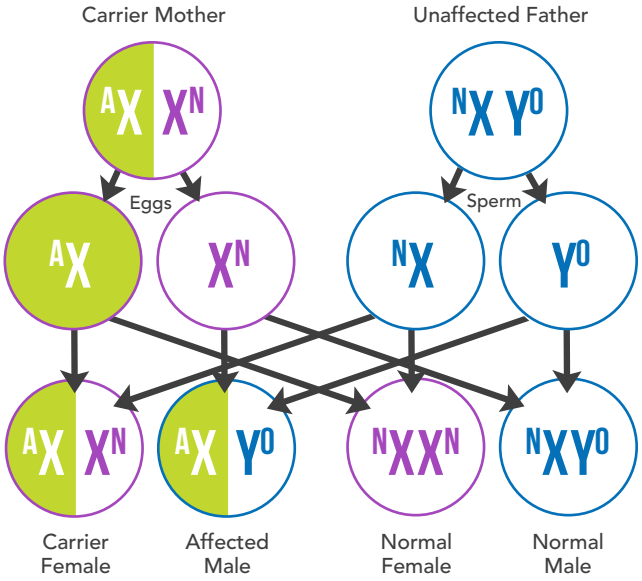
The chances of a woman who carries the faulty gene having an affected child is different based on the gender of the child. If the father is a non- carrier, there are four possible combinations in every pregnancy (See Figure 24:3).

- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and X-linked recessive gene mutation from his mother. He will, therefore, be affected.
- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and the working copy of the X-linked gene from his mother. He will not be affected by the condition.
- 1 chance in 4, (25% chance) that a daughter will inherit both working copies of the X-linked genes: one copy from her father and one from her mother. In this case, she will not only be unaffected by the condition, but she will also NOT be a carrier of the X linked recessive gene mutation.

- 1 chance in 4, (25% chance) that a daughter will inherit from her father the working copy of the X-linked gene and the faulty X-linked recessive gene mutation from her mother. She will be a genetic carrier of the condition like her mother and will usually be unaffected.

To summarize, if the offspring is a boy, there is 50% chance he will be affected by the disease. If the offspring is a girl, there is a 50% that she will be a genetic carrier of the disease. The outcome of future pregnancies will not be affected by previous pregnancies, meaning that it is possible for all (100%) of the boys in a family where the mother is a carrier to be affected with X-linked conditions.

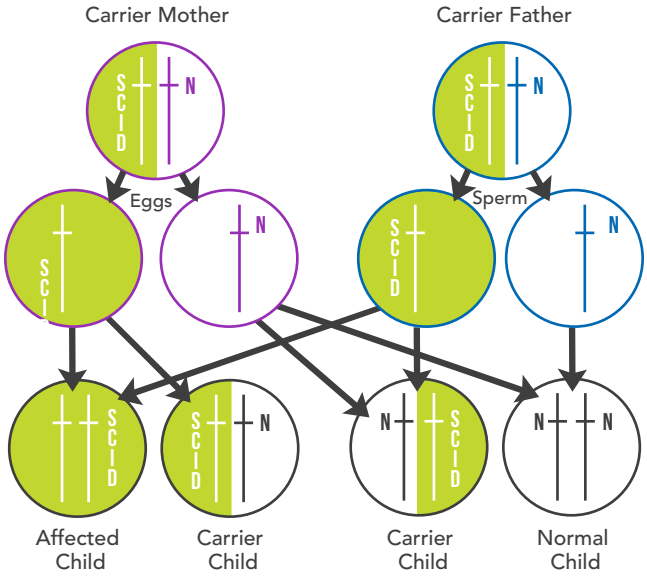
Figure 24:3 X-Linked Recessive Inheritance - Carrier Mother



Autosomal Recessive Inheritance

Genes present on one of the 22 pairs of chromosomes/autosomes are known as autosomal. In autosomal recessive disease, two abnormal copies of the gene, typically one from each parent, must be inherited to cause symptoms of the condition. Usually, parents of the child affected by an autosomal recessive condition carry one copy of an abnormal gene and are unaffected because of normal functioning of the other gene. In this scenario, where both parents are carriers of an abnormal autosomal recessive gene, there is a 25% chance (1 in 4) that any offspring, irrespective of gender will be affected by the disorder. There is a 50% chance (1 in 2) that the offspring will be a carrier (have one abnormal gene), and a 25% (1 in 4) that the baby will not inherit the faulty gene, and therefore will not be affected by the condition or be able to pass it on to their children (See Figure 24:4). Chances remain the same for all future pregnancies, and the outcome of each pregnancy is not affected by previous pregnancies.

Figure 24:4 Autosomal Recessive Inheritance - SCID Example



The following are frequently recognized autosomal recessive deficiencies:

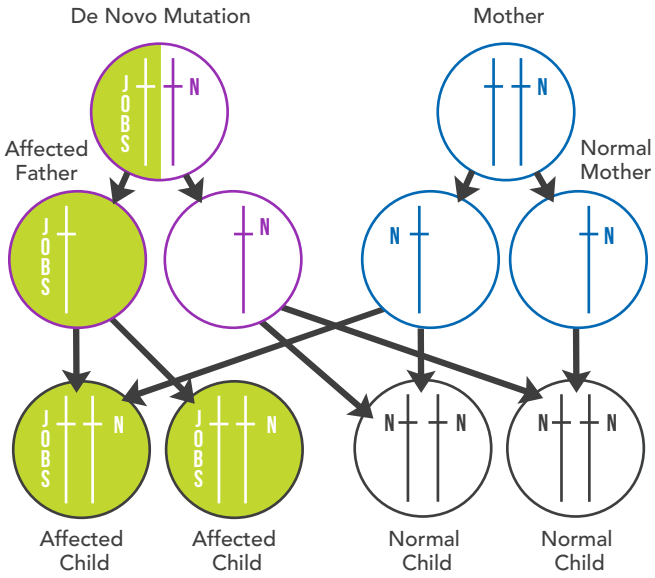
- Various forms of Severe Combined Immunodeficiency (SCID)
  - » Adenosine deaminase (ADA) deficiency
  - » Recombinase activating gene (RAG) deficiency
  - » Jak3 deficiency
  - » ARTEMIS SCID
- MHC class II deficiency
- Chronic Granulomatous Disease (CGD), three forms
- Leucocyte adhesion deficiency (LAD)
- Chediak-Higashi syndrome
- Familial forms of hemophagocytic lymphohistiocytosis (HLH).

The incidence of autosomal recessive diseases is rare. Most affected infants do not have any previous family history. However, consanguineous marriages and increased frequency of asymptomatic carriers of mutations in certain populations (such as ARTEMIS SCID in Navajo populations) increase the incidence of such diseases.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is a mode of inheritance where only one copy of the faulty gene is needed for the disease to occur irrespective of the normal gene inherited from the other parent. This affects both males and females, and there is a 50% chance (1 in 2) of the offspring of an affected parent to have the disease. The risk is the same in every pregnancy (See Figure 24:5). Many times, a patient affected with a condition associated with autosomal dominant disease will be the first affected person in their family. In this case, the faulty gene developed after the joining of egg and sperm during fertilization.

Figure 24:5 Autosomal Dominant Inheritance - Jobs Syndrome Example



Examples of Autosomal Dominant Inheritance:

- Hyper IgE Syndrome, due to mutations in STAT3 (Jobs syndrome)
- Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (a form of neutropenia – low neutrophil counts), also known as WHIM syndrome
- Some rare forms of defects in the IFN-γ/IL-12 pathway
- STAT1 and STAT3 gain of function disorders of immune regulation

Carrier Testing

With increasingly well-defined immunodeficiencies, it has now become possible to make a molecular diagnosis by analyzing recognized patterns and proteins present or absent in a particular disorder. DNA analysis can be performed to identify the presence of an abnormal gene. Once the diagnosis is confirmed, DNA samples from family members can be analyzed to establish if they are carriers or not.

In cases that do not fit a typical pattern or where initial genetic testing does not make a diagnosis, there are now other advanced techniques that may identify the underlying genetic cause. These include next-generation sequencing (NGS) or high throughput sequencing:

- Whole genome sequencing (WGS) involves reading an individual's entire DNA sequence,
- Whole exome sequencing (WES) involves reading the sequences of all the protein-coding genes, and
- NGS panel is sequencing a particular group of disease genes.

These techniques allow precise diagnosis in increasing numbers of families. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

Prenatal Diagnosis

In families where an immunodeficiency has been recognized, some parents may wish to know whether future babies are affected by the disorder. Testing to determine whether unborn babies are affected is possible in most situations where the immunodeficiency has a known genetic cause, such as XLA or RAG1 SCID. However prenatal testing is not possible if the genetic cause has not been defined despite a well characterized clinical immunodeficiency, such as most cases of Common Variable Immune Deficiency (CVID).

Methods of prenatal diagnosis include:

- Chorionic villus sampling (CVS) or amniocentesis associated laboratory techniques for prenatal diagnosis: DNA (deoxyribonucleic acid) from the fetus can be obtained by CVS or amniocentesis. These procedures can be performed to obtain a fetal sample for chromosome, gene or biochemical testing. CVS is usually scheduled at 10-13 weeks of pregnancy and involves the retrieval of a tiny sample of the developing placenta from the womb. Amniocentesis is typically performed at 16 to 17 weeks of pregnancy and involves the withdrawal of fluid

containing fetal cells that surrounds the fetus. Both procedures have a small risk of miscarriage that should be balanced against the benefits of the testing. Two techniques of DNA analysis are:

1. Mutation analysis: This method is 100% reliable if the mutation is known
2. Linkage analysis: If the mutation is unknown, but the diagnosis is definite, prenatal diagnosis may be possible using linkage analysis. This will be slightly less reliable than mutation detection.

- Noninvasive prenatal testing (NIPT), sometimes called noninvasive prenatal screening (NIPS), is a method of determining the risk that the fetus will be born with certain genetic abnormalities. This testing analyzes small fragments of DNA that are circulating in a pregnant woman's blood. Unlike most DNA, which is found inside a cell's nucleus, these fragments are free-floating and not within cells, and so are called cell-free DNA (cfDNA). These small fragments usually contain fewer than 200 DNA building blocks (base pairs) and arise when cells die off and get broken down and their contents, including DNA, are released into the bloodstream.
- During pregnancy, the mother's bloodstream contains a mix of cfDNA that comes from her cells and cells from the placenta. The placenta is tissue in the uterus that links the fetus and the mother's blood supply. These cells are shed into the mother's bloodstream throughout pregnancy. The DNA in placental cells is usually identical to the DNA of the fetus. Analyzing cfDNA from the placenta provides an opportunity for early detection of certain genetic abnormalities without harming the fetus.
- NIPT is a screening test, which means that it will not give a definitive answer about whether or not a fetus has a genetic condition. The test can only estimate whether the risk of having certain conditions is increased or decreased. In some cases, NIPT results indicate an increased risk for a genetic abnormality when the fetus is actually unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the fetus is actually affected (false negative). Because NIPT analyzes both fetal and maternal cfDNA, the test may detect a genetic condition in the mother.
- Enzyme analysis: Concentration and/or function of the enzyme that is known to be defective can be measured. Examples are adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP), deficiencies which both cause forms of SCID. Both of these enzymes can be analyzed in a chorionic villus sample taken at 11 to 12 weeks of gestation.
- Pre-implantation genetic diagnosis (PGD): This is a useful, viable option for couples who are at high risk of bearing a child with a single gene disorder. It involves in vitro fertilization (IVF) of a number of eggs, followed by genetic testing by analysis of a single cell from each embryo, and subsequent implantation of one to three normal embryos. Implantation of an unaffected embryo via IVF in individuals with SCID, LAD, CGD, and XLA have been previously reported. Evidence supporting the efficacy of PGD in the detection of some immunodeficiencies such as Wiskott-Aldrich syndrome, X-linked Hyper IgM Syndrome (HIGM), X-linked hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID); Ataxia-Telangiectasia is also available.

Gamete donation (use of donor egg or sperm) to conceive a child via IVF for infertile couples can be associated with risk of inheritable forms of PI, particularly if the health status of the donor with regard to immunodeficiency has not been established.

In conclusion, PI is a group of inherited diseases caused by genetic abnormalities that weaken the immune system. They could be inherited by one of three modes, X-linked recessive, autosomal recessive, or autosomal dominant. It is undeniable that raising a child with PI places physical, emotional, and financial burden on families, and many families might wish to maintain current family size to avoid the possibility of having another affected child. Those choices are very personal. It is recommended that parents are well-informed by healthcare professionals such as pediatricians, genetic counselors, immunologists and obstetricians on current medical advances relating to the diseases. Lately, there have been new developments in understanding the genetic causes of these rare diseases, and genetic counseling is highly recommended in families with a known history of PI as it allows option for early detection, diagnosis, and treatment.

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Chapter 25
Laboratory Tests

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Laboratory studies are necessary to determine the presence of a primary immunodeficiency disease (PI). This is usually prompted by an individual experiencing some clinical problems, particularly recurrent and/or chronic infections. Information regarding the types of organisms, the sites of infection, and the therapies required to treat the infections often help focus the laboratory studies. The individual's medical history and physical exam direct the appropriate choice of laboratory tests.

Normal vs. Abnormal Laboratory Values

Proper interpretation of any laboratory value depends on comparison of the result to the appropriate established normal reference ranges that in some cases are age-specific. To determine what is normal, the laboratory test is performed on a group of healthy individuals, usually adults and equally divided between males and females. These results are used to determine what the normal range is, using a variety of statistical approaches. A common statistical measurement is called a 95% confidence interval, which is the range that includes 95% of the results from normal tested subjects (as in a bell curve). It is important to note that when the definition of the normal range is set as a 95% confidence interval, 5% of the selected normal population will fall in the abnormal range (both high and low), even though they were originally selected as being normal. This is one of the challenges with using statistical methods to define a normal range and must be remembered when evaluating a test result falling near either end of the normal range.

Using the measurement of height as an example, normal individuals can be just above or just below a normal range (or 95% confidence interval) and still be normal. Someone 1 inch taller than the 95% confidence interval is not necessarily a giant, and someone 1 inch shorter is not necessarily a short person. In fact, by definition, 2.5% of normal individuals will be below the 95% confidence limit, and 2.5% will be above. The fact that 5% of otherwise normal healthy individuals will fall outside the normal range is important when looking at laboratory results—finding a value outside of the reference range does not automatically represent an abnormality. The clinical relevance of an abnormal laboratory finding must be based on the clinical history as well as the size of the difference from the normal range.

Characteristics of the group, such as the age of the group, used to determine the normal range are crucial since the immune system undergoes substantial development during infancy and childhood. The range of test values that are normal in infancy will be quite different when the child is 2 or 20 years old.

Consequently, all studies in children must be compared with age-matched controls. If the laboratory reporting test results does not provide age specific information, it is important to consult with a specialist who knows the age-specific reference ranges. Optimally, the laboratory doing the test should provide this, but if unavailable, there are published age-specific reference ranges.

The most common laboratory tests used to evaluate immune disorders are used to identify:

1. Antibody deficiencies
2. Cellular (T cell) defects
3. Neutrophil disorders
4. Complement deficiencies

These four major categories of tests for PI are described hereafter. Another emerging laboratory test for the diagnosis of PI is genetic testing. In the past, genetic tests were available mainly in

research settings, but now, several commercial labs offer genetic sequencing for the identification of known mutations causing various types of PI.

Antibody Deficiency (or Humoral Immune Function)

The standard screening tests for humoral immune function starts with measurement of immunoglobulin (Ig), or antibody, levels in the blood serum. These consist of IgG, IgA, IgM, and sometimes IgE levels. The results must be compared to age-matched controls.

There are also tests for specific antibody production. These tests measure how well the immune system can make antibodies against vaccines, as a marker of how well the antibody arm of defense is functioning. There are two main pathways of antibody production being tested, the T cell dependent pathway measured by the antibody response to protein antigens, such as tetanus and diphtheria toxoids, and the T cell independent pathway measured by the antibody response to carbohydrate antigens, such as those found in the pneumococcal polysaccharide vaccine (PPSV) known as PNEUMOVAX. In this approach, the person is immunized with these common vaccines, and blood samples are obtained immediately prior to and approximately four weeks after the immunization to evaluate how well the individual forms specific antibodies.

In some instances, the person may have already been immunized with these vaccines as part of their normal care and will already have circulating antibodies (if they make antibodies), while in other instances the individual may have little or no specific antibody prior to the immunization. The use of different types of vaccines is necessary because certain people with recurrent infections (and normal or near normal immunoglobulin levels) have been identified with an abnormality in the response to carbohydrate antigens but a normal response to protein antigens. (See Selective Immunoglobulin Deficiency: IgA and IgM Chapter.)

It is worth noting that during the maturation of the immune system, the response to carbohydrate antigen vaccines lags behind the response to protein antigen vaccines. (This is the reason for having a childhood version of the pneumococcal vaccine, the PCV13, which makes it easier for infants to respond to Streptococcus pneumoniae). The interpretation of vaccine responses is best done by an allergist/immunologist provider who deals with individuals with PI on a regular basis.

The ability to evaluate the antibody response in a person already receiving Ig replacement therapy is more difficult. This is because Ig is rich in most of the specific antibodies that are generated following immunizations. When immunized with common vaccines, it is difficult to tell the difference between the antibody provided by the Ig replacement therapy and any that might have been made by the individual. The solution to this is to immunize with vaccines that are not normally encountered by the general population and therefore are unlikely to be present in Ig preparations. Uncommon vaccines, such as typhoid or rabies vaccine, can serve this purpose.

It is important to note that in a person with a previously confirmed defect in antibody production, stopping therapy to recheck for antibody levels and immunization response is unnecessary and may place the individual at risk of acquiring an infection during the period when the Ig replacement therapy is stopped. In someone whose diagnosis of an antibody immunodeficiency is unclear, however, it may be necessary to stop Ig replacement therapy for a period of four to six months so that the individual's humoral immunity can be adequately assessed.

Additional studies used to evaluate people with antibody deficiencies include measuring the different types of lymphocytes in the blood using a test called flow cytometry. The B cell is the lymphocyte that has the ability to produce antibodies. B cells may be absent in certain immune disorders associated with antibody, such as X-linked Agammaglobulinemia (XLA). This test can also evaluate the ability of the B cells to mature.

In addition, analysis of DNA can be used to confirm a particular diagnosis, such as the gene encoding Bruton tyrosine kinase (BTK) associated with XLA. Finally, there are studies done in specialized laboratories to assess Ig production by cultured lymphocytes in response to a variety of different kinds of stimuli.

Cellular (T cell) Immunity

The laboratory evaluation of cellular or T cell immunity focuses on determining the numbers of different types of T cells and evaluating the function of these cells.

The first test to evaluate for T cell immunity occurs without most people knowing about it, as all states in the U.S. now screen for very low T cells numbers at birth. This occurs through the newborn screening program, a program to detect severe treatable genetic defects in otherwise healthy looking infants. All newborns have a blood sample drawn, obtained through a heel prick, that is sent to the state laboratory where a screening test called the TREC assay is performed. This measures the number of T cells in the blood at birth, and is an excellent way to screen for severe deficiencies of T cells, as can be seen in Severe Combined Immunodeficiency (SCID). If this is abnormal, an immunologist in the state is contacted and further testing is recommended. As of December 2018, all newborns born in the U.S., including all 50 states, Washington, DC, and Puerto Rico, are screened for severe T cell immunodeficiency. This newborn screening should make the successful treatment of SCID and other related severe T cell immunodeficiencies easier since infants with these conditions will be identified at birth and appropriate treatment, such as hematopoietic stem cell transplantation (bone marrow transplantation) or gene therapy, can be readily undertaken. (See Newborn Screening Chapter.)

Outside of the newborn period, the simplest test to evaluate possible decreased or absent T cells is a complete blood count (CBC) and differential to establish the total blood (absolute) lymphocyte count. This is a reasonable method to assess for diminished T cell numbers, since normally about three-quarters of the circulating lymphocytes are T cells and a reduction in T cells will usually cause a reduction in the total number of lymphocytes, or total lymphocyte count. One must be careful, however, as individuals can have fairly normal absolute lymphocyte count but still have a significantly low T cell count. The actual T cell count can be confirmed by using flow cytometry with markers specific for different types of T cells.

The measurement of the number of T cells is often accompanied by cell culture studies that evaluate T cell function. This is done by measuring the ability of the T cells to respond to different types of stimuli, including mitogens (such as phytohemaglutinin [PHA]) and antigens (such as tetanus toxoid, candida antigen). The T cell response to these various stimuli can be measured by observing whether the T cells divide and grow (called proliferation) and/or whether they produce various proteins important in immune responses called cytokines (such as interferon). There are an increasing variety of functional tests that are available to evaluate T cells. An immunologist is the best person to undertake this interpretation.

Many types of PI are associated with specific genetic defects. This is particularly true of SCID in which more than 20 different genetic causes have been identified. These can all be evaluated using current technology for mutation analysis, and this is the most accurate means to establish the definitive diagnosis.

Neutrophil Function

The laboratory evaluation of the neutrophil begins by obtaining a series of white blood cell counts (WBC) with differentials. The WBC and differential will determine if there is a decline in the absolute neutrophil count (neutropenia). This is the most common abnormal laboratory finding when an individual presents with a clinical history that suggests defective neutrophil immunity. Usually more than a single CBC and differential is necessary to diagnose neutrophil problems.

A careful review of the blood smear is important to rule out certain diseases that are associated with abnormalities in the structure of the neutrophil, or the way it looks under the microscope. Sometimes a bone marrow biopsy is needed to see if the neutrophils are being made properly. If these initial screening tests of neutrophil numbers were normal, testing would then focus on two possible types of PI: Chronic Granulomatous Disease (CGD) and Leukocyte Adhesion Deficiency (LAD). Both of these disorders have normal or elevated numbers of neutrophils, and each of these disorders has distinctive clinical features that can help to direct the appropriate evaluation.

Laboratory testing to diagnose CGD relies on the evaluation of a critical function of neutrophils that kills certain bacteria and fungi—the creation of reactive oxygen. This process, called the oxidative burst, can be measured using a number of different methods. Currently, the most commonly used and most reliable test uses flow cytometry to measure the oxidative burst of activated neutrophils using a specific dye (dihydrorhodamine 123 or DHR), referred to as the DHR test. The DHR test has been used for more than 20 years, and it is extremely sensitive in making the diagnosis. This test can also be helpful in identifying carriers of CGD. (See Inheritance Chapter.) Because of its excellent performance, this test has become the standard in most laboratories supporting clinics that see individuals with CGD regularly. In the past, a dye reduction test called

the Nitroblue Tetrazolium (NBT) test was used but this test had greater variability in its interpretation. The best confirmation of the specific type of CGD is suggested by the results of the DHR test, but it requires confirmation by either specifically evaluating for the defective protein involved or its related gene mutation underlying the disease.

Laboratory testing for the most common form of LAD Type 1 involves flow cytometry testing to determine the presence of a specific protein on the surface of neutrophils (and other leukocytes). When this protein is absent or significantly decreased, the movement of neutrophils to sites of infection is hampered and produces a large increase in the number of these cells in the circulation as well as an increased susceptibility to bacterial skin, oral, and other infections.

Laboratory testing for the most common form of LAD Type 1 involves flow cytometry testing to determine the presence of a specific protein on the surface of neutrophils (and other leukocytes). When this protein is absent or significantly decreased, the movement of neutrophils to sites of infection is hampered and produces a large increase in the number of these cells in the circulation as well as an increased susceptibility to bacterial skin, oral, and other infections.

Complement Deficiency

The standard screening test for deficiencies in the complement system is the total hemolytic complement assay or CH50. In situations with a defect in one complement component, the CH50 will be almost completely negative. Specialized complement laboratories can provide additional testing that will identify the specific complement component that is defective. There are some extremely rare conditions in which there are defects in another complement pathway (the alternate pathway). These can be screened for by using a functional test directed specifically at this pathway, the AH50 test. The complement cascade can also be initiated by the mannose-binding lectin pathway, and there are some individuals with a deficiency in mannose binding lectin, although the clinical relevance of the laboratory finding is inconclusive. (See Complement Deficiencies Chapter.)

Innate Immunity

Laboratory tests are also available to measure the function of the various elements of innate immunity. This includes determining the number and activity of lymphocytes, such as natural killer cells, as well as the function of various cell surface receptors such as the toll-like receptors.

Genetic Testing

Genetic testing (mutation analysis) has become increasingly common in the diagnosis of PI in recent years and is likely to continue to expand in its application as the testing becomes more affordable. These tests allow for the rapid screening for mutations in hundreds of genes that affect the immune system. Some tests are arranged in panels that screen for well-known disease causing mutations while other more in depth tests can look at the genetic code in more detail and uncover variations in immune genes that may be of significance but whose purpose may not be fully known. This data must be interpreted by a provider with experience in the analysis of this complex data set. Many healthy people have genetic changes in these genes, since the variant must be in the right place to affect function of the gene. This technology is already being used in clinical medicine and is rapidly advancing.

Summary

Laboratory testing plays a central role in the evaluation of the immune system. All results must be compared to age-appropriate reference ranges. An accurate medical history, family history, and physical examination are critical in developing the best strategy for laboratory evaluation. This typically begins with screening tests, followed by more sophisticated (and costly) tests chosen based on the initial test results. The range of laboratory testing available to evaluate the immune system continues to expand. This has been driven in part by the recognition of new clinical syndromes associated with recurrent and/or chronic infections.

The direct link between clinical findings and laboratory testing has extended our understanding of PI. The continuation of this trend and laboratory testing of the future will likely be even more sophisticated and help provide further answers to the underlying basis of the expanding range of PI.

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Chapter 26
Newborn Screening

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Newborn Screening for Severe Combined Immunodeficiency

What Is SCID?

Severe Combined Immunodeficiency (SCID), pronounced "skid," includes some of the most severe forms of primary immunodeficiency diseases (PI), and is characterized by an absence of T cells and little or no B cell lymphocyte function (NK lymphocytes are also affected in some cases), resulting in life-threatening infections that lead to death unless the immune system is restored through treatment. Treatment is usually done by either hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, or, in certain types of SCID, through enzyme replacement therapy and/or gene therapy. SCID is caused by genetic (inherited) defects. Most babies born with SCID appear well at birth. Prior to the development of a newborn screening (NBS) test in 2008, these babies were diagnosed only after they developed serious infections. Now, it is possible to diagnose and treat infants before the development of life-threatening infections.

What is the screening test for SCID?

All newborn babies in the U.S. have blood from a heel stick spotted onto a filter paper and dried. Using a sample from this Newborn Dried Blood Spot (DBS), states in the U.S. perform over 30 tests for conditions such as phenylketonuria and congenital hypothyroidism. These tests are performed routinely on all newborns. Usually the blood spot is collected at the birth hospital (or at home when there is a home birth), and then they are sent to the state Newborn Screening laboratory. Each state performs these tests on a few hundred to thousands of infants each week. Abnormal results require follow-up with additional tests to confirm the diagnosis and a visit to their doctor or a specialist.

While originally intended to screen infants for common conditions, newborn screening tests are also performed for rare conditions that result in significant disease or carry a high risk of death early in life. Early diagnosis of these conditions is important so that early treatment can be started to reduce some of the bad outcomes, and in some cases treat the disease. As of December 2018, every state in the U.S., as well as Washington, DC and Puerto Rico, undertakes NBS for SCID for every child born, measuring a circular piece of DNA, the T cell receptor excision circle (TREC), using a small (1/8") disc punched out of the DBS. This test has been effective in identifying infants with most forms of SCID, as well as infants with other conditions causing very low T cells.

Why Screen for SCID at Birth?

Since SCID is inherited, prior to the use of NBS, only families that previously had a child with known or suspected SCID had the opportunity to identify SCID at birth in subsequent children, before the onset of symptoms. In these families, the infants diagnosed soon after birth had a better chance of survival with fewer complications. This demonstrated the importance of early recognition, or pre-symptomatic identification of SCID, and early initiation of treatment. Not only was this linked to higher survival rates but also to less hospitalizations and lower healthcare costs. Based on this evidence and information from pilot screening in Wisconsin, population-based newborn screening was recommended for SCID. After this recommendation was published in 2010 and followed by years of advocacy by organizations including the Immune Deficiency Foundation (IDF), each year more states began implementing NBS for SCID. As mentioned earlier, as of December 2018, every state in the U.S., as well as Washington, DC and Puerto Rico, screens for SCID.

How Does the TREC Test Identify Infants with SCID?

The TREC test uses a polymerase chain reaction (PCR) to measure the amount of TREC DNA molecules from the DBS. The number of copies of TREC DNA correlates very well to the number of new T cells coming out of the thymus gland after they go through the proper development. Healthy newborn babies usually have a large number of T cells in their blood and approximately one copy of TREC per 10 T cells. The number of TREC in the blood drops very rapidly with age,

and adults typically have very low numbers of TREC in their blood. The absence (or near absence of) T cells and TREC is a very reliable way of identifying an infant who has SCID. Occasionally, some of the mother's T cells can be found in the baby's blood, so measurement of T cell numbers alone might not diagnose SCID. Since the mother's T cells will have a low TREC number, the newborn screening test would still be abnormal and signal the presence of possible SCID. It is important to remember, however, that the TREC test does not always diagnose SCID. We will discuss some of the other conditions that can also cause an abnormal TREC test. That is why secondary or confirmatory testing is critical.

What other conditions cause low or absent TREC at birth?

Low T cells at birth (causing the low/absent TREC) can be caused by other conditions causing a low production of T cells, including:

- Extreme prematurity (mainly infants born before 30 weeks)
- DiGeorge (22q11.2 deletion) syndrome
- Jacobsen syndrome
- Trisomy 21 (Down syndrome)
- CHARGE syndrome
- A defect in FOXN1 causing poor thymus development
- DOCK8 deficient Hyper-IgE syndrome
- Ataxia-Telangiectasia
- Other forms of combined immunodeficiency

Additionally, the TREC may be low due to losses of T cells in the intestines (intestinal lymphangiectasia, other gastrointestinal malformations) in babies with congenital cardiac disease or who have had cardiac surgery, or in babies with severe hydrops (generalized swelling). Rarely low TREC can be caused by destruction of T cells as seen in neonatal leukemia and some forms of acute HIV infection. Lastly, there is a group of infants with an abnormal TREC newborn screen who have low CD4 T cells for unknown reasons. These infants have been described as having idiopathic T cell lymphopenia.

What Is a "False Positive" Test?

The term false positive means that an abnormal test result happens in an unaffected person. Most of the time this occurs due to an error in the testing. The TREC test also measures the number of copies of another unrelated control gene to check the performance of the test in case the PCR fails to detect any TREC. This can occur for a variety of technical reasons from the way the blood spot was collected to problems performing the test in the laboratory. Therefore, if both TREC and the control gene fail to amplify, the PCR test is deemed unsatisfactory, and the state newborn screening laboratory will ask for a new blood spot to be collected.

What Happens Next for Infants with Low or Absent TREC?

If the TREC DNA is very low but the control gene DNA level is satisfactory, a liquid blood sample, collected through a venipuncture, will be tested to measure the total number of lymphocytes, and the numbers of T, B and natural killer (NK) cells by flow cytometry (a highly technical laser instrument that can detect and measure single cells labelled with a fluorescent dye). It is recommended that the proportion or number of naïve and memory T cells by flow cytometry also be measured to identify whether these T cells could come from the mother because T cells from the baby should be mostly naïve T cells. The blood sample for T cell measurement might be collected by the pediatrician, but the results are usually viewed by specialists working with the newborn screening program. All infants with abnormally low numbers of T cells should be seen as soon as possible by a pediatric immunologist or a specialist with experience diagnosing and caring for infants with SCID and other types of PI.

The immunologist will usually order additional tests to diagnose the cause for the low T cell numbers. These tests can include: measures of T cell function, determining whether any T cells seen in the baby's blood are from the mother, and genetic tests to identify the genetic cause of SCID or to identify any other suspected syndrome.

How Well Does TREC Testing Identify Infants with SCID?

TREC based NBS has been shown to be a good test for identifying infants who may have SCID. Over 10 states in the U.S. have now published their cumulative experience over several years showing that infants with abnormal TREC at birth are referred to treatment centers and can undergo treatment much earlier than previously. Information is still being collected on an ongoing basis. As more states publish data on their implementation of SCID NBS, we will have more information on the outcomes of these programs. The Newborn Screening Translational Research Network (NBSTRN) collects information nationally on diagnoses and screening test performance. At this time, there are no reports of infants with typical SCID (for example, those with absent T cells) who were missed due to a TREC test. There are rare forms of T cell defects, however, where some T cells develop but have poor function, such as atypical forms of SCID due to ZAP 70 deficiency, MHC Class II deficiency, or combined immune defects due to NF kappa-B essential modulator (NEMO) deficiency. In addition, one individual with late-onset adenosine deaminase (ADA) deficiency (ADA-SCID) had a normal TREC early on.

What Steps Occur If SCID Is Suspected?

If SCID or another significant T cell deficiency is suspected, it is a priority to take immediate steps to protect the infant from developing any infections. Infants should not attend daycare, and exposure to persons with possible infections should be avoided. Starting immunoglobulin (Ig) replacement therapy, prophylactic antibiotics, and antiviral and antifungal medications is important. Live vaccines, such as the rotavirus (oral) vaccine, should be avoided. If the infant requires a blood transfusion, the doctors and hospital should use blood that is depleted of white blood cells (or irradiated to destroy any viable lymphocytes) and does not contain any cytomegalovirus (CMV). Mothers are not advised to breast feed their infants. The risk of transmission of CMV through the breast milk is significant in any mother who has previously had an infection with CMV. This risk persists for years after exposure to CMV. Many mothers are tested for the CMV antibody during their pregnancy; this does not guarantee, however, that they are not exposed to CMV later in pregnancy or after delivery. Commercial infant formula or pasteurized breast milk are safe alternatives.

What Is Next for Newborn Screening for Other Types of PI?

The use of PCR testing for other types of PI has been considered, such as Kappa rearrangement excision circles (KRECs) to estimate immature B cell numbers that are low both in some forms of SCID and in those with a lack of immunoglobulin due to the absence of B cells, such as in X-linked Agammaglobulinemia (XLA). In the future it may be possible to sequence the entire genome and identify a myriad of diseases or predispositions to common multifactorial immune disorders. This testing is still in the research stage and will need to be fully studied to better understand the relationship between a gene mutation and the development of a disease to ensure that only disease causing mutations will be identified.

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Chapter 27

Infections in People with Primary Immunodeficiency Diseases: Antibiotic and Antifungal Therapy

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Infections are the hallmark of a primary immunodeficiency disease (PI). For many individuals, a PI diagnosis is suspected and made only after the individual has had recurrent infections or infections that are uncommon or unusually severe. This section discusses common infections and their treatment.

Infections in a Person with PI

Anyone can get an infection, and everyone does. But an infection in a person with PI may require different treatment than a similar infection in a person with a normal immune system. For example, the person with a PI may require a longer course or higher dose of antibiotics than someone who does not have a PI.

An individual's primary care provider should be the first point of contact when a person with PI is ill. The provider may then want to confer with the immunologist about the management and treatment of a particular infection. The immunologist needs to know about the infections, as this knowledge may affect treatment. For example, individuals with antibody deficiency who receive immunoglobulin (Ig) replacement therapy may need to have their dose adjusted if they are experiencing frequent breakthrough infections.

The goals of medical treatment and supportive care are to reduce the frequency of infections, prevent complications and prevent an acute infection from becoming chronic and potentially causing irreversible organ damage. The affected individual, family/caregivers, and members of the healthcare team must work together and effectively communicate among each other if these goals are to be accomplished.

A description of several kinds of infections and their treatment follows. Many other infections including skin infections, deep abscesses, bone infections, meningitis, and encephalitis (infections of the brain) are not covered here, but these may also occur in individuals with PI.

Remember that the suffix "itis" means an inflammation of a particular body part, like tonsillitis (inflammation of the tonsils) or appendicitis (inflammation of the appendix). The inflammation is usually caused by an infection but not always.

Eye Infections

Conjuctivitis

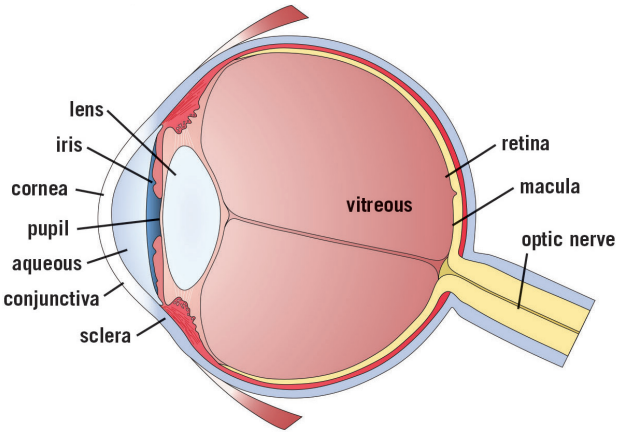
Conjunctivitis, or pink eye, is an inflammation or infection of the lining of the eyelid and of the membrane covering the outer layer of the eyeball (conjunctiva). It can be caused by bacteria, viruses, environmental allergies, or chemical irritants such as smoke or soap. Conjunctivitis may occur by itself or in association with other illnesses, such as the common cold. The symptoms commonly associated with conjunctivitis are redness and/or swelling of the eyelids, tearing, and discharge of mucus or pus. These symptoms are frequently accompanied by itching, burning, and sensitivity to light.

In the morning, it is not unusual to find the eyelids stuck together from the discharge that has dried while the eyes were closed during sleep. These secretions are best loosened by placing a clean washcloth or cotton ball soaked in warm water on each eye. After a few minutes, gently clean each eye, working from the inner corner to the outer corner of the eye. **Meticulous hand washing is necessary for anyone coming in contact with the eye discharge in order to prevent the spread of the infection as conjunctivitis is usually very contagious.**

It may be necessary to be seen by a physician if vision is significantly affected or if symptoms persist, in order to determine the type of conjunctivitis.

The eye discharge may be cultured to determine if the infection is bacterial or viral. Topical antibiotics (ointment or eye drops) may be prescribed if the infection is bacterial in nature. If the inflammation is caused by an irritant, avoidance of that irritant will be important.

Figure 27:1 The Eye



Ear Infections

Otitis Media

Otitis Media is an infection of the middle ear and is usually caused by bacteria or viruses. A small tube called the Eustachian tube connects the middle ear with the back of the throat and nose. In the infant and small child, the tube is shorter and more horizontal than in the adult, and provides a ready path for bacteria and viruses to gain entrance into the middle ear and not drain out. In some infections and allergic conditions, the Eustachian tube may actually swell and close, preventing drainage from the middle ear.

The characteristic symptom associated with otitis media is pain, caused by irritation of the nerve endings in the inflamed ear from inflammatory secretions or changes in ear pressure. A baby or young child may indicate pain by crying, head rolling, or pulling at the infected ear(s). The older child or adult may describe the pain as being sharp and piercing. Restlessness, irritability, fever, nausea, and vomiting may also be present. Pressure in the infected eardrum tends to increase when the individual is in a flat position. This explains why pain is often more severe at night, causing the individual to wake up frequently. As fluid pressure increases within the eardrum, pain becomes more severe and the eardrum may actually rupture. The appearance of pus or bloody drainage in the ear canal is an indication of a possible eardrum rupture. Although pain is usually relieved when the eardrum ruptures, the infection still exists.

Whenever an ear infection is suspected, the patient should be seen by a healthcare provider. Antibiotic therapy is usually started in order to treat the infection. Analgesic (pain killing) ear drops may also be prescribed to help with pain. A follow-up examination may be recommended to be sure that the infection has cleared and that no residual fluid remains behind the eardrum. Repeated episodes of otitis media may actually cause hearing impairment or loss.

For children with repeated episodes of otitis media, a procedure called a myringotomy may be recommended. In this procedure a small hole is made in the eardrum and a tube placed in the hole, to promote drainage of fluid from the middle ear and equalize the pressure between the ear canal and middle ear.

Upper Respiratory (Sinus and Throat) Infections

Rhinitis

Rhinitis is a term used to describe an inflammation of the nose. It is usually caused by bacteria, viruses, chemical irritants, and/or allergens. Symptoms may include sneezing, difficulty in breathing through the nose, and nasal discharge (rhinorrhea). The nasal discharge may vary from thin and watery, to thick and yellow or green. It is generally accepted that green or yellow-green nasal discharge is a sign of acute infection, but this may not always be the case.

Acute Sinisitus

Sinusitis is an inflammation of one or more of the sinuses. The sinuses are small cavities, lined with mucous membranes, located in the facial bones surrounding the nasal cavities. The purpose of the sinuses is thought to be to decrease the weight of the skull and to give resonance and timbre to the voice. The basic causes of sinusitis are the blockage of normal routes of sinus drainage and infections spread from the nasal passages. Pain, particularly in the forehead and cheekbones, and tenderness over the face in these same areas are characteristic symptoms. In addition, there may be pain in and around the eyes, and in the teeth of the upper jaw. The pain and headache associated with sinusitis is typically more pronounced in the morning due to accumulated secretions in the sinuses during sleep.

Being in an upright position during the day facilitates sinus drainage and usually provides some temporary relief. Depending on the amount of sinus drainage, there may be cough, throat irritation, bad breath, and decreased appetite. Sinusitis may be accompanied by a fever.

A sinus infection can be difficult to treat in an individual with PI and may require a longer course of antibiotics than would be usually prescribed. Many individuals get benefit from the use of daily sinus rinses to keep the sinuses free of accumulating secretions. It is important to boil water or to use purchased distilled water for sinus rinses to make sure the water itself doesn't contain unwanted pathogens. Repeated or prolonged episodes of acute sinusitis may lead to chronic sinusitis and damage to the mucosal surfaces.

Acute Coryza

Coryza, also known as upper respiratory infection (URI) or the common cold, is an acute inflammation of the upper respiratory tract (nose and throat or nasopharynx). Early symptoms include a dry tickling sensation in the throat, followed by sneezing, coughing, and increased amounts of nasal discharge. There may also be symptoms of fatigue, and generalized aches and discomfort. A cold is usually caused by rhinovirus. Symptomatic treatment may bring some relief, but there is no antibiotic currently available that will kill or inactivate rhinovirus. Taking an antibiotic will not cure a cold any quicker. A cold generally lasts about a week. But if a cold lasts more than a week and is accompanied by a fever, productive cough, and/or difficulty breathing, it may be more than a cold and a primary care provider should be seen.

Influenza

Influenza, or flu (a short form of the word influenza), is a term that is often used generically to describe the fever, body and joint aches, cough, congestion, etc. that we associate with many common respiratory viruses. True influenza, however, is caused only by an influenza virus, and it may be more severe and dangerous than other common respiratory viruses. Flu season is generally in the fall and winter. Flu may occur sporadically or in epidemics. Usually epidemics occur every two to four years and develop rapidly because of the short incubation period of the disease.

The incubation period is the time from when a person is exposed to an infection to the time symptoms appear. Symptoms of the flu include sudden onset of high fever, chills, headache, muscle ache, weakness, fatigue, and runny nose. Vomiting and diarrhea may also be present. Sometimes a bacterial infection of the ears, sinuses, or even lungs may develop during or after the flu.

There are anti-viral drugs available to treat the flu, but they must be started shortly (one or two days) after the onset of symptoms in order for them to be effective. There is also some evidence to suggest that these drugs may prevent the flu or decrease its severity if taken after someone has been exposed to the flu. Influenza can be a very serious infection, particularly in someone with PI, and seeking medical attention is highly recommended.

Pharyngitis

Pharyngitis describes an inflammation of the throat (sore throat). It is usually caused by a bacterial or viral infection but may also be caused by simple irritation. Symptoms include a raw or tickling sensation in the back of the throat, and there may be difficulty swallowing. Sometimes these symptoms are accompanied by a fever. Sore throats that are caused by Streptococcus pyogenes (strep throat) can cause other diseases such as rheumatic fever or kidney inflammation if they are not treated. If an individual has a sore throat, they should seek medical attention; a quick test or culture to determine if it is a strep throat infection is usually indicated.

Tonsillitis

Tonsillitis is an inflammation of the tonsils. The most common causes are viral illnesses for which antibiotics do not work. Some people have chronic tonsillar infections, and it may be recommended that the tonsils be removed (sometimes along with the adenoids).

Adenitis or Lymphadenitis

Lymphadenitis, or swollen glands, is an inflammation of the lymph nodes. Lymph nodes are present all over the body, but particularly in the neck, axillae, and groin areas. The lymph system functions to help the immune system respond to infection. For example, the lymph nodes in the neck can become inflamed as the body is recovering from an upper respiratory infection. This is called reactive lymphadenopathy because it is a normal response, or reaction, to an infection. It is also possible for the lymph nodes to become inflamed because they themselves are infected. Enlarged lymph nodes on a single side of the neck generally indicate a bacterial infection, while enlargement on both sides usually indicates a viral infection but not always.

Lower Respiratory Infections

Croup

Croup is a general term used to describe an infection, usually in children, which causes narrowing of the air passages leading to the lungs. Croup can be caused by viruses or bacteria. The child's temperature may be normal or slightly elevated. The onset of croup may be sudden or occur gradually. In some instances, the onset occurs at night, and the child may awaken with a tight barking cough and respiratory distress.

Breathing is difficult due to the narrowing of the trachea (windpipe). Croup can be a frightening experience for both the parents and child. Unfortunately, the child's anxiety may increase the severity of the symptoms. It is important for the parents to remain as calm and as reassuring as possible. Urgent medical attention may be needed. Depending on the severity of symptoms, advice may be sought from the primary care on-call provider, and sometimes an emergency room visit is in order.

Acute Bronchitis

Acute bronchitis is an inflammation of the bronchi, which are the major branches off the trachea (windpipe). It often accompanies or follows an upper respiratory infection. Symptoms include fever and cough. At the onset, the cough is usually dry but gradually becomes more productive in which the person may cough up mucus or phlegm.

Pneumonia

Pneumonia is an acute infection of the lungs and can be caused by bacteria, viruses and/or fungi. Symptoms include chills, high fever, cough, and chest pain associated with breathing. Symptoms of pneumonia should always be reported to the primary care provider. In some people with a PI, bronchiectasis may develop if there are repeated episodes of pneumonia. Bronchiectasis is an irreversible condition where the airways become widened and scarred. After this occurs, it becomes difficult to clear the airways of mucus and bacteria, which leads to even more serious lung infections.

General Care of Respiratory Infections

Respiratory infections may be merely bothersome, like a cold or more serious like pneumonia. Management of these infections is directed toward the relief of symptoms and the prevention of complications. The primary care provider may recommend a medication to relieve fever and general body aches. Antibiotics may be prescribed to treat infections that are caused by bacteria. Expectorants may be prescribed to liquefy (water down) mucus secretions and make them easier to cough up. Decongestants to shrink swollen mucous membranes may also be recommended. Fluids should be encouraged to promote adequate

hydration. Drinking a variety of non-alcoholic beverages is important. Beverages served with crushed ice can be soothing to a sore throat. Warm beverages, such as tea, may promote nasal drainage and relieve chest tightness.

During the acute phase of any of these types of illnesses, there may be a loss of appetite. This is generally short lived. It is usually effective to have small frequent feedings of liquid and light foods. Once the appetite returns, a high-caloric, high-protein diet to replace the proteins lost during the acute phase of the illness might be recommended.

General comfort measures also include rinsing the mouth with plain water at regular intervals. This will relieve the dryness and bad taste that often accompanies illness and mouth breathing. A vaporizer may be helpful in increasing room humidity. However, if a vaporizer is used, daily cleaning is imperative to prevent contamination with molds. A coating agent (such as petrolatum or lip balm) can provide relief and protection to irritated lips and nose. Adequate rest is important. If persistent coughing or post nasal drip interferes with rest, elevation of the head and shoulders with extra pillows during periods of sleep should be attempted. Sometime a cough suppressant can be prescribed at night to prevent interruption of sleep.

Respiratory infections tend to be easily passed from one individual to another. The person who is ill should always be encouraged to cover the mouth and nose when sneezing and coughing. Soiled tissues should be promptly discarded. Hand washing is the most important method to prevent the spread of the infection. An alcohol-based hand sanitizer should be used frequently. If the hands are visibly soiled, soap and water is best. In some cases of bronchitis and pneumonia, coughing and breathing deeply at regular intervals should be encouraged as coughing protects the lungs by removing mucus and foreign particles from the air passages. Deep breathing promotes full expansion of the lungs, reducing the risk of further complications. In some situations, the primary care provider may order chest

postural drainage, chest physiotherapy, or sinus postural drainage, which are all ways of helping to loosen and clear mucus.

Gastrointestinal (GI) Infections

Diarrhea

Diarrhea is characterized by frequent, loose, watery bowel movements (stools). Diarrhea is a symptom and may indicate an infection or inflammation of the GI tract. Infections may be caused by viruses, bacteria, fungi or parasites. The primary care provider may order stool cultures to determine the cause of the infection. Certain medications may also cause diarrhea. Diarrhea may be mild to severe in nature. Whether it is mild or severe depends on the frequency, the volume and the consistency of the stools. Diarrheal illnesses may be accompanied by fever. In some cases severe diarrhea can cause dehydration. Infants, young children, and the elderly are at the greatest risk of serious problems associated with dehydration. Diarrheal illnesses may sometimes be accompanied by vomiting, further increasing risks of dehydration. Signs of dehydration can include:

- Loss of skin elasticity
- Dry parched lips, tongue, and mucus membranese
- Thirst
- Decreased urine output
- In infants, depressed or sunken fontanelles (soft spots on the head)
- An appearance of sunken eyes
- Behavioral changes ranging from restlessness to extreme fatigue and weakness

The general care of diarrhea focuses on the replacement of lost body fluids and salts, and the prevention of dehydration. When diarrhea is mild, changes in the diet and increased fluid intake may compensate for fluid losses. The primary care provider may suggest a clear liquid diet (avoiding dairy products), including weak tea, sports drinks, bouillon, and flattened soft drinks (without carbonation). As clear liquids are tolerated and the frequency and volume of stools decrease, the diet may be gradually advanced. In case of severe dehydration, hospitalization and intravenous fluids may be necessary.

General comfort measures include coating the rectal area with a petroleum jelly preparation. This will help protect the skin and reduce irritation from frequent diarrheal stools. Soiled diapers and clothing should also be changed immediately. The older child and adult may be encouraged to rinse his or her mouth with water regularly. This helps to relieve mouth dryness and bad taste associated with illness and is especially important after vomiting.

In infectious diarrhea, several measures are used to reduce the chances of spreading the illness to other family members. It may be easier for the infected person to use disposable cups, dishes, and utensils. Soiled diapers, clothing and linens should be kept separate and washed separately from other family laundry. Bathrooms should be cleaned with a disinfectant solution as often as necessary. Frequent hand washing with soap and water is essential for everyone, especially before and after handling soiled diapers or linens.

Bloody diarrhea and diarrhea accompanied by urgency and severe abdominal cramping may be signs of illnesses other than infections. These symptoms should always be reported to the primary care provider. Diarrhea can be caused by many things in addition to infections including certain drugs, malabsorption, inflammatory bowel diseases, like ulcerative colitis or Crohn's disease, etc., and additional testing may be required to determine its cause. Bacterial causes of diarrhea do not always require antibiotics, and antibiotic therapy may sometimes prolong symptoms.

Sometimes, antibiotics themselves may cause diarrhea. The job of antibiotics is to kill bacteria. In some cases, they kill good bacteria that normally live in the GI system as well as the disease causing ones. A prescriber may recommend taking a probiotic when someone is on antibiotics. The probiotic will replace some of the good bacteria that have been killed by the antibiotic.

Other GI Infections

Any of the gastrointestinal organs can become inflamed. Examples of these disorders include hepatitis (liver), gastritis (stomach), pancreatitis (pancreas), cholecystitis (gall bladder), or colitis (large intestine). This inflammation may be caused by infection. Symptoms can include pain, yellowing of the skin and/or eyes (jaundice), diarrhea, nausea, or loss of appetite. Medical attention should always be sought for these types of symptoms.

Bloodstream Infections

The blood can become infected with any kind of germ (bacteria, fungus, or virus). The general term for this is sepsis. These are extremely serious infections usually accompanied by high fever and signs of severe acute illness. It is necessary for the blood to be drawn and cultured to see if infectious organisms are present. Very often, blood stream infections require treatment with intravenous antibiotics

Infections at Unusual Locations or with Unusual Organisms

Infections that occur with defects in the innate immune system may be quite different from infections that affect individuals with defects in T cells or individuals with defects in B cells/antibody production.

For example, children with Chronic Granulomatous Disease (CGD), which is a defect in the innate immune system, are usually healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria Serratia marcescens, an organism that very rarely causes infections in other types of PI and any infant with an infection with this particular organism should be tested for CGD. Infections in CGD may involve any organ or tissue, but the skin, lungs, brain, lymph nodes, liver, and bones are the usual sites of infection and where abscess formation is common. Infections may rupture and drain with delayed healing and residual scarring. Infection of lymph nodes (under the arm, in the groin, in the neck) is a common problem in CGD, often requiring drainage or surgery along with antibiotics. Pneumonia is also a common problem in CGD. Pneumonias due to the fungus Aspergillus may come on very slowly, initially only causing fatigue, and only later causing cough or chest pain. Fungal pneumonias often do not cause fever. In contrast, bacterial infections (Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia) usually come on very quickly with fever and cough. Nocardia in particular causes high fevers and lung abscesses that can destroy parts of the lung. With CGD, it is particularly important to identify infections early and treat them completely, usually for a long period of time, so it is critical to seek medical attention early. If pneumonia is found it is very important to figure out exactly which microorganism is the cause, which may require a biopsy, usually done with a needle or a bronchoscope and not surgery. Treatment may require many weeks. Liver abscesses occur in about a third of individuals with CGD. They can start as fever and fatigue but may also cause mild pain over the right upper abdomen. Staphylococcus aureus causes most liver abscesses. Abscesses can also develop in the brain or bones (osteomyelitis) and can involve the spine, particularly if a fungal infection in the lungs spreads into it. (See Chronic Granulomatous Disease Chapter.)

Treatment of Infections

There are many anti-infective drugs: antibacterial, antifungal, antiviral, and anti-parasitic. The term antibiotic usually refers to a drug that fights bacterial infections. Anti-infective drugs are very specific. Different infections require different treatment. While penicillin is an excellent antibacterial antibiotic, it does not kill every kind of bacteria and has no effect at all on a virus or a fungus. If antibiotic therapy is indicated, the antibiotic prescribed should be one that will kill or inactivate the disease causing organism. Taking the medication as prescribed is very important, and every effort should be made not to miss any doses. Every infection does not necessarily need to be treated with an antibiotic or an anti-infective. The body has many defenses and mechanisms to fight off and kill infections. These defenses are present, even in people with PI. For example, the skin and mucus membranes are the first line of defense against many infections. Phagocytes (germ-killing white blood cells) usually work very well in people with antibody deficiencies just as antibodies are produced and work effectively in people with certain phagocyte problems. Some infections are mild and will resolve on their own, even in someone with PI.

Taking anti-infectives (antibiotics) may cause unwanted side effects and may require monitoring by a physician or laboratory testing. Antibiotics can cause upset stomach, vomiting, or diarrhea when taken over short periods of time such as days to one to two weeks. Longer courses of antibiotics (several weeks) may cause decreasing blood counts and kidney irritation, or require monitoring of drug levels. Antifungal medication may cause similar side effects as antibiotics as well as liver irritation, and may interfere with other medications, causing increase or decrease levels of those medications. Doctors should be consulted about possible side effects before taking any medication.

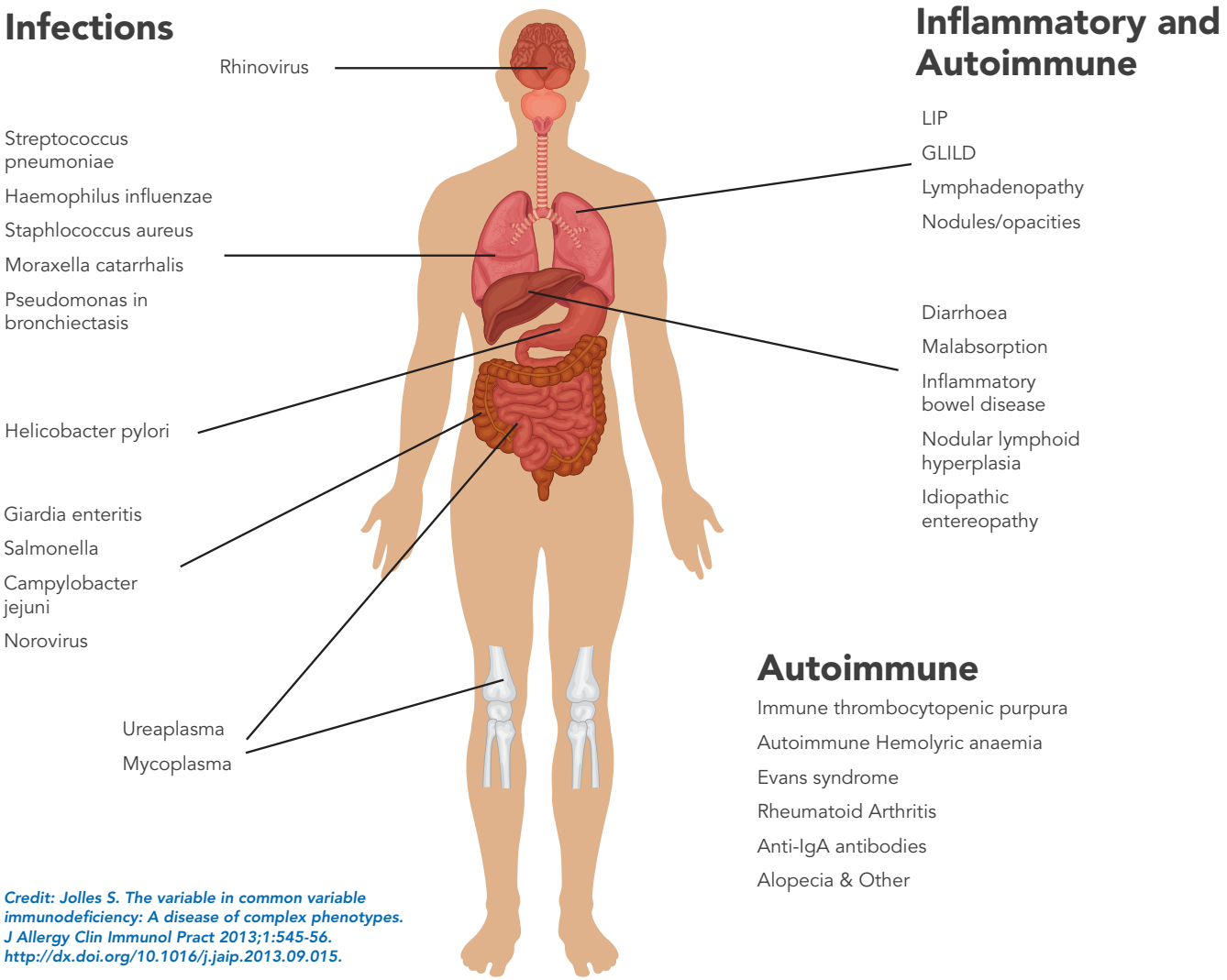
Sometimes prophylactic (or preventive) antibiotics may be prescribed for individuals with some types

of PI. For example, people with CGD usually receive daily antibiotics to protect them against certain kinds of infections.

People with cellular immune defects may take antibiotics to protect them against a particular kind of pneumonia. Prophylactic antibiotics are not, however, routinely recommended for all people with PI. There can be risks associated with antibiotic therapy. For example, drug-resistant organisms can develop or severe diarrhea can occur if normal body, non-pathogenic organisms are killed by an antibiotic. Only an immunologist can determine if prophylactic antibiotics are appropriate.

It is always important to try and determine the cause of a particular infection in someone with a PI. In order to determine what the right drug is, it may be necessary to get a culture. For example, if an individual has a respiratory infection with a cough, sputum that is coughed up can be sent to the lab to identify what the infecting agent is and its sensitivity to different antimicrobial agents. Cultures can be obtained on any type of drainage or body fluid including the blood. Sometimes, a biopsy of a tissue needs to be done. This involves taking a sample of a particular tissue and testing it to see if infection is present. For example, during a colonoscopy, tiny samples of the tissue from the intestinal wall are taken and examined by the pathologist to determine if an infection or other kind of inflammation is present.

Figure 27:2 Infections and autoimmune and/or inflammatory complications in CVID. The predominant organisms and sites of infection are shown on the left, with the inflammatory and autoimmune complications on the right.



Credit: Jolles S. The variable in common variable immunodeficiency: A disease of complex phenotypes. J Allergy Clin Immunol Pract 2013;1:545-56. http://dx.doi.org/10.1016/j.jaip.2013.09.015.

Summary

While infections of all kinds (acute, chronic, frequent, or recurrent) are always going to be problematic for people with PI, it is important to remember that prevention and early intervention are always the best approaches. A healthy lifestyle that includes adequate rest, nutrition, and exercise can go a long way to preventing infections. Similarly, a common-sense approach to prevention that includes such measures as frequent handwashing and avoiding others who are ill can also be highly effective. Once symptoms of an infection are present, however, seeking medical care in a timely manner is critical so that infections can be diagnosed early and treated appropriately, thereby preventing complications.

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Chapter 28
Immunoglobulin Replacement Therapy

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Immunoglobulin (Ig) replacement therapy is one of the most important and successful therapies for people with primary immunodeficiency diseases (PI) that affect antibody production. The therapy is both lifesaving and often lifelong, and it plays a huge role in the lives of many people with PI. The first commercial Ig for intravenous use was approved in 1981 for people with antibody immune deficiency.

What Is Immunoglobulin Replacement Therapy?

There are several specific medical therapies available for people with PI involving antibody deficiencies. Antibody deficiencies account for more than 50% of the disorders. These illnesses, such as Common Variable Immune Deficiency (CVID), X-linked Agammaglobulinemia (XLA), and other disorders, are characterized by a lack of and/or impaired antibody function.

Immunoglobulin or Ig, also known as gamma globulin or immune globulin, refers to the liquid plasma component of blood that contains immunoglobulins or antibodies. These antibodies have the important role in the immune system of neutralizing bacteria and viruses, and enhancing the phagocytosis and destruction of bacteria, certain viruses, and other pathogens.

When antibody molecules recognize a microorganism as foreign, they physically attach to it and set off a complex chain of events involving other components of the immune system that work to eventually destroy the infection. Antibodies vary with respect to their specialized functions in the body. These variations are determined by the antibody's chemical structure, which in turn determines the class of the antibody (or immunoglobulin). There are five major classes of antibodies (IgG, IgA, IgM, IgD and IgE). IgG has four different subclasses (IgG1, IgG2, IgG3, IgG4). IgA has two subclasses (IgA1 and IgA2). Only the IgG is purified from plasma in the production of therapeutic Ig products, so Ig used for treatment contains 95-98% pure IgG with only small amounts of other plasma proteins including some IgA and IgM.

It is important to understand that the Ig given to people with PI partly replaces what the body should be making, but it does not stimulate the individual's own immune system to make more Ig. Since Ig only replaces the missing end product but does not correct the person's defect in antibody production, Ig replacement therapy is usually necessary for the individual's lifetime. In addition, the Ig only provides temporary protection. Most antibodies, whether produced by their own immune system or given in the form of Ig replacement, are used up or metabolized by the body and must be constantly replenished. Approximately half of the infused antibodies are metabolized over three to four weeks, so repeat doses of Ig are required at regular intervals. Ig replacement therapy reduces the susceptibility to infections, can optimize health, and improve quality of life. As with any treatment, however, individual risks and benefits should be discussed with a healthcare provider.

Before starting Ig replacement therapy, it is important that the provider completes all the immune studies to demonstrate that the individual's immunoglobulins

are not only low but also that the individual does not make specific antibodies. People who do not have antibody disorders normally make antibody during and after natural infections and in response to immunization with vaccines. Immunologists generally use tetanus toxoid and pneumococcal vaccines (Pneumovax® or Prevnar®) to test the ability of the person to make specific antibodies. Blood is drawn before giving the vaccine to measure the vaccine specific antibody levels. After vaccination, a second blood sample is drawn four to six weeks later to determine how well specific antibodies are made to these vaccines. It is important that the individual completes this second blood draw to determine the response to the vaccine within this four to six-week timeframe. These results provide important information about the individual's immune condition and insurance companies often review this information before approving Ig replacement therapy. Once Ig replacement therapy is started, it is not possible to get accurate results for these important tests without stopping Ig treatment for a few months.

History

Gamma globulin derived from human plasma was first introduced as a treatment option in 1952 when gamma globulin was injected intramuscularly (IM) to treat people with recurrent infections who had antibody immune deficiencies[1]. Dosing was very difficult because only small amounts of gamma globulin could be given in each painful shot. Much scientific investigation in the 1960s and 1970s finally led to a suitable gamma globulin product that could be used intravenously in the early 1980s. People with antibody disorders have been successfully treated with intravenous immunoglobulin replacement therapy (IVIG) for over 30 years.

With the discovery of well-tolerated preparations of IVIG in the 1980s, the suboptimal, painful IM administration was no longer used[2]. This shift to IVIG changed the face of PI treatment. In primary or secondary hypogammaglobulinemia (low IgG), Ig replacement therapy protects against infections by providing an adequate amount of IgG in the blood[3]. Human immunoglobulin plays an important role in the treatment of many diseases, including diseases for which there is no other alternative treatment[3,4]. Currently, more than 100 inflammatory and autoimmune disorders are also treated with IVIG.

Route of Administration

Ig replacement therapy is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). SCIG can be given in two ways: conventional or facilitated. The facilitated method uses an additional enzyme medication to increase the amount of Ig that can be delivered during each subcutaneous infusion. The individual with PI or caregiver and the prescriber should have a discussion about which route of administration is most appropriate. There are advantages and disadvantages for each route of administration (see Table 28:1). IVIG has allowed infusion of higher doses over a short time and historically has been the standard route of administration. It must be administered by a healthcare professional.

SCIG was utilized as early as the 1970s[5], but it did not gain approval from the Food & Drug Administration (FDA) in the U.S. until 2006. This therapy does not require venous access and is associated with the slow release of Ig from the subcutaneous tissues into the blood, which enables IgG levels to remain consistent and steadier between infusions[6].

Currently, among those receiving Ig replacement therapy in the U.S., approximately 50% use IVIG and 50% use SCIG. The individual with PI or caregiver and the prescriber need to make a decision on the route of therapy that is best for the individual person. All options are clinically effective. All therapies, regardless of route, must be individualized to meet the individuals' needs.

Manufacturing

There are more than 25 different Ig preparations available worldwide. The preparations vary in a number of ways, including the distribution of IgG subclasses, stabilizers, and infusion details. All Ig products are made from human source plasma. Source plasma is different than recovered plasma, which is collected through whole blood donation where plasma is separated from its cellular components. This source plasma is pooled from thousands of plasma donations by a process called plasmapheresis in which the liquid part (plasma) is separated from the red and white cells. The red and white cells are then returned to the patient. This allows a specific donor to return to the plasmapheresis center monthly.

Considerations for Choosing a Route of Administration for Ig Replacement Therapy

Table 28:1

	Intravenous Immunoglobulin (IVIG)	Facilitated Subcutaneous Immunoglobulin (fSCIG)	Subcutaneous Immunoglobulin (SCIG) (Conventional)
Frequency of Dosing	Every three to four weeks.	Every two, three, to four weeks.	From daily to every 14 days.
IgG Level	Achieves an initial high concentration of IgG that decreases gradually over approximately 21 days.	There is an initial peak (day 4), although not as extreme as with IVIg, and decreases gradually over 21 days.	No variation in IgG level once steady state is achieved; level stays constant.
Access	Requires intravenous (IV) access (NOT a port).	Does not require IV access. Individual can do their therapy independently once appropriately trained.	Does not require IV access. Individual can do their therapy independently once appropriately trained.
Needle Sticks	Usually one (to establish IV access).	One to two.	One to four or more, depending on dose and preference.
Time of Infusion	Usually three to four hours.	Usually three to four hours.	Variable. Data supporting safe, rapid (less than 30 minute) infusions and individuals who manually push their dose as rapidly as tolerated.
Ancillary People	Requires healthcare professional to establish IV access and monitor infusion.	Individuals can establish their own subcutaneous access once trained, but therapy requires a committed individual with PI or caregiver.	Individuals can do their own SCIG once trained.
Intra-infusion Systemic Side Effects	Possible, including chills, rigors, blood pressure changes, nausea/vomiting, aches.	Possible, but to a lesser degree than with IVIG.	Usually no systemic effects but localized burning or itching is possible.
Pre-medication	Sometimes necessary.	Sometimes necessary.	No, as drug is not biologically available for 24-36 hours.
Intra-infusion Local Side Effects	Not usually, unless IV infiltrates.	Sometimes some itching and burning.	Sometimes some itching or burning.
Post-infusion Side Effects	Systemic side effects possible.	Both local and systemic post-infusion side effects are possible.	Redness and swelling at the site of the infusion which decrease with subsequent infusions.
Cost	Cost for drug and nursing/ infusion center.	Cost for drug and supplies.	Cost for drug and supplies.

Usually a pool or lot of Ig product is derived from approximately 10,000 donors. This ensures that a pool or lot of Ig contains a broad spectrum of specific antibodies that are found in the general population which then provide protection to people with PI. The product contains at least 90% intact IgG molecules. All Ig products licensed in the U.S. must be made from source plasma that has been collected in the U.S.

Safety

There are multiple safety steps in the production of Ig: donor screening, viral removal, and inactivation of viruses.

All plasma donors undergo a very rigorous screening process that includes a detailed history of infections and risk behaviors, and testing of their plasma for certain viruses using very sensitive techniques. Donors cannot give their plasma unless they pass this screening. Donors are asked specific questions about risk factors that could affect the safety of the donation and are excluded from donation if risk factors are identified. Plasma centers can look at the donation history for each donor. The FDA also requires blood centers to maintain lists of unsuitable donors to prevent further donations from these rejected donors. As an added protection, donors must return to donate within a set timeframe for rescreening. If a donor does not return within that timeframe, their prior plasma donation is discarded.

After donation, the individually donated plasma is tested for infectious agents before being pooled with plasma from other donors. Once the plasma is pooled, the entire pool is tested for the markers of HIV and hepatitis A, B, and C viruses. The pooled plasma is then divided up and different methods of fractionation and filtration help to separate out the IgG molecules. At multiple times throughout this process, the pool is tested for viral safety before additional safety measures are implemented.

In the mid-1990s, rare clusters of non-A, non-B hepatitis (now called hepatitis C) were documented after the use of some IVIG products. This prompted the addition of an extra viral inactivation step in the manufacturing process. Now multiple safety measures, including pasteurization, low pH, low pH with pepsin, and solvent detergent help dissolve the lipid enveloped viruses, including hepatitis C. An additional safety step is chromatography, a technique widely used to obtain pure ingredients from mixtures. More recently, a final ultrafiltration or depth filtration step has been added to remove the possibility of transmission of prion related diseases (mad cow disease). Transmission of HIV, which is destroyed in the first ethanol fractionation step in the production of Ig, has never been documented with the use of any Ig replacement therapy.

Dosing

Ig replacement therapy is typically dosed based on the recipient's weight. Many factors, however, are considered when the medication is prescribed. Typically, a starting dose is between 400 to 600mg/kg/month. Doses are adjusted for clinical efficacy, with the expectation of minimizing the frequency and severity of recurrent infections while minimizing side effects of the medication. IgG levels are usually monitored over time and correlated with the response to therapy.

With SCIG, there is a steady level of IgG present in the bloodstream due to the more frequent dosing regimens (Figure 28:1) and slower rate of absorption.

With IVIG, the dosing at longer intervals may cause peaks and valleys, called troughs (Figure 28:2). The goal is to keep the levels of Ig in the blood stream above a certain level even even when the level is at its lowest (the trough level) right before the next infusion is due.

Intravenous Immunoglobulin (IVIG) Replacement Therapy

Uses: IVIG is given through a vein. Most immunologists strongly discourage the use of central catheters to administer IVIG due to the increased risk of serious blood infections and the development of blood clots. Placing a central venous catheter, also known as a port, due to poor venous access increases the risk of infections and blood clots, and it should be strongly discouraged. Given the very serious risk involved with the use of implantable ports, individuals should instead consider switching to the subcutaneous route of administration (SCIG) if there is a vein access problem.

IVIG is typically given every three-four weeks at a dose determined by the prescriber. Infusions can be given in various settings including an inpatient or outpatient infusion suite, physician office, or in the home. IVIG is administered by a healthcare professional, and the procedure is scheduled in advance. In special extenuating circumstances, individuals can be instructed to self-infuse this therapy after they are stable on the treatment as long as IV access can be established. The medical

Figure 28:1

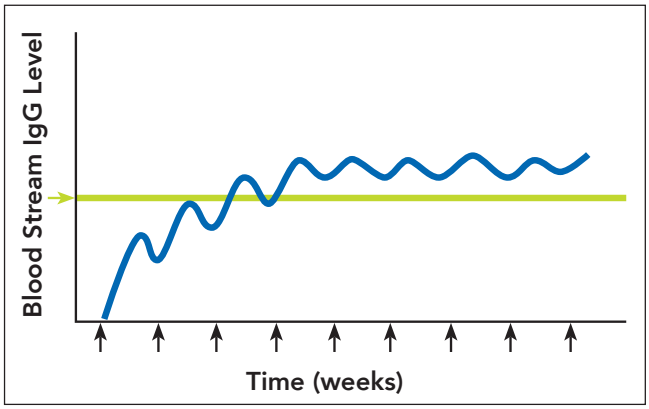
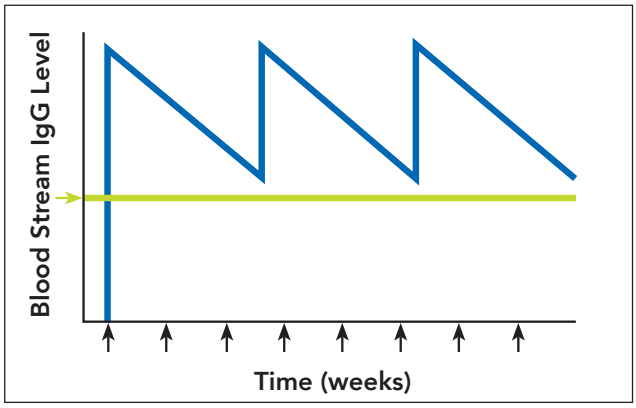


Figure 28:2



professional should, however, stay with the individual for the length of the infusion because of the risk of serious side effects, such as anaphylaxis.

The following are considerations for switching from IVIG to SCIG administration:

- Extreme prematurity (mainly infants born before 30 weeks)
- DiGeorge (22q11.2 deletion) syndrome
- Jacobsen syndrome

Side Effects: Although IVIG has been safely and effectively administered since the early 1980s, IVIG can cause adverse effects, both localized and systemic. Systemic reactions to IVIG infusion occur in approximately 3% to 15% of individuals receiving treatment. The side effects are usually self-limiting and can be avoided by decreasing the rate of the infusion, good hydration, and/or making sure that the product is at room temperature when it is infused.

Individuals may be at increased risk for developing an adverse reaction if they have never received IVIG, have active infections or pre-existing conditions (such pneumonia or bronchiectasis), or are switching products. Individuals with a history of migraine headache may be at risk for a post-infusion headache reaction. The prescriber of the therapy can modify IVIG dosing by decreasing the rate of infusion or adding other medications to the prescription. Medications such as acetaminophen, diphenhydramine, non-steroidal anti-inflammatory drugs, or corticosteroids can help prevent side effects during and after an infusion. It is important to know, however, that repeated use of corticosteroids used to manage IVIG side effects may lead to long-term problems associated with repeated steroid use. While IVIG brands differ by manufacturer, the listed side effects are virtually identical on each package insert. Some common infusion reactions are headache, nausea, fever, chills, flushing, wheezing, vomiting, backache, muscle aches, joint aches, or chest tightness. Side effects experienced during an infusion of Ig are almost always related to the rate of the infusion, such as infusing too fast, or relate to the temperature of the product. Stopping or slowing the infusion is usually the only intervention needed to alleviate these symptoms. Sometimes a switch in product is successful in alleviating these side effects as some may simply tolerate one brand better than another.

Some side effects can happen up to 72 hours after an infusion of Ig. These delayed symptoms are not usually associated with the rate of infusion. Some rare side effects include:

- Aseptic meningitis (inflammation of the meninges, the membranes that surround the brain and spinal cord) has been seen up to 72 hours after infusion of IVIG and may be more prevalent in people with a history of migraine headaches. Hydrating prior to IVIG may protect from this side effect. It is important to note that every person who develops a post-infusion headache does not necessarily have aseptic meningitis. A prescriber should be notified if the individual experiences severe headaches that do not respond to standard medications such as acetaminophen or non-steroidal anti-inflammatory drugs, like ibuprofen.
- Anaphylaxis is very rare and may be associated with anti-IgA IgE antibodies (there are no labs that can test for these IgE antibodies) in some people who have totally absent IgA. The role of anti-IgA antibodies in causing anaphylaxis in people with IgA deficiency receiving Ig

replacement therapy is still controversial[7]. The newer liquid IVIG products have low concentrations of IgA. In addition, reactions due to anti-IgA antibodies do not occur with SCIG, and SCIG has been safely given to people with PI suspected of having anti-IgA IgE antibodies.

- Acute renal failure has been seen after infusion of IVIG; 90% of these cases, however, are associated with sucrose-based products, which are no longer in use and are not necessarily associated with the timing of the infusion. Individuals over age 65 or who have pre-existing kidney disease may be at an increased risk of adverse effects on the kidney.
- Blood clots, such as thrombotic side effects and embolisms, have been associated with IVIG infusions. The relationship between IVIG infusion and an increased risk of blood clots is thought to be due to a plasma contaminant (Factor XIa) that all manufacturers test for in the final product and eliminate, if present to reduce this risk. Risk factors for blood clots include heart disease, advanced age, previous thrombotic event, clotting disorder, hypertension, diabetes, high cholesterol, renal disease, obesity, and immobility[8]. Adequate hydration prior to administering the IVIG is very important as is not exceeding the recommended rate of infusion.
- Hemolytic anemia is a rare but reported side effect of IVIG. The risk of significant hemolysis (breakdown of blood cells) appears greater in those who receive high dose IVIG for autoimmune disorders than in those who are receiving replacement therapy.

What Side Effects to Report to the Prescriber: The individual with PI or caregiver is responsible for reporting any side effects or discomforts experienced during or after an infusion of IVIG to the prescriber of the therapy and to the nurse administering the therapy.

Side effects to report include but are not limited to:

- Headache
- Body aches
- Fever/chills
- Diarrhea
- Muscle cramps
- Nausea and vomiting
- Symptoms of infection

Optimized Infusion Experience: A nurse trained in the administration of this therapy and the appropriate place of administration for IVIG is important. Many of the side effects that happen during an infusion are related to rate. The nurse should be experienced in infusing this medication and aware of when to slow down the rate of infusion or stop the infusion if necessary. If individuals are aware of steps that they can take to prepare for each infusion, the infusion process will be much smoother. It is important to be well hydrated going into an infusion of IVIG. This will not only help the nurse get an IV started, but it will decrease the risk of headache and other side effects after each infusion. Prescribed pre-medication is designed to prevent side effects. It is important to take the pre-medication as prescribed. Individuals or caregivers should record the infusion experience on a calendar or journal so that any adverse experience can be reported to the nurse and the prescriber prior to the next infusion so that adjustments can be made to the rate, pre-medications, dose, etc.

Monitoring: Routine lab tests may be ordered by the prescriber to monitor IVIG treatment. This may include measuring IgG levels just before the next infusion is due. It is also necessary to monitor other blood levels such as total blood counts and measures of kidney and liver function. Most importantly, the prescriber will want to monitor the person for infections to make sure IVIG is having the desired effect of decreasing serious infection.

Subcutaneous Immunoglobulin (SCIG) Replacement Therapy

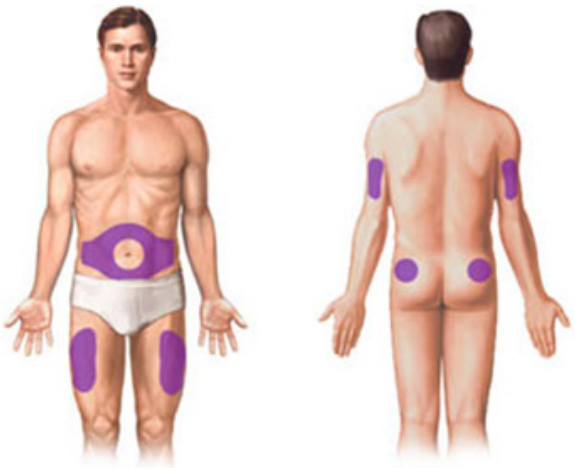
Subcutaneous immunoglobulin replacement therapy (SCIG) has gained popularity in the U.S since the 2000s. SCIG has increased the options available for people needing Ig replacement therapy for PI and certain neuromuscular diseases. Currently, there are several products available that can be administered subcutaneously using a number of regimens. These products differ based on concentration, stabilizers, and infusion specifics.

SCIG Regimens: Greater flexibility in the dosing and an increase in the number of products available has contributed to the expanded use of SCIG. The following are currently available for subcutaneous use: 10% preparations, 20% preparations, and

facilitated SCIG (a 10% SCIG preparation plus an enzyme called hyaluronidase). In general, SCIG regimens require the individual with PI or caregiver to learn how to self-administer at home. Both forms of SCIG allow for self-administration at home. Facilitated SCIG may be administered at home or in-office administration with a nurse, depending on insurance coverage and preference.

SCIG is usually infused under the skin, into the subcutaneous layer of the abdomen, thighs, or outer buttocks at one or multiple sites, depending on the volume being infused (Figure 28:3). The total monthly dose is calculated by the prescriber, then divided according to the interval between infusions (usually weekly or biweekly for conventional SCIG and every three-four weeks for facilitated SCIG). The number of needle sticks (sites) is also calculated for the individual depending on the volume and the concentration of the SCIG to be infused. Larger intervals between infusions require larger volumes of product to achieve the same total dose. Conventional SCIG can be given daily, weekly, every two weeks, or multiple times per week, as long as the total monthly dose is divided appropriately. Dosing daily involves subcutaneous injection of small volumes without the need for a pump, using only a syringe. Facilitated SCIG can be given every three-four weeks to deliver the total monthly dose at once into the subcutaneous space. This is facilitated by the use of human bioengineered hyaluronidase. Hyaluronidase is a naturally occurring enzyme in the subcutaneous tissues that is injected into the subcutaneous space before the Ig to expand the subcutaneous space and allow more medication to be infused into each site. The effects of the hyaluronidase enzyme are very short lived, and the tissues revert back to normal in 24 to 48 hours. The benefit of this therapy is a decrease in the frequency of infusions as it allows for an entire three or four-week dose to be administered at one time.

Figure 28:3 Sites for infusion of SCIG



The length of the infusion varies depending on the volume infused, but generally takes up to one to two hours (or less). For SCIG, some of the standard (less concentrated) 10% IVIG preparations can be used via the subcutaneous route. Currently there are several 20% (more concentrated) preparations indicated for subcutaneous use only that allow for smaller volumes to deliver the same dose with fewer needle sticks. With the 20% preparations, site volumes can range from 30ml to 60ml per site depending on the individual's tolerance. In facilitated SCIG, about 300-600ml can be delivered in one site or divided into two or more sites as tolerated.

In general, SCIG is delivered using a small needle attached to tubing and a syringe that is placed in either an automatic mechanical pump or an electric programmable pump. Both pumps are portable. Alternatively, some individuals may prefer or better tolerate SCIG delivered by subcutaneous push, meaning that a small amount of SCIG is injected daily under the skin without the use of a pump. The Ig products come in a variety of vial sizes depending on the manufacturer. Several needle and tubing sizes are available, and troubleshooting problems with SCIG often involves reviewing that the equipment being used, such as needle sets, tubing, pump, etc., are appropriate for the individual receiving the therapy.

Dosing: As in IVIG, the typical starting dose is between 400 to 600mg/kg/month. The monthly dose is divided into infusions daily, weekly, or every two weeks. In contrast, facilitated SCIG enables the whole monthly dose to be infused every three to four weeks. Doses are adjusted to clinical effect, with the expectation of minimizing the frequency and severity of recurrent infections. IgG levels are monitored over time, correlated with clinical outcomes, and the dose is adjusted as necessary. With SCIG, there is a steady level of IgG (no peaks or troughs like IVIG) present in the bloodstream due to the more frequent dosing. With facilitated SCIG, there are peak and trough levels but the peak levels are not as high and trough levels are not as low, as with IVIG.

Optimized Infusion Experience: Several variables involved with SCIG allow optimization of the infusion experience. Some of these variables include number of needle-sticks, infusion sites, volume infused/site, needle length, and pump type. The number of needle-sticks may be reduced by increasing the volume infused per site. Fewer sites are needed with the more concentrated 20% products. Conversely, more sites may be needed if the less concentrated solutions are used. With facilitated SCIG, which delivers the whole month's

dose at once, the dose can be divided between one to two sites, depending on how the infusion is tolerated. If the individual is experiencing discomfort using the abdomen, other sites such as the thighs can be used. If the individual prefers to dose every month rather than weekly or every two weeks, then facilitated SCIG using one to two sites may be the best choice. For those who have issues with tolerating infusions, smaller volumes of SCIG daily may be needed. Several needle lengths are also available that can be tried; the important thing is to use a needle long enough to insure that the Ig is being administered into the subcutaneous tissues rather than the skin. A variety of infusion pumps are available ranging from a simple and portable mechanical pump to more complicated programmable pumps. Most importantly, SCIG can provide freedom of scheduling for those who self-infuse, resulting in fewer school and workday losses.

Side Effects: In general, SCIG is associated with fewer systemic adverse events than IVIG. SCIG is an option to consider when IVIG is not well tolerated, when there is poor venous access, or when the individual's lifestyle is more compatible with SCIG than IVIG. SCIG can be considered for children, adults, pregnant women, the elderly, and for individuals with IgA deficiency secondary to having antibodies against IgA (very rare). Systemic side effects are usually mild. Severe reactions rarely occur, but individuals who have had severe reactions to IVIG might be at a higher risk. Pre-medication is usually not required for SCIG. The most common adverse reaction reported is local redness, swelling, and irritation at the injection site. Usually these mild localized reactions improve with repeated infusions. In rare cases, the injection site reactions can be severe. To improve or avoid the infusion site reactions, and decrease the chance of other problems, individuals need thorough training to ensure that proper technique is used to access the subcutaneous tissue. Local skin reactions may be due to inadequate needle length preventing the Ig from being infused into the subcutaneous tissue. For those with fear of needles, a topical numbing medicine or ice can be applied to the skin prior to the subcutaneous infusion.

Monitoring: With SCIG, there is a steady state level of IgG in the circulation due to more frequent infusions of smaller doses and the fact that the Ig is more slowly absorbed. Peak and trough levels are not as extreme, and the level is more consistent on a daily basis. Routine lab work including blood counts and markers of liver and kidney functions should be monitored. None of the currently available products for SCIG, are stabilized with sucrose, making renal complications less likely. Smaller doses given subcutaneously also minimize risks due to fluid overload.

Practical Considerations: Many practical considerations should be taken into account when deciding if SCIG is the right choice. SCIG requires more frequent administrations (daily, weekly, every two weeks), unless the facilitated SCIG route is chosen (every three to four weeks). Medical supervision is not required for home infusion, so the ability of the individual to adhere to the treatment regimen is an important consideration. If there is a fear of needle-sticks, training strategies for self-infusion including numbing creams should be considered. Manual dexterity, or the ability to make coordinated hand and finger movements to manipulate objects, is also required to draw up SCIG and manage the pump. SCIG provides the freedom to administer Ig at home or anywhere else at any time of day. This flexibility and control have been shown to enhance the quality of life for many individuals[9]. SCIG is associated with a lower rate of systemic side effects, making this route of administration a good option for those experiencing unwanted adverse effects from IVIG. Administration of more frequent, smaller volumes provides a steady level of Ig, avoiding high peak levels that may be associated with side effects of IVIG, such as headaches and symptoms of wear-off. SCIG should be given serious consideration for college students and those individuals whose jobs require frequent travel. Individuals should remember that there are many options available for therapy and that they should thoroughly discuss these options with their prescribers.

Summary

The goal of Ig replacement therapy for antibody disorders—no matter the route of administration—is to provide protection from infection. An individual's adherence to therapy is paramount to achieving this goal. Any barriers to therapy, real or potential, need to be addressed appropriately.

It is also important to remember several things when considering Ig replacement therapy:

- **Not all infections can be prevented.** After starting Ig replacement therapy, individuals may still get infections. It is hoped, however, that

Table 28:2

	Intravenous Immunoglobulin (IVIG)	Facilitated Subcutaneous Immunoglobulin (fSCIG)	Subcutaneous Immunoglobulin (SCIG) (Conventional)
Who?	Indicated for adult and pediatric individuals with PI.	Indicated for adult and pediatric individuals with PI.	Indicated for adult individuals with antibody deficiencies.
How?	Usually administered by a nurse.	Self-administered.	Either self-administered or given by a nurse.
Where does it go?	Infused directly into the bloodstream through a vein.	Infused or injected under the skin into the subcutaneous tissues of the arms, belly, outer buttock or the thighs.	Infused under the skin into the subcutaneous tissues of the belly, outer buttock or the thighs.
When?	Usually given every three-four weeks.	Can be given on a flexible schedule from daily to every two weeks.	Can be given every three-four weeks.
How long?	Can take two-six hours to infuse.	Can take five minutes to two hours to infuse or inject.	Can take one-2 hours to infuse.
Where is it given?	Can be infused at home, in a hospital or an outpatient infusion center depending on insurance and patient preference.	Usually administered in a home setting after the patient is trained to be independent.	Can be infused at home or in an outpatient infusion center depending on insurance and patient preference.
Side effects?	Individuals can have side effects that are often related to the rate of infusion and can be treated and prevented with other medications, given before or after the treatment.	Skin can be red and irritated at the site of injections. This often improves with each injection.	Skin can be red and irritated at the site of injections. This often improves with each injection. The volume per injection is larger than standard subcutaneous (under the skin) injection, so the volume is more visible under the skin, and may take 48-72 hours to totally absorb.

the frequency and severity of infections will be significantly decreased so that permanent organ damage, like bronchiectasis can be prevented

- **"One size does not fit all."** An individualized Ig replacement therapy regimen must be developed for each individual and modified as necessary to achieve treatment goals and the needs of each person.
- **Once a diagnosis of PI involving antibody production and/or function has been made, Ig replacement therapy will probably be needed lifelong.** In some instances, reevaluation of the diagnosis may be undertaken. This must be done cautiously as Ig replacement therapy must be stopped for four months to obtain accurate repeat lab tests.

The following chart (Table 28:2) is designed to facilitate a discussion between individuals and caregivers living with PI and their healthcare providers when immunoglobulin (Ig) replacement therapy is determined to be the treatment of choice and is deemed medically necessary. Decisions on which therapy is best should be made with some of these factors in mind.For more information, refer to the IDF Guide to Ig Therapy that contains frequently asked questions and troubleshooting SCIG therapy.

Resources

Information regarding the Ig products currently licensed in the U.S. is available from each specific manufacturer via the individual corporate websites. Companies who manufacture Ig replacement therapy offer a wealth of valuable information for individuals and families living with PI. Learn more about the companies, their products, general information about PI and/or reimbursement assistance programs on their websites.

For a complete, updated list of Ig products, manufacturers, and details, visit the IDF website: www.primaryimmune.org/ig-products. Please note that manufacturers and products are subject to change.

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Adapted from: Chapter 24 Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 29

Hematopoietic Stem Cell Transplantation

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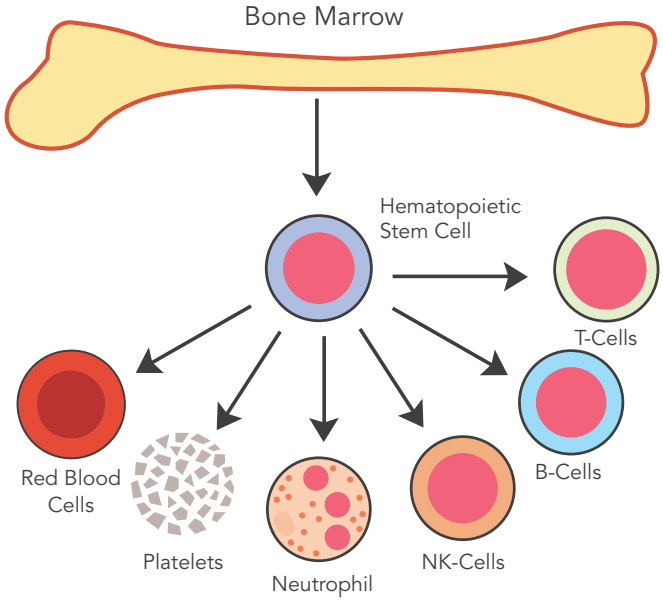
Primary immunodeficiency diseases (PI) cause a wide spectrum of symptoms with varying severity. Some forms of PI are mild and don't cause significant harm, or may be effectively treated with agents like immunoglobulin (Ig) replacement therapy. Other forms of PI are so severe that individuals have a very poor quality of life or can die as a result of their disease. When PI is likely to cause significant harm or death to someone, allogeneic hematopoietic stem cell transplantation (HSCT) may be the best treatment option. Some common indications for allogeneic HSCT include Severe Combined Immunodeficiency (SCID), Wiskott-Aldrich Syndrome (WAS), Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome, X-linked Lymphoproliferative Disease (XLP), Hyper IgM Syndrome, Combined Immune Deficiency (CID), and Hemophagocytic Lymphohistiocytosis (HLH). Allogeneic HSCT can also be considered for other forms of PI. The following will review the basics of allogeneic HSCT for PI.

Overview

Immune system cells develop from special cells that live in the bone marrow called hematopoietic stem cells. Hematopoietic stem cells produce all blood cells including red blood cells, platelet-producing cells, and immune system cells such as neutrophils, T cells, B cells, and NK cells (Figure 29:1).

Hematopoietic stem cells can be transferred from one person to another person. This requires a very specialized procedure called an allogeneic HSCT. The person who receives the stem cells is called a recipient of HSCT. The term, allogeneic, indicates that the stem cells given to the recipient came from someone else, the hematopoietic stem cell donor. If an allogeneic HSCT is successful, the donor's hematopoietic stem cells will replace the recipient's own cells. The donor cells will live in the recipient's bone marrow and make blood and immune system cells.

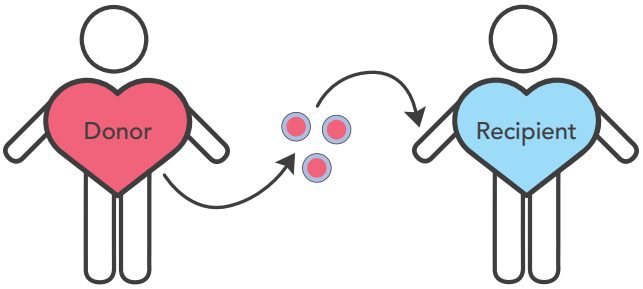
Figure 29:1 Hematopoietic Stem Cell Produces All Blood Cells



People with PI essentially have broken pieces in their immune system. Immune system cells may be missing or just not work properly. An allogeneic HSCT can replace an individual's own hematopoietic stem cells with stem cells that will produce normal immune system cells. In this way, a person's immune system can be fixed. Allogeneic HSCT also fixes any problems with other blood cells. For example, platelets will be fixed in those with WAS who have a successful allogeneic HSCT. Unfortunately, problems outside of the blood or immune system will not be fixed. For instance, if an individual with IPEX has diabetes before transplant, they will still have diabetes after transplant, because the cells in the pancreas that make insulin have been destroyed by this disease, and HSCT cannot replace pancreatic cells.

Hematopoietic stem cells may be collected from the bone marrow, the peripheral blood, or from umbilical cord blood, so HSCT procedures may be called bone marrow transplants, peripheral blood stem cell transplants, or cord blood transplants depending on the source of the stem cells. The transplant itself does not require surgery for the recipient, as the hematopoietic stem cells are typically infused into a large vein in the same way that a patient receives a blood transfusion. (Figure 29:2)

Figure 29:2 Hematopoietic Stem Cell Transplantation (HSCT)

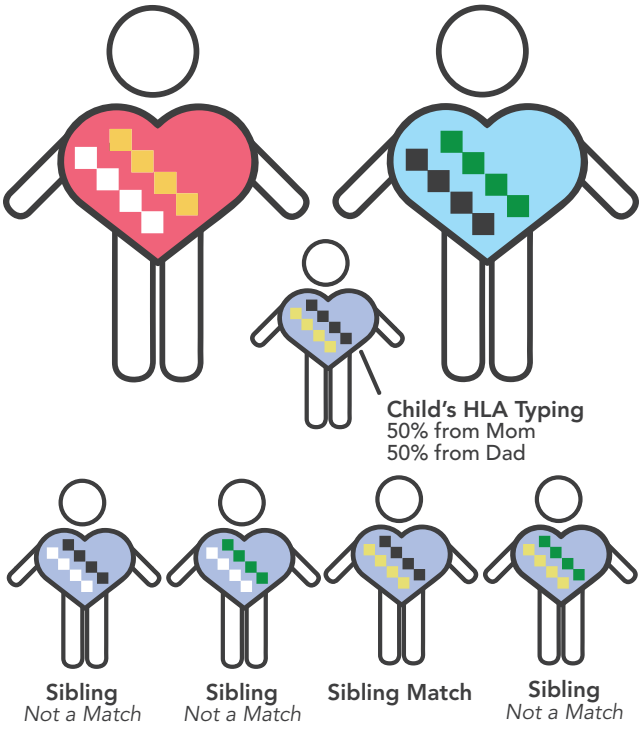


Finding a Donor

Before having a transplant, a suitable donor must be found. Finding a donor can take several weeks or months. The first thing that happens is a blood test is done to learn about a person's human leukocyte antigen (HLA) typing. The immune system uses HLA proteins on cells to help determine which cells belong to the body and which don't, so HLA matching increases the chances of transplanted donor cells being successfully incorporated into the recipient's body. A donor must be found who has the same or almost the same HLA typing results. HLA-matched donors are the best donors because when HLA typing is the same between a donor and recipient, the chances of complications, such as graft rejection and graft versus host disease (GVHD), are low. Transplant providers typically look at 8 to 12 HLA alleles (markers) or genes when trying to find a matched donor. A fully matched donor would be an 8/8, 10/10, or 12/12 (depending on the testing lab) HLA matched donor.

If the individual with PI has siblings, the brothers and sisters will have HLA typing done to determine if they are a match. Everyone has two sets of HLA genes. One set is inherited from the mother, and the other set is inherited from the father. Typically, each full brother or sister (same mother and same father as the recipient) has a 25% chance of being a full match to their affected sibling (Figure 29:3). It is important that potential sibling donors are evaluated for PI before being used as donors.

Figure 29:3 Example of Human Leukocyte Antigen (HLA) Typing in a Family



If there are no sibling donors available, the search will move to several national and international donor registries to look for a matched unrelated donor. If there are no matched donors, a mismatched donor may be considered. If only one HLA allele is different between the person with PI and the donor, that would be noted as a 7/8, 9/10, or 11/12 HLA mismatch. Having an HLA mismatch increases the risks of graft rejection and GVHD—the greater the mismatch, the greater the risks of rejection or GVHD.

Sometimes, a parent may be used as a donor. Parents are typically only a half match to their children, so this type of transplant is called a haploidentical transplant. This type of transplant must be done in a special way because there is a high risk of graft rejection or acute GVHD. Donor T cells must be removed from the graft or otherwise destroyed to decrease the risk of severe GVHD.

Graft Sources

Hematopoietic stem cells can come from three sources: bone marrow grafts, cord blood grafts, and peripheral blood stem cell grafts. Bone marrow grafts are harvested from the pelvic bones of donors using large needles after the donor is put to sleep. Cord blood grafts are collected from the umbilical cord at the time of a baby's birth, and processed in a special way to allow the cord blood to be frozen and stored until it is used. Peripheral blood stem cell grafts are collected from a donor's veins after the donor receives several days of a special medicine that causes stem cells to leave the bone marrow and circulate in the bloodstream. A central venous line or large intravenous lines (IVs) are placed in the donor's veins, a machine is used to remove and collect the stem cells from the blood, and the blood minus the stem cells is then returned to the donor. This process takes several hours. Sometimes more than one peripheral blood stem cell collection is performed in order to get more stem cells.

Preparing for Allogeneic HSCT

Some individuals with PI may be fortunate enough to be able to have an allogeneic HSCT at their nearby hospital, but many will have to travel to specialized centers for transplantation. This can be difficult for families and can be emotionally and financially challenging. Individuals with PI and their families will usually meet members of the transplant team, which can include physicians, nurse practitioners, social workers, psychologists, nurses, and financial counselors. These team members can help prepare recipients and their families for the impact the transplant will have on family life, and they can help provide support and assistance with all aspects of the transplant. Staff at the hospital, in collaboration with the families, will often work with insurance companies to get approval for the transplant.

The time spent at a transplant center can vary from center to center, and it also varies from person to person. However, recipients and families can generally expect to stay at the transplant center for at least three to six months before returning home. Allogeneic HSCT are generally performed in the hospital, but once recipients are healthy enough, they can be discharged from the hospital and return to the transplant clinic several times a week.

Pre-transplant Evaluations

Recipients typically have a large battery of tests and procedures done before transplant to make sure they are healthy enough to have a transplant. Healthcare providers may find hidden problems that need to be addressed prior to transplant, such as infections or organ function problems. Immunologists and transplant providers will typically order many blood tests as well as imaging studies, such as computerized tomography (CT) scans, ultrasounds, and/or magnetic resonance imaging (MRI). Special tests of kidney function will be done. The heart will be evaluated with an echocardiogram (ECG, EKG), an ultrasound of the heart. If recipients are old enough, pulmonary function testing will be done. Some may need procedures such as a bone marrow biopsy, lumbar puncture, bronchoalveolar lavage, or gastrointestinal endoscopy prior to allogeneic HSCT. All of these tests usually take a few weeks to complete.

Consent for Transplant

Before having a transplant, a recipient and/or family must give consent to proceed with the transplant. Members of the transplant team will meet with the recipient and/or family to go over the process and the risks and benefits in detail. Recipients and families should ask questions and be sure that they understand the proposed treatment before proceeding.

The Transplant

HSCT is different than organ transplants, for example of liver, lung, or kidney, in several ways. As mentioned before, the transplant itself is not a surgery, because the stem cells are given in the vein similar to a transfusion. Also, HSCT recipients need special preparation to receive the stem cells that solid organ patients don't need. The process of replacing the stem cells in the bone marrow requires an inpatient stay of about six to eight weeks. This inpatient stay is what most people think of as the transplant. After discharge, full recovery of the immune system to a normal immune system occurs as an outpatient, and is a process that takes many months, up to a year. Unlike solid organ transplant

recipients, HSCT recipients are able to wean off of immune suppressive medications if all goes well because the new immune system becomes accustomed or tolerant to the patient's body.

Most need a long-term central venous line placed prior to transplant. This ensures that venous access will be available for chemotherapy, stem cell infusion, medications, IV fluids, and lab work that will be done throughout the transplant process. It also avoids the need for repeated IV placement and venipuncture. Central lines are usually placed in large veins in the chest or neck, and recipients and parents can learn to take care of them.

What happens during the inpatient hospitalization can be thought of as similar to what happens if you replant a garden. If you imagine that the immune system is a garden that has weeds in it, instead of healthy plants, first you need to use some weed killer to get rid of the weeds. For stem cell transplant, the weed killer is what is called a conditioning regimen, in other words a combination of different medications to destroy the patient's own immune and bone marrow cells to prepare for receiving the donor stem cells. Conditioning regimens vary from center to center and from person to person. In general, conditioning regimens may consist of chemotherapy and serotherapy, and the regimen is given over many days prior to receiving the hematopoietic stem cells. Chemotherapy medications are given to essentially kill the recipient's own hematopoietic stem cells. This helps to make space in the bone marrow for the donor's stem cells to grow. Common chemotherapy agents include busulfan, fludarabine, melphalan, cyclophosphamide, and thiotepa, but other agents may be used. Serotherapy medications are antibody therapies, often monoclonal antibodies that are toxic to immune system cells. These agents can help prevent graft rejection, and they also help prevent GVHD. Common serotherapy agents include alemtuzumab and anti-thymocyte globulin. Different conditioning regimens have different intensities, which refers to how strong the chemotherapies are and how effectively they kill a person's bone marrow. Higher intensity regimens are very effective and are called myeloablative regimens. Lower intensity regimens, such as partial myeloablative regimens, may be less effective, but they are associated with fewer risks. The choice of conditioning regimen depends on each individual and the individual's diagnosis. In certain situations, conditioning may not be given. This is particularly true for some individuals with SCID and depends on the type of donor.

After the conditioning regimen is completed, the hematopoietic stem cells are given. The planned day of stem cell infusion is called Day 0. Stem cells are given through the central line like a blood transfusion. After Day 0, recipients typically remain in the hospital for several weeks while doctors wait for the new stem cells to grow. Similar to the garden analogy, once the weeds are gone, you can plant the seeds, but there is a period of time when the garden is empty because it takes time for the healthy plants to grow. During this time, there are no blood cells being produced by the bone marrow, so it is common to need blood and platelet transfusions. Recipients will be watched closely for any signs of infection, and they may need pain medicines, medicines for nausea, and fluid and nutrition support. Frequent blood tests will be performed to monitor for any signs of organ dysfunction. Most will receive medications to help prevent GVHD. These medications suppress the immune system. Common examples include cyclosporine or tacrolimus. Transplant teams will monitor the recipient's blood counts with a blood test called a complete blood count (CBC). When the stem cells start to work, the numbers of particular blood cells will start to rise; this is called engraftment. Once there are signs of engraftment, a special blood test will be done to determine what percentage of the cells are from the donor, called an engraftment or chimerism study. Once the blood counts recover to a safe level, recipients may be able to transition to outpatient care at the transplant center. Recipients will have a lot of oral medications, and many will need some IV medications, IV fluids, or IV nutrition during the early outpatient treatment phase. Home healthcare services, depending upon an individual's insurance coverage, may be utilized to help with these needs.

Early Transplant Complications

Allogeneic HSCT can have many complications. It is difficult to estimate the risks for each individual, but common complications are noted below.

Mucositis and Nausea, Vomiting, Diarrhea:

Chemotherapy can damage the lining of the mouth, throat, stomach, and intestines. This can be very mild or more problematic depending on the intensity of the conditioning regimen. Recipients may have ulcers, nausea, pain, vomiting, diarrhea, and sometimes bleeding. This improves as the blood counts start to recover a few weeks after transplant. Recipients may need pain medications, anti-nausea

medications, and nutrition and fluid support. These symptoms improve once the recipient engrafts with donor cells.

Graft Failure: If donor stem cells don't grow (primary graft failure) or don't last (secondary graft failure), a recipient is said to have graft failure. An individual will often have a second transplant if this occurs.

Graft Rejection: Sometimes graft failure is suspected to occur because a recipient's immune system attacked it. This is called graft rejection. An individual will often have a second transplant if this occurs.

Anemia: Recipients usually require blood transfusions early after transplant. After successful engraftment, the recipient changes blood type from their blood type to the blood type of the donor. Once the donor marrow is producing a good amount of red blood cells, the recipient will generally no longer need transfusions.

Bleeding: Recipients have low platelet counts and are prone to bleeding after transplant. They often receive platelet transfusions for several weeks after transplant to prevent bleeding. After successful engraftment, they generally no longer need transfusions.

Mixed Chimerism: If a donor's stem cells grow, but the recipient's stem cells also grow after transplant, an individual is said to have mixed chimerism. This will be evident on the engraftment study. Mixed chimerism is more likely to happen with lower intensity conditioning regimens. In general, mixed chimerism is okay for many individuals with many types of PI, as long as there are enough donor cells to keep the individual healthy. The level of donor cells needed and type of donor cells needed, depends on the disease for which that the individual was treated.

Acute Graft Versus Host Disease (GVHD): In the first few months after transplant, a donor's immune system may recognize a recipient's as being foreign, and mount an attack against the recipient's own tissues, just as it would fight an infection. For this reason, HSCT recipients take immune suppressive medicines for approximately six months after transplant to prevent GVHD. Sometimes despite the preventative medications, GVHD still occurs. The most common signs of acute GVHD are rash or diarrhea. It can also affect the liver or other organs. Acute GVHD can be mild or severe. It is usually treated with steroids and other immune suppressive medications.

Chronic GVHD: Chronic GVHD typically occurs later than acute GVHD and can last a long time. It can affect several organs including the skin, mouth, gastrointestinal tract, eyes, lungs, and genitourinary tract. It is usually treated with steroids and other immune suppressive medications.

Infections: Individuals with PI are prone to infections prior to allogeneic HSCT, but the risk goes up further with transplant. Recipients are monitored very closely for infections during and after transplant. Several anti-microbial medications are given to prevent infections, and Ig replacement therapy may be given regularly. Recipients are treated aggressively for any sign of infection. It is important that the recipient or caregivers call immediately if the recipient has a fever or other signs of infection after discharge from the hospital after undergoing an allogeneic HSCT.

Organ toxicity: Chemotherapy can damage organs such as the liver and lungs. Certain transplant medications can damage the kidneys. Organ function is another thing that will be closely monitored after transplant.

Transplant-associated thrombotic microangiopathy (TMA): TMA is characterized by injury to little blood vessels during or after transplant. This can lead to blood clotting in the little blood vessels and organ dysfunction.

Death: Even though transplant outcomes are now very good for most individuals with PI, survival is not 100%. As a gross estimation, chances of survival can be considered to be approximately 80% for most individuals with PI. However, if a matched (HLA) sibling is available as a donor, survival data is closer to almost 100%. Chances of survival may be higher or lower depending on several factors such as diagnosis, age, pre-existing complications, donor relation, and HLA match, as well as other variables.

Hospital Discharge

Once a recipient's donor cells are producing enough neutrophils and platelets to keep the patient safe, they may be ready for discharge. Recipients must not have fevers or bleeding, and they need to be able to take their medications as prescribed. Recipients and/or caregivers must be comfortable taking care of the central line, and they may also need to learn to give IV fluids, IV nutrition, and even some IV medications

outpatient. Once a recipient is discharged, they will usually come back to the transplant clinic several times a week for lab work, examinations, and infusions. Often recipients are discharged to housing that is close to the transplant center, particularly if their own homes are some distance away. Recipients can still develop complications after discharge, including infections, organ toxicities from medications, and GVHD.

By Day +100, some recipients are ready to return to their own homes and can usually just continue to follow up just with their local healthcare providers. Recipients often still need to take several medications for the first year after transplant, including immune suppressive medications to prevent GVHD. Until they have full recovery of immune cell numbers and are successfully weaned off of immune suppressive medications, they should still remain isolated. Neutrophils recover just a few weeks after transplant, but T cells require many months and B cells may take one to two years. Healthcare providers can do blood tests to see how an individual's immune system is recovering and make recommendations about when it is safe to stop isolation. Once the immune system is fully recovered, recipients should receive routine re-vaccination following transplant.

Long-Term Follow Up

By one to two years post-transplant, most recipients have good immune system recovery and do not need frequent follow up. It is generally recommended that an individual should return for follow up yearly or every other year, as this long term follow up is important to monitor them for late complications of transplant. These late complications are mostly related to the conditioning medications given to prepare the recipient for transplant, but they may also be related to organ damage caused by infection or immune dysregulation before the transplant. The severity and likelihood of late complications related to allogeneic HSCT is variable. Some complications include endocrine problems such as thyroid function, growth, or puberty issues. Fertility may be affected. Individuals who develop chronic GVHD need special long-term follow up. The transplant team can tell recipients and caregivers more about what long-term monitoring may be needed.

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Chapter 30
Gene Therapy

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Gene therapy may provide an alternative for those individuals with severe forms of PIs, who may be treated with Hematopoietic Stem Cell Transplantation (HSCT) from a haplo-identical parent or unrelated donor. These types of transplants may be complicated by a problem called graft versus host disease (GVHD) where the body tries to reject or fails to accept the new cells. In contrast, GVHD is not a problem after gene therapy because the individual is transplanted with their own Hematopoietic Stem Cells (HSC), negating the need for a HSC donor.

To add a normal copy of the gene, we take advantage of the ability of some viruses (retroviruses) to penetrate into cells and to insert their genes into the individual's own DNA. For the purpose of gene therapy, viruses have been modified so that their own genes have been removed and replaced with the normal copy of the human gene that is causing the PI. The genes carried into HSC by the virus are permanently in the stem cell's DNA and will be passed on to all of the blood cells made from the HSC, giving them the normal gene. The new gene does not go into other cells of the body besides the blood cells and will not prevent an individual from passing the disease gene on to their future offspring. Because PI is caused by gene defects that affect blood cells, this can be sufficient to treat the disease in the affected person. To directly fix genes that carry mutations, techniques have been developed to directly edit genes in human cells to repair mutations. Gene editing uses designer proteins, such as the CRISPR system, to find a single gene among the entire human genome in each cell, and modify that gene to correct a mutation causing PI. Gene editing in HSC has advanced to clinical trials for several conditions (such as HIV, thalassemia) and is coming to the clinic for several more conditions, including some types of PI, sickle cell disease, and other illnesses.

To perform gene therapy, the individuals with PI are both the donors and recipients—their own stem cells are collected, the gene is corrected in the cells, and then their cells are given back into them (by an intravenous infusion). HSCs are first isolated from their bone marrow or from their peripheral blood, and the cells are then cultured in the laboratory for a few days, usually with some growth factors to activate them. During this time, the gene is added or edited in the cells. The gene-corrected cells can then either be transplanted back to the individuals directly, or frozen and given back later. The cells that have the added gene or the fixed gene of interest in their chromosomes will pass it to all the cells that will be generated when these cells divide. Most gene therapy has used chemotherapy to support the engraftment of the corrected stem cells, but generally less chemotherapy is necessary for gene therapy than is needed for transplants from another donor.

Until now, gene therapy has been used to treat individuals with Severe Combined Immunodeficiency (SCID) secondary to adenosine deaminase (ADA) deficiency (ADA-SCID), X-linked SCID, X-linked Chronic Granulomatous Disease (XCGD), and Wiskott-Aldrich Syndrome (WAS). The first clinical trial of gene therapy was at the National Institutes of Health in 1990 and treated a 4-year-old girl with ADA-SCID. The design of this first trial did not attempt to correct the defective HSC, only the T cells. This girl is now clinically well and still has about 25% of her circulating T cells carrying the corrected ADA gene more than 20 years after her treatment. After this initial clinical trial demonstrated that gene therapy could be carried out safely and that gene-corrected T cells could survive for years and function normally, follow-up trials were initiated attempting to treat other children with ADA-SCID by targeting HSC from the bone marrow for gene correction. The results have been excellent, with most of the nearly 100 individuals with ADA-SCID attaining a significant long lasting increase of the T and B cell count and a remarkable improvement of immune function. Importantly, no episodes of serious adverse reactions have occurred in the individuals with ADA-SCID treated by gene therapy.

The next type of PI to be treated by gene therapy was X-linked SCID. These trials also targeted the HSC using a retrovirus to deliver the gene. Beginning

with a groundbreaking study in Paris followed by a similar experience in London, there were 20 babies with X-SCID treated with gene therapy. In these infants, gene therapy was performed without any chemotherapy prior to the transfusion of HSC that had been cultured with the virus. Eighteen of these individuals are currently alive. In 17 of these 18 children gene therapy alone was sufficient to restore development of T cells and immune function, and no other treatment was needed.

Unfortunately, while the X-SCID was corrected, six of these individuals developed leukemia as a complication of the retrovirus vector. Five of the children's leukemia was able to be treated, but one child died. More recent trials for X-SCID have used the next generation viruses designed to avoid the risk of leukemia and have led to similar immune benefits as in the early trials, but without any cases of leukemia to date.

Clinical trials of gene therapy for WAS and XCGD are ongoing. Gene therapy trials, using either viral addition or editing, are also ongoing or under development for individuals with other types of PI including: Artemis-deficient SCID, Leukocyte Adhesion Deficiency, RAG 1/2 deficiency SCID, X-linked Hyper IgM Syndrome (XHIGM), X-linked Agammaglobulinemia (XLA), Immunodysregulation-Polyendocrinopathy-Enteropathy-X-linked disease (IPEX), and more. One of the limitations of gene therapy, compared to HSCT from a related donor or tissue matched unrelated donor that can be used for any PI, is that gene therapy is a more personalized medicine and requires a specific virus or editing system to be developed for each different form of PI. Gene therapies have not yet been tested for more complex diseases like Common Variable Immune Deficiency (CVID) where all the responsible genes are not yet known, and there are many different genes that have been found among individual patients.

Overall, the growing experience with gene therapy for ADA-SCID, XSCID, WAS, and XCGD has demonstrated that it is possible to successfully treat PI by inserting a normal copy of the gene into the individual's HSC. Clinical trials are ongoing for many types of PI. It is likely that a larger number of types of PI will be treated by gene therapy in the future.

Chapter 31
Immunizations

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Overview

Vaccines have played a vital role in preventing infections within our society. Because of immunizations, common life-threatening infections, such as polio, smallpox, measles, mumps, and rubella, are now rarely seen in modern society. For individuals with primary immunodeficiency diseases (PI), vaccination remains an important defense against infections. Most people with PI are able to make normal responses to vaccines, and immunizations will help to protect them against infections that could be dangerous in the setting of their PI.

Immunizations are designed to produce immunologic memory so that the immune system can respond rapidly and neutralize an infection before it becomes harmful. In this process, routine vaccines are generally categorized into two types: nonviable and viable (live).

Nonviable vaccines can contain either fragments of microbes or whole microbes that have been fully inactivated. These vaccines cannot directly cause an infection. Examples include the immunizations against tetanus, diphtheria, whooping cough, Haemophilus influenzae (Hib), pneumococcus, and influenza (the injectable form of the vaccine).

Viable vaccines, on the other hand, contain weakened microbes that do not usually cause disease in healthy people. In individuals with various types of PI, however, these weakened microbes can sometimes cause significant illness. Examples of viable immunizations include the measles-mumps-rubella (MMR), oral poliovirus (OPV), rotavirus, yellow fever, intranasal influenza, the older zoster vaccine and chickenpox vaccines. The Bacille Calmette-Guerin (BCG) vaccine is another viable immunization that is not routinely used in North America. It is important to note that the OPV and BCG vaccines are contraindicated in most, if not all, types of PI. A new non-viable vaccine (Shingrix) for preventing shingles and the painful complications, such as postherpetic neuralgia, is available. It is not known how effective this vaccine is in people with PI. However, if the T cell function is mostly intact and the antibody immune deficiency is variable, such as in mild Common Variable Immune Deficiency (CVID), IgG Subclass Deficiency, or Selective Antibody Deficiency, etc., this vaccine may be of benefit.

Guidelines for Immunizations in People with PI

Because various types of PI can differ so vastly in terms of what part of the immune system is not working properly, decisions regarding the administration or withholding of various immunizations should always be made at the discretion of the clinical immunologist who is caring for the affected individual. Nonetheless, broad guidelines concerning immunizations in PI offer insights regarding what may be safe and beneficial. For the purposes of guidelines for immunizations, PI can generally be categorized into five broad groups. (See Table 31:1)

The first category consists of individuals with primary T cell defects and is subdivided into severe deficiency and mild deficiency. Severe Combined Immunodeficiency (SCID) and complete DiGeorge Anomaly fall into the severe classification, and all immunizations are contraindicated in affected children prior to correction of the PI by hematopoietic stem cell or thymic transplantation. Persons with mild or partial T cell deficiency, on the other hand, should receive all nonviable immunizations, although some may not be fully effective. Viable immunizations can be given, depending upon the degree of T cell deficiency, and special care should be exercised concerning administration of the chickenpox, herpes zoster, and MMR vaccines.

The second category includes people with primary B cell defects. It is further divided into severe deficiency and mild deficiency. X-linked Agammaglobulinemia (XLA) and Common Variable Immune Deficiency (CVID) are examples

of conditions that fall into the severe category, whereas IgA Deficiency and Specific Antibody Deficiency and Specific Antibody Deficiency serve as examples of mild B cell deficiencies. Children and adults with severe B cell defects cannot make antibodies to vaccines and will usually be receiving immunoglobulin (Ig) replacement therapy. Use of nonviable immunizations is therefore safe but may not be helpful, unless induction of T cell immunity is desired. Annual nonviable influenza immunization is recommended for that reason. Very little data is available to guide decisions to administer or withhold viable vaccines despite overall recommendations to avoid them. **It should be noted that antibodies in Ig replacement therapy can neutralize any immunizations, rendering them less effective.** For mild B cell defects, all immunizations can usually be given safely, although some may be less effective. In some individuals, healthcare providers may measure antibody titers to determine whether certain vaccines are necessary or likely to be helpful. For people with concerns about infections by bacteria covered with polysaccharides, combined testing is recommended for protective levels of antibodies to both the nonviable 23-valent polysaccharide pneumococcal vaccine and the nonviable Salmonella typhi polysaccharide Vi vaccine. All parties should be aware that different laboratories may measure the pneumococcal antibody titers differently, and results must therefore be interpreted cautiously. Children and adults who have difficulty making antibodies to polysaccharide vaccines should be administered the corresponding protein-conjugated forms of the immunizations, if available. The safety of rotavirus immunization has not been studied in this population, and administration of the OPV and BCG vaccines is contraindicated.

The third category encompasses individuals with phagocytic cell defects. Examples include Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), and Chediak-Higashi syndrome (CHS). Nonviable vaccines can be given safely in these conditions. Immunizations containing viable bacteria are contraindicated. The decision to use viable viral vaccines will depend upon the specific disease. For instance, individuals with CGD should receive viable viral immunizations, but certain viable viral immunizations may not be safe for individuals with LAD or CHS.

The fourth category involves persons with complement deficiency. Nonviable immunizations are recommended and may need to be administered more frequently than usual (every 3 to 5 years). A few viable vaccines are not recommended, but most viable immunizations can be given safely.

The final category consists of individuals with other defects in innate immunity. Nonviable vaccines can be given safely, although in some of these conditions, they may not be effective. Meanwhile, the safety and efficacy of viable immunizations will depend upon the specific condition and must be approached on an individual basis.

Importance of Immunization of Close Contacts

Of utmost importance, all close contacts surrounding individuals with, including household members, family members, and caretakers, should be immunized fully and regularly. They should be given all of the nonviable immunizations, especially the injectable influenza vaccine, in accordance with recommended schedules. Even viable immunizations (with the exception of viable influenza in individuals close to someone with SCID and OPV in all PI situations) should be kept updated. If signs of infection, such as skin blisters following chickenpox vaccination, appear in a close contact after immunization, the individual with PI may need to be temporarily isolated away from the contact and assessed by a healthcare provider. Nevertheless, this practice of immunizing close contacts protects the child or adult who has PI by decreasing the likelihood that they will become exposed to the microbes that cause disease in the community which can cause severe illness in the individual with PI.

Summary

Immunizations are strongly recommended and encouraged for the protection of people with PI. Nonviable immunizations cannot directly cause infections in any person. With a proper understanding of the type of PI an individual has, viable vaccines can be appropriately administered or withheld, depending upon the situation. Thus, most affected children and adults can be safely vaccinated. Lastly, immunization of people surrounding individuals with PI must be promoted and practiced to minimize their risk for infections.

Expert Recommendations for Common Immunizations in Patients with PI

Table 31:1

Vaccine	Primary defect						
	T cell function		B cell function		Phagocytic function	Complement	Other innate immune function
	Severe	Mild	Severe	Mild			
Nonviable immunizations							
Hepatitis B (HepB)	N	Y	N	Y	Y	Y	Y
Diphtheria, tetanus, acellular pertussis (DTaP)	N	Y	N	Y	Y	Y	Y
Haemophilus influenzae, type B (Hib)	N	Y	N	Y	Y	Y	Y
Pneumococcal conjugate (PCV13)	N	Y	N	Y	Y	Y	Y
Inactivated poliovirus (IPV)	N	Y	N	Y	Y	Y	Y
Inactivated influenza (IIV)	N	Y	Y	Y	Y	Y	Y
Hepatitis A (HepA)	N	Y	N	Y	Y	Y	Y
Meningococcal (MenACWY)	N	Y	Y	Y	Y	Y	Y
Human papillomavirus (HPV)	N	Y	Y	Y	Y	Y	Y
Pneumococcal polysaccharide (PPSV23)	N	Y	N	Y	Y	Y	Y
Zoster recombinant (RZV)#	N	Y	N	Y	Y	Y	Y
Viable immunizations							
Rotavirus (RV)	N	N	N	Y	*	Y	*
Measles, mumps, rubella (MMR)	N	*	N	Y	*	Y	*
Varicella (VAR)	N	*	N	Y	*	Y	*
Attenuated influenza (LAIV)	N	N	N	N	N	N	*
Zoster live (ZVL)	N	*	N	Y	*	Y	*
Bacille Calmette-Guerin (BCG)	N	N	N	N	N	Y	*

Y = recommended, N (shaded boxes) = not recommended, * = recommendation depends upon the specific immunodeficiency, # - Shingrix zoster vaccine

Chapter 32

Autoimmunity in Primary Immunodeficiency

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The immune system is a complex set of organs, cells, proteins, and other substances. Primary immunodeficiency diseases (PI) are characterized by abnormalities in these substances that can lead to an increased susceptibility to infection. Many times, abnormalities in the immune system that lead to PI also cause immune dysregulation, which is an immune response that is not properly controlled or restrained. One form of immune dysregulation is called autoimmunity, in which the immune system is misdirected to attack normal parts of the body such as cells, tissues, or organs.

Definition

A normal immune system makes proteins known as antibodies. Antibodies recognize, prevent, and resolve infections in the body. Autoimmunity occurs when the immune system makes antibodies against itself—these are known as autoantibodies. Sometimes people with PI cannot make "good" antibodies to protect against infection but make "bad" autoantibodies, which then cause autoimmune disease.

Medicines that suppress the immune system (and therefore shut down the inappropriate immune response) are used to treat autoimmune conditions. Immune suppressive medications, however, may also suppress the "good" antibodies as well as the "bad" autoantibodies. Additionally, some immune suppressant medications can also decrease the number of types of white blood cells. These side effects of immune suppressive medications may result in an increased chance of developing a serious infection. Managing the good effects and the side effects of immune suppressant medications in an individual who has an underlying immune deficiency can be complex, as the goal is to avoid infections while still controlling the autoimmune disease. It is best to use a team approach when using immunosuppressive treatment, joining the skills of the immunologist with the appropriate specialist, which may include gastroenterology, rheumatology, pulmonology, endocrinology, nephrology, dermatology, and/or hematology.

Autoimmune complications have been reported in a wide range of types of PI. Certain types of PI have autoimmune disease as their primary problem. Examples include Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dysplasia (APECED or APS-1); Autoimmune Lymphoproliferative Syndrome (ALPS); and Immune dysregulation, Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome.

Some others are frequently associated with autoimmune complications. Examples include Common Variable Immune Deficiency (CVID), Wiskott-Aldrich Syndrome (WAS), IgA deficiency, Good Syndrome, Hyper IgM Syndrome, Idiopathic T-cell Lymphopenia (ICL), and Complement Deficiencies.

Rather than great detail on the previously mentioned diagnoses, the focus here is to provide an overview of the types of immune dysregulation and autoimmunity that can occur in various types of PI.

Autoimmune Cytopenias

The development of autoantibodies that bind to and destroy blood cells is the most common autoimmune disease seen in PI. The blood cells affected include the red blood cells (RBCs), platelets, and white blood cells (WBCs). Cytopenia is the general term used to describe low numbers of blood cells.

Red Blood Cells

The RBCs carry oxygen to the body's tissues. Oxygen is necessary for the body's tissues to perform their functions. Anemia is the term used to describe a low number of RBCs. Autoantibodies against RBCs can cause destruction of these cells. This destruction is called autoimmune hemolytic anemia (AIHA).

Symptoms associated with AIHA include fatigue, headache, dizziness, fainting, and a decrease in the ability to exercise. The person sometimes looks pale. In severe cases, the individual can develop a yellow discoloration to the skin and eyes, known as jaundice. The spleen may become enlarged as it traps the damaged red blood cells. The body tries to compensate for the decreased capacity to carry oxygen by working the lungs and heart harder.

Platelets

Injuries to the tissues can cause bleeding. Platelets help create blood clots to stop bleeding. A low number of platelets is called thrombocytopenia. When autoantibodies are formed against the platelets and cause thrombocytopenia, it is known as idiopathic thrombocytopenic purpura (ITP). ITP can cause abnormal bleeding. Individuals frequently notice increased bruising, sometimes in unusual areas or without known trauma to the area. They may develop a pinpoint red rash caused by small hemorrhages called petechiae. They may notice nosebleeds that are more frequent and difficult to resolve. The gums may bleed easily. The urine may have an orange, pink, or red color. Stools may appear black and look like tar, which can indicate bleeding in the intestinal tract. Rarely, bleeding in the brain can cause altered mental status or death.

White Blood Cells

There are many different types of WBCs. Neutrophils are WBCs that have a major role in responding to infections. A low number of neutrophils is called neutropenia. Autoimmune neutropenia (AIN) occurs when antibodies are produced against neutrophils.

One of the most important symptoms associated with AIN is fever, as this may indicate a serious infection. Other signs of infection such as coughing, vomiting, diarrhea, and rash may also be present. Serious infections can progress rapidly in people with AIN, and they may require evaluation in the emergency room or admission to the hospital. Antibiotic therapy is urgently needed in these cases. Individuals with AIN may also have ulcers or sores develop in the mouth, esophagus, or intestine. The gums may also become inflamed and red.

Diagnosis of Autoimmune Cytopenias

Autoimmune cytopenias are diagnosed with blood tests. Typically, a complete blood count (CBC) is the blood test performed to establish the presence of a cytopenia. A CBC is a test that measures the number of red blood cells, different types of white blood cells, and platelets in the bloodstream. Additional blood tests can determine if an autoantibody is present. A specialist such as a clinical immunologist, hematologist, or oncologist typically evaluates individuals for these disorders. Sometimes a bone marrow sample needs to be obtained to determine if there is a problem with production of blood cells.

Treatment of Autoimmune Cytopenias

Autoimmune cytopenias may be temporary and require little to no treatment. If treated, the goal of therapy is to remove the autoantibodies and let the body replenish the blood cells. Several treatments have been used including intravenous immunoglobulin (IVIG) replacement therapy, steroids, chemotherapy drugs, and other immune suppressive drugs. The therapy that is best for a particular patient is based on many factors. Autoimmune cytopenias often respond well to therapy. At times, however, symptoms may recur or may require long-term treatment. Individuals rarely require blood transfusions except in extreme circumstances. In all cases, individuals with cytopenias require close follow-up by their specialist.

Most individuals can be treated successfully and have no major restrictions on their daily activities. Individuals with platelet counts that remain low, however, may have to refrain from activities with a higher risk of injury, such as contact sports.

Autoimmune Lung Disease

There are multiple causes of lung disease in individuals with PI including infection, malignancy, and autoimmunity. Differentiating between these can be difficult. In most cases of lung disease, the autoimmunity is not due to formation of an antibody, but an abnormal accumulation of white blood cells in the lung tissues, causing inflammation and damage. Sometimes white blood cells accumulate in a specific part of the lung known as the interstitium, which is the site where oxygen is taken up from the lung to the bloodstream. Too many white blood cells in the interstitium can cause a disease called interstitial lung disease, in which the ability of oxygen to be absorbed into the bloodstream is impaired.

Some individuals with certain types of PI develop clusters of immune cells in the lung, called granulomas. Granulomas are sometimes formed in an attempt to contain an infection that cannot be resolved, or because the immune cells are not being regulated properly, a situation that sometimes occurs in PI. Two types of PI that often have granulomas in the lung are Chronic Granulomatous Disease (CGD) and CVID. Individuals with CVID sometimes develop both interstitial lung disease and granulomas in the lung. This disease is called Granulomatous Lymphocytic Interstitial Lung Disease (GLILD). Recent studies show GLILD can also occur in other rare forms of PI that are similar to CVID. Occasionally, individuals with Ataxia-Telangiectasia and APECED will develop a different type of interstitial lung disease, which can also decrease the ability of the lung to absorb oxygen. Without proper treatment, the inflammation caused by interstitial lung disease can be so severe that it will cause scarring (fibrosis) of the lung and permanently impair the ability of the lung to absorb oxygen.

Symptoms of Autoimmune Lung Disease

In most cases, the symptoms of interstitial lung disease develop slowly over time. Individuals with CGD can develop symptoms more quickly due to an infection causing lung inflammation. Individuals may notice a decrease in their endurance with every day activities. They may find themselves having to cut back on exercise, such as biking or running. These changes are often attributed to other causes, which may delay the diagnosis of the lung disease. Individuals often complain of a cough, which is usually non-productive. Enlargement and rounding of the toenails and fingernails, termed clubbing, is not specific to PI or to lung damage, but they are a clue that the lungs should be evaluated. In some cases, the lung damage can lead to a severe lowering of blood oxygen causing individuals to have a bluish tint to their skin or mucous membranes. This is known as cyanosis. Fever is not a typical finding, unless infection is also present. On the lung exam, a practitioner may hear abnormal breath sounds such as crackles, wheezes, or a decrease in the amount of air moving in and out of the lung with breathing. Often these symptoms lead to the incorrect diagnosis of asthma or a lung infection by physicians not familiar with autoimmune lung diseases in PI.

Diagnosis of Autoimmune Lung Disease

Chest X-rays are useful for diagnosing infections (pneumonia). A chest X-ray can sometimes be normal, however, even when there is still significant lung disease present. A chest CT scan is a much better test to detect lung abnormalities even when the chest X-ray is normal. In individuals with CVID and GLILD, changes on the chest CT scan will often appear before the patient has symptoms.

Breathing tests, called pulmonary function tests (PFTs), can demonstrate how well the lungs are working. Changes in PFTs can be found in interstitial lung disease and other types of lung disease. However, individuals often must lose a significant amount of lung function to show symptoms that lead to ordering of the PFTs.

In some cases, a lung biopsy is needed to make the correct diagnosis and define the correct treatment course. A lung biopsy is a surgical procedure usually done by making a small incision in the chest and inserting a small scope and instruments to obtain a piece of lung tissue. The lung biopsy is evaluated by a pathologist, a doctor who performs a variety of tests on the lung tissue including a microscopic examination. The tests performed by the pathologist can determine the specific type of lung disease that is present, such as cancer, infection, interstitial lung disease, granuloma.

Treatment of Autoimmune Lung Disease

Individuals with cancer are referred to an oncologist (cancer doctor) for continuing care. Individuals with infections are treated with antibiotics. Inflammatory changes in the lung are usually treated with drugs that suppress or alter the immune system. The

most common medicine used is corticosteroids (like prednisone), which can be given through an inhaler, by mouth, or intravenously (IV). Steroids can be effective but may not provide long-term improvement. Steroids can cause side effects such as high blood pressure, high blood sugar, osteopenia (weak bones), hyperlipidemia (high cholesterol), and stress on the kidney and eyes if used for a long period of time. Other immune suppressive medicines, such as cyclosporine and sirolimus, are sometimes helpful. Some types of lung disease respond to one type of immunosuppressant medication but not another. IVIG, in addition to other drugs, can sometimes improve the inflammation in the lungs.

Without treatment, interstitial lung disease can progress and cause permanent lung damage. Fibrosis, cannot be reversed. It is very important that your doctor has the correct diagnosis of your specific lung disease and expertise in treating the disorder in order to insure the best outcome.

Autoimmune Skin Disease

Skin conditions due to autoimmunity or immune dysregulation can be seen in individuals who have PI. Common skin conditions like eczema or psoriasis are also seen in people with normal immune systems as well. Sometimes, skin disease is one of the earliest symptoms of a PI and can lead to further testing to identify an immune deficiency. In addition to skin disorders that are autoimmune or inflammatory in nature, other abnormal skin symptoms, such as dry, sparse hair; abnormally formed teeth and fingernails; and absent sweat glands, can be seen in certain types of PI but are not due to autoimmunity. These will not be covered in detail here.

Eczema

Eczema, also known as atopic dermatitis, is generally a mild skin disease and is the most common skin disease in PI. Often referred to as "the itch that rashes," eczema typically begins as patches of dry, itchy skin that worsen and erupt into rash as they are scratched. It is not unusual for individuals with PI who have other autoimmune manifestations to also have eczema. Some types of PI are, however, associated with more severe eczema. Examples include WAS, Hyper-IgE Syndrome (HIES), IPEX syndrome, and certain forms of Severe Combined Immunodeficiency (SCID). In these disorders, the eczema may be difficult to treat with the usual therapies.

Psoriasis

Psoriasis is another type of autoimmune skin disease that may be confused with eczema. The typical rash in psoriasis are called plaques and may appear as red, raised, itchy, and painful. These lesions have a silvery scale on the surface of the plaques that often bleeds if it is removed. Plaques of psoriasis occur most frequently on the scalp or on the elbows or knees. Psoriasis can occur in a number of types of PI.

Hair and Skin Pigmentation Changes

Multiple types of PI can have autoimmunity that affects the hair and skin coloring (pigment). Some individuals develop alopecia, or patches of baldness, as a result of autoantibodies against hair producing cells. Alopecia areata refers to round circular areas of hair loss. Some individuals also develop vitiligo, or loss of the pigment in the skin. The affected area of skin will appear white in color. The contrast of the surrounding skin will determine how apparent the change is. The affected areas often change somewhat over time. Vitiligo and alopecia are most commonly associated with APECED, CVID, IPEX, and genetic disorders such as 22q11 deletion (Di-George) syndrome, although they can develop in a wide range of PI.

Diagnosis of Skin Diseases

Most of the time, a knowledgeable healthcare provider can diagnose skin disorders just by physical exam. If a rash is unusual, however, a skin biopsy is sometimes needed to determine the type of rash. Biopsies are typically taken from the area where the rash is most evident using a sharp punch that cuts and removes a small circular piece of skin tissue. A pathologist will look at the specimen under a microscope to determine the type of rash. This is typically a very minor procedure that can be done in the office with local numbing of the skin.

Treatment of Skin Diseases

While not typically life threatening, autoimmune and inflammatory disorders of the skin can lead to significant emotional distress and in rare situations can lead to permanent changes in appearance.

Severe rashes, like eczema, may serve as an entry point for bacteria and other organisms to enter the bloodstream due to the breakdown in the skin barrier.

Mild skin conditions can be diagnosed and treated by a primary care provider or an immunologist, but more severe skin conditions often require diagnosis and treatment by a dermatologist. Treatment for most conditions typically begins with local application of moisturizing lotions and steroid ointments directly to the rash. If this is not sufficient to control the symptoms, stronger steroid creams or other immunosuppressant medications can be applied. In rare cases, immunosuppressant medications may be needed to treat severe disease.

Autoimmune Gastrointestinal Disease

Autoimmune gastrointestinal diseases refer to problems in the mouth, esophagus, stomach, intestines, and liver. These are common among individuals with PI, particularly individuals with CVID, CGD, IPEX, X-linked Agammaglobulinemia (XLA), APECED, WAS, Omenn syndrome, NEMO deficiency, and others. This is likely due to the fact that the intestines are constantly exposed to bacteria, other organisms, and food, which all have the potential to cause irritation in the stomach and intestines. The immune system plays an important role in protecting the body from invasion by the bacteria present in the bowel.

Mucosal Changes

Autoimmune or inflammatory diseases of the gastrointestinal tract can break down the mucous membranes that line the mouth, esophagus, stomach, and intestines. This can cause a variety of symptoms including: geographic tongue, an abnormal appearance of the tongue that can be mistaken for an oral yeast infection (thrush); gingivitis or inflammation of the gums; oral ulcers or canker sores; abdominal pain; diarrhea that may be watery or bloody; an urgency to stool after eating; and weight loss despite a reasonable diet. Similar symptoms can also be present in individuals with PI who have bowel infections with organisms such as Giardia, Cryptosporidium, rotovirus, norovirus, or Clostridium difficile. Because both autoimmune and infectious complications can lead to serious problems in individuals with PI, it is important that new gastrointestinal symptoms be evaluated when they occur. In rare cases, persistent gastrointestinal symptoms can be a sign of cancer in the bowel, which is more common in some types of PI than in the general population.

Liver Inflammation

The liver is part of the gastrointestinal system and plays many important roles in the normal function of the body. Among the most important roles of the liver are:

- Breakdown of nutrients absorbed from the intestines
- Production of important blood proteins, such as clotting factors
- Processing of certain medications
- Removal of waste products from the blood
- Excretion of these into the bile

Autoimmune or inflammatory disease of the liver, which can occur in PI, can cause temporary or permanent damage that can alter one or more of the liver's important functions. This may lead to accumulation of fluid in the abdomen (ascites), elevated bilirubin in the blood leading to jaundice, blood clotting abnormalities, etc.

CVID and CGD are among the types of PI most commonly associated with autoimmune or inflammatory liver disease, but this has also been observed in APECED, IPEX, X-linked Hyper IgM syndrome, and others. Certain infections, such as Hepatitis (A, B, or C), Cytomegalovirus (CMV), and Epstein Barr virus (EBV) can also cause severe liver inflammation and damage. Symptoms of infection and autoimmunity can be similar, so individuals should always be tested for these specific infections as treatment of infection and autoimmunity will be different.

Diagnosis of Gastrointestinal Disease

The diagnosis of gastrointestinal disorders in PI often requires a combination of approaches. Individuals will undergo a physical exam, laboratory tests on blood and stool, and radiology tests. Physical exam findings may include oral or anal ulcers, abdominal tenderness, fluid in the abdomen (ascites), enlargement or tenderness of the liver, cracks or fissures around the anus, weight loss, and poor growth for children.

Laboratory tests include a complete blood count and an examination of the stool to determine whether the individual may be losing blood through the stomach or intestines. Lab tests will measure inflammation with a C reactive protein (CRP) and erythrocyte

sedimentation rate (ESR); albumin and pre-albumin levels as a rough measure of nutritional status; and AST, ALT, and Bilirubin levels as a measure of liver irritation. To evaluate for a bowel infection, testing of the stool is performed to identify bacteria or viruses. Samples of stool are also stained and evaluated under the microscope for the presence of specific parasites or other organisms.

Radiologic tests that may be helpful include an abdominal X-ray, abdominal and liver ultrasounds, and a CT scan of the abdomen after contrast material has been swallowed. Sometimes the only way to make a diagnosis of either bowel or liver inflammation is to obtain a piece of tissue that can be evaluated under the microscope by a pathologist. For certain conditions, the physician may want to pass a scope into the esophagus, stomach, and intestines to directly see those areas. They may also perform biopsies and other tests in the liver. This is done by obtaining a small piece of liver tissue with a biopsy needle inserted through the skin and into the liver. Both of these procedures are typically done by a gastroenterologist, a doctor who specializes in the treatment of intestinal disorders.

Treatment

In general, immunosuppressant medications are used to treat autoimmune or inflammatory disorders of the bowel in most individuals with PI. The treatment plan has to balance the risks of the treatment against the risks of the disease. It may be helpful to work with a nutritionist to provide advice about an appropriate diet and vitamins. In some cases, including the bowel disease associated with CVID or CGD, steroids are often the first line of therapy, and in many cases, they may be sufficient to control symptoms. In contrast, the severe bowel disease associated with IPEX syndrome or Omenn syndrome typically requires stronger immunosuppressive medications. For individuals with PI who have significant gastrointestinal symptoms, it is essential to have a gastroenterologist involved to assist with diagnostic testing and directing treatment.

Autoimmune Kidney Disease

The kidney is made up of a large number of tiny filtration units. Each unit is called a glomerulus. The job of the kidney is to remove waste products and control fluid balance. The most common form of autoimmune kidney disease in PI is called glomerulonephritis, which is inflammation and destruction of the glomerulus units. This leads to decreased kidney function which can worsen over time if not treated. Glomerulonephritis is often seen in individuals with complement deficiencies, particularly complement components C1, C2, C3, or C4. Autoimmune kidney disease can also be seen less commonly in other PI including CVID and APECED.

Symptoms of Autoimmune Kidney Disease

In many cases, the first sign of autoimmune kidney disease is elevated blood pressure. The affected individual may have blood or protein in the urine. With glomerulonephritis, blood in the urine may not appear pink, but instead it is more likely to cause the urine to have a color closer to that of tea or cola. Blood and protein are easily detected in the urine using test strips that are frequently called urine dipsticks. If there is a large amount of protein loss in the urine, it can lead to fluid retention and swelling (edema) of the legs and feet.

Diagnosis of Kidney Complications

When kidney disease is suspected, common blood tests are helpful to determine if the kidneys are not working properly. Evaluation of the urine for the presence of blood, protein, inflammatory cells, and electrolytes is also typically performed. In many cases, a kidney biopsy is needed to make the correct diagnosis and define the correct treatment course. A kidney biopsy is usually done by inserting a biopsy needle through the skin and into the kidney to obtain a small piece of tissue, which is then evaluated by a pathologist, who performs a variety of tests on the kidney tissue, including a viewing under the microscope.

Treatment of Autoimmune Kidney Disease

Individuals with autoimmune kidney disease are often referred to a nephrologist (kidney doctor) for evaluation and management of the kidney problems. Blood pressure medications are typically prescribed to manage the elevated blood pressure, and immunosuppressants are used to control the autoimmune process.

Autoimmune Endocrine Disease

The endocrine organs secrete hormones that play important roles in maintaining basic body functions. The major endocrine organs include the pituitary gland in the brain, the thyroid and parathyroid glands, the pancreas, the adrenal glands, and the gonads (testicles or ovaries). Autoantibodies against endocrine organs can cause significant health problems. Individuals who have endocrine autoimmunity are often referred to an endocrine specialist (endocrinologist) for evaluation and management.

Thyroiditis

The thyroid gland secretes thyroid hormones, which play an important role in maintaining the metabolic rate of the body. Individuals with hypothyroidism (abnormally low thyroid hormone levels) typically gain weight, have a slow heart rate, feel cold and fatigued, are constipated, and have coarse hair and stiffening in the skin. In contrast, individuals with hyperthyroidism (abnormally high thyroid hormone levels) typically lose weight, have a rapid heart rate, feel hot and energetic, and have thin hair. Autoantibodies directed against the thyroid can cause either hypothyroidism or hyperthyroidism. Autoimmune thyroid disease is the most common autoimmune disease among the general population. In certain types of PI, including CVID and IPEX syndrome, the incidence is even higher.

Diagnosis of thyroid autoimmunity is typically made by a series of blood tests. Hypothyroidism is treated by taking supplements of thyroid hormone. Hyperthyroidism often has to be treated by decreasing the thyroid's ability to make thyroid hormone. This may require surgical removal of part of the thyroid, radiation treatment to the thyroid gland, or use of other drugs. This is always done under the direction of an endocrinologist.

Diabetes

Diabetes (abnormally elevated blood sugar levels) can be caused by not making enough insulin (Type 1), or the body's cells cannot use the insulin properly (Type 2). Type 1 diabetes (T1D) is caused by autoantibodies against the islet cells in the pancreas that produce insulin. Once islet cells are destroyed, they do not recover. When the number of islet cells producing insulin drops to a low level, individuals develop diabetes. T1D is very common in some PI such as IPEX syndrome where it occurs in approximately 70% of individuals. Incidence is also higher in other PI, including IPEX, CVID, APECED syndrome, and others.

T1D is typically diagnosed by checking the urine for the presence of glucose (sugar) and checking the blood for elevated glucose levels. If these do not decrease as expected after eating or if they are high even when a patient is fasting, then diabetes may have developed. Identification of autoantibodies directed against the islet cells can help confirm that the process is autoimmune.

Treatment of T1D typically involves giving insulin either via shots or an insulin pump. Even though T1D is autoimmune mediated, it is not yet clear whether the use of immunosuppressive drugs early in the course of disease will change the need for insulin treatment or not.

Other Autoimmune Endocrine Disorders

The parathyroid gland controls calcium levels in the body. Autoimmunity against this gland is rare, but can be seen in APECED syndrome. The parathyroid gland can be underdeveloped in some syndromes such as DiGeorge or CHARGE syndrome.

Diagnosis of Endocrine Complications

As mentioned previously, diagnosis of endocrine complications revolves around identifying abnormal levels of specific hormones in the blood or in measuring abnormal electrolyte or glucose levels in the blood. The identification of specific autoantibodies in the blood is helpful in confirming that the process is autoimmune in nature.

Treatment

In general, most autoimmune endocrine disease leads to a deficiency of very important hormones that are supposed to be made by the endocrine organs. Treatment typically involves administering replacement hormone to try and achieve normal levels. In the case of the thyroid, autoimmunity can also cause increased function, which requires removal or destruction of at least part of the gland to correct the problem.

Autoimmune Musculoskeletal Disease

Arthritis (inflammation of the joints) is a common problem in the general population. Arthritis can either occur as a result of wear-and-tear on the joints (osteoarthritis) or as a result of autoimmune attack of the joints (as in rheumatoid arthritis). There is no evidence that the incidence of osteoarthritis is

higher in individuals with PI, but some types of PI are associated with a higher incidence of certain autoimmune arthritis syndromes.

For example, both DiGeorge syndrome and Selective IgA Deficiency have been associated with an increased risk for developing Juvenile Idiopathic Arthritis (JIA), a type of arthritis that affects children. Approximately 20% of individuals with XLA develop arthritis at some point, although it is often usually mild and temporary. In contrast, individuals with CVID can develop rheumatoid arthritis or psoriatic arthritis (a type of arthritis that often accompanies psoriasis – see previous Autoimmune Skin Disease section). These can cause significant pain and limitation of daily activities and can lead to permanent damage to the joint.

Unlike arthritis, myositis (inflammation of the muscles) is relatively uncommon in PI.

Symptoms of Autoimmune Musculoskeletal Disease

Typical signs and symptoms of arthritis include pain and stiffness of the joints, joint swelling, and sometimes warmth or redness over the joints that have arthritis. The stiffness is often worse after not moving the joint, for example in the morning after sleep or after resting, and often improves somewhat with activity. When the arthritis is active and flaring, individuals may also have fevers, feel fatigued, and may have decreased appetite.

Diagnosis of Musculoskeletal Complications

A physical exam by an experienced healthcare provider is extremely helpful in diagnosing arthritis. Individuals are often referred to an arthritis specialist (rheumatologist) for evaluation.

Blood tests can help to determine whether there is ongoing inflammation. Measurement of specific autoantibodies in the blood can also be helpful for making a diagnosis. Radiology tests including X-rays, CT scans, and MRI scans of inflamed joints can be helpful in determining if there is ongoing inflammation and whether the joint has signs of damage from the arthritis. Sometimes, obtaining a sample of the fluid from inside the joint for testing can be helpful in making a diagnosis and ruling out infection in the joint. This is typically done by withdrawing the fluid from the joint with a needle and syringe.

Treatment of Autoimmune Musculoskeletal Disease

Treatment of arthritis often requires the use of immunosuppressants. Steroids like prednisone are among the most commonly used. These can be given by mouth, injected into the blood through an IV, or injected directly into the inflamed joints. They are often very effective for a time but may not provide a long-term effect. To improve the chances for control of the arthritis, other non-steroid drugs are often added. Since giving immunosuppressant medicines to a person with PI may suppress their immune system even more, making them more susceptible to certain types of infections, these treatments often need to be coordinated between an immunologist and a rheumatologist.

Expectations for Autoimmunity in Primary Immunodeficiency Diseases

Significant autoimmune or inflammatory disease is common among individuals with PI. Early recognition and treatment of these symptoms is critical for optimizing quality of life and decreasing complications associated with PI. This requires that individuals and their healthcare providers be aware of signs and symptoms that may suggest an autoimmune disease, and that appropriate diagnostic testing and treatment be initiated in a timely fashion. Maintaining a balance between the immunosuppression used to control the autoimmune process while avoiding compounding the defects of the underlying PI, requires close cooperation between the individual with PI (and/or their caregiver) and the various specialists involved in their care. Treatment may require frequent dosage adjustments or changes in overall approach to reach the desired balance.

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Chapter 33

Supplemental, Complementary, and Alternative Medicine in Primary Immunodeficiency

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Complementary and alternative medicine (CAM) has been gaining popularity in Western culture as the list of conventional therapies for primary immunodeficiency diseases (PI) is limited relative to other medical conditions. Benefits and risks of these kinds of therapies are mostly anecdotal or theoretical, with little to no well-designed clinical trials existing to support their use. Use of these kinds of therapies should be discussed with an individual's healthcare provider. It must be remembered that they are to be used as complementary—in addition to, not as an alternative to conventional medicine.

Introduction

There are over 350 different types of PI that interfere with the body's immune system. These deficiencies can be attributed to the improper functioning or absence of a required component of the immune system. Medications offered by your health care provider are frequently aimed at enhancing the protection against infections that occur in these immune deficiencies. Depending on the type of PI a person has, medications may be part of everyday treatment. For example, people with Chronic Granulomatous Disease (CGD) take protective antifungal and antibacterial medications every day. People with some antibody disorders, like X-linked Agammaglobulinemia (XLA), require immunoglobulin (Ig) replacement therapy. In the US, the Food and Drug Administration (FDA) requires that all prescribed medications be rigorously tested before they are approved for use. This process often requires years of research and development. But once approved, this process allows the prescriber to understand the risks and benefits of the drugs, and they can then prescribe them based on this understanding, what is called evidence-based decision making.

CAM therapeutic modalities, such as Traditional Chinese Medicine (TCM), Ayurvedic medicine, acupuncture, yoga, chiropractic medicine, and massage therapy, continue to gain widespread popularity in the U.S. and throughout the global economy due to their perceptive impact on immune health. CAM is viewed as a group of diverse medical and health care systems, practices, and products that are not generally considered part of the conventional allopathic (Western) medical practices. Complementary medicine commonly signifies "in addition to" rather than "a substitute for" clinical interventions used with conventional allopathic medicine. On the other hand, alternative medicine is occasionally used in place of conventional medicine. This is a distinction reflected by the National Institutes of Health—National Center for Complementary and Alternative Medicine (NCCAM).

The use of CAM is gaining interest in Western countries because of its reputed effectiveness, low cost, and favorable safety profiles. People are often interested in CAM therapy for chronic conditions either because they are unsatisfied with conventional therapies or because they have

concerns regarding side effects of synthetic drugs. Here, the use of supplements as part of CAM therapies will be addressed.

Supplements

Supplements are part of CAM therapies. They include vitamins, herbals, pro-biotics, and fish oils. It is important to recognize that supplements are not held to the same standard as conventional medicines. They are not regulated by the FDA. Accurate and reliable information on different supplements is hard to find, and recommendations are often based on personal beliefs and experiences rather than evidence obtained from well-designed studies as with conventional medicines. For this reason, all of the different ways in which a supplement acts on the body is often not known. Although some products are thought to stimulate the immune system based on observations in healthy volunteers or in animal studies, it is not known if the desired effects will be seen in people with PI. It is also not known what the supplements effect will be on other drugs an individual may be taking or other diseases a person might have.

Daily multivitamins are marketed as a way to ensure one gets all the minerals and vitamins needed to remain healthy. Daily supplementation is often excessive as most people get all the vitamins and minerals they need from their diet. Short of the cost, there is often no harm in taking one or two of these a day. However, there is no literature to suggest daily supplementation with a multivitamin improves immune function in people with PI. Vitamin A (retinol), vitamin B6 (pyroxidine/pyridoxal phosphate), and vitamin E are naturally found in many foods and are thought to play a vital role in supporting a healthy immune system. However, there are no studies to suggest there is any benefit to excess supplementation in people with PI.

Additional supplements include L-arginine and zinc. L-arginine is a building block (called an amino acid) that is needed to make proteins in your body. A person gets it from eating red meat, fish, poultry, and dairy. There are conflicting studies regarding whether or not taking L-arginine stimulates immune function in people with secondary immunodeficiencies (such as HIV). However at this time there are no studies suggesting it may be beneficial in people with PI. Zinc is a mineral that is involved in many physiologic processes in the body. There is debate regarding whether or not supplementation is beneficial or harmful in people with secondary immunodeficiencies. However, there are no studies that look at the effect of excess zinc supplementation on immune function in individuals with PI.

Herbal supplements are plants used in traditional healing practices that are believed to have medicinal properties. Their proposed benefits are often well advertised despite not being backed by evidence gathered from well-designed clinical trials. Complicating the studies that do exist are questions regarding herbal potency and quality (chemical content). For example, how much does the strength of a supplement vary from pill to pill? Unfortunately, the possible harms are not typically advertised as manufacturers are not required to do so. Reporting of adverse effects linked to supplements is voluntary and very difficult to prove. For example, there are no standard lab tests for herbal blood levels a doctor can order. Thus there is very little known about how these supplements interact with drugs and diseases.

There are many herbs that are currently advertised as able to boost immunity. These include astralagus, ashwagandha, cat's claw, echinacea, goldenseal, and European mistletoe. There is presently no research to support their use in people with PI. However, they are often well tolerated when used in small amounts. It is important to know there are no studies on optimal dosing. This is important because some supplements, such as astralagus, may cause immunosuppression in larger doses.

Fish oil, obtained by supplements or by eating fish, contains fatty acids that have been shown to lower triglyceride levels. Fish oil is typically tolerated well, with common side effects being belching and odorous breath. However, like astralagus, there is some data to suggest mega doses of fish oil may cause suppression of the immune system.

A growing trend over the past decade has been the supplementation of probiotics. The idea is that the human gastrointestinal tract is made up of hundreds/thousands of strains of known bacteria and some unknown that all compete for nutrients and space to grow. "Good" bacteria help with tasks ranging from the breakdown of food to preventing bad bacteria from making a home in the gastrointestinal tract. Probiotics are bacteria that are considered beneficial to their host. Some foods, such as yogurt and cheese, naturally contain these bacteria. Probiotics have been well-studied for certain allergic and infectious indications, and have been found useful in preventing antibiotic-associated diarrhea. However, they have been implicated in severe bloodstream infections in individuals with inflammatory bowel

disease. Although the bacteria used in probiotic supplements are considered to be safe, theoretical concerns have been proposed regarding probiotic safety in people with PI. There are a few case reports where probiotics have harmed individuals with PI.

Conclusion

When considering supplement use, it is important to remember that most have not been studied as being possible therapeutic options for people with PI. Some products may have absolutely no clinical evidence behind them and their proposed benefit to the immune system is theorized based on laboratory observations. Risks of supplement-drug and supplement-disease interactions are for the most part unknown. High-quality studies are needed to better understand the risks and benefits of using these products. It is important to remember that these interventions are at the very most complementary and not alterative because they should be used with, not in the absence of, modern medicine. If you wish to incorporate CAM into your care, it is important to first speak with a physician to determine if and which CAM is right for you.

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Supplements Summary

Table 33:1

Integrative Therapy	Vitamins	Herbals	Probiotics	Fish Oil
Products Advertised as Beneficial	Daily Multivitamin, ß-Carotene, L-Arginine, Vitamin A, Vitamin B6, Vitamin E, Zinc	Astralagus, Ashwagandha, Cat's Claw, Echinacea, Ginseng, Goldenseal, European Mistletoe	Probiotics	Fish Oil
Overview of Risks	Very little risk of physical harm. However, supplementation with vitamins and minerals is often unnecessary in individuals with immunodeficiencies.	Potential for harm is often theoretical. Supplement-disease and supplement-drug interactions are based on theoretical mechanisms of action supported by limited research. Additionally, different studies may use different types of plants and different methods of preparing the herb. Risk is highlighted by plants such as Astralagus, which may suppress the immune system in larger doses.	Potential for harm is theoretical. Severe bloodstream infections attributed to these bacteria have been found in individuals with irritable bowel disease, showing potential to be of a risk. No literature exists examining this risk in immunocompromised individuals. Also, there is no equivalence between probiotics – even of the same species.	Potential for harm is theoretical. Avoid consuming greater than 3 grams of fish oil supplements daily as it may lead to suppression of the immune system.
Overview of Benefits	Insufficient evidence to support claims that excess supplementation benefits people with primary immunodeficiencies.	Insufficient evidence to support claims that supplementing with these herbs benefits people with primary immunodeficiencies.	Insufficient evidence to support claims that supplementing with probiotics benefits people with immunodeficiencies.	Insufficient evidence to support claims fish oil supplements benefit people with immunodeficiencies.

Chapter 34
Secondary Immunodeficiencies

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Overview

Individuals who are suffering from frequent or unusual infections often have concerns about how well their immune systems work, knowing that the body's defense against infections is the most important function of the immune system. Immunodeficiency is the word that describe conditions characterized by an abnormal function of the immune system, resulting in an increased risk of developing infectious diseases. In addition, some immunodeficiency disorders are associated with increased risk of cancer and inflammatory conditions. The integrity of anatomical barriers, our skin and the lining of the respiratory and digestive tracts, are part of our immunity. Abnormal barriers are a risk factor for the occurrence of frequent infections.

Immunodeficiencies can be classified into **primary** or **secondary**, according to the cause of the abnormality in the immune system. When a genetic change is the direct cause of the immunodeficiency, it is called a **primary immunodeficiency**. If the immune system is not working properly due to other causes, it is called a **secondary immunodeficiency**.

Secondary immunodeficiencies present with a wide variety of types and severity. They are far more common than primary immunodeficiency diseases (PI). A well-known secondary immunodeficiency is due to the infection by the human immunodeficiency virus (HIV), which leads to the acquired immunodeficiency syndrome (AIDS). Other common causes of secondary immunodeficiency include the use of medications that decrease the immune response, chemotherapy drugs used to treat cancers, and conditions associated with significant loss of proteins in the gut or renal system.

It is important to determine whether an individual with frequent or severe infections has a secondary immunodeficiency. Treatment of the primary problem can lead to subsequent recovery of the abnormal immune function.

Select Causes

HIV infection and other infections

HIV infection targets and destroys CD4 T cells, a subset of immune system cells. These cells are essential to produce an effective immune response. According to the Center for Disease Control and Prevention, there were more than 37 million people living with HIV worldwide in 2017, most of them in Africa. In the U.S., it is estimated that over one million people are HIV infected. Fortunately, advances in prevention, early diagnosis, and effective anti-HIV medications are reducing the incidence of new infections. Individuals with HIV present with a loss of CD4 T cells. Without CD4 T cells, the immune system cannot produce an effective immune response. HIV infected individuals who don't receive treatment suffer from frequent and debilitating infections by other common and uncommon microbes. With the use of anti-HIV medications and control of the virus infection, the immune response usually recovers, and these other severe infections occur less frequently.

In contrast to the persistent immunosuppression associated with HIV infections, infections with other pathogens, for example the viruses that cause influenza and measles, are associated with transient impairment of the immune response. During or shortly after this period of impaired immune responses, these individuals have an increased risk of secondary bacterial infections.

Malignancies

Immunodeficiency occurs in individuals with cancer or malignancies as a result of multiple factors. Besides the effects of anti-cancer medications and radiation therapy on white blood cells, lymphocytes, and neutrophils, malignant conditions might directly compromise the immune function. Decreased serum IgG level in adults might be one of the first signs of the presence of a blood malignancy, such as chronic lymphoma. Chronic lymphocytic lymphoma (CLL) is a blood cancer characterized by the uncontrolled proliferation of

B cells, usually in individuals over 60 years of age. Malignant B cells are immature, and individuals might develop frequent respiratory infections and also autoimmune disorders.

Age: Prematurity, Neonatal Period and Elderly

The immune system starts developing in the first weeks of gestation, with the formation of blood cells and continues to develop even after the baby is born. During the last three months of gestation, maternal antibodies are transferred to the fetus, providing protection in the first few months of life until the newborn's own immune system makes protective antibody levels. A neonate's early immune responses might not be optimal and thus they are at risk of developing some severe infectious diseases.

Infants who are born prematurely are at higher risk for infection because immature barrier function (GI tract, skin), and immaturity of the immune system. These infants also may have decreased levels of maternal antibody because their premature birth prevented some of the transfer of antibody that occurs in late pregnancy.

The immune response in people of advanced age is characterized by decreased ability to generate immune responses to new pathogens. There is also slow tissue repair, of importance to heal skin and mucosal barriers that deter entrance of infectious agents.

Use of Medications That Suppress the Immune System Function

The use of medications to reduce the immune response and the inflammation caused by autoimmunity can increase the risk of infections. The list of these medications, collectively known as immunosuppressive drugs, is long and continues to expand. Immunosuppressive drugs include: corticosteroids, cyclosporine, rapamycin, rituximab, tumor necrosis factor inhibitors, and interleukin inhibitors. Each of these drugs has a different mechanism of action and produce specific effects in the immune system.

Corticosteroids, such as hydrocortisone and prednisone, have been used for decades to control inflammation. The immune suppressing effects of corticosteroids occurs with oral prolonged and high doses. In order to reduce the immunosuppressive effects, corticosteroids may be administered with limited schedules or topically, such as skin or inhaled, to achieve minimal systemic absorption.

Medications That May Decrease the Serum Immunoglobulins and/or Suppress the Immune Function

- **Systemic corticosteroids**
- **Chemotherapeutic agents**
  - Cyclophosphamide
  - Methothrexate
  - Mycophenylate
- **Immunosuppressants**
  - Cyclosporine
  - Rapamycin
  - Tacrolimus
- **Immunosuppressive biological agents**
  - Rituximab
  - Adalimumab
- **In some individuals anti-seizure medications**
  - Phenobarbital
  - Hydantoin
  - Carbamazepine
  - Valproic acid
- **Other medications**
  - D-Penicillamine
  - Gold therapy
  - Captopril

Conditions Leading to Loss of Proteins

Immunoglobulins (Ig) are proteins that can be lost through the gastrointestinal tract and kidneys resulting in low serum IgG levels. If the production of antibodies is not affected, increased susceptibility to infections is variable. Chronic or recurrent diarrhea and other gastrointestinal diseases can lead to protein loss in the stool, a condition called protein losing enteropathy. In some kidney diseases, protein is lost in urine. Individuals with low serum levels of albumin and IgG should be evaluated for these possibilities—protein-losing enteropathy or nephrotic syndrome. Treatment of these conditions can reduce the loss of serum IgG and antibodies in the stool or urine.

Malnutrition

Malnutrition is a leading cause of immunodeficiency worldwide, though uncommon in the U.S. and other countries. Severe restriction of protein and calorie intake result in inadequate cell metabolism that affect

all body functions, including the immune system response. Shortage of nutrients limits lymphocyte proliferation in response to antigens and reduces production of antibodies. Lymphocyte proliferation and antibody production are fundamental for an effective immune response. Specific vitamins, like vitamin A, and minerals that play essential roles in cell metabolism and function are also of significance for the normal function of the immune system. Malnutrition affects the integrity of the skin and mucosa, which may serve as ports of entry for pathogens. A balanced diet is essential for the immune system. An immunodeficiency secondary to malnutrition may be reversed with adequate nutrition.

Abnormal Barriers as a Risk Factor for Frequent Infections: Allergy Inflammation

Skin and mucosal tissues are considered integral components of the immune system. Disruptions of these barriers increases susceptibility to infections. One of the most common conditions associated with frequent infections is allergic disease. Although the allergic response depends on the immune system, it is an unwanted response and not an immunodeficiency. Allergic individuals have sensitivity to specific substances in the environment collectively called allergens, such as grass pollen, dust mite or cat hair. Exposure to environmental allergens might result in local inflammation of the nose, throat, lungs, eyes, and skin. This inflammation produces swelling of tissues and production of secretions that increases the risk of recurrent upper respiratory infections.

Diagnosis and Treatment

When an individual is found to have an abnormality in the immune system, the next step is to find whether there is a factor that can explain it. Secondary immunodeficiencies are common and often can be treated. A complete clinical history and physical exam is usually revealing of potential factors affecting the immune system, such as prolonged use of corticosteroids. Routine urine and blood testing might also be useful. For example, excessive loss of protein found in urine might explain low serum levels of IgG. It is also important to keep in mind that both a primary and a secondary immunodeficiency can occur at the same time.

Once the cause of a secondary immunodeficiency is defined, the main objective of the medical management is to treat this cause, when possible. For example, measures to control protein loss in stools. While this specific treatment is initiated, other objectives of management include treating current infections and using preventive measures to reduce the risk of further infections. Preventive measures to consider include: Ig replacement therapy when there is antibody deficiency, antibacterial and antifungal prophylaxis for recurrent bacterial infections and fungal infections, respectively. If the cause of the secondary immunodeficiency cannot be treated or is persistent, periodic follow up visits are recommended to ensure prompt diagnosis and treatment of infections.

Select Common Causes of Secondary Immunodeficiencies

- Recurrent use of corticosteroids, or other immunosuppressive medications
- Use of monoclonal antibodies targeting the immune system, such as rituximab (anti-B cells)
- Immunoglobulin losses via the gastrointestinal or urinary tract
- Malignancies
- Human immunodeficiency virus (HIV) infection

Chapter 35
Chronic Sinusitis

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Chronic sinusitis, often called chronic rhinosinusitis (CRS) due to involvement of both the nose and sinuses, is a common medical condition affecting over 10% of the general population. In primary immunodeficiency diseases (PI), CRS is a very common complication due to the increased risk of infection and inflammation associated with many forms of PI. Additionally, CRS is often a prominent presenting symptom of PI such that screening for PI should be considered in individuals with severe and persistent CRS that does not respond to usual treatments. The following will briefly review CRS in PI including contributing factors, evaluation, and treatment.

Background

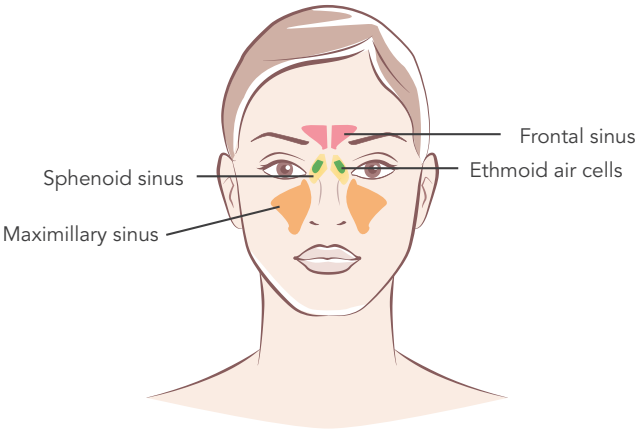
The sinuses are hollow cavities in the skull that have important functions:

- Warming, humidifying, and filtering air before it goes into the lungs
- Improving the quality of our voice and speech
- Reducing the overall weight of the skull

The tissue lining the nose and sinuses can swell or contract with changes in temperature, humidity, and exposure to particles or allergens.

The paranasal sinuses of the head and face include specific cavities named for their location within the skull: maxillary, ethmoid, frontal, and sphenoid. (Figure 35:1) Normally, these sinuses have a specific drainage pattern by which cilia (tiny hair-like cells) continuously sweep mucous, microbes, and other particles out of the sinuses through ostia (small openings) into the nose and subsequently the throat. When inflammation from infection, allergy, or other irritants causes swelling of the sinus tissues, these ostia can become obstructed leading to accumulation of mucous, fluid, or bacteria. The ostiomeatal complex is an additional potential trouble spot in the sinuses. This is a series of narrow, bony openings along the inside wall of the nose. The ostiomeatal complex is a common drainage pathway for the frontal, maxillary, and ethmoid sinuses, and it is important for normal sinus drainage and ventilation. If the ostiomeatal complex is blocked due to swelling, mucous accumulation, or an anatomical abnormality, this can act as a bottleneck and lead to chronic inflammation in multiple sinus cavities due to the lack of normal drainage. Typically with an acute viral or bacterial sinus infection that resolves, inflammation only lasts for several days; this is known as acute sinusitis. But if inflammation persists, CRS may develop. Any of the sinuses can be affected by CRS though the maxillary and ethmoid sinuses are most often involved.

Figure 35:1 Cavities of the Paranasal Sinuses



The chronic nasal and sinus inflammation of CRS can be due to several factors and is exacerbated in PI by the susceptibility to infection as well as the inability to adequately control inflammation. CRS is often divided into specific categories: CRS without nasal polyps, CRS with nasal polyps, allergic rhinosinusitis, and allergic fungal rhinosinusitis. Most people with PI are affected by CRS without nasal polyps, but it is important to consider the possibility of other

subtypes. Typically CRS with nasal polyps and allergic fungal rhinosinusitis can be identified by specific characteristic findings on sinus imaging (CT scans) or direct examination by rhinoscopy.

Symptoms

Common symptoms of CRS include chronic nasal obstruction (blockage), persistent mucous production from the nose or down the back of the throat (post-nasal drip), facial pain or pressure, and a reduction or loss in the sense of smell. Chronic cough is also a common symptom and may be seen more frequently in children than adults. These primary sinus and respiratory symptoms of CRS are important to recognize and report to a healthcare provider so that appropriate evaluation and treatment can be pursued. Studies suggest that uncontrolled CRS may contribute to other problems including fatigue, sleep disturbances, ear pain or pressure, dizziness, bad breath, and throat irritation. The course of CRS can be quite variable from person-to-person but involves chronic recurrent sinus symptoms lasting more than 12 weeks. Some individuals with CRS have constant, persistent sinus symptoms with episodes of modest worsening or improvement over time. Others have more distinct intermittent episodes of sinus symptoms with short asymptomatic periods in between.

Causative and Contributing Factors

CRS is a chronic inflammatory process that likely begins with an acute bacterial sinus infection. In most cases, an antibiotic and/or the immune system will clear the infection and sinus symptoms will resolve over several days. However, in some individuals, the infection or inflammation fails to resolve leading to a chronic inflammatory process that causes prolonged, persistent symptoms. This is particularly true in PI where the immune response may be inadequate to effectively control or clear an infection. The role of chronic or recurrent bacterial infection in the ongoing symptoms of CRS is controversial. The exact causes for the development of CRS are not entirely known and remain an area of ongoing research but identified factors contributing to CRS include the following:

Allergy: Environmental allergies are the most common risk factor for CRS in the general population. Allergic inflammation in the nose and sinuses may lead to chronic inflammatory symptoms and obstruction that additionally increases the risk of recurrent sinus infections. Most allergic people who develop CRS are reactive to perennial (year-round) rather than seasonal allergens. Perennial allergens typically involve chronic exposure and include dust mites, indoor/outdoor molds, and animal dander.

Immunodeficiency: Impaired immune responses increase the frequency and severity of infectious sinusitis leading to CRS complications. Individuals with antibody deficiency conditions, such as Common Variable Immune Deficiency (CVID), hypogammaglobulinemia, Specific Antibody Deficiency (SAD), etc., are frequently affected by CRS, though other types of PI may also develop this complication.

Anatomical abnormalities: Significant obstruction of normal sinus drainage may increase the risk of recurrent bacterial infection and subsequent inflammation. Obstruction can be caused by allergic inflammation as described above but also can be due to structural tissue abnormalities: large nasal polyps, congenital formations such as concha bullosa (air cells in the nasal turbinates), deviated septum, or sinus cysts. In addition, previous sinus surgeries can sometimes lead to structural abnormalities due to scarring or disruption of the tissues that normally clear the sinuses using very fine-hair like structures (cilia) to sweep mucous, particles, allergens, and infectious organisms out of the sinus cavities.

Smoking: Active smoking is an important risk factor for CRS. Tissue inflammation in the nose and sinuses is caused by chronic exposure to the particles and chemicals found in tobacco or marijuana smoke.

Airborne irritants and pollutants: Chronic respiratory exposure to irritant chemicals (mostly a concern in occupational settings) may increase the risk of CRS. Frequent exposure to more common air pollutants, such as engine exhaust particles and carbon monoxide, may also increase CRS symptoms though it is unclear if these exposures play a causative role.

Evaluation

Evaluation for CRS starts with the clinical history to identify chronic sinus symptoms as described previously. This should include documentation of the primary symptoms of chronic obstruction, persistent mucous production, facial pain or pressure, and reduced sense of smell. Typically, symptoms are present for months (less than 12 weeks). The medical history should include information about any conditions or exposures known to be associated

with CRS (as described above) and determine any previous diagnostic tests, treatments, or procedures (such as sinus surgery) for the condition. A physical examination should be conducted to look for signs of nasal and/or sinus inflammation. Findings may include purulent (colored) mucous, swelling, or polyps in the sinuses. Rhinoscopy or nasal endoscopy may be performed to better visualize the nasal and sinus cavities. This involves the use of a slender fiberoptic scope inserted into the nose, usually after medication is given by nasal spray to temporarily shrink the nasal tissues. Radiographic imaging such as CT scans may also be performed to assess the deeper sinus tissues. Important CT findings in CRS include mucosal thickening, obstruction of the sinuses due to structural abnormalities, and fluid or mucous collections within specific sinus cavities. Additional important diagnostic tests to consider in the evaluation of CRS include allergy testing (skin or blood tests) to identify environmental allergies and laboratory testing for immunodeficiency if not already completed. In individuals with persistent infectious symptoms that have been unresponsive to antibiotics, sinus cultures can be considered to guide additional antibiotic therapy. However, cultures should be collected from the deep sinuses via nasal endoscopy; culture swabs from the anterior nose are not accurate and should not be used to guide treatment.

Management

Once CRS is diagnosed by a healthcare provider based on the evaluation above, the management plan will often consist of multiple components. It is important to recognize that CRS generally cannot be cured, but appropriate treatment can usually reduce symptoms and the burden of the condition.

Treatment of PI: In PI, a first important step in managing CRS is to ensure proper treatment is provided for the underlying immunodeficiency. For many individuals, this involves appropriate immunoglobulin (Ig) replacement therapy with dose adjustments made over time by the treating healthcare provider to prevent infections as effectively as possible while avoiding side effects. However, CRS may occur and persist despite Ig replacement therapy, likely due to multiple factors other than infection that contribute to the condition. Thus, CRS remains very common in PI, even with Ig replacement therapy. Studies support a reduction in the frequency and severity of sinusitis symptoms with Ig replacement therapy in types of PI that involve antibody deficiency. The effect of higher dosing of Ig replacement therapy in CRS has not been firmly established.

Antibiotics: The role of antibiotics in treating CRS is currently unclear. Antibiotic treatment is recommended for the treatment of acute bacterial sinusitis in individuals with PI due to the increased risk of more severe infectious complications in this population. However, the chronic persistent sinus symptoms of CRS are unlikely to be due to a simple persistent bacterial infection and treatment with antibiotics alone is unlikely to be effective. As CRS is driven by multiple factors and a complex inflammatory response, management plans frequently require non-antibiotic treatment aimed at controlling inflammation. Thus, prolonged or chronic antibiotic treatment for the management of persistent CRS symptoms is generally not recommended; rather antibiotics should be reserved for treatment of clear acute bacterial sinusitis exacerbations. However, when evidence of persistent bacterial infection is present (persistent purulent colored mucous, findings on CT scan or by direct rhinoscopy), a prolonged course of antibiotics for four to six weeks may be beneficial. Rarely, longer antibiotic courses are considered, but the associated risks and side effects should be carefully evaluated. Antibiotics should be selected by the healthcare professional based on suspected or confirmed causative bacteria. Gradual improvement in symptoms is expected over the course of antibiotic treatment. If symptoms fail to improve, consideration should be given to obtaining a culture from the sinuses (typically done by ear, nose, and throat specialists) to guide further treatment. CRS can sometimes be complicated by specific infections such as Staphylococcus aureus, Pseudomonas aeruginosa, and anaerobes. These may require very specific antibiotic regimens so proper cultures are important in determining the most effective treatment. As noted earlier, antibiotics alone are usually insufficient to treat or control CRS and other non-antibiotic therapies must be used.

Nasal irrigation: One of the most effective management procedures is daily sinus rinses with a saline solution to physically remove mucous, particles, allergens, and infectious organisms. Irrigation also improves the function of sinus cilia that naturally clear the sinuses. Larger volume rinses with a neti-pot, squeeze bottle, or water pick with nasal irrigating device are thought to be more effective than low volume saline nasal sprays. To reduce the

risk of contamination or infection, it important to use distilled water or water sterilized by boiling or other means. A variety of over-the-counter saline packets are available, or it is possible to make buffered saline solution weekly using available recipes.

Intranasal corticosteroids: Topical steroids are an important anti-inflammatory medication for the treatment of CRS. These are most commonly given by nasal spray with several formulations available over-the-counter or by prescription. Nasal corticosteroids work slowly to reduce inflammation such that daily use for several weeks is necessary to see maximal benefits from the treatment. Nasal irrigation first followed by intranasal steroids seem to work best. Additionally, spray technique is important to ensure optimal results and to avoid injury to the anterior nose, so it is important for individuals to review this with their healthcare provider. For CRS that is unresponsive to nasal steroid sprays, short-term use of nasal rinses with a diluted steroid solution may be more effective in some cases.

Anti-leukotriene drugs: Leukotrienes are an inflammatory mediator that can contribute to the symptoms of mucous production and sinus swelling in some people with CRS. Medications that specifically block the effects of leukotrienes can sometimes be helpful for symptom control when added to other treatment measures. Medications in this class include montelukast, zafirlukast, and zileuton.

Allergy treatment: Effective allergy treatment is an important part of controlling CRS. This is most often achieved with the anti-inflammatory intranasal steroids and/or anti-leukotriene medications listed above. Oral or nasal antihistamines can also be useful to relieve symptoms of itching, sneezing, or dripping. Allergen immunotherapy (injections or sublingual tablets or drops) can be considered though the efficacy of this desensitization therapy for individuals with PI is unknown.

Oral corticosteroids: Short courses of oral corticosteroids such as prednisone may be useful in managing severe flares of CRS. However due to the considerable side effects and risks, systemic corticosteroids are rarely used for this purpose, and this is particularly true in PI where avoidance of the immunosuppressive effects is preferred.

Smoking cessation: Smoking causes chronic inflammation of both the upper and lower airway such that smoking cessation is an important part of improving CRS symptoms. In addition, it is also recommended that household members be encouraged to stop smoking since secondhand smoke has similar toxicity.

Additional medical therapies in development: Since CRS can be difficult to treat in some individuals, additional treatments are being studied. These include nebulized or topical antimicrobials for the sinuses, the placement of sinus devices that slowly deliver local medications to the sinus tissues, and targeted antibody medications (biologics) aimed at blocking specific inflammatory pathways. The benefit of these approaches for CRS has not been firmly established and the safety in PI conditions is not known.

Sinus surgery: Sinus surgery for CRS should be considered only when comprehensive maximal medical therapy has failed to result in substantial symptom improvement. In some instances, identified anatomical abnormalities or obstructions may need to be addressed by sinus surgeons in an effort to restore proper sinus drainage. Occasionally, severe inflammation cannot be improved with medication and removal of affected tissues is necessary for future medical therapy to be effective in controlling CRS. If sinus surgery is considered, it is very important that medical therapy be implemented or continued as well so that improvements achieved with surgery can be maintained following the procedure. Individuals with PI should be sure to discuss any planned surgical procedure with their immunodeficiency specialist so that appropriate PI expertise is available throughout the surgical period.

Summary

CRS is a chronic inflammatory condition affecting individuals with and without PI. The condition may be complicated in PI by susceptibility to recurrent infection which makes condition-specific PI treatment a critical part of CRS management. However, CRS is clearly multifactorial, and treatment or prevention of infection alone is insufficient to control symptoms in most cases. Therefore it is important for individuals with PI and CRS to consider and discuss all contributing factors with their healthcare team. Often, a multidisciplinary team that includes the primary care provider, immunologist, allergist, and ENT specialist is helpful in optimizing treatment outcomes.

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Chapter 36

Gastrointestinal (GI) Complications in Primary Immunodeficiency Diseases

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Introduction

The gastrointestinal (GI) tract includes all the organs from the mouth to the anus. This tract is responsible for the intake of nutrients, their digestion, absorption, and final elimination. Understanding the structure and function of the gut can help explain the symptoms and signs of GI complications of primary immunodeficiency diseases (PI).

For instance, the mouth provides for the first processing (chewing, macerating) and digesting (salivary enzymes) of food and the esophagus is a muscular tube that efficiently transfers the swallowed food to the stomach. The stomach further grinds down the food and also continues the process of digestion. The food passes to the small intestine where it mixes with bile (from the liver) and digestive enzymes (from the pancreas) to undergo the most thorough digestion and prepares the digested food for absorption across the bowel wall into the bloodstream. Finally, the remnants of the digested food are passed into the colon where fluid is absorbed back into the body and stool is prepared for elimination.

In the past decade, the rich collection of bacteria and other microbes (the gut microbiome) that live in the colon at the highest concentrations, but is found throughout the GI tract, have been of great interest to researchers who are defining the roles of these organisms in human health and disease. Given the fact that these communities of gut microbes can be affected by the immune deficient state itself (seen in animal models) as well as by repeated exposure to antibiotics (common in individuals with PI), the state of the gut microbiome may also be necessary to consider when evaluating GI complications of PI.

Evaluating GI Symptoms

The types of GI problems that can occur can be quickly linked to the organ involved or sometimes be harder to pinpoint by questioning alone. For instance, trouble swallowing, like food getting stuck, etc., heartburn, and even chest pain can come from the esophagus. Upper abdominal pain and vomiting poorly digested food can come from the stomach. Unexplained weight loss and diarrhea can come from disturbances in small bowel digestion and/or absorption of food while slower bowel pattern with pain and even vomiting after meals could come from small bowel obstruction. Lastly diarrhea and lower abdominal pain along with a sense of stool urgency and pain on elimination can come from the colon. However, many symptoms and signs including abdominal pain, changes in bowel habits, bloating and upset stomach as well as all types of GI bleeding from the upper or lower gut, most often cannot be diagnosed just by asking questions. Often special tests are needed to make an accurate diagnosis.

The most common tests that a GI specialist (gastroenterologist) relies upon include upper endoscopy (where a scope is introduced through the mouth into the GI tract to look at the esophagus, stomach, and upper small bowel) and colonoscopy (where a scope is introduced into the anus to look at the anus to the beginning of the colon and even into the end of the small intestine. Beyond just looking at the lining of the gut for abnormalities, these procedures allow for samples of gut contents to be taken as well as tissue samples (biopsies) for inspection under the microscope. In addition, special x-rays of the intestines and abdomen are used (often to examine the rest of the small bowel that is beyond the reach of the usual scopes) to detect an abnormal appearance. Unfortunately, biopsies cannot be obtained from these radiographic procedures.

There are other studies that can be used to assess the GI tract:

- Stool can be cultured for infectious organisms.
- The upper small intestine can be checked for inappropriate growth of bacteria (called small intestinal bacterial overgrowth) by using a hydrogen breath test.
- The small intestine checked for normal absorption (using d-xylose).
- Special endoscopy studies can be done using a much longer scope (double balloon endoscopy).
- Video endoscopy is done with a pill-sized camera that is swallowed. As it travels through the bowel, pictures are taken.
- Manometry (pressure monitoring) can be done to assess the function of the esophagus. This measures the strength and coordination of muscular contractions.
- Monitoring of pH can be done to assess for abnormal acid exposure that could cause damage to the esophagus and gut mucosa.

Major Types of GI Complications in PI

The major GI complications fall into three main categories: infectious, idiopathic inflammatory/autoimmune, and neoplastic (cancer). Certain types of PI seem to increase the risk for gastrointestinal complications (from mild to severe). Individuals with Common Variable Immune Deficiency (CVID) and Chronic Granulomatous Disease (CGD) have some of the most frequent and significant gut manifestations, and these are discussed in more detail below. It should be appreciated, however, that not every individual with PI will necessarily have GI complications, and if GI disease develops, it may not always be a direct result of the PI.

GI Complications by Specific PI Diagnosis

Selective IgA Deficiency

Selective IgA Deficiency (SIgAD) is generally asymptomatic and without GI complications. However, SIgAD is associated with a higher frequency of celiac disease. Special attention to proper screening tests is needed (use of genetic testing as well as IgG-based serum antibodies) for these people. People with SIgAD can also be affected by increased infections with gut pathogens as in CVID. Individuals with SIgAD may acquire infections with a protozoa called Giardia lamblia when swimming in lakes and streams, so they should be avoided. Chlorinated pools and oceans are usually fine. SIgAD is also associated with enlargement of the lymph nodes in the gut (nodular lymphoid hyperplasia) that can be associated with malabsorption. Associations between SIgAD and autoimmune intestinal disease occurs including chronic hepatitis, biliary cirrhosis, ulcerative colitis and regional enteritis.

Common Variable Immune Deficiency

Individuals with Common Variable Immune Deficiency (CVID) can have high rates of gut infections (up to 60% of individuals might experience at least one) despite the use of IgG replacement. Among the infectious agents, Giardia lamblia, non-typhoidal Salmonella, and Campylobacter jejuni are mostly seen, but Cryptosporiudium may also be found. People with CVID, like those with SIgAD, can also be affected by increased infections with gut pathogens and may acquire infections with a protozoa called Giardia lamblia when swimming in lakes and streams. Individuals with CVID should avoid lakes and streams because of this potential infection, but chlorinated pools and oceans are usually fine.

Clostridium difficile and viruses (cytomegalovirus) may be encountered in people with CVID. C. difficile usually occurs when people are taking antibiotics that kill good bacteria as well as bad pathogenic bacteria. Because of the wide use of antibiotics in individuals with CVID, one would think that the occurrence of C. difficile infections would be higher compared to the normal population; however, this has not been found to be true.

People with PI do have a higher rate of gastric Helicobacter pylori infection than do people with normal immune systems. Infection with H. pylori is important to detect as it is a World Health Organization (WHO) Class 1 carcinogen with chronic infection associated with gastric cancer.

Another GI infection that can lead to persistent diarrhea is Norovirus that can be very difficult to treat; individuals need to be very vigilant on cruise ships where Norovirus infections have been commonly reported.

Finally, small intestinal bacterial overgrowth (SIBO), a condition where collections of bacteria normally found in the lower GI tract are growing at high concentrations in the upper GI tract (where they interfere with nutrient digestion and absorption causing diarrhea and weight loss) is present in up to 30% of individuals with CVID with chronic GI symptoms.

The autoimmune/inflammatory GI complications of CVID include an idiopathic enteropathy that is an intestinal disease of unknown cause that affects the small bowel. The bowel looks normal to the eye but appears inflamed and damaged when looked at through the microscope. This condition typically causes symptoms of very chronic diarrhea combined with inability to absorb nutrients leading to severe weight loss. Much less frequently, obvious ulceration resembling Crohn's disease might occur. CVID-associated autoimmune disease involving the GI tract also includes type II gastritis that can lead to loss of acid production and vitamin B12 deficiency (pernicious anemia).

Nodular lymphoid hyperplasia also occurs in CVID and can lead to chronic diarrhea. Lastly, cancer complications of intestinal lymphoma and gastric adenocarcinoma (related to autoimmune gastritis) have been reported.

Chronic Granulomatous Disease (CGD)

The most common gastrointestinal complaints in individuals with CGD are abdominal pain and diarrhea (with or without rectal bleeding). GI symptoms usually begin before age 10, sometimes preceding the diagnosis of CGD.

While infectious diarrhea (especially Salmonella and C. difficile) occur in CGD, an inflammatory bowel disease also develops:

- In the mouth, ulcers and dental abscesses cause pain and difficulty eating; in the esophagus, feeding difficulties can result from narrowing by strictures (scarring) and altered muscle function related to granulomatous inflammation and fibrosis;
- In the stomach, loss of function and volume due to thickened wall leads to vomiting, pain, and weight loss;
- In the small and large intestine, diarrhea, bowel obstruction (large granulomata block the gut), rectal bleeding and rectal pain can result from ulcers, anal fissures and abscesses.

Feeding difficulties and the chronic inflammatory state itself predispose to growth delay that often affects children with CGD.

Liver abscesses also can complicate CGD in up to 45% of individuals. These individuals often have fever, abdominal pain, fatigue, and, less often, abdominal tenderness and liver enlargement. A high level of suspicion, especially in the setting of fever with or without abdominal pain, should instigate a search for a hepatic abscess.

Types of PI with Less Frequent GI Complications

Individuals with the rare X-linked recessive Wiskott-Aldrich Syndrome (WAS) can develop a non-infectious colitis resembling ulcerative colitis with rectal bleeding increased by the accompanying low platelet counts. Successful hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, for WAS can also be a curative treatment for colitis.

Rare mutations that affect IL-10 activity lead to early onset inflammatory bowel disease (EOIBD). Individuals present with colitis within weeks of birth that has features of Crohn's disease. HSCT can be a curative therapy for this condition.

Individuals with X-linked hyper-IgM syndrome (type 1) can have Cryptosporidia infectious diarrhea, inflammation of the bile ducts (sclerosing cholangitis), cirrhosis and cancer of the hepatobiliary system. Rarely non-infectious colon inflammation has been reported. HSCT, preferably done before chronic complications occur, is the only potential for curative treatment.

X-linked lymphoproliferative syndrome 2 (XIAP deficiency) can present with very early-onset anal skin inflammation in up to 20% of individuals.

Lastly, the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) has the gut lining as a major site affected by inflammation, and this complication produces a watery, sometimes bloody, diarrhea and inability to absorb nutrients. Treatment requires HSCT, but the gut disease may be managed temporarily with corticosteroids and immunosuppressants.

Summary

The GI tract is a major site of symptoms related to PI including increased infections, inflammation, and rarely cancer. Individuals and caregivers with their healthcare providers need to be aware of the potential for the development of GI disorders associated with PI. Early diagnosis and appropriate treatment can be effective in preventing long-term complications of these conditions.

Chapter 37
Clinical Trials

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Clinical trials, also known as protocols or clinical research studies, are experiments that use a scientific approach to explore whether a new medication, treatment, or device is safe and effective for human use. This process is the final drug development step before a new drug or treatment is approved by the Food and Drug Administration (FDA) and made available to people. Clinical trials are key in advancing new medical knowledge and patient care.

Overview

Human testing is necessary to develop safe and effective treatments with acceptable side effects, while providing the greatest therapeutic benefit. Before any new medications or treatments are studied in humans, they are studied in laboratory animals to determine whether they are safe enough to test in humans. Animal studies must be evaluated to determine if they are safe. They must also show some positive outcomes before human testing begins.

To make sure that a new product being tested will work for different groups of people, it is important that the participants in the clinical trials are from different ages, genders, and disease groups. This is the best way to test potential treatments to see whether they should be approved for a larger group. However, clinical studies of new treatments are often first studied in adults prior to enrolling children, unless the condition for treatment predominantly affects children. A treatment could be a drug, medical device, or a biologic (made from living organisms or containing components of living organisms), such as a vaccine, blood product, or gene therapy.

Types of Clinical Trials

There are several types of clinical trials or studies. Some involve treatments or interventions, and some are observational that collect data or information only.

Treatment or Interventional: Involve a medical treatment or intervention such as medications, psychotherapy, new devices or new approaches to surgery, or radiation therapy. *Example: new type of intravenous immunoglobulin (IVIG) replacement therapy.*

Prevention: Look for better ways to prevent disorders from developing or returning. Different kinds of prevention research may study medicines, vitamins, vaccines, or lifestyle changes. *Example: low salt diet to prevent high blood pressure.*

Diagnostic: Look at better ways of identifying or diagnosing a particular disorder or condition. Screening studies are also a type of diagnostic research designed to learn better ways of detecting disorders. *Example: newborn screening for Severe Combined Immunodeficiency (SCID).*

Natural History: Study the evolution of a disorder (often present since birth) over the lifetime of an individual, to see the possible complications or changes in the disorder, and learn about recognizing and managing these problems to reduce their severity. *Example: natural history study of Common Variable Immune Deficiency (CVID).*

Treatment or Interventional Trials

Development of new drugs or treatments can take 10 to 15 years before FDA approval, and many treatments are determined to be ineffective or

unsafe during this prolonged development process. The process is done in a step-by-step approach called Phase(s). Each phase of the process must be safely completed before moving on to the next.

Phase I Trials

These trials test a drug or a treatment in a small group of people usually the first time in humans. This may be done in a group of healthy individuals depending on the treatment or condition being studied. The purpose is primarily to determine a safe dose of the medication and determine possible side effects.

Phase II Trials

The drug or treatment is given to a larger group of people affected by the medical condition being treated to get initial efficacy data and determine the best dose(s) for safety and efficacy.

Phase III Trials

The study drug or treatment is given to an even larger group of individuals with the medical condition to prove effectiveness and monitor for side effects. Depending on the disease entity there is placebo group (subjects who do not get the investigational drug and may receive a similar looking pill or liquid or IV that does not contain any type of medication) for comparison to the investigational drug. The study of new immunoglobulin (Ig) products for replacement therapy does not include a placebo group of subjects since it would be unethical to exclude individuals with PI from getting Ig replacement therapy. This study often compares the new treatment to the currently used treatment to determine safety and efficacy. Phase III studies are typically the final step before the FDA considers whether to approve a medication or treatment.

Phase IV Trials

These trials are for study drugs or treatments that have been approved by the FDA. Phase IV studies are designed to get additional long-term safety information on a treatment as it is used when prescribed to individuals.

Participating in Clinical Research

Deciding to take part in clinical trials is something only you can decide once you have information about the study from the study doctor (investigator) and team. There are possible benefits as well as risks so you should discuss these and understand any concerns fully before making your decision.

Participation in clinical trials may allow you the benefit of a treatment option that is not otherwise available. Your participation allows you an active role in a decision that affects your life or the life of your child so careful consideration and discussion with your care team is necessary.

Informed Consent

Prior to enrolling into a clinical trial, you will be asked to sign an informed consent form. This is a document that describes, in detail, what the trial is about, what is expected of you if you participate, the potential risks, possible benefits, and any financial compensation offered. All subjects participating in a clinical trial will need to sign an informed consent document. As a subject you have rights, the most important of which is that you have the right to withdraw your consent from participating in the study **at any time** without it affecting your care. Informed consent is an ongoing process and you should be updated to any changes in the study or new findings that may affect your willingness to participate.

Unknown Side Effects and Risks

There is always a chance the treatment or medicine will not work. Known side effects will be described in the Informed Consent document but there may be other side effects that are not known by the study team at the time you start the study.

Randomization

This is a process used in some trials to prevent favoritism with one treatment versus another. One group receives the actual study treatment or medication, while the other will receive the most widely accepted treatment (standard approved treatment). Comparing the results from these two groups often shows which treatment is more effective and/or has fewer side effects. Before you decide to participate, you should understand your chance of being randomized into either group is about equal, like the flip of a coin. The doctor does not decide on what treatment or drug you get, it is usually done randomly by a study statistician or pharmacist.

Placebo

Placebos, which are inactive 'look-alike' drugs, are rarely used in primary immunodeficiency drug studies. However, in a placebo study there is the possibility that you may not be selected to be in the group receiving the actual drug being tested and will not know this until later in the trial.

Blinding

This is a term used in clinical trials which means that neither you or your doctor will know if you are getting the experimental treatment or standard treatment. This is done to reduce bias.

Protections and Safeguards

To assure patient safety and ethical practices, all clinical research is reviewed by an institutional ethics or review board. This panel reviews the proposed study to make sure it is ethical, that the risks do not outweigh the possible benefits and that concerns related to special populations such as children or pregnant women are addressed. There are also federal government agencies: The Office of Human Research Protection and The Food and Drug Administration (FDA) that have oversight over all clinical research conducted in the U.S.

You also have the right to privacy if you choose to participate in a clinical trial. You will be assured that the research staff will not share your health information with anyone without your consent.

Resources

- ClinicalTrials.gov: www.clinicaltrials.gov/ct2/about-studies/learn
- FDA: www.fda.gov/patients/clinical-trials-what-patients-need-know
- National Institutes of Health: www.nih.gov/health-information/nih-clinical-research-trials-you

Chapter 38
General Care

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The diagnosis of a primary immunodeficiency disease (PI) means different things to different people. For most, it represents both an end and a beginning. It is the end of what may have been a lengthy quest for answers to the questions: Why am I always sick? Why do I have more infections than anyone else I know? Why is my child sicker than his siblings or friends? This quest can involve multiple healthcare providers, a long period of diagnostic testing, and, perhaps, even a misdiagnosis. Nevertheless, once a diagnosis has been made, it represents a beginning—the beginning of a life spent moving forward while dealing with a chronic illness.

It is seldom necessary to make major life changes in response to a diagnosis of PI, but some modifications may be needed. The individual's new normal may need to be defined in the context of the condition. It is important to remember that most people with PI are able to live full lives. A diagnosis of PI is merely a part of that life; it should never become the life. Adopting a healthy lifestyle is the key to making sure that this is the case.

General Health Measures

Hygiene

General principles of good hygiene are essential for everyone, including people with PI and their families. This includes regular bathing or showering, and the use of soap. For some, the use of germ-killing soaps may be recommended. **Regular handwashing should be routine**—before and after eating, after blowing the nose, after coughing—anytime there is a concern that germs have gotten onto one's hands. It is important to remember that to be truly effective, hands must be washed vigorously for at least 15 seconds. This is generally longer than most people think. It usually takes 15 seconds to sing "Happy Birthday."

Individuals should avoid touching the nose or eyes, especially after touching a doorknob or flat surface. Viruses can remain alive on these surfaces for long periods and are easily transmitted from the hands.

When hands are not visibly dirty, alcohol-based hand sanitizers can be an alternative to hand washing. They have the advantage of being portable and easy to use. These products have been shown to reduce the occurrence of colds and other viral infections. Individually wrapped disposable hand wipes are another great alternative to soap and water.

Tooth brushing and dental care are also key components to maintaining good hygiene. People with some immunodeficiencies are especially prone to gum disease and to infections that come from having decayed teeth. Regular visits to the dentist, as well as brushing and flossing multiple times daily, are essential.

A common sense approach to infection prevention is generally the best policy to follow. In addition to the maintenance of good hygiene, individuals should avoid exposure to people who have signs of illness or an obvious infection. This includes people who are coughing or have a fever. During flu season, it is wise to consider staying away from places where there are large crowds of people like a shopping center or movie theatre. With the recent measles outbreaks, it is also advisable to avoid social gatherings in which there is a group of parents who do not vaccinate their children. Some individuals choose to wear a

mask. It is best to consult the care provider about this. Masks tend to get moist from nasal or oral

secretions quickly. As soon as masks become moist, they are no longer effective. People who wear masks sometimes have a false sense of security and forget about other, more effective, preventative measures like frequent handwashing.

Many people with PI have questions about flying or travel. Depending on the specific type of PI a person has, travel to a particular place might not be advisable. For example, in some parts of the world yellow fever is a serious problem. The vaccine for this disease is a live viral vaccine and contraindicated for some people with antibody deficiencies. Travel to an area where there is yellow fever would not be a good idea for these individuals. Similarly, travel to a part of the world where healthcare services are not readily available might not be a particularly good idea. It is always wise for the individual with a PI to consult the immunology team when considering extensive travel. Consultation with a provider specializing in travel medicine may also be indicated.

Nutrition

A healthy and balanced diet provides the elements necessary for appropriate growth and development, as well as body repair and maintenance. While good dietary habits are important for everyone, they are especially important for an individual with a PI. A lack of adequate nutrition can predispose people to developing many illnesses, including infections for which someone with a PI is already susceptible.

Dietary guidelines for Americans encourage eating a variety of foods including starch and fiber, achieving and maintaining an ideal body weight, and limiting the intake of fat, cholesterol, sugar, salt and alcohol. (See Figure 38:1). The primary healthcare provider is an excellent resource for direction and advice regarding a healthy diet.

Special Diets

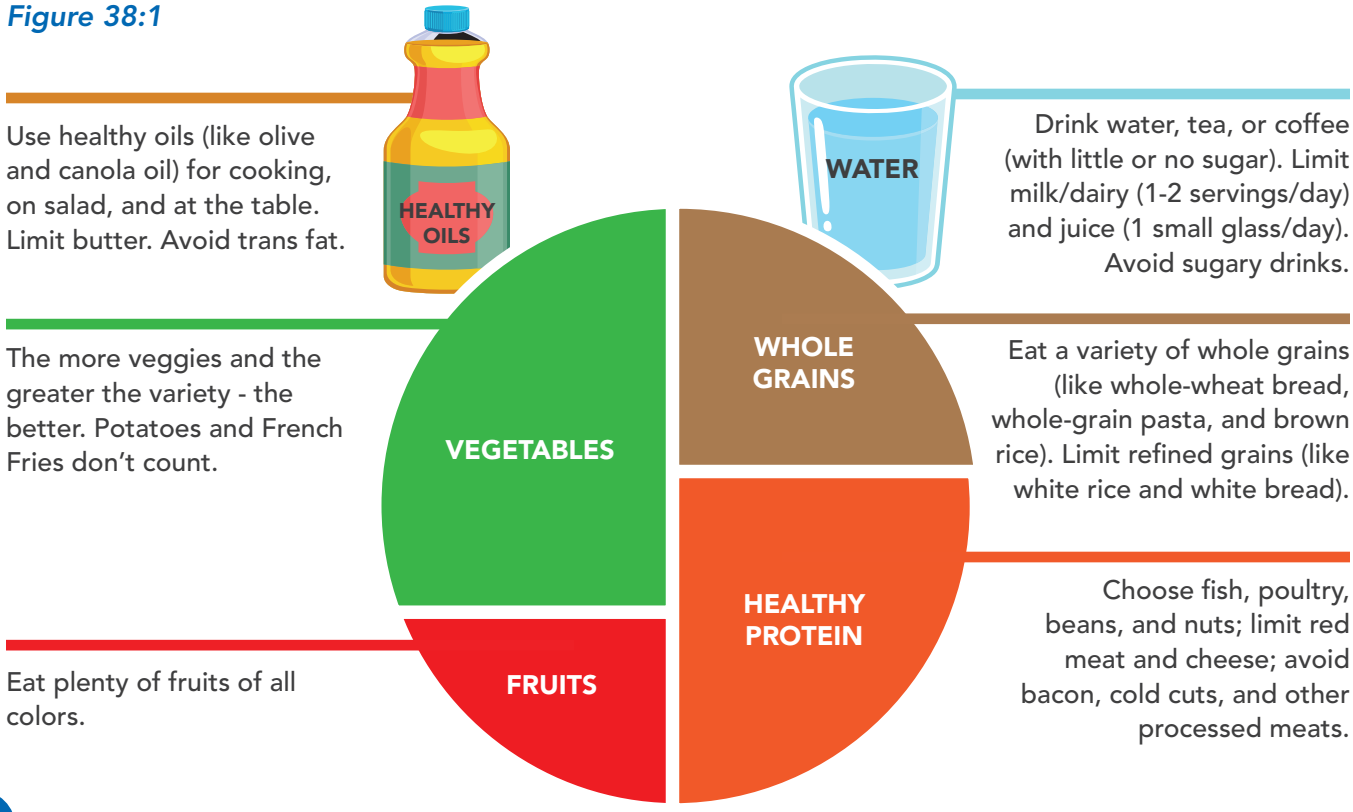
Unless the individual with a PI has another condition like diabetes, food allergies, or gluten sensitivity, special diets are not usually needed. During times of acute illness, though, dietary modification may be necessary. For example, when an individual has a gastrointestinal (GI) "bug" with nausea and vomiting and/or diarrhea, the healthcare provider may recommend a clear liquid diet. The provider will give instruction for the dietary modification.

Special Dietary Interventions

In some circumstances, if individuals are unable to eat or drink normally or are unable to absorb nutrients from their GI tract, there are ways to assist them in getting and maintaining adequate nutrition.

Enteral nutrition, feeding directly into the stomach or small intestine via a special tube, may be recommended for those individuals who cannot eat

Figure 38:1



enough calories to ensure adequate nutrition or drink enough fluids to avoid becoming dehydrated. This method of feeding may be suggested for those who have swallowing difficulties, such as those individuals with Ataxia-Telangiectasia. It may also be a short-term solution for those who develop mucositis (inflammation of the mucus lining of the GI tract) during hematopoietic stem cell transplantation, also known as bone marrow transplantation.

Two common methods of enteral feeding are with a nasogastric (NG) tube or a gastrostomy tube (GT). An NG tube is a small, flexible plastic tube that is inserted through the nose and threaded down the esophagus into the stomach. In infants, these tubes can be passed through the mouth instead of the nose. A GT is a feeding tube that is surgically implanted directly into the stomach through the abdominal wall. These types of tubes can also be placed into the duodenum or jejunum, the upper two parts of the small intestine, and bypassing the stomach. Prescribed amounts and types of liquids are administered through the tubes either continuously or at regular intervals. There are many commercial products designed to be given in tube feedings. These products differ in the amounts of calories, nutrients, and the other components that they contain. The healthcare provider will decide which is the best product for an individual to use.

Total parenteral nutrition (TPN) and hyperalimentation are the terms used for nutrition administered intravenously. TPN is used to maintain the nutritional status of an individual who is very ill, malnourished, or unable to absorb nutrients from the GI tract. TPN solutions usually contain protein, carbohydrates, fats, electrolytes, vitamins, water, and essential trace minerals. Various types of intravenous catheters are used for TPN. Nutrition via TPN is usually a short-term solution designed to meet an individual's immediate nutritional needs.

Nutritional Supplements

There are thousands of nutritional supplements available at supermarkets, specialty stores, pharmacies, and on-line. These include vitamins, minerals, herbal supplements, botanicals, pro-biotics, and naturopathic products. Many of these products are marketed aggressively and make claims to improve health by "boosting" the immune system. These supplements are not considered to be drugs by the United States Food and Drug Administration (FDA) and so are not FDA regulated. Virtually anything can be put into these products, and manufacturers can put anything they wish to on the labels.

There is no scientific data to support that any of these products improve health or strengthen the immune system. Extreme caution should be used before taking these products. Some of these products can be harmful or interact adversely with the medications an individual is taking. The healthcare provider should always be consulted before an individual takes any of these products. Sometimes the provider will recommend a pro-biotic, vitamin, or mineral supplementation. Some of these products may require a prescription. The important thing to remember is that these products are not a substitute for a healthy, balanced diet.

Day Care

Families who have children with PI may need to use daycare just like those families with immunocompetent children. Unfortunately, all children in day care are exposed to lots of easily transmitted infections. It is not uncommon for a child to have seven to eight viral infections during the first year of daycare. While most of these infections are not serious and are self-limited, they, nevertheless, have an effect on quality of life as well as parental stress. Exposure to infections tends to be greater in larger daycares. Parents may choose smaller day cares or home day-care settings. They may choose to forego daycare, instead hiring a nanny or au pair. Parents need to consider carefully their options, weighing the benefits of daycare like providing the child with peer socialization, against the potential risks of infection.

Exercise

A healthy lifestyle always includes exercise. Regular physical activity should be encouraged for all people—including people with normal immune systems and those with PI. Physical activity is good for the body and good for the mind, as well. Regular activity is an excellent stress and anxiety reducer. Activities such as swimming, biking, running, and walking promote lung function, muscle development, strength, and endurance. In general, people who get regular exercise are known to have fewer infections than those who do not exercise. Organized sports may be an excellent outlet for children who are struggling to cope with their illness. By competing on a team with other children, it may help the child with PI to feel that he or she is not so different and just a "regular kid" like everyone else.

Some kinds of exercise may be contraindicated for people with specific types of PI. People with

low platelet counts should not engage in contact sports. People with Chronic Granulomatous Disease (CGD) should never swim in fresh water. Likewise any individual with PI should be cautious about swimming in lakes or streams because of the increased susceptibility to a protozoa called Giardia.

The immunology healthcare team can recommend appropriate types of exercise if there is a specific concern. Nevertheless, everyone should get their steps in!

Sleep

Getting enough sleep is critical for everyone, not just those who have a chronic illness. Adequate rest is an essential requirement for good health. Most research studies support getting a consistent number of hours of sleep each night as well as having consistent bed times and waking times. While sleeping in on a Saturday morning may be a special treat, it may not be the best thing to do to insure good health. Erratic or inconsistent sleep patterns have been shown to have negative effects on the immune system.

Some helpful sleep guidelines include:

- Going to sleep and getting up at roughly the same time everyday.
- Avoid late nights.
- Avoid consuming caffeine, such as coffee, tea, cola, in the evening.
- Avoid eating heavy meals in the evening or snacking right before bedtime.
- Minimize potential disturbances during the night (Don't go to sleep with the television in the bedroom on). Overall, limit screen time on any device before bed.
- Avoid long naps in the daytime that might interfere with the regular sleep schedule.

Adequate amounts of sleep are also important for children. They usually require more sleep than adults do. Children age 3 and younger require daytime naps in addition to their nighttime sleep.

Stress

The notion that people get sick more often when they are under stress is supported by scientific data. Chronic illness alone is considered a major life stressor. Some studies suggest that stress has a negative impact on immune function and that reducing stress can actually improve

Age Appropriate Sleep

Table 38:1

Age	Average Sleep Requirement (in hours)
Newborn (0 to 2 months)	12 to 18*
Infant (3 to 11 months)	14 to 15*
Toddler (1 to 3 years)	12 to 14*
Pre-schooler (3 to 5 years)	11 to 13*
School-age (5 to 10 years)	10 to 11
Teen (10 to 17 years)	8.5 to 9.25
Adults (26 to 64)	7 to 9
Seniors (65+)	7 to 8

*Includes nap

Adapted from the National Sleep Foundation Guidelines (www.sleepfoundation.org)

immune function. Many stress reducers are easy to incorporate into one's daily life. These include massage therapy, biofeedback, meditation, and hobbies. Physical activity, even a walk around the block after lunch and adequate sleep, including a power nap can also help with stress reduction.

If you find that you are unable to deal with the stressors in your life, you should **absolutely** discuss these concerns with your healthcare providers. They can assist you or refer you to someone who can help you to deal effectively with your issues. You should **never** feel that nothing can help you to deal with the problems that overwhelm you and keep you from living and enjoying your life.

Primary Care

Seeing a primary care provider regularly for health maintenance screening is important for everyone, but even more so for the person with PI. Many types of PI are associated with other illnesses. For example, it is known that people with Common Variable Immune Deficiency (CVID) have a higher incidence of autoimmune disease. The primary care provider who knows the individual well and sees them regularly may be the first person to recognize a symptom of one of these autoimmune conditions. Similarly, the first sign of a problem in a child may be seen by the primary care provider in the regularly assessed parameters that may indicate failure to grow or develop properly.

Immunization

Perhaps the greatest advances made to improve general health over the past 225 years have been the development of vaccines to protect individuals from some of the worst diseases in our environment. Many people with PI, especially those with antibody disorders, have questions about vaccines.

People with many kinds of PI are fully capable of making protective levels of antibody to vaccines. Vaccines are very important for these people. They include people with complement deficiencies, phagocytic disorders like CGD, and even people with some antibody disorders like those with Selective IgA Deficiency. However, there are others with PI who are unable to develop protective immunity following vaccination. In some of these cases, the vaccine itself may pose a threat to the recipient.

People with CVID, Severe Combined Immunodeficiency (SCID), significant T cell deficiencies or agammaglobulinemia should never receive live vaccines. These include the vaccines for chicken pox (varicella), measles (rubeola), German measles (rubella), mumps, smallpox, yellow fever, oral polio, oral Salmonella typhi vaccine, or rotavirus. These vaccines could actually cause the disease they are supposed to prevent in the people with these conditions. Infants with SCID are at the greatest risk for this problem. As some of these live viruses are shed in body fluids and stool for up to two weeks following vaccination, it might be necessary to limit contact between anyone recently immunized with these vaccines and an infant with SCID. For those people receiving immunoglobulin (Ig) replacement therapy, the infused antibodies should give them adequate protection against any shed virus. It's best to talk to an individual's immunology providers if there are any vaccine questions.

The usefulness of vaccination when one is receiving Ig replacement therapy is not fully understood, in part to the complexity of the range of underlying immune defects in those being treated with Ig replacement therapy. Assessing these peoples' antibody responses to vaccines is confounded by the antibody present in the Ig. However, it is possible that these individuals' T cells will be stimulated by inactivated vaccines, and therefore there is potential for some benefit. Thus, the viral influenza vaccine is generally recommended for individuals with CVID, and certain other individuals with antibody deficiency, such as IgG Subclass Deficiency, Selective IgA Deficiency and Selective Antibody Deficiency.

Some individuals with milder forms of PI affecting humoral immunity such as those with Selective IgA Deficiency, mild hypogammaglobulinemia, and partial DiGeorge Syndrome can safely receive all vaccines. Again, the immunology providers are the best people to advise regarding whether an individual should or shouldn't get a particular vaccine.

Purified protein, polysaccharide, or non-viable whole-agent vaccines pose no infectious risk to individuals who have problems making antibodies and are receiving Ig replacement therapy. However, for most vaccines the antibody response is not likely to be protective and these individuals rely on the antibodies they receive in their Ig for protection. For this reason, many immunologists do not recommend routine vaccination for individuals on Ig replacement therapy as they believe there is little benefit to be gained. New vaccine agents are the exception to this rule. For example, it is well known that the influenza strain changes from year to year. In a given year, there may not be a protective level of influenza

antibody in the Ig pool. Antibody to a new influenza strain will not be present in Ig replacement therapy for approximately two years, which is roughly the time between plasma collection to production of a lot of Ig. Many immunologists recommend an annual influenza vaccine for their individuals on Ig replacement therapy for this reason.

The Immune Deficiency Foundation (IDF) recommends that families of people with PI receive all recommended immunizations. The only exception is oral polio vaccine, which can be transmitted. If a close contact develops a rash after varicella vaccination, isolation of the person with PI is recommended with administration of zoster immunoglobulin. This is especially important in the case of highly communicable diseases like influenza, which change from year to year. Even if people with PI do not benefit from receiving the vaccine directly, they will certainly benefit from having a cocoon of protection from their immunized family members. (See Immunizations Chapter.)

General Care during Times of Acute Illness

Even after a diagnosis of a PI has been made and appropriate treatment has been initiated, people with PI are still going to get sick. It is the hope that these illnesses are reduced in intensity and number, but it is unrealistic to think that they will be eliminated. When acutely ill, people with PI should always:

- Seek medical advice. Do not ignore symptoms such as a cough or fever and think they will just go away.
- Never self-treat. Taking leftover antibiotics or those prescribed for another family member is never a good idea.
- Follow the healthcare providers' advice. If 14 days of antibiotics are prescribed, take them all. Do not stop after a week because things have improved. If there is a recommendation to stay home from work or school, then stay home.

Undertreating or trying to ignore an acute illness may seem okay in the short run, but it can absolutely have long-term negative consequences.

Summary

The diagnosis of a PI is a life-changing event. It can be viewed in a positive way. The diagnosis and treatment are the first steps on the road toward wellness and an improved sense of well-being. Adopting a healthy lifestyle and complying with the advice and recommendations of the entire healthcare team can maximize the potential for a normal, full life.

Adapted from: Chapter 23 General Care. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.

Chapter 39

Women's Health and Primary Immunodeficiency Diseases

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The diagnosis of a primary immunodeficiency disease (PI) can occur at an age just prior to or during childbearing years. Since a delay in diagnosis of many years, even decades, is not uncommon in milder forms of PI, many individuals struggle through adulthood raising families while in poor health prior to the knowledge of their PI. Studies investigating the impact of PI on puberty, fertility, pregnancy, or menopause are lacking, and therefore it is difficult to make recommendations or discuss expectations for most individuals. However, we have learned a great deal from the community of individuals living with PI.

Puberty and Fertility

In general, puberty, menarche, and fertility are not directly affected by a diagnosis of PI, but the disorders are diverse and may affect people differently. For example, the onset of puberty may be delayed especially if nutrition is poor or for individuals who are underweight. Additionally, types of PI that are associated with endocrine system abnormalities can affect normal physical maturity and delay puberty. Likewise, chronic gastrointestinal problems can result in low weight and poor nutritional status that too can affect onset of puberty and fertility. Some medications can affect hormones that signal the body to start puberty or may affect fertility. Fortunately, for many people with PI, puberty will be achieved as expected.

Pregnancy and Newborn Outcomes

Pregnancy can be affected by PI. The most information available on the ability to become pregnant and pregnancy outcomes are for people with Common Variable Immune Deficiency (CVID) and other antibody deficiencies. The diagnosis of CVID or milder forms of antibody deficiencies is frequently delayed by many years. Many symptomatic individuals with antibody deficiencies and CVID have entered and completed their childbearing years prior to a diagnosis, despite a history of symptoms.

An IDF survey published in 2015 provided the first descriptive analyses of responses from females with CVID and hypogammaglobulinemia regarding fertility and pregnancy in this population. In this internet-based IDF survey of female individuals who self-identified as having a diagnosis of an antibody deficiency, responses to questions regarding pregnancies and outcomes from 490 women with CVID and 100 with hypogammaglobulinemia were evaluated.

Fertility as measured by the percent of women who had had a birth was reported at 70%, which was statistically significantly lower compared to the general U.S. population reported at 85%, but the rates of spontaneous pregnancy loss were comparable. Out of 966 pregnancies reported in the survey, 695 (72%) resulted in a live birth. The majority of the pregnancies reported progressed without complication and with continuation of immunoglobulin (Ig) replacement therapy; 23% reported an increase in Ig dosing during pregnancy. The rates of spontaneous abortions reported by survey respondents for first and second pregnancies were no greater than the reported U.S. national average, and terminations of pregnancies by respondents were noted to be less than the 2010 US national average. About 75% of all respondents reported that they did not have difficulty getting pregnant. Of those who had a child with a PI, 60% indicated that this did not have an impact on their decision to have more children. Timing of diagnosis

and pregnancy was evaluated as follows: for thoseand pregnancy was evaluated as follows: for those respondents whose antibody deficiency was already diagnosed at the time of the first pregnancy, over 70% reported concerns regarding their ability to have children, the child developing a PI, or the pregnancy endangering their health. Meanwhile, those who did not have their diagnosis at the time of the first pregnancy expressed little concern. Those who were diagnosed prior to their first pregnancy were more likely to indicate concerns regarding the diagnosis having an impact on their decision to have or try to have children. The results of this survey are encouraging given that females with CVID and hypogammaglobulinemia were able to get pregnant and carry the pregnancy to term.

The next largest study conducted in Czech Republic reported from the Czech National Registry of Reproduction Health on 54 women with CVID and their reported 115 pregnancies. Similar to the U.S. survey, only eight (15%) women followed had a diagnosis of CVID at the time of their first pregnancy. Eighty-eight pregnancies (77%) resulted in live births. This report noted as well that women undiagnosed and symptomatic had more spontaneous abortions; however, pregnancy complications such as low birth weight babies, preeclampsia/eclampsia, and a higher number of stillbirths occurred among the non-symptomatic, symptomatic untreated, and symptomatic treated women equally. This led the authors to conclude that women with CVID are at higher risk with respect to their pregnancies and should be followed accordingly.

Genetic testing can be performed during the prenatal period to detect a PI in which the genetic abnormality causing the disorder has been identified. (See Inheritance Chapter.) However, for CVID, the genetics are not known in the majority of individuals, and therefore prenatal testing is not possible. Newborn antibodies are primarily from the mother in the early months of life, and therefore testing newborn antibody levels will not be conclusive to determine an antibody deficiency in newborns. Screening in this way for antibody deficiency is not recommended until after one to two years of age. The IDF survey reported 15% of the births to mothers with CVID resulted in a child with a diagnosed humoral PI. Forty-four percent were diagnosed as CVID and Selective IgA Deficiency was seen in 14% of children. In the Czech National Registry of Reproduction Health children born to mothers with CVID had a similar rate of Selective IgA Deficiency at 15%.

Since the majority of pregnancies reported in the U.S. and Europe occurred without serious adverse events or excessive complications despite the majority of mothers untreated for their PI, this is a reassuring finding that PI has less harmful consequences on fertility and pregnancy outcomes than would be feared.

Women should discuss their reproductive health and family planning with their healthcare providers and immunologists. The IDF survey demonstrated concerns about the ability to become pregnant and have children in 50% of the respondents that knew of their diagnosis of PI before they had children in comparison to 25% of undiagnosed and untreated women.

Ig replacement therapy, either subcutaneous (SCIG) or intravenous (IVIG), has not been well studied in large numbers of pregnant women, although pregnant women have been treated with Ig replacement therapy without incident or adverse effect.

Ig replacement therapy is well tolerated and has specific benefits to the mother, the developing infant, and the newborn. In a healthy maternal placenta, IgG from the mother is actively transferred to the developing infant in the uterus. The transport of maternal IgG begins just beyond 28 weeks into pregnancy, steadily increases and peaks at about 36 to 38 weeks. Since a newborn is fully reliant on the protective IgG transferred from the mother for the first several months of life after birth, Ig replacement therapy during pregnancy is critical for the mother and child. Several small studies have documented the safety and efficiency of the transfer of Ig replacement therapy during pregnancy. Newborns whose mothers receive Ig replacement therapy have similar IgG levels as newborns whose mothers have a normal immune system.

Despite the general evidence of safety, there is some misunderstanding about Ig replacement therapy during pregnancy especially when individuals are not followed by immunologists. It is important to have a healthcare team focused on health of the mother and the child. Women should be followed by a high-risk obstetrician and an immunologist. The immunologist ideally will help guide healthcare decisions with the obstetrician.

It is not uncommon for individuals with PI to feel their healthcare providers do not fully understand their immune disorder and special considerations, especially for women during their pregnancy. In a

study published by Hansen and others, pregnant women on Ig replacement therapy for PI were surveyed to gauge their confidence in their healthcare provider throughout their prenatal visits. Nine women on Ig replacement therapy had full-term deliveries. Although all women surveyed had a good experience with respect to their prenatal care, the women felt marginalized and unheard when discussing their PI and need for Ig replacement therapy. Ig replacement therapy in pregnancy needs to be continued in pregnancy; however, dosing strategies during pregnancy are unguided. In the survey conducted by IDF, the majority of the U.S. pregnant women's IgG dosing remained unchanged: 25% had a dose increase, 13% received Ig more often, and 1% stated their dose was decreased. Reason for the changes were not collected. Given the increase in plasma volume during the third trimester of pregnancy, increasing the dose of Ig replacement therapy should be considered.

In pregnancy beginning around 28 weeks, the placenta develops specialized function to remove IgG from the mother's circulation into the developing infant's circulation. Studies conducted in pregnant women with normal immune systems are well studied and show the transfer of IgG of all subclasses into the developing infant's circulation. Thus at week 36 of pregnancy, IgG of diverse protection for viruses and bacteria are transferred to the baby and are equal if not slightly higher than the mother's. Although not formally studied, due to the shift in active transport of IgG to the developing child at 32 weeks and beyond, without the ability to make more IgG, mothers with antibody deficiency might need more Ig replaced to continue the same level of Ig prior to pregnancy and earlier in pregnancy. Therefore, it is best to test Ig levels throughout the pregnancy, especially in the third trimester, to watch for trends in Ig and adjust the amount of Ig replacement therapy to levels where the mother feels her best and continues to maintain levels most protective.

Studies done on Ig replacement therapy show the very same trend; therefore regardless of whether the mother is making her own antibodies or if antibodies are replaced through Ig replacement therapy, the developing infant has the same level on par with the mother including the same protective diversity. There are small studies that have shown similar results in mothers with PI on Ig replacement therapy.

Post Pregnancy

Breastfeeding

Breastfeeding is beneficial to the mothers and their newborns. Protective IgA is transferred through breastmilk. Breastmilk is rich in many proteins and factors that support immunity outside of transferred antibodies. These beneficial factors support many aspects of newborn development, and therefore is encouraged when possible. One exception can be in the case of newborns where there is a concern for Severe Combined Immunodeficiency (SCID) or other significant T cell immunodeficiency. In these individuals, there is a risk of transmission of cytomegalovirus (CMV) via breastmilk from mothers with a prior history of CMV infection. CMV infection can be fatal or lead to permanent organ damage in infants with SCID or significant T cell deficiency. Therefore, many immunologists will recommend against breastfeeding in this situation.

Caring for a Newborn

Newborn children and throughout early years will be protected with vaccinations to prepare their immunity from serious infections. Children with normal immune systems born to mothers with PI should receive all vaccinations on time as recommended by the CDC (Centers for Disease Control and Prevention) including live vaccines. Live vaccines unlike other vaccines have weakened pathogens in the make-up of the vaccine that could cause an infection in persons with PI if exposed to the vaccine virus. Children receiving live vaccines might have some of the infectious components of the live vaccines shed in their stools but not in their saliva. Examples of these vaccines received early in life include the rotavirus vaccine (2 months), and the MMR and varicella (both one year). Caution is advised when considering whether to administer live viral vaccines to the close contacts of individuals with PI; generally, this risk is greater in individuals with PI with a T cell deficiency.

The developing immune system in children will be naïve and their exposure to other children in shared nanny care, preschool, and outings can wreak havoc on households caring for recurrent but usual illnesses in children. For parents with PI on Ig replacement therapy, the infections are generally no more than expected for households with parents with normal immune systems. For siblings with PI, it may be preferred to limit some exposure with their siblings when sick, but often this is not possible. It will be important to discuss infections and childhood

activities with an immunologist as certain exposures will be pertinent to discuss depending on the specific type of PI.

Menopause

There are no published reports on the specific concerns facing women with PI and menopause. Individuals with PI experience autoimmunity and other complications such as chronic gastrointestinal symptoms. A delay in diagnosis for many individuals can mean their respiratory infections and symptoms have been erroneously managed as asthma. Management of asthma, autoimmune disease, and chronic gastrointestinal symptoms are usually with corticosteroids or prednisone. Frequent courses of prednisone are associated with accelerated bone loss and risk for osteopenia and osteoporosis. Nutritional concerns as well as limited mobility due to illness or joint disease can compound the effects of corticosteroids or prednisone. Many individuals with PI have active inflammation that may play a role in bone health. Therefore, it is possible to diagnose osteopenia and osteoporosis earlier than expected for similarly aged women and men without PI and should be addressed with a healthcare provider. Weight bearing exercise, supplements, and medications should be adjusted to minimize risk for bone loss. Individuals with PI experience autoimmunity and other complications such as chronic gastrointestinal symptoms. A delay in diagnosis for many individuals can mean their respiratory infections and symptoms have been erroneously managed as asthma. Management of asthma, autoimmune disease, and chronic gastrointestinal symptoms are usually with corticosteroids or prednisone. Frequent courses of prednisone are associated with accelerated bone loss and risk for osteopenia and osteoporosis. Nutritional concerns as well as limited mobility due to illness or joint disease can compound the effects of corticosteroids or prednisone. Many individuals with PI have active inflammation that may play a role in bone health. Therefore, it is possible to diagnose osteopenia and osteoporosis earlier than expected for similarly aged women and men without PI and should be addressed with a healthcare provider. Weight bearing exercise, supplements, and medications should be adjusted to minimize risk for bone loss.

Lastly, individuals with PI may be at a higher risk for cancer. A competent immune system will help remove cancer cells as a part of a functioning immune system, a natural surveillance against harm. Therefore, questions regarding cancer screening for individuals with PI need to be addressed. It is recommended by the U.S. Preventive Services Task Force, CDC, and American Cancer Society to have age appropriate screening for breast, cervical, and uterine cancer (women), colorectal cancer, prostate cancer, and lung cancer (based on risk factors). Fortunately, these cancers are not greatly increased in individuals with PI and a change in routine recommendations for screening is likely not necessary. The exceptions to these published guidelines are based on an individual's exposures (occupational and recreational), lifestyle, family history, and other individual risks and should be discussed with an immunologist to determine individual screening timelines.

Unfortunately, lymphoma is one cancer that has been most strongly associated with several forms of PI. There is no appropriate screening for lymphoma and individuals with PI might have symptoms that resemble lymphoma, such as persistent large lymph nodes, fevers, and weight loss that are unexplained. It was once thought that women had a much higher risk of lymphoma than men did. A recent publication demonstrated that men and women with PI have near equal risk of lymphoma and women are not at higher risk for developing lymphoma than men. Research is needed to develop better tools to screen for lymphoma in individuals with PI that are noninvasive and do not add to cost burden or excessive worry for individuals and their families.

Summary

From various surveys in different countries and registries, females with PI who had antibody deficiencies (humoral deficiencies) reported relatively good rates of fertility and pregnancies ending in live births. Breastfeeding is beneficial in many aspects of newborn development, and therefore should be encouraged when possible. The one exception are infants with SCID or severe T cell deficiencies in which breastfeeding should be avoided. Vaccination of newborns and children is important. Generally, there is little risk for parents with PI on Ig replacement therapy. However, this risk is greater in individuals with PI with a T cell deficiency, and caution is advised. In older women with PI, bone health is a concern; screening for osteopenia and osteoporosis should be considered at a younger age.

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Chapter 40

Employment and Primary Immunodeficiency Disease

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For people with primary immunodeficiency diseases (PI), employment is about more than just making money and job satisfaction. You need a job that will allow you to perform at a high standard with your disorder and will offer good health insurance benefits. There are many people with PI who have amazing jobs, and you can be one of them.

Job Selection

Let's face the facts—depending upon your type of PI, there might be some jobs that will not be appropriate for you. However, as a rule, there is no limit to the types of employment a person with a PI can have. There are many ways to work in a field you are passionate about with some adjustments. For example, there are many people with PI who successfully work in the medical field while taking necessary precautions with respect to infectious diseases. Fortunately, the job market has innumerable opportunities that could be a great fit for you.

Whether or not you would be a good candidate for employment will be based on a few basic principles:

- You have skills that employers will know how to apply to a variety of workplace settings.
- You have a positive attitude despite having a chronic illness.
- You display initiative and self-motivation.
- You show that you are determined to have a successful career even though you have PI.

The best job plays to your strengths. Remember that you are not the only one with limitations—everyone has limitations in one way or another.

Disclosing Your Diagnosis

Legally, you do not have to disclose to your employer that you have PI unless it affects completing essential job functions, and you are seeking a reasonable accommodation to perform the job. A reasonable accommodation is any modification or adjustment to a job, practice, policy, or the work environment that allows an individual with a disability to participate equally in an employment opportunity without creating an undue burden for the employer.

- **Potential Employer**: You have no legal obligation to disclose your PI to a potential employer when applying or interviewing for a job unless you have an immediate need for a reasonable accommodation.

A potential employer may not ask you if you have any disability during the application or interview period before offering you a job. An employer may only ask disability/medical-related questions if it makes a job offer to you that is conditioned upon meeting the reasonable and legitimate physical and medical requirements of the job. If the employer rescinds the job offer, the reason must relate to the job requirements only.

- **Current Employer**: Once on the job, you do not have to disclose your PI to your employer unless you have an immediate need for a reasonable accommodation.

Your employer may only ask about your disability if there is a reasonable basis for the employer to think that you are: unqualified to do the job; need a reasonable accommodation; or pose a direct threat to your own health or safety or the health or safety of others.

For more information about disclosure in the workplace from the U.S. Department of Labor Office of Disability Employment Policy, visit: www.dol.gov/odep/pubs/fact/ydw.htm.

Medical Coverage and Health Benefits

It is critical to consider the type of health insurance benefits offered by the employer. Insurance plans can differ greatly from one to the next even within the same company. Researching health insurance plans when you have a PI can be complicated, but choosing the right plan is critical. It can help you to save money and ensure the appropriate treatments are covered. (See Health Insurance Chapter.)

If you are applying or interviewing for a potential job, it is entirely appropriate to ask about health insurance benefits. Health benefits are considered compensation and should be investigated in the same way a salary is investigated. Note, the potential employer cannot ask about any disability or medical concerns in response to you asking for health benefit information.

Other Employee Benefits

In addition to health insurance benefits offered by the employer, you should also investigate the other benefits offered as well. Employers often provide short-term and long-term disability insurance coverage or wellness plans.

- **Short Term Disability.** Short-term disability (STD) insurance covers leave from work for a temporary disability, such as pregnancy, accidental injuries, and illnesses. STD insurance replaces a portion of your income, which is a huge benefit. The percentage of income paid depends on the insurance plan. The replacement income comes from the insurance company, not the employer. Some states with STD insurance: California, Hawaii, New Jersey, New York, and Rhode Island.

Note, many STD insurance plans do not cover preexisting conditions, such as PI, or do not cover such conditions until the expiration of a certain period such as 12 months. Also, some may cover preexisting conditions but have certain specific conditions which are excluded. Be sure to investigate these rules.

- **Long Term Disability.** Long-term disability (LTD) insurance picks up where STD insurance leaves off. Once the STD benefits expire (generally after three to six months), LTD insurance pays a percentage of your salary, usually 50 to 60%, depending on the policy. The benefits last until you can go back to work or for the number of years stated in the policy.

It's important to note that like STD insurance many LTD insurance plans do not cover preexisting conditions, such as PI, or do not cover such conditions until the expiration of a certain period of time such as 12 months. Also, some may cover preexisting conditions but have certain specific conditions which are excluded. Be sure to investigate these rules.

- **Unpaid Medical Leave.** Even if you are excluded from STD insurance due to PI being a preexisting condition, you may be entitled to medical leave under the Family and Medical Leave Act (FMLA). This Federal law provides protections when you miss work because of PI or you need to care for a child/spouse with a PI. You may also be entitled to medical leave under the Americans with Disabilities Act (ADA). State workers' compensation laws and/or medical leave laws may have additional provisions that apply as well.
- **Cobra Insurance.** The Consolidated Omnibus Budget Reconciliation Act (COBRA) gives workers who lose their health benefits the right to choose to continue group health benefits provided by their plan under certain circumstances.

  In the event that you lose your health coverage for a qualifying event, your employer will send you an election notice within 14 days after your last day on the health insurance plan. You will then have 60 days to decide whether to elect COBRA continuation coverage. You will then have 45 days after electing coverage to pay the initial premium. Expect to pay the total premium (both your employer's and your contribution to the premium) plus 2% for administration expenses. Also, another important note is that the premiums are not tax deductible, like they are when they are deducted from payroll.

COBRA defines certain qualifying events that would cause an individual to lose health coverage. The type of qualifying event will determine who the qualified beneficiaries are and the amount of time that a plan must offer the health coverage to them under COBRA. A plan, at its discretion, may provide longer periods of continuation coverage.

- **Qualifying Events for Employees (18 months coverage)**
  - Voluntary or involuntary termination of employment for reasons other than gross misconduct
  - Reduction in the number of hours of employment
- **Qualifying Events for Spouses**
  - Voluntary or involuntary termination of the covered employee's employment for any reason other than gross misconduct (18 months)
  - Reduction in the hours worked by the covered employee (18 months)
  - Covered employee's becoming entitled to Medicare (36 months)
  - Divorce or legal separation from the covered employee (36 months)
  - Death of the covered employee (36 months)
- **Qualifying Events for Dependent Children**
  - Loss of dependent child status under the plan rules (36 months)
  - Voluntary or involuntary termination of the covered employee's employment for any reason other than gross misconduct (18 months)
  - Reduction in the hours worked by the covered employee (18 months)
  - Covered employee's becoming entitled to Medicare (36 months)
  - Divorce or legal separation of the covered employee (36 months)
  - Death of the covered employee (36 months)

Additional information on COBRA benefits can be found at: www.dol.gov/general/topic/health-plans/cobra.

Legal Protections: Federal and State Governmental Policies

For those living with a PI, there are several Federal and State laws that provide protections.

Americans with Disabilities Act: The Americans with Disabilities Act (ADA) states that employers with more than 15 employees may not discriminate against a qualified individual on the basis of disability in regard to job (application hiring, promotion, firing, compensation, job training etc.). According to the ADA, a disability is:

- A physical or mental impairment that substantially limits one or more major life activities of an individual (PI qualifies under this definition).
- A record of such an impairment, or
- Being regarded as having such impairment

This means that you cannot be eliminated from consideration for employment or from your job because of your PI if you have the skills, experience, education, or other requirements for the job you already have or the job you want, and you can perform the essential functions of the position with or without reasonable accommodation.

The ADA requires employers to offer a reasonable accommodation to employees with a disability. As described earlier, a reasonable accommodation is any modification or adjustment to a job, practice, policy, or the work environment that allows an individual with a disability to participate equally in an employment opportunity without creating an undue burden for the employer. Reasonable accommodations may include: modifying a work schedule; acquiring or modifying equipment; time off for medical appointments; telecommuting arrangements; or many other accommodations.

As a result, you may be eligible for certain reasonable accommodations to permit you to perform your job despite some restrictions of your PI. For more general information about the ADA, visit www.ada.gov, and additional information about reasonable accommodations is available at www.eeoc.gov/policy/docs/accommodation.html.

Family and Medical Leave Act: The Family and Medical Leave Act (FMLA) allows qualified employees working for a company with more than 50 employees to take unpaid, job-protected leave for specified family and medical reasons, with continuation of group health insurance coverage under the same terms and conditions as if the employee had not taken leave. Qualifying reasons for FMLA leave include but are not limited to:

- A physical or mental impairment that substantially limits one or more major life activities of an individual (PI qualifies under this definition)
- A record of such an impairment
- Being regarded as having such impairment

Eligible employees may take up to 12 weeks of unpaid leave under FMLA. The leave does not have to be consecutive and can be taken intermittently.

Additional information about FMLA is available at www.dol.gov/whd/fmla/.

U.S. Equal Employment Opportunity Commission: Another important government agency that is a valuable resource is the U.S. Equal Employment Opportunity Commission (EEOC). The EEOC is responsible for enforcing federal laws that make it illegal to discriminate against a job applicant or an employee because of the person's race, color, religion, sex (including pregnancy), national origin, age (40 or older), disability, or genetic information. It is also illegal to discriminate against a person because the person complained about discrimination, filed a charge of discrimination, or participated in an employment discrimination investigation or lawsuit. For more information, visit www.eeoc.gov/eeoc/index.cfm.

Chapter 41
Health Insurance

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Treatment of primary immunodeficiency diseases (PI) has evolved over the years, and there are effective, lifesaving treatments available to those diagnosed with these rare, chronic disorders. However, these treatments often come at a significant financial burden to the individual with PI and their families. The majority of people with PI rely on some form of insurance to assist with expenses, but dealing with health insurance and understanding the maze of issues involved can be overwhelming.

Often health insurers require additional paperwork to justify the use of the therapy prescribed. Added red tape and follow-up phone calls can be frustrating. Even individuals who have adequate insurance coverage often face expensive insurance premiums or high co-payments or coinsurance. Many people living with PI may be confused about their insurance options. Others simply lack affordable health insurance. Medicare beneficiaries have additional questions to consider.

IDF Patient Insurance Center

The Immune Deficiency Foundation understands these challenges and maintains the IDF Patient Insurance Center: www.primaryimmune.org/insurance. While not designed to solve each and every problem, the information provided there will help prepare you to be your own best advocate. Regardless of how you and your family obtain your health insurance, it is ultimately your responsibility to understand your plan. It is up to you to choose the plan that is right for you and your family's healthcare needs.

Individuals living with PI need to make educated decisions about their coverage options. Do a thorough plan comparison to determine what plan best fits your needs. Things to look at include:

- What is my premium?
- What is my out-of-pocket maximum?
- What are my deductibles?
- Is deductible included in the out-of-pocket maximum or is it in addition to the maximum?
- How is immunoglobulin (Ig) replacement therapy covered?
- Do I have a coinsurance or a flat co-pay?
- Do I have options for site of care?
- Are my doctors in the plan's network?
- Are there out-of-network benefits?

These are basic things to consider. More information is available in the IDF Patient Insurance Center.

You may need to contact the insurance carrier or get assistance from your benefits or human resources department in obtaining the answers to these questions. Once you have these questions answered, you can make an informed choice.

Understanding your plan can have a huge impact on both your health and your finances. When it comes to your healthcare insurance coverage, never hesitate to ask questions and search for as many resources as possible.

Visit the IDF Patient Insurance Center: www.primaryimmune.org/insurance.

Chapter 42

Infants and Children Living with PI

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When a child is diagnosed with a primary immunodeficiency disease (PI), each member of the family is affected. The family must come to terms with the illness and be prepared to adjust schedules and priorities. With proper anticipation and realistic expectations, quality of life can be normal.

Helping a Child Understand

Children's understanding of PI depends on where they are in terms of their cognitive development. They adjust differently to illness and family life at each developmental stage. Here is information about how children cope at different ages and how a parent/caregiver can help a child better understand their diagnosis.

Infants and Toddlers (ages 0 to 2) are just beginning to develop trust and security, and they usually do not have an understanding of their diagnosis. They may experience challenges to their development of trust and security when they experience pain, restriction of motion, and separation from parents. A parent/caregiver can help by staying with the child for medical procedures and hospitalizations as well as holding, comforting, and interacting with the child as much as possible. Bringing a favorite stuffed animal, pacifier or blanket along to treatments may be helpful as well.

Preschool Children (ages 3 to 4) are ready to begin to be independent and eager to make choices. They may understand what it means to get sick, but they may not understand why and how. Being in the hospital or adjusting to medication schedules can sometimes take away their freedom and choices. Children may try to challenge limits set by parents as a way to exert some control. A parent/caregiver can help by being firm and consistent with things the child does not have a choice over (such as taking medications, going to the doctor, etc.). However, when possible, let them make some decisions, like what medication to take first, what chair to sit in when getting blood drawn, and what color bandage to use or which site to use for their treatment. Rewarding a child for making positive choices about their health is also important. Do not make promises to the child that cannot be kept. For instance, do not promise a child that it will only be one poke or that there will not be any blood draws at any certain office visit. Broken promises can damage trust in this age range.

Early School Age Children (ages 5 to 10) are developing a stronger sense of control over their environment. They may have a greater understanding about their disease, but these reasons may not be entirely logical. Children in this developmental stage may believe they caused their illness by thinking bad thoughts, acting out, or by not following rules at home. At this stage, children are also beginning to notice that they may seem different from their peers. When these emotions are not dealt with, they can lead to sadness, anger, anxiety, or withdrawal. Parents can have a big influence on how their child responds to feeling different. Remind them that they are not alone. Engage in an ongoing dialogue about what they are experiencing and encourage them to share their feelings. Parents can help by making sure their child knows that their diagnosis is not their fault and that they did nothing to cause it. It may also be beneficial to allow children to participate in the management of their care. For example, allowing the child to communicate with their doctor or help keep track of their medication schedule can go a long way in helping the child develop a stronger sense of control.

Parents can help children cope with their disease and treatments by encouraging them to practice on a doll or stuffed teddy bear with a toy doctor kit. Letting the child take the doll or bear's temperature or blood pressure, listening to its breathing, or even practice painful procedures (such as shots, blood draws, infusions, etc.) can help relieve anxiety the child may be feeling. Parents/caregivers should participate in this play, but it is important for the child to take the lead.

Older School Age Children (age 11+) want to be more independent from their parents. Relationships with friends and social activities are exceptionally important to children of this age. Children may feel frustrated, angry, and left out if they are forced to miss activities due to illness or restriction. Children of this age may also start to struggle with not wanting to take their medicine, especially if they are feeling well. They may not feel as though they need it any longer. While they are better able to understand their diagnosis and its treatment, they should not be expected to react as adults do. Parents/caregivers can help by explaining to the child how important medications can be in the management of PI, even when they begin to feel better. With the approval of the child's healthcare provider, the child should participate in school or other activities whenever possible. Be sure to include the child in discussions with their medical team when possible. Encourage the child to prepare for a medical visit by writing down questions to ask. This will help children feel included and give them a greater sense of control over the situation. Listening to the child is always essential, and it may be helpful to encourage the child to express emotions through play, art, drawing, music or reading.

Normalizing a Child's Life

Parents of a child living with PI may be faced with challenges, difficulties, and decisions that other parents will never have to face. This may be overwhelming; however, there are ways to support the child and help the family cope.

Medical

Explain the diagnosis to the child in ways he or she can understand. One of the most important things parents can do for children with PI is to provide accurate age-appropriate information and encourage children to ask questions. Children who lack information about their diagnosis tend to make up information that is often inaccurate and scarier than the actual circumstances. It is important to let children know that the diagnosis is not their fault and that it is not a punishment. Make sure the child knows that the parents/caregivers are there to answer any questions they may have. Having open and honest communication with the child helps build trust and a sense of security, and it helps the child cope better. It is important to let the child know that the parents/caregivers trust the healthcare team so the child, in turn, can learn to trust providers.

Become informed about special medical issues affecting the child. These may include:

- Infection precautions, including school, sleepovers, camps, and airline travel
- Use of antibiotics if they get sick or following known exposures
- Vaccines for the child and family
- Avoidance (if necessary) of swimming, gardening, playing in the leaves, etc.
- Precautions about school sports if necessary
- Nutrition
- Dental hygiene
- Genetic counseling of parents
- Insurance issues

Prepare the child for medical procedures. Children need to know what to expect before medical appointments. Explain, in an age-appropriate way, the reasons why procedures are being done, who will be doing it, what equipment will be used, and whether or not it will be painful or uncomfortable. This will give the child an opportunity to ask questions, build trust, and cope in their own ways instead of worrying about the unknown. It is important to give consistent and accurate information. For example, do not tell the child that something will not be painful or uncomfortable when it will be. Child life specialists are available at many hospitals and can help prepare children for hospitalization, surgery, and various medical procedures.

Emotional

Help the child deal with feelings about the diagnosis. Try to understand the many emotions that children experience regarding their PI. Parents/caregivers can help the child cope with difficult emotions by talking openly about how everyone experiences similar emotions at times in their life—isolation, anxiety, sadness—for various reasons. Providing routine and predictable times to check in with a child gives them opportunities to talk and to share, and it gives parents/caregivers opportunities to reassure them that their feelings are normal and acceptable. Parents/caregivers can ask questions in a way to get a child talking by using open-ended questions. "What kind of questions do you have?" is very different than "Do you have any questions?" Parents/caregivers can also ask questions about specific

behavior: "Lately, you have been getting angry about things that do not normally bother you. Why do you think that is?" Finally, provide ways to help the child get rid of unhappy feelings. Some examples include using play or art to express their emotions.

Give a child choices whenever possible. Many children living with PI tend to think they have little control over their lives. Children need opportunities to make choices—to have power over any part of their lives they can control. This can be done by offering the child choices whenever possible (such as what they would like for dinner, what activity they would like to do that day). When appropriate, it can also help to have the child participate in making small decisions about their treatment (such as what arm to get a shot in, what day of the week or month to take their treatment, what site to use to get their infusion, etc.).

Social

Prepare the child for the reactions of others. Children with PI often do not know how or what to tell others about their illness and symptoms, particularly at times when they look healthy on the outside.

Parents/caregivers can help by teaching the child a simple and short explanation of the diagnosis. Make sure they are comfortable explaining what is necessary to stay well. It may help to role-play examples of how to answer questions that others might ask and to handle any teasing that might occur. Be sure to include siblings in these discussions as well, as they often experience similar situations with their peers.

Look for role models. Many children with PI feel different and isolated. Being around others with the same diagnosis can often help them in this regard.

- The Immune Deficiency Foundation (IDF) offers many ways for children and families to interact throughout the year at events held across the country: www.primaryimmune.org/events. Children often benefit from having contact with others who have the same illness.
- Parents/caregivers can also connect online through IDF Friends, www.idffriends.org, or in the IDF Facebook groups, www.facebook.com/ImmuneDeficiencyFoundation.
- Additionally parents/caregivers can request IDF to connect them with a trained peer support volunteer that has experience living with a child who has PI: www.primaryimmune.org/idf-peer-support-program.

School

Living with a PI may disrupt a child's schooling. It is important for parents/caregivers to meet with teachers, counselors, nurses, and administrators to explain their child's PI and the potential impact on school (such as frequent absences, fatigue, activity restrictions). Consider what parents and other children in the class should be told about the child's diagnosis, if anything. One issue that should be discussed with a child's teacher and school nurse includes a reminder to other parents/caregivers in the classroom to keep children who have infectious symptoms home in order to limit exposures to infections. For instance, ask the teacher to review protocol surrounding fever or vomiting with class parents. A plan should be developed to help the child keep up with schoolwork when they cannot attend school. An excellent free resource to help coordinate with a child's school is the IDF School Guide, available to order or download at: www.primaryimmune.org.

Family Life

A diagnosis of a chronic illness such as PI affects the entire family system. Research shows that how well a child with a chronic illness copes depends on how the entire family is supported. A family that has healthy coping skills is more likely to follow treatment and care plans, and to be active in seeking support.

Chronic illness can affect a family in many ways. Some parents/caregivers may experience increased worry, stress, problems with sleep or appetite, sadness, anger, a sense of loss, and even a feeling of relief. These conflicting emotions can be difficult to deal with, but they are a normal part of the coping process. Parents/caregivers may have less time for each other and for social activities they once enjoyed. Planning for fun times may be difficult due to the unpredictability of the child's illnesses. Financial worries may also increase.

Siblings may experience a wide range of emotions when their brother or sister is living with a PI. These emotions often include anger, guilt, embarrassment, sadness, loneliness, fear, and confusion. Siblings may also experience jealousy if they receive less attention. It is important to talk with siblings about their feelings and not to simply dismiss them, thinking they will get over it on their own.

Families can benefit from strategies that help them to relieve stress, share responsibilities, gain support, and explore emotional worries. Approaches include:

- **Help the child lead as normal a life as possible.** To whatever extent possible, try to treat the child with a PI just like any other child. At the same time, parents/caregivers need to take into consideration the child's health and any special needs that they may have. This can be a balancing act, but it is important for parents/caregivers to encourage their child's participation in activities that involve other children of the same age.
- **Maintain family routines.** As much as possible, maintain regular family routines (such as wake-up times, mealtimes, bedtimes, regular activities, chores, discipline, etc.) as this can help offset some of the disruption experienced due to living with a PI. Children typically do better when their daily routines are predictable and consistent. Of course, this is not always possible, but every effort should be made to maintain structure and schedules for family members. Continue to enforce the usual discipline in the household. Setting and enforcing limits that are fair to all family members will decrease resentment in siblings.
- **Help the other children cope.** A child living with a PI may demand a lot of parental attention. Siblings may feel jealous, angry, lonely, and worry about their sibling and about their parents/caregivers. They also might worry that they might get the disease. Explain the disease to siblings. Try to get them to ask questions and to express their concerns. Parents need to keep lines of communication open with all of their children. It often helps children feel like an important member of the family if they can have a part in caring for their sibling in some way. One way to help siblings is by focusing on fun family activities when the child with a PI is healthy. It can be beneficial for parents to spend individual quality time with each child, letting each of them know how much they are loved, valued, and appreciated.
- **Make having fun together as a family a priority.** Living with a child's PI may cause the whole family to be under increased stress. Getting support from each other may be harder during times of stress, but it is also even more important. Spend time together that is not focused on the disease and make it a priority to carve out time for whole family activities. It is equally as important to have special alone time just for parents/caregivers and even for one-on-one parent-child dates.

Coordinating The Child's Healthcare

When a child is diagnosed with a PI, parent/caregivers become part of the child's healthcare team and their main advocate. The role in monitoring the child's symptoms, responses to treatments, and communicating the observations and concerns is vital to the medical team's assessment and treatment of the child. In many cases, more than one provider will be involved in caring for the child; therefore, coordinating communication and keeping comprehensive and accurate records of the child's medical course is essential. Many parents/caregivers suggest that a journal is an invaluable tool to document events affecting the child's medical care. There are also online personal health records that can be helpful.

Recommended information to record:

- Brief history leading to the diagnosis, written by a parent/caregiver or the child's healthcare provider.
- Copies of laboratory evaluations confirming the diagnosis.
- Current list of providers caring for the child with accurate addresses and phone numbers.
- Chronology of important events, specifically noting types of treatment and therapy, changes in therapy and subsequent responses to that therapy, surgeries and/or hospitalizations.
- List of the child's current medications.
- Allergies to medications.
- Immunization record.
- Current insurance information.
- Explanations of benefits (from the insurance company) can be kept in the journal or separately but should be periodically reviewed for accuracy.

Insurance concerns that arise are more easily resolved through accurate record keeping. A journal or online health record will be useful if the child should need to see a new provider, especially in an emergency. This form of accurate record keeping shortens the lengthy, often repeated history-taking sessions by new providers, allowing more time to focus on the immediate issues at hand. It is wise for more than one person in the family to be aware of the child's medical routine. A well-documented

medical record maintained by parents/caregivers can be extremely helpful for those times when others care for the child.

In addition to bringing a journal to each medical visit, additional suggestions when visiting a medical professional include:

- **Prepare questions**: Have a list of questions prepared in writing.
- **Take notes**: Document the visit by writing details about the visit. When possible, take another family member or friend along. It is always wise to have more than one person familiar with the child's medical routine.
- **Plan ahead**: Be prepared for a change in plans or long office visits. Sometimes parents/caregivers and the child will go for tests immediately after the visit or the visit could be extended for other reasons. If this is the case, make arrangements for other children.
- **Communicate directly with the child**: Encourage the healthcare professional to communicate directly with the child when possible. Although the child may be young, it is always appropriate for them to build a relationship with their healthcare providers.
- **Ask for written instructions**: Request written instructions concerning medicines and treatments. This helps avoid mistakes by all parties, and provides written instructions to be placed in the journal or scanned and saved into an online personal health record.
- **Prepare a tote bag**: Designate a special tote bag just for these medical visits and include the following items:
  - Toys and/or activities: It may not be wise to share toys at the doctor's office to reduce exposure to germs. You can also prepare age-appropriate activities to engage them.
  - Books: Take along favorite books or a new book to help the child stay occupied and calm during long waiting periods.
  - Game device or smart phone: These are also useful for distraction and to alleviate boredom.
  - Notebook: Parents/caregivers or another family member can take notes.
  - Contact list: Include a contact list with names and phone numbers of family, friends, and school personnel.
  - Snacks: Bring snacks in case the visit may be extended.

Being a Child's Advocate

A parent/caregiver is their child's best advocate. It is important to communicate concerns and questions to the child's providers. Using a journal or an online personal health record will help remind a parent/caregiver about what to discuss with the child's provider at various visits. Overall, parents/caregivers should follow their intuition. They generally know when something is going on with their child.

How to Advocate for a Child:

- Ask questions about the child's diagnosis, treatment, and plan. Ask again if there is something unclear.
- Inquire about what can be done to improve the child's health, such as diet, physical activity, sleep, and social activities.
- Maintain consistent communication with the school as the child may miss school days.
- Know the child's insurance policy and communicate if there are any changes to the provider.
- If the child receives immunoglobulin (Ig) replacement therapy, make notes of how it is going and/or any side effects.
- Build positive relationships with the child's providers, teachers, and therapists. Know whom to call when.
- Ask about resources for further information at the local, state, and national level.
- Connect with IDF for additional resources: www.primaryimmune.org or 800-296-4433.

Transitioning Responsibility to the Child

As children develop, they begin to form their own thoughts and opinions of their care. When it is appropriate, offer choices to the child. This helps the child build confidence because they have some control over decision-making and will prepare the child to participate and eventually take over their healthcare in adolescence and adulthood. The better prepared the child is, the easier the transition will be.

When to Ask for Help

Having a child with a PI forces the entire family to cope with many changes and stressors. It can cause emotional and behavioral challenges for the child, parents, siblings, and extended network offamily and friends. Because of these challenges, family members may be more likely to experience adjustment difficulties as they learn to adapt.

It is important to support the child's emotional and behavioral needs as well as the needs of the entire family. Counseling services can be a valuable part of the child's treatment plan. The most successful families tend to be those who are working together as a team to face the new responsibilities of managing a long-term illness. They build on their family's strengths to cope with the new stress and can help the family grow closer together.

Every situation is unique, but there are similarities in how children and families react to the stress of living with PI. Adjustment difficulties commonly observed in children with chronic health conditions and/or in their parents and siblings include the following:

- Disturbance of mood: feelings of anxiety, fear, sadness, depression, hopelessness, irritation, anger, emptiness, and/or guilt; frequent worrying; disinterest or lack of pleasure in activities formerly of interest.
- Behavior difficulties: mood swings, temper outbursts, aggressive behavior, not cooperating with medical care, changes in activity or energy level, separation anxiety or clinging behavior, regressive behaviors, reenactment of their situation/trauma, and/or acting out by not listening, fighting, or even hitting.
- School issues: academic problems, change in school performance, and/or difficulty with concentration.
- Social issues: isolation from peers, feeling disconnected from people, lack of interest in things they previously enjoyed, and/or fights with friends.
- Self-esteem issues: sense of being different, low self-confidence, and/or negative comments about the way they look or feel.
- Family issues: increased strain in relationships, different perceptions of issues, blame, communication difficulties, fights with siblings, and/or ignoring other family members.
- Parent issues: time-management difficulties, financial worries, marital stress, guilt, self-blame and/or blame of others, grief, and/or discipline problems
- Physical issues: changes in eating, sleep disturbances, stomachaches, headaches, tiredness, and/or over-activity.

Remember that it is a sign of strength to be able to ask for help from counselors and other support professionals. Support can be sought at any time. Parents/caregivers do not need to wait for a crisis. In fact, it is better to arrange for support sooner rather than later. Also, it is normal to experience the need for support at some times and not at others. Adjustment is an ever-changing process.

Addressing the Needs of the Parents/Caregivers

Parents/caregivers should remember to take care of themselves. Addressing personal needs will allow a parent/caregiver to provide better care for the child.

Learn about a child's diagnosis. Being knowledgeable allows parents/caregivers to make informed decisions about their child's care and to know which behaviors and symptoms are normal and which are not. It also helps parents answer questions their child may have about their disease.

Practice self-care. This may seem like a difficult task for many parents/caregivers. Nevertheless, it is vital for parents to take care of themselves. Otherwise, they will not be able to give good care. It is important to get connected with other parents who know what it is like to have a child living with a PI. Allow others to help and be sure to carve out time to do something you enjoy. Find someone to listen to the worries and make it a priority to spend quality time with the partner on a regular basis. Learn to deal positively with the stress by eating right, exercising, keeping a journal, and spending quality time with the children.

Remain hopeful. Coping with PI can be discouraging and scary at times. It is important to stay positive and hopeful. Do not ignore or dwell on worries and negative feelings. Instead, recognize and address them in a positive manner. Trying to find the positive side of things enables parents/caregivers to teach their children a valuable lesson as well as maintaining their own peace of mind.

Chapter 43

Adolescents Living with Primary Immunodeficiency Diseases

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Adolescence is a time of great transition physically, cognitively, socially, and emotionally. Adolescents diagnosed with a primary immunodeficiency disease (PI) and their families face not only the day-to-day challenges of any family, but they also must learn to manage the effects of a rare and chronic disease while nurturing growth towards adulthood. Regardless of when an adolescent was diagnosed, they face some unique challenges, and it is important to help them manage the impact of PI as they strive to achieve the developmental steps or stages of a teenager.

Although typical adolescent trials may be more stressful and confusing for those living with PI, you and your adolescent can work together to overcome challenges and enjoy this unique time preparing for the transition into adulthood.

Normalizing Your Adolescent's Life

During this life stage, adolescents develop the skills needed to establish and maintain family and social relationships. Education continues as they begin to make decisions about their future life goals. They typically go through a series of steps in this maturation process, commonly having both successes and setbacks in navigating the path toward adulthood. School and social time with friends are often the focus as adolescents begin to explore their independence and separate from prior parental attachments. This can be difficult for both parents and adolescents. A balance must be achieved between maintaining an optimum level of health and being able to actively participate in desired activities. In addition, PIs manifest differently in each individual. Therefore, families must make choices that best suit their adolescent's physical and mental health, as well as abilities.

You can help your adolescent through this time by teaching coping skills to manage day-to-day issues associated with PI while helping them live a normal life.

Begin a dialogue with them, so that they can become a part of their health-related decision-making that impacts their life. Lead off any discussion by asking about their feelings, views, and experiences. This approach helps to establish a respectful discussion in both directions.

Helping your adolescent maintain a balanced life.

Teens who best manage their diagnosis are those who find a balanced approach to PI and to life. It is understandable that adolescents would often want a break from focusing on PI, yet neglect of symptoms or treatment routines can lead to serious health setbacks. An emphasis should be placed on both managing their condition (the signs, symptoms and treatments) and maintaining overall health itself (the activities and relationships that promote a healthy lifestyle). The Immune Deficiency Foundation (IDF) Teen Program offers opportunities for teens to help them learn about living with PI and to connect with others. Contact the IDF at **www.primaryimmune.org** to learn more.

Coordinating with their school.

Living with a PI may disrupt schooling, and as previously mentioned, school is an integral part

of an adolescent's life. You and your adolescent should meet with teachers, counselors, nurses and administration to explain the PI and the potential impact on school, such as frequent absences, fatigueand illness. Work with these professionals to develop a plan to help them keep up with schoolwork when they are absent. A good resource to help you coordinate with their school is the IDF School Guide, which can be ordered or downloaded at www.primaryimmune.org.

Encouraging a healthy social life.

Encourage your adolescent to explore their talents and interests, and help them to set realistic expectations based upon their individual capabilities and medical needs, and focus on their strengths. Encourage participation in athletics, music, dance or whatever peaks their interest. Having fun outside of family, school and medical appointments will build confidence and help them cope with periods of illness.

Allow your adolescents to participate in school and social activities whenever possible to help them understand that they are living a valuable life with purpose and enjoyment. Remember that school and social events are central to teenagers, and missing out because of a PI can be very difficult for them. Acknowledge such disappointments while balancing their health. There is always a chance that they can become ill since germs exist everywhere, but preventing them from participating in group events can create feelings of anxiety and depression. Making simple modifications, such as using hand sanitizer, avoiding shared beverages, and staying away from actively coughing individuals, can allow them to participate.

There are some restrictions that people with certain PIs must follow. For example, those with thrombocytopenia should avoid contact sports. Football or soccer is risky for those with Chronic Granulomatous Disease (CGD) because of exposure to dust or grass. Restrictions should be determined with the immunology team.

Teenagers already struggle with identity issues and confidence, and feeling different can further complicate this matter. Although they might not want to share information about their diagnosis with peers, it is important to develop strategies to help them educate peers and to explain their condition, including the appropriate terms for diagnosis and treatment. Then, they are prepared if they decide to share this information. Because PIs are rare, adolescents may not know others their age with the same illness. They must develop strategies to cope with questions and misconceptions they may come across. If they are able to clarify peer questioning and talk about their experiences, peers will be less likely to gossip about the condition.

Assure them that they can disclose as much or as little information as they want. They may not feel comfortable telling everything to everyone. They can choose to confide in some and to provide minimal information to others. This is completely their decision. Make sure that you do not publically share more information about their PI than your adolescent does. Respect their wishes when it comes to this.

Start conversations about dating not only to encourage positive decisions but also to help you get to know your teenagers as they mature. Dating is a hallmark of adolescence, and speaking to your son or daughter about how to talk about their PI and safety concerns is important. Although rejection is a normal part of dating and people reject others for all sorts of reasons, reiterate that if someone rejects them because of PI, that person is not the right person for them. It is important to let them know their value and that people with PI date, marry, have children and lead full lives.

Maintaining Family Life with Adolescents Living with PI

Parenting issues in adolescence can be intensified by chronic conditions. Families may struggle to find a balanced approach to maintaining their family life and addressing the health issues. Time, activities and family decisions may require daily modifications. In addition, adolescents with PI often feel guilty that they are burdening their parents with the additional pressures of their illness. Be sure to let them know all the wonderful things that they add to your life, so that you can let them know how valued they are.

Adolescents and their families who best cope with an ongoing health problem typically follow a pattern during the maturation process. In early adolescence, parents are more involved in overseeing and modeling positive healthcare practices. Later, parents should encourage increased involvement and independence. Finally, as they move toward adulthood, parents should encourage them to take main responsibility for managing the disease, with family members as more distant supporters.

Increased attention to medical care and modifications to the family routine may cause strain amongst siblings. Siblings can feel jealous of the

attention given to the brother or sister who has a PI. Acknowledging the impact of a chronic illness upon siblings not diagnosed with PI is important. Praising siblings for their patience and acknowledging the challenges of having a family member with PI can help decrease resentment and validate the siblings' experience. Encourage sibling input on family decision-making, so they feel that their suggestions are also important.

When two or more children in the family have PI, there can be a greater connection and shared understanding gleaned from the common experience. There may be less resentment between siblings than if one child did not have the disease. However, the emotional impact can vary based on individual personalities, coping skills and different degrees or manifestations of the disorder. It is important to individualize every child's needs and not to generalize experiences.

Preparing for Tough Questions from Adolescents Living with PI

Common questions or issues that you may hear from your son or daughter:

I hate being treated differently! Why can't I be just like everybody else?

It will vary in each individual how much they wish to express their uniqueness or how much they want to blend in with the crowd. Helping them find their own distinctive qualities and talents will help build confidence.

What do I tell my friends about PI?

This may be related to the question about being treated differently. It also involves learning relationship skills of trust building and sharing. They can benefit from a trusted peer who can understand and offer personal support. Conversely, they can be hurt by less mature peers who use personal information as a way to bully or tease. Help them make wise choices in their friendships and personal sharing. Encourage them to take advantage of the IDF Teen Program, which includes weekend events exclusively for teens with PI, to learn more about their disease and to connect with others.

How do I handle my PI at school?

When asked this, you may want to determine if they mean the social aspect of school and/or the academic side. They may be asking about how to deal with teachers, coaches, assignments, and team requirements. While a long-term goal is self-responsibility, some school issues may require you to help establish positive relationships with school personnel and include them in setting realistic expectations for balancing health and school performance. Consult the IDF School Guide, which can be ordered or downloaded at www.primaryimmune.org.

Why do I have to go see my physician/take my medications/continue my treatments?

As adolescents acquire new levels of responsibility, there will be times that they will want to do things differently. Begin by listening to their concerns. It is possible that a treatment or management regimen made when children were younger can be changed or modified to meet the needs of older children. Some of the questions about care may relate to a healthy need to have a greater sense of control over their life. This may be a good time to review their current responsibilities throughout their life, not only with healthcare but also with home responsibilities, schoolwork and recreational activities. Having a greater sense of control in other areas often helps balance the sense of lacking control that can come with living with PI. Schedule an appointment between your adolescent and their immunology team to discuss why taking medications and continuing treatment is important.

Am I going to be dealing with this disease forever?

Younger adolescents may ask this when they realize that PI will not be like other health problems they have experienced, like a sprained ankle or broken bone, which has healed and is now forgotten. This may be about that balance of addressing the illness and health aspects of their diagnosis, and realizing how health and wellness habits will help them. Older adolescents may ask this when they are thinking about their future—career plans, college plans or developing relationships. Discuss how they can apply earlier learning experiences to these new challenges, and suggest talking with their healthcare providers.

Why do I have to have this disease? It's not fair!

"Why me?" is a question often asked by those with a chronic condition. This is a very tough question, and is often asked by parents as well. This may be a question about their particular diagnosis and how the immune system works. Often, though, this question is looking beyond scientific answers and looking more toward personal beliefs and values about life. Assure your adolescent that this is not their "fault." Remind your child that there are many who are also living with PI, and that it is not a punishment, but

something they just have to learn to manage and life with. Creating a positive mindset will help them to better take control of their condition and life.

Offering Resources and Professional Assistance

Many adolescents with PI often feel misunderstood. As much as family and friends may attempt to empathize the impact of these diseases, only individuals with PI can really understand what this disease feels like. Encourage them to connect with peers with PI through the IDF Teen Program. Having others to relate to is invaluable in providing encouragement. Not only can it foster supportive friendships, but involvement with others with PI can also help them feel that they are neither alone nor different from others. IDF Teen Escape weekends, which are held each year in various cities throughout the country, are designed to help teens develop coping skills, promote and nurture friendships and provide educational guidance for those living with PI. IDF holds biennial National Conferences and Regional Conferences, during which there are programs for teens. Teens may not feel they need to attend such programs, but those who do attend have said they've had extremely positive experiences. For more information about programs and resources for teens, contact IDF: www.primaryimmune.org. Almost everyone is connected on social media today and there are support groups for every possible subject available almost instantly. Make sure that they do not confuse any posted public information as a substitute for professional advice. Anyone can write anything on social media.

Seek professional assistance if they display symptoms of depression or anxiety. They can feel isolated as well as overwhelmed by the impact of feeling ill, limitations in productivity and awareness of financial burdens. It is important for you to recognize the signs and symptoms of depression and contact a mental health professional. Symptoms of depression include:

- Shifts in overall mood and outlook
- Changes in eating and sleeping patterns
- Negative self-talk
- Increased isolation
- Irritability, anger
- Hopelessness, tearfulness

Coping for Parents with Adolescents Living with PI

Parents of children with chronic illness not only worry about their children's physical and emotional care, but they also carry the extra burden of managing financial and insurance issues. This can be incredibly stressful. Of course, children require support, but parents also need to receive some extra, outside assistance. Having a place to vent about how difficult this challenge can be is important and receiving support from friends, family and partners is necessary. Just as it is imperative that adolescents are connected to the PI community, parents should be too. Having a connection to another parent who understands your experience can be helpful. Parents of individuals with PI may understand your experience more than friends and family who have not had this experience and may find it difficult to relate to the daily pressures of dealing with PI. Taking care of your emotional well-being can make it easier for you to manage caring for any adolescent with PI. IDF offers a variety of resources and programs to connect you with other parents on the IDF website: www.primaryimmune.org.

Coordinating Your Adolescent's Healthcare

Managing your adolescent's healthcare calls for a high level of communication and teamwork among healthcare providers, family members, and the adolescents themselves. Knowing what local resources are available and creating positive relationships with healthcare providers, teachers, and others involved with your teens' life increases the chance that your children's healthcare needs can be effectively met.

Adolescents are more likely to make positive choices if they feel they have some say in the decision-making process. Find providers who are willing to work with you and them, and allow for private time between the children and providers. Your adolescents may want to share concerns about issues that they do not want to share with you. Some level of privacy is appropriate and necessary. Keep in mind that they will be more likely to share information and therefore receive better care if they feel heard and develop a good relationship with healthcare providers.

Planning appointments around their school and social activities allows them to maintain social relationships, which are key to emotional well-being.

Try to schedule their doctors' appointments, infusions and/or blood draws on the same day or a day and time that does not interfere with school or social activities.

In conversations with your adolescents and healthcare providers, develop a personalized list of successful approaches to managing your children's health:

- What health and wellness habits have been most successful in keeping your adolescents happy?
- What routines for diet, rest and leisure have been the most refreshing?
- What activities have promoted the most success with physical fitness?
- What medications and treatments have been most reliable in managing the symptoms of their disease?

Having a personalized understanding of your teen's PI, medications and treatment, and strategies for health and wellness will help encourage good habits. In addition, parents who model good health and wellness habits in their own lives will provide positive examples to follow. Along with modeling, make sure that they have a full understanding of specific health concerns and treatments, and how preventative care and an emphasis on wellness can help. Reinforce and praise efforts to take responsibility for their health, and emphasize how this is an important sign of maturity. With appropriate support, they can develop lifetime habits of positive coping skills for health challenges.

Being Your Adolescent's Healthcare Advocate

As your children's advocate, you work to make sure their needs are being met by the healthcare team. With younger children, the parent is the chief advocate. As a caregiver, the parent is in the position to tell the healthcare providers what happens every day and supply the healthcare provider with critical information. As children mature during adolescence, they must begin to learn to advocate for themselves. To be effective advocates, it is important that you both learn as much as possible about the disease, treatment options and available resources, and that everyone builds positive relationships with the healthcare providers.

Recommended information to record and keep readily available in a record, either digital or print:

- Brief history leading to the diagnosis, written by you or a healthcare provider
- Copies of laboratory evaluations confirming and supporting the diagnosis
- Current list of healthcare providers caring for your adolescents with accurate addresses and phone numbers
- Chronology of important events such as infections and surgeries, specifically noting types of treatment and therapy, changes in therapy and subsequent responses to the treatment, therapy, infection, surgeries and/or hospitalizations
- List of all current medications they're taking
- Allergies to medications
- Infusion log for those receiving immunoglobulin (Ig) replacement therapy
- Immunization record
- Current insurance information
- Explanation of benefits records can be kept in the journal or separately but should be periodically reviewed for accuracy

While you are going to begin this record, it is important to encourage them to gradually take over this responsibility.

How you can advocate for your adolescents:

- Ask questions about the diagnosis, treatment and plan. If you do not understand, ask again.
- Inquire about what can be done to improve their health such as diet, physical activity, sleep and social activities.
- Maintain consistent communication with the school.
- Know your insurance policy and communicate to your provider if there are any changes.
- If they receive Ig therapy, make note of how it is going and/or any side effects.
- Build positive relationships with their providers, teachers and therapists. Know whom to call and when.
- Ask about and seek out resources for further information at the local, state and national level.

- Connect with IDF for additional resources: www.primaryimmune.org or 800-296-4433

Planning for Life after High School

Having this disease should not impede your adolescent from pursuing post-secondary education and/or living independently, but it might influence some decisions in terms of obtaining healthcare and living conditions. Some may choose to live at home and attend a local college or university. Others choose to attend school and/or live on their own, sometimes far from home. Consider what is best for your adolescent. Have your college-bound student contact student support services at their colleges of choice to discuss the diagnosis and specific needs, as well as possible resources and accommodations. Connecting with the health service is important, especially if they are receiving immunoglobulin replacement therapy. Some colleges and universities will not allow intravenous Ig infusions on campus. While subcutaneous therapy may be allowed, shipping of drugs and supplies may be problematic, especially if all mail and deliveries come to a centralized location.

When researching new providers and facilities, you need to understand your adolescent's insurance benefits and what providers and facilities are covered. The location of the potential healthcare providers may influence decisions about where to live or attend school. If they plan to relocate after high school or attend college away from home, you and your adolescent should research immunologists and resources in that area. Your current providers may be helpful in making recommendations. Many immunologists are associated with major universities so your adolescent might want to consider these types of schools. If your children move out of state, it is also important to remember that hospitals and clinics may not be able to accept the orders from your current healthcare provider. Your adolescent should establish care, if possible, before moving day to give the healthcare provider time to get to know them and have time to request any required pre-authorizations for treatment from the insurance plan. It is also key to make sure that the health insurance is accepted as in-network even when out of state in order to maintain their care.

If they receive Ig therapy and are relocating and/or going away to college, it may not always be necessary to change infusion providers. If they are receiving infusions through a specialty pharmacy in a homecare setting, they may be able to continue with the same provider. Be sure to check with their current infusion provider several months before moving. Additionally, if a change in providers is required, their current provider should participate in coordinating the care and transition to the new provider. If they receive infusions in a clinic or outpatient hospital setting, it will be important to coordinate the care in advance with as much notice as possible. Additionally, the receiving clinic will likely need to get a new insurance authorization to provide care. Failure to obtain a new authorization could result in denied claims.

Transitioning Responsibility to Your Adolescent

During childhood and adolescence, parents have the responsibility of making all healthcare decisions. Once they turn 18, they are legally considered an adult. At that point, parents need written permission from their children to access healthcare records and to speak with the healthcare team and health insurance company. To prepare for this transition, adolescents should begin actively participating in their care early on and understand their diagnosis, treatment and insurance. When appropriate, allow them to make choices that ultimately meet the determined goal. This helps them build confidence because they have some control over decision-making and it prepares them to participate and ultimately take care of themselves in adulthood.

Planning the transition of care should begin in early adolescence. The primary care providers and immunology team should be involved to insure a smooth transition, and the plan for independence should be tried and tested long before the adolescent turns 18 or lives away from home. Testing the transition plan would involve having your adolescents become independent with current healthcare providers and to gradually take on more and more responsibility for themselves and their care.

For more information about how to help transition care to your adolescent, use the IDF Transition Guide, which can be downloaded or ordered on www.primaryimmune.org.

On the following pages are checklists to be completed by your adolescents to help them prepare for the transition to adulthood, and can also be found in the IDF Transition Guide.

Transition Skills Checklist

Ages 12-14

Yes	No	Almost	General Information
			I can tell someone the name of my primary immunodeficiency.
			I can describe the effect of primary immunodeficiency disease on my body.
			I can share my medical history with a doctor or nurse.
			I can list my medication and food allergies.
			I tell my parents about changes in my health.
			My parents keep a personal health record for me.
			My parents and I carry a medical summary, such as the in case of emergency (ICE) report
Yes	**No**	**Almost**	**Medications and Treatment**
			I can list the proper names of my medications, the dosage and times they should be taken.
			I can explain why each medication is necessary, the result of not taking it as prescribed and its side effects.
			I take all medications as prescribed and notify a parent when the supply is low.
			I use and take care of medical equipment/supplies and notify a parent if there is a problem or supplies are low.
			I can list medical tests that need to be completed regularly.
Yes	**No**	**Almost**	**Medical Appointments**
			I tell my doctor or nurse about how I am feeling.
			I answer at least one question during a medical appointment.
			I ask at least one question during a medical appointment.
			I spend some time alone with the healthcare provider during a medical appointment.

Transition Skills Checklist

Ages 12-14 (cont.)

Yes	No	Almost	Medical Appointments
			I talk with my parents and healthcare providers about the medications and treatments I need.
			I tell the healthcare provider I understand and agree with the medication or treatment prescribed.
Yes	**No**	**Almost**	**Understanding the Healthcare System**
			I know the date and reason for my next medical appointment.
			I know the names of my healthcare providers and how to contact them.
			I know the name of my health insurance and the importance of being insured.
Yes	**No**	**Almost**	**Healthcare Transition**
			I am taking more responsibility for my healthcare.
			I have talked to my parents and healthcare providers about whether I will need to see new providers when I'm an adult.
			I have talked to other teens about their healthcare transition experience.

Transition Skills Checklist

Ages 15-17 (cont.)

Yes	No	Almost	General Information
			My parents and I keep a personal health record.
			I carry a medical summary.
			I can explain why each medication is necessary, the result of not taking it as prescribed, its side effects and the management of side effects.

Transition Skills Checklist

Ages 15-17 (cont.)

Yes	No	Almost	Medications and Treatment
			I can select medication for a minor illness, such as a headache.
			I can refill a prescription.
			I can list medical tests that need to be completed regularly and make sure they are scheduled.
Yes	**No**	**Almost**	**Medical Appointments**
			I answer many questions during a medical appointment.
			I ask many questions during a medical appointment.
			I spend most of the time alone with the healthcare provider during a medical appointment.
			I decide with my parents and healthcare providers about the medications and treatments I need.
			I can contact the appropriate healthcare providers to tell them about changes in my health.
Yes	**No**	**Almost**	**Understanding the Healthcare System**
			I can explain the difference between a specialist and primary care physician.
			I can explain legal rights and responsibilities available to me when I am 18.
			I can explain how my health insurance works (provider network, deductible, co-pays).
Yes	**No**	**Almost**	**Healthcare Transition**
			I know if my health care providers will stop treating me at a certain age.

Transition Skills Checklist

Ages 15-17 (cont.)

Yes	No	Almost	Healthcare Transition
			I have talked to my parents and healthcare providers about things I should think about if I need to see new providers when I'm an adult.
			I have identified some healthcare providers that will care for me when I'm an adult.
			I have talked to other teens and young adults about their healthcare transition experience.

Transition Skills Checklist

Ages 18 and Up (cont.)

Yes	No	Almost	General Information
			I keep a personal health record.
			I carry a medical summary.
Yes	**No**	**Almost**	**Medications and Treatment**
			I understand and/or arrange payment for my medications, equipment and treatments.
Yes	**No**	**Almost**	**Medical Appointments**
			I check myself in at appointments and provide my insurance card.
			I answer all questions during a medical appointment.
			I ask the questions during a medical appointment.
			I am alone or choose who attends a medical appointment with me.
			I decide with the healthcare provider about the medications and treatments I need.

Transition Skills Checklist

Ages 18 and Up (cont.)

Yes	No	Almost	Medical Appointments
			I locate and share healthcare information with my providers and in making decisions about my care.
			I sign medical consent forms.
Yes	**No**	**Almost**	**Understanding the Healthcare System**
			I can explain the difference between a specialist and primary care physician.
			I can explain legal rights and responsibilities available to me when I am 18.
			I can explain how my health insurance works (provider network, deductible, co-pays).
Yes	**No**	**Almost**	**Healthcare Transition**
			I have decided which things I should consider when selecting a new healthcare provider.
			If necessary, I have transitioned to a new healthcare provider.
			If necessary, I have shared medical information with a new provider.

Chapter 44

Young Adults Living with Primary Immunodeficiency Diseases

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Young adulthood is a time of independence and self-exploration when we separate from our parents and make choices about education, career, lifestyle, peer and romantic relationships. The transition to adulthood is a challenging time in general, but the impact of primary immunodeficiency diseases (PI) requires some unique life adjustments. The physical aspects of PI get the most attention, but the emotional ones are just as important.

It is important to have the necessary emotional support and skills to deal with chronic illness. Everyone experiences their disease differently. By using your individual strengths and coping skills along with the support of family, friends, and your healthcare team, you will succeed and lead a fulfilling and productive life.

Normalizing Your Life

Having a primary immunodeficiency disease impacts your daily life and your life choices; however, it is the decisions you make that will help you enjoy a normal, healthy life.

Maintain balance. Those who best manage their disease are those with a balanced approach to the disease and to life. It is normal to want a break from focusing on your disease, but neglecting symptoms or treatment routines can lead to serious health problems. It is critically important to manage your disease and treatments, while maintaining your relationships and the activities essential to your healthy lifestyle.

Make positive choices. The choices that you make affect your health. Young adults, living on their own and/or attending college, may be living in close quarters, keeping irregular sleep schedules with late night studying, recreation, sexual activity, and may have new access to alcohol or drugs.

Incorporating positive choices into your life in these areas is an important skill. If you attend college, take a manageable course load. If you have a job, make sure it suits both your interests and abilities. Balance your responsibilities and your recreation. Remember the importance of balance in all aspects your life. Know your limits!

Be active. Participate in healthy recreational activities. Managing a chronic illness is demanding. As a young adult you assume the role of healthcare manager as well as the other responsibilities of adulthood. It is important to take an emotional break from your disease and make time for recreational activities that you enjoy. As a young adult you are finding your place in the world beyond the shelter of your family. Rise to the challenge of fitting your diagnosis into your life, rather than fitting your life into your diagnosis.

Manage transition. Maintain an ongoing dialogue with your parents and talk about your changing roles in managing your care. If you were diagnosed as a child, your parents played a large role in your healthcare. Being responsible for your own care can be a big shift for you, and it may be difficult for your parents to let go. They may fear that you may not make the best choices. Yet, it is essential that you are able to manage your own healthcare at your own pace. Keeping the lines of communication open while utilizing your parents for support and guidance if needed will be beneficial as you manage your transition.

Build a support system. Your relationship with your family and friends will evolve as a young adult. You will learn to take care of yourself independent of your family and under different living conditions. Your friends and significant others will be important resources for help if you are ill. Asking for support when you need assistance can be difficult, so assess which of your family members and friends are best suited to help with your potential needs. Some may be helpful with logistics, like picking up medications when necessary or taking you to a procedure or appointment. Others may be sources of emotional support, who can listen to your frustrations or help you to make sensible decisions.

Talking with Others about Your Diagnosis

Primary immunodeficiency diseases (PI) are rare, so most people are unaware of the diseases and their effects. You will encounter people who have never met someone with primary immunodeficiency disease before. You may face resistance from fellow students and coworkers who think that you are faking it or always sick. Pressures regarding performance and attendance can be difficult. Develop strategies and explanations to respond to people's questions and misconceptions. People often do not understand that their comments or lack of understanding about your illness can undermine your sense of self-worth and leave you feeling misunderstood or alone.

Sometimes, while trying to explain what PI is, you may hear "You don't look sick." Although not usually intended in a negative way, this can be irritating and for some, particularly because other well-known chronic illnesses are not treated the same.

Work to develop a comfortable way to deal with comments like this. See these statements as chances to empower yourself and educate others. Sharing information about your experience with PI can help people develop an awareness and understanding of PI and other invisible illnesses.

Dating and Partner Choices

Peer and romantic relationships are a top priority for young adults. Making positive choices is important for maintaining your physical and emotional health.

Safe sex practices and clear communication with any sexual partner is vital to prevent potential health risks from infections. When you want to enter a long-term romantic relationship, you will want to make sure that your partner accepts and supports you, including your medical condition. Although it may be difficult because of fears of rejection or of being misunderstood you will need to reveal and discuss your diagnosis with your partner.

When to tell someone is a personal choice. It is best not to tell too early or too late. Although disclosing too early before you really know a partner can lead to rejection; waiting too long may make them feel that they were not trusted. Remember, healthy relationships are built on trust. Carefully consider finding the right time to have a discussion.

Before you can be comfortable sharing such personal details, you must first be comfortable in your own acceptance of your diagnosis. Prepare yourself to answer personal questions in a sincere manner and be aware of what you would like to share.

Anticipate questions like:

- Is this contagious?
- Can you have children?
- Will your children inherit this disorder?

Other questions about your diagnosis will surely follow.

Preparing the answers to these types of questions and knowing what you are comfortable sharing will help decrease your anxiety and feelings of vulnerability.

If you need resources about how to answer such questions.

- Consult your immunology provider
- Role-play these discussions with family or friends
- Contact the Immune Deficiency Foundation (IDF) to connect with someone who has had similar experiences through peer support: www.primaryimmune.org or 800-296-4433.

Life is about choices. Choosing the right romantic partner can be very satisfying. Choosing to marry and/or have children or not is your choice. Choosing to enjoy and live a full life even though you have a primary immunodeficiency disease is one of the most important choices that you can make.

Pursuing Career Education

Many young adults with PI continue their education in colleges, universities, and vocational and career schools.

Having a primary immunodeficiency should not stop you from pursuing your life goals, continuing your education, finding a career, and living independently; but it will need serious consideration in your decision.

Some of you may choose to attend a local college or university and live at home. Others may choose to go away to college, sometimes far from home. In either case you will need to have access to healthcare and suitable living conditions to properly care for yourself during your education.

Become knowledgeable about your rights and responsibilities as a student as well as the responsibilities that post-secondary schools have to accommodate your diagnosis.

If you need to request special living accommodations at a school, work with the admissions office to identify the person to best help you. You should be prepared to discuss your diagnosis, accommodations, and other specific needs to be able to get the necessary resources.

Additional information regarding post-secondary education is available in this handbook. (See Adolescents Living with Primary Immunodeficiency Diseases Chapter.) You can also consult the IDF School Guide or IDF Transition Guide: Pediatric to Adult Care, which can be ordered or downloaded at www.primaryimmune.org.

Making Employment Decisions

When making employment decisions, consider your strengths and make changes that address your limitations. Although you may be anxious about having a primary immunodeficiency disease and making a career choice; remember that everyone has limitations. Make choices based on your own interests, abilities and health needs. This will lead to a successful career and a positive life.

Because of your diagnosis, understand your rights and benefits and learn how to communicate with your employer. Insurance coverage is a critical consideration in choosing a career. (See Health Insurance chapter.)

To learn more about choosing health insurance, visit the IDF Patient Insurance Center: www.primaryimmune.org/insurance.

For more information about your rights, contact these government agencies:

- U.S. Department of Justice Civil Rights Division, Office of ADA: www.usdoj.gov
- U.S. Department of Labor, Employment Standards Administration, Wage and Hour Division: www.dol.gov
- U.S. Equal Employment Opportunity Commission (EEOC): www.eeoc.gov

Managing Stress

Learning how to cope with the emotional stress of living with a primary immunodeficiency disease is vital. Managing pain, dealing with the unpredictability of illness, and missing out on recreational, social, and family activities may trigger feelings of sadness, isolation, and anger. You may benefit from sharing your feelings with close friends and family.

Negative changes in your overall outlook, feelings of hopelessness, sadness, irritability, and isolation may indicate that you may be experiencing clinical depression. If you need further help to cope, seek professional assistance. Talk to a therapist; and prevent disrupting your daily life.

You can connect with others in the primary immunodeficiency community who "get it" and understand the complications unique to these diseases can be very powerful.

IDF offers many programs to make those interpersonal connections. You can participate in the Young Adult Forum on IDF Friends (www.idffriends.org), an online community specifically for individuals and families living with PI. Contact the IDF and connect directly with another young adult through peer support. Attend an in person event, like the IDF National Conference, IDF Regional Conference or a local education meeting and connect with others who have PI. You may form valuable relationships that can be both rewarding and supportive. Visit IDF's Calendar of Events at www.primaryimmune.org/events to learn more.

Being Your Own Healthcare Advocate

If you choose to move away from home or change any of your providers, you will need to create a new healthcare team. If you were diagnosed as a child, your parents made all healthcare decisions for you. Once you are 18, you are legally an adult. After that, your parents need your written permission to access your healthcare records and to speak with your healthcare team or insurance company. It is important that you work with your parents and your healthcare providers to help you to become your own healthcare advocate and manager.

The transition of care from a pediatric setting to an adult setting is a major step for parents and young adults alike. To successfully assume responsibility for your own care, you need to become familiar with all aspects of your care.

The following information and resources will help you on your way to becoming your own healthcare advocate.

Information to record and keep readily available in a journal, either paper or digital:

- Brief history leading to the diagnosis, written by you or your physician
- Copies of laboratory evaluations confirming the diagnosis
- Current list of physicians caring for you with accurate addresses and phone numbers
- Chronology of important events such as infections and surgeries, specifically noting types of treatment and therapy, changes in therapy and subsequent responses to the treatment, therapy, infection, surgeries and/or hospitalizations
- List of your current medications
- Allergies to medications
- Infusion log if you receive immunoglobulin (Ig) replacement therapy
- Immunization record or lack of immunization
- Current insurance information
- Explanation of benefits records can be kept in the journal or separately but should be periodically reviewed for accuracy

Advocating for yourself:

- Ask questions about your diagnosis, treatment and plan. If you do not understand, ask again.
- Understand the treatments you are receiving and why they are important to your overall, long-term health.
- Inquire about what can be done to improve your health such as diet, physical activity, sleep and social activities.
- If attending school, maintain consistent communication with the school in the event you miss days.
- Know your insurance policy and communicate if there are any changes to your provider.
- Understand the difference between a primary care physician and a specialist.
- Build positive relationships with your providers, therapists, etc. Know whom to call when.
- If you receive Ig therapy, make note of how it is going and/or any side effects.
- Ask about resources for further information at the local, state and national level.
- Connect with IDF for additional resources: www.primaryimmune.org or 800-296-4433.

Understanding the Importance of Treatment

As a young adult, you make decisions for yourself. In order to make wise choices, you need to fully understand your specific diagnosis, medications and treatment. You must also know the consequences of not adhering to your current treatment. For most, treatment is lifesaving as well as lifelong.

Educate yourself. Become an expert; know your personal health history. Have the important details from your health records available, in a folder or in cloud storage that you can easily access.

Learn about your specific diagnosis and treatment. Utilize the IDF and its resources. If you find information on the internet, make sure that it is current and correct. Validate it with your health care team. Consult your immunologist so that you fully grasp the vital role of your treatment to your overall, long-term health.

Finding New Healthcare Providers

When searching for new providers and facilities, fully understand your insurance benefits and which providers and facilities are covered. Request a case manager from your insurance carrier. The case manager can help you navigate your particular insurer's rules and regulations, obtain authorizations, and navigate through their network. Be sure to choose healthcare providers who best suit your needs and who are in your network. Out of network providers or sources of care can carry a hefty price tag.

The location of the potential healthcare providers may influence your choices about where to attend school and live. If you relocate to attend college away from home, search for immunologists and health care systems in that area. Many immunologists are associated with universities, so consider those universities and cities. Consult your current providers for recommendations. Visit www.primaryimmune.org to access the IDF Physician Finder for help locating a specialist.

If you are moving out of state, remember that hospitals and clinics may not be able to accept the orders from an out of state physician. As a new patient in a new health care system, it may take longer than you expect to get an initial appointment. Establish care, get an appointment, and arrange to transfer your medical records before moving day. Your new healthcare provider will need time to get authorization for treatment, and review your records.

Visiting your New Provider

Be prepared and organized for your first visit. Remember, your communication is vital to your long term health.

When you first meet your new provider, treat your visit like a date.

- Introduce yourself.
- Shake hands.
- Make eye contact.
- Sit close.
- Pay attention.
- Silence your phone, and don't text or take calls during your visit.
- Let your expectations be known up front, say the reason for your visit.
- Be concise, stick to the details.
- Use words that you're comfortable with. If you don't understand the words you're hearing, ask.
- When sharing personal information tell the truth. If you smoke, drink, do drugs, take herbs, see alternative care providers, your provider is there to help not to judge.
- If you didn't comply with treatment, or follow doctor's orders. If you didn't buy your medicine or couldn't afford it; say so.
- Don't be afraid to ask a question because you might think it is a dumb question or think your doctor knows best.
- Know your medications, bring them with you or at least a list.
- Bring your records, especially if you've seen someone else or had a new problem. Keep a folder or an app with your info, immunization records, tests etc.
- Don't bring a stack of internet searches; bring a list of questions you have based on your searches. Ask them early, not at the end of the visit. Take notes. Don't leave with unanswered questions.
- Ask how the office works, who to talk to for results, emergencies, after hours.
- Review and confirm your treatment plan.
- Schedule your next follow up visit.

Locating Infusion Providers for Immunoglobulin Therapy

Many infusion companies are part of a national or regional system so it may or may not be necessary to change infusion providers when relocating. To find out, check with your current infusion provider several months before moving. If a change in providers is required, your current provider should participate in the transition of care to your new provider.

If you plan to get your infusions in a new clinic or outpatient hospital setting, arrange your care with as much advance notice as possible. Check with student health services at your new college. Some may not allow infusions in a dormitory and arrangements

may have to be made for infusions at the student health center or a local hospital/infusion center. Additionally, the new clinic will likely need to get a new insurance authorization to provide care. Check with your insurance company or case manager to make sure that the new site is in network. Failure to obtain a new authorization could result in denied claims or delays in therapy which could impact your health.

Summary

As a young adult, you make choices that will impact your overall health. Maintain balance in all aspects of your life. Build strong relationships with family and friends, pursue a career that suits your interests and abilities, and make time for recreation.

It is your responsibility to be in control of your healthcare. Build a support system for yourself. Use all the resources available to you from IDF, and other local and national resources to help you. Take the necessary steps to stay healthy. Learn how to manage your stress. Make informed decisions and keep good records. Continue your healthcare with compatible providers no matter where you are.

Be courageous, recognize your strengths, manage your primary immunodeficiency disease, set your goals, and live and enjoy every moment of your life.

Chapter 45

Adults Living with Primary Immunodeficiency Diseases

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Many adults with primary immunodeficiency diseases (PI) live full lives. Those who are well-informed and working with an attentive healthcare team can often pursue a career and live an active, productive life.

Introduction

Although the first PI were identified in children, the medical community soon realized that adults can have a PI as well. Advances in medicine, as well as earlier diagnosis and treatment of the childhood immunodeficiency diseases, have allowed many born with a PI to grow into adulthood. In other cases, many children born with apparently normal immune systems go on to develop a PI later in adolescence or adulthood. Unfortunately, the Immune Deficiency Foundation (IDF) survey research has shown that adults with an undiagnosed PI will, on average, experience symptoms of their immunodeficiency for more than a decade before a diagnosis is made.

No matter how old you were when you were diagnosed, it is important to learn about your condition and to choose healthcare providers with whom you can work comfortably. In addition, you should consider the psychosocial aspects of living as an adult with PI.

Normalizing Your Life

PI affects people in different ways, but, like everyone else, individuals with a PI need to feel a sense of accomplishment and purpose and contribute to the world around them. To best manage your life and your health, you need to educate yourself about your disease, build a collaborative relationship with your healthcare providers, and take care of yourself physically and emotionally.

Accept your new diagnosis. Some recently diagnosed individuals may experience a combination of relief, fear, and denial upon diagnosis. In such cases, it can be a relief for you to finally have a firm diagnosis and an identified treatment plan. At the same time, it can be frightening to have confirmation of a documented illness that is of a chronic nature. This is especially the case for individuals who already may be struggling with one or more conditions which may interfere with their level of functioning and quality of life. You can work towards accepting your diagnosis by creating a support system with family, friends, and healthcare providers to help you effectively manage the impact of a primary immunodeficiency on your life.

Educate yourself about your health issues. You will be better equipped to manage health issues successfully if you understand them and the potential impact they can have on your life. This is true of your PI as well as any other health issues you may have. Almost no one is likely to care about your health and well-being as much as you do. The diagnosis of any illness, particularly a chronic illness, can challenge your sense of independence and control over life. Educating yourself not only provides you with information about how to care for yourself and gives you the confidence to make decisions about your treatment but it can also help to restore and reaffirm a sense of independence and control. Self-education is a continual process and IDF provides a wealth of information for you. Ongoing research frequently provides new information about these diseases and their treatment, so it is important to review existing information, to register for IDF communications and mailings at www.primaryimmune.org, and to continue asking questions of your healthcare providers. Ensure that while educating yourself about your disease that you use reputable sources like www.primaryimmune.org or www.nlm.nih.gov. Always consider the source of the information that you find; if it sounds too good to be true, it probably is.

Choose a quality healthcare team. It is essential to have a healthcare provider who understands your health problems. Seek out an immunologist who specializes in PI and make sure that you feel comfortable with that person. They should welcome and encourage your questions and input. Individuals who are involved in their own healthcare decisions tend to do better than those who are not as involved, so it is in your best interest to find healthcare providers who consider you a partner in the treatment process. Although many healthcare providers are pressed for time, most of them appreciate if you are curious, willing to learn about your health issues and treatments, and want to collaborate in your care. IDF can help you locate a specialist in your area, go to www.primaryimmune.org.

Build strong social relationships. It is particularly important to build and maintain strong relationships, both inside and outside the family, and to remain connected socially. Schedule quality family time. Meet friends for lunch or coffee. Volunteer your time for a worthy cause. Engaging in activities outside of managing your health will ultimately benefit your health. It is also important to learn to ask for and accept help from the people in your life. Family members and friends often want to help and contribute to your sense of well-being. They can be a valuable resource for you.

Connect with others like you. Individuals living with chronic illnesses, especially unusual or rare disorders such as PI, often feel isolated and alone. Contact with other individuals who live with these diseases is a way to both gather knowledge and acquire an important sense of connection with others who share your experience. IDF can put you in touch with others living with PI through its peer support program and can provide information about regular educational meeting opportunities that occur at various regional and national locations.

Maintain a positive attitude. If there are activities in which you can no longer engage, focus instead on what you can do. Consider the gifts and abilities you have and use them to contribute to the world and people around you.

Family Life for Adults Living with PI

Maintaining strong and healthy family relationships can be a special challenge when you have a chronic illness, but these relationships are vital to your health. Consider your family as your team. You and your family must work together to remain strong and caring and communication is the key. Your family members should share their thoughts and feelings with each other on a regular basis. One of the most effective ways to do this is to share a daily meal together. This is a great opportunity to share your experiences, plan family activities and outings, and reminisce about good times spent together. In addition, everyone must make a contribution to the team. Everyone needs to feel a sense of accomplishment and to feel good about themselves and their contributions. In some cases, because of your health, you may no longer be able to work or complete other tasks for which you have been previously responsible within the family. You need to discuss the changes in your roles or responsibilities and work with your family members.

It is very common for those with PI to take out their frustrations on family members when they are feeling overwhelmed, angry, or stressed. Remind yourself that you may be feeling upset about your situation and are not necessarily angry with other family members. At times, it is important to share that thought with your family. Consider what other family members need or want as well. Usually you will find that it is exactly what we all want: love, understanding, and appreciation.

Having Children

If you and your partner consider growing your family, it is important to understand the genetic implications of PI. Some PI are genetic, meaning they are passed down from parent to child. Your health care provider or a genetic counselor can address these questions and concerns. (See Inheritance Chapter.)

Managing Stress

Not everyone with the same disease is affected in the same way. It is typical to experience increased stress as they face unexpected illness, hospitalizations, and missed work. They may simply be unable to manage their usual responsibilities and may require the help of others while they recuperate. Some can become absorbed in their own problems and feel angry, hopeless, or depressed. The amount of stress some feel and the way they cope vary greatly in each individual. Recognizing and managing this psychological stress can be challenging, but it is important to identify stress and how it affects your physical and emotional health, as well as to develop effective ways of coping.

The best ways to address and manage stress differ from person to person and sometimes it takes time to understand your limits. Keep in mind a variety of activities that help you manage stress. Remember that you may not be as efficient when you are stressed or overwhelmed with fatigue, so it is of no benefit to push yourself at those times. Make time for rest and relaxation. Take a nap, learn how to meditate or use deep breathing or other relaxation exercises. Make time to read for pleasure or enjoy music. Exercise is also an excellent way to relieve stress, whether you walk, ride a bike or engage in a more strenuous workout. Know the kinds of stress-reducing activities that are helpful to you and best suited to your lifestyle and physical abilities.

Many individuals benefit from speaking with a mental health professional, such as a psychiatrist, a clinical psychologist, a social worker, or a pastoral counselor. If you are wondering how you will know when it is time to seek help, consider the following suggestions:

- When your feelings and/or your behavior regularly interfere with your ability to function on the job, at home or as a member of your family.
- If you are trying to move forward but feel stuck or if you feel uncomfortable to the point that you feel a need to do something as soon as possible.
- When your family members become overwhelmed, unable to manage or struggle to manage everyday stress or when relationships seem to be falling apart.

The first step in seeking help is to contact your insurance company to review your mental health coverage and benefits. You will want to know any in- and out-of-network deductibles and co-pays and if there are any restrictions on the type of professionals you can see. Your insurance company can usually provide you with a list of mental health professionals in your area who are participating providers with your plan. Another way to identify a potential therapist is to get a recommendation from someone you trust, like a family member, friend, your healthcare provider, or clergy. In addition, most state psychological associations or state social work associations have referral services to help you identify a suitable professional.

Employment with PI

When choosing a job or career, adults with PI must think in terms of ones that are suitable for their condition. Depending on the nature of your condition, you may or may not be limited physically. However, there may be complications that need to be considered. Factors like time and stress and how they affect your condition and treatment cannot be ignored. You may need to limit your exposure to large numbers of other individuals who may transmit infections.

In seeking employment, be aware that there are laws against discriminating against an applicant based on a chronic health condition. However, that does not mean that the laws are easy to enforce. You may want to familiarize yourself with these laws.

Those living with PI work in all kinds of jobs. For many, the health insurance coverage associated with employment is the most problematic. Small employers, for instance, may not be able to cover you, so choosing an employer who can provide adequate health insurance may be important while considering careers. New Health Insurance Portability and Accountability Act of 1996 (HIPAA) legislation has improved the ability to transfer insurance coverage from job to job once you are insured. The Family Medical Leave Act (FMLA) also ensures continued employment in the face of prolonged work absences due to illness. Disability in this population is not common but can happen. You need to be prepared should this occur. (See Employment Chapter.)

Relocation

Adults with a PI may find it necessary to relocate to another city or state for education or employment. It is vital that you notify your healthcare provider of any plans to relocate as soon as possible to ensure that there are no disruptions in your medical care or treatment. Notifying your healthcare provider as soon as possible ensures that there will be time to address the following:

- Establishing care with new healthcare providers. Your current provider may be able to recommend a new provider or you can contact the IDF for a provider in your area. Often providers have long wait list for new patients, so it is important to make an appointment for as soon as possible after you relocate.
- Signing a release of medical records. In order for your current provider to send your medical records to your new provider you must sign a release of medical information form.

- Needing to continue therapy. Once you relocate, your current provider may no longer be able to order and/or refill your medications. If you are receiving Ig replacement therapy, new authorizations may need to obtained and care transferred to a new center. In order to prevent a lapse in your treatment, this authorization will need to be obtained as soon as possible after you relocate. Discuss with your healthcare provider how you will continue to receive treatment prior to your relocation.

Most healthcare providers are familiar with patients relocating and will be able to work with you to ensure your transition is as smooth as possible.

Health Insurance for Adults Living with PI

Health insurance is a concern that all people with a PI must face. Decisions regarding school or employment may be affected by insurance coverage. This issue cannot be taken lightly by anyone with a pre-existing condition. If you allow your insurance to lapse or do not look into the options that exist before coverage terminates, your ability to qualify for insurance may be seriously jeopardized. It is important for an engaged or married couple to face the issue of health insurance realistically and understand its importance in career decisions.

It is also essential that you understand how the Affordable Care Act (ACA) of 2010, also known as healthcare reform, affects you. The law puts in place strong consumer protections and provides new coverage options. (See Healthcare Chapter.)

Coordinating Your Healthcare and Being Your Own Healthcare Advocate

It is essential for you learn how to coordinate your healthcare, become your own healthcare advocate, and establish a relationship with your healthcare providers. Communication is key.

Effective communication is essential in all relationships. It needs a sender, a message, and a receiver. It is a two-way process and is not complete until the receiver understands the message.

To improve your care, it is important to pay careful attention to the communication with your healthcare team. Your healthcare team includes anyone who helps you get the care that you need and can include doctors, nurses, ancillary therapists, case managers, and social workers. Support personnel and insurance providers may also be key people.

Ways to help you communicate with your healthcare providers so you can be heard and understood:

- Treat each healthcare appointment as if it is an important meeting. Remember, communication is more than just words. You have probably waited a while for the appointment, and it will not last as long as you might like, so make the most of your face-to-face time. Silence your cell phone. Make your visit personal, minimize distractions; do not bring the whole family or kids into the exam room. Remember, it is an important meeting, and you do not need any interruptions.
- Be prepared. Plan ahead and do your homework. Get any necessary insurance authorizations ahead of time. This will help you to keep organizational noise down.
- Bring your medical information to your visit. You can keep a journal, create a folder, make computer documents, or use an online personal health record. **However, you choose to document your healthcare, make sure to include:**
  - A brief history leading to the diagnosis, written by you or your healthcare provider
  - Copies of laboratory evaluations confirming the diagnosis
  - A current list of providers caring for you along with their accurate addresses and phone numbers
  - The chronology of important events, specifically noting types of treatment and therapy, changes in therapy and subsequent responses to that therapy, surgeries, and/or hospitalizations
  - A list of your current medications
  - Allergies to medications
  - Infusion log if you are currently receiving immunoglobulin (Ig) replacement therapy
  - An immunization record or lack of immunizations
  - Current insurance information

- Prepare and feel comfortable asking your questions. Ask questions, but be concise. Ask your questions early, not at the end of your visit so that the provider has a chance to carefully answer your questions.
- Bring a list of the most important questions that you have.
- Never be afraid to ask a question because you think it might be seen as dumb or because you feel that the provider knows best.
- If you do not understand the meaning of the words that your provider is using, do not be afraid to say so.

- **At your initial visit, ask questions like:**
  - Whom should I talk to in the office when I need to get a message to you?
  - What should I do when I get sick after hours or on the weekend?
  - Which hospital do you admit your patients to?
  - May I contact you by e-mail if I have a question?
- Be sure to take notes electronically or bring a notebook and pen along.
- Express your concerns in your own words. Use words with which you are comfortable. Tell the provider what the reason for your visit is, it will help them focus on what you need.
- Forget your stereotypes about your providers. Remember, healthcare providers are people, just like you, with a job to do. Their job is to help you find a way to stay as healthy as possible. It is important to find providers with whom you can be yourself around. They are your partners in your healthcare.
- Be honest. Do not be afraid to talk about what goes on in your bathroom or your bedroom. If you smoke, drink, take illicit drugs, use herbs or see alternative care providers, say so. Remember, your healthcare information is private and law protects that privacy. Whatever you do, do not be afraid to tell the truth. Your relationships with your healthcare providers are intimate ones. It is their job to help you, not to judge you. If you did not follow their advice, did not adhere to the treatment plan, or did not buy the medicine because your insurance did not cover it and you could not afford it, tell them. How else will they know if what they thought should work was effective?
- Advocate for yourself. No one knows how much your disease affects your life better than you do. No one understands the changes you have to make every day to deal with your treatment as you do. To live your life to the fullest, you need to be your own healthcare advocate.
- Ask questions of your providers about your diagnosis, treatment, and plan. If you do not understand, ask again.
- Inquire about what can be done to improve your health. Consider such things as diet, physical activity, sleep, and social activities.
- In terms of school or work, maintain consistent communication with your school and/or your employer in the event that you miss days and understand their policies and procedures.
- Know your insurance policy and let your provider know if there are any changes—especially if those changes mean you have to change providers or your therapy and medications will no longer be covered.
- If you receive Ig therapy, make note of how it is going and/or any side effects. Keep an infusion log, including date, time, product name, and product lot number.
- Build positive relationships with your providers. Know whom to call and when.
- Ask about resources for further information at the local, state and national level.
- Connect with IDF for additional resources: www.primaryimmune.org or 800-296-4433.

Remember, communication is how we all relate to each other. Think about the things that you need to stay healthy. Think about how you can best communicate those needs. By doing this you will have some of the tools you need to successfully coordinate your healthcare and be your own advocate. No matter what your diagnosis is, this is your life. Make the most of it.

Chapter 46

Senior Adults Living with Primary Immunodeficiency Diseases

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Primary immunodeficiency disease (PI), frequently thought of as a disease occurring in infants and children, may in fact be more common in adults. Health care providers who think of PI as a pediatric disorder may miss the diagnosis of PI in older adults and geriatric individuals. The convenience and efficacy of antibiotics may also masquerade the diagnosis of PI, resulting in prolonged delay of the correct diagnosis. In the geriatric age group, there are special problems and special needs which require attention:

- Complications: Many senior adults have had PI for years and, consequently, have developed complications such as chronic lung disease (including bronchiectasis), chronic sinusitis (often with a history of multiple sinus surgeries), and infections with microorganisms resistant to multiple antibiotics.
- Comorbid diseases: Comorbid diseases such as heart disease, diabetes, kidney disease, arthritis, and other chronic medical problems, take on significance of enormous proportions when combined with PI.
- Frailty: Due to possible physical and mental issues, some seniors may not be able to navigate the requirements of taking care of PI themselves.
- Third party coverage and bureaucracy: This age group is almost always covered by government insurance (Medicare). Medicare regulations are not always "PI Friendly" making the effective care of these individuals difficult.

The Senior Individual

This age group includes the population of 60 years and older. Little has been written about PI in this age group, and the prevalence of PI in this age group has not been appreciated until recent evaluation from a large database (see Figure 46:1) and from unpublished data from the Immune Deficiency Foundation. Immunodeficiency in the senior population looks significantly different than it does in younger groups. Unlike children, who may have many different kinds of immune deficiency disorders, the majority of adults with PI have antibody immune defects. Some may have a recent diagnosis of PI, while others, have had their diagnoses for decades. Similar to younger individuals, seniors may present with severe or frequent bacterial infections or infections with unusual organisms.

Common Variable Immune Deficiency (CVID) and Specific Antibody Deficiency (SAD) are the most common diagnoses in these individuals. Studies have shown that as these individuals increase in age, they often have an increased number and severity of comorbid conditions. Another more recent change has been the "uncovering" of PI or triggering of secondary immunodeficiency (SID) due to biologics used to treat a comorbid disease. These comorbid disease complications have been described in other sections, but they may have an increased significance in this age group, and produce greater risks for some interventional diagnostics and therapies.

Progression of PI Related Problems

Sinopulmonary disease may progress over time, leading to multiple sinus surgeries and insidious, progressive lung disease. Lung disease may include bronchiectasis with resistant organisms, COPD, pulmonary fibrosis with hypoxemia, and granulomatous lung disease. Early recognition and treatment may help to control the progression. However, some may eventually require aggressive intervention and/or oxygen supplementation.

Gastrointestinal disease may lead to increased intestinal infections, malnutrition, protein and fluid loss from chronic diarrhea, including loss of immunoglobulin (IgG).

Inflammatory bowel disease, malabsorption and bacterial overgrowth syndrome may occur as well. Malignancies also increase with age. Unexplained weight loss, fatigue, and careful examination for anemia and blood loss in the stool can alert the physician to gastrointestinal malignancies.

Careful and vigilant monitoring for proliferative diseases (lymphoma, myeloma and leukemia) is extremely important as increasing age incurs a higher incidence of malignancies leading to the need for chemotherapy. Chemotherapy itself has profound effects on individuals and more so in seniors. Sometimes, either before or after chemotherapy, the individual is found to have decreased IgG with or without infections. If no prior laboratory studies documenting Ig levels are obtained before the treatment of lymphoma or leukemia, it may be impossible to say which disease occurred first (CVID or lymphoma or leukemia).

Secondary immunodeficiency can occur when another disease, such as lymphoma, leukemia, myeloma or benign monoclonal gammopathy, abnormal proteins in the blood, causes a decrease in IgG and possibly in other serum immunoglobulins, including IgA and IgM. Ig replacement therapy may be required in these disorders. In addition, treatment of these malignancies with chemotherapy or certain biologics (rituximab and ocrelizumab, etc.) may exacerbate an underlying immunodeficiency by destroying lymphocytes which produce immunoglobulins.

Consequences of Aging

Aging leads to worsening of other diseases including diabetes mellitus, kidney disease, neuropathies, dementia, arthritis, Parkinson's disease, and hypertension. Many of these diseases or disorders may have profound implications on how Ig therapy will be given. This includes dose, frequency and route of administration, product selection and site of care. Less rapid administration and lower doses in older individuals are important in geriatric individuals, especially in those with renal disease. Further, this age group has a higher risk for blood clots including phlebitis (inflammation of the blood vessels), myocardial infarction, stroke, and pulmonary embolism (clots in the lungs). This risk is higher in individuals with previous thrombotic conditions or blood clotting diseases, particularly for those with limited mobility.

While Ig replacement therapy may be administered by either intravenous immunoglobulin replacement therapy (IVIG) or subcutaneous immunoglobulin replacement therapy (SCIG), it may be medically necessary to choose the subcutaneous route in individuals with underlying renal disease, severe heart disease, clotting disorders, hypertension or other conditions where large volumes of IVIG, if infused rapidly, may be detrimental. Infusions with IVIG can also transiently increase the osmolarity (thickness of the blood) which may have adverse effects on clotting and kidney function.

Administration of Immunoglobulin

As previously mentioned, there are two ways in which you can receive Ig replacement therapy, IVIG and SCIG. In general, many go towards SCIG, governed by convenience, safety and insurance prerogatives. A study has shown that seniors can tolerate and self-administer SCIG safely. Even those on anticoagulants can safely administer SCIG. Generally, someone who is newly diagnosed with very low IgG levels are given a "loading dose" of IVIG followed a week later by weekly or biweekly SCIG. The reason for this process is to get protective levels of serum IgG up rapidly.

Some elect to receive IVIG because it is given every three to four weeks, rather than weekly, and do not wish to self-infuse. However, because of insurance considerations, particularly Medicare, and convenience considerations, many elderly individuals self-infuse at home. Currently, it is unknown how many receive their treatments through IVIG or SCIG. While SCIG may be convenient for some, it may present special problems for many elderly individuals who have physical limitations. Self-infusions require a number of preparatory steps to infuse, some of which may not be possible for those with arthritis, poor eyesight, muscle weakness or other frailties. Oftentimes a caregiver is required for those with SCIG, although in one study 83% self-infused. If there is no caregiver, this therapy may present considerable obstacles to self-infusion. Other concerns are that Medicare does not pay for nursing support for self-infusion. A significant problem is that SCIG in nursing homes or attended care settings may be difficult because of cost considerations.

Insurance Issues

The majority of individuals in this age group have Medicare coverage and it is important to talk to someone who can advise you on your different plan options. You can contact your State Health Insurance Assistance Program (SHIP) to find trained counselors who can tell you the plans you are eligible for and assist you in finding the answers to your questions regarding coverage. To find your state's SHIP program contact information, go to http://bit.ly/SHIPprograms.

There are many options when it comes to Medicare so understanding your plan's coverage is extremely important. Choosing the wrong plan can impact your health and finances. For more information visit the IDF Patient Insurance Center: www.primaryimmune.org/insurance. If you have further questions, contact IDF: 800-296-4433 or www.primaryimmune.org/ask-idf.

Summary

PI is more common in adults than children. As a special group, seniors, may be the most complicated to treat for all the reasons described above.

References

PI is more common in adults than children. As a special group.

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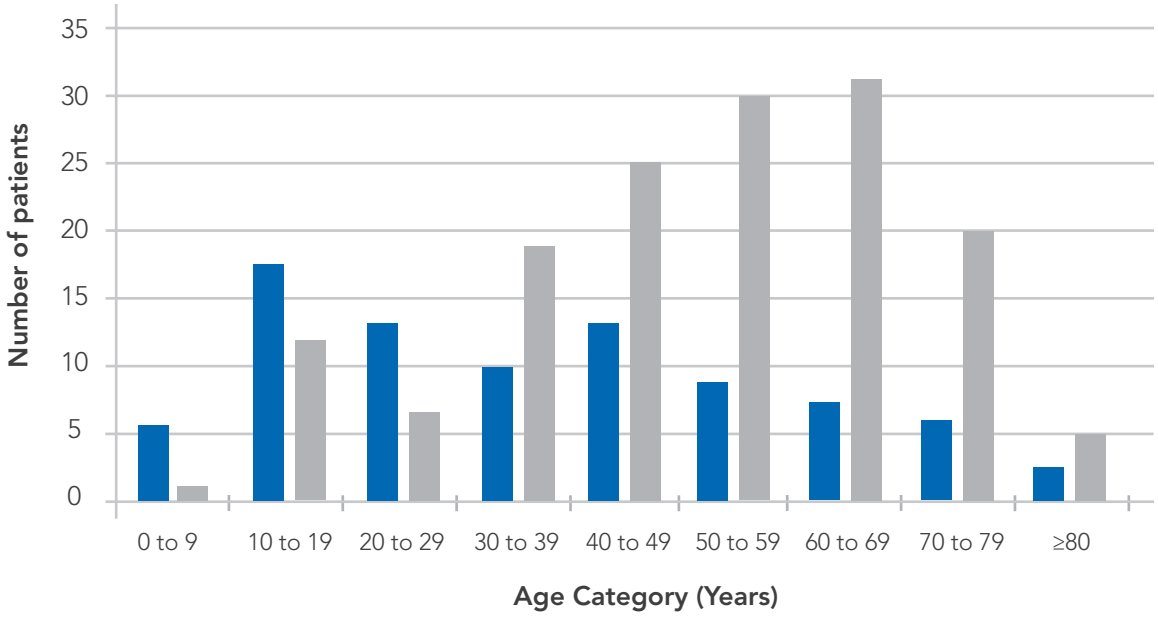
Age distribution of 235 individuals with PI in the Consortium of Independent Immunology Clinics patient registry.

Figure 46:1



Glossary

Note – More detailed information of each item may be found online.

Acquired immune deficiency syndrome (AIDS): A secondary immunodeficiency caused by infection with the HIV (human immunodeficiency virus).ituximab and ocrelizumab, etc.) may exacerbate an underlying immunodeficiency by destroying lymphocytes which produce immunoglobulins.

Acute: An adjective describing an illness which is usually short in duration and of recent onset.

Adenosine Deaminase (ADA): An enzyme essential for the development of the immune system and normal brain function.

Agammaglobulinemia: An almost total lack of immunoglobulin or antibodies.

Amniocentesis: The withdrawal of amniotic fluid surrounding a fetus in order to perform prenatal genetic testing.

Anaphylaxis: A life-threatening systemic allergic reaction.

Androgen: A male sex hormone.

Anemia: A condition in which the blood is deficient in red blood cells, in hemoglobin or in total volume.

Antibodies: Protein molecules that are produced and secreted by certain types of white blood cells (B lymphocytes, plasma cells) into the tissues and serum in response to stimulation by an antigen; their primary function is to fight bacteria, viruses, toxins and other substances foreign to the body.

Aspergillus: A species of fungi (mold) which is particularly a problem for individuals with Chronic Granulomatous Disease and/or some T cell defects.

Antigen: Any foreign substance that provokes an immune response when introduced into the body; the immune response usually involves both T lymphocytes and B lymphocytes.

Ataxia: An unsteady gait or general incoordination caused by neurological abnormalities.

Autoantibody: An antibody produced by the immune system in reaction to any of its own cells, cell products and tissues.

Autoimmune disease: A disease that results when the body's immune system reacts against the person's own cells or tissues.

Autosomal recessive inheritance: A form of inheritance where the characteristic, or disease, is inherited from both parents.

Autosomes: Any chromosome other than the sex chromosomes (X and Y).

Bacteria: Single cell organisms (microorganisms) that can be seen only under a microscope. Although there are thousands of different kinds of bacteria in our environment and in or on our bodies, only a few actually cause disease in human beings. Patients with certain kinds of immune defect may have problems with specific kinds of bacteria that do not cause disease in individuals with a normal immune system. Certain other kinds of bacteria infect both immune deficient and normal individuals, but the immune deficient individuals have more trouble clearing this infection and therefore the infection may progress to develop organ damage or other serious consequences.

B lymphocytes (B cells): White blood cells of the immune system derived from the bone marrow and involved in the production of antibodies.

Bone marrow: Soft tissue located in the hollow centers of most bones; the marrow contains developing red blood cells, white cells, platelets and cells of the immune system.

Bradykinin: A protein that causes blood vessels to dilate (enlarge) and results in a decrease in blood pressure.

Bronchiectasis: A dilation and disruption of the tubes (bronchi) leading to the air sacs of the lung; usually the consequence of recurrent (chronic) lung infections.

Carrier detection: The detection of a genetic characteristic in a person who carries the characteristic (or disease) in their genes but does not have the disease.

CD 40 ligand: A protein found on the surface of T lymphocytes; some individuals with X-linked Hyper IgM Syndrome have a deficiency in this protein.

Cellular immunity: Immune protection provided by the direct action of some immune cells, usually referring to T cell immunity.

Chromosomes: Physical structures in the cell's nucleus that carry genes; each human cell has 23 pairs of chromosomes.

Chronic: Descriptive term used to describe an illness or infection that may be recurrent or last a long time.

Chorionic villus sampling (CVS): Retrieval of a sample of the developing placenta from the womb in order to perform prenatal genetic testing.

Combined immunodeficiency: Immunodeficiency when both T- and B lymphocytes are inadequate or lacking, or not functioning properly.

Complement: A complex series of blood proteins that act in a definite sequence to affect the destruction of bacteria, viruses and fungi.

Complete blood count: A blood test that includes separate counts for red and white blood cells and platelets.

Congenital: Present at birth or born with the health problem.

Consanguineous (or Consanguinous): Descended from the same family or ancestors.

Cord blood: Blood obtained from the umbilical cord and placenta at birth.

Cryptosporidium: An organism that can cause gastrointestinal symptoms and liver disease; may be present in drinking water.

Cytokines: Proteins secreted by cells that affect the activity of other cells and are important in controlling immune responses and inflammation. Interleukins and interferons are cytokines.

DNA (deoxyribonucleic acid): Found in the cell nucleus, DNA carries genetic information.

Eczema: Skin inflammation with redness, itching, oozing and scaling. Also called atopic dermatitis, and is usually seen in allergic individuals but also can occur in people with PI.

Endocrine system: The glands in the body that produce hormones.

Eosinophilia: An increase in the number of granular white blood cells that stain with the dye eosin (eosinophils), which occurs with some allergies and parasitic diseases.

Febrile illness: An illness accompanied by fever.

Ficolins: Soluble molecules of the innate immune system, which recognize carbohydrate molecules on pathogens, apoptotic and necrotic cells and activate the complement system.

Fungus: Member of a class of relatively primitive microorganisms including mushrooms, yeast and molds.

Gammaglobulin (or Gamma globulin): The protein fraction of blood that contains immunoglobulins or antibodies. It usually refers to the IgG fraction of immunoglobulins as defined by their position in serum protein electrophoresis methods.

Gamma interferon: A cytokine primarily produced by T lymphocytes that improves bacterial killing by phagocytes; used in the treatment for chronic granulomatous disease.

Gene: A unit of genetic material (DNA).

Gene (or genetic) testing: Testing performed to determine if an individual possesses a specific gene or genetic trait.

Gene therapy: Correction of genetic diseases by providing a correct or normal form of the abnormal gene which is causing the disease.

Genotype: One gene or a set of genes that determine certain traits or disease characteristics (phenotype). (Also see entry "phenotype.")

Graft-versus-host disease (GVHD): A medical reaction that occurs following transplanted tissues from a genetically different person. Transplanted immune lymphocytes in the donated tissue or bone marrow recognize the recipient as foreign and attacks the tissues of the recipient.

Graft rejection: The immune response of the recipient to the transplanted organ or tissue resulting in its rejection.

Granulocyte: A white blood cell of the immune system characterized by the presence of granules in the cytoplasm. Neutrophils, eosinophils and basophils are examples of granulocytes. Some granulocytes (especially neutrophils) ingest (phagocytose) foreign material such as germs (bacteria). (Also see entry on "phagocyte.")

Granuloma (pl. Granulomata): A mass of granulation tissue typically produced in response to infection, inflammation or the presence of a foreign substance.

HLA Haplotype: A particular combination of genes clustered on the sixth human chromosome that determines histocompatibility. (Also see entries for "histocompatibility antigens" and "MHC.")

Human leukocyte antigen (HLA): The name for a large group of genes in humans on chromosome 6 that code for cell surface proteins that determine tissue type (histocompatibility antigens). This complex of genes is also called the major histocompatibility complex (MHC). (See entries on "histocompatibility antigens" and "Major histocompatibility complex.")

Helper T lymphocytes (Helper T cells): A subset of T lymphocytes that help B lymphocytes and T lymphocytes to become activated to exert their protective functions.

Heterozygous mutation: Each diploid cell (most cells of the body except sperm and eggs) has two copies of every gene, one inherited from the mother and one from the father. Any given gene may contain a mutation. If only one of the two copies of the gene contains the mutation it is called a heterozygous mutant.

Histocompatibility antigens: Proteins on the surface of many cells of the body, including the cells of the immune system, which are relatively unique to each individual and are responsible in providing a signal to the immune system whether a cell is part of the self or foreign like an invading organism. (Also see entries for "human leukocyte antigen" and "MHC.")

Homozygous mutation: Each diploid cell (most cells of the body except sperm and eggs) has two copies of every gene. Any given gene may contain a mutation. If both copies of the gene contain the same mutation it is called a homozygous mutation.

Homozygous mutation: Each diploid cell (most cells of the body except sperm and eggs) has two copies of every gene. Any given gene may contain a mutation. If both copies of the gene contain the same mutation it is called a homozygous mutation.

Humoral immunity: Immune protection provided by soluble factors, such as antibodies which circulate in the body's fluids.

Hypocalcemia: An abnormally low concentration of calcium in the blood.

Hypogammaglobulinemia: Lower than normal levels of immunoglobulins (or antibodies) in the blood.

Hypoparathyroidism: A disorder in which the parathyroid glands in the neck do not produce enough parathyroid hormone (PTH).

Hypoplasia: The failure of an organ or body part to grow or develop fully.

IgA: An immunoglobulin found in blood but mostly and secreted into tears, saliva and on the mucous membranes of respiratory and intestinal tracks.

IgD: An immunoglobulin that makes up only 0.25% of the immunoglobulins in the plasma. IgD on the surface of B-lymphocytes are important in B-cell differentiation. The function of IgD is poorly understood but may have a role in the allergic response.

IgE: An immunoglobulin found in trace amounts in the blood and responsible for allergic reactions.

IgG: The most abundant and common of the immunoglobulins. It is the only antibody that can cross the placenta from the mother to the developing fetus. It is the only immunoglobulin class that is commercially available for treating immunodeficiency.

IgM: An immunoglobulin found in the blood. IgM functions in much the same way as IgG, but is formed earlier in the immune response. It is also very efficient in activating complement.

Immune response: The response of the immune system against microbial organisms and foreign substances that threatens the body.

Immunocompetent: Capable of developing an immune response.

Immunocompromised: A state in which a person's immune system is weakened or absent. Individuals who are immunocompromised are less capable of battling infections because of an immune response that is not properly functioning.

Immunodeficiency: A state of either a congenital (present at birth) or an acquired abnormality of the immune system that prevents adequate immune responsiveness. (Also see entries for "primary immunodeficiency" and "secondary immunodeficiency.")

Immunoglobulin replacement therapy: The intravenous, intramuscular or subcutaneous injection of immunoglobulin on a regular basis to treat antibody deficiency.

Immunoglobulins (Ig): Another name for antibody; there are five classes: IgA, IgD, IgG, IgM and IgE.

Incubation period: The period between the infection of an individual by a pathogen and the manifestation of the disease it causes.

Insertional mutagenesis: Mutation caused by the insertion of new genetic material into a normal gene.

Intention tremor: A slow tremor of the extremities that increases on attempted voluntary movement and is observed in certain diseases of the nervous system (e.g., Parkinson's disease).

In vitro: Outside of a living environment; refers to a process or study taking place in test tubes, etc.

In vivo: Inside a living environment; refers to a process or study taking place in the body.

Intravenous immunoglobulin (IVIG) infusion: Immunoglobulin (gamma globulin) therapy injected directly into the vein.

Killer lymphocytes: T lymphocytes or natural killer cells that directly kill microorganisms or cells that are infected with microorganisms.

Kinin: Any of various polypeptides that are formed locally in the tissues and cause dilation of blood vessels and contraction of smooth muscle.

Leukemia: Type of cancer affecting the white blood cells.

Leukocyte (white blood cell): A group of small colorless blood cells that play a major role in the body's immune response. There are five basic types of leukocytes: monocytes, lymphocytes, neutrophils, eosinophils and basophils.

Live vaccines: Live viruses and bacteria are contained in the vaccine. In seriously immunocompromised individuals, live vaccines can sometimes transmit the disease they were designed to prevent. Examples of common live vaccines include oral polio, rotavirus, measles, mumps, rubella, BCG and chicken pox.

Lymph: Blood plasma-like fluid that contains lymphocytes and granulocytes, but no red blood cells, that circulates through the tissues of the body in small vessels called lymphatics. Lymph is collected from the tissues and lymph nodes via the lymphatic vessels and is rejoined with the circulating blood in a venous connection found near the neck called the thoracic duct.

Lymph nodes: Small bean-sized organs of the immune system, distributed widely throughout the body. Each lymph node contains a variety of specialized compartments that house B lymphocytes, T lymphocytes, dendritic cells and macrophages.

Lymphocytes: Small white blood cells, normally present in the blood and in lymphoid tissues that bear the major responsibility for carrying out the functions of the immune system. There are two major forms of lymphocytes, B lymphocytes and T lymphocytes, which have distinct but related functions in generating an immune response.

Lymphokines: A class of cytokines specifically secreted by lymphoid cells that are important in regulating inflammation and immune responses and for recruiting other cells to participate in immune and inflammatory responses.

Lymphoma: A type of cancer of the lymphocytes.

Macrophages: A phagocytic tissue cell of the immune system that functions as a scavenger in the destruction of foreign antigens (as bacteria and viruses) and serves as an antigen-presenting cell. (See entry on "antigen presenting cell.")

Major histocompatibility complex: (MHC) A series of genes on chromosome 6 that direct the synthesis of the proteins on the surface of many cells of the body, including the cells of the immune system, which are relatively unique to each individual and provide our tissue type.

Malignancy: Cancer.

Metabolism: A general term which summarizes the chemical changes within a single cell, and the body as a whole, which results in either the building up or breaking down of molecules.

Microorganisms: Very, small living organisms that can only be seen with a microscope, usually one-cell organisms, which include bacteria, protozoa, and fungi.

Molecules: The smallest unit of a chemical compound.

Monocyte: Phagocytic cell found in the blood that acts as a scavenger, capable of destroying invading bacteria or other foreign material; these cells develop into macrophages in tissues.

Monokines: Chemical messengers produced and secreted by monocytes and macrophages.

Mucosal surfaces: Surfaces that come in close contact with the environment, such as the mucous membranes of the mouth, nose, gastrointestinal tract, eyes, etc; IgA antibodies protect these surfaces, or mucus membranes, from infection.

Mucocutaneous Candidiasis: A group of syndromes with common features including chronic noninvasive Candida infections of the skin, nails, and mucous membranes and associated autoimmune manifestations. It is caused by genetic faults in the immune system

Multifactorial immune disorders: Conditions or diseases arising from a combination of genetic and non-genetic causes, including environmental factors.

Neurology: A branch of medicine concerned with the structure, functions, and diseases of the nervous system.

Neisseria: A group of bacteria that colonize the mucosal surfaces and includes different bacteria that cause meningitis, gonorrhea and other illnesses.

Neonate: A newborn baby, specifically a baby in the first 4 weeks after birth.

Neutropenia: A lower than normal amount of neutrophils in the blood.

Neutrophils: A type of granulocyte, found in the blood and tissues that can ingest microorganisms. The major cellular component of pus. (See entry on "granulocyte.")

Nystagmus: Involuntary, usually rapid movement of the eyes.

Opportunistic infection: An infection that occurs only under certain conditions, such as in immunodeficient individuals. Not normally a pathogen for individuals with intact immune systems.

Organism: An individual living thing.

Osteomyelitis: Infection in the bone.

Parasite: A plant or animal that lives, grows, and feeds on or within another living organism.

Parathyroid gland: Small glands found in the neck near the thyroid that secrete parathormone and control the normal metabolism and blood levels of calcium. (Also see entry on "hypoparathyroidism.")

Petechiae: Pinhead-sized red spots resulting from bleeding into the skin.

Phagocyte (also phagocytic cell): A general class of white blood cells that ingest microbes and other cells and foreign particles; monocytes, macrophages and neutrophils are types of phagocytes. (Also see entry on "granulocyte.")

Phagosomes: A compartment inside a phagocyte in which pathogenic microorganisms can be killed and digested.

Phenotype: The constellation of traits that result from one or more specific genes (genotype). (Also see entry on "genotype.")

Phenotypic variability: The differences in certain traits or disease characteristics that can be associated with a single genotype. (Also see entry on "genotype.")

Phenylketonuria (PKU): A genetic disorder in which the body cannot normally process the amino acid phenylalanine (Phe), part of many proteins that are found in certain foods.

Plasma cells: Antibody (immunoglobulin)-producing cells that develop from B lymphocytes.

Plasmapheresis: A process in which whole blood is taken from an individual's circulation and then treated, usually by centrifugation, to separate the plasma (that is saved) from the cells and corpuscles, which are then then returned to the individual's body.

Platelets: Smallest of the blood cells; their primary function is associated with the process of blood clotting.

Pneumatocele: An air or gas filled cyst that most often develops within lung tissue.

Polymorphism: The quality or state of existing in or assuming different forms.

Polysaccharides: Complex sugars.

Primary immunodeficiency: Immunodeficiency that is intrinsic to the cells and tissues of the immune system, not due to another illness, medication or outside agent damaging the immune system.

Prophylaxis: Medical therapy initiated to prevent or guard against disease or infection.

Protein: A class of chemicals found in the body made up of chains of amino acids (building blocks); immunoglobulins (antibodies) are one example of proteins.

Pyogenic infection: Any infection that results in pus production.

Purpura: Bluish spots (bruises) on the skin occurring in individuals with low blood platelets (thrombocytopenic purpura) or severe blood stream infections (septic purpura).

Recurrent infections: Any infections that occur repeatedly, usually (but not always) affecting the same set of organs in one individual.

Secondary immunodeficiency (SID): Immunodeficiency due to another illness or agent, such as human immunodeficiency virus (HIV), cancer, or chemotherapy.

Sepsis: An infection of the blood.

Sinopulmonary: Of or relating to the paranasal sinuses, the middle ear and the pulmonary airway from the nose down to the terminal bronchi and air sacs in the lungs.

Spleen: An organ in the abdominal cavity; it is directly connected to the blood stream and like lymph nodes contains B lymphocytes, T lymphocytes and macrophages.

Staph or Staphylococcal: Staphylococcus, a type of bacteria, is commonly referred to as "staph." There are more than 30 types, but Staphylococcus aureus causes most staph infections.

Stem cells: Cells from which all other cell types are derived. There are also stem cells that only give rise to a limited number of other cells such as the hematopoietic stem cell (HSC) from which blood cells and immune cells are derived. The bone marrow is rich in hematopoietic stem cells.

Subcutaneous immunoglobulin (SCIG) infusion: Administration of gamma globulin directly under the skin into the subcutaneous tissues.

T cell anergy: A tolerance mechanism in which the lymphocyte is intrinsically functionally inactivated following an antigen encounter, but remains alive for an extended period of time in a hyporesponsive state.

Telangiectasia: Dilation of the small blood vessels, usually in the skin and eyes.

Thrombocytopenia: Low platelet count.

Thrush: A fungal disease on mucous membranes of the mouth caused by Candida.

Thymus gland: A lymphoid organ located behind the upper portion of the sternum (breastbone). The thymus is the chief source and educator of T lymphocytes. This organ increases in size from infancy to adolescence and then begins to shrink.

Titer: A measurement of the amount or concentration of a substance in a solution. It usually refers to the level in the blood of antibodies binding a specific antigen.

T lymphocytes (or T cells): Surfaces that come in close contact with the environment, such as the mucous membranes of the mouth, nose, gastrointestinal tract, eyes, etc; IgA antibodies protect these surfaces, or mucus membranes, from infection.

Unusual infectious agents: These are normally non-pathogenic agents or those not generally found in humans, which can cause serious disease in immunocompromised patients. (Also see entry for "opportunistic infection.")

Vaccine: A substance that contains components from an infectious organism which stimulates an immune response in order to protect against subsequent infection by that organism.

Vacuole: A cavity or vesicle containing fluid in the cytoplasm of a cell.

Vectors: Modified viruses or other carriers used to deliver genetic material into a cell; used in gene therapy to insert normal genes in cells.

Venipuncture: The collection of blood from a vein, usually for laboratory testing.

Virus: A submicroscopic microbe causing infectious disease; can reproduce only in living cells.

White blood cells: See "leukocyte."

X-linked recessive inheritance: A form of inheritance where the characteristic, or disease, is inherited on the X-chromosome. As such, it almost always is only seen in boys (male offspring).

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